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Epidemiological Basis of Tuberculosis Eradication*

9. Changes in the Mortality of Danish Tuberculosis Patients since 1925

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The authors have carried out an analysis of the mortality among Danish patients with tuberculosis whose condition was diagnosed between 1925 and 1954 in order to obtain a picture of the trend of tuberculosis mortality over a period during which a dramatic improvement in the prognosis of the disease has taken place. The data originate from clinical records and follow-up during 10 years of all notified cases fulfilling certain conditions in Århus, the largest provincial town in Denmark.

The mortality of the patients was highest immediately after diagnosis and decreased during the 10 years they were followed. The relative changes during the follow-up period, however, appeared to be the same in all patient groups and this fact has greatly simplified the comparison of the mortality among patients diagnosed in the different calendar years.

Analysis of the data according to year of diagnosis showed a consistent and substantial decrease in the mortality of young patients before the antituberculosis drugs came into use. This was true even within groups of patients with similar radiological findings. For patients over 45 years of age, however, there was no significant decrease in mortality before 1950.

INTRODUCTION

Physicians who have been working in the field of tuberculosis for many years will have a general impression that the prognosis for patients with pulmonary tuberculosis has improved dramatically during recent decades, but a more precise estimate of the magnitude of these changes or of the speed with which they have occurred is difficult to obtain. During the same period there have been other changes in the tuberculosis situation which confuse the picture. In most of the countries for which data are available it appears, for example, that the age composition of the patients has changed; in former years tuberculosis was mainly a disease of young people but today a large proportion of the patients belong to older age-groups. Furthermore, the clinical picture of the patients diagnosed today seems to be less severe than that found in previous years. It is therefore difficult for clinicians to appreciate to what extent their impression of improved prognosis is influenced by these changes.

The credit for the improved prognosis is usually given to the antituberculosis drugs introduced during the 1940s and 1950s. It would, however, be of some interest to study the conditions existing before the drugs came into use; was the situation stationary or was the prognosis for tuberculosis patients already improving then? In other words, did the drugs come as an isolated phenomenon or were they only the coping stones on a development that had started earlier?

Only a few studies have been published on this problem. Berg (1941) and Tattersall (1947) found no conclusive evidence of decreasing mortality among tuberculosis patients during the periods 1910-34 and 1921-40, respectively. Lowe (1954), studying the survival of patients with respiratory tuberculosis notified in Birmingham during each of the years 1930, 1935, 1940, 1945, 1947, 1949, 1950 and 1951, found no decrease in the mortality for the years 1930, 1935 and 1940, but a consistent decline since 1945.

The purpose of the present paper is to give a picture of the mortality among Danish patients with pul-

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monary tuberculosis diagnosed between 1925 and 1954 and to give quantitative estimates of the changes that have occurred. The study was conducted by following the patients for 10 years and establishing who died during this observation period and when death took place.

There are certain conditions in Denmark that facilitate studies of this kind and make the results relatively reliable. First, pulmonary tuberculosis has been reportable since 1905; according to the law, any doctor who finds a patient in need of treatment for the disease must notify the local health officer. Denmark is also covered with a net of public county chest clinics that are responsible for directing the tuberculosis control work within their areas. These clinics work in close collaboration with the health officers and the general practitioners and the latter will always refer patients with pulmonary symptoms to the chest clinic for further examination. The clinic will also provide for the necessary treatment, which is given without cost to the patient. Because of these conditions it is possible from the records of the chest clinics to obtain information about practically all known cases of tuberculosis within their areas. The information obtained may thus be regarded as referring to tuberculosis patients in general; it does not refer to a group that has been selected with regard to income or other factors affecting the prognosis. It may also be mentioned that the municipal registers are very effective in Denmark and it is relatively easy to trace the patients even if they move out of the clinic's area.

The data presented in this paper concern the patients with pulmonary tuberculosis from the municipality of Århus; this is the second largest town of Demark and has now a population of about 120 000 inhabitants. Although these patients constitute only a small percentage of all patients in Denmark, they may probably be taken as fairly representative of Danish tuberculosis patients as a whole. The facilities for diagnosis and treatment have been very much the same for patients in all parts of the country and the population is relatively homogeneous with regard to social and economic conditions. It should also be mentioned that the incidence of tuberculosis in Århus has been practically the same as in the whole country during the period under review.

MATERIAL AND METHODS

The basic data for the study were obtained from the records kept in the chest clinic in Århus. The cases contained in the files were included in the present study if they fulfilled the following conditions:

(1) Tubercle bacilli should have been demonstrated in their sputum or gastric washings (it follows from this rule that cases found *post mortem* have not been included). The first time that bacilli were found is here used as the time of diagnosis.

(2) The patient should be a resident of the municipality of Århus. For example, military recruits from other parts of the country who were stationed in Århus have not been included.

(3) The patient should be aged 16 years or more at the time of diagnosis.

(4) The diagnosis should have been made in the period 1925-54, both years included.

The chest clinic in Århus was actually not established until 1926 but at that time the clinic obtained from the public health service all notifications concerning bacillary cases reported from the town; it has thus been possible to extend the study to all cases diagnosed since 1 January 1925.

From the clinical records the following particulars were obtained: date of diagnosis, sex of patient and age at time of diagnosis, the method by which tubercle bacilli were demonstrated, X-ray status at diagnosis, treatment given during 10 years after diagnosis, and information on whether the patient died during the same period.

Bacteriological methods

Up to 1930 the only method used for demonstration of tubercle bacilli was direct microscopy of sputum. Thereafter culture of gastric washings and of sputum was gradually introduced and this method had come into general use by 1940. From that year all bacteriological examinations were carried out by the Statens Seruminstitut, Copenhagen, which functions as the central tuberculosis laboratory for the country. Because of the change in methods it is hardly possible to select patients with similar bacteriological status for the various periods of diagnosis.

X-ray status at diagnosis

This information is based on a full-size X-ray taken at the time of diagnosis and all the films have been read and classified by one of the authors (Buhl). More detailed radiological information, i.e., tomographical, is available for several patients diagnosed in recent years but an attempt was made to disregard such information during reading of the large X-rays.

It may therefore be assumed that the classification of the patients according to X-ray status has been done with a high degree of uniformity for the entire period.

The classification used in the present study is very simple: it is a four-way classification providing information on whether one lung or both lungs were affected and whether or not cavitation was present.

X-ray films are not available for 69 patients. The greater proportion of these patients were very ill and could not be transported to the X-ray department.

Information on death

Each patient was followed for a period of 10 years, i.e., an investigation was made into whether the patient was alive 10 years after the diagnosis, and if this was not the case, whether he died during the first, second or third year and so on up to the tenth year. If the clinic had lost contact with the patient by the end of 10 years, an attempt was made to contact him again. If he had moved out of the county, information was sought from the clinic which was now responsible for him; if his movements were not known, he was traced through the municipal registers. For the few patients (less than 20) who had moved out of the country, the information was sought from the patients' parents, siblings, or children (a record of their names and addresses was kept by the clinic).

As a result of these efforts information on survival or death has been obtained for all the patients fulfilling the four conditions mentioned above and the errors on this point appear to be negligible.

The data described above provide information about the over-all mortality among the patients and, deliberately, no attempt was made to exclude deaths in which the cause of death was considered to be something other than tuberculosis. The reasons for adopting this attitude will be given in the " Discussion ".

