Untreated Inactive Pulmonary Tuberculosis

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Risk of Reactivation

GEORGE W. COMSTOCK, M.D., Dr.P.H.

THE RELAPSING TENDENCY of pulmonary tuberculosis is widely known and well documented. In 1938, Puffer, Stewart, and Gass (*1*) reported from the Williamson County (Tenn.) Tuberculosis Study that 12 percent of white persons classified as having minimal arrested tuberculosis and 15 percent of those having latent apical tuberculosis had become worse during a 3-year period of observation. Reisner and Downes (*2*) investigated the relapse rate among a sample of persons with productive, fibrotic, or calcific minimal tuberculosis who attended the ambulatory chest clinics of the New York City Department of Health. They found 5 percent of whites and 14 percent of nonwhites had developed active disease in 5 years. Among a group of upstate New York patients, diagnosed by the staff of Hermann M. Biggs Memorial Hospital between 1937 and 1947 as having minimal arrested tuberculosis, the risk of developing active tuberculosis during the 10 years following diagnosis was 13 percent (*3*).

Similar studies have been made in other countries. Kallquist (*4*), reporting from Sweden on the experience of 312 persons considered to have inactive or probably inactive tuberculosis, noted that 8 percent had shown evidence of active disease within a period of 8 years. A comprehensive report on the Danish Tuberculosis Index by Groth-Petersen, Knudsen, and Wilbek (*5*) included observations on 560 persons never previously reported as tuberculosis cases because their chest roentgenograms were considered to show fibrosis only. Within 4 years, nearly 2 percent had developed active disease. In south India, Frimodt-Møller (*6*) found an average annual reactivation rate of 6 percent for persons classified as probably having inactive tuberculosis and 1 percent for those initially considered to have clinically insignificant, inactive disease.

Although the foregoing studies have indicated considerable variation in the average annual reactivation rate, a variation that could be related both to differences in the definitions of a case and in the living conditions of the study populations, all agreed that the risk of reactivation was substantial. And yet there is surprising variation in the period of observation recommended for persons with inactive pulmonary tuberculosis. Some health departments do not advise any followup of persons with newly diagnosed minimal inactive disease; others advise periodic examinations for 5 years or longer. Such variation in public health practice suggested the need for further information on the importance of relapses among persons with inactive disease as a source of active tuberculosis.

Information gathered by the Muscogee County Tuberculosis Study was used to estimate the prognosis of untreated inactive pulmonary tuberculosis. The discovery and prolonged observation of all cases of tuberculosis in the community has been one of the major

Dr. Comstock is with the Tuberculosis Branch of the Communicable Disease Center, Public Health Service, Washington, D.C.

goals of this study since its inception in 1946 (*7*). Consequently, casefinding activities in this area have been more extensive than is often possible. Communitywide photofluorographic surveys were conducted in 1946 and again in 1950 (*8,9*). In addition, the number of chest X-ray examinations made by the health department each year approximated one-sixth of the total population. The medical profession and allied agencies in the community have been highly cooperative in reporting tuberculosis cases, usually relinquishing responsibility for followup supervision to the study. As a result, it is believed that nearly all known cases have been reported to and supervised by the study.

All persons with definite or suspected tuberculosis were advised to obtain quarterly or semiannual examinations until their disease had shown no evidence of activity for at least 5 years. Although routine followup was then discontinued, subjects were advised to be examined annually and were sent reminders of these examinations as long as they continued to live in the area. Facilities for sputum examinations have also been readily available, with cultures for mycobacteria a routine part of the examination since 1947. Sputum specimens were requested at the beginning and end of the routine followup period, and also whenever clinical or roentgenographic evidence of possibly active disease was noted. Almost all patients with a history of productive cough complied with the requests for specimens. Many, however, denied this symptom and failed to submit specimens. Gastric lavages were rarely performed.

