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What can we learn by following the development of tuberculosis from one generation to another?

Kristian F. Andvord

TO CONTRIBUTE to a clearer understanding of what I will later explain in detail, I would first like to briefly outline some of the important features of tuberculosis. Although these are largely well-known facts, they may often be overlooked.

I will start by the characteristic curve of age-specific mortality of this disease, with its two maxima and two minima, and emphasize how little variation there really is in this curve, both with regard to the disease in general as well as to variation over time. It may rise or decline slowly over time, but the form of the curve remains the same. Thus, it may be of great interest to mention that Professor Gärtner in 1893 pointed out the striking similarity between the mortality curve of tuberculosis and the overall mortality curve, and that tuberculosis in this respect is reminiscent of a constitutional disease, showing a characteristic pattern across different age groups.

Furthermore, I would like to draw attention to another extraordinary feature, which in my view has received little attention, namely the very different appearance of tuberculosis before and after the fourth to fifth year of life.

It appears that, from the second part of childhood onwards, the human body develops a very different resistance against primary infection with tuberculosis bacilli than that which is apparent during the first year of life. This resistance is presumably partly physiological in nature, dependent on age itself, and partly an expression of an inborn immune process. The well-known feature that the extent of the disease gradually increases while its intensity decreases can hardly be explained otherwise than that such an immune process gradually changes the soil and thereby increases the resistance of the human body. While during the first three or four years of life we find relatively few, but severe, cases with very high mortality, in contrast, during the remainder of life the majority of the primary infections are of a benign nature, with low mortality. This applies to populations where tuberculosis has been prevalent for at least a few generations. I do not doubt that here at home, in many of the more isolated areas, we may find real primary infections on a non-immunized soil also among adults and adolescents, the so-called malignant primary lesion phthisis ('Primärherdphthisen') to quote Redeker.

With regard to this, I take pleasure in citing a few of Professor Redeker's remarks from his recent work on the onset and development of pulmonary tuberculosis among adults. On page 46 he writes, 'The exogenous re-infection must be one of the most important causes of the endogenous re-activation', and further on, 'the exogenous super-infection is both immunobiologically as well as anatomically strongly connected with exacerbation of an already existing focus'.

These two vaguely formed statements, which have now received 'general scientific acceptance', according to the Professor, tell us that the primary infection during childhood should be regarded as a prerequisite for the development of pulmonary tuberculosis in adult life. Not less so because, again according to Redeker, we must assume that in as many as thirty per cent of cases it has not been possible to identify any source of transmission whatsoever.

After dwelling on these particular aspects of the mortality and morbidity of tuberculosis, we will now proceed with my main subject, an examination of what we can learn by following the development of tuberculosis from one generation to another.

The relation between infection during the first years of childhood and pulmonary tuberculosis, which develops 15–20 years later, is not completely clear. During my ongoing research in this field it gradually became clear to me that by following each cohort of the population from birth onward—by generation, in other words—it should be possible to determine the significance that a rise or decline in childhood tuberculosis mortality may have on the following periods of life.

It was the characteristics and course of the disease in Kristiansand that gave me the first proof that my opinion had to be correct. As early as the late 1880s, an accelerating decline in childhood tuberculosis emerged, whereas on the other hand the mortality of pulmonary tuberculosis remained high year after year

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despite increasing preventive efforts. A decrease in mortality among adults did not appear until 20 years later, approximately in 1905, but from then on this decrease accelerated. My hypothesis is that during those 20 years, generations grew up that were less and less severely infected with tuberculosis, and as a result tuberculosis mortality in adults also had to decrease in a similar manner with time.

It was evident that studying the development of tuberculosis over generations only in towns or small parts of the country would be insufficient to obtain reliable results. Migration would have too great an influence. It would be much more appropriate to study the country as a whole, and fortunately the available health statistics enable us to follow the tuberculosis mortality within different population groups with relative certainty, at least since 1896. Based on a preliminary evaluation, I sensed that I was on the right track. Through Professor Meidells' advice and amiable guidance I understood what might be achieved with statistics in this field, although I was warned against drawing too far-reaching conclusions from these figures, since, according to the Professor, "the course of numbers always can be interpreted in different ways and, therefore, only gives presumptive evidence for the hypothesis, which appears to be confirmed."

