

STUDIES ON THE EPIDEMIOLOGY OF SARCOIDOSIS IN THE UNITED STATES: THE RELATIONSHIP TO SOIL AREAS AND TO URBAN-RURAL RESIDENCE

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During World War II, there were 350 recognized cases of sarcoidosis among American Armed Forces personnel. These cases, chosen in a relatively unselected manner, afford an admirable opportunity for investigation into some of the aspects of the epidemiology of this disease. Preliminary studies of this group have demonstrated a striking concentration of patients' birthplaces in the Southeastern United States (1, 2). Although cases in negroes predominated, the observed geographic localization could not be accounted for solely by the distribution of the negro population in the United States. The present investigation, which was concerned with factors which might have influenced this unusual case distribution, revealed an association between the distribution of the cases and certain soil areas. Furthermore, a higher incidence of the disease was found among servicemen from the more rural areas of the Southeast. These correlations may serve as additional localizing factors for further studies on the epidemiology of sarcoidosis.

MATERIAL AND METHODS

Of the 350 cases of sarcoidosis diagnosed in World War II servicemen, there were 334 living at the time of this study. Only these were investigated since the compilation of epidemiologic data would be incomplete in those deceased. In many patients the disease was discovered accidentally by routine x-ray examination taken during the course of hospitalization or upon separation from service. The diagnoses of sarcoidosis were made in American military hospitals scattered over the

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world. In all instances the biopsy specimens were reviewed and confirmed by the Armed Forces Institute of Pathology. A record of the induction chest film and physical examination was available on all patients. The complete records of all hospitalizations on each patient were studied and an analysis of the clinical data is in preparation. The standards for verification of the diagnosis have been previously reported (1, 2). The present analysis has been restricted to 297 of these cases, 37 were excluded because of the lack of availability of data to clearly establish locale of residence or diagnosis.

The minimum information on these cases consisted of identifying data including race, birthplace, residence at the time of entry into the military service, *i.e.*, "induction residence", and clinical and pathological reports which conformed to the criteria for the diagnosis of the disease, as proposed by the National Research Council (1). Additional consideration was given to those cases whose birthplace and induction residence were in the same or adjacent counties. For convenience, these cases have been arbitrarily designated "lifetime residents".

Figures giving the total number of persons serving in all the military services from the beginning of conscription to December 2, 1946, were obtained through the courtesy of the National Selective Service. These data, available by county and state of induction and race, were used as a basis for calculating race specific attack rates. Since the numerator consists of servicemen, a denominator representing the source of this group would be needed for calculation, hence the use of this Selective Service data. While certain factors of bias, such as omission of females, older persons and those rejected from military duty, are recognized in these rates, this military service information represented the most appropriate denominator that was available. The rates by induction residence, in turn, were selected because factors of migration, particularly the movement of Negroes from the Southeast to the northern industrial centers, prolonged the determination of accurate rates by birthplace.

The soil classification data which were used in this study were obtained through the courtesy of the Division of Soil Survey, United States Department of Agriculture. By the use of a recent map, showing the soil regions of the South, the various counties in Alabama,

Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Texas were placed in one of 91 categories, depending upon the predominant soil series charted for each county. The soil series, in turn, were combined into larger groups on the basis of similarities in topography, profile, and parent materials, to

form the soil areas characteristic of the Piedmont Plateau, Middle and Lower Coastal Plain, and other physiographic divisions of the Southeast. These soils are contained for the greater part in 8 of the 36 great soil groups thus far recognized in the United States, namely, the Red-Yellow Podzolic soils, Rendzinas, Alluvial soils,

TABLE I

Cases of sarcoidosis in the Armed Forces during World War II, according to states, by race, birthplace, and induction residence

State	Number of cases					
	Birthplace			Induction residence		
	Total	White	Negro	Total	White	Negro
Region I (South Atlantic Gulf Coast)						
Alabama	31	5	26	27	5	22
Arkansas	13	4	9	14	3	11
Florida	11	1	10	15	—	15
Georgia	26	3	23	20	3	17
Louisiana	13	2	11	12	2	10
Mississippi	22	3	19	19	2	17
North Carolina	36	4	32	29	4	25
South Carolina	30	2	28	15	2	13
Texas	23	4	19	20	6	14
Virginia	18	2	16	14	2	12
Total	223	30	193	185	29	156
Region II (Middle Atlantic and Border)						
Delaware	1	—	1	1	—	1
District of Columbia	—	—	—	6	—	6
Maryland	3	—	3	4	—	4
New Jersey	2	2	—	7	1	6
New York	13	12	1	18	15	3
Oklahoma	3	2	1	3	1	2
Pennsylvania	3	3	—	14	4	10
Tennessee	8	4	4	8	3	5
West Virginia	3	2	1	2	1	1
Total	36	25	11	63	25	38
Region III (Rest of Country)*						
Arizona	—	—	—	1	—	1
California	1	—	1	6	4	2
Connecticut	—	—	—	1	1	—
Illinois	5	3	2	8	5	3
Indiana	3	3	—	4	3	1
Iowa	2	2	—	—	—	—
Kansas	1	—	1	2	1	1
Kentucky	1	1	—	1	1	—
Massachusetts	4	4	—	4	4	—
Michigan	2	1	1	8	3	5
Missouri	2	1	1	3	2	1
Montana	1	1	—	1	1	—
Nebraska	1	1	—	1	1	—
North Dakota	1	1	—	—	—	—
Ohio	3	1	2	6	2	4
Utah	1	1	—	1	1	—
Washington	2	2	—	2	2	—
Wisconsin	1	1	—	—	—	—
Total	31	23	8	49	31	18
U. S. Total	290†	78	212	297	84	212

* No cases were recognized from 11 states: Colorado, Idaho, Maine, Minnesota, Nevada, New Hampshire, Oregon, Rhode Island, South Dakota, Vermont, Wyoming.

† Seven white cases were foreign born.

TABLE II
Sarcoidosis attack rates among World War II servicemen, by race and induction residence, according to regions of the United States

	Selective service population			Sarcoidosis cases by induction residence			Attack rates per 100,000			Ratio N/W
	Total	White	Negro	Total	White	Negro	Total	White	Negro	
Region I (South Atlantic Gulf Coast)	2,955,135	2,291,056	664,079	185	29	156	6.3	1.3	23.5	18/1
Region II (Middle Atlantic Border)	4,238,992	3,953,837	285,155	63	25	38	1.5	0.6	13.3	22/1
Region III (Rest of U. S.)	7,037,448	6,820,041	217,407	49	31	18	0.7	0.5	8.3	17/1
Total	14,231,575	13,064,934	1,166,641	297	85	212	2.1	0.7	18.2	26/1
Ratio of Rates: Region I/Region III							9/1	3/1	3/1	
Region I/Region II							4/1	2/1	2/1	

Reddish-Chestnut soils, Ground-Water Podzolic soils, and Lithosols.⁴

The urban-rural distribution data which were used in this study were obtained from the 1940 census report. The population characteristics utilized in the urban-rural classification included population density, as defined by population per square mile, and total population. In relation to the negro cases, the population of negro inhabitants of a county classified as rural by the Bureau of Census was used. For this part of the study a total of 185 cases was studied. Each of these patients had entered military service from one of the ten Southeastern states, the area in which the highest incidence of the disease was found. An attempt was made to characterize the county areas of residence as predominantly rural or urban on a relative basis and to consider attack rates among servicemen from county areas of varying urban-rural composition.