STUDY POPULATION

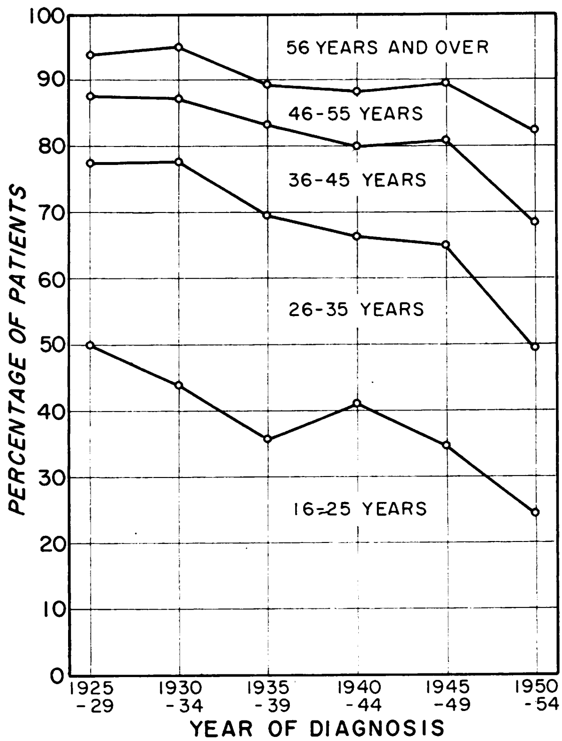
The total number of patients included in the study was 1517 and the distribution of the patients according to sex and period of diagnosis is shown in Table 1. There are more females than males among the patients but in later years the difference is only small. The figures show a slight decrease by calendar year except for the immediate post-war period 1945-49. It should be mentioned that the incidence of tuberculosis in Århus has decreased more than is indicated by these figures because the population has increased by more than 50% during the period.

TABLE 1
NUMBER OF TUBERCULOSIS PATIENTS BY YEAR OF DIAGNOSIS AND SEX

Year of diagnosis	Males	Females	Both sexes
1925-29	139	175	314
1930-34	111	126	237
1935-39	114	119	233
1940-44	111	120	231
1945-49	139	147	286
1950-54	107	109	216
Total	721	796	1 517

The age composition of the patients has changed during this period of 30 years, as shown in Fig. 1 (the data for this figure are given in Appendix Table 1). There is a clear trend toward older ages with calendar time; patients more than 45 years old constituted only 12% of the cases diagnosed in 1925-29, but by 1950-54 the proportion had increased

FIG. 1
AGE OF PATIENTS ACCORDING TO YEAR OF DIAGNOSIS



to 32%. Moreover, half of the patients from the first 5-year period were between 16 and 25 years old, but in the last 5-year period this age-group comprised only a quarter of the patients. The average age at the time of diagnosis was 30 years in 1925-29, 34 years in 1935-39 and 39 years in 1950-54.

The radiological findings at the time of diagnosis have also changed considerably during the period, as seen from Fig. 2. In 1925-34, 60% of the patients showed cavities, but by 1950-54 only 20% had this condition. During the same period the proportion of patients with both lungs affected decreased from nearly 60% to less than 40%. These data show that the clinical picture of the patients diagnosed in later years was less severe than that in previous years.

Some information about the treatment—in addition to rest in bed—given to the patients is presented in Table 2. This table shows the number of patients given various kind of treatment; some patients received several kinds of treatment and others none. It will be seen that pneumothorax has been widely used throughout the whole period. None of the patients diagnosed before 1940, and only few of those from 1940 to 1944, received chemotherapy, but about one-third of the patients in the period 1945-49 and more than 90% of those in 1950-54 were treated with antituberculosis drugs.

EVALUATION OF MORTALITY

Before going into the analysis of the mortality among the Danish tuberculosis patients some general remarks about evaluation of mortality should be made. The term " mortality " is commonly used by physicians in discussions and papers but what in fact is the precise meaning of this term?

The mortality in a population group is often described by means of the proportion of persons who died during a period of 1, 5, or 10 years. There are, however, some problems connected with the use of such proportions for comparative purposes. In order to illustrate these problems, let us assume that in one population group 80% died during 10 years and that in another population group only 20% died during the same period. To some it would seem natural to conclude that the mortality in the former group was 4 times higher than in the latter, but this is not necessarily correct; it depends on how

FIG. 2
SEVERITY OF RADIOLOGICAL FINDINGS AMONG PATIENTS ACCORDING TO YEAR OF DIAGNOSIS

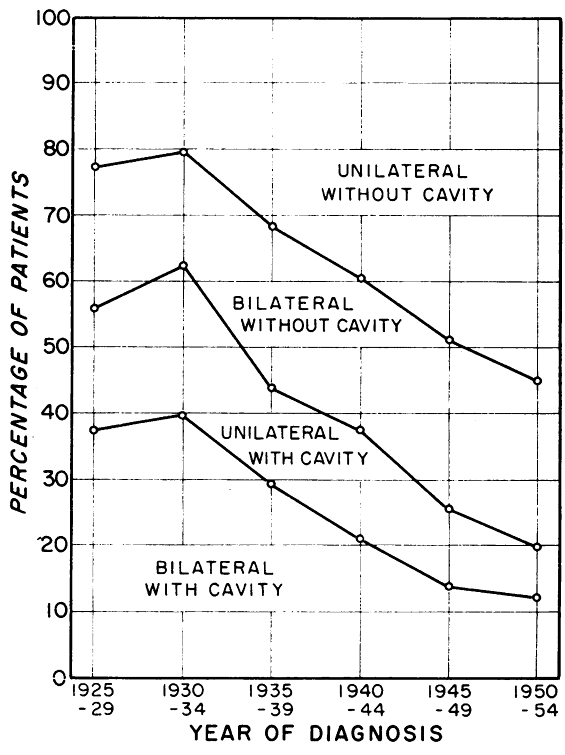


TABLE 2
TREATMENT GIVEN TO PATIENTS WITHIN 10 YEARS AFTER DIAGNOSIS

Type of treatment	Number of patients given specified treatment among those diagnosed in					
	1925-29	1930-34	1935-39	1940-44	1945-49	1950-54
Pneumothorax or pneumoperitoneum	90	136	135	126	154	99
Surgery	22	20	16	26	60	55
Chemotherapy	—	—	—	14	99	198
Total number of patients	314	237	233	231	286	216

mortality is defined. Instead of using the 10-yearly death rates we might, for example, characterize the mortalities in the two groups by means of the annual death rates. If it is assumed that the annual death rate (r) has remained the same during all 10 years of observation, the proportion of survivors after one year is $1-r$, after 2 years $(1-r)^2$ and after 10 years $(1-r)^{10}$. We can thus calculate the annual death rate in the first population group by the relation $(1-r_1)^{10} = 0.20$, from which we find $r_1 = 14.9\%$. By similar calculations for the second group we find $r_2 = 2.21\%$.

Therefore, if we base our evaluation of mortality on annual death rates we come to the conclusion that the mortality in the former group was 6.7 times higher than in the latter group.

It should be noted that the annual death rate in the first population group is much more than one-tenth of 80%, or 8%. It is higher because many persons die during the first years and so towards the end of the observation period there are few survivors exposed to death; a constant annual rate of 8% will therefore result in only 57% deaths during 10 years. In the second population group, on the other hand, in which the mortality is much less, the population exposed to death does not decrease much during the 10 years. Therefore, the annual death rate in this group does not deviate much from one-tenth of 20%.

The above example shows that one gets an impression of a greater difference between the mortality in the two population groups by using annual rates instead of 10-year rates. But then, we shall obviously get still different impressions by operating with rates for other periods, for example, 2 years or 1 month. We might even get an impression of equal mortality by using a rate for a sufficiently long period of, for example, 100 years. But which of these rates gives the best impression of the difference between the two groups?

