

Some Factors in the Epidemiology of Histoplasmin Sensitivity in Williamson County, Tennessee*

L. D. ZEIDBERG, M.D., M.P.H., F.A.P.H.A., ANN DILLON, M.S.P.H., F.A.P.H.A., AND R. S. GASS, M.D.

Tennessee Department of Public Health, Nashville, Tenn.

WHEN the Williamson County Tuberculosis Study was initiated almost twenty years ago, the clinician and roentgenologist usually experienced little difficulty in making an x-ray diagnosis of tuberculosis. A soft infiltrate seen in the upper lung field of a chest film was inevitably labelled tuberculous, and calcified pulmonary nodules were almost never believed to be anything but calcium deposited in a primary tuberculous lesion. Yet, during the first analysis of material three years after the Study began, a curious observation was made that was destined to upset certain well established dicta, and to lead to the eventual realization that "all that calcifies is not tuberculosis." Roentgenological and clinical diagnoses of tuberculosis, made according to the then accepted criteria, were found to be associated with negative tuberculin reactions in a significant number of instances. The investigators first concluded that "tuberculin testing of contacts does not identify all individuals who have been infected."¹ Investigation of school children in Williamson County in 1937 revealed that calcified pulmonary lesions were present in negative reactors to tuberculin just

about as frequently as in positive reactors.² Subsequent studies done in 1939³ and in 1941⁴ strengthened the original observations, and the investigators were perplexed. Did these findings indicate that the tuberculin test was not as specific as had been believed, or did some agent other than the tubercle bacillus produce lesions which resembled tuberculosis? Christie and Peterson at Vanderbilt University applied themselves to the problem. Using several antigens in addition to tuberculin, to test a group of children with calcified pulmonary lesions, they discovered that many more reacted to histoplasmin than to tuberculin.⁵ In a comprehensive review of the subject, and from their own findings, they concluded that "an immunologic relationship between histoplasmin sensitivity and the problem of pulmonary calcification" was suggested by the accumulated evidence. Palmer's studies supported the observation and conclusion.⁶

Since these first significant reports, the literature has been liberally studded with accounts of other investigations of histoplasmin sensitivity and histoplasmosis, but a number of crucial factors in their epidemiology remain obscure. As yet the source of *Histoplasma capsulatum* in nature has not been determined, nor has its mode of transmission been established. These are but two of the most significant problems. No solution for them is offered here, but it is hoped

* Presented before the Epidemiology Section of the American Public Health Association at the Seventy-eighth Annual Meeting in St. Louis, Mo., October 31, 1950.

This investigation was made possible by the financial assistance of the International Health Division of the Rockefeller Foundation.

that some clues may be provided by the observations that have been made during the past five years in Williamson County.