RESULTS

Geographic distribution

The breakdown of cases by states is shown in Table I. The states have been divided into three geographic areas on the basis of the relative incidence of the disease. Region I, which had the highest incidence of sarcoidosis, was composed of the nine South Atlantic and Gulf Coast states of Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Texas, and Virginia plus Arkansas. In these states there was a total of 223 cases by birthplace, 30 whites and 193

negroes; and 185 by induction, 29 whites and 156 negroes. The difference of 37 negroes indicates the migration of this group out of the section. Region II which had the next highest incidence was contiguous to Region I and comprised the District of Columbia, the five Middle Atlantic States of Delaware, Maryland, New Jersey, New York and Pennsylvania, plus Tennessee, West Virginia and Oklahoma. In these states there was a total of 36 cases by birthplace, 25 whites and 11 negroes; and 63 by induction, 25 whites and 38 negroes. The difference of 27 negroes represents the migration into this industrial region. In the remainder of the country, Region III, there were 31 cases by birthplace, 23 whites and 8 negroes; and 49 by induction, 31 whites and 18 negroes.

Attack rates for sarcoidosis, specific for race and induction residence, are summarized in Table II for the three regions. In the South Atlantic Gulf Coast States, Region I, the overall attack rates are 1.3 and 23.5 for whites and negroes, respectively. The overall rate in the Middle Atlantic and Border States, Region II, was 1.5 per 100,000, 0.6 for whites and 13.3 for negroes. In Region III, the remainder of the country, the overall rate was 0.7 per 100,000, 0.5 among whites and 8.3 among negroes. It is apparent from these attack rates that a marked predominance of the disease exists among negro inductees of all regions, with the remarkably consistent negro-to-white ratios of 18 to 1, 22 to 1, and 17 to 1 for Regions I, II, and III, respectively. It is possible, however, that the disproportionately larger num-

⁴ The classification and nomenclature of soils used in this study is that of Soils and Men, U. S. Dept. of Agr. Yearbook of Agriculture, 1938, Part IV, pp. 861-1161, with some modifications outlined in the issue of Soil Science and Soil Classification, Vol. 67, No. 2, 1949.

TABLE III

Sarcoidosis attack rates among World War II servicemen, by race and induction residence, according to the states of the South Atlantic Gulf Coast region

State	Selective service population			Attack rates per 100,000			$\frac{(O-E)^2}{E}$ (for Negro cases)
	Total	White	Negro	Total	White	Negro	
Alabama	272,843	202,648	70,195	9.9	2.5	31.3	1.83
Arkansas	189,327	156,550	32,777	7.4	1.9	33.6	1.41
Florida	208,787	157,599	51,188	7.2	0	29.3	0.75
Georgia	292,172	220,912	71,260	6.8	1.4	23.9	0.01
Louisiana	242,943	170,620	72,323	4.9	1.2	13.8	2.88
Mississippi	211,667	125,592	86,075	9.0	1.6	19.8	0.51
North Carolina	349,809	276,260	73,549	8.9	1.4	34.0	3.43
South Carolina	179,664	125,201	54,463	8.3	1.6	23.9	0.00
Texas	716,250	626,258	89,992	2.8	1.0	15.6	2.39
Virginia	291,673	229,416	62,257	4.8	0.9	19.3	0.46
Total	2,955,135	2,291,056	664,079	6.3	1.3	23.5	$X^2 = 13.67$ $0.20 > p > 0.10$

ber of negro, as compared to white, emigrants from the Southeast may have altered the negro-to-white attack rate ratios for Regions II and III.

In comparing rates between the regions, it can be seen that the overall rate for Region I, 6.3 per

100,000, is nine times as great as that for Region III, 0.7 per 100,000. However, a large part of this difference is due to the disproportionate rates between the two races, since a ratio of less than 3 to 1 is observed between the respective

DISTRIBUTION OF CASES OF SARCOIDOSIS AMONG AMERICAN ARMED FORCES PERSONNEL BY BIRTHPLACE

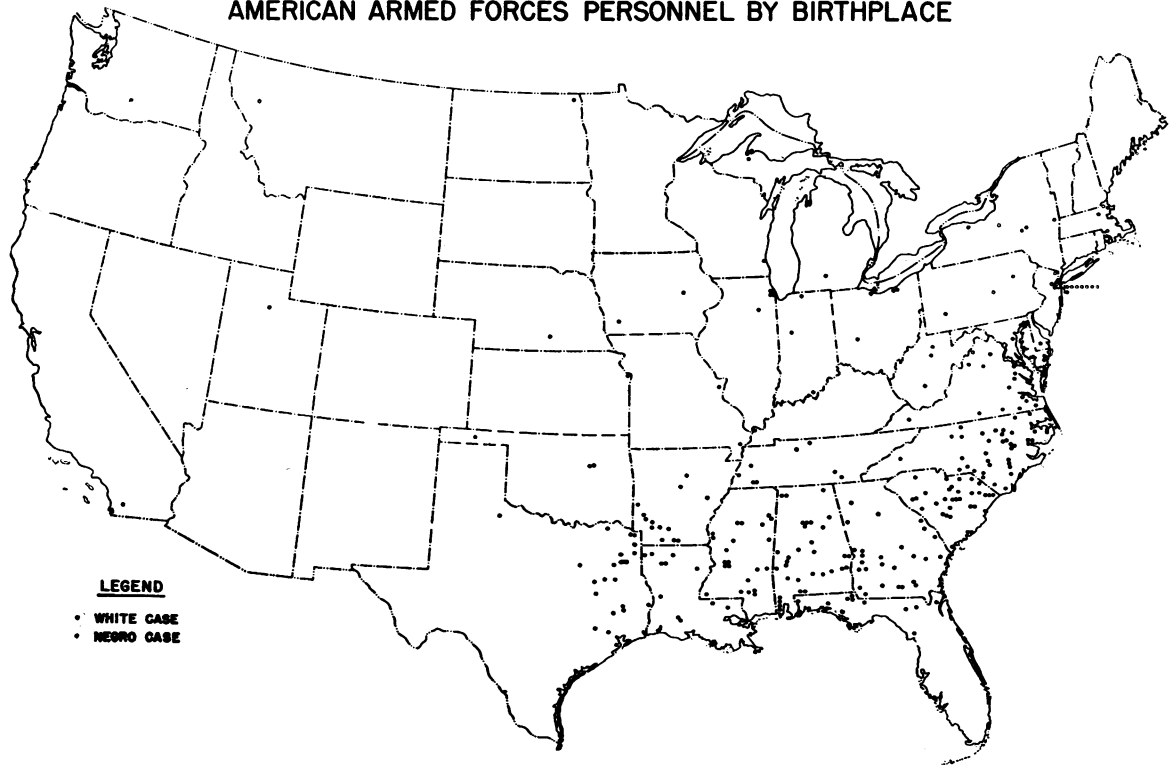


FIG. 1. THE DISTRIBUTION, BY BIRTHPLACE, OF 290 CASES OF SARCOIDOSIS RECOGNIZED AMONG WORLD WAR II SERVICEMEN

Each dot represents the birthplace of a single case. Seven additional cases were foreign-born.

