Even though histoplasmosis seems to be an infectious disease at present restricted to limited areas of our country, and blastomycosis a disease still more firmly hemmed in, there are conditions about which those of us, who are happily outside the present boundaries of their spread, need to know all we can learn about them.

Incidence of Tuberculin, Histoplasmin, and Blastomycin Reactors Among a Group of School Children

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SINCE no recent survey of tuberculin sensitivity had been made, and since there was no comprehensive study of histoplasmin sensitivity by age in school children in the area of Cincinnati, Ohio, it was felt that current information on the prevalence of sensitivity to these antigens would be of interest. Cincinnati has been shown to be in an area where histoplasmin sensitivity is extremely high.[1, 2] Indeed, it appears to be on the northeastern border of the high area, as sensitivity has been demonstrated to decrease both to the north and to the east.

The recent report of 12 cases of blastomycosis from Cincinnati makes this city one of the centers of the disease so far as reported cases are concerned.[3] The exact incidence of this disease and its importance as a clinical and epidemiological problem remain to be defined. The most pressing question relates to the prevalence of the infection. Is it a rare and usually fatal disease, or does it, like coccidioidomycosis and histoplasmosis, occur also as an extremely common primary type of infection? One way of determining the possibility of the occurrence of widespread infection would be to do skin tests with blastomycin. For this reason skin tests with this antigen were also performed.

The present paper reports the skin test reactions to tuberculin, histoplasmin, and blastomycin in 7,194 school children between the ages of 5 and 19 years in Hamilton County, Ohio.

MATERIAL AND METHOD

The study was carried out between May 5 and May 15, 1952. Tuberculin, histoplasmin and blastomycin tests were done simultaneously by intradermal injection of 0.1 ml. of the appropriate antigen. The tuberculin and blastomycin tests were made at points widely separated on the left forearm and the

histoplasmin test on the right forearm. The tests were performed by teams of experienced individuals, each giving one injection to avoid any confusion in the antigens. The readings were made 48 hours after injection by four physicians with long experience in skin testing. The transverse diameter of edema and erythema was measured and recorded for each test. Reactions in which the area of induration measured 5 mm., or more, in transverse diameter at 48 hours after injection were considered to be positive.

The tuberculin employed was Purified Protein Derivative (PPD-S), furnished by Dr. Florence B. Seibert of the Henry Phipps Institute of Philadelphia, Pa. A dose of 0.0001 mg. was employed. The histoplasmin (Lot HKC-5) was prepared and titrated by the method of Shaw, Howell, and Weiss.[4] It was employed in a dilution of 2:1,000. The blastomycin (Lot B-7) was furnished by Dr. Arden Howell of the Public Health Service. This material had been standardized on infected guinea pigs[5] and was employed in a dilution of 1:1,000.

Skin tests were given and read on a total of 7,582 persons in 15 grade and high schools in the Cincinnati area. Of these, 191 were white adults and 197 were Negro children. Both these groups were excluded from the analysis. About 90 per cent of the school population of the 15 schools accepted the tests, the percentage reaching 98 in some schools.

In addition to the skin testing, a 70 mm. x-ray of the chest by portable x-ray units was obtained on each individual. Retakes on 14 x 17 films were made when indicated. The Tuberculosis Division of the Ohio State Department of Health and the Anti-Tuberculosis League of Cincinnati provided the staff and x-ray units for this part of the survey. Reports of the skin tests and x-ray findings were sent to parents and physicians.

In the analysis of the results, only those who had lived 80 per cent, or more, of their lives in Cincinnati or Hamilton County were considered as lifetime residents. All others were considered as nonlifetime residents.

The 6 communities selected for the survey are areas in Hamilton County, adjacent to the City of Cincinnati. It was thought that the more suburban areas were preferable from the point of view of permanence of residence, compared to the downtown areas of the city where there is a rapid change in school population. However, the city areas were represented by the City of Norwood. This is a residential and industrial area with a population of over 50,000 which is completely enclosed by the City of Cincinnati. The population is composed mostly of industrial workers.