Initial Study Population

The population from which the cases of untreated inactive pulmonary tuberculosis were drawn comprises all persons who were first reported to the Muscogee County Tuberculosis Study as having definite or suspected tuberculosis between January 1, 1946, and January 1, 1956, and who also met the following criteria: (*a*) at the time these persons were reported, they lived in Muscogee County, and were 15–65 years of age; (*b*) before being reported, they had never been advised to be hospitalized for tuberculosis; (*c*) 2 years after the first report, they were still registered as having suspected or definite pulmonary tuberculosis and were not known to have extra-pulmonary tuberculosis.

Table 1. Year in which members of initial study population were reported to the Muscogee County Tuberculosis Study as tuberculosis cases or suspects

Year	Number	Percent
Total	1, 327	100. 0
1946	477	35. 9
1947	95	7. 2
1948	62	4. 7
1949	82	6. 2
1950	225	17. 0
1951	87	6. 5
1952	87	6. 5
1953	73	5. 5
1954	79	6. 0
1955	60	4. 5

A total of 1,327 persons met these criteria. The year in which they were first reported to the study is shown in table 1. More than one-third were detected in 1946, the year of the first community survey. One-sixth came to attention in 1950, largely as the result of the second survey. Although the proportion discovered in each of the other years has been quite constant, this actually reflects a decline in the morbidity rate owing to the increase in population of Muscogee County, Ga., from 95,638 persons in 1946 to 158,623 in 1960.

The composition of the initial study population and the type of examination which led to the recognition of tuberculosis are shown in table 2. Almost 70 percent of the cases were in whites and 30 percent in Negroes. However, since considerably fewer Negroes than whites reside in the county, the morbidity rate was slightly higher among Negroes. Slightly more than half of the whites but only one-third of the Negroes were over the age of 45 years. A much higher proportion of Negroes than whites were classified as having advanced disease, 44 percent contrasted with 23 percent. For both races, the proportion of advanced tuberculosis was larger among the younger age groups.

Almost half of the group was brought under supervision as the result of the two mass surveys. If persons detected by survey-like procedures such as preemployment and foodhandler

examinations are also included, more than three-fifths were found among presumably healthy groups. Only a few were identified because they had been in contact with a case of active tuberculosis. A third of the total group was classified as symptomatic, having been referred for examination by private physicians or hospital clinics or self-referred. Many contacts were in the category of symptomatic referrals. These persons had no evidence of tuberculosis on routine contact examinations, but returned for reexamination when symptoms developed rather than waiting for their next routine followup examination. As might be anticipated, a high percentage of advanced cases came from the group of symptomatic referrals. Although older persons did not participate well in the community surveys, a surprisingly large proportion of those with minimal or suspected diseases among them were discovered this way.

Active and Inactive Tuberculosis

Arriving at an appropriate definition of active tuberculosis was not as simple as might appear at first glance. Primarily, a definition was desired which would designate persons who were truly ill and whose tuberculosis was sufficiently severe to require a major change in their lives. It did not seem important to study the incidence of disease manifested only by isolated demonstrations of acid-fast bacilli or by minor roentgenographic changes.

No single criterion seemed adequate to designate significantly active tuberculosis. Even the finding of acid-fast bacilli with the cultural characteristics of *Mycobacterium tuberculosis* was far from satisfactory. In this part of the world, acid-fast bacilli have been isolated with considerable frequency from certain healthy population groups (*10*). Some of these organisms could have been mistaken for *M. tuberculosis*, particularly in the earlier days of the study. But the major reason for not accepting this single criterion was the fact that tubercle bacilli were isolated from a sizable segment of this study group on only a single occasion, with no other evidence of active disease on prolonged bacteriological and roentgenographic observation. Although one widely used standard would automatically classify these persons as having active tuberculosis (*11*), their disease did not then and has not yet shown any evidence of becoming a real health problem.