**DISTRIBUTION OF CASES OF SARCOIDOSIS AMONG
AMERICAN ARMED FORCES PERSONNEL
BY INDUCTION RESIDENCE**

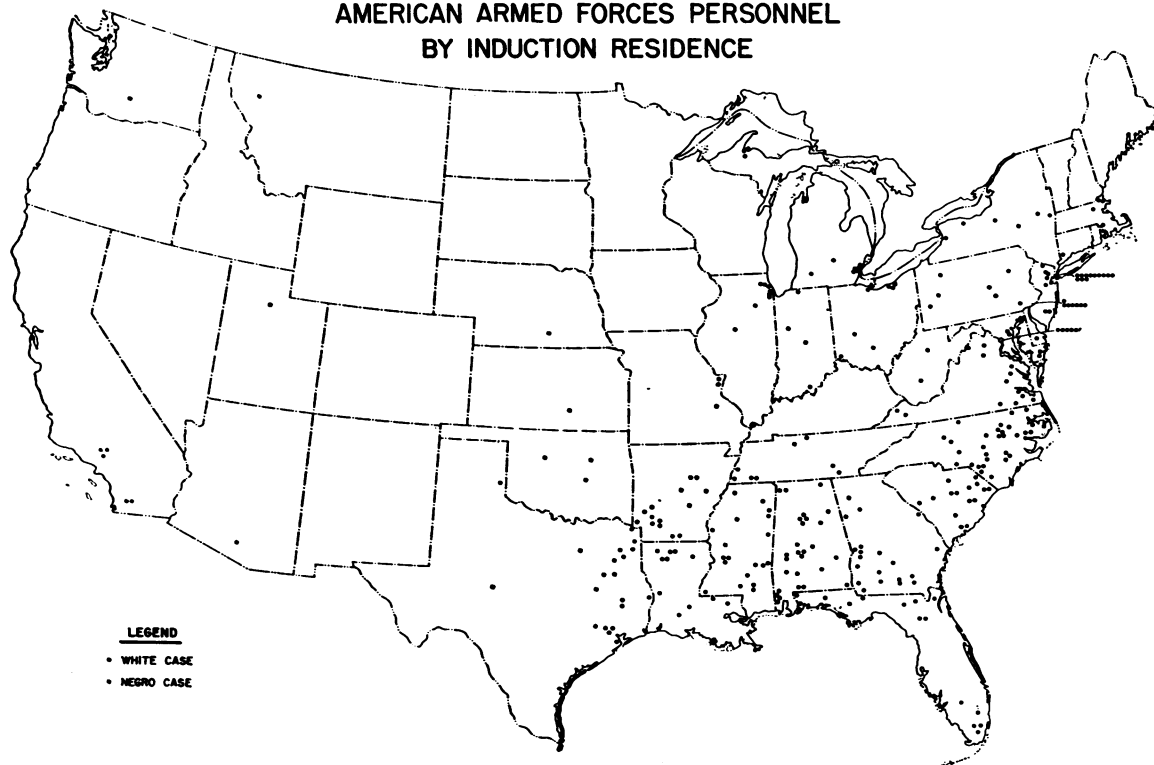


FIG. 2. THE DISTRIBUTION, BY RESIDENCE AT THE TIME OF INDUCTION INTO THE ARMED FORCES, OF 297 CASES OF SARCOIDOSIS RECOGNIZED AMONG WORLD WAR II SERVICEMEN

Each dot represents the induction residence of a single case.

negro and white rates for these regions. Similarly, the 4 to 1 ratio between the overall rates of Regions I and II, 6.3 and 1.5, respectively, also reflects the disproportionate rates between the negroes and whites.

It is evident, therefore, that the higher attack rate for sarcoidosis in the negro and the large negro population in Region I account, in part, for the concentration of cases in this area. However, the 3 to 1 ratio of rates in negroes for Regions I and III clearly indicates the presence of some localizing factor, aside from race, which influences the distribution of the cases.

In attempting to disclose what this factor (or factors) might be, subsequent considerations were focused on the ten states of Region I. Attack rates specific for race and induction residence were first determined for each of these states, as shown in Table III. Because of the small number of white cases, comparisons were made between the negroes only. In the table, the observed inci-

dence of the disease among negro inductees for each state has been compared with the expected incidence on the basis of the overall rates for the area. It is evident that the variations obtained are not great. Although the negro attack rate for North Carolina, 34.0 per 100,000, is somewhat greater than that for the rest of the area, 22.2 per 100,000, this difference is only of questionable statistical significance. Thus, when comparing individual states as units in this manner, it is apparent that no definite concentration of the cases by induction residence exists in any one state.

Relation of the disease to the fall line

Reference to Figures 1 and 2 will reveal certain peculiarities in the distribution of the cases in the Southeast, both by birthplace and induction residence. Within the Carolinas, a greater number of residences appear in the eastern portion of the states. Concentrations also appear in Southern

**DISTRIBUTION OF SARCOIDOSIS IN 10 SOUTHEASTERN STATES
BY INDUCTION RESIDENCE
IN RELATION TO THE "MODIFIED" FALL LINE AREA**

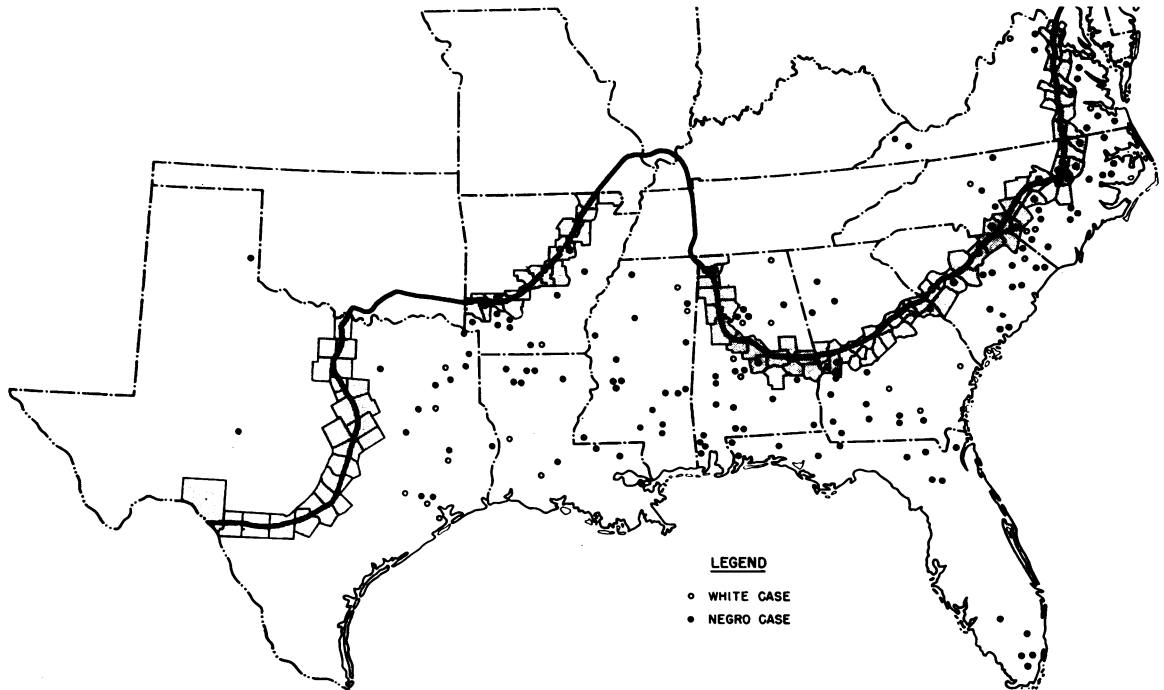


FIG. 3. THE DISTRIBUTION, BY INDUCTION RESIDENCE, OF 185 CASES OF SARCOIDOSIS IN THE 10 SOUTH ATLANTIC GULF COAST STATES OF REGION I IN RELATION TO THE FALL LINE AND "BORDER COUNTIES"

Each dot represents the induction residence of a single case. The heavy line represents the approximate location of the fall line and the shaded area indicates the "border" counties.

Georgia and in the area where Texas, Louisiana, and Arkansas are contiguous. This distribution corresponds very closely with the physiographic area known as the Atlantic and Gulf Coastal Plain. Until relatively recent geologic times, this area was covered by the sea and was delineated along its westernmost and northernmost extent by the former coast line, which is now known as the fall line (3). The approximate position of this former coast line is shown by the heavy line on Figure 3.

Comparisons were next made of the race specific attack rates by induction residence for the areas within the Southeastern states in relation to this geologic landmark. In arriving at these rates, counties were assigned to the "above" or "below fall line" category, depending upon their localization. Since the former coast line transects many contemporary county borders, and since the

determination of its exact location in any region may be difficult, the counties traversed by and adjacent to the fall line, which have been designated as border counties, were considered separately. The term "modified" fall line was introduced to represent the composite area of these border counties and is depicted in Figure 3 by the stippled area.