PREVALENCE OF HISTOPLASMIN
SENSITIVITY
In these studies of histoplasmin sen-

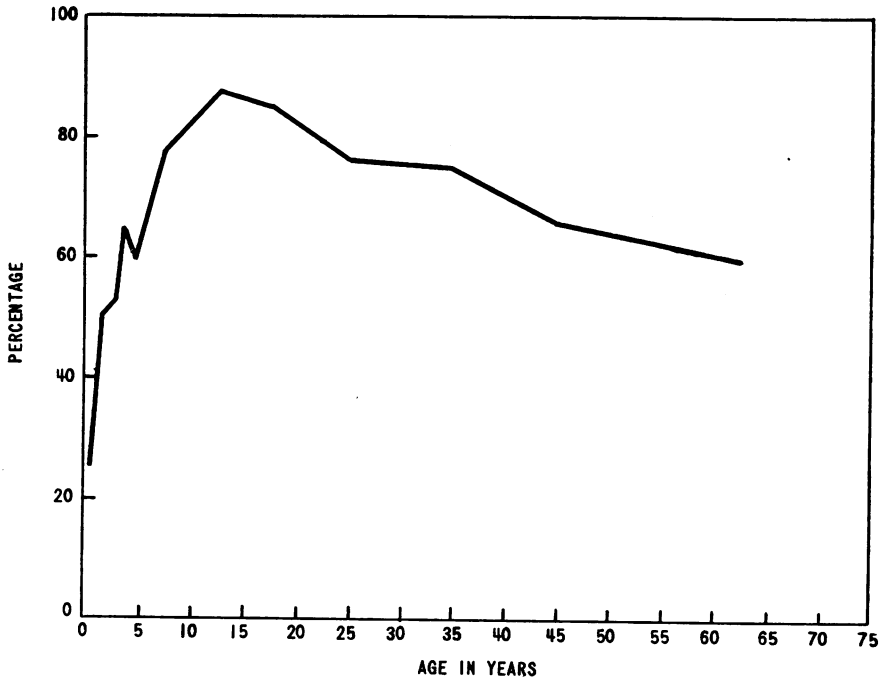
TABLE 1

Number of Persons Tested with Histoplasmin and Number and Percentage Positive, by Color, Sex and Age Group, Williamson County, Tennessee, August, 1945-July, 1950

Age in Years	Total			Male			Female		
	Number Tested	Positive		Number Tested	Positive		Number Tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
	Total								
Total	5,044	3,610	71.6	2,164	1,560	72.1	2,880	2,050	71.2
Under 1	251	62	24.7	132	34	25.8	119	28	23.5
1	287	145	50.5	157	84	53.5	130	61	46.9
2	238	124	52.1	112	59	52.7	126	65	51.6
3	234	153	65.4	114	79	69.3	120	74	61.7
4	183	108	59.0	96	58	60.4	87	50	57.5
5-9	1,055	818	77.5	501	394	78.6	554	424	76.5
10-14	982	856	87.2	453	389	85.9	529	467	88.3
15-19	615	521	84.7	245	213	86.9	370	308	83.2
20-29	287	219	76.3	59	50	84.7	228	169	74.1
30-39	359	266	74.1	80	66	82.5	279	200	71.7
40-49	220	143	65.0	68	44	64.7	152	99	65.1
50 and over	333	195	58.6	147	90	61.2	186	105	56.5
	White								
Total	3,868	2,806	72.5	1,647	1,201	72.9	2,221	1,605	72.3
Under 1	182	49	26.9	90	24	26.7	92	25	27.2
1	209	113	54.1	116	62	53.4	93	51	54.8
2	169	93	55.0	79	44	55.7	90	49	54.4
3	173	114	65.9	88	62	70.5	85	52	61.2
4	132	78	59.1	65	39	60.0	67	39	58.2
5-9	817	638	78.1	399	314	78.7	418	324	77.5
10-14	786	689	87.7	358	312	87.2	428	377	88.1
15-19	431	368	85.4	166	147	88.6	265	221	83.4
20-29	223	173	77.6	45	39	86.7	178	134	75.3
30-39	293	220	75.1	65	51	78.5	228	169	74.1
40-49	180	118	65.6	61	40	65.6	119	78	65.5
50 and over	273	153	56.0	115	67	58.3	158	86	54.4
	Colored								
Total	1,176	804	68.4	517	359	69.4	659	445	67.5
Under 1	69	13	18.8	42	10	23.8	27	3	11.1
1	78	32	41.0	41	22	53.7	37	10	27.0
2	69	31	44.9	33	15	45.5	36	16	44.4
3	61	39	63.9	26	17	65.4	35	22	62.9
4	51	30	58.8	31	19	61.3	20	11	55.0
5-9	238	180	75.6	102	80	78.4	136	100	73.5
10-14	196	167	85.2	95	77	81.1	101	90	89.1
15-19	184	153	83.2	79	66	83.5	105	87	82.9
20-29	64	46	71.9	14	11	78.6	50	35	70.0
30-39	66	46	69.7	15	15	100.0	51	31	60.8
40-49	40	25	62.5	7	4	*	33	21	63.6
50 and over	60	42	70.0	32	23	71.9	28	19	67.9

* Percentage not figured when less than 10 persons were tested.

