

## REPRINTS AND REFLECTIONS

# Continued Studies of Tuberculosis considered as a generation illness<sup>1,2</sup>

Kristian F Andvord

My studies of tuberculosis as a generation illness have brought, I believe, some clarity to many obscure points around the course and behaviour of the disease, and as during the last couple of years, I have made further observations in this area I shall now allow myself to present these to the Society. Firstly, I must make some explanatory remarks.

Ladies and gentlemen, as some of you will perhaps recollect from my previous lecture in spring of last year, these generation studies are built on five year groups, taking into account age groups and generations. It is known that, as a basis for these mortality values, lies the respective countries' total population, and the generation groups begin thus with about 3.5 million children under five years of age in England's case, 300,000 for both Denmark and for Norway, and with about 500,000 for Sweden. In addition, it can be further pointed out that all these mortality rates are calculated in the same way for all the countries. Of the last five year group (that for 1926–1930) we now know the tuberculosis mortality figures for 4 of these 5 years and it is the mean value here which is indicated with a broken line on my graphs.

Before I go into detail about what the generation graphs themselves can tell us, I shall first allow myself to show a table (Table 1) which, in Norway's case, shows the mortality relationships, before, during and after the characteristic decline in deaths from tuberculosis, which as we know began during infancy and early childhood in 1900–1905.

On the uppermost line, marked as A: mortality rates per 10,000 during the first 5 years of life from 1871–1875 to 1926–1930; on the lower line marked as B: the corresponding values during 20 to 25 years of age from 1891–1895 to 1926–1930. The inclined arrows then indicate the values corresponding to the same generations.

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The quality of the original figure/ did not permit better reproduction. The figure/ is/ are available in the electronic version of this paper at *International Journal of Epidemiology* online.

<sup>1</sup> Lecture at the Norwegian Society for Medicine, published Norwegian Journal of Medicinal Science, vol 93, 1932.

<sup>2</sup> Translated by Joan Linden Kristiansen, Fredrikstad, Norway.

For infancy and early childhood years we find high and steady values, lying between 31.6 and 37.2 per 10,000 until 1901–1905 when the drop to 20.0 per 10,000 starts, and later continues to 9.4 per 10,000 during 1926–1930. For the age groups 20–25 years of age we also show here high and steady values, lying between 42.3 per 10,000 and 47.4 per 10,000 from 1891–1895 and the same for the 1921–1925 period; as it was first then that a smaller drop from 45.0 per 10,000 to 42.8 per 10,000 appears and then for the five year period afterwards we see a considerable drop to 31.5 per 10,000.

During the twenty years from 1901–1920, it appears therefore that the tuberculosis mortality for adults seems not to be influenced by the prophylaxis which seemingly must be considered as one of the most important factors for the large and steady decline of the child mortality rate which takes place during the same two decades.

And vice versa, the real decline in mortality for the age group 20–25 first takes place when the generations from 1900–1910, with their declining values from age group to age group, have reached adulthood. Thus, this notable drop for the adults in the 1920's to 1930's neither comes too early nor too late.

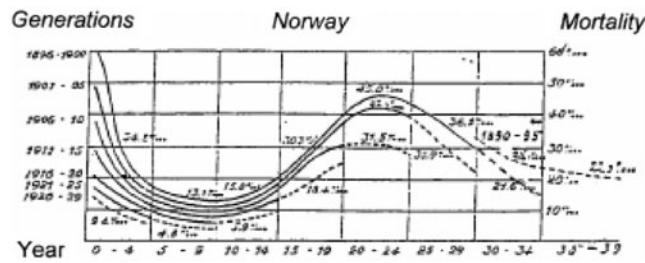
Can one, by objective consideration of these facts, find any better explanation for this than to assume that these tuberculosis mortalities described here, for the age groups 20–25, cannot have been primary infections that have occurred in adulthood but must, in the main, arise from infections during childhood, as the mortality for this population group as adults first starts to decline from that time when they have been replaced by less and less seriously affected generations? This view should at least be kept in mind during my presentation. And now I will proceed to describe the generation curves as they now exist.

