Nationwide Histoplasmin Sensitivity and Histoplasmal Infection

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RESULTS of skin testing with histoplasmin and the diagnosis of clinical cases of histoplasmosis have made it clear that where people live is of prime significance in the risk of becoming infected with the fungus *Histoplasma capsulatum*.

The purpose of this paper is twofold: to depict State-to-State variations in indigenous sources of sensitivity to histoplasmin, as measured by the prevalence of reactions among young men who have lived all their lives in one State, and to distinguish, in some regions, between the reactions caused by infection with *Histoplasma* and cross-reactions attributable to infection with other agents. In dealing with geographic units as large as States, the presence of small and perhaps isolated areas of both high and low prevalence will be obscured. State figures, on the other hand, can provide a broad picture of geographic variations across the 3,000 miles from the Atlantic to the Pacific coasts.

Several earlier reports from this office have described nationwide variations in the prevalence of histoplasmin sensitivity and variations in the sizes of reactions observed in different geographic areas (*1–4*). These reports were based on material collected in several studies of young adults during 1945–52. More recently, it has been possible to obtain material in a single study, in which the same histoplasmin, techniques, and procedures were used for giving skin tests, at the same time and place, to large numbers of young men (Navy recruits) from all parts of the country. Results of this newer study confirm and extend the conclusions drawn from the previous material, which was collected, on the average, about 10 years earlier.

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Materials and Methods

For more than 4 years, in a cooperative study with the U.S. Navy, all recruits have been skin tested as they come into the Navy's training centers, at Great Lakes, Ill., and San Diego, Calif., where all recruits receive their basic training. Within the first few weeks after arrival, they are given four skin tests: tuberculin PPD–S, histoplasmin, PPD–B prepared from the Battey type of *Mycobacterium*, and a fourth test with one of a number of other mycobacterial or fungal antigens. PPD–S and histoplasmin have been used as routine tests given to all recruits since the program started. PPD–B was added as a third routine test in June 1958.

The skin tests are given by Navy corpsmen. For each test, 0.1 ml. of diluted antigen is injected intracutaneously into the volar surface of the forearm. Tuberculin and histoplasmin are given in the upper and lower part of the left arm, PPD–B and the fourth antigen on the right arm.

The reactions are read by Public Health Service nurses who are assigned full time to the two training centers and transferred at intervals from one center to the other. The reason for exchanging the staff is to distribute systematic reader differences among recruits from all parts of the country, since most recruits from the eastern States are sent to Great Lakes and those from the western and Gulf States are sent to San Diego. The reactions are read, generally after 2 days, by measuring the transverse diameter of palpable induration in millimeters. Only the measurements are recorded; no judgment is made by the field staff as to whether a reaction might be classed as positive or negative.

The histoplasmin used in the study, identified as batch H–42, is a culture filtrate of *H. capsulatum*. H–42 was prepared in 1947 by Dr. Arden Howell, Jr., of the Public Health Service (*5, 6*). Since 1952, H–42 has been used as the Reference Histoplasmin No. 1 by the Biologics Control Laboratory, Division of Biologics Standards, National Institutes of Health (*7*). The 1:100 dilution used for testing in this program is the same strength which has been used for almost all of the testing done with H–42—probably close to 1 million tests—in this country and abroad over the last 10 years (*8*).

Study Group

A total of 374,187 recruits were available for testing during 1958–61. Of the total, 352,372 specified their race as white, and of these, 340,244 were 17–21 years old on arrival at the training centers. For the sake of homogeneity, the study group is therefore limited to white recruits 17–21 years of age. A relatively small proportion, 15,977, had to be excluded because their records were incomplete for a variety of reasons: not tested, reactions not read, failure to give age, race, residence history, and so on. An additional 8,461 were excluded because they had not been tested with all three routine tests—tuberculin, histoplasmin, and PPD–B. Although the present report deals only with results of the histoplasmin tests, it was desirable for technical reasons connected with tabulating the material to use the identical study group for analysis of results with each of the three antigens used routinely. Since PPD–B was not introduced as a routine test until June 1958, most of those excluded for not having all three tests were recruits who came into the Navy during the first half of 1958.

The only other selecting factor was residence. The study group is limited to men who had lived all their lives before entering the Navy in the conterminous United States. At the time of the skin tests, each recruit was asked to complete a residence history form, listing all of the places he had lived for 6 months or more since birth. From this information, all but 9,580 could be grouped into three broad residence categories: lifetime in a single county (category 1), lifetime in more than one county but in only one State (category 2), or lifetime in more than one State but never outside the conterminous United States (category 3). Those who could not be classified in one of the three categories had lived for 6 months or longer in the two States, Alaska and Hawaii, which are not conterminous, in U.S. territories or possessions, or in other countries.

Thus, the study group for the present report is composed of 306,226 white males, 17–21 years of age when they entered the Navy, whose records were complete, who were tested with all three routine tests, and who had lived all their lives in the conterminous United States.

Breakdown of the study group by State (table 1) shows that California, New York, and Pennsylvania each contributed more than 20,000 recruits; only Delaware, Nevada, and the District of Columbia contributed fewer than 1,000. The table also gives the numbers classified as lifetime one-State residents (categories 1 and 2 combined) and residents of more than one State (category 3). Residents of more than one State were assigned to the State named as their permanent address, on the assumption that they

Figure 1. Percentage of lifetime residents among all recruits from each State

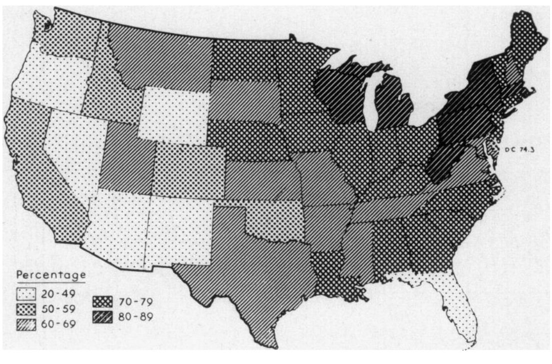


Table 1. Summary data and results of histoplasmin tests for 306,226 recruits, by State of residence