FIGURE 1—Percentage of Persons Positive to Histoplasmin by Age, Williamson County, Tennessee, August, 1945–July, 1950



sitivity, persons in all age groups have been included. However, efforts were concentrated on children under 5 years of age because in this age group was offered the best opportunity to observe the evolution of histoplasmin sensitivity and calcification. Between August, 1945, when the program began, and July, 1950, 5,044 individuals have been tested with histoplasmin.* Of these, 2,164 were males and 2,880 females; 3,868 were white and 1,176 colored. Children under 5 years of age comprised 24 per cent of the total number tested, those 5–19 years of age, 53 per cent, and individuals 20 years of age and over, 24 per cent. Table 1 shows the number of persons tested with histoplasmin, and the number and percentage positive, by color, sex, and age group.

* The histoplasmin used in these studies was obtained from Drs. Christie and Peterson. Antigen from the same lot was used practically throughout. It was administered intracutaneously in doses of 0.1 ml. of a 1–100 solution. Results were read in 48 hours.

The prevalence of histoplasmin sensitivity was found to rise abruptly from 25 per cent in the first year of life to a peak of 87 per cent at 10–14 years of age, and then to decline gradually as shown in Figure 1. The pattern of this curve was similar for males and females, and for white and colored persons.

No difference was noted in the percentage of positive reactors by sex, but the percentage of colored persons who reacted was slightly less than that of white persons. The greatest difference in sensitivity for white and colored was observed in children under 5 years of age, where, for colored females, the percentage of positive reactors was unusually low. The explanation for this unexpected finding is not clear. It may be due to the influence of some hidden selective factor, for certainly there is no evidence that individuals in this group are either less susceptible or less exposed to the sensitizing agent.

The observations noted above are not

entirely in accord with those reported by Emmons, *et al.*⁷ and by Furcolow, *et al.*⁸ In Furcolow's study there was no difference in histoplasmin sensitivity by sex up to the age of 20, but thereafter the proportion of sensitized individuals was higher for males than for females. Emmons also reported a higher occurrence of allergy in adult males. In both of these studies, selected adult groups were tested. Furcolow's study group was composed predominantly of urban males in local or federal government service. In Williamson County the population is about 75 per cent rural in residence, and the only selective factor which operated in this study was the usual unavailability of working males for testing.

Since the occurrence of sensitivity is similar among adult males and females in Williamson County, it may be inferred that, where reported differences have been observed, they result rather from an inequality of exposure than from any real sex difference in susceptibility to infection with the agent.

The collected data indicate that the sensitizing agent which produces allergy to histoplasmin is quite liberally distributed in Williamson County, and that all segments of the population come in contact with the agent. The rising frequency of sensitivity with age up to 15 years may be explained by increasing opportunities for exposure as children grow older and expand their activities. The decline in sensitivity which occurs after the age of 15 may be due to several factors. It may result either from a loss

of allergy in previously sensitized individuals whose opportunity for exposure to the agent diminishes in later life; or from the eventual development of immunity in some people who have had repeated exposures to the agent. It is interesting to note that Furcolow's data show a similar decline in sensitivity with later age, but in his study the peak of sensitivity was reached later than in ours, and most of the subsequent decline appeared to be in the females.

LOSS OF SENSITIVITY

Between August, 1945, and July, 1950, 855 persons were retested at least once with histoplasmin (Table 2). Of this number, 506 had been positive and 349 negative on the first test. Of those positive on the first test, 426, or 84.2 per cent, were still positive when retested. One hundred and eighty-two, or 52.1 per cent, of those negative on the first test had acquired sensitivity by the time of the second test.

Attention was focused particularly on those who were originally positive because they offered the best possibility of obtaining information on the allergenic potency of the sensitizing agent, and on the enduring qualities of the allergy. Eighty of the 506 individuals who were positive on the first test were found to have reverted to negative after an average interval of 25 months. The total reversion rate was 15.8 per cent, but it was by no means uniform at all ages, as shown in Table 3 and Figure 2.