We start with Norway (fig. 1) as we have more knowledge about the generations here and we see, as previously mentioned, how these mortality curves decline steadily in an almost schematic way, follow each other from age group to age group, and what is especially noticeable is the law-directed course of the diagrams, as each curve clearly shows both to what

**Table 1** The course of tuberculosis mortality in the age classes

A: 0 – 5 years, B: 20 – 25 years

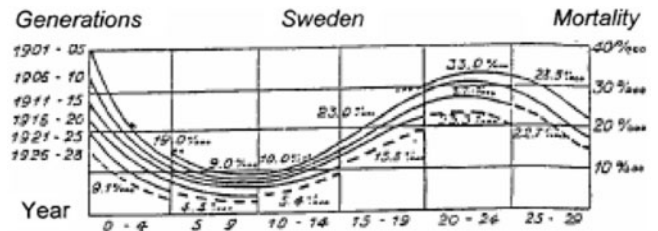
	1871	1876	1881	1886	1891	1896	1901	1906	1911	1916	1921	1926
	1875	1880	1885	1890	1895	1900	1905	1910	1915	1920	1925	1930
<b>A</b>	35.1 ‰/1000	36.2 ‰/1000	37.7 ‰/1000	32.6 ‰/1000	31.6 ‰/1000	34.4 ‰/1000	26.0 ‰/1000	20.3 ‰/1000	16.8 ‰/1000	13.9 ‰/1000	11.2 ‰/1000	9.4 ‰/1000
<b>B</b>					42.3 ‰/1000	44.7 ‰/1000	47.4 ‰/1000	45.3 ‰/1000	44.6 ‰/1000	45.0 ‰/1000	42.8 ‰/1000	32.5 ‰/1000



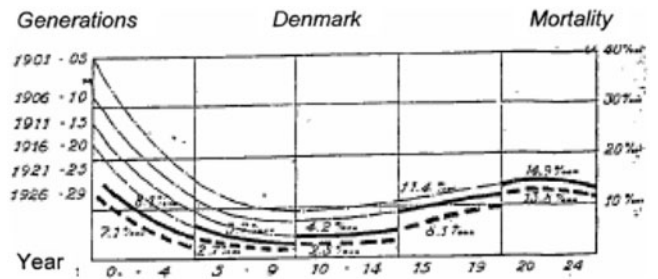
**Figure 1**

extent the generation is affected and, at the same time, tells us the direction of the probable course. It was this characteristic parallelism and uniformity of the course from one generation group to another which Professor Meidell referred to so regularly and which he maintained was a nearly certain proof that there must be certain realities behind these mortality values. The total picture reminds us, as I have said previously, about a rolling, steadily decreasing, wave which, in the case of Norway, comprises seven five-year generations including the one from 1896–1900 which started with a tuberculosis mortality rate of 34.2 per 10,000 for the first years of life, upto and including the one from 1926–1930 which has now started with 9.4 per 10,000; whilst the generation group from 1896–1900 can be followed through 35 years, the group from 1926–1930 has just begun. The other curves fill, as we can see, the in-between section, and at the extreme right one can see the last part of the curve for 1890–1895; it shows how these older generations, before the characteristic drop started, in all probability will come to represent high mortality values throughout life.

Therefore, this presentation with the generation curves, appears to indicate very clearly that if the tuberculosis mortality starts to fall during the early years of life then the drop continues within the same generation, and further from age group to age group,



**Figure 2**



**Figure 3**

at least through the years we have been able to follow the course of the generations i.e. 35–40 years.