The use of roentgenographic change also seemed inadequate as the only criterion for active disease, particularly in view of the demonstrated difficulties in getting agreement even among experts in classifying tuberculosis from chest roentgenograms (*12,13*). And again there

Table 2. Percentage of tuberculosis cases in initial study population discovered by specified types of examination, by race, stage of disease, and age group

Race and initial stage of disease	Age group (years)	Number of cases	Percent	Discovered by—			
				Mass surveys	Other survey-like examinations	Contact examination	Symptomatic referrals
White							
Minimal and suspected	15–44	281	100.0	39.1	23.5	5.3	32.0
Minimal and suspected	45–64	418	100.0	60.5	10.3	1.7	27.5
Advanced	15–44	117	100.0	22.2	14.5	10.3	53.0
Advanced	45–64	97	100.0	37.1	12.4	3.1	47.4
Negro							
Minimal and suspected	15–44	139	100.0	56.8	26.6	5.0	11.5
Minimal and suspected	45–64	94	100.0	70.2	16.0	3.2	10.6
Advanced	15–44	144	100.0	21.6	20.8	7.6	50.0
Advanced	45–64	37	100.0	35.2	21.6	5.4	37.8
Total		1,327	100.0	46.3	17.2	4.5	32.0

were a number of persons with roentgenographic evidence of active tuberculosis but with no other evidence of active disease even on prolonged followup.

After careful consideration, it appeared that the most appropriate weighting of the various diagnostic factors could be achieved by defining the onset of significantly active disease as the time when hospital treatment was first recommended. This definition had several advantages. First the recommendation for hospitalization was an event which could be clearly recognized and dated from the records. Most important, the decision to recommend hospitalization indicated the recognition of a significant adverse change in a patient's condition. While bacteriological and roentgenographic findings obviously influenced this decision much more than any other factor, the use of clinical judgment manifested in the recommendation for hospital treatment appeared to be the most satisfactory method of discounting isolated or inconsistent findings which might otherwise inflate the proportion of insignificantly active cases. Recommendations for hospitalization were not materially affected by the availability of hospital beds or by enthusiasm for ambulatory treatment. Throughout the period of this study, hospital beds were available with little or no delay for Muscogee County patients. Furthermore, hospital treatment was almost always recommended for persons believed to have active progressive tuberculosis, only a few exceptions having occurred in recent years.

Inactive tuberculosis was defined as the absence of significantly active tuberculosis for at least 2 years after the individual was reported to the study as a tuberculosis case or suspect. The classification of the 1,327 persons in the initial study population 2 years after they had first been reported as a tuberculosis case or suspect is shown in table 3. In this period, 314 persons were thought to have active tuberculosis, the majority within a few weeks of initial report. Five persons without evidence of active disease are known to have died during this 2-year period; the remaining 1,008 comprise the inactive cases for this analysis. The majority had only suspected or minimal disease initially. Relatively few of the persons with inactive disease had advanced tuberculosis because there were not many advanced cases in the initial study group. Moreover, 70 percent were classified as having active disease before 2 years had elapsed.

Method of Analysis

The analysis includes observations on all persons in the study population through June 30,

Table 3. Classification of study population 2 years after initial report as tuberculosis case or suspect, by race, initial stage of disease, and age group

Race and initial stage of disease	Age group (years)	Initial study population	Classification 2 years after initial report		
			Active disease	No active disease	
				Dead	Alive
White					
Minimal and suspected	15–44	281	20	0	261
Mimimal and suspected	45–64	418	3	3	412
Advanced	15–44	117	89	0	28
Advanced	45–64	97	40	1	56
Negro					
Minimal and suspected	15–44	139	10	1	128
Mimimal and suspected	45–64	94	4	0	90
Advanced	15–44	144	125	0	19
Advanced	45–64	37	23	0	14
Total		1, 327	314	5	1, 008

Table 4. Subsequent development of active disease among 1,008 persons classified as having inactive tuberculosis, according to bacteriological and roentgenographic findings

Bacteriological findings	Roentgenographic findings	Number of persons	Percent	Active disease		No active disease	
				Number	Percent	Number	Percent
Total		1, 008	100. 0	68	6. 7	940	93. 3
Positive	Active	62	100. 0	60	96. 8	2	3. 2
Positive	Never active	24	100. 0	2	8. 3	22	91. 7
Never positive	Active	22	100. 0	5	22. 7	17	77. 3
Never positive	Never active	900	100. 0	1	. 1	899	99. 9