The mathematical solution of this dilemma is simple. Instead of operating with a rate related to one period or another we shall do away with the period; that is, we shall introduce a new measure which is obtained when the length of the period goes toward zero. This measure is called, by statisticians, the *force of mortality* and it characterizes the risk of death at a certain moment. The force of mortality might be said to provide the most explicit expression of the risk of death because there is no need to specify a period to which it relates. It is, of course, impossible to make a direct observation of the force of mortality but it is possible to derive estimates of it from observations made over any period of time.

If it is assumed that the force of mortality (μ) has not changed in time, it is related to the proportion of survivors after t years (${}_tp$) by the formula $\mu = \frac{-\text{Log}\,{}_tp}{t}$, where Log stands for the natural logarithm (see Annex). By applying this formula to the above example we find for the first population group $\mu_1 = \frac{-\text{Log}\,0.20}{10} = 0.161 = 16.1\%$, and for the second group $\mu_2 = 2.23\%$.

The interpretation of this result is that the risk of death in the first population group was 7.2 times higher than in the second group.

In our opinion it is the risk of death which is of main interest in studies of mortality and the sharpest measure of that risk is the force of mortality. We have therefore adopted the force of mortality for characterizing the mortality among the patients under study.

RESULTS OF ANALYSIS

Trends in mortality of tuberculosis patients during the observation period

A first impression of the mortality trend during the 10 years that the patients were followed may be obtained from the survival curve, i.e., the curve showing the proportion of survivors after 1, 2, . . . 10 years. Curves for 6 different patient groups are given as examples in Fig. 3 (the basic data for the curves are to be found in Appendix Table 1). The curves have been selected to represent patients with very different mortalities and they include patients diagnosed at various ages and in various years. These curves show a steep drop during the first years of observation and then a flattening-off, suggesting that the mortality is highest immediately after diagnosis and decreases during the following years. In order to learn more about the trends in mortality, the negative logarithms of the proportion of survivors are shown in Fig. 4; these values again are depicted on a logarithmic scale. It will be seen that these curves have a similar form and are located at different levels. This similarity suggests (see Annex) that the mortality in the various patient groups follows the same trend during the observation period, but is at different levels. More specifically, it suggests that the force of mortality in a group of patients can be described as a product of two factors —one factor (which is the same for all patient groups) characterizing the changes in mortality during the

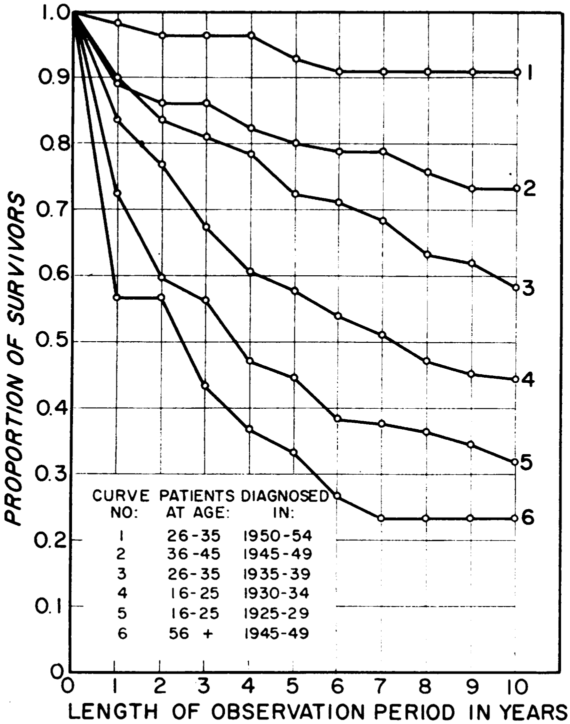


FIG. 3

EXAMPLES OF SURVIVAL CURVES FOR PATIENTS DIAGNOSED AT DIFFERENT AGES AND IN DIFFERENT YEARS

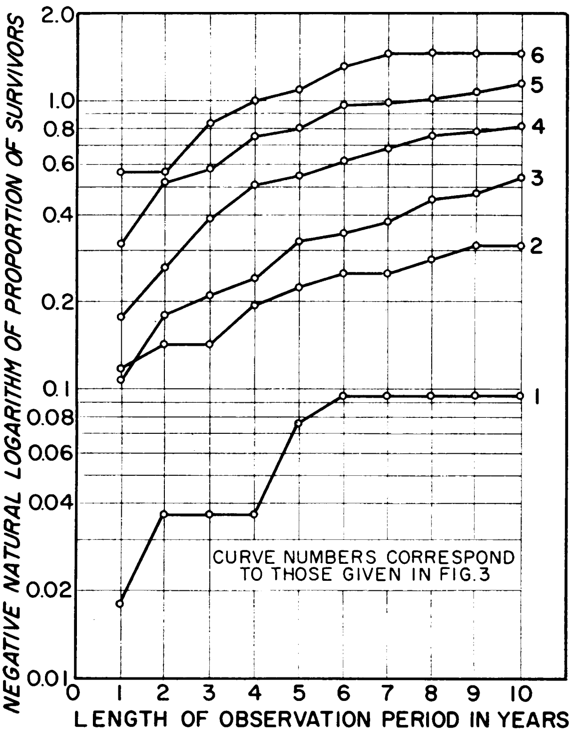
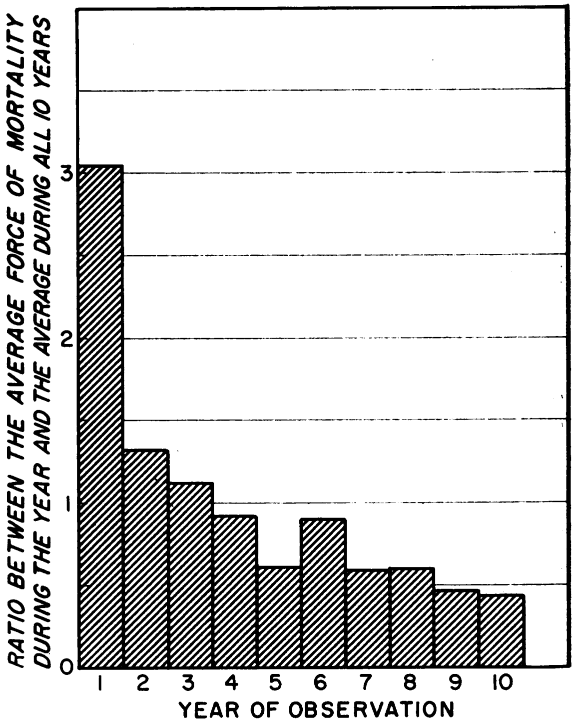


FIG. 4

LOGARITHMIC TRANSFORMATION OF THE DATA GIVEN IN FIG. 3

FIG. 5
ESTIMATED TREND IN MORTALITY OF PATIENTS DURING THE OBSERVATION PERIOD



observation period, and another factor characterizing the level of mortality in that particular group.