Table 1 shows the development of tuberculosis mortality per 10 000 for the country as a whole within the various population cohorts from 1896–1900 until and including 1927. The cohorts consist of 5-year groups and each of these comprise approximately 300 000 individuals for the first few years of life, out of which an estimated 200 000 will remain when the cohort has reached the age of 20. It is thus the entire population of the country that we follow here, generation-wise. The fewer and fewer age groups in each of these cohorts until the year 1927 is, of course, caused by the fact that they begin at a later and later point in time. While the first cohort, i.e., that of 1896–1900, can be followed for 32 years, the cohort of 1921–1925 can be followed for only 7 years.

Very precise data on tuberculosis mortality for previous generations for the country as a whole are not available. However, all accessible evidence suggests that the mortality had been high in the years prior to the study period. In particular, the mortality during the first years of childhood seemed to be high in the period 1875 to 1885.

Table 1 Tuberculosis mortality per 10 000 within the various 5-year cohorts in Norway from 1896–1900

Population cohorts from	Age groups						
	0–4	5–9	10–14	15–19	20–24	25–29	30–35
1896–1900	34.2	13.1	15.0	30.3	45.0	36.8	21.8
1901–1905	26.0	11.6	12.6	29.7	42.8	32.5	
1906–1910	20.3	9.5	10.9	27.4	34.0		
1911–1915	16.8	8.1	9.5	19.4			
1916–1920	13.9	6.4	6.3				
1921–1925	11.2	5.45					
1926 & 1927	10.2						

First in the table we have the 5-year cohort for 1896–1900, the group that shows the highest mortality rates overall with 34 per 10 000 for the first few years of life, a minimum of 13 between 5 and 9 years, and then another maximum of 45 per 10 000 when the cohort reaches the ages of 20 to 25.

The second cohort, that of 1900–1905, is the first to show a noticeable decrease in the mortality among both children and the other age groups, and if we review the mortality of the next cohorts we discover the same regular decrease from one cohort to another as long as we can follow it.

To illustrate the development of tuberculosis over the last 20 to 30 years more clearly, I transferred the values to curves (Figure 1), one for each cohort, or in other words, one for every new generation. We see here how the curves, steadily decreasing, follow each other through the age groups, each generation with its own characteristic curve. Within a generation, relatively high mortality for the early years of childhood seems to correlate to similarly high rates for adults after 20 to 25 years. On the other hand, a decrease in the mortality during the first few years of life is followed by a similar fall in mortality among adults. If we consider these mortality curves from one generation to another, sequentially as a total entity, as a big rolling wave, it becomes evident that they will encounter a certain leveling off, the cause of which in my view has to be related to an immunization process regulated by nature itself.

The steady pre-determined shape of the curve is particularly striking. Every individual curve clearly expresses the degree to which a generation is affected and at the same time explains how further developments will take place. Furthermore, we should recognize the obvious decrease in childhood tuberculosis, particularly during the last few decades.

And if we ask ourselves: Where do we stand in our fight against tuberculosis? What have we accomplished? Then, in my opinion, these generation curves give us a clear answer. As I hope to prove, collaboration between the different disciplines of treatment on one hand, and a clear understanding of nature's self-protecting forces on the other, have brought about a situation that bodes particularly well for the future.

We start by looking at the development of tuberculosis during the first five years of life. What has not yet been accomplished by intensive prevention together with improved conditions for children? The mortality has decreased gradually from cohort to cohort, for a total reduction of 60 per cent. Indeed, now, in 1926–1927, 650 fewer children die per year than at the turn of the century.