Of the infants, under 1 year of age

TABLE 2

Number of Persons Retested with Histoplasmin According to Results of First and Second Tests, Williamson County, Tennessee, August, 1945-July, 1950

Result of First Test	Total		Result of Second Test			
	Number	Per cent	Positive		Negative	
			Number	Per cent	Number	Per cent
Total	855	100.0	608	71.1	247	28.9
Positive	506	100.0	426	84.2	80	15.8
Negative	349	100.0	182	52.1	167	47.9

FIGURE 2—Percentage of Persons Positive to Histoplasmin on First Test Who Were Negative on Second Test, by Age at First Test, Williamson County, Tennessee, August, 1945–July, 1950

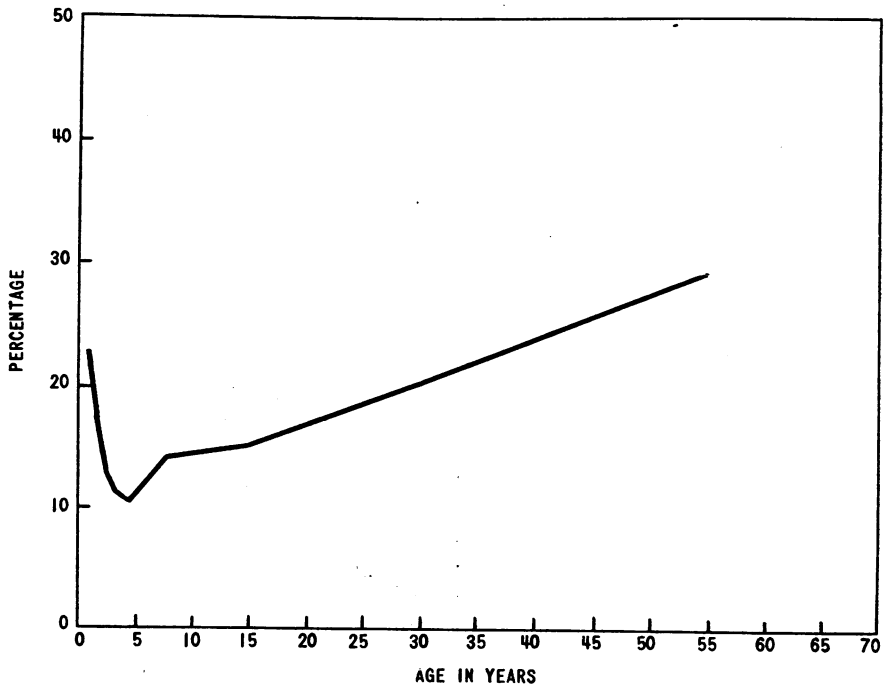


TABLE 3

Number of Persons Positive to Histoplasmin on First Test Who Were Retested and Number and Percentage Negative on Second Test, by Age at First Test, Williamson County, Tennessee, August, 1945–July, 1950

Age in Years	Total	Negative	
		Number	Per cent
Total	506	80	15.8
Under 1	30	7	23.3
1	53	9	17.0
2	40	5	12.5
3	62	7	11.3
4	41	4	9.8
5–9	97	14	14.4
10–19	107	16	15.0
20–39	45	9	20.0
40 and over	31	9	29.0

when first tested, 23 per cent were negative when retested. The reversion rate then fell abruptly but steadily at each succeeding age until it reached a low point of about 10 per cent at age 4. The percentage of individuals who became negative then increased with age

to a high point of 29 per cent in those 40 years of age and over.

It is apparent that histoplasmin allergy is of a much lower order of endurance than tuberculin allergy. But if allergy in the observed group was not permanent, neither was the anergy that developed in those who reverted. In a small number of individuals who had a series of histoplasmin tests, some have gone from positive to negative to positive again. More information about such vacillations of sensitivity should be available in the future as a result of the program which has now been instituted of retesting individuals at 6 month intervals.