1960, with the total period of observation ranging from 4½ to 14½ years. Because 2 years had to elapse before a person could be classified as having inactive disease, the potential range of observation for cases of inactive tuberculosis was 2½ to 12½ years. Two modifications were made in applying the life table method of analysis to the findings of this study. The first modification was the use of two different assumptions regarding the development of active tuberculosis among persons withdrawn from observation because they moved away or discontinued examination. Assumption 1 is that the development of active disease could only be determined during the period in which the subjects were under observation. The period of observation would thereby be counted from the date of report to the date of last examination before July 1, 1960. This assumption understates the person-years of observation and thus overestimates the risk of developing active disease. Assumption 2 is that significant reactivation would become known for surviving members of the study population even if they did not continue to be examined by the study, and that their experience can thus be counted through June 30, 1960. This assumption is based on the probability that persons developing significantly active tuberculosis after discontinuing observation would seek medical care, and that their physicians would then request their previous chest roentgenograms. In this way, the study would learn that reactivation had occurred. Assumption 2 overstates the person-years of observation, mainly because most deaths which occurred among persons who moved away did not become known to the study. It probably also understates the number of reactivations. On both counts, assumption 2 tends to underestimate the risk of reactivation.

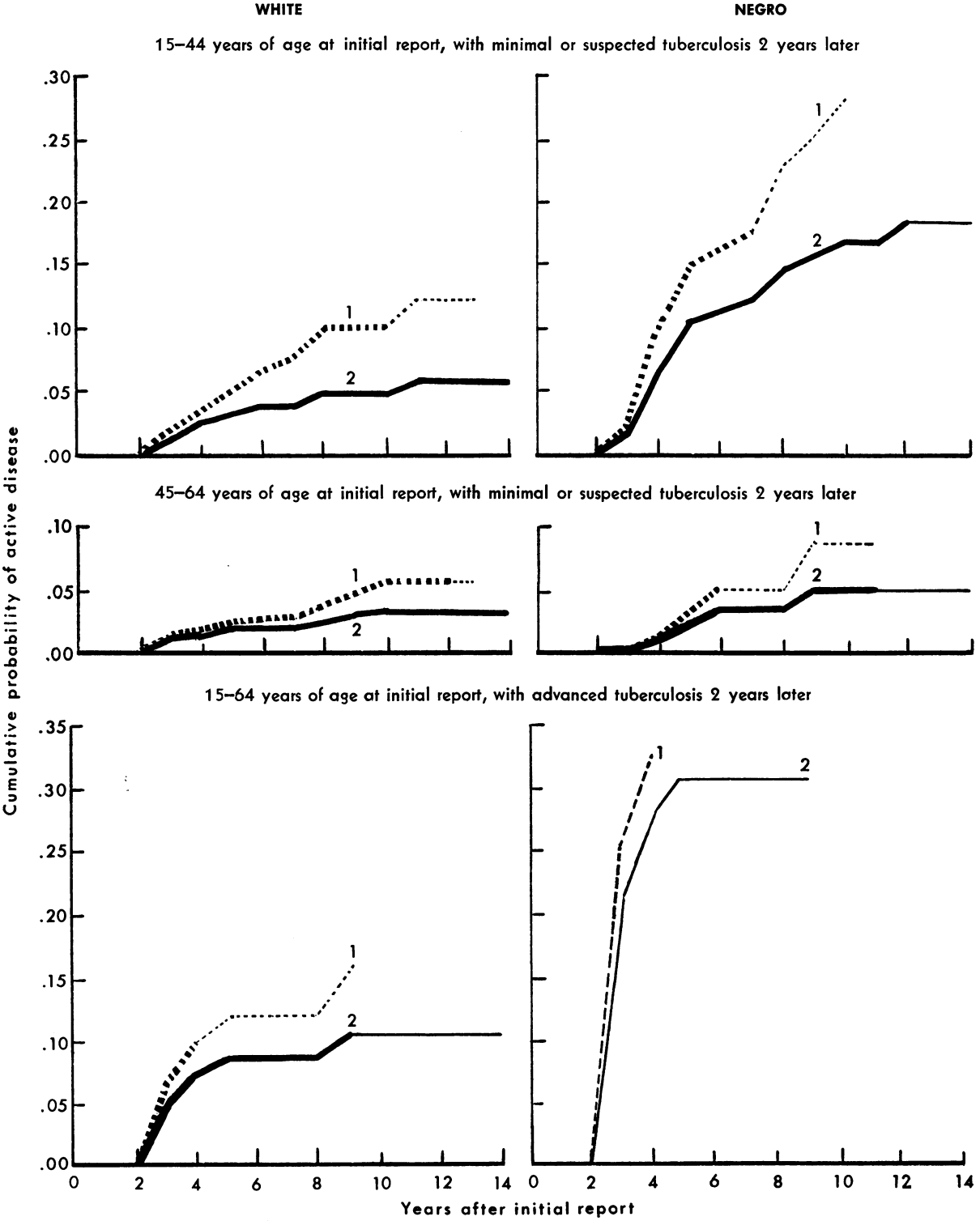
The second modification of the usual life table technique was to apply it in two steps. First, the standard approach was used in the analysis of the findings for the first 2 years of observation. For those who passed through this 2-year period without having active tuberculosis and who were thereby designated as having inactive tuberculosis, the calculation of time-specific and cumulative risks was again undertaken, with the beginning of the third year as the starting period.