Furthermore, for the age groups 5–9, and 10–14 years, the mortality has decreased by at least 40 to 50 per cent, and now, around 1920, at least 400 fewer

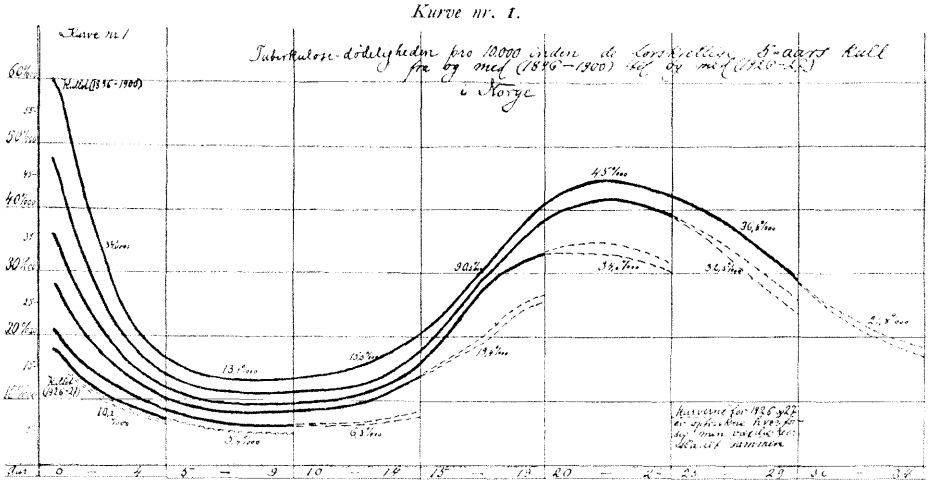

Figure 1 Tuberculosis mortality per 10 000 within the various 5-year cohorts from 1896–1900 to 1926–1927 in Norway. The curves for 1926 and 1927 are drawn separately, but the values were added together. Reproduced with the kind permission of the Editor of the Journal of the Norwegian Medical Association (Andvord K F. Hvad kan vi lære ved å følge tuberkulosens gang fra generasjon til generasjon? Norsk Magazin for Lægevidenskapen 1930; 91: 642–660.)

children die in this period of life than 20 years earlier. Does anybody doubt that institutions such as our coast hospitals, tuberculosis sanatoria, school hygiene and colonies for children at risk of tuberculosis have all contributed to both a reduction of mortality and a strengthening of the rising generation so that they can better tolerate the strong strain at the age of 15–20 years? With regard to this, I will also draw attention to Division Doctor Øverland's observation of the importance of diet, particularly at the age of rapid growth and development.

In the age groups between 15 and 30 years, where pulmonary tuberculosis dominates the picture, we still find a decrease in mortality of at least 600 cases (20–25%) during the last ten years. It is difficult to say how big a part of this decrease can be attributed to our therapeutic efforts, but I am fully convinced that our current sanatorium treatment annually returns a sizeable number of either completely healthy, or at least employable individuals, to the country. Overall, at least 1700 (approximately 30%) fewer individuals under 30 years of age died of tuberculosis in this country in 1926–1927 than by the turn of the century. This is a very remarkable result, and I am of the opinion that our fight against tuberculosis is based on secure foundations, and that we have all the encouragement we need to continue along those lines.

But, apart from these obvious conclusions, the generation curves can clarify other and possibly even more important issues. I think, in particular, of what they can tell us with regard to the further development of tuberculosis. There are clear indications that during the last 25–30 years a generation has grown up that is progressively less severely infected, or better immunized, than the previous generation. Based on these observations, we can assume with a reasonable degree of certainty that in the following decades the mortality of pulmonary tuberculosis, as well as the overall mortality of the disease, will continue to decrease. We can predict the further development of tuberculosis by following the direction in which the curve for each individual generation is already set from childhood.

As small proof hereof, and of the fact that tuberculosis mortality in the long run must undoubtedly be guided by certain rules, I will report the results of a small experiment that I did last year.