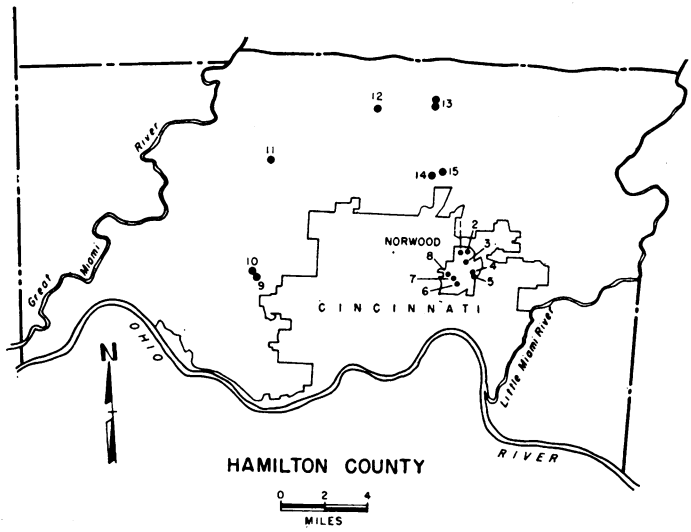
Figure 1 shows the location of the 15 different schools in Hamilton County, Ohio. There were 10 public and 5 parochial schools included in the survey. Bridgetown and Colerain are semirural residential areas. The Village of Greenhills is a housing development located in a rural area. The Village of Glendale is a residential area in a rural section, while the Village of Wyoming is largely residential, but adjoins industrial areas of Cincinnati. Both Glendale and Wyoming are, in general, suburban residential areas of high economic level. As shown on the map, none of the communities are located on the Ohio or Little Miami Rivers.

RESULTS

In Table 1 and Figure 2 are shown the number and per cent of positive reactors to tuberculin, histoplasmin, and blastomycin among the 7,194 white children tested in the 15 schools. One of the most striking findings evident from the study of these data is the low rate of reaction to tuberculin. It is seen that the rate rises slowly from less than 1 per cent at age 5 to about 5 per

FIGURE 1

Map of Hamilton County, Ohio, Showing Location of Schools Where Tests Were Conducted



1. Norwood View
2. St. Peter and Paul
3. North Norwood
4. St. Matthew
5. Sharpsburg
6. Williams Avenue
7. Allison Avenue
8. St. Elizabeth
9. Bridgetown
10. St. Aloysius
11. Colerain
12. Greenhills
13. Glendale
14. St. James
15. Wyoming

cent at age 13. It continues at about this level through age 18. The fact that only 10 persons were tested in the 19-year-old group makes the higher rate in this group of no significance. It is impressive, however, that little more than 5 per cent of the children aged 13–18 reacted to tuberculin. It is interesting to note that the over-all rate among the 197 Negro children tested was 14.2 per cent, compared with the rate of 3 per cent among white children.

The histoplasmin rates in Hamilton County are extremely high, as shown in

TABLE 1

Number and Per cent Positive Reactors to Tuberculin, Histoplasmin, and Blastomycin Among 7,194 White School Children in Hamilton County, Ohio

		Age Nearest Birthday															
		5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
Number Tested		270	643	776	727	858	781	763	607	669	463	237	160	140	90	10	7,194
								Tuberculin									
Pos.	Number	2	12	8	12	16	23	30	19	32	28	13	10	6	4	1	216
	Per cent	0.7	1.9	1.0	1.7	1.9	2.9	3.9	3.1	4.8	6.1	5.5	6.3	4.3	4.4	10.0	3.0
								Histoplasmin									
Pos.	Number	41	119	170	187	290	283	299	262	333	245	148	93	92	72	8	2,642
	Per cent	15.2	18.5	21.9	25.7	33.8	36.2	39.2	43.2	49.8	52.9	62.5	58.1	65.7	80.0	80.0	36.7
								Blastomycin									
Pos.	Number	12	22	51	61	91	86	111	91	123	88	53	32	28	23	3	875
	Per cent	4.4	3.4	6.6	8.4	10.6	11.0	14.5	15.0	18.4	19.0	22.4	20.0	20.0	25.5	30.0	12.2