Suspected and minimal tuberculosis were combined into a single category because the risk was essentially the same for both of them. Moderately and far advanced tuberculosis were combined because of the small numbers in each group. For persons with advanced tuberculosis, so few survived the first 2 years without having active disease, that the two age groups had to be combined; even so, the numbers of advanced inactive cases are small.

Results

The bacteriological and roentgenographic findings for the 1,008 persons classified as having inactive tuberculosis are shown in table 4. Of the 68 for whom hospital treatment for tuberculosis was recommended, 60 had both positive bacteriological and roentgenographic evidence of active tuberculosis at some time; only 1 had neither of these two criteria. Of the 940 persons for whom hospital treatment was never recommended, 2 had both bacteriological or roentgenographic evidence of active disease.

Cumulative probability of reactivation of inactive pulmonary tuberculosis, by race, age, and initial stage of disease, according to two different assumptions (1 and 2) regarding followup observations



NOTE: Heavy line indicates that the population base is 50 or more persons; thin line indicates that the base is 20–50 persons.

The use of positive bacteriological and roentgenographic findings together as a criterion of active tuberculosis would have altered but little the proportion of persons classified as having reactivated disease. Parenthetically, it may be noted that a major factor in the discrepancy between positive bacteriological findings and the roentgenographic classification of active tuberculosis was the conscious attempt to record the interpretations of chest roentgenograms without regard to other findings. Had these interpretations been completely independent, it is likely that disagreement between the two criteria would have been even greater.

For inactive cases, the risk of developing active disease is shown in the chart for each of the two assumptions regarding followup.

A summary of the risk for inactive cases from the third through the seventh years of observation appears in table 5. Of 1,008 persons who had not developed active tuberculosis in the first 2 years of observation, 68 were considered to have developed active disease, 53 of them during the next 5 years. The risk was greater for Negroes than for whites, greater for those with advanced disease, and among persons with only minimal or suspected tuberculosis initially, greater for younger than older persons.

The most reasonable estimate of the probability of developing active tuberculosis lies between the two extremes shown in table 5 and the chart. For Negroes with advanced inactive tuberculosis, the risk of developing active tuberculosis within a 5-year period was somewhat greater than 30 percent, and for whites approximately 10 percent. For persons with minimal or suspected disease who were under the age of 45 years, the risk of reactivation was approximately 15 percent for Negroes and 5 percent for whites. For older persons with minimal or suspected disease, the rate approximated 4 percent for Negroes and 2 percent for whites.

The risk of reactivation for inactive cases was greatest shortly after the subjects were placed in that category, and tended to diminish thereafter. Among persons with little evidence of disease initially, it appeared that the risk of reactivation approached zero for whites and older Negroes after about 8 years of observation. For younger Negroes with minimual or suspected tuberculosis initially, the risk of reactivation remained high throughout this study.