On the basis of the reported observations, I attempted to calculate the mortality curve for 1927. In April, last year, Chief Physician Heitmann received these calculated rates in a sealed envelope for safekeeping. In September this autumn, the envelope was opened for comparison with the mortality rates, which were made available from the Central Bureau of Statistics. The comparison of both rates is shown in Table 2. The average error is approximately 1 per

Table 2 Tuberculosis mortality per 10 000 in 1927 within the various age groups

Age group (years)	Registered values	Values estimated by Andvord
0–4	10.5	9.5
5–9	5.4	5.3
10–14	5.9	6.5
15–20	19.8	19.5
21–24	33.1	36.0
25–29	31.6	33.0
30–39	22.2	20.6
40–49	15.7	15.9
50–59	14.6	13.0
60–69	15.3	14.3
70–79	13.9	12.0

That is, an error of 1.1 per 10 000.

Table 3 Tuberculosis mortality per 10 000 within the various 5-years cohorts in Sweden from 1891–1895 to 1926

Population cohorts	Age group (years)						
	0–4	5–9	10–14	15–19	20–24	25–29	30–34
1891–1892					33.0	28.5	
1896–1900		8.9	10.1	23.0	31.4	24.2	
1901–1905	18.8	8.2	9.6	22.1	27.1	23.0	
1906–1910	16.4	7.7	8.5	18.3	25.0		
1911–1915	15.5	7.3	6.6	15.6			
1916–1920	14.0	5.1	5.3				
1921–1925	11.0	4.2					
1926	8.3						

Table 4 Tuberculosis mortality in England and Wales per 10 000, by generation

A Within the 10-year cohorts from 1851–1860 to 1881–1890

Population cohorts from	Age group (years)					
	0–4	5–9	10–14	15–19	20–24	25–35
1851–1860	57.8	(20–30 years later)			32.4	37.0
1861–1870	54.7	—			25.0	30.4
1871–1880	52.3	—			19.4	23.0
1881–1890	44.9	—			15.8	18.9

B Within the 5-year cohorts from 1896–1900 to 1926–1927

Population cohorts from	Age group (years)						
	0–4	5–9	10–14	15–19	20–24	25–29	30–35
1896–1900	36.0	6.9	5.7	11.3	16.2	14.6	
1901–1905	32.0	6.4	**5.9**	**13.4**	15.8	13.5	
1906–1910	25.8	6.0	**6.6**	**11.3**	13.4		
1911–1915	19.9	**6.3**	4.2	9.8			
1916–1920	16.0	3.5	3.4				
1921–1925	11.4	3.35					
1926 & 1927	9.25						

10 000, and if I had thought it over more precisely it would have been even less.

I mention these remarkably consistent features of the disease also to underline how highly unlikely it would be that these almost 'predestined' tuberculosis mortality rates for adults could be ascribed to the more or less random acute primary infections with relatively short incubation time.

According to Professor Meidell, the life insurance companies have previously made certain efforts with regard to examining the evolution of tuberculosis mortality within each generation. However, in medical science such analysis has not been done previously, and it has thus been difficult to find statistical material that could be used for comparison. The mortality rates should comprise the whole of the country concerned and be calculated in a uniform manner, with respect to both age groups and population groups. The statistical material from Sweden could be used, and with the kind help of general secretary Dr Neanders and office chief Arosenius, I succeeded in rearranging these data for generations similarly to what I did with our own data (Table 3, Figure 2).

It should be noticed that the complete statistics for causes of death for Sweden in its entirety are available only from 1911, and that the age group 20–30 is not divided until the year 1923. Thus, some of the values in Table 3 are merely estimates and should therefore be interpreted with caution, according to Mr Arosenius.

