Histoplasmosis: Study of Reactors to Histoplasmin

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THIS study of the reactors to histoplasmin as compared to those reacting to tuberculin was carried out at Berea College, Berea, Ky., by the Student Health Service with coöperation of the State Department of Health of Kentucky.

Berea College is located on the border of the Southern Appalachian mountain area. Most of the students come from the mountain counties of 8 states—Kentucky, Tennessee, Virginia, West Virginia, North Carolina, South Carolina, Georgia and Alabama, mostly from rural homes. The largest group comes from Kentucky.

Histoplasma capsulatum infections have been found in part of this area. The Berea College Student Health Service has carried on a tuberculosis case finding study since 1931. Thousands of roentgenograms have been made. Many students were found with lung calcifications who had a negative tuberculin test. Some of these were rejected by Selective Service on the basis of roentgenograms.

The publication of the studies of Christie and Peterson[1, 2] and the report of Palmer[3] demonstrated by the means of skin tests the probability of benign histoplasmosis in part of this area. We questioned whether the lung calcifications in our students might have this histoplasmosis as an etiological factor. Previous reports by Darling[4–6] and Parsons[7] had suggested this condition as a fatal infection only rarely seen. After correspondence with Dr. Palmer and Dr. Christie concerning our situation and program, we instituted a special study in November, 1946.

Histoplasmin was obtained from the U. S. Public Health Service. It was used in 1:1,000 dilution; 0.1 ml. was injected in the forearm intradermally. Purified Protein Derivative of Tuberculin (Parke, Davis & Company) was used for the Mantoux test which was given at the same time. The dosage was 0.0001 mg. on advice of Dr. Palmer.[8]

All tests were read in 48 hours. Chest roentgenograms, using 14 x 17″ x-ray films, were made possible by the cooperation of the Tuberculosis Control Division of the Kentucky State Department of Health. Flat films were taken of about 1,200 students. On 1,004 of these we had complete data, and they are included in Table 1. Incomplete information was largely in the field of residence data.

The films were read by the writer and by Dr. E. N. Maxwell of the Kentucky State Department of Health. They were read independently and, also, together, to correlate results. Readings were made without knowledge of the skin test reactions. Data were obtained in regard to age, sex, and residence.

The tables show the results of analyzing the total data. If a person had moved about so that there was no one long continued residence, we left residence unclassified. No one knows how long a residence is required to become

a reactor. If all but four years had been in a home county or adjoining county, the residence was classified. In many cases the numbers from a given county were so small as to have little statistical significance. This is also true of some state groups. The figures are given for what they may be worth.

The majority of those tested fell in the age group between 16 and 24. The numbers in other age groups are too small for statistical purposes. They include faculty members and some faculty children. Data on some of the younger children, who have lived in Berea only, suggest that a long residence is not necessary to become sensitized to histoplasmin. The other age groups are included to complete the picture as we found it. Thirty-three per cent of those tested reacted to the Mantoux test, 41 per cent of the males and 25 per cent of the females. Fifty per cent of those tested reacted to histoplasmin, 58 per cent of the males and 44 per cent of the females. Some of the skin test results

TABLE 1

Summary of Skin Tests by Age Groups and Sex

		Mantoux Test			*Histoplasmin Test*		
		Pos.	*Neg.*	*Per cent Pos.*	*Pos.*	*Neg.*	*Per cent Pos.*
Under 12	Male	1	2	33	3	0	100
	Female	0	1	0	1	1	100
	Total	1	3	25	4	1	100
13–15	Male	2	24	8	16	10	61
	Female	0	27	0	13	14	48
	Total	2	51	4	29	24	55
16–18	Male	47	113	29	75	86	46
	Female	45	196	18	81	153	36
	Total	92	309	23	156	239	39
19–21	Male	44	69	39	66	51	59
	Female	67	218	23	129	151	46
	Total	111	287	28	195	202	48
22–24	Male	54	56	50	67	41	62
	Female	19	50	27	35	33	51
	Total	73	106	40	102	74	58
25–27	Male	27	36	43	41	21	66
	Female	11	10	50	11	9	55
	Total	38	46	45	52	30	63
28–30	Male	15	6	72	11	9	55
	Female	5	0	100	4	1	80
	Total	20	6	77	15	10	60
Over 30	Male	37	10	79	34	10	77
	Female	31	13	70	29	20	59
	Total	68	23	74	63	30	69
Total	Male	227	316	41	313	228	58
Total	Female	178	515	25	303	381	44
Grand Total		405	831	33	616	609	50