It is interesting to speculate on possible explanations for the varying reversion rates at different ages. The ubiquity of the sensitizing agent in Williamson County is apparent from the prevalence data presented above. Persistence of

allergy must be an expression either of a continued, active, first infection, or of reinfections. In infants under 1 year of age, reversion rates are high while prevalence is relatively low. Both observations point to a comparatively infrequent opportunity for first infection and for reinfection at this age. In the older ages, the reversion rates are the highest, but the prevalence of sensitivity has declined from its peak. Again, this may be an expression of a declining frequency of contact with the sensitizing agent. It is also possible, however, that after repeated reinfections some immunity may develop, and this immunity is apt to be manifested most in older people who have had a long experience with the agent. It is hardly likely that the explanation lies in progressive desensitization produced by repeated exposures, because experiments done with tuberculin indicate that massive doses administered over prolonged periods are required to accomplish anergy. These conditions could hardly be expected to occur in nature, even if it is assumed that tuberculin and histoplasmin allergy are comparable.

INFLUENCE OF SEASON

As the study progressed, it was noted that the prevalence of histoplasmin sensitivity varied at different times of the year, and from one year to another. Not all segments of the population were

tested throughout the year, so it was not possible to make an overall analysis of sensitivity by season. The most sustained observation was made of children under 5 years of age, and since they comprised about one-fourth of the whole, analysis of the data was made for this group alone. The data are shown in Table 4 and Figure 3 for two periods of time, August 1945, to December, 1949, and for January to July, 1950. The 1950 findings are presented separately because tabulations for only the first 7 months of the year are available, and the 1950 percentages have been so much higher than in the past that undue weight would have been cast on the January to July data of previous years.

Prevalence of sensitivity is at its lowest in children under 5 years of age during the winter and early spring. A rise occurs throughout the summer to a peak in the early fall, and then there is a decline. The 1950 curve parallels that of previous years, but is on a higher level.

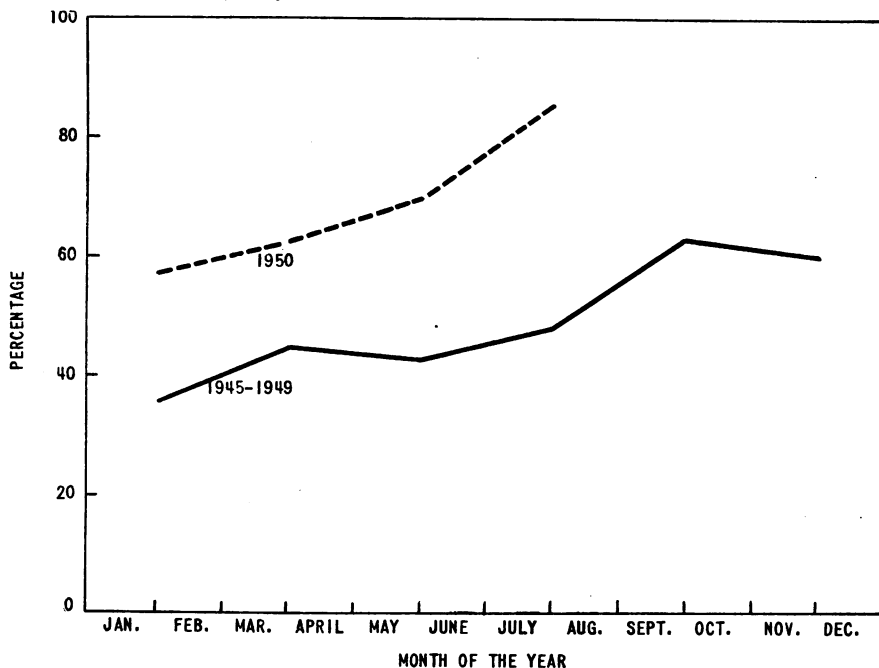
The pattern of the curve for children under 2 and for those 2-4 years of age is similar, but varies in degree. The greatest seasonal variation is noted in children under 2 years of age, as shown in Table 5. Here the variation is significantly greater than could have occurred by chance. For the 2-4 year age group the differences are within the limits of probability.