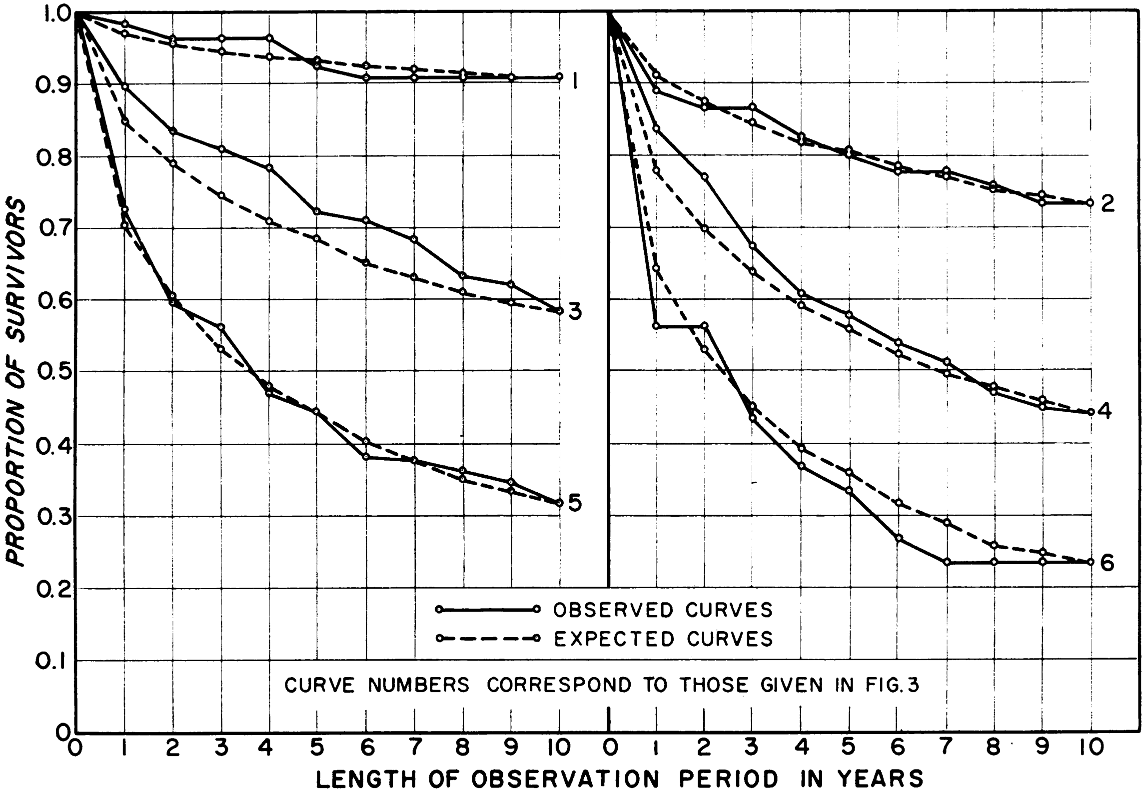
In order to examine this hypothesis the first-mentioned factor, i.e., the trend in mortality during the observation period, has first been estimated as explained in the Annex. The resulting estimates based on all patients in the study are given in Fig. 5. The mortality is seen to be very high during the first year of observation, but it drops as early as the second year to about 40% of the former level. During the following years the mortality decreases more slowly and by the end of the observation period it is approximately one-sixth of that found during the first year.

As a second step in the examination of the above hypothesis, the factors characterizing the level of mortality in each patient group were estimated as described in the Annex. With these estimates, as well as that for the trend during the observation period, it was possible to calculate the survival curves that would be expected if the above hypothesis holds true. These expected values for the curves of Fig. 3 are shown in Fig. 6, and it appears that the agreement between observation and expectation is fairly good. A detailed analysis of the data for all 30 patient groups given in Appendix Table 1 has shown that the deviations between observed and expected numbers of deaths appear to be quite unsystematic; they show no apparent trend by year of diagnosis, age at diagnosis, or year of observation. It is therefore concluded that the above hypothesis will provide a sufficiently accurate model for describing the mortality among the patients.

The apparent similarity in mortality of the patients is fortunate because in the following section we shall compare the mortality in various groups of tuberculosis patients and it follows from the model that such comparisons can be made in a very simple way—by comparing the factors characterizing the level of mortality. We may therefore express the difference in mortality among two groups as simply as, for example, that the mortality in group A was 60% higher than that in group B. If, on the other hand, the changes in mortality during the observation period had been different in different patient groups, the result of a comparison would have had a more complicated form such as, for example, that during the first 2 years after diagnosis the mortality in group A was 50% higher than in group B, and

FIG. 6

THE SURVIVAL CURVES OF FIG. 3 AND EXPECTED CURVES BASED ON HYPOTHESIS DESCRIBED IN TEXT



during 3-10 years after diagnosis the mortality of the two groups was equal.

Because of the similarity in the mortality of the patients during the observation period, however, we shall need only one figure—an index—for characterizing the level of mortality in a particular patient group. The index used in the following is the average of the force of mortality to which the group has been exposed during the 10 years of observation.

When these data are presented in the following section the reader should keep in mind that the mortality changed during the observation period as outlined in Fig. 5; for example, during the first year it was 3 times the average of 10 years and during the ninth and tenth observation years it was slightly less than half the average.

Mortality according to year of diagnosis

A picture of the level of mortality among patients according to year of diagnosis is given in Fig. 7, which shows the average force of mortality during 10 years for all patients diagnosed in the 5-year groups 1925-29 up to 1950-54. The data show a consistent and rapid drop in mortality from 10% in 1925-29 to only 2% in 1950-54.

A more detailed picture of the trend is given in Fig. 8, which shows similar data separately for patients diagnosed at the ages of 16-25 years, 26-35 years, 36-45 years, and 46 years and over. It will be seen that the drop in mortality by year of diagnosis is steepest in the youngest age-group; by 1935-39 the mortality had dropped to one-third of that in 1925-29 and by 1950-54 it had come down to one-fiftieth of the initial level. In patients diagnosed at the ages of 26-35 years and 36-45 years there is also a consistent decrease with year of diagnosis but the relative decrease is less than in the youngest age-group; among the patients diagnosed in 1950-54 the mortality was a little more than one-tenth of the level for 1925-29. In patients aged 46 years or more the picture is somewhat different. In this group the mortality has apparently remained unchanged up to 1949; it

FIG. 7
MORTALITY OF PATIENTS ACCORDING TO YEAR OF DIAGNOSIS

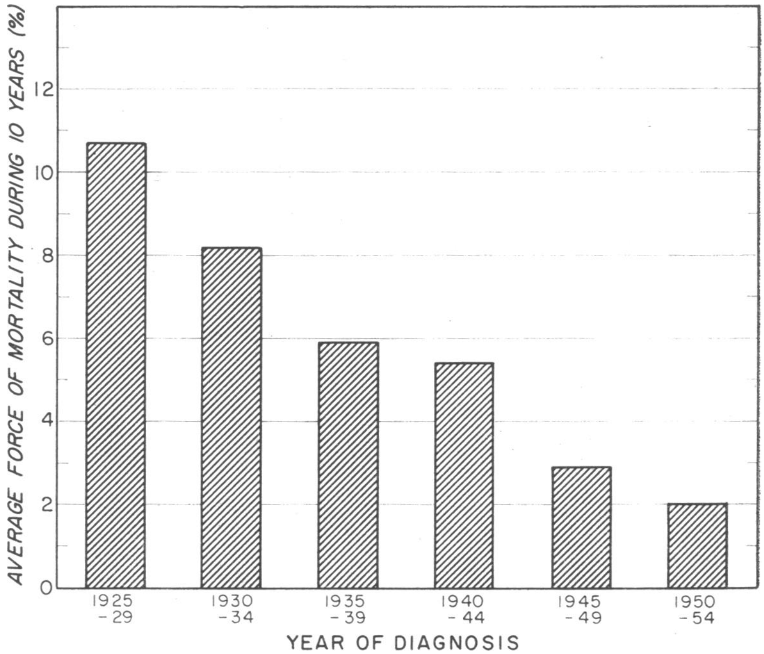
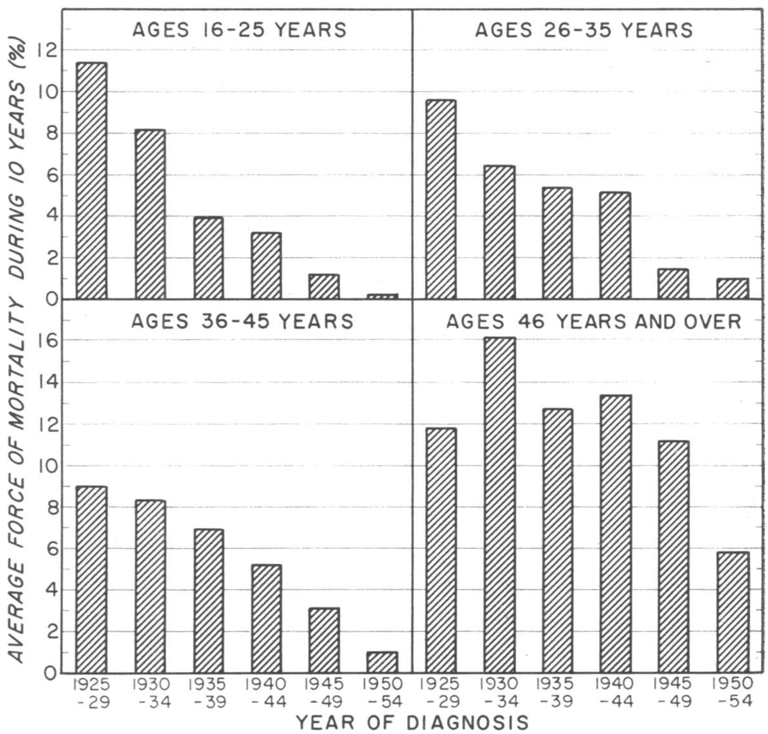