382 individuals reacted to the Histoplasmin test but not Mantoux.
224 individuals reacted to both tests.
168 were negative to the Histoplasmin test but reacted to Mantoux.

TABLE 2

Summary of Skin Tests by Residence

(Mountain Counties of 8 States Contrasted with Plain Counties)

	Mantoux Test			*Histoplasmin*				
	Pos.	*Neg.*	*Per cent Pos.*	*Pos.*	*Neg.*	*Per cent Pos.*	*Positive to Both*	*Negative to Both*
Kentucky								
Mountain	184	328	36	302	207	59	113	136
Plain	33	56	37	66	23	74	25	17
Total	217	384	41	368	230	61	138	153
Tennessee								
Mountain	11	38	22	27	20	47	8	17
Plain	2	8	20	7	2	77	1	2
Total	13	46	22	34	22	60	9	19
West Virginia								
Mountain	25	41	38	22	44	33	11	29
Plain	9	19	32	10	17	37	3	10
Total	34	60	34	32	61	37	14	39
Virginia								
Mountain	17	60	22	24	52	32	6	41
Plain	1	10	9	4	7	36	0	6
Total	18	70	20	28	59	32	6	47
North Carolina								
Mountain	15	63	19	14	64	26	2	51
Plain	2	11	15	1	13	12	0	10
Total	17	74	18	15	77	23	2	61
South Carolina								
Mountain	1	5	17	1	5	17	1	4
Plain	1	5	17	2	3	40	1	3
Total	2	10	17	3	8	27	2	7
Georgia								
Mountain	1	4	20	1	5	17	0	4
Plain	2	5	28	0	7	0	0	5
Total	3	9	25	1	12	7	0	9
Alabama								
Mountain	10	10	50	14	6	70	7	2
Plain	2	2	50	1	3	25	1	2
Total	12	12	50	15	9	65	8	4
Ohio	5	19	20	14	8	63	2	6
New England States	4	5	44	2	7	22	2	5
North Atlantic States	3	15	17	8	9	47	3	9
North Central States	8	11	42	13	6	68	5	3
South Central States	0	3	0	2	1	66	..	..
South Western States	0	1	0	1	0	100	..	..
Mid-western States	3	7	30	6	4	60	1	2
Western States	4	4	50	2	6	25	1	3
Foreign	16	15	50	8	23	38	6	13
Residence short time 1 place	46	84	35	63	67	48	24	46
Residence not given	0	1	0	1	0	100	..	..
Grand Total	405	831	33	616	609	50	223	226

were questionable. These are not recorded in the tables but they account for the differences in totals with Mantoux compared to totals with histoplasmin test. Table 1 presents a summary of the test results by sex and age. (Statistical data were compiled with the assistance of the State Department of Health.)

The summary of the results of tuberculin tests in 91 colleges this same year showed 22.6 per cent males and 9.4 per cent females as reactors, or 19 per cent of both.[9]

Table 2 classifies the reactors according to residence. It willl be noted that the highest percentage of reactors was found in those giving Kentucky and Tennessee as their residence. Because most of our students come from the mountain counties of the South we have separated the residence by mountain area and so-called plain area of those states. The number with residence out of the mountains and in other states is too low for statistical value but shows our findings.