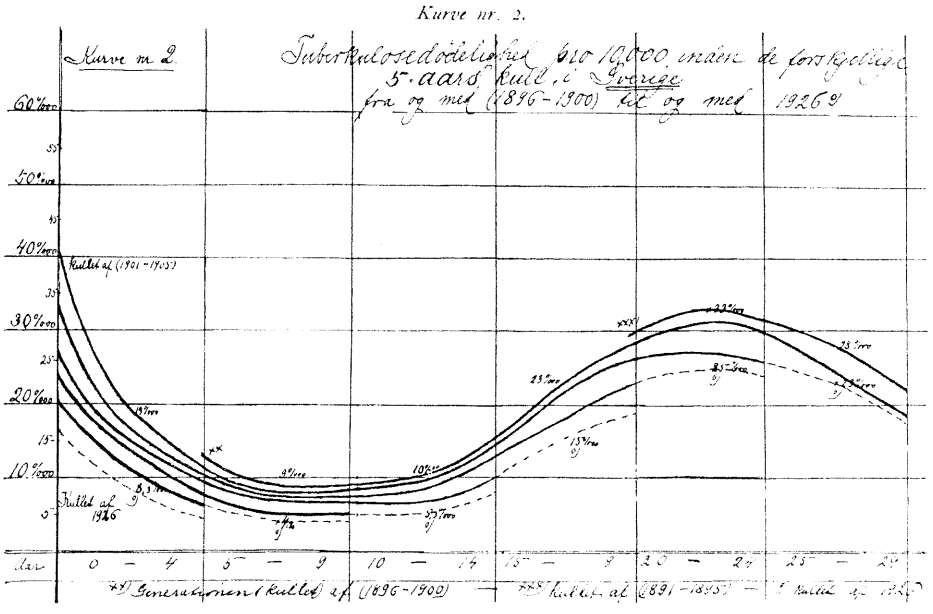

Figure 2 Tuberculosis mortality per 10 000 within the various 5-year cohorts in Sweden from 1896–1900 to 1926. o) Cohort from 1926; xx)1896–1900 cohort; xxx)1891–1895 cohort. Reproduced with the kind permission of the Editor of the Journal of the Norwegian Medical Association (Andvord K F. Hvad kan vi lære ved å følge tuberkulosens gang fra generasjon til generasjon? Norsk Magazin for Lægevidenskapen 1930; 91: 642–660.)

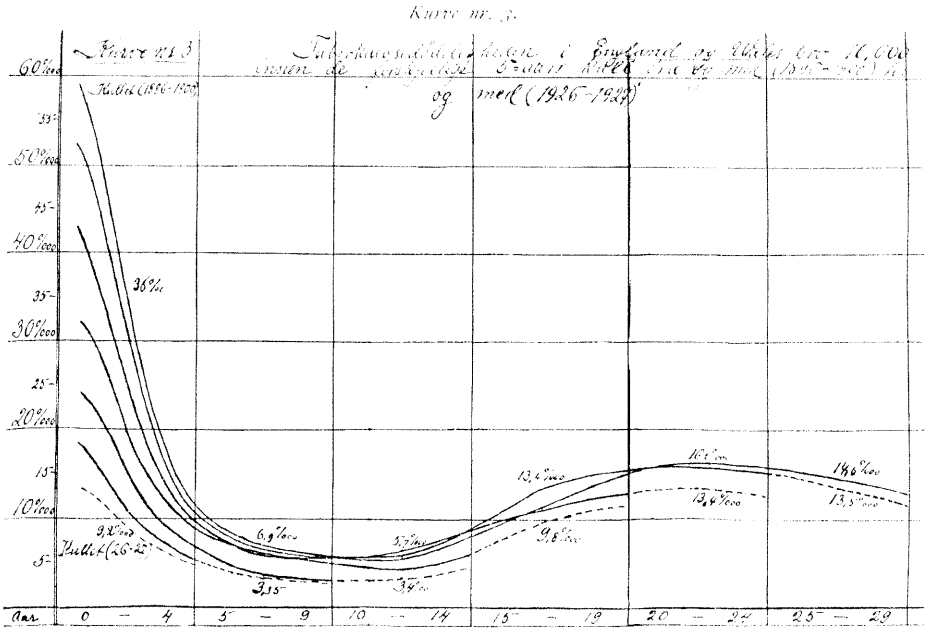

Figure 3 Tuberculosis mortality in England and Wales per 10 000 within the various 5-year cohorts from 1896–1900 to 1926–1927. Reproduced with the kind permission of the Editor of the Journal of the Norwegian Medical Association (Andvord K F. Hvad kan vi lære ved å følge tuberkulosens gang fra generasjon til generasjon? Norsk Magazin for Lægevidenskapen 1930; 91: 642–660.)