FIG. 8
MORTALITY OF PATIENTS ACCORDING TO AGE AT DIAGNOSIS AND YEAR OF DIAGNOSIS



is only among the patients diagnosed in 1950-54 that a significant decrease (to about half) is noted.

The trend in mortality according to year of diagnosis has been studied separately for male and female patients. For the purpose of this analysis it was necessary to combine age-groups with similar mortality in order to obtain reliable estimates of the mortality. In Appendix Table 2 basic data are given for 2 age-groups—16-45 years and 46 years and over—and the estimated mortality level for the younger age-group is given in Table 3.

The trend in mortality by year of diagnosis is seen to be similar in the two sexes and there is not much difference between the mortality of male and female patients.

It is generally assumed that the prognosis of pulmonary tuberculosis depends on the chest X-ray findings at the time of diagnosis. As the cases diagnosed in later years showed less serious X-ray findings than those diagnosed in the 1920s and 1930s, this change might partly account for the observed drop in the mortality according to year of diagnosis. It would therefore be of interest to study the trends in mortality separately for patients with specific types of X-ray findings at the time of diagnosis.

TABLE 3

MORTALITY OF PATIENTS AGED 16-45 YEARS ACCORDING TO YEAR OF DIAGNOSIS AND SEX

Year of diagnosis	Average force of mortality during 10 years (%)		
	Males	Females	Both sexes
1925-29	10.0	11.0	10.5
1930-34	8.1	7.0	7.5
1935-39	5.6	4.4	5.0
1940-44	3.9	4.2	4.1
1945-49	1.9	1.4	1.6
1950-54	1.2	0.4	0.7

Estimates of the mortality among patients in the age-group 16-45 years with break-down into 4 categories of X-ray findings—unilateral processes with and without cavity, and bilateral processes with and without cavity—are shown in Fig. 9 (the basic data may be obtained from Appendix Table 2). In all 4 groups there is a clear downward trend according to year of diagnosis; in particular, there would seem

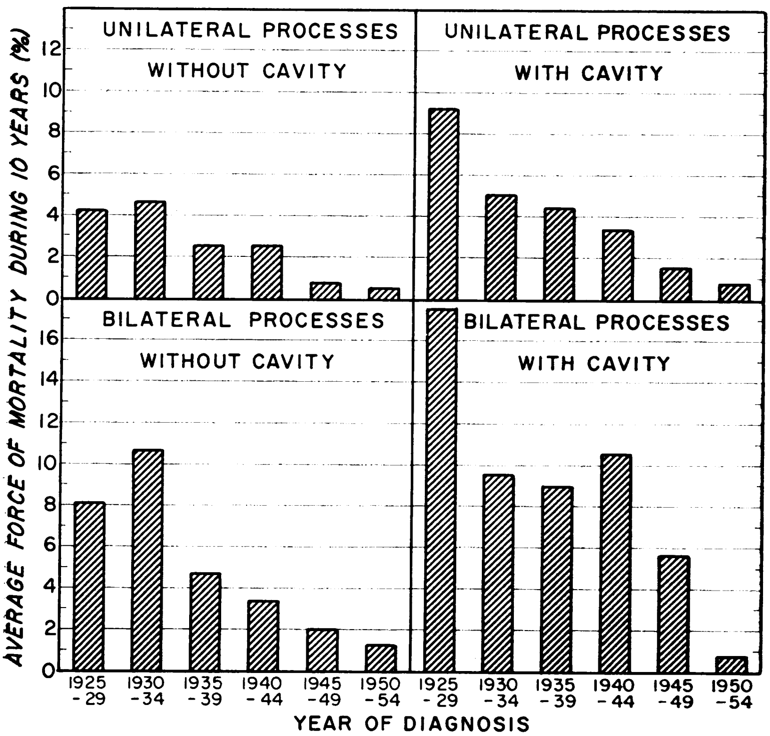


FIG. 9

MORTALITY OF PATIENTS AGED 16-45 YEARS ACCORDING TO INITIAL RADIOLOGICAL FINDINGS AND YEAR OF DIAGNOSIS to be little doubt that the mortality was decreasing with the year of diagnosis even during the period 1925-44. The relative decrease in mortality during the years 1925-44 does not seem to be very different in the 4 categories but the estimates of this decrease are not very reliable because of the few observations, especially for the period 1950-54.

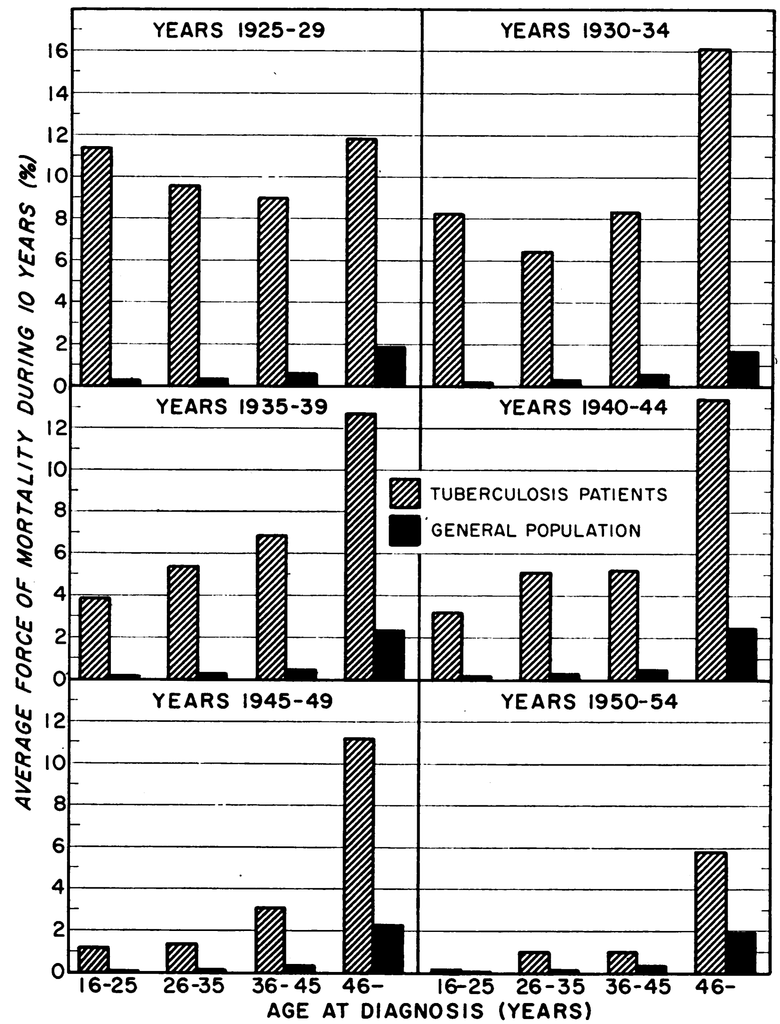
The data in Fig. 9 confirm the general observation among clinicians that the prognosis depends to a large extent on the X-ray findings at the time of diagnosis: the mortality was definitely higher in patients with bilateral processes than in those with unilateral processes and it was higher when cavitation was seen than when no cavity was seen.