Table IV indicates *negro* attack rates by induction residence for the areas of the ten states of Region I in relation to the "modified" fall line. It can be seen that for each state a greater number of cases in negroes occurs in the "below fall line" area. Similarly, the attack rate is greater for this area in each of the states, with the exception of Texas. The overall rate for the "below fall line" area in four of the states, Alabama, Georgia, North Carolina, and South Carolina, is 49.0 per 100,000 or five times greater than the

overall "above fall line" rate of 10.0 per 100,000 for these states. In three other states, Arkansas, Texas, and Virginia, the differences in attack rates between the "above" and "below fall line" areas are not statistically significant. However, in two of these, Arkansas and Virginia, the trend of the rates is the same as that observed in the four states where the differences are significant. Thus, we have a distinct intrastate concentration of the cases in the coastal plain area which appears to be unaccountable for by population distribution within these states.

Relation to other geographic factors

A number of ecological factors were explored for a possible explanation of this unusual localization. Among these were meteorologic conditions (4), the distribution of plant and animal life (5, 6), agricultural practices (7), and overall population densities (8). It was found that none of these factors was overtly associated with the distribution of the cases.

Since the fall line delineates, among other things, the boundaries of geologic formations (9) and major soil groups in the Southeast, attention was directed to a consideration, in a qualitative fashion, of surface materials. A close association appeared to exist between the residences of the cases and some of the soils of the coastal plains. This correlation was strengthened by several additional observations. In the Mississippi Valley, relatively few cases were noted although this is an area with a large negro population. The Alluvial soils, which are found there, differ significantly in character from the other soils of the Southeast. Furthermore, in the area where Texas, Louisiana, and Arkansas are contiguous, there is a reappearance of some of the soils which are present along the eastern portion of the coastal plain. The concentration of cases in this general region appeared to strengthen the preliminary correlation of the cases with these soils. Therefore, a more detailed and quantitative study was made of this relationship.

TABLE IV

Sarcoidosis attack rates among World War II Negro servicemen, by induction residence, according to areas in relation to the "modified" fall line in the South Atlantic Gulf Coast states

State	Area in relation to "modified" fall line	Negro selective service population	Negro cases by induction residences	Attack rates per 100,000	X ² of differences between Negro rates
Alabama	Above	28,751	4	13.9	7.66
	Below	25,760	15	58.2	
Arkansas	Above	2,142	—	—	0.46*
	Below	23,543	8	34.0	
Florida	Below	51,188	15	29.3	—
Georgia	Above	30,721	3	9.8	5.81
	Below	26,636	11	41.3	
Louisiana	Below	72,323	10	13.8	—
Mississippi	Below	86,075	17	19.8	—
North Carolina	Above	33,498	3	9.0	10.38
	Below	21,745	12	55.2	
South Carolina	Above	17,237	—	—	5.67*
	Below	26,214	11	42.0	
Texas	Above	5,318	2	37.6	1.30
	Below	74,301	12	16.2	
Virginia	Above	22,101	4	18.1	0.21
	Below	24,767	6	24.2	
Total	Above	139,768	16	11.4	11.07
	Below	432,552	117	27.0	
	Border	91,759	23	25.1	

* Corrected for continuity.

SOIL REGIONS OF THE SOUTH

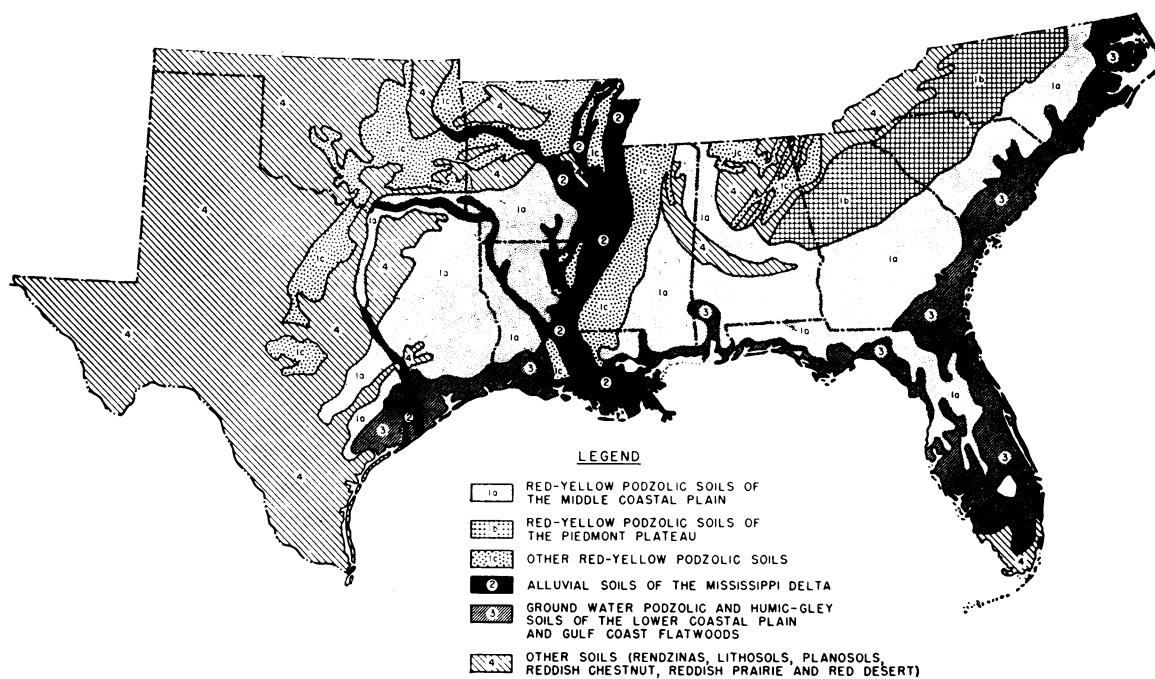


FIG. 4. THE GENERAL PATTERN OF THE GREAT SOIL GROUPS IN THE SOUTHEAST

Local details have been submerged in order to present a general view of the significant features on a small map.

Soils of the southeast

The general pattern of the soil areas in the Southeast is shown in Figure 4.⁵ These soils can be differentiated on the basis of well-defined morphological and other characteristics, such as chemical composition, geologic precursors, native vegetation, and topography (10, 11).

The Red-Yellow Podzolic soils form the dominant group in this region, extending from Virginia to Texas. These have light-colored sandy surfaces overlying firm, red to yellow subsoils. They are generally well drained, strongly leached, and low in organic and mineral plant nutrients.

On the basis of variations in one or more of their characteristics, these leached soils can be further classified among a number of subgroups.

⁵ Since identical soil classification data were not available for Virginia, the subsequent analysis has been restricted to nine of the states in Region I. Older soil classification schemes (10) indicated that the inclusion of Virginia did not significantly alter the correlations obtained between race specific attack rates for sarcoidosis and residence in certain soil areas.

In Figure 4 are outlined The Red-Yellow Podzolic soils of the Middle Atlantic Coastal Plain, subgroup "1a," those of the Piedmont Plateau, subgroup "1b," and a miscellaneous subgroup, "1c."

The Alluvial soils occupy the flood plains in the Southeast and form the dominant soils of the Mississippi Valley. They are soils in early stages of profile development, having been affected very little by processes of soil formation. In general, the Alluvial soils in this region are relatively high in organic matter, poorly drained, and neutral in reaction. These have been designated as group "2" in Figure 4.

The Humic-Grey and Ground-Water Podzols are poorly drained soils which occur extensively along the Atlantic and Gulf Coasts. These soils, group "3" in Figure 4, generally have light-grey sandy leached layers and usually contain little organic matter. Most of these have been derived from beds of unconsolidated sands and sandy clays of relatively recent geological origin.

The remaining soils in the Southeast are com-

TABLE V

*Sarcoidosis attack rates among World War II Negro servicemen, by induction residence, according to soil areas of the South Atlantic Gulf Coast states **

Soil group	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000	$\frac{(O-E)^2}{E}$ (for Negro cases)
Red-Yellow Podzolic soils of the Middle Coastal Plain (1a)	188,049	82	43.6	30.65
Red-Yellow Podzolic soils of the Piedmont Plateau (1b)	92,542	6	6.5	11.72
Other Red-Yellow Podzolic soils (1c)	63,995	11	17.2	1.21
Alluvial soils of the Mississippi Delta (2)	55,881	6	10.7	4.09
Ground-Water Podzolic and Humic-Clay soils of the Lower Coastal Plain (3)	116,376	23	19.8	0.83
Other soils† (4)	84,979	16	18.8	0.91
				$X^2 = 49.41$ $p < 0.001$
Totals	601,882	144	23.9	

* Includes Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Texas.