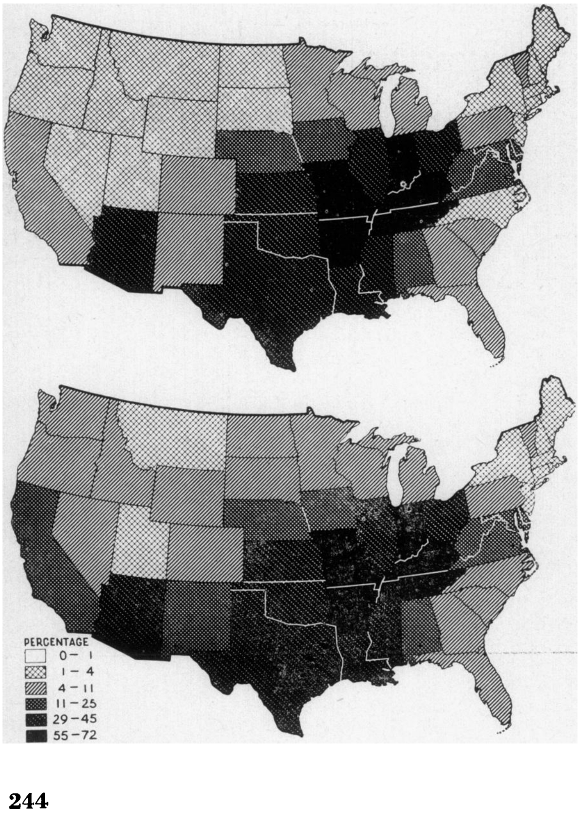
State of residence	Number of recruits			Percent lifetime one-State residents in study group	1960 white male population 15–24 yrs. of age [1] (thousands)	Percent in study group	Percent of lifetime one-State residents with reactions of—		Percent of total study group with reactions of—		Provisional estimates of percent of lifetime one-State residents with—	
	Lifetime in State	Not lifetime in State	Total study group				4 mm. or more	6 mm. or more	4 mm. or more	6 mm. or more	Specific reactions	Cross-reactions
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Total United States [2]	212,462	93,764	306,226	69.4	10,431.8	2.94	18.5	17.1	20.0	18.6		
Alabama	3,125	1,244	4,369	71.5	166.2	2.63	23.6	21.6	25.4	23.5	22	2
Arizona	782	2,366	3,148	24.8	83.5	3.77	31.2	24.8	34.5	29.4	4	26
Arkansas	2,172	1,409	3,581	60.7	98.3	3.64	61.2	59.6	60.2	58.3	59	3
California	15,090	14,554	29,644	50.9	984.3	3.01	6.7	4.7	11.6	9.6	1	5
Colorado	2,409	2,230	4,639	51.9	118.1	3.93	4.1	2.3	9.2	7.4	2	2
Connecticut	3,083	1,063	4,146	74.4	142.3	2.91	1.3	.6	2.0	1.2	<1	<2
Delaware	418	312	730	57.3	23.8	3.07	18.9	18.2	21.1	20.1	18	<2
Dist. of Columbia	387	134	521	74.3	25.6	2.03	23.0	21.4	22.3	20.7	22	<2
Florida	2,416	4,600	7,016	34.4	252.7	2.78	5.2	4.2	10.6	9.7	2	2
Georgia	4,122	1,546	5,668	72.7	217.7	2.60	9.0	7.3	10.4	8.9	5	4
Idaho	1,046	1,032	2,078	50.3	46.5	4.47	1.7	.7	5.6	4.1	<1	<2
Illinois	10,354	3,328	13,682	75.7	550.6	2.49	36.4	34.9	37.6	36.1	34	<2
Indiana	6,026	2,330	8,356	72.1	291.6	2.87	55.9	54.4	55.3	53.9	56	<2
Iowa	4,923	1,584	6,507	75.7	172.8	3.77	23.6	22.3	24.4	23.0	22	<2
Kansas	3,324	1,995	5,319	62.5	138.7	3.83	33.3	31.0	35.1	32.9	29	4
Kentucky	2,855	1,128	3,983	71.7	215.2	1.85	71.5	69.9	71.2	69.5	72	<2
Louisiana	3,928	1,325	5,253	74.8	150.2	3.50	29.7	27.0	31.7	29.1	18	12
Maine	1,639	487	2,126	77.1	67.3	3.16	1.1	.5	1.3	.8	<1	<2
Maryland	2,679	1,259	3,938	68.0	171.0	2.30	25.1	24.1	24.7	23.8	24	<2
Massachusetts	7,123	1,397	8,520	83.6	313.1	2.72	1.2	.5	1.6	.8	<1	<2
Michigan	12,003	2,765	14,768	81.3	444.4	3.32	6.4	5.5	9.0	8.1	5	<2
Minnesota	6,539	1,896	8,435	77.5	210.6	4.01	5.5	4.4	5.9	4.8	4	<2
Mississippi	1,587	757	2,344	67.7	98.0	2.39	44.8	43.2	45.0	43.3	42	3
Missouri	5,993	2,724	8,717	68.8	253.9	3.43	61.7	59.7	62.3	60.3	61	<2
Montana	1,271	844	2,115	60.1	43.0	4.91	2.4	1.3	3.7	2.5	<1	<2
Nebraska	2,545	1,057	3,602	70.7	87.9	4.10	12.7	11.0	14.5	13.0	9	4
Nevada	130	526	656	19.8	17.4	3.78	3.8	2.3	10.2	8.8	<1	<2
New Hampshire	1,003	538	1,541	65.1	39.8	3.87	1.0	.3	1.0	.5	<1	<2
New Jersey	6,813	2,582	9,395	72.5	320.2	2.93	2.5	1.4	2.8	1.9	1	<2
New Mexico	931	1,421	2,352	39.6	66.3	3.55	10.8	8.4	16.7	14.6	4	6
New York	17,228	2,831	20,059	85.9	875.6	2.29	3.1	2.3	3.5	2.7	2	<2
North Carolina	4,269	1,226	5,495	77.7	278.2	1.98	2.9	2.3	4.0	3.3	2	<2
North Dakota	1,187	414	1,601	74.1	44.1	3.63	2.8	1.6	4.0	2.7	1	<2
Ohio	13,406	4,199	17,605	76.1	547.0	3.22	34.6	33.6	35.4	34.3	35	<2
Oklahoma	2,922	2,017	4,939	59.2	152.6	3.24	41.6	38.7	42.1	39.5	36	6
Oregon	2,777	3,074	5,851	47.5	107.5	5.44	2.0	.9	5.9	4.7	<1	<2
Pennsylvania	17,564	2,671	20,235	86.8	624.8	3.24	6.6	5.8	7.1	6.3	6	<2
Rhode Island	969	279	1,248	77.6	61.2	2.04	.7	.1	1.0	.3	<1	<2
South Carolina	2,423	797	3,220	75.2	138.5	2.32	7.0	5.6	7.5	6.2	2	5
South Dakota	1,054	590	1,644	64.1	43.1	3.82	2.2	1.1	4.1	3.2	1	<2
Tennessee	3,411	1,614	5,025	67.9	220.9	2.27	68.8	66.8	67.3	65.3	67	2
Texas	10,780	4,996	15,776	68.3	607.1	2.60	35.7	32.3	35.6	32.4	29	7
Utah	1,127	695	1,822	61.9	64.4	2.83	1.4	.5	3.7	2.4	<1	<2
Vermont	765	316	1,081	70.8	26.9	4.03	4.7	3.4	5.3	4.0	4	<2
Virginia	2,637	1,340	3,977	66.3	258.2	1.54	19.3	18.7	18.8	18.2	19	<2
Washington	4,084	3,482	7,566	54.0	187.0	4.05	2.6	.8	5.0	3.3	<1	<2
West Virginia	3,295	843	4,138	79.6	121.8	3.40	15.7	14.8	16.3	15.3	15	<2
Wisconsin	5,374	1,346	6,720	80.0	240.4	2.80	5.5	4.7	6.1	5.3	5	<2
Wyoming	474	601	1,075	44.1	21.4	5.02	1.1	.4	7.2	6.0	<1	<2

[1] Reference 19.
[2] Excluding Alaska and Hawaii.

were living in that State at the time they entered the Navy. The percentages of one-State residents out of the total number from each State are shown in figure 1 (and column 4, table 1). The percentages are generally lower in the western than the eastern States, with the exception of Florida. Nevada and Arizona, with 19.8 and 24.8 percent, have the lowest proportion of one-State residents; New York and Pennsylvania, with 85.9 and 86.8 percent, have the highest.

Variations among the States in their contribution to the study group are indicated by the estimates in column 6, table 1. These estimates are based on the number of recruits from each State as a percentage of the 1960 census population in the State of white males 15–24 years of age, which is probably the most appropriate group for which figures are available. For the total study group the percentage is 2.9. The percentages among the States range from a high of 5.4 for Oregon down to 1.5 for Virginia. Most of the western States show percentages above that for the total study group, while lower percentages appear more frequently for States in the generally more populous east and midwest.

Figure 2. Percentage of recruits with histoplasmin reactions of 4 mm. and more among lifetime residents (upper section) and all recruits (lower section) from each State



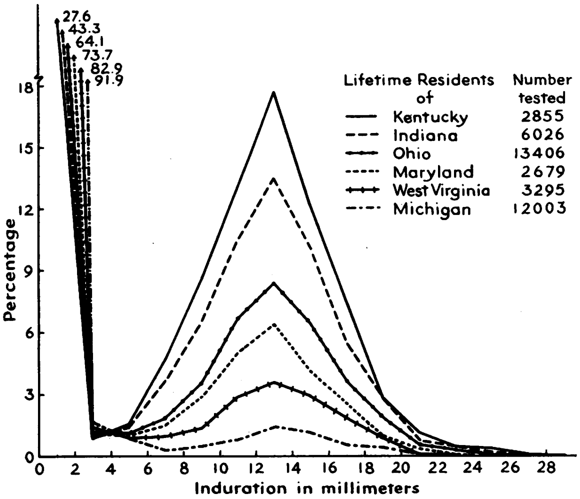
Additional specific information on the representativeness of the study population is not yet available, and it must suffice for now to indicate that the study group obviously does not include men with recognizable defects or disease. Moreover, there are indications that the more well-to-do segments of the general population tend to be under-represented. Despite these and other possible selective factors, the study population may be the most representative sample of young white men for the country as a whole that can be obtained in large numbers.

Results

Prevalence of reactions to histoplasmin. Results for recruits from each State are summarized in table 1 (columns 7–10) in terms of the percentages with reactions of 4 mm. and more and with reactions of 6 mm. and more. Detailed data from which the percentages are derived may be found in table 2. The two maps in figure 2 show the percentage of recruits with reactions of 4 mm. and more among those classed as lifetime residents of the State and among all recruits whose permanent home address is in the State. The map for lifetime residents reflects variations in prevalence of indigenous sources of sensitivity to histoplasmin, whereas the map for all present residents (lifetime plus those now living in the State) shows the effect of migration on the prevalence of histoplasmin sensitivity in the State.

The highest prevalence rates among lifetime one-State residents are found in the east-central part of the country—Missouri, Indiana, Kentucky, Tennessee, and Arkansas—where more than 55 percent react to histoplasmin. (Were it not for the very low prevalence among the large number of recruits from the Chicago area, Illinois would also be in the highest bracket.) In many of the adjoining States the rates range from 29 to 45 percent, in others from 11 to 25 percent. Toward the southeast the frequency of reactors drops more rapidly, to less than 11 percent in Georgia and less than 4 percent in North Carolina. The rates are also below 4

Figure 3. Frequency distributions of sizes of histoplasmin reactions for lifetime residents of six States



percent throughout the northwestern tier of States; they are again higher in the Mexican border States.

Prevalence rates in many of the western States are notably affected when account is taken of all recruits now living in the State. This is not surprising in view of the predominantly westward trend of migration from the eastern and central States, where indigenous sources of sensitivity are much higher than in the west. People take their histoplasmin sensitivity with them when they move.

Table 1 also shows how the percentages of "reactors," particularly in the northwestern and New England States where the rates are low, may be affected substantially by raising the criterion from 4 mm. to 6 mm.; Arizona, too, is notably affected. On the other hand, for most of the central States where the rates are high, the effect of raising the criterion is small. Material presented in the following section should make apparent the advantage of using different criteria for estimating the percentages of "reactors" in different parts of the country.

Evidence of cross-reactions. A reaction to histoplasmin does not necessarily represent sensitivity caused by infection with *H. capsulatum;* cross-reactions are known to occur as a result of other systemic mycotic infections. Unless account is taken of possible cross-reactions, the prevalence of histoplasmal infection, as determined by the percentage of "reactors," may be grossly overestimated for some geographic areas. The reason for this is seen in the distributions of the sizes of reactions among population groups in different parts of the country.

Percentage frequency distributions of the sizes of reactions to histoplasmin for lifetime residents of six adjoining States are shown in figure 3. These curves, based on 2-mm. groupings, are derived from table 2. Though the frequencies of measurable reactions range from a high of more than 70 percent in Kentucky to a low of about 8 percent in Michigan, all six distributions are bimodal in form, that is, composed of two segments, one showing a peak at 0–1 mm., the other at 12–13 mm. The inverted J-shaped curve formed by the left-hand segment and the fairly symmetrical curve around a central value of 12–13 mm. formed by the right-hand segment suggest that the population may be separated into two groups: one group with no reactions or only very small "insignificant" reactions, presumably attributable to nonspecific factors such as reaction to the diluent, needle trauma, errors, and the like; the other group with apparently "significant" reactions resulting from infection with some sensitizing agent or agents.