Comparison of the mortality of tuberculosis patients with that of the general population

Until now we have been dealing with the over-all mortality among the patients. This is based on deaths from all causes and one would assume that some of these deaths would have occurred even if the persons under study had not suffered from tuberculosis. One may therefore wonder how large a part of the mortality shown above is excess mortality, i.e., in some way connected with the fact that this was a group of tuberculosis patients, and how large a part is " natural " mortality.

In order to throw some light upon this problem, the mortality of the patients and the mortality in

FIG. 10
MORTALITY OF PATIENTS ACCORDING TO YEAR OF DIAGNOSIS AND AGE AT DIAGNOSIS IN COMPARISON WITH MORTALITY OF THE GENERAL POPULATION



the general population of Denmark are presented in Fig. 10. The latter data are based on the life-tables that are published by the Statistical Department of the State of Denmark every fifth year and show the mortality in a group of the general population with the same age and sex composition as the patients.

It can be seen that among the patients diagnosed in the years 1925-34 only a small part of the mortality is accounted for by " natural " mortality. In those years pulmonary tuberculosis imposed a huge excess death risk upon the sufferer from the disease and it would appear that this extra risk was nearly the same for all age-groups, i.e., apparently it was independent of the general mortality in the group.

Among the patients diagnosed in 1950-54 the picture is very different. A relatively large part of the mortality in this group was due to " natural " mortality, i.e., pulmonary tuberculosis was still a killing disease but much less so than before. It would also appear that the extra death risk undergone by the patients in this period is closely related to the mortality among the general population of the same age. In fact, the death risk among the patients was approximately three times higher than that among the general population.

These data would thus indicate that the effect of the disease has changed profoundly during the period studied; at the beginning of the period, the disease acted as an independent killer and inflicted a high additional death risk on young and old alike. In recent years the disease has had much less influence on mortality and its influence also has appeared to depend on the general conditions in the host—among young patients, in whom the general mortality is low, the additional death risk was much less than among old patients.

DISCUSSION

The killing effect of a chronic disease like tuberculosis may be studied in several ways. The method applied in this paper is first to compute the over-all mortality among the patients and then to relate the findings to the mortality in the general population. Another, and more direct method, would have been to limit the study to the deaths among the patients that were caused by tuberculosis. Information on the cause of death might have been obtained from the death certificates, which are nearly always issued by a physician in Denmark.

There is, however, a risk that by including in the study only deaths reported to be caused by tuberculosis an underestimate of the effect of tuberculosis on mortality is obtained. The fact that the doctor has stated the underlying cause of death to be other than tuberculosis does not necessarily mean that this disease played no role at all. It would seem possible, for example, that tuberculosis makes some patients more prone to accident or suicide. It would even seem likely that tuberculosis, by undermining the patient's health, makes him more vulnerable to other diseases and that certain diseases take a fatal course more often when associated with tuberculosis.

It may also be pointed out that the cause of death is not always determined with a high degree of accuracy. There may be a great deal of doubt as to the cause of death, especially when the patient has been suffering from several diseases or conditions at the time of death, which is increasingly frequently the case as the average age at death increases. Whether the certifying physician in such cases puts one or another disease as the underlying cause of death can hardly be unaffected by his personal experience and interests.

Because of these considerations we think that more objective and probably more reliable information on the fatal effect of tuberculosis is obtained by including all the deaths occurring among the patients in the analysis.

On the other hand, it must be admitted that the method used here—i.e., comparing the over-all mortality among the patients with that of the general population—also has its limitations. One objection to the method is that the comparison should be made rather between the tuberculosis patients and *the remaining (non-tuberculous) part* of the population. Data for the last-mentioned group can only be computed for the last period of diagnosis, 1950-54, because reliable estimates of the prevalence of tuberculosis are not available for the years before 1950. It is, however, easy to see—even without data—that this objection cannot seriously affect the general trends in the excess mortality presented above. It is true that for the early years of diagnosis, when the prevalence of tuberculosis was high and the mortality of patients was also high, the mortality of the non-tuberculous population was probably considerably lower than that of the general population. But during these years the excess mortality among the patients was so high that a correction would be relatively insignificant. And during the later periods of diagnosis, when the prevalence of tuberculosis and the mortality of tuberculosis patients were both lower, the mortality of the non-tuberculous population can only have been a trifle lower than that of the general population.

A more serious objection to our method is that one cannot be sure that the excess mortality observed among the patients is *due to* tuberculosis only; it is possible, for example, that the disease occurs relatively frequently in certain segments of the population in which the over-all mortality is higher than in the general population. It would seem possible to investigate this problem in special studies; but until such studies have been made, the possibility cannot be excluded that a part of the excess mortality among the patients is due to causes other than the disease, for example, poor social conditions. Despite this limitation it is presumably still of interest to present a factual account of the excess mortality among the patients.

The most striking finding in the present study is the decrease in the mortality of young Danish tuberculosis patients during the period 1925-44. As seen from Fig. 9, the excess mortality among the patients diagnosed in 1940-44 at ages 16-45 years was approximately half of that among patients of the same ages diagnosed in 1925-29. This would seem to indicate that even among patients with similar radiological findings half of the extra death risk carried by the patients diagnosed during the period 1925-29 had disappeared before the anti-tuberculosis drugs came into use.

It must, of course, be admitted that the X-ray classification used here is crude since within each X-ray category there may be considerable differences with regard to severity of disease. Therefore, the possibility cannot be excluded that, by using a more detailed classification of the X-ray findings, the drop in mortality would have been less pronounced. However, in view of the fact that the classification was very relevant for the prognosis and since it appears unlikely that a shift towards more mild cases would occur in all four categories, it would still seem well established that there was an appreciable improvement in the prognosis for young tuberculosis patients during the years 1925-44.

The reasons for this improvement are not known. During these years new methods of treatment were not introduced and the methods applied are now considered to be only slightly effective. Improvements in social conditions may therefore be suggested as a possible explanation for the improved prognosis. But if this is correct why was there no decrease in the mortality of the older patients during this period? One possible explanation is that the support provided by the social progress had less effect in the older patients; in other words, that more effective means were required for curing tuberculosis in these age-groups than in younger age-groups. This agrees with clinical observations, and the results found in 1950-54 might also lend some support to this explanation.

The improvements occurring among the patients diagnosed in 1945-49 and 1950-54 would seem easier to explain. During these years an increasing proportion of the patients were given chemotherapy and, as the effectiveness of the drugs is well established, there is little doubt that they have played a large role in the reduction of mortality during these years.