TABLE 4

Number of Children under 5 Years of Age Tested with Histoplasmin and Number and Percentage Positive by Season of the Year, Williamson County, Tennessee, August, 1945-December, 1949, and January-July, 1950

Month of the Year	1945-1949			1950		
	Number Tested	Positive		Number Tested	Positive	
		Number	Per cent		Number	Per cent
Total	1006	464	46.1	187	128	68.4
January-February	102	36	35.3	16	9	56.2
March-April	187	83	44.4	79	49	62.0
May-June	316	133	42.1	51	35	68.6
July-August	242	114	47.1	41	35	85.4
September-October	112	70	62.5			
November-December	47	28	59.6			

FIGURE 3—Percentage of Children under 5 Years of Age Positive to Histoplasmin, by Season, Williamson County, Tennessee, August, 1945–December, 1949, and January–July, 1950



Several possible explanations may be offered for the seasonal variations in histoplasmin sensitivity. The sensitizing agent may be present in greater abundance at some seasons than at others; or, if a vector is involved in the transmission of the agent, the vector population may vary with season. A third explanation for the observed seasonal variation may lie in the habits and customs of the population. Children under 2 are more apt to be confined indoors during cold

and rainy weather than older children, and it is precisely these seasons that correspond with the periods of lowest sensitivity. Also, children under 2 years of age have a rather limited horizon of activity compared to older children. Infants and those under 2 may not come in contact with the agent unless it is brought to them, whereas older children may be exposed to the agent at its source in nature while they are engaged in outdoor play.

TABLE 5

Number of Children under 5 Years of Age Tested with Histoplasmin and Number and Percentage Positive for Two Age Groups, Williamson County, Tennessee, August, 1945–December, 1949

Month of the Year	Under 2 Years			2-4 Years		
	Number Tested	Positive		Number Tested	Positive	
		Number	Per cent		Number	Per cent
Total	450	154	34.2	556	310	55.8
January-February	47	10	21.3	55	26	47.3
March-April	77	23	29.9	110	60	54.5
May-June	151	43	28.5	165	90	54.5
July-August	102	37	36.3	140	77	55.0
September-October	54	32	59.3	58	38	65.5
November-December	19	9	47.4	28	19	67.9

As has been noted above, the 1950 prevalence is on a much higher level than had been observed during preceding years. This difference cannot be accounted for by any change in procedure, technique of administration of the histoplasmin, or potency of the histoplasmin. A tentative explanation may lie in the unusual weather conditions that have prevailed in Williamson County during 1950. The winter and spring were exceptionally mild and rainy. Summer was relatively cool, and July, especially, was marked by excessive rainfall. These correlations are not entirely conjectural, as will be demonstrated in the next section on the effect of dampness on sensitivity. Local weather bureau meteorological data for the past five years are now being analyzed with the hope that some suggestive explanations for the yearly variations in histoplasmin sensitivity may be found.

EFFECT OF DAMPNESS

An epidemiologic investigation of homes in which at least one child under 5 years of age had been tested with histoplasmin and x-rayed was undertaken during the summer of 1946.* Two

hundred and seventy-one homes in which there were 546 children under 15 years of age who had been tested were investigated for economic status, source of drinking water, types of grain cultivated, presence or absence of various animals in and around the house, and dampness of the home and environment. Certain criteria for judging dampness were arbitrarily established.† Analysis of the data revealed that there was no association between histoplasmin sensitivity and any of the factors investigated, with the exception of dampness. Data concerning cows and rodents were suggestive but not conclusive.