Nevertheless, these generation curves show a remarkable resemblance to the Norwegian ones. We find the same regular overall decrease from generation to generation, and the same proportional relation between mortality during the first years of childhood and mortality among adults. It may be of interest that every generation includes approximately half a million individuals.

In order to include observations from other countries, if possible, I discussed further with Director Jahn, who suggested that I find out whether or not the British data could be used, while at the same time very

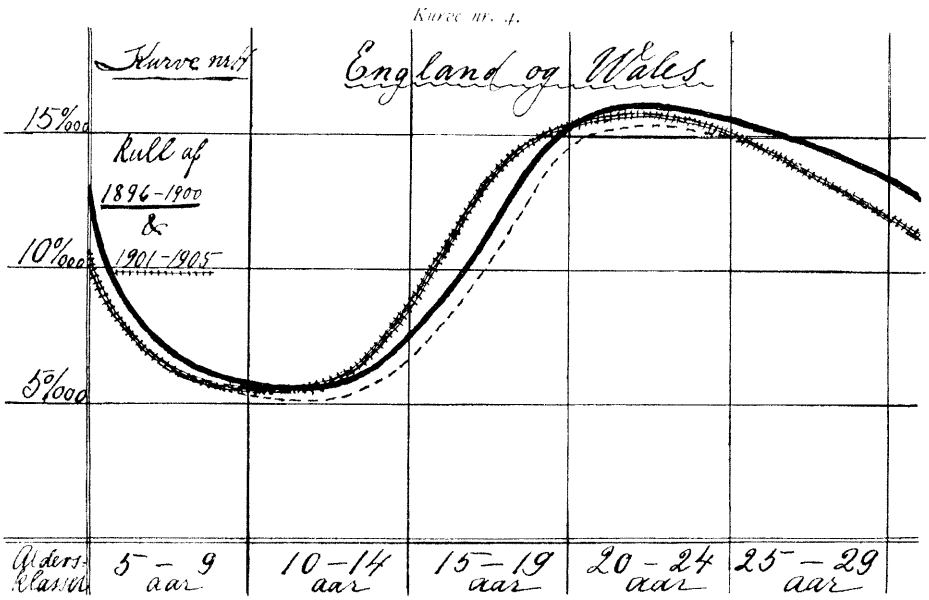

Figure 4 England and Wales cohorts from 1896–1900 and 1901–1905. Reproduced with the kind permission of the Editor of the Journal of the Norwegian Medical Association (Andvord K F. Hvad kan vi lære ved å følge tuberkulosens gang fra generasjon til generasjon? Norsk Magazin for Lægevidenskapen 1930; 91: 642–660.)

Table 5 Tuberculosis mortality per 10 000 within the various cohorts in Denmark from 1921

Population cohorts from	Age group (years)					
	0–4	5–9	10–14	15–19	20–24	25–29
1901–1905					14.9	
1906–1910				11.2	13.3	
1911–1915			4.2	7.8		
1916–1920		3.7	2.9			
1921–1925	8.1	2.8				
1926–1928	7.4					

kindly offering the assistance of his office in this matter. Everything went as hoped, and I obtained statistical data on tuberculosis from England and Wales, rearranged in five-year groups in the same way as was done for the Norwegian and Swedish data, and for the same period of time, from 1896–1900. I will now present these data. Despite the development of tuberculosis mortality in England and Wales having been slightly different from what we observe here, and despite the war obviously having put its stamp on the development of some of these curves, we find the same characteristics in these generation curves as outlined for our country and for Sweden.