Thus, the course of the generation curves decide, for a very essential part of the mortality value, the load with which the curve starts and this forms an intimate, almost proportional relationship between the two mortality maxima, one for the first years of life and one for the age group 20–25. It augers well for the future that the tuberculosis mortality rate within the growing generations in this country has decreased remarkably during the later years. For the last started generation, the one from 1926–1930, Denmark shows 7.1 per 10,000, England shows 8.8 per 10,000, Sweden shows 9.1 per 10,000, and Norway shows 9.4 per 10,000, and we see that Norway is fast

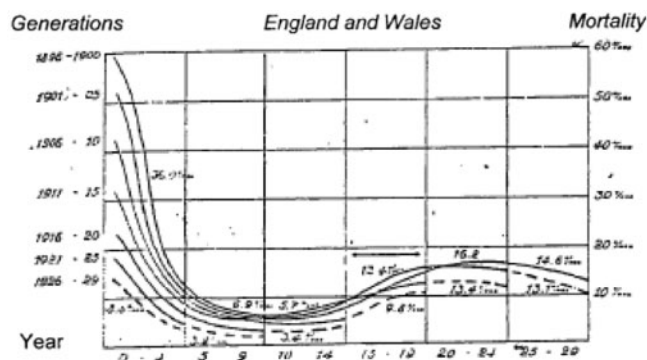


Figure 4

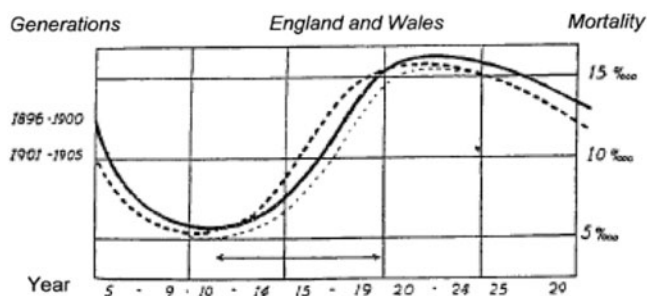


Figure 5

approaching the corresponding values of the other Nordic countries.

Then we get to Sweden (fig. 2) and Denmark (fig. 3). For these two countries the necessary statistical values are only available from 1911 and 1920, respectively, but, in spite of this, we also find here the same characteristic picture of the course of the tuberculosis mortality for the generations, but the curves flatten out and become less steep as the mortality values here lie at a lower level, especially with regard to the first years of life and the ages between 20 and 30. Sweden is almost a horse's head in front of us and Denmark is a good step ahead of Sweden and, if we therefore compare our mortality values with those of these two countries, then we can get an even better picture of the direction of the probable course we can assume we will experience.

At the same time, we must not forget that this so called "regular course" of the curves, to a greater or lesser extent, is shown to be influenced by deviations sometimes in an increasing, sometimes in a decreasing, direction. As far as Norway is concerned, a relatively small but noticeable increase of the tuberculosis mortality is found for the age group 15-20, within the 1901-1905 generation, as this curve, as we have just seen, during its relatively large increase at this time, almost coincides with the above lying curve.

Statistically, a noticeable excess of tuberculosis mortality was found amongst our young women, and one assumed it was a female problem as they had, to a

**Table 2** Reduction in tuberculosis mortality during the five last years in the age group 20-25

	Initial Mortality per 10,000	Reduced mortality per 10,000	Rate of Reduction
Denmark	14.9	13.8	8%
Sweden	27.1	23.8	12%
England	15.8	13.4	15%
Norway	42.8	31.5	26%

large extent, during these years, moved in from the country to the large cities, and had not tolerated the associated physical and psychological strains, particularly at this stage of life. An even more extraordinary rise in tuberculosis mortality we find for England (figs. 4 and 5) within the growing population group during the war years, the increase, as we can see here, is of a completely temporary nature as the respective generation curves fall back to the regular course very quickly.

But we have also deviations in the opposite direction, that is not increases but, for example, an unexpected or large drop in the tuberculosis mortality; I refer to the large drop which has just taken place in Norway between the 20 and 25 years age group within the 1906-1910 generation, a considerable fall from 42.8 per 10,000 to 31.5 per 10,000, which is even more noticeable when we, as here in this table 2, gather these values and compare with the corresponding values for the other Nordic countries. The tuberculosis mortality for the same time period, measured in percent, has sunk in Norway three times more than in Denmark, and twice that in Sweden.