† Includes Rendzinas, Lithosols, Plenosols, Reddish Chestnut, Reddish Prairie and Red Desert soils.

posed of a heterogeneous group of shallow, stony soils (Lithosols), clay pan soils (Planosols), black soils (Rendzinas), and subhumid and semi-arid soils (Reddish-Prairie and Reddish-Chestnut), all of which have been combined into group "4" in Figure 4.

Negro attack rates by soils

Race specific attack rates for negroes by induction residence were determined for the various soil areas in the Southeast, as shown in Table V. Although the number of white cases in relation to each soil group was too small to make valid comparisons of the attack rates between the groups, the trends observed were similar to those among the negro patients.

The negro attack rates range from 6.5 per 100,000 for the soils of the Piedmont Plateau above the fall line to 43.6 per 100,000 for the soils of the Middle Coastal Plain below the fall line. The attack rate for the Alluvial soil area is somewhat low, 10.7, but the remaining rates appear to be quite uniform. Thus, rates of 17.2, 19.8, and 18.8 per 100,000 were noted for the group "1c," group "3," and group "4" soil areas, respectively.

It is apparent that the greatest differences in attack rates exist between the soils of the Middle Coastal Plain and those of the Piedmont Plateau, where a ratio of almost 7 to 1 in these rates is observed. This ratio should be contrasted to the much smaller 3 to 1 ratio which was found be-

tween the negro attack rates for Regions I and III.

No significant localization of the cases by induction residence appeared to exist within the Red-Yellow Podzolic soils of the Middle Coastal Plain itself. Thus, negro attack rates in relation to this particular soil group for each of the nine Southeastern states, as shown in Table VI, are essentially equivalent. The one exception, perhaps, is North Carolina, where the rate of 71.3 per 100,000 is somewhat higher than those for the other states. Even with this elevated rate, however, the total chi square of the differences, 10.48, is not statistically significant.

TABLE VI

Sarcoidosis attack rates among World War II Negro servicemen from the "1a" soil area, according to states

State	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000	$\frac{(O-E)^2}{E}$ (for Negro cases)
Alabama	27,175	13	47.8	0.12
Arkansas	10,464	7	66.9	1.25
Florida	10,001	6	60.0	0.58
Georgia	27,059	13	48.0	0.12
Louisiana	18,574	5	26.9	1.19
Mississippi	20,898	8	38.3	0.13
North Carolina	22,449	16	71.3	3.92
South Carolina	19,374	5	25.8	1.38
Texas	32,055	9	28.1	1.79
				$X^2 = 10.48$ $0.20 < p < 0.30$
Totals	188,049	82	43.6	

Race specific attack rates were determined for each of the seventeen minor soil series which compose the leached soils of the Middle Coastal Plain. Because of the generally small number of cases, it was difficult to compare the rates, which were found to be quite variable. However, no significant concentration of induction residences was observed in relation to any of these soil series, as can be observed from Figure 5. There, the approximate locations of the individual soil series are indicated by the alphabetical characters. Thus, the factor (or factors) which influence the concentration of cases by induction residence in the Middle Coastal Plain area appears to be distributed with some uniformity.

Factors of migration

Admittedly, these efforts to quantitate the association of the cases of sarcoidosis with certain

soil groups are crude. However, the previously mentioned influence of migration, particularly for the negroes, seems to minimize the observed differences. For example, of the 52 negroes inducted from Regions II and III, only 17 were born in this area; 35 had been born in the Southeast. Of these 35 migrants, 22, or 63 per cent were born in the area of the Middle Coastal Plain soils. Since it is reasonable to assume that the majority of these individuals had migrated to northern areas as recently as the pre-war period of national mobilization, exposure to the soils may have been of considerable duration.

The uncertainties introduced by migration can be minimized by considering only those cases whose birthplace and induction residence were located in the same or adjacent counties, the so-called "lifetime residents." It would seem reasonable to assume that these individuals had a pro-

DISTRIBUTION OF SARCOIDOSIS IN 9 SOUTHEASTERN STATES BY INDUCTION RESIDENCE IN RELATION TO CERTAIN OF THE RED-YELLOW PODZOLIC SOILS

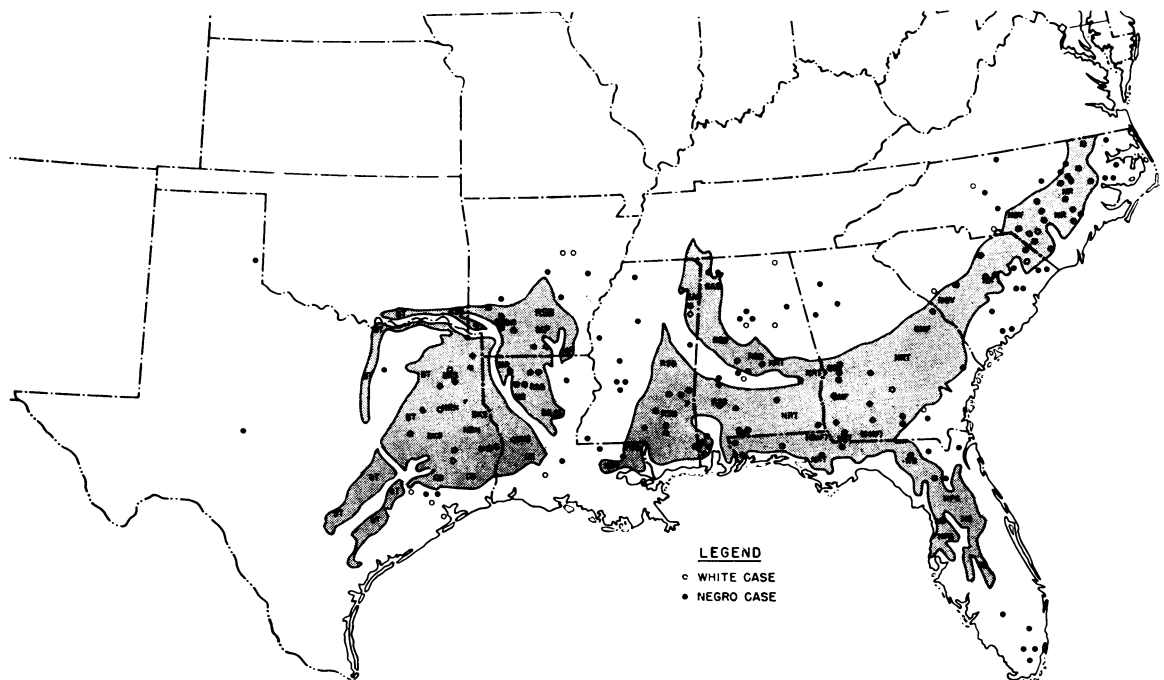


FIG. 5. THE INDUCTION RESIDENCES OF A GROUP OF 171 CASES OF SARCOIDOSIS IN NINE OF THE SOUTH ATLANTIC GULF COAST STATES

The residences are shown in relation to the 17 minor soil series, indicated by the alphabetical characters which compose the "1a" Red-Yellow Podzolic soils.

longed contact with the soils in and about their county of induction, whereas a similar assumption would be less likely to apply in the case of the migrants. Of the 113 negroes with sarcoidosis inducted from Region I who could be classified as "lifetime residents," 73 came from the Middle Coastal Plain soil area and 4 from the leached soil area of the Piedmont Plateau. The total negro selective service populations for these areas, inclusive of immigrants and permanent residents, were approximately 188,000 and 93,000, respectively. While these figures are not deemed sufficiently comparable to calculate valid attack rates, the crude rates which may be derived are 39 per 100,000 and 4 per 100,000 indicating differences of 10 to 1 or greater. As noted previously, the attack rates based on the total number of cases inducted from these areas were 43.6 per 100,000 and 6.5 per 100,000, respectively, representing a difference of slightly less than 7 to 1.