RÉSUMÉ

Les auteurs se sont proposé de présenter un tableau de la mortalité parmi les Danois atteints de tuberculose pulmonaire diagnostiquée entre 1925 et 1954. Les données de base proviennent des archives du Centre de lutte contre la tuberculose pulmonaire d'Aarhus, la plus grande ville de province du Danemark. Les malades en cause paraissent représentatifs de ceux du pays tout entier et ne constituent probablement pas un groupe sélectionné sous le rapport du revenu ou d'autres facteurs affectant le pronostic. Il s'agit uniquement de personnes pour lesquelles le bacille tuberculeux a été mis en évidence dans des crachats ou des produits de lavage d'estomac; en outre, toutes avaient plus de 15 ans et résidaient à Aarhus au moment du diagnostic. Dans ce groupe de 1 517 malades, tous les décès survenant dans les dix ans qui ont suivi le diagnostic ont été enregistrés.

La structure du groupe a subi des changements notables au cours de la période 1925-1954. Il y a eu une nette augmentation de la proportion représentée par les groupes d'âge les plus élevés; d'autre part, la gravité de la maladie au moment du diagnostic, telle que la révélait l'examen radiologique des poumons, a été moindre vers la fin de la période qu'au début. Si la chimiothérapie a été très peu appliquée aux sujets dont la tuberculose a été diagnostiquée avant 1945, la proportion des malades soumis à un traitement de ce genre a été d'un tiers pour

les cas diagnostiqués entre 1945 et 1949, de plus de 90% pour les cas diagnostiqués de 1950 à 1954.

Une section de l'article est consacrée à une discussion générale des méthodes de comparaison de la mortalité. Les auteurs soulignent qu'une comparaison directe des taux de mortalité n'est pas satisfaisante, car les résultats dépendent de la longueur de la période employée pour calculer ces taux. Ils suggèrent donc d'utiliser aux fins de comparaison la mortalité instantanée, qui ne fait pas intervenir de facteur de durée et constitue, par conséquent, une mesure « pure » du risque de décès.

On a, en premier lieu, analysé les données de façon à dégager les tendances de la mortalité au cours des dix ans pendant lesquels les malades ont été suivis. Après avoir atteint un maximum immédiatement après le diagnostic, la mortalité a baissé, d'abord rapidement, puis plus lentement. Cette tendance s'est manifestée pour toutes les années de diagnostic et pour tous les âges au moment du diagnostic. Ainsi, quel que soit le sous-groupe de malades considéré, la mortalité peut être représentée par un modèle mathématique simple: le produit de deux facteurs, l'un, commun à tous les sous-groupes, correspondant à l'évolution de la mortalité pendant la période d'observation, l'autre correspondant au niveau de la mortalité dans chaque sous-groupe. Cela simplifie les comparaisons entre les diverses séries annuelles de cas diagnostiqués, puisqu'il suffit de prendre en considération le dernier facteur mentionné.

Il ressort de l'analyse des données relatives à l'ensemble des malades que, pour tous, la mortalité a diminué de 1925 à 1954. La répartition des données selon l'âge au moment du diagnostic indique que la baisse a été maximale pour le groupe d'âge 16-25 ans, un peu moins forte pour les sujets âgés de 26 à 45 ans. En ce qui concerne les malades de plus de 45 ans, la mortalité n'a pas décru notablement avant 1950.

On a aussi étudié la mortalité chez les malades de 16 à 45 ans classés selon le type des constatations radiologiques faites lors du diagnostic. Même avec de tels sous-groupes, constitués chacun de sujets présentant une atteinte d'importance analogue au moment du diagnostic, on a noté partout une baisse de la mortalité pendant la période 1925-1954.

Enfin, on a comparé la mortalité parmi les malades à celle de la population générale du Danemark. Pour les cas diagnostiqués de 1925 à 1929, l'excédent de mortalité a été considérable et apparemment indépendant de l'âge. Pour les cas diagnostiqués de 1950 à 1954, il a été bien moindre et, semble-t-il, étroitement lié à la mortalité générale du groupe d'âge. En fait, la mortalité moyenne des malades au cours de la période d'observation a été à peu près trois fois plus forte que celle de la population générale du même âge.

La présente étude a porté sur la totalité des décès, quelle qu'en soit la cause, chez les malades, et non pas seulement sur les décès dus à la tuberculose. Les avantages et les limites de cette méthode sont discutés. On suggère quelques explications possibles de tendances observées dans la mortalité.

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Annex

STATISTICAL CONSIDERATIONS

RELATIONSHIP BETWEEN THE FORCE OF MORTALITY AND THE PROBABILITY OF SURVIVAL

The force of mortality (μ) is a mathematically convenient means of describing the death risk in a population. It depends, normally, on the age (x) and is defined as follows: the probability of a person dying between the ages x and $x + dx$ is $\mu_x dx$. The force of mortality is related to the number of survivors at age x (l_x) by the formula:

$$l_x - l_{x+dx} = l_x \mu_x dx, \text{ or } \frac{1}{l_x} \cdot \frac{dl_x}{dx} = -\mu_x, \text{ or } l_x = ke^{-\int_0^x \mu_\tau d\tau}$$

The probability ${}_tp_x$ that a person of age x will survive for t years is therefore

$${}_tp_x = \frac{l_{x+t}}{l_x} = e^{-\int_x^{x+t} \mu_\tau d\tau}$$

In the special case when μ is constant between x and $x + t$ we have the simpler relations:

$${}_tp_x = e^{-t\mu}, \text{ or } \mu = -\frac{\operatorname{Log} {}_tp_x}{t}$$

(Here and in the following Log means the natural logarithm.)

DEVELOPMENT OF MODEL FOR DESCRIBING THE MORTALITY OF TUBERCULOSIS PATIENTS AND ESTIMATION OF PARAMETERS

Estimates of the probabilities of survival may be obtained from the observed survival curves and we may thus obtain information about the force of mortality from the observed data. It will be seen, however, that the relationship between the probability of survival and the force of mortality is quite complicated. In order to get expressions which have a simpler relation to the force of mortality it would seem natural to introduce the negative natural logarithm of the proportion of survivors because

$$-\operatorname{Log} {}_tp_x = \int_x^{x+t} \mu_\tau d\tau$$

It has been observed (Fig. 2) that when the negative natural logarithms of the proportion of survivors after 1, 2 . . . 10 years are plotted on a logarithmic scale the curves for various patient groups show a similar form but are at different levels. This would seem to suggest that for any patient group P_v

$$\log \int_x^{x+t} \mu_\tau^{(v)} d\tau = k_v + \mathrm{F}(t)$$

where k_v is a constant characteristic for the group P_v, and $F(t)$ is the same for all groups. It follows that

$$\int_x^{x+t} \mu_\tau^{(v)} d\tau = \operatorname{antilog} k_v \cdot \operatorname{antilog} F(t) = K_v \cdot G(t)$$

and thus that $\mu^{(v)}$ has the form

$$\mu^{(v)}_{x+t} = K_v \cdot g(t)$$

during the period of observation.