Because the reactivation rate was so much greater for Negroes than whites, it seemed worthwhile to study the association between the risk of reactivation and the degree of skin pigmentation among Negroes. Starting in 1951 skin pigmentation of Negro patients was assessed according to a 3-point scale—dark, medium, and light. The number of subjects in each category is shown in table 6, with medium

Table 5. Probability of reactivation of inactive tuberculosis among 1,008 persons during the third through seventh years after initial report as tuberculosis case or suspect

Race and initial stage of disease	Age group (years)	Number classified inactive	Number with active disease in third through seventh years	Probability of active disease in third through seventh years (percent)	
				Assumption 1	Assumption 2
White					
Minimal and suspected	15–44	261	11	7.7	4.3
Minimal and suspected	45–64	412	7	2.4	1.8
Advanced	15–64	84	7	11.8	8.5
Negro					
Minimal and suspected	15–44	128	15	17.6	12.0
Minimal and suspected	45–64	90	3	4.8	3.5
Advanced	15–64	33	10	36.6	30.6
Total		1,008	53		

and light combined since there were only 32 subjects classified as having light skin pigmentation.

The subjects with no classification of skin color are largely those who were diagnosed early in the study period and whose period of routine followup was completed prior to the time skin color was being recorded. Skin pigmentation was recorded for no one whose last examination occurred before 1951, contrasted with 88 percent of those last examined after 1955. This difference accounts in large measure for the higher rate of active disease observed among the group whose skin color was recorded. Persons with active disease were more likely to have been observed by the study over a prolonged period, and therefore to have been under observation at a time when it was the practice to record skin pigmentation.

There was no association between the degree of skin pigmentation and the likelihood of having active disease in the 2 years after the subject was first reported as having definite or suspected tuberculosis, nor with the risk of reactivation during the next 12 years. Adjustments for minor differences between the three groups with respect to age and extent of disease caused a slight decrease in the differences between the rates.

Discussion

All prognostic studies of tuberculosis suffer from the lack of a satisfactory method of distinguishing active from inactive disease. Under the most widely accepted standard (*11*), the yield of "active" cases would increase in direct proportion to the diligence with which currently available diagnostic techniques are applied. At the same time, the true significance of "active" cases found in this way would diminish with increasing diligence of diagnosis. The definition of active disease used in this paper, while open to criticism on a number of counts, does have the advantage of designating a group of patients who would be considered truly ill from tuberculosis by nearly everyone. For this reason, the results reported here are more generally applicable to the experience of others than if the definition of active tuberculosis included borderline cases about which there would be much less agreement.

Some will still be concerned about leaving in the base population patients whose disease was technically active, notably those with positive bacteriology for whom hospitalization was not advised. To the extent that this procedure may have been in error, the cases of active disease are too few and the population remaining at risk is too large. On both counts, broadening the definition of active tuberculosis would obviously increase the reactivation rates. Indeed, if such borderline cases had been included, the rates of reactivation after 2 years of observation would have been increased by 60 percent. Unfortunately, it is impossible to estimate how much more the rates might have been increased by still more diligent investigation, and so a reliable upper limit cannot be set. On the other hand, the rates in this study may safely be con-

Table 6. Active tuberculosis among Negro cases and suspects, by degree of skin pigmentation and period after initial report

Degree of skin pigmentation	Period after initial report					
	First 2 years			3d through 14th years		
	Initial population	Active cases		Inactive cases	Active cases	
		Number	Percent		Number	Percent
Total	414	162	39. 1	251	35	13. 9
Dark	132	57	43. 2	75	12	16. 0
Medium and light	134	65	48. 5	69	10	14. 5
Not stated	148	40	27. 0	107	13	12. 1

sidered a lower limit for the true rates, and to approximate very closely the true rates for clinically significant active tuberculosis.

In any event, followup of persons with inactive disease should receive high priority as a procedure for finding active tuberculosis. Few, if any, other groups in this country will experience a comparable incidence of active disease. Furthermore, most inactive cases of tuberculosis come to light through ordinary methods of casefinding already available in most communities. Identifying individuals with inactive tuberculosis thus presents no unusual problems.