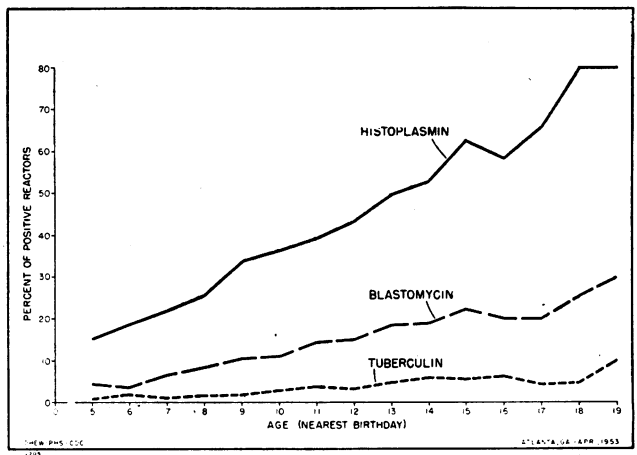


FIGURE 2

Per cent of Positive Reactors to Tuberculin, Histoplasmin, and Blastomycin Skin Tests Among 7,194 White School Children in Hamilton County, Ohio

Table 1 and Figure 2. Over 20 per cent are positive to this test by the age of 7 years and 80 per cent are positive by age 18. As in other studies,[2] the rate among males was slightly higher than among females (38 as compared with 33 per cent).

The percentage of positive blastomycin reactors was 12.2. However, there were essentially no positive blastomycin reactors among children who did not react also to histoplasmin. One-third (33 per cent) of the histoplasmin reactors gave a positive reaction to blastomycin. The blastomycin reactions were smaller than the histoplasmin reactions in 97 per cent of the children. Only one child reacted to blastomycin and not to histoplasmin, and this child could not be retested.

The relationship of the size of the blastomycin and the histoplasmin tests in the same children is shown in Table 2. This table emphasizes the consistent finding that the histoplasmin reaction was almost always larger than the blastomycin reaction in the same child. Of the 1,164 children who showed some reaction to blastomycin only 38 (3.3 per cent) showed reactions to blastomycin larger than to histoplasmin, and of these the greatest difference was 6–8 mm. which occurred in 2 children. Of the 875 blastomycin reactors showing a positive reaction, all but 11 (1.3 per cent) showed larger reactions to histoplasmin.

TABLE 2

Comparison of the Size (in mm.) of the Histoplasmin and Blastomycin Reactions in the Same Child

Blastomycin Size in mm.	*Histoplasmin (Size in mm.)*						
	0	*1–4*	*5–10*	*11–14*	*15–20*	*21 or over*	*Total*
0	4,413	91	580	636	287	23	6,030
1– 4	27	21	68	112	56	5	289
5–10	1		82	351	183	29	646
11–14			2	71	93	10	176
15–20				8	34	10	52
21 or over						1	1
Total	4,441	112	732	1,178	653	78	7,194

TABLE 3

Number and Per cent of Positive Reactors to Histoplasmin Among "Lifetime" Residents of Specified Schools in Hamilton County, Ohio

School Number			Age Nearest Birthday								
			5–6	7–8	9–10	11–12	13–14	15–16	17–18	19	Total
1.	Number	Positive	13	19	24	31	31	3			121
		Tested	88	72	80	74	46	8			368
	Per cent	Positive	14.8	26.4	30.0	41.9	67.4	37.5			32.9
2.	Number	Positive	3	17	17	19	19	2			77
		Tested	20	87	80	71	53	6			317
	Per cent	Positive	15.0	19.5	21.3	26.8	35.9	33.3			24.3
3.	Number	Positive	13	11	29	30	35	4			122
		Tested	57	68	71	69	61	7			333
	Per cent	Positive	22.8	16.2	40.9	43.5	57.4	57.1			36.6
4.	Number	Positive	3	27	27	29	28	6			120
		Tested	17	92	79	74	64	6			332
	Per cent	Positive	17.7	29.3	34.2	39.2	43.7	100.0			36.1
5.	Number	Positive	20	14	27	29	22	3			115
		Tested	68	52	79	49	41	4			293
	Per cent	Positive	29.4	26.9	34.2	59.2	53.7	75.0			39.3
6.	Number	Positive	11	33	27	38	40	6			155
		Tested	58	93	74	68	65	10			368
	Per cent	Positive	19.0	35.5	36.5	55.9	61.5	60.0			42.1
7.	Number	Positive	12	17	37	34	26	1			127
		Tested	41	62	85	65	41	2			296
	Per cent	Positive	29.3	27.4	43.5	52.3	63.4	50.0			42.9
8.	Number	Positive	8	9	31	34	28	7			117
		Tested	66	99	108	88	71	8			440
	Per cent	Positive	12.1	9.1	28.7	38.6	39.4	87.5			26.6
9.	Number	Positive	17	9	28	25	19	4			102
		Tested	99	54	75	65	44	5			342
	Per cent	Positive	17.2	16.7	37.3	38.5	43.2	80.0			29.8
10.	Number	Positive	6	13	37	28	39	1			124
		Tested	18	103	129	89	83	2			424
	Per cent	Positive	33.3	12.6	28.7	31.5	47.0	50.0			29.3
11.	Number	Positive	13	44	84	57	64	70	58	2	392
		Tested	78	147	169	120	118	100	70	3	805
	Per cent	Positive	16.7	29.9	49.7	47.5	54.2	70.0	82.9	66.7	48.7
12.	Number	Positive	9	28	40	49	35	33	18	1	213
		Tested	96	124	141	107	69	57	29	1	624
	Per cent	Positive	9.4	22.6	28.4	45.8	50.7	57.9	62.1	100.0	34.1
13.	Number	Positive	2	27	23	37	24	23	22	1	159
		Tested	9	79	65	79	44	41	28	1	346
	Per cent	Positive	22.2	34.2	35.4	46.8	54.5	56.1	78.6	100.0	45.9
14.	Number	Positive	1	7	14	15	12	1			50
		Tested	13	74	60	64	36	1			248
	Per cent	Positive	7.7	9.5	23.3	23.4	33.3	100.0			20.2
15.	Number	Positive	13	10	18	21	24	21	22		129
		Tested	76	65	76	68	61	41	35		422
	Per cent	Positive	17.1	15.4	23.7	30.9	39.3	51.2	62.9		30.6
Total	Number	Positive	144	285	463	476	446	185	120	4	2,123
		Tested	804	1,271	1,371	1,150	897	298	162	5	5,958
	Per Cent	Positive	17.9	22.4	33.8	41.4	49.7	62.1	74.1	80.0	35.6