Madison County of Kentucky, in which Berea is located, is on the border of the mountains and the Blue Grass area. Over 100 individuals living in the county were tested with 70 per cent reactors.

Table 3 emphasizes the importance of the tuberculin test if we are to find those who have been infected. Lung calcifications alone cannot be used in this area as evidence of primary tuberculosis. Fifty-one per cent of those found with lung calcification had negative Mantoux tests. Only 13 per cent of those positive to Mantoux and not to histoplasmin test showed lung calcification, while 22 per cent of those positive to both showed calcification. There were 71 individuals with x-ray findings identical with those usually called calcification due to tuberculosis who had no reaction to the Mantoux test but were positive to the histoplasmin test. Histoplasmosis must be considered in the future in the differential diagnosis of lung calcifications found on reontgen-ray examination along with tuberculosis, coccidioidomycosis and sarcoidosis.

Table 3, classification of the roentgen-ray findings, is self explanatory. The questionable cases and those with no films recorded are included to show their distribution in the skin tests.

Clinical signs and symptoms of fatal histoplasmosis were reported by Parsons and Zarafonetis,[7] McLeod, Emmons, Ross and Burke,[10] and Christie.[1, 2, 11] We are especially interested in the symptomatology of subclinical cases discov-

TABLE 3

Summary of Roentgen-Ray Findings

Classification	*Pos. Mant. Pos. Hist.*	*Pos. Mant. Neg. Hist.*	*Neg. Mant. Pos. Hist.*	*Neg. Mant. Neg. Hist.*
1. Negative	118	124	246	327
2. Definite hilar calcification	5	3	15	4
3. Probable hilar calcification	3	0	4	3
4. Definite parenchymal calcification (1–4 foci)	15	4	21	1
5. Probable parenchymal calcification (1–4 foci)	8	1	6	2
6. Parenchymal calcification (5 or more foci)	0	1	0	0
7. Definite hilar and parenchymal calcification	15	3	16	4
8. Probable hilar and parenchymal calcification	3	1	2	0
9. Definite hilar calcification, probable parenchymal	0	1	4	1
10. Probable hilar and definite parenchymal calcification	1	0	3	0
11. Questionable calcification	7	6	9	10
12. Parenchymal infiltration or cavitation	0	4	0	0
13. No x-ray	49	19	56	76
14. Other chest pathology	0	1	1	1
Total positive x-rays	50	18	71	15

Two previously unknown active cases of pulmonary tuberculosis were discovered in this survey.

ered by the skin test and roentgenogram studies. We have not that information now. Long-term studies should be carried out with children living in areas where the tests show a high percentage of reactors to histoplasmin. Careful clinical history recorded as the children grow older, plus repeated skin tests and roentgen examinations, may reveal a symptom complex. We know that children develop histoplasmin reactions early in life and show extensive pulmonary calcification as well. So these studies must be begun early in life.

Some question the validity of the assumption that we are really discovering subclinical cases of histoplasmosis in this way. Others question the specificity of the test. And there are those who disagree with the assumption that the lung calcification revealed in a study such as this may actually be due to histoplasmosis. But there does seem to be good circumstantial evidence, and thus far no other explanation has been found to fit the picture.

These studies emphasize the importance of the histoplasmin test in this area. They show that the tuberculin test continues to have importance since we cannot differentiate by films between the lung calcification of primary tuberculosis and this condition.

SUMMARY

1. Results of skin tests using tuberculin and histoplasmin in students at Berea College are shown in tables.

2. The finding of 50 per cent positive reactors to histoplasmin further confirms this area as one infected with the fungus.

3. The tables show the relationship between reactors to tuberculin and histoplasmin and the x-ray studies of the group.

4. A significant number of students with negative tuberculin tests but positive histoplasmin tests showed lung calcification.

5. The tuberculin test is still an important procedure in the diagnosis of tubercular lung calcification.

6. Emphasis is placed on the need for long continued studies of small children in this area to discover the symptomatology of subclinical histoplasmosis.

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