Because the right-hand segment of each distribution resembles the normal probability fre-

Figure 4. Frequency distributions of sizes of histoplasmin reactions for lifetime residents of two groups of States and theoretical distribution of "negative" reactions

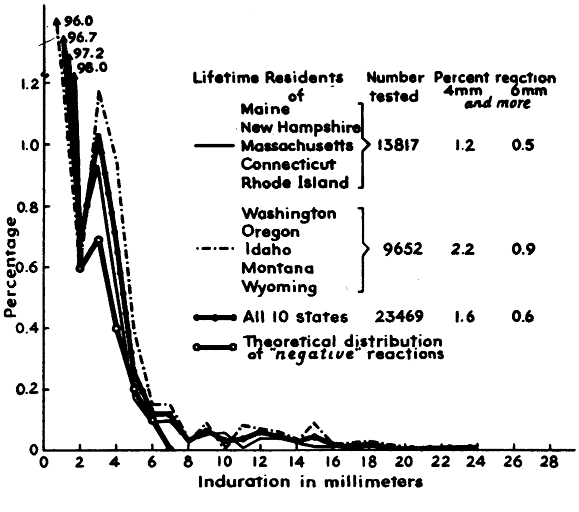


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Table 2. Frequency distributions of sizes of reactions to

State	Residence in State	Total tested	Reaction to histoplasmin (induration in millimeters)												
			0–1	2	3	4	5	6	7	8	9	10	11	12	13
Alabama	Lifetime	3,125	2,336	23	30	26	34	31	36	36	49	71	65	79	62
	Not lifetime	1,244	851	9	9	12	13	27	17	18	23	24	20	34	46
Arizona	Lifetime	782	514	13	11	18	32	29	25	22	25	33	16	13	8
	Not lifetime	2,366	1,472	17	35	61	48	89	88	55	67	83	53	81	54
Arkansas	Lifetime	2,172	813	8	21	17	19	61	56	67	86	137	115	154	153
	Not lifetime	1,409	574	3	8	18	11	44	34	23	56	67	92	98	81
California	Lifetime	15,090	13,763	125	188	170	135	134	67	61	79	94	69	60	41
	Not lifetime	14,554	11,854	97	177	146	147	153	134	108	158	191	189	225	204
Colorado	Lifetime	2,409	2,271	13	27	28	15	11	2	3	2	3	3	9	8
	Not lifetime	2,230	1,863	18	18	29	16	15	7	10	22	23	30	37	29
Connecticut	Lifetime	3,083	3,001	21	20	17	4	3	4	2	1	2		3	3
	Not lifetime	1,063	1,001	9	11	4	8	1	1	3	3	5	6	2	3
Delaware	Lifetime	418	334		5		3		2	6	6	4	6	6	8
	Not lifetime	312	233	1	3	3	1		3	2	6	14	11	6	5
Dist. of Columbia	Lifetime	387	292	2	4	1	5	1	4	4	6	9	8	10	6
	Not lifetime	134	105	2		1	1	1	1	3	3	1	1	7	
Florida	Lifetime	2,416	2,245	18	28	14	9	13	8	7	14	8	10	13	1
	Not lifetime	4,600	3,923	29	28	31	12	30	21	24	47	59	62	69	57
Georgia	Lifetime	4,122	3,675	30	48	34	33	24	33	16	25	33	29	35	29
	Not lifetime	1,546	1,291	15	19	11	7	8	15	14	15	27	14	24	17
Idaho	Lifetime	1,046	1,012	9	7	7	4	1	2		2			1	
	Not lifetime	1,032	914	6	14	15	4	5	4	8	6	8	9	7	4
Illinois	Lifetime	10,354	6,432	66	87	77	74	131	149	166	244	311	356	471	360
	Not lifetime	3,328	1,908	12	27	30	28	50	49	73	82	126	128	189	152
Indiana	Lifetime	6,026	2,606	15	36	39	50	109	112	166	231	330	307	422	385
	Not lifetime	2,330	1,050	6	20	10	23	30	60	42	97	101	126	147	125
Iowa	Lifetime	4,923	3,692	29	40	43	21	38	40	43	56	82	100	136	105
	Not lifetime	1,584	1,135	6	16	14	13	16	9	19	18	35	35	50	44
Kansas	Lifetime	3,324	2,177	15	25	38	38	70	70	54	73	110	97	115	103
	Not lifetime	1,995	1,205	7	22	24	19	28	41	38	58	58	75	91	68
Kentucky	Lifetime	2,855	789	12	12	13	33	64	73	107	137	198	213	280	227
	Not lifetime	1,128	322	5	8	3	16	20	31	44	51	83	77	104	86
Louisiana	Lifetime	3,928	2,688	19	56	44	62	78	83	63	107	101	106	115	91
	Not lifetime	1,325	792	13	18	14	20	35	30	26	37	37	46	54	50
Maine	Lifetime	1,639	1,596	11	14	9		1	2		1	1		1	1
	Not lifetime	487	473	2	2	1	1	1		2			1	2	
Maryland	Lifetime	2,679	1,975	8	23	15	12	23	17	32	45	63	74	98	73
	Not lifetime	1,259	941	6	13	5	2	9	9	13	27	26	22	42	31
Massachusetts	Lifetime	7,123	6,895	55	84	38	15	8	7	2	5	5	1	2	1
	Not lifetime	1,397	1,330	9	11	6	6	2	1	1	7	4	1	7	3
Michigan	Lifetime	12,003	11,035	72	129	71	31	28	25	23	34	42	54	87	80
	Not lifetime	2,765	2,157	16	30	13	15	18	16	33	39	64	55	57	50
Minnesota	Lifetime	6,539	6,064	36	79	50	20	19	3	10	11	17	30	37	29
	Not lifetime	1,896	1,730	12	18	11	6	7	8	9	2	5	6	18	10
Mississippi	Lifetime	1,587	856	8	12	13	12	34	34	31	51	58	80	81	66
	Not lifetime	757	410	1	2	10	6	18	19	11	17	28	36	33	39
Missouri	Lifetime	5,993	2,245	18	33	44	76	151	128	165	284	353	372	466	368
	Not lifetime	2,724	973	8	12	20	37	50	60	63	130	173	151	218	191
Montana	Lifetime	1,271	1,222	4	15	9	5	7	2				2		1
	Not lifetime	844	779	7	9	8	5	2	1	1	3	3	5	7	2

histoplasmin for 306,226 recruits, by State of residence

Reaction to histoplasmin (induration in millimeters)													Residence in State	State
14	15	16	17	18	19	20	21	22–23	24–25	26–27	28–29	30+		
69	53	45	32	16	11	5	6	6	4				Lifetime	Alabama.
29	31	24	16	9	12	5	6	6	1	1	1		Not lifetime	
7	5	3	2	2	1	2			1				Lifetime	Arizona.
36	35	25	21	14	12	7	2	4	6		1		Not lifetime	
109	109	84	55	37	26	8	11	15	6	2	3		Lifetime	Arkansas.
72	72	45	29	20	19	12	7	13	9		2		Not lifetime	
23	24	14	13	11	9	4	1	3	2				Lifetime	California.
155	171	136	97	65	54	21	20	28	15	5	4		Not lifetime	
3	5	1	2			1			2				Lifetime	Colorado.
21	28	25	7	9	6	4	1	6	2	3	1		Not lifetime	
1		1											Lifetime	Connecticut.
2	2	1									1		Not lifetime	
12	6	3	7	3	3	1	1	1	1				Lifetime	Delaware.
7	6	3	4	3	1								Not lifetime	
13	8	7	2	3		1		1					Lifetime	Dist. of Columbia.
1	1	2	1	1	1	1							Not lifetime	
12	6	4	3		1			2					Lifetime	Florida.
70	39	30	24	14	11	6	6	4	2	1	1		Not lifetime	
24	12	16	8	5	3	3	1	1	3	1		1	Lifetime	Georgia.
14	21	12	6	8	4	1	1		1		1		Not lifetime	
	1												Lifetime	Idaho.
4	6	4	8	2	1	1	1	1					Not lifetime	
389	295	236	191	109	75	41	33	29	18	8	6		Lifetime	Illinois.
117	114	67	57	41	32	6	15	15	6	2	1	1	Not lifetime	
318	295	196	131	106	69	30	20	34	11	3	2	3	Lifetime	Indiana.
152	109	73	59	45	26	16	7	12	10	2	1	1	Not lifetime	
82	121	94	54	49	23	13	18	28	10	4	2		Lifetime	Iowa.
38	44	28	28	14	10	3	5	2		2			Not lifetime	
69	88	45	43	38	13	8	4	18	7	3	3		Lifetime	Kansas.
62	51	40	23	29	17	12	5	13	9				Not lifetime	
206	141	126	84	41	39	22	10	15	10	1	1	1	Lifetime	Kentucky.
78	55	44	32	27	22	6	6	4	2	1	1		Not lifetime	
78	78	41	22	32	22	12	8	12	4	2	3	1	Lifetime	Louisiana.
40	39	29	15	16	2	2	3	4	2	1			Not lifetime	
1				1									Lifetime	Maine.
1			1										Not lifetime	
65	48	45	25	15	10	4	4	3	2				Lifetime	Maryland.
24	26	23	15	11	7	3		4					Not lifetime	
1	2				1		1						Lifetime	Massachusetts
3	2	1	1	1	1								Not lifetime	
60	70	44	37	32	20	5	7	8	4		2	3	Lifetime	Michigan.
63	50	36	15	11	8	5	4	7	1	1		1	Not lifetime	
32	33	18	14	9	10	9	3	3		1	2		Lifetime	Minnesota.
16	11	9	5	3	2	2	1	1	2		1	1	Not lifetime	
56	76	28	24	26	17	10	8	4	1	1			Lifetime	Mississippi.
26	33	22	11	12	6	7	3	3	4				Not lifetime	
352	252	198	155	118	76	39	21	48	17	7	6	1	Lifetime	Missouri.
163	151	114	58	52	25	19	9	20	7	9	5	1	Not lifetime	
1	1			1	1								Lifetime	Montana.
1	5	2	1	2				1					Not lifetime	