To be able to demonstrate, evaluate and follow these rather temporary deviations it is of great importance to study the course of the mortality from generation to generation.

Thus, it would be of great interest to look closely at what factors have had the most positive or negative effect during such deviations, but unfortunately we cannot tackle these important issues here.

At least, there are very encouraging and remarkable results which the fight against tuberculosis can demonstrate at home here in Norway.

During the last three decades, from the five year period 1896-1900 the total mortality from tuberculosis up to 1920 has been reduced from 31.0 per 10,000 to 15.8 per 10,000, the mortality per 10,000 has thus been halved and the number of deaths from tuberculosis has been reduced from 6726 to 4420, i.e. 2300 in total. The institutions, the men and women, that during the years of the struggle, have carried the burden and who have keenly striven to work for the cause, to these men and women we certainly owe a debt of gratitude and they deserve our warmest appreciation for the work well done; not

least when we take into consideration the difficult conditions that existed in our country, particularly to begin with.

The etiological conditions regarding tuberculosis have with us, as elsewhere, been the subject of thorough scientific investigations and it has become clearer and clearer how differently the disease appears clinically and prognostically when it is from a younger or older date within the respective geographic regions. This was made clear, as we recall, through Heitmann's presentation of the mortality of tuberculosis within the southernmost and northernmost counties in Norway. During his presentation here at our Society in the spring of 1930, the consultant proposes that according to his opinion one immediately starts to consider biological conditions i.e. on the question of whether a generation immunity exists, a kind of immunity that contributes to the decline of the illness, where it has reigned for years as a community disease and that the lack of this can be a contributing factor to the large increase in the northernmost counties.

Through Heitmann we invariably come to the description of the different ways individuals react to a tuberculosis infection. The interesting studies and examinations which, during the later years have been carried out in the Scandinavian countries regarding the primary tuberculosis behaviour especially in adulthood have, I would suggest, contributed much directly, as well as indirectly, to throw light on these conditions, at the same time as they have invariably taught us to more critically consider the importance and extent of the Pirquet reaction. It is, in particular, investigations by Schell and Heimbeck, Arborelius, Heckscher and Würtzen, that I am thinking of, and I shall now attempt to draw a number of practical conclusions from these in the light of what my generation curves can tell us.

It is apparent that the above mentioned studies regarding the behaviour of primary tuberculosis have, in the main, been carried out within the part of the Scandinavian population which has now reached the age of between 30–35 years and which therefore belongs to the generation period 1901–1905, and if we examine the tuberculosis mortality within this period for the 20–25 year age group, the part of life which is relevant here, then we find the following values for the three Nordic countries: for Norway 42.8 per 10,000, for Sweden 27.1 per 10,000, and for Denmark only 14.9 per 10,000. Therefore, we find during the years 1920–1925, within the same race, same generation and age group a remarkably large mortality difference for these three countries as Norway has nearly three times the number of deaths as Denmark (Table 3).

These mortality values within the age group 20–25 mentioned here comprise both the cases where the beginning was in infancy, and where it must be

**Table 3** The generation period 1901–1905 for the three Nordic countries which demonstrate for the age group 20–25 (1920–1925), a tuberculosis mortality of:

Norway	42.8 per 10,000
Sweden	27.1 per 10,000
Denmark	14.9 per 10,000

considered as a consequence of primary infection in adulthood. Therefore it is of the utmost importance to try to unravel which part of this mortality can be attributed to the one or the other of these phases of life.

In connection to what we have just demonstrated with regard to the pronounced mortality differences that appear to be present within the three Nordic countries, we shall now proceed to investigate in what way the living population in these same countries, notably also during adulthood, reacts to an acute tuberculosis infection.