Table 4 is divided into two time intervals: the upper section from 1851 until 1890 comprises four 10-year cohorts arranged generation-wise, but more schematic in that the mortality values have only been indicated for the two maxima for the age groups 0–4 and 21–35 years. The lower part, from 1896 to 1927, is, on the other hand, presented in 5-year cohorts in the same way as was done for Norway and Sweden.

The relatively high mortality for the first years of life is obvious, especially during the last century. Furthermore, the same regular fall in mortality from one generation to another is present also for this country. And without exception, a decrease in mortality during the first years of life is followed by a similar decrease when the cohort has reached adult age.

However, during and after the war years, we find a remarkable increase in tuberculosis mortality among the succeeding generation, as illustrated in the tables by highlighting the five values that apply. It is evident that this extraordinary increase, where one would expect a decrease, was entirely temporary in nature. The respective generation curves very soon fall back into their regular pattern. In Figure 3 this cannot be seen easily because it is rather difficult to distinguish the individual lines. However, it is very clear from Figure 4, where I have indicated the two curves that apply in different ways, and we can see here how the generation from 1901–1905, which begins with values under the previous one, shoots over it between 12 and 20 years of age, and then from 25 years of age follows the expected pattern.

It is noteworthy that every generation here includes approximately 3 million people.

Finally, I would like to show a table and curves demonstrating the development of tuberculosis in Denmark, again produced generation-wise (Table 5 and Figure 5). Thanks to Director Doctor Ostenfeldt's kindness, I received those data a few days ago. The data comprise the whole of Denmark, but unfortunately go back no further than 1920, and as a result we only obtain knowledge on a few of the 5-year

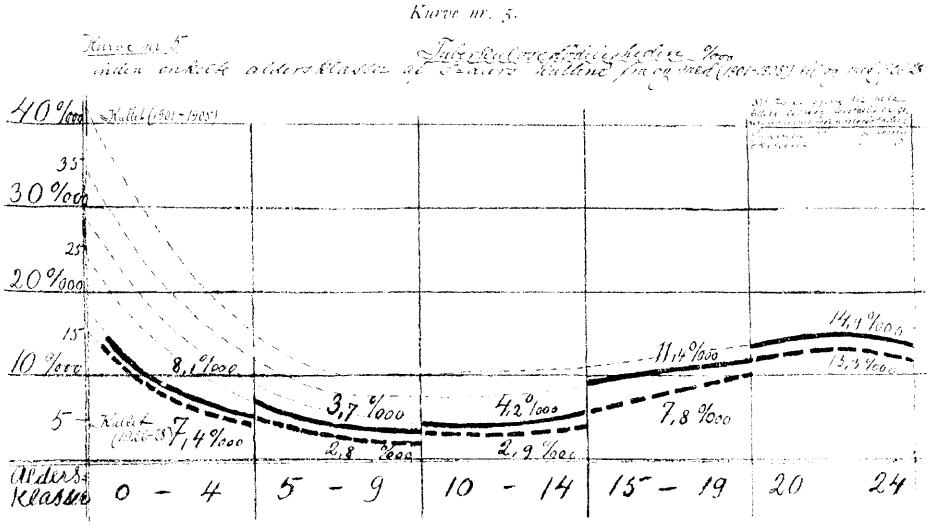

Figure 5 Tuberculosis mortality (in Denmark) per 10 000 within separate age groups of the 5-year cohorts from 1901–1905 to 1926–1928. NB: To make the figure more comprehensible, the first part of each cohort curve has been sketched schematically and loosely (with a dotted line). Reproduced with the kind permission of the Editor of the Journal of the Norwegian Medical Association (Andvord K F. Hvad kan vi lære ved å følge tuberkulosens gang fra generasjon til generasjon? Norsk Magazin for Lægevidenskapen 1930; 91: 642–660.)