Unfortunately, chronological residence data are not available for all the cases from Region I. If such were at hand, it would be feasible to determine man-years of experience for all the soil areas. The significant correlations obtained by use of "lifetime residents" suggest that such a method of analysis would strengthen the relationship between sarcoidosis and the soils of the Middle Atlantic Coastal Plain.

Urban-rural occurrence of the disease

By grouping the counties of the ten Southeastern states according to population density, sarcoidosis attack rates can be calculated for white and negro servicemen from these composite county areas. In Table VII the rates for negro military personnel are shown. It can be seen that an inverse relationship exists between these rates and county population density. For the counties with 19 or fewer inhabitants per square mile, presumably those which are most rural in character, the rate of 48.7 per 100,000 is highest. On the other hand, a much lower rate, 15.2 per 100,000, is found among the servicemen from the counties with population densities of 100 or more people per square mile, areas which presumably are most urbanized. The attack rates among negro servicemen from counties with intermediate population densities lie in between these extremes.

TABLE VII

*Sarcoidosis attack rates among World War II Negro servicemen from 10 South Atlantic Gulf Coast states * according to population density of county of induction*

Population density of county of induction	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000	$\frac{(O-E)^2}{E}$
Less than 20	20,560	10	48.6	5.63
20-49	219,332	71	32.4	7.38
50-99	187,434	39	20.8	0.57
100 and over	236,753	36	15.2	6.91
Total	664,079	156	23.5	$X^2 = 20.49$ $p < 0.001$

* Includes Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Texas, and Virginia.

† Population per square mile (1940), from County Data Book, U. S. Bureau of the Census, 1947.

The overall differences between these rates are statistically highly significant ($X^2 = 20.49$, $p < .001$). The small number of white cases in relation to each county group made it difficult to evaluate the differences between the attack rates observed. However, the overall trend of these rates was the same as that found among negro servicemen.

Figure 6 illustrates the population density distribution for the counties of the ten-state region. In comparing this with Figure 3, which illustrates the distribution of the cases of sarcoidosis in relation to the modified fall line, it appears that the more densely populated counties are located in the area of the Piedmont Plateau (above the fall line) whereas the distribution of the less densely populated counties appears to conform to that of the Atlantic Coastal Plain (below the Fall line).

In view of the previously demonstrated correlation between race specific attack rates for sarcoidosis and residence in certain soil areas in the Southeast, it was deemed desirable to determine whether urban-rural localizing factors were acting independently of these soil associations. Therefore, attack rates were computed for servicemen from the various soil areas of the Southeast according to the population density distribution of the various counties.

These rates for negro servicemen from the Red-Yellow Podzolic soil area of the Middle Atlantic Coastal Plain in nine of the Southeastern states having identical soil classification data are

**POPULATION DENSITY DISTRIBUTION BY COUNTIES
IN SOUTHEASTERN STATES**

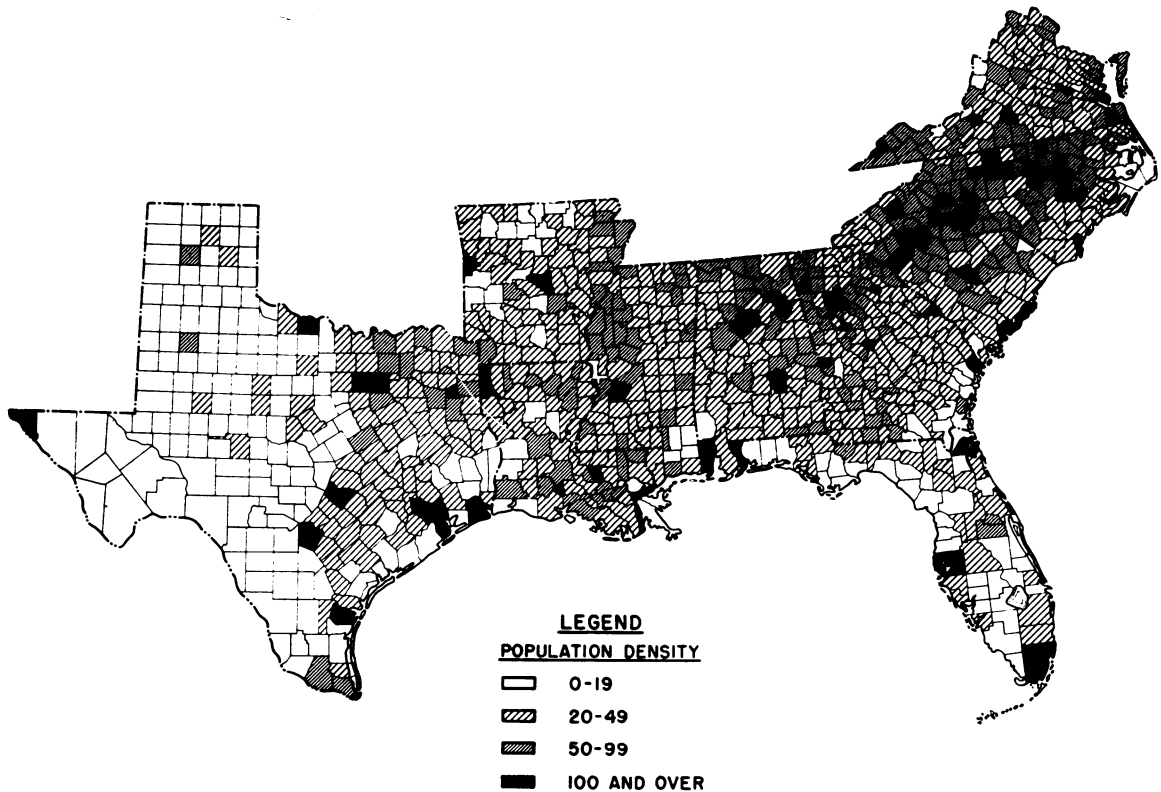


FIG. 6. THE POPULATION DENSITY DISTRIBUTION BY COUNTIES IN TEN SOUTHEASTERN STATES

Population density is expressed as number of inhabitants per square mile and refers to Bureau of the Census data from the 1940 census.

shown in Table VIII. This "1a" soil area, as designated previously, represents the site of maximal intraregional concentration of the cases, both

TABLE VIII

Sarcoidosis attack rates among World War II Negro servicemen from the Middle Coastal Plain soil area, by induction residence, according to population density of county of induction*

Population density† of county of induction	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000
Less than 20	7,639	7	91.6
20-49	93,612	37	39.5
50-99	56,000	25	44.6
100 and over	30,798	13	42.2
Total	188,049	82	43.6

* Middle Coastal Plain Soil area in 9 states, including Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Texas.

† Population per square mile (1940), from County Data Book, U. S. Bureau of the Census, 1947.

by birthplace and induction residence. The rate of 91.8 per 100,000 among the servicemen from the counties with lowest population densities, 19 or fewer inhabitants per square mile, is more than twice as great as the overall rate of 41.7 per 100,000 among servicemen from the more densely populated counties. Although the number of cases in the former category is small, the difference between these rates is statistically significant ($p < 0.04$). The remaining attack rates among servicemen from counties with population densities of 20-49, 50-99, and 100 or more inhabitants per square mile, show no consistent downward trend, in contrast to the findings for the whole of the ten-state region.

On the other hand, the attack rates among negro servicemen from the remaining soil areas of the nine-state region exclusive of the "1a" Middle Coastal Plain area are shown in Table IX.

TABLE IX

Sarcoidosis attack rates among World War II servicemen from nine South Atlantic Gulf Coast states, exclusive of the Middle Coastal Plain soil area, according to population density of county of induction*

Population density† of county of induction	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000
Less than 20	12,640	3	25.7
20-49	108,294	27	24.9
50-99	114,060	11	9.6
100 and over	178,779	21	11.7
Total	413,773	62	15.0

* Includes Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Texas.