Table 2. Frequency distributions of sizes of reactions to

State	Residence in State	Total tested	Reaction to histoplasmin (induration in millimeters)												
			0–1	2	3	4	5	6	7	8	9	10	11	12	13
Nebraska	Lifetime	2,545	2,169	18	35	23	19	18	18	15	21	28	20	23	25
	Not lifetime	1,057	839	8	9	10	5	11	9	3	9	17	15	27	11
Nevada	Lifetime	130	120		5		2	1							1
	Not lifetime	526	458	1	5	4	3	3	1	2	5	6	5	6	4
New Hampshire	Lifetime	1,003	985	2	6	5	2	1							
	Not lifetime	538	526	1	5	1	1	1							1
New Jersey	Lifetime	6,813	6,537	44	65	48	24	17	10	12	4	6	9	8	8
	Not lifetime	2,582	2,457	11	16	11	3	9	2	4	8	9	8	11	5
New Mexico	Lifetime	931	812	4	14	18	5	7	4	6	9	11	10	7	7
	Not lifetime	1,421	1,096	9	24	13	13	24	14	17	16	35	25	22	30
New York	Lifetime	17,228	16,424	92	170	99	45	41	26	24	22	29	40	47	39
	Not lifetime	2,831	2,620	26	24	17	9	5	4	6	10	5	15	23	23
North Carolina	Lifetime	4,269	4,065	40	42	17	7	6	5	11	4	8	7	12	13
	Not lifetime	1,226	1,106	9	12	10	4	3	1	3	7	7	13	13	7
North Dakota	Lifetime	1,187	1,132	6	16	10	4	2		2	1	2	3	1	2
	Not lifetime	414	374	3	6	3	3	1		3	3	4	2	2	
Ohio	Lifetime	13,406	8,596	60	105	77	67	122	135	207	279	426	481	602	505
	Not lifetime	4,199	2,559	26	32	27	14	40	43	62	92	153	156	207	178
Oklahoma	Lifetime	2,922	1,670	8	29	32	53	62	84	60	98	110	105	152	119
	Not lifetime	2,017	1,126	7	18	16	29	49	46	39	62	79	73	98	86
Oregon	Lifetime	2,777	2,663	17	42	22	8	3	2	1	4		5	3	2
	Not lifetime	3,074	2,737	12	33	30	13	18	14	8	20	29	29	26	20
Pennsylvania	Lifetime	17,564	16,123	108	165	91	53	56	49	50	65	98	92	117	110
	Not lifetime	2,671	2,371	14	24	11	9	11	3	6	19	21	28	27	33
Rhode Island	Lifetime	969	947	10	5	4	2		1						
	Not lifetime	279	270	1	2	1	2		1		1				1
South Carolina	Lifetime	2,423	2,212	9	33	18	16	15	11	13	21	16	16	10	8
	Not lifetime	797	705	7	12	4	3	5	9		7	6	6	10	7
South Dakota	Lifetime	1,054	1,002	7	22	6	5	3		1		1	2	1	1
	Not lifetime	590	540	2	3	3	2	1	2	1	4	3	4	1	5
Tennessee	Lifetime	3,411	1,038	8	17	23	45	82	102	113	143	215	208	298	237
	Not lifetime	1,614	568	2	11	11	21	45	46	42	51	84	108	132	115
Texas	Lifetime	10,780	6,719	71	138	161	210	261	242	219	305	387	301	416	303
	Not lifetime	4,996	3,144	30	54	64	78	95	99	97	125	168	164	184	154
Utah	Lifetime	1,127	1,096	5	10	6	4	3				1			
	Not lifetime	695	635	2	6	9	5	4	3	2	3	2	3	10	4
Vermont	Lifetime	765	718	3	8	6	4	1	1		4	2		2	4
	Not lifetime	316	295			2	2	2		1	2		2		1
Virginia	Lifetime	2,637	2,081	20	26	9	8	20	12	30	34	64	57	80	49
	Not lifetime	1,340	1,083	5	14	4	5	7	5	13	12	17	22	30	31
Washington	Lifetime	4,084	3,905	28	46	53	19	3	8	1	2		1	3	2
	Not lifetime	3,482	3,152	27	33	37	17	12	11	15	16	15	11	25	20
West Virginia	Lifetime	3,295	2,732	18	28	17	12	9	23	24	23	49	45	75	43
	Not lifetime	843	677	4	6	3	8	4	5	10	5	13	14	16	20
Wisconsin	Lifetime	5,374	5,003	33	41	33	13	16	11	10	10	22	20	31	37
	Not lifetime	1,346	1,212	5	13	8	4	3	4	3	8	9	4	12	15
Wyoming	Lifetime	474	464	2	3	1	2				1				1
	Not lifetime	601	520	2	7	6	4	3	4	1	3	11	4	5	8
All States	Lifetime	212,462	169,741	1,243	2,105	1,614	1,381	1,818	1,718	1,885	2,624	3,540	3,535	4,582	3,724
	Not lifetime	93,764	70,356	530	899	805	722	1,015	985	981	1,462	1,938	1,962	2,496	2,130

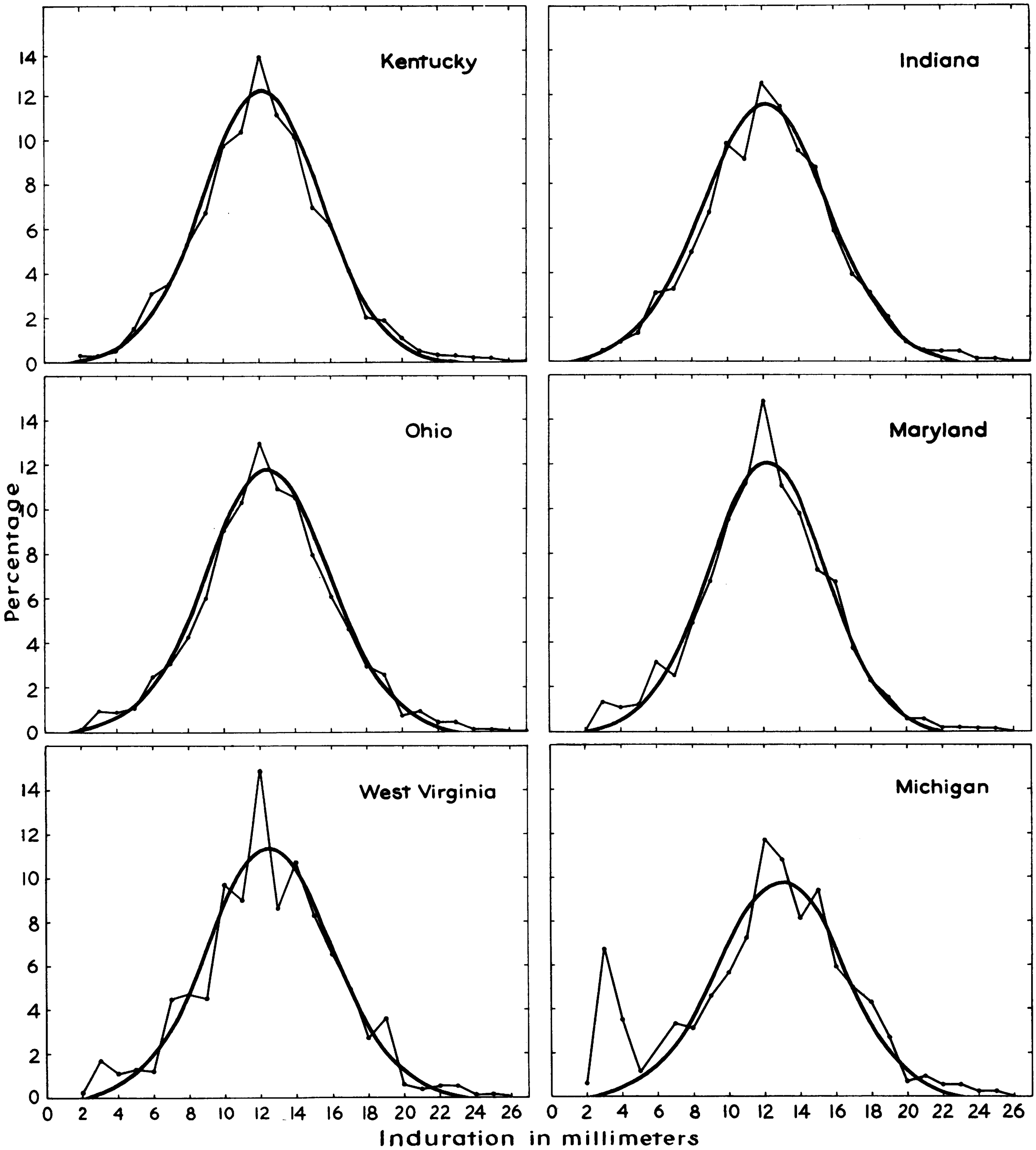
histoplasmin for 306,226 recruits, by State of residence—Continued