There appeared to be a positive association between dampness and histoplasmin sensitivity (Table 6, Figure 4). In damp environments the percentage of children under 15 years of age who reacted to histoplasmin was 86.1; in dry environments near a creek the percentage was 66.1; and in dry environments without a creek, it was 48.9. Apparently the association was not influenced by age except in the very dry environment, where children under 5 years of age experienced a relatively low occurrence of sensitivity. It may be inferred that

TABLE 6

Number and Percentage of Children under 15 Years of Age Reacting to Histoplasmin according to Dampness of Environment, by Age Group, Williamson County, Tennessee, 1946

Age in Years	Damp			Dry with Creek			Dry		
	Number Tested	Positive		Number Tested	Positive		Number Tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
Under 15	72	62	86.1	245	162	66.1	229	112	48.9
Under 5	30	25	83.3	95	58	61.1	98	30	30.6
5-9	21	20	95.2	99	65	65.7	78	47	60.3
10-14	21	17	81.0	51	39	76.5	53	35	66.0

* This program was under the direction of Dr. H. C. Stewart, former Director of the Williamson County Tuberculosis Study, with the assistance of Dr. Robert Nesbitt.

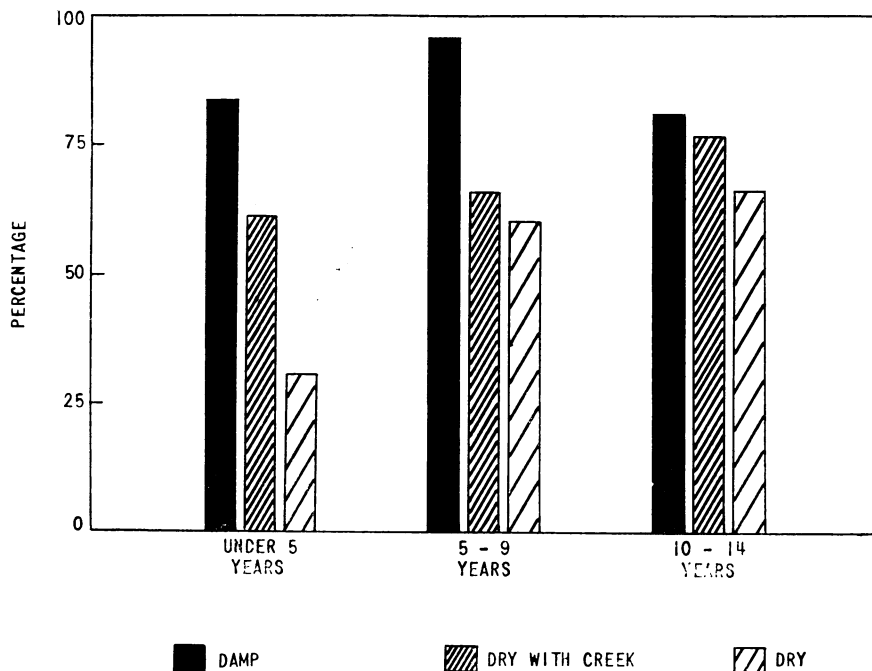
† 1. Damp—evidence of moss in the yard and on trees, creek or pond 100 yds. or closer to the house.

2. Dry with creek—house dry, but creek or pond within 100 yds. of house.

3. Dry—house dry, creek or pond (if any) more than 100 yds. from house.

children of this age are not frequently exposed to infection, in or near the home, if the environment is dry, and since their activity at any appreciable distance from home is limited by their age, they do not have the same opportunity for exposure to the sensitizing agent as children of school age.

FIGURE 4—Percentage of Children under 15 Years of Age Positive to Histoplasmin, according to Dampness of Environment, by Age Group, Williamson County, Tennessee, 1946



This correlation between dampness and histoplasmin sensitivity is reasonable considering the nature and growth characteristics of fungi. If dampness is indeed a factor in determining the prevalence of histoplasmin sensitivity, the observed yearly variations may well be explained by differences in precipitation and humidity from year to year.