† Population per square mile (1940) from County Data Book, U. S. Bureau of the Census (1947).

Rates of 23.7 and 24.9 per 100,000 were obtained for servicemen from counties with population densities of 19 or fewer, and 20 to 49 inhabitants per square mile, respectively. The overall rate for these composite county areas, 24.9 per 100,000, is statistically significantly higher ($p < 0.001$) than the overall rate of 10.9 per 100,000 observed among servicemen from counties with greater population densities, 50 to 99, and 100 or more inhabitants per square mile, respectively. Again, there is no consistent downward trend in the rates as shown in Table VII for the entire ten-state region, but the qualitative relationships remain unchanged, *i.e.*, higher attack rates prevail among servicemen from counties with low population densities, which presumably are most rural in character. These findings suggest the presence of a rural localizing factor in the occurrence of sarcoidosis which may be independent of any primary soil relationship.

By grouping the counties of the "1a" Middle Coastal Plain soil area according to population size, a similar correlation can be demonstrated, as shown in Table X. Here, a threefold difference is evident between the attack rate of 124.4 per 100,000 among negro servicemen from counties with the smallest total populations, less than 10,000 inhabitants, and the overall rate of 41.1 per 100,000 among servicemen from counties with the smallest total populations, less than 10,000 inhabitants, and the overall rate of 41.1 per 100,000 among servicemen from counties with more than 10,000 inhabitants. Although the former rate is

based on only seven cases, the difference between these rates is statistically significant ($p < 0.01$). Again, no consistent downward trend in the rates is apparent among the more populous counties; however, the rate among servicemen from counties with populations of 100,000 or more, is only 25.7 per 100,000, a somewhat lower value than the others.

A further suggestion of the rural localization of sarcoidosis is provided by other Bureau of the Census data. Table XI presents the attack rates among negro servicemen from the Middle Atlantic Coastal Plain soil area according to the proportion of inhabitants classified as "rural," *i.e.*, those residents in communities with less than 2500 people, among the negro population of each county. A direct correlation exists between these rates and the percentage of "rural" negro inhabitants. Thus, among negro servicemen from counties where 90 to 100 per cent of the negroes are in the "rural" category, the attack rate of 54.7 per 100,000 is highest. This declines to a rate of 29.0 per 100,000 for the servicemen from counties with less than 49 per cent "rural" negro inhabitants. Although the differences between these rates are only of borderline statistical significance, the trend is in conformity with previous findings.

Admittedly, these attempts to demonstrate a rural localization of sarcoidosis among World War II servicemen are also crude. The factor of migration, among others, again introduces some uncertainty in the interpretation of the findings and the unavailability of residence data pertaining to

TABLE X

Sarcoidosis attack rates among World War II Negro servicemen from the Middle Coastal Plain soil area, by induction residence, according to population size of county of induction*

Population size† of county of induction	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000
Less than 10,000	5,622	7	124.5
10,000-19,999	30,502	14	45.9
20,000-49,999	95,854	39	40.7
50,000-99,999	40,514	18	44.4
100,000 and over	15,557	4	25.7
Total	188,049	82	43.6

* Middle Coastal Plain soil area in nine states, including Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Texas.

† 1940 population, from County Data Book, U. S. Bureau of the Census, 1947.

TABLE XI

Sarcoidosis attack rates among World War II Negro servicemen from the Middle Coastal Plain soil area, by induction residence, according to per cent of rural inhabitants among Negro population of county of induction*

Per cent of rural inhabitants among Negro population of county of induction†	Negro selective service population	Negro cases by induction residence	Attack rates per 100,000
90-100	58,546	32	57.7
70-89	63,367	26	41.0
50-69	31,697	14	44.2
Less than 50	34,439	10	29.0
Total	188,049	82	43.6

* Middle Coastal Plain soil area in Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Texas.

† From 1940 Bureau Census Data.

the pre-induction period precludes any attempt to correct for this variable. The importance of the latter is evident from the findings on the follow-up studies of 40 cases in the ten-state Southeastern region. Sixteen, or 40 per cent of these patients, lived in a community with a population of 2500 or greater at the time of their induction into the armed forces, and by the criteria of the Bureau of the Census, could be termed "urban" inhabitants. However, chronological residence histories from these sixteen individuals revealed that eleven had spent more than half their lives on farms or had engaged in farming as an occupation prior to military service, and therefore must have had prolonged contact with rural environments. It would seem likely that similar residence information from more intensive follow-up studies of all the cases would serve to strengthen the relationship between the disease and previous rural residence.

DISCUSSION

An analysis of the residence data from this group of 297 military cases of sarcoidosis revealed a distinct concentration of their birthplaces and induction residence in the Southeast. Within this region, a significant correlation was observed between race specific attack rates and residence in areas defined by the distribution of certain specific soil groups. In addition, significantly higher attack rates were noted among military personnel from the Southeast whose residences at the time of entry into the armed forces were located in the relatively rural counties, as evidenced by low popu-

lation density and small population size of these areas.

Since sarcoidosis is not a reportable disease, there is a paucity of morbidity data from which any comparison might be made with the cases which occur in the general population. Israel and Sones (12) have recently described their experiences with cases of sarcoidosis seen in Philadelphia. Of the 74 negroes in their group, 64 were born in the South, a distribution greatly disproportionate to the estimated percentage of southern-born negroes in that city.

Some data from a group of civilian cases of sarcoidosis in North Carolina (13) and South Carolina (14) provided an opportunity to compare the geographic localization of these cases with that observed among the military group. Of a total of 14 individuals suspected of having tuberculosis but later diagnosed as sarcoidosis, during 1949 and 1950 in South Carolina, 12 resided in the "below fall line" area. Nine of these resided within counties containing the leached soils of the Middle Coastal Plain as the predominant soil types. In North Carolina, 17 deaths were reported from Boeck's sarcoid from 1949 to 1951. Of the total, four resided in counties above the fall line, six lived in "border" counties and seven resided in the "below fall line" area. Of the 13 deaths in "border" and "below fall line" counties, nine had lived where the leached Middle Coastal Plain soils abounded. Thus, these data, while inappropriate for the computation of sarcoidosis attack rates for different areas, would appear to be consistent with the observations on the military cases inducted from these states.

On the other hand, in analyzing the birthplaces of 177 patients with sarcoidosis diagnosed at the Mayo Clinic from 1940 through 1951, Carr and Gage (15) did not find that the disease was more common in patients who came from the Southeastern part of the United States than in those who came from other areas. Apparently, such factors as age, sex, race, and severity of disease could not explain the difference in distribution from that which had been reported for the group of military cases (2). It should be pointed out, however, that the comparison between the geographic distribution of cases and the total population at the Mayo Clinic does not provide any precise information as to the relative incidence of the disease

among an unselected population in a given area. The series of Carr and Gage therefore is not strictly comparable to the military group.

The evidence that Boeck's sarcoid occurs with greater frequency among inhabitants of rural areas is in accord with the suggestion that soils may be determinants in the occurrence of the disease. Longcope and Freiman (16) in confirming an earlier observation of Lomholt (17), noted that sarcoidosis often affected farm laborers and those who live in country districts. Whitehead (18) and Cone (19) refer to similar observations. In relating calcareous crystalline material in soils to the pathogenesis of lesions characteristic of sarcoidosis, Refvem (20) noted ". . . that people living in the country are preferably attacked by Boeck's disease, especially farmers, gardeners, etc." Israel and Sones (12) reported that of ten cases of sarcoidosis in white persons seen in Philadelphia only one had been a life-long resident of that city. They noted that "Sarcoidosis would appear to be extremely rare among what is the largest group in this country, the native-born urban white."