Reaction to histoplasmin (induration in millimeters)													Residence in State	State
14	15	16	17	18	19	20	21	22–23	24–25	26–27	28–29	30+		
21	24	19	16	12	4	5	2	6	3	1			Lifetime	Nebraska.
19	15	17	6	9	3	5	5	2	2			1	Not lifetime	
1													Lifetime	Nevada.
1	11	1	2	4	2	1		1					Not lifetime	
1		1											Lifetime	New Hampshire.
1						1							Not lifetime	
4	5	5	2	2	1	1	1						Lifetime	New Jersey.
9	10	2	3	2				2					Not lifetime	
5	4	2	5					1					Lifetime	New Mexico.
16	21	12	12	8	2	4	4	2	2				Not lifetime	
34	21	24	14	14	7	4	3	6	3				Lifetime	New York.
12	13	5	8	3	1		1	1					Not lifetime	
15	4	3	3	2	3	1	1						Lifetime	North Carolina.
6	11	4	2	3	2	2	1						Not lifetime	
1	1	2	1	1									Lifetime	North Dakota.
2	4		2	1	1								Not lifetime	
485	370	284	213	133	120	34	41	39	11	6	6	2	Lifetime	Ohio.
153	144	93	76	56	34	18	9	15	8	3		1	Not lifetime	
87	96	42	37	31	15	11	7	6	6		1	1	Lifetime	Oklahoma.
69	79	42	37	19	12	5	7	12	5		1	1	Not lifetime	
1	2		1	1									Lifetime	Oregon.
19	23	16	7	5	6	3		3	2	1			Not lifetime	
117	88	58	50	25	22	7	3	10	6			1	Lifetime	Pennsylvania.
26	15	18	14	11	4		1	1	3			1	Not lifetime	
													Lifetime	Rhode Island.
													Not lifetime	
4	7	3	3	3	1	2	1	1					Lifetime	South Carolina.
4	5		3	2		2							Not lifetime	
1		1						1					Lifetime	South Dakota.
5	1	3	1	5	1		1	1	1				Not lifetime	
213	187	139	103	90	55	21	17	33	12	8	4		Lifetime	Tennessee.
97	95	57	38	25	19	14	12	14	5	1		1	Not lifetime	
249	247	158	120	109	53	29	23	30	23	2	3	1	Lifetime	Texas.
105	130	90	65	55	34	15	14	12	13	5	2		Not lifetime	
			2										Lifetime	Utah.
1	1	4		1									Not lifetime	
2	1	1	1	2	3	1		1					Lifetime	Vermont.
2	1	3	1			1		1					Not lifetime	
46	37	23	13	10	8	4	1	4			1		Lifetime	Virginia.
22	20	13	14	5	12	3	1	1	1				Not lifetime	
1	4	2	1	1	1			2			1		Lifetime	Washington.
24	16	9	11	9	8	2	2	5	4			1	Not lifetime	
54	42	33	25	14	18	3	2	5	1				Lifetime	West Virginia.
18	13	9	8	5	1	2	1			1			Not lifetime	
18	23	18	10	10	6	2	2	5					Lifetime	Wisconsin.
10	9	14	6	3	1	1		2					Not lifetime	
													Lifetime	Wyoming.
5	4	5	2	3	1		1	1		1			Not lifetime	
3,344	2,892	2,067	1,524	1,114	747	343	261	381	168	50	46	15	Lifetime	All States.
1,806	1,743	1,212	852	643	423	218	162	224	125	40	24	11	Not lifetime	

quency curve, an attempt was made to fit a normal curve to the observed results for each of the six States. To do this, it was desirable to deal only with the right-hand segment, representing the presumably infected group, as 100 percent, so that results for the six States could be readily compared. This required removal of the "negative" or uninfected segment of each population—those with insignificant reactions to the test.

Ideally, a theoretical distribution of negative reactions should be derived from observed re-

Figure 5. Normal probability frequency curves fitted to observed distributions of "not negative" reactions for lifetime residents of six States



sults in a population in which no one has a reaction that might represent significant sensitivity. The closest we could come to the ideal in the present material was in five States in the northwest and five in New England where the frequencies of significant reactions to histoplasmin were the lowest in the country. Figure 4 gives the observed frequency distributions for these groups of States and a theoretical curve showing what we consider a reasonable, though admittedly arbitrary, estimate of the frequency of negative reactions at each millimeter from 0–1 through 6 mm. The estimates are somewhat below the observed frequencies, partly because of unaccountable and seemingly erratic variations among the States in the frequencies of very small reactions, and partly because some significant reactions can be expected to be very small. Thus, as shown in figure 4, all reactions of 0–1 mm. were considered to be "negative" and to constitute 98.0 percent of the theoretical negative distribution. The remaining 2.0 percent of the theoretical distribution was distributed as shown: 0.6 percent at 2 mm., 0.7 percent at 3 mm., 0.4 percent at 4 mm., 0.2 percent at 5 mm., and 0.1 percent at 6 mm.

Figure 5 shows results for the six States represented in figure 3 after removal of the theoretically negative segment of the population. The remaining reactions, those considered "not negative," range upward from 2 mm.; the frequency distributions, by single millimeters of induration, are based on the total number not negative as 100 percent. By use of the repetitive analog computer described in 1959 by Noble, Hayes, and Eden (*9*) and placed at our disposal by Dr. Hayes of the National Heart Institute, a normal Gaussian curve was fitted to each distribution. Fitting a normal curve to an observed distribution with the computer does not involve a numerically computed "best fit" according to a set of mathematical assumptions. Rather, the computer provides a mechanism for projecting normal curves, the parameters of which may be varied continuously as the operator wishes. The actual fitting of an observed curve involves, in effect, the manual adjustment of several dials, one controlling the value of the parameter representing the mean of the distribution, another the standard deviation, and another the total frequency. The decision as to what combination of parameters gives the best fit depends therefore on the operator's judgment, based on visual comparison of the observed and projected curves.

The values of the parameters for the fitted normal curves shown in figure 5 are given in the upper section of table 3. The means range from 12.2 through 12.9 mm., the standard deviations from 3.3 through 3.6 mm. That normal curves with such similar means and standard deviations fit so well the distributions from

Table 3. Percentages of recruits with reactions considered "not negative," and estimated frequencies of infection with H. capsulatum based on normal curves fitted to observed results for lifetime residents of selected States

State of lifetime residence	Total number tested	Recruits with reactions considered "not negative"		Fitted normal curve		Estimated percent infected with *Histoplasma* among the—	
		Number	Percent	Mean (mm.)	S.D. (mm.)	"Not negative"	Total tested
Kentucky	2, 855	2, 050	71. 8	12. 2	3. 3	100	72
Indiana	6, 026	3, 367	55. 9	12. 2	3. 5	100	56
Ohio	13, 406	4, 635	34. 6	12. 5	3. 5	100	35
Maryland	2, 679	664	24. 8	12. 2	3. 3	95	24
West Virginia	3, 295	507	15. 4	12. 6	3. 5	97	15
Michigan	12, 003	743	6. 2	12. 9	3. 6	88	5
Arizona and New Mexico	1, 713	360	21. 0	12. 3	3. 4	29	6
Louisiana	3, 928	1, 185	30. 2	12. 8	3. 6	59	18
Nebraska	2, 545	332	13. 0	12. 8	3. 6	71	9
Florida, Georgia, and South Carolina	8, 961	663	7. 4	12. 5	3. 4	44	3

States with such widely different frequencies of reactions, in our opinion, constitutes statistical evidence that we are dealing with homogeneous populations, that is, populations infected and sensitized by one and the same agent. (The excess frequency of 3 and 4 mm. reactions in Michigan is referred to near the end of the section on results.) At the present time, we are assuming that the sensitizing agent is *Histoplasma.* These results also suggest that specific sensitivity to histoplasmin, once acquired, does not wane in the absence of repeated infection and also that repeated infection does not boost the size of the reaction to histoplasmin. If either waning or boosting occurred, one could expect deviations from the normal curve; in the case of waning, a relative increase of small reactions, particularly where the prevalence of reactions is low, as in Michigan, and in the case of boosting, a relative increase of large reactions, particularly where the prevalence of reactions is high, as in Kentucky.

Sizes of reactions to histoplasmin are distributed quite differently in residents of several other parts of the country, as illustrated in figures 6 and 7. Each distribution in figure 6 is paired with one or a combination of several of the distributions in figure 3 with about the same total frequency of reactions of 2 mm. or more. The curve for Arizona and New Mexico, compared with the curve for West Virginia and Maryland, shows a relative deficit of large reactions and proportionately many more of the smaller reactions. The same kind of difference, though not so pronounced, is seen in the other three pairs of distributions. Infection with *Coccidioides immitis* is known to be prevalent in the southwest, and a substantial proportion of the reactions to histoplasmin in this region unquestionably are small because they are cross-reactions (*2,3,10–12*). But *Coccidioides*, as far as is now known, does not exist in Louisiana, Nebraska, and the southeast; yet in these regions, too, we find a disproportionate increase in the frequency of small reactions. These should, we believe, also be considered cross-reactions,

Figure 6. Frequency distributions of sizes of histoplasmin reactions for lifetime residents of four different regions, paired with results for lifetime residents of other regions with similar percentages of reactions of 2 mm. or more