Comparison of the rates of reaction between lifetime and nonlifetime residents of Hamilton County reveals that the lifetime residents showed 35.6 per cent positive to histoplasmin while the nonlifetime residents showed 42.0 per cent positive. This finding that nonlifetime residents show a somewhat higher rate of reaction than lifetime residents was also observed in Kansas City.[6]

Variation in skin test rates in different schools — Considerable differences in rates of reaction were found in the various schools.

The rates of reaction to histoplasmin by age for each of the 15 schools are shown in Table 3. For the purpose of

this comparison only lifetime residents of each school were considered. Quite marked variations in over-all sensitivity rates are evident as the rates for various schools vary from 20 to 43 per cent even in schools where the same age groups were studied. The rate for all of the 5,958 lifetime residents was found to be 35.6 per cent.

For purposes of comparison of the different schools, it is possible to construct theoretical annual conversion rates, assuming such rates to be constant, by a modification * of the method of Manos.[7] These rates give an estimate of the yearly rate at which persons are being infected among the population under study or the yearly rate at which persons negative to the histoplasmin skin test "convert" to a positive skin test. This method simplifies comparison of the schools, since each school can be represented by a single "conversion" rate. The annual "conversion" rates for the 15 schools are seen below:

School	*Location*	*Annual Conversion Rate with Standard Error*
1. Norwood View	Norwood	7.5 ± 1.8
2. St. Peter and Paul	"	3.0 ± 0.5
3. North Norwood	"	7.3 ± 2.1
4. St. Matthew	"	4.3 ± 0.5
5. Sharpsburg	"	6.3 ± 2.2
6. Williams Ave.	"	8.8 ± 1.2
7. Allison Ave.	"	7.8 ± 1.6
8. St. Elizabeth	"	6.8 ± 2.2
9. Bridgetown	W. Central	5.8 ± 1.5
10. St. Aloysius	"	6.1 ± 2.0
11. Colerain	Northwest	10.0 ± 1.2
12. Greenhills	North	7.5 ± 0.5
13. Glendale	"	7.4 ± 1.3
14. St. James	"	4.3 ± 0.9
15. Wyoming	"	5.0 ± 1.0

It is seen that the lowest rates occur in schools 2, 4 and 14, all of which are parochial schools. The rates vary from 3.0 to 4.3 in these 3 schools. The two other parochial schools (8 and 10) also show fairly low rates, 6.8 and 6.1, respectively. It is interesting to note that although three of the lowest schools (2, 4 and 8) occur in the City of Norwood, the school with the second highest rate observed (6), also is in Norwood, as is the third highest (7). The school with the highest rate (11) was a rural centralized school. The remaining schools showed rates intermediate between the highest and the lowest. It is interesting to note that public and parochial schools which were adjacent (9 and 10, 14 and 15) showed almost the same rates.