Table 6 The 5-year period 1920–1925 (tuberculosis mortality in selected 5-year cohorts in Denmark, England, Sweden and Norway)

	Age groups (years)		
	0–4	5–9	20–25
Denmark	8.1	3.7	14.9
England	11.4	3.5	15.8
Sweden	11.0	5.1	27.1
Norway	11.2	6.4	42.8

cohorts, from 1901–1905 onward. Despite this, the Table shows two important things that completely agree with what has been presented for the other countries, namely, the curves' gradual and regular decrease and their characteristic course. In addition, we see that Denmark shows the lowest overall mortality rates. It may therefore be of interest to compare the rates for the examined countries, for example, for the period 1920–1925, and for the three most important age groups: 0–4, 5–9, and 20–25 (Table 6).

From this comparison it seems that the immunization process of the populations and generations must have worked fastest and strongest in Denmark, next comes England, then Sweden, and finally, Norway. In my view, this is also very natural, taking into account the size and population density of the respective countries. However, it is also evident that we have made considerable progress in our control of childhood tuberculosis during the most recent decades here in Norway, considering that the mortality of childhood tuberculosis is now at approximately the same level as in England and Sweden, a sign bearing good promise for the future.

As we can see, tuberculosis is on the decline everywhere, and the change in the curves tells us clearly that, perhaps even before a decade has passed, the maximum mortality in adults may be below 10 per 10 000, at least as far as Denmark is concerned.

In general, the tuberculosis mortality presented by generation shows a characteristic and most regular wave pattern, which has decreased over several decades, although to a different degree, in virtually the entire civilized world. In England, this decrease in mortality rates had already begun in the middle of the last century, at least as far as children are concerned, while here in Norway there was no evidence of a decrease in the mortality rates for this age group until approximately the 1880s. The decrease takes place from one generation to another, and every new population segment seems to be more resistant to the tuberculosis bacillus than the previous one. Every generation has its own distinct curve, as the degree of infection during the first years of life becomes an indicator for the mortality rates in the following age groups. A decrease in tuberculosis mortality during the first childhood years is thus always followed by a similar fall 20 to 25 years later among adults, a series of facts that undoubtedly must be of great significance for a clearer understanding of the onset and development of the disease.

As the older generations with their relatively high tuberculosis mortality represent the end point of the heavily burdened generations from the 1850s to the 1860s, we will now undoubtedly reach a period with gradually decreasing mortality. The mortality will also decrease among older people, because the generation that is now growing up has been both better immunized and less infected during their childhood than the previous generations.

In short, it appears that the curves tell us that the more we can contribute to a reduction in childhood tuberculosis mortality, the more we will indirectly contribute to a decreased overall mortality.

Thus, the most important objective of our treatment must be to know nature's self-regulating and self-protecting forces and, thereafter, to obtain as good a cooperation with them as possible. We must also remember that although each generation from childhood on is predestined to experience a certain tuberculosis mortality, this burden can be influenced within certain limits either for better or for worse.

If these statistical observations prove correct and can be confirmed by similar observations from still other countries, we should consider tuberculosis to be a generational disease, and that it is the infection during childhood and a steadily operating immunization process that seems to determine the course and development of the disease. Consequently, adult pulmonary tuberculosis as a cause of death has to be regarded as a secondary, or even tertiary process.

We know little about how the above-mentioned immunity develops. It may be inherent, but, in my opinion, it may also be acquired through lactation. We hope continued studies in this field will produce more clarity in this regard.

The use of generation curves will be invaluable for following tuberculosis mortality from one cohort to another, and will thus enable us to determine both what we have achieved and what we can expect to achieve in our fight against the disease.

Originating from several generations of the total populations of various countries, these statistical data can possibly be interpreted and explained differently. However, we cannot get around the facts. I am convinced that the approach of following and comparing by generation also for the course of other diseases may help us to better understand the importance and extent of the inborn immunobiologic processes.