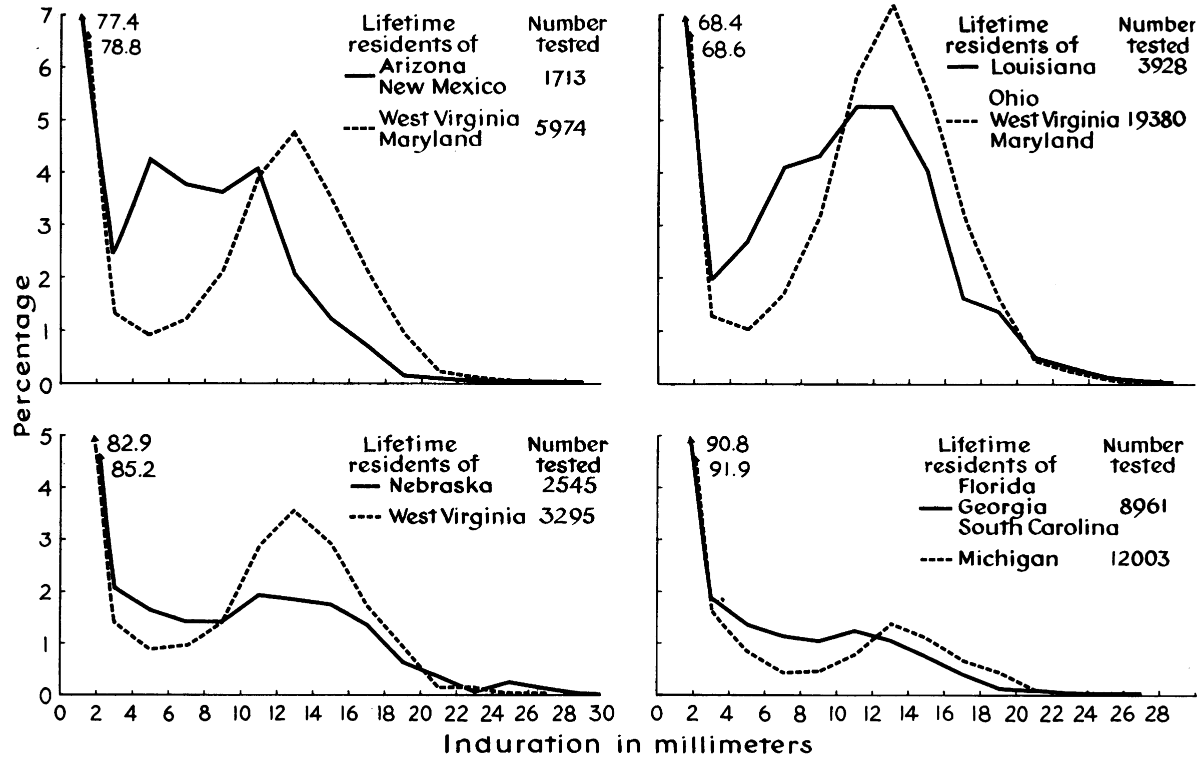
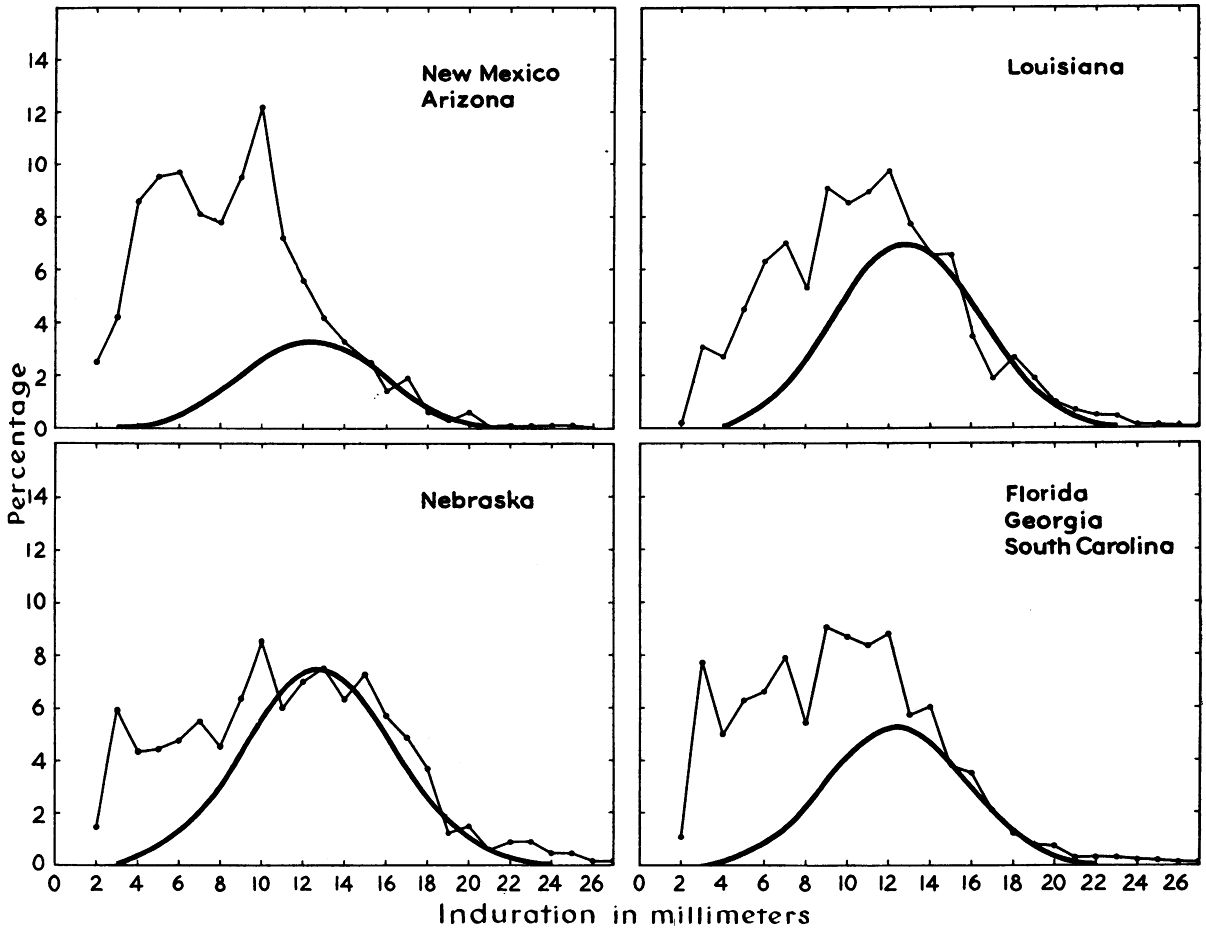


Figure 7. Normal probability frequency curves with parameters similar to those in figure 5 fitted to observed distributions of "not negative" reactions for lifetime residents of four different regions



though not attributable to coccidioidal infection.

In addition to the evidence of cross-reactions to histoplasmin in these regions, there are varying proportions of large reactions similar in size range to those ascribed to specific histoplasmal infection in the distributions with which they are compared. On the assumption that distributions of reactions to histoplasmin caused by specific histoplasmal infection, whereever it occurs, will approximate normal curves with means and standard deviations similar to those shown in figure 5, an attempt was made to fit such normal curves to the distributions shown in figure 6. Results, shown in figure 7 and the lower section of table 3, were obtained with the analog computer described above.

Table 3 also shows that an estimated 29 percent of the "not negative" recruits from Arizona and New Mexico, or roughly 6 percent of the total number tested, have reactions that might be ascribed to histoplasmal infection; many of the remainder are considered cross-reactions owing to infection with *Coccidioides.* In Louisiana and Nebraska, roughly two-thirds of the histoplasmin reactions appear to represent histoplasmal infection, in the three southeastern States, less than half; the remainder are attributed to some other, unrecognized, sensitizing agent or agents.

As will be discussed later, relative excesses of small reactions to histoplasmin are not limited to the regions discussed above, although they are seen most clearly in the several States selected for illustration.

Histoplasmin reactions in the northwest and *northeast.* The very low frequency of large reactions to histoplasmin in the northwestern States, as shown in figure 4, raises some questions as to their source. Because of the high frequency of migration to the northwest from the east-central States (where histoplasmin sensitivity is high), even a few errors of omission in the residence histories of the recruits would have a significant effect. Indigenous sources of infection, though a possibility, seem fairly unlikely since the few reactors were widely scattered throughout the region rather than concentrated in single counties or localities. We therefore decided to question a sample of the recruits from the five States and wrote to each one who had a reaction of at least 5 mm., asking for a detailed list of all places he had ever lived or visited, even for as short a time as 1 week. The information obtained in this way is summarized in the upper section of table 4.

Replies were received from 71, or 59 percent, of the 121 men to whom letters were sent. A history of having been in areas where they might have acquired histoplasmin sensitivity was obtained from 26 out of the 71; of those 26, nearly three-quarters (19) had reactions of 8 mm. or more. In contrast, among the 45 who had never been outside the northwest, only one-third (14) had reactions of 8 mm. or more. Putting it another way, of 38 with reactions of less than 8 mm., 18 percent had lived outside the northwest; of 9 with reactions 8–10 mm., 33 percent; and of 24 with 11 mm. or larger, 67 percent. Thus, the larger the reaction, the greater the likelihood that the recruit had been in an area where histoplasmin sensitivity is more prevalent than in his home State. These results, though not conclusive, suggest that more than half of the men, especially those with larger reactions, could have acquired their histoplasmin sensitivity outside their home States. On the other hand, if the few scattered reactions found among recruits who had never left the State are in fact evidence of indigenous sources of infection with *Histoplasma* in the northwest, then such sources would seem to be located in areas where people rarely go.

Similar letters were sent to a corresponding sample of the recruits from five New England States, where the frequency of reactions is also very low (fig. 4). Here, as shown in the lower

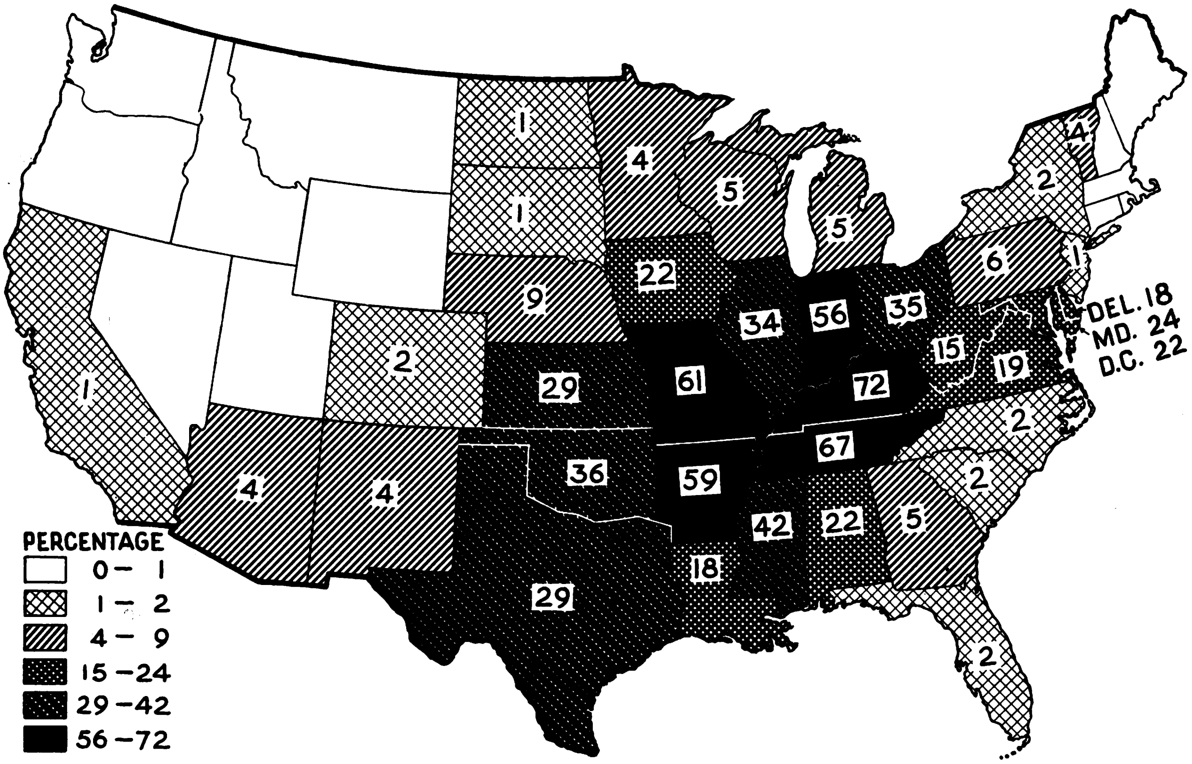
Table 4. Information received from recruits from two selected groups of States, in reply to letters asking for detailed residence history since birth