The percentage of children positive to the tuberculin test varied for the different schools from 0.7 per cent positive to 5.4 per cent positive. The highest percentage of positive reactors (5.4, 5.2, 4.5, and 4.1) all occurred in Norwood (schools 7, 3, 1, and 4) probably reflecting the industrial crowding in this city. The lowest percentage of positive reactors (0.7 per cent) was found in school 14, a suburban parochial school.

DISCUSSION

The three-fold purpose of this survey was to define the tuberculin, histoplasmin, and blastomycin rates in the Cincinnati area. While the tuberculin rates are, in general, low and reflect credit upon the control program in the area, the rates among Negroes and in industrial communities still are high compared to the other areas surveyed. The establishment of these basic tuberculin rates by age for the Cincinnati area should present a useful tool for physicians in attempting to evaluate the results of a positive tuberculin test on any individual child. It is obvious that the previous concept that most persons are positive to tuberculin is erroneous, especially as far as children are con-

* This modification weights the original observations proportionally to $\frac{n}{p(1-p)}$ rather than weighting their logarithms by $\frac{n(1-p)}{p}$. It was adapted by Myron J. Willis of the Communicable Disease Center, Public Health Service, to whom the authors express their appreciation.

cerned. Data on the prevalence of tuberculin sensitivity by age, done with standardized tuberculin, are of great importance in evaluating the tuberculosis problem. The rates of reaction presented herein for Hamilton County are directly comparable to those for Kansas City,[6] since the same tuberculin was employed. For comparison with Kansas City the children of Norwood were considered together as representing an urban area, surrounded by the City of Cincinnati. The rates by age for Norwood are almost the same as the rates for similar aged children in Kansas City. The tuberculin rates for the combined suburban schools, exclusive of Norwood, are, however, about half those found in the Norwood and Kansas City areas. Tuberculin rates in urban areas are usually higher than in rural areas; hence this finding was not unexpected.

In contrast to the relative infrequency of tuberculin reactors in the survey schools, histoplasmin reactors occurred frequently. Children 5 years of age showed a rate of 15 per cent. The rate rose steadily, to reach a high of 80 per cent positive at age 18. This rate curve is similar to that of Kansas City,[6] but a little lower.

The importance to physicians of the finding of the very high histoplasmin rate in the area is obvious. It is apparent that consideration of fungus etiology should enter into the diagnosis of any lung lesions in young children, especially if there is a poor response to antibiotic therapy. Also, since the rates among apparently normal school children are so high, the value of the skin test as an indicator of active disease is decreased. Serological tests are the best indicators of activity.

Perhaps the most important finding of the survey relates to the blastomycin reactors. One of the most interesting questions relative to blastomycosis is whether this disease is a rare, usually fatal disease, or whether widespread primary infections occur, of which the disseminated fatal disease is a rare complication. The latter condition has been found to exist with both coccidioidomycosis and histoplasmosis, once regarded as rare and fatal diseases, now as widespread and relatively benign infections. The occurrence of fatal cases of blastomycosis in Cincinnati made this an area where these possibilities could be tested, assuming that the organism produces skin sensitivity as readily as the other two fungi. It was necessary to have a specific skin testing material and to employ it at specific titer.[5] The blastomycin used was prepared and titered in the same manner as the histoplasmin antigen. Based on the previous work with Coccidioides and Histoplasma, one would expect that if Blastomyces, were prevalent, a large number of persons would react to blastomycin, and that the individual reactions to blastomycin would be larger than to histoplasmin. Actually, just the reverse was observed; reactions to blastomycin occurred in only 12 per cent; whereas 33 per cent reacted to histoplasmin. Only one-third of the histoplasmin reactors also reacted to blastomycin. Only one person reacted to blastomycin who failed to react also to histoplasmin. The size of the reactions to blastomycin was almost always smaller than the size of the reactions to histoplasmin. These findings point to the conclusion that blastomycin reactions are cross-reactions rather than specific reactions. Cross-reactions between histoplasmin and blastomycin have been demonstrated in animals and man.[5, 8] In the case of experimentally infected animals, reactions to the specific antigen were frequent and large; whereas cross-reactions or reactions to the heterologous antigen were less frequent (from 12 to 16 per cent) and smaller in size. These findings parallel those of the present survey where 12 per cent of blastomycin reactions were observed. Murphy[9] has

reported that a "majority" of 31 blastomycin reactors observed in North Carolina reacted to histoplasmin, usually with a reaction of over 10 mm. of induration.