The higher attack rates of sarcoidosis among the rural inhabitants of the Southeastern United States, its apparent predilection for negroes and for those living in certain soil areas presents a challenging and perplexing problem. If sarcoidosis is a manifestation of a single etiologic agent, the widespread occurrence of cases in this country would indicate that such an agent is not confined to the Southeast. However, the distinct aggregation of military cases in this area and the suggestion of a similar distribution among civilian cases leads to speculations which may point to further investigation.

It is conceivable that the observed geographic localization of the disease is the result of a) the presence of a highly favorable environment in areas within the Southeast for the growth, propagation, or transmission of an etiologic agent or agents, or b) an alteration in the susceptibility of the population of these areas which predisposes them to the action of some agent which elsewhere might possess a very low grade or altered pathogenicity.

The role of possible host factors in the localization of sarcoidosis is suggested by experiences with pellagra in this country. The concentration of the latter disease in the Southeast could be re-

lated largely to the socio-economic status and consequent dietary habits of the affected population, with contributory or secondary factors, such as infectious diseases, influencing its incidence at a particular time or place (21). Similarly, dietary peculiarities and the socio-economic status of the population in certain areas of the Southeast may enhance their resistance to the inciting factor of sarcoidosis; however, little information is available on this point.

The data pertaining to the unusually high incidence of sarcoidosis among negroes in this country also suggest an influence of host susceptibility. Of the total of 523 cases reported in the American literature up to 1952, 385, or 73.4 per cent, were of this race (16). The 26 to 1 ratio between the overall negro and white attack rates in the present series of cases emphasizes this racial predilection. In contrast are the reports from Europe and elsewhere which indicate a high frequency of sarcoidosis in the white race (22). Schönholzer found 67 cases of sarcoidosis among 516,879 Swiss army recruits subjected to mass radiographic examinations, an incidence of 13 per 100,000 (23). This rate compares much better with the overall attack rate in negroes of 18 per 100,000, than the white rate of 0.7 per 100,000 among American servicemen. Although these two series are not strictly comparable, the results suggest that factors other than inherent racial susceptibility may be influencing the higher prevalence of sarcoidosis among negroes in this country. Thus, sociologic and environmental factors, such as those suggested to account for the significantly higher incidence of venereal diseases among this group (24), may similarly contribute to a susceptibility for Boeck's sarcoid.

The possible concentration of an etiologic agent in some of the soils of the Southeast is brought to mind by the somewhat similar distribution of hookworm disease in the sandy areas of this region (25), and the greater prevalence of this parasitic infection among rural inhabitants (26). Furthermore, recent epidemiologic studies of various mycotic diseases, particularly histoplasmosis and coccidioidomycosis, indicate that their distribution is restricted to regions containing soils favorable for the growth and dissemination of the causative fungi (27-29). By analogy, it can be postulated that some helminth, bacterium, fungus, or virus

giving rise to sarcoidosis may find certain of the Red-Yellow Podzolic soils of the Southeast the best natural media in which to thrive and thus result in the described localization of the disease.

Other factors, such as the role of intermediate vectors, may account for the circumscribed distribution of Boeck's sarcoid. The Southeastern localization of typhus and malaria can be correlated with the distribution of the tropical rat flea (*Xenopsylla cheopis*) and certain species of mosquitoes (*Anopheles quadrimaculatus*) (30, 31). In these instances the concentration and migration of the rat, as well as climatic conditions (32, 33), and the presence of impounded water and other suitable breeding places (34), rather than any specific soil characteristics, appear to be the factors which confine these respective arthropods to this region. However, certain insects are restricted to specific soil areas, thereby localizing disease agents for which they are the natural vector. Acute conjunctivitis in the South and the distribution of the sand gnat, (*Hippelates pusio*), may be such a case in point (35, 36). Again by analogy, it is possible that some intermediate arthropod vector, in close association with certain soils, serves as an effective transmitter of the etiologic agent of sarcoidosis. However, the lack of any evidence to incriminate an intermediate vector in the transmission of the disease and the lack of any knowledge concerning an arthropod distribution which conforms to that observed for the military cases casts some doubt upon such an hypothesis.

The *plant and animal life* of the soil areas in which cases of sarcoidosis are concentrated bear scrutiny for a possible etiologic relationship to the disease. In addition, the *chemical differences* between the various soils of the Southeast might have some relation to the localization of Boeck's sarcoid.

In regard to the latter, the Red-Yellow Podzolic soils of the Piedmont Plateau (where relatively few cases of sarcoidosis resided) contain a strikingly lower percentage of silica and higher percentages of alumina and potash than do the soils of the middle Atlantic Coastal Plain (10). These differences and the resemblance of the pulmonary forms of sarcoidosis to some of the pneumoconioses suggest the possibility that soils may be directly implicated in the pathogenesis of

Boeck's sarcoid. In support of this are the observations of Refvem, who demonstrated crystalline material, which he assumed to be derived from calcareous spars in the soil, in biopsy specimens of 4 of 100 patients with sarcoidosis (20). Ayres, Ober, and Hamilton are of the opinion that many of the strictly localized sarcoid lesions of the skin, following trauma, are actually a form of silicosis (37), and similar contentions have been made by other workers (38, 39). Experimentally, Gardner was able to reproduce in rabbits, guinea pigs, and rats, granulomatous lesions resembling those of sarcoidosis, following the administration of particles of silicon dioxide (40).

Suggestions have been made of a relationship between sarcoidosis and the chronic form of beryllium poisoning (41). Although there are many similarities in clinical features between the two, certain differences have been found (42). Furthermore, as Freiman has noted (43), the relatively recent industrial use of beryllium compounds makes these agents unlikely causes for any great numbers of cases of sarcoidosis. However, the inability of Dutra, Cholak, and Hubbard (44) to recover abnormal quantities of beryllium from some lesions of chronic berylliosis, illustrates the difficulty of evaluating possible relationships.

The possibility does exist that exposure to unusual amounts of *naturally-occurring* beryllium in the soils of the Southeast might have accounted for the aggregation of cases in the middle Atlantic Coastal Plain. Soils in this area were derived from the granitic rocks of the Appalachian Mountains which represent the major concentration of beryllium containing surface ore in the United States. Similarly, such beryllium containing rocks have their greatest concentration in Europe in the Scandinavian countries where sarcoidosis is quite prevalent. Analysis of soil samples obtained in close proximity to the lifetime residence of several of the military cases revealed, by the specific gravity flotation method, the presence of occasional small fragments of beryllium containing rock (44). Chemical and spectrographic analyses carried out by Hodge, Toribara, Steadman, Cholak, and Hubbard, confirmed the presence of beryllium in these samples, although not in any unusual concentrations (45, 46). However, the need for caution in relating sarcoidosis to berylliosis and other forms of pneumoconioses which

might result from any association with soils must be stressed, in view of the diversity of agents that can induce tissue reactions closely simulating the sarcoid granuloma.

Many hypotheses relating to factors of host susceptibility or to characteristics necessary for the propagation and transmission of an etiologic agent may be invoked to account for the observed concentration of cases in certain areas of the Southeast. Undoubtedly, other possibilities exist which have not been mentioned. Any working hypothesis should be in accord with the available epidemiologic knowledge of sarcoidosis in this country; namely, its apparent predilection for negroes, its concentration in certain soil areas, and its apparent greater relative frequency among rural inhabitants. The newly defined hyper-endemic sarcoidosis area in the Southeast would appear to warrant more intensive study in an effort to elucidate the many obscurities still surrounding the etiology and pathogenesis of this disease.

SUMMARY

An epidemiologic study of 350 cases of sarcoidosis in military personnel during World War II has indicated the occurrence of this disease with a significantly greater frequency among those whose birthplace is in the Southeastern United States. Residence in a rural area further favors development of the disease.

The ratio of negro to white cases of 18 to 1 accounts in part only for this geographic distribution. The occurrence of sarcoidosis is greater in patients living within certain regions of this endemic area. A close association between the distribution of certain soil types with these regions was noted. Thus, residence in rural areas of the Southeast, particularly of negroes, within regions of a fine sandy soil type appears to favor the development of sarcoidosis. The possible implications of these findings are discussed.

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