State of lifetime residence	Number of recruits sent letters	No reply [1]	Reply received		Reaction size of those who had—					
					never left the region			been outside the region		
			Number	Percent	5–7 mm.	8–10 mm.	11 or more mm.	5–7 mm.	8–10 mm.	11 or more mm.
Washington	52	20	32	61.5	15	1	3	1	1	11
Oregon	33	18	15	45.5	6	4	1	2	------	2
Idaho	11	3	8	72.7	3	1	1	1	1	1
Montana	21	7	14	66.7	7	------	2	3	------	2
Wyoming	4	2	2	50.0	------	------	1	------	1	------
Total	121	50	71	58.7	31	6	8	7	3	16
Connecticut	19	12	7	36.7	2	1	1	------	1	2
Rhode Island	4	1	3	75.0	3	------	------	------	------	------
Massachusetts	40	25	15	37.5	4	4	3	2	1	1
New Hampshire	5	1	4	80.0	2	------	2	------	------	------
Maine	7	2	5	71.4	3	1	------	------	1	------
Total	[2] 75	41	34	45.3	14	6	6	2	3	3

[1] Including 10 letters returned by the post office marked "unclaimed" or "unknown": 2 from Washington, 3 from Oregon, 1 from Montana, 1 from Connecticut, and 3 from Massachusetts.

[2] Since the letters were sent in the fall of 1961, an additional 17 recruits with reactions of at least 5 mm. and classified as lifetime residents of these five States were added to the study group.

Figure 8. Provisional estimates of the percentage of recruits infected with Histoplasma among lifetime residents of each State



section of table 4, out of 34 who replied only 8 had ever lived or visited in States outside the New England area, and 6 of the 8 had reactions of 8 mm. or more. However, among the total of 18 with reactions of 8 mm. or more, two-thirds (12) had never left the area. Thus, in contrast to the situation in the northwest, it seems likely that sources of infection are present in one or more of these five States. This likelihood is supported by material (not included in this report) showing that reactors from Vermont and New York tend to be concentrated primarily among residents of the northern portions of both States, indicating indigenous sources of infection in that region.

Provisional estimates of the frequency of specific reactions and cross-reactions. Based on the analytical procedures described above, an attempt was made to estimate the percentage of recruits from each State whose reactions to histoplasmin might reasonably be attributed to specific histoplasmal infection and the percentage with cross-reactions ascribed to infection with some other agent or agents. The material is limited to lifetime residents of each State because we are interested in the geographic distribution and variations in prevalence of indigenous sources of histoplasmin sensitivity. The estimates are shown in figures 8 and 9 and the last two columns of table 1.

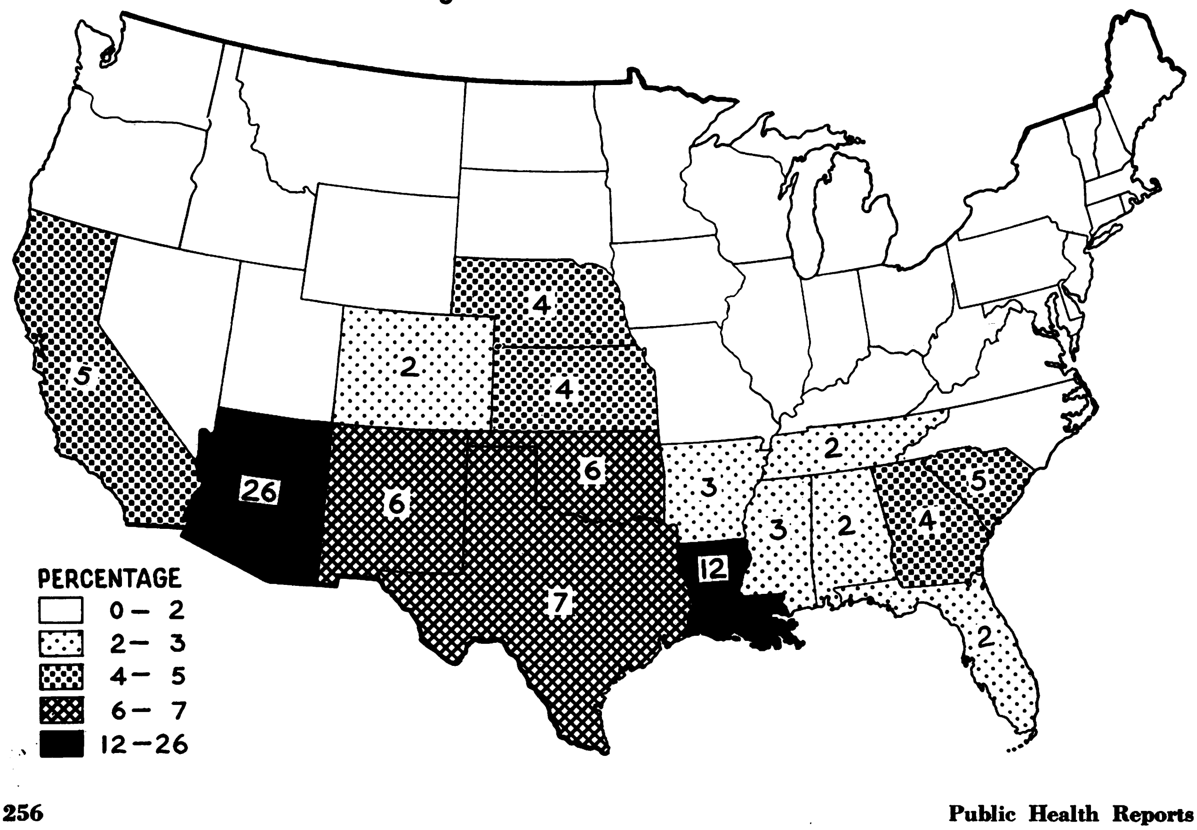
Provisional estimates of the frequency of histoplasmal infection take account in some instances of the possible effect of errors in residence histories, as discussed earlier in regard to recruits from the northwestern and northeastern States. Although only recruits from those two regions were queried directly, similar results could be expected from States with high migration rates such as California, Nevada, Arizona, New Mexico, and Florida. However, even after allowing for some errors in residence histories, we still find varying but small percentages of recruits whose reactions should, we believe, be tentatively regarded as evidence of histoplasmal infection. The critical question is whether or not such reactions signify indigenous sources of histoplasmal infection.

We are provisionally suggesting, for example, that about 4 percent of the recruits from Arizona and New Mexico have reactions to histoplasmin caused by histoplasmal infection acquired in those States. To be considered, of course, is whether within these and other western States there are areas where *Histoplasma* is present, or whether the source was outside the State and our findings represent deficiencies in obtaining accurate residence histories. Also to be considered is whether some of the reactions which we are now attributing to histoplasmal infection in some other areas may actually represent cross-reactions attributable to infection with some other agent so closely related antigenically to *Histoplasma* that it causes reactions approaching in size those caused by histoplasmal infection.

As to provisional estimates of the frequency of cross-reactions to histoplasmin, we found it prudent, for several reasons, not to try to estimate frequencies below 2 percent. In most of the New England States, for example, there is very little evidence of any indigenous histoplasmin sensitivity, either specific or otherwise. On the other hand, in States such as Missouri and Kentucky there are indications of cross-reactions in some counties, but they tend to be obscured by the high frequencies of reactions attributed to histoplasmal infection throughout most of that area. Still another situation exists in the northwestern and Great Lakes States, where the existence of cross-reactions must also be suspected. The appreciable excess of reactions measuring 2, 3, and 4 mm. in these areas may represent sensitization by an agent that gives much smaller cross-reactions to histoplasmin than, for example, does coccidioidal infection.

One further point should be mentioned regarding cross-reactions to histoplasmin. In Arizona, where we presume a frequency of 26 percent cross-reactions to histoplasmin, coccidioidal infection may not be the only source. The distinctly two-peaked distribution of sizes of reactions, one peak at 6 mm., another at 10 mm., suggests the presence of not one but two sources of cross-sensitivity. *Coccidioides* is no doubt one of the sources, perhaps the major one,

Figure 9. Provisional estimates of the percentage of recruits with cross-reactions to histoplasmin among lifetime residents of each State



but it seems not at all improbable that the agent or agents responsible for the cross-sensitivity in Louisiana and other Gulf States may also occur in Arizona. This source, or sources, could be highly prevalent in Louisiana, judging from the provisional estimate of 12 percent cross-reactions in recruits from that State. If, as with coccidioidal infection, roughly 40 percent of those infected have cross-sensitivity to histoplasmin (*2*), the frequency of infection with the unknown agent could be about 30 percent among young men in Louisiana.