There are several possible interpretations of these data. Among these is the assumption that the blastomycin is not specific for Blastomyces infection. It must be stated, however, that the methods of standardization were the same as for histoplasmin, the specificity of which is widely acepted. Another assumption is that Blastomyces infection does not sensitize as readily as Histoplasma or Coccidioides, and hence the skin reactions would fail to occur even if the antigen was specific. Some evidence suggesting this is found in the case reports of blastomycosis, since all cases have not reacted to blastomycin.[10, 11] Still another assumption is that blastomycosis, unlike histoplasmosis and coccidioidomycosis, does not exist as a widespread mild infection; but that infection with this fungus is infrequent, serious, and often fatal. Against this hypothesis is the parallelism between the course and history of these three systemic mycoses. The existence of a common antigen has been commented upon; the frequency of animal cases and of lung infection in cases of Blastomyces parallels that with the other two fungi. The growth and appearance of the organism in ordinary laboratory media are quite similar to Histoplasma, and the temperature and humidity requirements for growth of both organisms are similar. Also, Blastomyces will grow on bark or soil in the laboratory.[12]

In view of the limitations mentioned above, it is not possible to rule out the existence of subclinical forms of blastomycosis by these studies. Certainly, however, no evidence was found to support the existence of widespread infection. Further studies of the problem are urgently needed. There appears to be no doubt that cases of blastomycosis frequently occur in Cincinnati,[3] Lexington, Ky.,[13] and around Durham, N. C.;[9] yet prolonged search in the Kansas City area has failed to reveal a single case, even though both histoplasmin and blastomycin rates are quite similar to those found in Cincinnati.[14]

SUMMARY

The skin reactions to tuberculin, histoplasmin, and blastomycin of 7,194 school children in the Cincinnati, Ohio, area are reported.

1. The tuberculin rate was low, 3 per cent for the entire group of white children, with variation by age from less than 1 per cent at 5 years to 6 per cent at 14 years of age.

2. The rate of histoplasmin reactors was high, increasing with age from 15 per cent at 5 years to 80 per cent at 18 years. There was considerable variation in histoplasmin sensitivity, both within and between the different communities.

3. The rate of reaction to blastomycin is about one-third the rate of reaction to histoplasmin. With one exception, positive blastomycin reactions were found only in the presence of positive histoplasmin reactions. It appears from these findings that the blastomycin reactions are cross-reactions.

4. The implications of these findings in the epidemiology of blastomycosis are discussed.

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New Korean School of Public Health

The first School of Public Health in Korea was opened on September 28 with 20 physicians enrolled. A severe shortage of qualified public health personnel is judged the immediate problem confronting public health officials in Korea. There is at present only a small number of trained Korean public health personnel—most of them trained in the United States from 1945 through 1950. The initial activity of the school is a basic three-month training course for a maximum number of students, with advanced graduate courses leading to a degree in public health to follow next year. The faculty consists of 25 Korean medical men, assisted by 20 United Nations specialists, most of whom are U. S. Army medical personnel on duty in Korea. Dr. Han Pum Sak, a graduate of the University of Michican School of Public Health, has been appointed acting dean of the school.

The school is the result of cooperative action by several organizations and public health leaders. A World Health Organization team of experts recommended establishment of such a school; the American-Korean Foundation Mission provided the funds, contributed by the Monsanto Chemical Company; the Harvard University School of Public Health participated in the preparation of the curriculum and collection of textbooks and other teaching materials which were flown to Korea; the school has been organized as a unit of the Seoul National University in conjunction with the Ministry of Health; full technical assistance of the R. O. K. Army Medical Field Service School faculty and of the U. S. Eighth Army Surgeon's office have been made available. Among the individuals who have taken leadership in formation of the school are Dr. Choi Chai Yu, Korean minister of health; Col. James P. Pappas, M.C., U. S. Army, chief of public health, Korean Civil Assistance Command; Howard A. Rusk, M.D., head of the second American-Korean Foundation Mission; and James Steven Simmons, M.D., dean, Harvard University School of Public Health.