The findings of this and other studies indicate the value of prolonged observation of inactive cases. Although the risk of reactivation may decrease with the passage of time after initial report, it remains sufficiently great to warrant supervision for at least 10 years after a suspected tuberculous lesion is recognized.

How frequently periodic examinations should be made is a much more difficult question. The answer depends to a considerable extent on whether reactivations tend to be acute and symptomatic, or chronic and insidious. It is not possible to be certain about this unless persons with inactive tuberculosis are examined frequently over a long period of time, and this was not done in the present study. However, many reactivations seemed to have occurred acutely, often causing the patient to seek medical advice before the next scheduled examination. Although some reactivations were truly insidious, these were exceptions. But even though the likelihood of detecting reactivations as early as possible increases with the frequency of examination, a schedule calling for very frequent examinations over a long period of time is not likely to be acceptable to the patients or to the examining agency. As a compromise, one might suggest routine examinations every 3 to 6 months for the first few years of observation with annual examinations thereafter. Prolonged followup with infrequent examinations may well be more valuable as a reminder that prompt medical evaluation should be sought when respiratory symptoms occur than as a direct measure to detect asymptomatic reactivation.

The followup routine for persons with inactive disease should obviously be tailored to the risk of reactivation. In this study, the risk was greater for persons with advanced tuberculosis, and greater among the young than the old. Females had only slightly lower reactivation rates than males. At all ages and at all stages of disease, the reactivation rates were greater for Negroes than for whites. The risk for young Negroes was particularly striking, and suggests that examinations for them might profitably be scheduled at more frequent intervals over a longer period than for other groups.

Why tuberculosis behaves differently in Negroes and whites has been a longstanding puzzle. There has been much speculation regarding the relative roles of nature and nurture; scientific evidence has been difficult to obtain. While the present study can hardly provide a definitive answer, some pertinent evidence was derived from a study of reactivation rates among Negroes with differing degrees of skin pigmentation. For, if susceptibility to tuberculosis were inherent in the Negro race, the group with dark skins might be expected to have higher reactivation rates than those with lighter skins. This was not the case. The lack of association between reactivation rates and degree of skin pigmentation suggests that environmental conditions may be more important than genetic factors in influencing the reactivation of inactive tuberculosis.

Summary

A total of 1,327 residents of Muscogee County, Ga., 15–65 years of age, were reported as having suspected or definite reinfection-type pulmonary tuberculosis between January 1, 1946, and January 1, 1956. None had previously been advised to accept treatment for tuberculosis.

Two years after being reported, 1,008 persons were classified as having inactive pulmonary tuberculosis with no evidence of extrapulmonary complications. Among these persons, the probability of developing active disease in the next 5 years was found to be substantial. For those with advanced tuberculosis initially, the risk was approximately 30 percent for Negroes and 10 percent for whites. For those under the age of 45 years with minimal or sus-

pected disease, the risk approximated 15 percent for Negroes and 5 percent for whites. For older persons with minimal or suspected tuberculosis, the risk was approximately 4 percent for Negroes and 2 percent for whites. The risk of reactivation among Negroes was not associated with degree of skin pigmentation. Long-term followup of persons with inactive disease appears to be an important means of detecting active tuberculosis.

NOTE: Persons interested in the tables giving more details of the life table analyses may obtain them from the author.

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Graduate Training

The Conference of Biological Editors at its annual meeting in New Orleans in March 1962 voted to:

1. Endorse the principle that English departments in secondary schools and colleges give training in writing scientific reports.

2. Recommend that teachers of biological sciences require written reports by students in their courses.

3. Recommend that teachers of science correct the English in science reports written for their courses.

4. Endorse an exploration of possibilities of greater cooperation between departments of English or journalism and departments of biological sciences. An example would be to permit a term paper on a science subject to serve both departments.

5. Endorse the principle that the writing and publication of reports be regarded as an essential and integral phase of fulfilled research.