Finally, from the material given in table 1, we roughly estimated the percentage of young white males in the United States as a whole who react to histoplasmin because of infection with *Histoplasma* and the percentage whose reactions to histoplasmin can be regarded as cross-reactions caused by other agents. Because the study population does not numerically represent the population of each State, it seemed best to base the estimate on the provisional rates shown in columns 11 and 12 and the populations shown in column 5 of table 1. Using these figures we estimate that about 17 to 18 percent of the young white males in the country react to histoplasmin because of infection with *Histoplasma* and that about 2 percent have cross-reactions caused by other agents. Altogether, nearly 20 percent are sensitive to histoplasmin, and about 9 out of 10 of those who are sensitive owe their sensitivity to infection with *Histoplasma*.

Discussion

If our histoplasmin skin test antigen were so specific that it educed reactions only in persons infected with *H. capsulatum* and so sensitive that all infected persons reacted, the present report could have been considerably shorter, simpler, and more precise. But less provocative. The problem of cross-sensitivity, involving recognition of its existence in different regions and identification of the causative agent or agents, is certainly not a new kind of problem to medical science.

To a large extent, the interpretation of results obtained with histoplasmin depends on the use of the quantitative approach to the study of skin reactions, a method which has been developed and has gained widespread acceptance in connection with tuberculin testing (*13–18*). It also takes account of our present knowledge of the existence, prevalence, and geographic distribution of infection with another systemic fungus, *C. immitis*. Six years ago, a report from this office on the prevalence of histoplasmin sensitivity among young adults in this country contained the statement, "All or most of the histoplasmin sensitivity found in California, Arizona and New Mexico probably represents cross-sensitivity by infection with *Coccidioides immitis*" (*1*). At that time, analyses of frequency distributions of sizes of reactions to histoplasmin in different geographic areas had only just begun. In later reports it was possible to show how the distribution of reactions differed in different areas, how the simple "percent positive" obscured those differences, and why, if many of the reactions in the southwest must be interpreted as cross-reactions, the evidence from several other regions was also indicative of cross-reactions, although apparently not caused by the same agent (*2–4, 6*). Material in this report further supports that evidence.

While it may be uncomfortable to have to reckon with unknown sources of cross-sensitivity to histoplasmin, the evidence can hardly be rejected simply because the causative agent or agents have not yet been found and identified. The situation might have been the same with histoplasmal infection were it not that histoplasmal infection does produce clinical disease in some persons and that the organism has been recovered, cultured, and identified and a skin test antigen prepared from it. Even so, widespread benign infection as well as most cases of histoplasmosis went unrecognized for a good many years because histoplasmosis was considered rare and invariably fatal.

From the analysis in the present report, it becomes possible to account for some of the otherwise incomprehensible variations in the distributions of reactions to histoplasmin among population groups in different geographic areas. *Coccidioides* infection as the predominant cause of cross-reactions in the southwest is readily acceptable. Our task now is to be on the alert, particularly in the Gulf and southeastern States, for signs of other fungi that may be infecting and sensitizing a good many people and, perhaps, causing clinically recognizable disease in only a few of them.

It also appears that the epidemiology of histoplasmosis, as well as other fungus infections, may well be strongly affected by the density and movement of populations in regions where the organism exists naturally. A highly potent but geographically limited focus of *Histoplasma*, for example, would be of little significance for human histoplasmosis unless it were frequented by human beings. Until people get there, and become infected, such foci will probably remain unknown.

Summary

Histoplasmin skin tests were given to a study group of 306,000 male Navy recruits as they entered the Navy's two training centers during 1958–61. The study was limited to recruits 17–21 years old who had specified their race as "white" and had indicated in a brief residence history that they had lived all their lives in the conterminous United States. Results are presented separately for the 212,000 classified as lifetime residents of a single State and the 94,000 who had lived in more than one State.

The frequency of reactions of 4 mm. or more varies among the States from 71.5 percent for lifetime residents of Kentucky to 0.7 percent for Rhode Island residents. Such figures provide an index of the prevalence of sensitivity to histoplasmin but not necessarily the prevalence of infection with the fungus *Histoplasma capsulatum*, since cross-reactions to histoplasmin occur in some regions as the result of infections with agents other than *Histoplasma*.

Frequency distributions of the sizes of reactions to histoplasmin in different parts of the country illustrate how, in some regions, the distributions of "not negative" or "significant" reactions, regardless of their frequency in the total group, approximate normal curves with similar means and standard deviations. They also show how, in other regions, normal curves with the same parameters can be fitted to only part of the observed distributions, leaving a relative excess of small reactions which are believed to represent cross-sensitization caused by infection with agents other than *Histoplasma*. While infection with *Coccidioides* may account for many of the cross-reactions in the southwest, unknown agents appear to be responsible in other parts of the country.

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Predicting Asthma Outbreaks

A preliminary study of asthma outbreaks in New Orleans (*Public Health Reports*, November 1962) described an apparent relationship between the number of hospital visits for treatment of acute asthma and the wind's speed and direction. This implied a possible connection between asthma outbreaks and emissions of contaminant substances into the air from sources in the immediate vicinity of New Orleans. In a single day, 100 or more visits might be reported.

To determine whether outbreaks related to air pollutants were occurring in other cities, hospital records and U.S. Weather Bureau summaries for Houston and Corpus Christi, Tex., were surveyed.

In Houston, emergency room records for 1955–59 revealed no relationship between wind direction and the number of visits to the Hermann Hospital for treatment of acute asthma. Visits never reached outbreak levels, the maximum being 7 or 8 a day.

In Corpus Christi, on the other hand, 1959–60 records revealed a distinct relationship between wind direction and visits to the Driscoll Foundation Children's Hospital and the County Charity Hospital for treatment of acute asthma. Cases were distributed geographically from the northeast sector of the city toward the southwest in association with north and northeast winds. Since Corpus Christi is bordered on the north by a ship channel, along which the heavier industry of the area, landfills, and shipping and docking facilities are located, this area might be a source of air pollution.

Failure to find a relationship between wind direction and asthma, as in Houston, does not rule out the possibility of asthma due to air pollution. Moreover, in Corpus Christi a detailed study of current events, rather than a review of records, would be needed to confirm that an air pollutant is responsible for the asthma and, if so, from what source.

The seasonal pattern of visits for emergency asthma treatment was similar in New Orleans, Houston, and Corpus Christi. In Houston the approximately 450 admissions per year ranged from 24 to 50 per month from December through June, dropped to 15–25 in July, August, and September, and reached a sharp seasonal peak of 50–100 for October and November. In Corpus Christi there were about 325 visits for emergency asthma treatment a year.

Each of the studies of the two cities required only about 2 weeks of clerical time in collecting the information from hospital records and about 4 days of professional time in collecting and analyzing the results. The methods employed may prove useful in determining radical patterns of asthma outbreaks related to air pollutants.—GUY R. NEWELL, JR., *medical undergraduate, Tulane University School of Medicine, at time of survey; now intern at Johns Hopkins Hospital, Baltimore, Md.*

Occupational Health Notes

Ventilation in Garages

A Cincinnati Health Department survey of garages during cold weather disclosed widespread deficiencies in ventilation. Air in 48 garages with capacities from 4 to more than 25 cars was analyzed by using an MSA squeeze bulb sampler.

Carbon monoxide concentration in 13 garages exceeded 100 ppm; it was between 25 and 100 ppm in 23 others. (These readings were not taken at peak periods.)

A drive to improve conditions was engendered by complaints from several sources. Owners were concerned with failure of some mechanics to use exhaust hoses. Service managers criticized owners who neglected defective mufflers and tailpipes. Mechanics reported frequent headaches, nausea, and loss of appetite.

Radioactive Wastes

Incineration of radioactive wastes by hospitals in Houston, Tex., has been investigated. Some hospitals licensed to do this by AEC store wastes for decay before incineration, and others store the ash on the premises.

Certain hospitals not licensed to incinerate assumed it was permissible to incinerate as long as the unburned wastes fell within established limits. At one such hospital, radioactivity in the ash exceeded permissible levels. When informed that the limits applied to the ash, the hospital discontinued incineration.

Auto Body Shops

California studies of automobile body repair operations, often poorly ventilated, with little or no suitable sanitary facilities, have pointed up several hazards:

- Skin contact with plastic body fillers, solvents, grease, and dirt.
- Inhalation of paint spray, solvent fumes, plastic dust (from grinding), and carbon monoxide.
- Exposure to flammable and explosive materials.

It has been observed that right-handed workers are likely to develop boils on the left side of the body (since more plastic dust is directed at that side during grinding operations). Multiple boils have been seen on the left forearm, under the left arm, on the left thigh, and particularly below the left knee, where dust is easily forced into the skin of the kneeling worker.

Innovation in Sewer Maintenance

Closed-circuit television is used in Pennsylvania for sewer and pipeline maintenance.

A section of the sewer is first rodded from manhole to manhole; then a television camera is attached to the rod and pulled through the line.

Personnel in an air-conditioned portable trailer watch the findings on the screen.

Silicosis in Sandblasting

Two patients with advanced silicosis were discovered among eight workers employed by a Massachusetts company to sandblast and clean external walls.

When the first was discovered, it was learned there had been no X-ray survey of these workers. One of the patients had developed silicotuberculosis, and the other, who was clinically asymptomatic, showed evidence of pulmonary deficiency after removal of a cancerous lobe of lung.

Phosdrin-Contaminated Clothing

Investigation of repeated illness of an 8-year-old California boy revealed it occurred only when he wore his jeans. The suspect jeans, which had been purchased at a salvage depot, were found to be impregnated with Phosdrin, a potent insecticide. In the next few weeks four other boys and two adults had similar symptoms, and one boy became critically ill.

Through radio, television, and newspaper publicity all purchasers of jeans from the same lot were urged to submit them to the local health department for laboratory testing. All recovered clothing was tested by the California Department of Agriculture, and one batch was found contaminated with up to 5 percent pure Phosdrin. Further investigation disclosed a container of Phosdrin had been punctured in transit with a consignment of jeans which had absorbed most of the spilled insecticide. The jeans had been stored 7 months before being placed on sale.