SUMMARY

1. Between August, 1945, and July, 1950, 5,044 individuals of all ages were tested with histoplasmin in Williamson County, Tennessee. Positive reactions occurred in 25 per cent of those under 1 year of age, then rose abruptly with age to a peak of 87 per cent in those 10-14 years of age. After the age of 15 years, the proportion of positive reactors declined steadily.
2. There was no significant difference in the percentage of positive reactors among males and females at any age, or *in toto*.
3. Colored people showed a lower proportion of positive reactors than white, with the

greatest difference manifested in those under 5 years of age.

4. Five hundred and six individuals who had been positive on first test, were retested at an average interval of 25 months. Of this number, 15.8 per cent had reverted to negative by the time of the second test. Reversion rates were highest in those under 1 year of age and in those 40 years of age and over.

5. Seasonal variation in allergy was studied in children under 5 years of age only. In this group histoplasmin sensitivity appeared to be at its lowest level in the winter and early spring. The percentage of positive reactions rose during the summer to a peak in the fall, and then declined.

6. Epidemiological investigation of 271 homes in which at least one child under 5 years of age had been tested, revealed an association between positive reaction and dampness of the environment. This association was particularly marked in children under 5 years of age.

7. Several possible explanations for the above observations have been offered.

REFERENCES

1. Stewart, H. C., Gass, R. S., Gauld, R. L., and Puffer, Ruth R. Tuberculosis Studies in Tennessee;

- A clinic study with reference to epidemiology within the family. *A.J.P.H.* 26:689 (July), 1936.
2. Gass, R. S., Gauld, R. L., Harrison, E. F., Stewart, H. C., and Williams, W. C. Tuberculosis Studies in Tennessee: Roentgenological evidence of tuberculous infection in relation to tuberculin sensitivity in school children. *Am. Rev. Tuberc.* 38:441 (Oct.), 1938.
 3. Gass, R. S., Murphy, William J., Harrison, E. F., Puffer, Ruth R., and Williams, W. C. Tuberculosis Infection in Relation to Tuberculin Sensitivity in School Children. *A.J.P.H.* 31:951 (Sept.), 1941.
 4. Gass, R. S., Harrison, E. F., Puffer, R. R., Stewart, H. C., and Williams, W. C. Pulmonary Calcification and Tuberculin Sensitivity among Children in Williamson County, Tennessee. *Am. Rev. Tuberc.* 47:379 (Apr.), 1943.
 5. Christie, A., and Peterson, J. C. Pulmonary Calcification in Negative Reactors to Tuberculin. *A.J.P.H.* 35:1131 (Nov.), 1945.
 6. Palmer, Carroll E. Non-tuberculous Pulmonary Calcification and Sensitivity to Histoplasmin. *Pub. Health Rep.* 60:513 (May), 1945.
 7. Emmons, C. W., Olson, B. J., and Eldridge, W. W. Cross Reactions of Histoplasmin. *Ibid.* 60:1383 (Nov.), 1945.
 8. Furcolow, M. L., High, R. H., Allen, M. F. Some Epidemiological Aspects of Sensitivity to Histoplasmin and Tuberculin. *Ibid.* 61:1132 (Aug.), 1946.

NOTE: The authors wish to express their gratitude to Drs. Amos Christie and J. C. Peterson for their advice and encouragement in the planning and execution of this study.

New Jersey Calls Regional Conference

An Eastern States Conference on Local Health Services and Civil Defense has been called by the Governor of New Jersey on the suggestion of his Commission on Local Health Services. The governors of Delaware, Pennsylvania, New York, and Massachusetts have accepted an invitation to be represented by a group of up to 25 citizens at a conference to work out ways and means for improving local health services, particularly in relation to civil defense, in their various states.

The Conference to be held January 22,

and 23 at the Nassau Tavern, Princeton, N. J., is being organized by Mrs. Frances Mancusi-Ungaro of Newark, in her capacity as chairman of a Subcommittee on Meetings of the Governor's Commission. The National Health Council, through its National Advisory Committee on Local Health Units, is serving in an advisory capacity. Plans for the Conference were made in early December at a meeting in Trenton attended by representatives from the health departments of the five states.