We shall first derive estimates of the function $g(t)$ from the data given in Appendix Table 1. These data will not permit an estimation of $g(t)$ in detail, but only averages of $g(t)$ for each year of observation and we shall therefore introduce the notations:

$$g_1 = \int_0^1 g(t)\,dt, \qquad g_2 = \int_1^2 g(t)\,dt, \qquad \ldots g_{10} = \int_9^{10} g(t)\,dt.$$

We shall also arbitrarily put

$$\sum_{s=1}^{10} g_s = \int_0^{10} g(t)\,dt = 10;$$

by so doing K_v will be an estimate of the average force of mortality during the 10 years of observation because

$$\int_0^{10} \mu^{(v)}_{x+t}\,dt = \int_0^{10} K_v g(t)\,dt = K_v \int_0^{10} g(t)\,dt = K_v \sum_{s=1}^{10} g_s = 10\,K_v \quad \text{and so } K_v = \frac{1}{10}\int_0^{10} \mu^{(v)}_{x+t}\,dt.$$

If the value of K for the first patient group given in Appendix Table 1 (patients diagnosed at ages 16-25 years in 1925-29) is called K_1, that of patients diagnosed at ages 26-35 years in 1925-29 is called K_2, etc. up to K_{30}, which is the value for patients diagnosed at ages 56 years and more in 1950-54, we shall find the following estimates of the products of K and g:

$$K_1 g_1 \approx -\text{Log}\,\frac{114}{157}, \quad K_1 g_2 \approx -\text{Log}\,\frac{94}{114}, \quad \ldots K_1 g_{10} \approx -\text{Log}\,\frac{50}{54}$$

$$K_2 g_1 \approx -\text{Log}\,\frac{65}{86}, \quad K_2 g_2 \approx -\text{Log}\,\frac{56}{65}, \quad \ldots K_2 g_{10} \approx -\text{Log}\,\frac{33}{36}$$

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$$K_{30} g_1 \approx -\text{Log}\,\frac{32}{38}, \quad K_{30} g_2 \approx -\text{Log}\,\frac{30}{32}, \quad \ldots K_{30} g_{10} \approx -\text{Log}\,\frac{16}{16}$$

By adding each column we shall obtain estimates

$$\text{of } g_1 \sum_{s=1}^{30} K_s, \quad g_2 \sum_{s=1}^{30} K_s, \quad \ldots g_{10} \sum_{s=1}^{30} K_s, \text{ i.e.,}$$

estimates of the g values multiplied by the same constant. But as we have already put

$$\sum_{s=1}^{10} g_s = 10$$

this does not present any difficulty. The resulting estimates of g are given opposite.

Year of observation	*Estimate of g*
1	3.05
2	1.33
3	1.11
4	0.92
5	0.61
6	0.90
7	0.58
8	0.60
9	0.47
10	0.43

Estimates of the K values are found by adding the rows given opposite. By adding, for example, the first row we find

$$K_1 \sum_{s=1}^{10} g_s \approx -\left(\text{Log}\,\frac{114}{157} + \text{Log}\,\frac{94}{114} + \ldots + \text{Log}\,\frac{50}{54}\right) = -\,\text{Log}\,\frac{50}{157}, \text{ i.e., } K_1 \approx -\frac{1}{10}\,\text{Log}\,\frac{50}{157} = 0.114.$$

It will be noted that in this model the estimates of the K values depend only on the proportion of survivors after 10 years.

APPENDIX TABLE 1

NUMBER OF SURVIVORS AMONG TUBERCULOSIS PATIENTS ACCORDING TO YEAR OF DIAGNOSIS, AGE AT DIAGNOSIS AND LENGTH OF FOLLOW-UP PERIOD

Year of diagnosis	Age at diagnosis	Number of patients diagnosed	Number of survivors after									
			1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
1925 - 29	16 - 25	157	114	94	88	74	70	60	59	57	54	50
	26 - 35	86	65	56	52	47	41	39	39	38	36	33
	36 - 45	32	22	19	17	15	14	14	14	13	13	13
	46 - 55	20	12	11	11	10	10	10	9	9	9	8
	56 +	19	8	6	5	5	5	4	4	4	4	4
1930 - 34	16 - 25	104	87	80	70	63	60	56	53	49	47	46
	26 - 35	80	66	63	59	56	55	53	51	48	46	42
	36 - 45	23	18	15	14	13	11	11	11	10	10	10
	46 - 55	18	10	9	7	7	7	6	5	5	5	5
	56 +	12	8	5	4	3	3	3	2	2	1	1
1935 - 39	16 - 25	83	75	69	66	64	62	61	60	59	58	56
	26 - 35	79	71	66	64	62	57	56	54	50	49	46
	36 - 45	32	26	22	20	19	19	19	18	17	16	16
	46 - 55	14	10	10	9	9	9	8	8	6	6	6
	56 +	25	18	14	11	9	7	5	5	5	5	5
1940 - 44	16 - 25	95	85	83	78	74	73	72	70	69	69	69
	26 - 35	58	52	47	45	42	38	37	37	37	37	35
	36 - 45	32	26	22	21	21	21	21	21	20	19	19
	46 - 55	19	16	15	13	13	11	9	9	7	7	7
	56 +	27	17	14	11	8	8	6	6	6	6	5
1945 - 49	16 - 25	99	94	91	90	88	88	88	88	88	88	88
	26 - 35	87	85	83	81	79	78	78	78	76	76	76
	36 - 45	45	40	39	39	37	36	35	35	34	33	33
	46 - 55	25	22	20	19	18	17	17	16	14	14	11
	56 +	30	17	17	13	11	10	8	7	7	7	7
1950 - 54	16 - 25	52	52	52	52	52	52	52	52	52	52	51
	26 - 35	55	54	53	53	53	51	50	50	50	50	50
	36 - 45	41	40	39	39	39	39	39	38	37	37	37
	46 - 55	30	28	28	27	27	27	26	25	24	23	22
	56 +	38	32	30	29	26	24	21	17	16	16	16

APPENDIX TABLE 2

INITIAL NUMBER OF PATIENTS AND NUMBER OF SURVIVORS AFTER 10 YEARS, ACCORDING TO YEAR OF DIAGNOSIS, AGE AT DIAGNOSIS, SEX AND INITIAL X-RAY FINDING

Year of diagnosis	Age at diagnosis	Sex	Initial number of patients (init.) and number of survivors (surv.) with initial X-ray findings										Total	
			Unilateral processes				Bilateral processes				Information not available			
			Without cavity		With cavity		Without cavity		With cavity					
			init.	surv.	init.	surv.	init.	surv.	init.	surv.	init.	surv.	init.	surv.
1925 - 29	16 - 45	M	28	19	16	6	21	10	38	7	19	3	122	45
		F	25	16	29	12	26	11	54	9	19	3	153	51
	46 and	M	2	1	2	1	7	2	5	-	1	-	17	4
	over	F	6	5	2	-	3	2	3	-	8	1	22	8
1930 - 34	16 - 45	M	13	8	13	9	18	5	44	18	2	-	90	40
		F	28	18	35	20	17	7	36	13	1	-	117	58
	46 and	M	3	-	3	1	4	2	9	1	2	-	21	4
	over	F	3	1	2	1	1	-	3	-	-	-	9	2
1935 - 39	16 - 45	M	25	21	10	5	29	17	26	10	3	-	93	53
		F	38	28	18	13	19	13	25	11	1	-	101	65
	46 and	M	4	3	1	-	2	-	12	2	2	1	21	6
	over	F	4	-	4	-	5	3	3	2	2	-	18	5
1940 - 44	16 - 45	M	31	26	10	8	20	13	18	7	2	1	81	55
		F	47	35	22	15	15	12	19	6	1	-	104	68
	46 and	M	6	2	5	3	12	2	7	-	-	-	30	7
	over	F	6	4	-	-	5	-	4	1	1	-	16	5
1945 - 49	16 - 45	M	57	52	14	12	23	17	11	6	1	1	106	88
		F	62	59	15	13	31	27	17	10	-	-	125	109
	46 and	M	11	6	1	-	11	4	9	1	1	-	33	11
	over	F	7	6	3	1	7	-	2	-	3	-	22	7
1950 - 54	16 - 45	M	33	31	5	4	15	12	8	7	-	-	61	54
		F	53	51	10	10	17	16	7	7	-	-	87	84
	46 and	M	21	11	2	2	14	8	9	3	-	-	46	24
	over	F	12	8	-	-	8	5	2	1	-	-	22	14