Thus, we will first look at the conditions in Denmark. According to the observations of Würtzen and Heckscher, it appears as if men and women in adulthood very seldom display clinical symptoms when they get their primary infection and their Pirquet reaction switches from – to +. At Oresund Hospital 22 pupils showed, in this context, no sign of the disease and Würtzen claims the reason for this benignity which the tuberculosis morbidity seems to exert in Denmark is that there might be a certain immunity that comes into play with regard to the primary infection in adulthood and the re-infections; the observations made at the hospital in Copenhagen by Meulengracht and Bechschoft-Nilsen support this.

Heckscher's examination of recruits gives similar results. Of 8,000 in service, 13.4% went from – to + Pirquet, and the consultant says that indications of unhealthy conditions were so rare that they could not be statistically evaluated, and Heckscher further says that the primary tuberculosis for the adult population in Denmark appears in very few cases as an illness.

He maintains, therefore, how much better the conditions are amongst the recruits in Denmark compared to Arborelius's reports from Sweden and further expresses the assumption that the different way tuberculosis behaves within the three Nordic countries can be associated to different biological and epidemiological factors which are, as yet, unknown.

With regard to the conditions in Sweden, it is clear from Arborelius's work that he regards the prognosis for the tuberculosis primary infection in adulthood to be relatively benign. For the recruits who became positive to the Pirquet reaction whilst in service, most of them were very mildly infected as clinical symptoms could only be reported in very few, probably only 4%; the annual mortality of primary infection in the 20–25 years-of-age group, should not account for

more than about 1 per million. In a letter to myself dated July 6 1931, Dr Arborelius asks me to regard these mortality values with some reservation and he writes that he could only follow his tuberculosis patients for too short a period and his prognosis studies related to a somewhat different material. Relatively speaking, we get the distinct impression that the Swedish population below 20 to 30 years of age does not display the same resistance to the primary infection as the Danish population, and if we come to Norway it seems that the conditions are less favourable than in Sweden.

In Norway, we have the interesting Scheel-Heimbeck's investigations from Ullevål as a comparison and as far as I can understand, it seems as if the clinically proven tuberculosis morbidity among the nurses who were infected during service goes up to 8-10% per year as a mean value and thus lies two, if not three times, higher than the corresponding value for Sweden. With regard to mortality the material has not been completed by the author but it would not surprise me if the value is shown to be much higher than in Sweden, probably going up to 2-2.5 per million.

The results from the investigations in the three Nordic countries concerning the receptivity for, and the frequency and course of the primary infection in adulthood, can, unfortunately, not be directly compared as the given values cannot be described as completely commensurable, for one thing because there does not appear to be full agreement about which clinical symptoms that must be regarded as pathognomic for the conception of "tuberculosis primary infection in adulthood". On the contrary, they provide us with very clear impressions of the relative circumstances between the countries within the mentioned generation. And we are well within our rights to state that while the Danish population must be considered as remarkably unreceptive for the primary infection in adulthood, and while Arborelius regards the prognosis for this disease as relatively benign for his recruits, then for us, especially in the north of Norway, the primary infection in adulthood is often of a more serious nature and probably the cause of a considerable part of the total tuberculosis mortality.

In 1923 I tried to assess on the basis of what was then known within the different disciplines to make up my mind about how large a part of the total tuberculosis mortality could be said to be attributed to the primary infections during adulthood. I then came to the conclusion that these infections probably were only responsible for 10-20% of the total mortality; this within populations with about 3 per million tuberculosis mortality and where the tuberculosis had been active for generations because, as I wrote at the time, "I have no doubt that in many of our isolated areas with a diffuse population, in areas where the

illness is of a relatively new date, it behaves in a completely different manner and there we will surely find different, several serious primary infections also among adults". I came to that conclusion ten years ago and, in the main, this view has only been strengthened by the subsequent studies.

The north of Norway, and here especially in Finnmark, is shown, as previously mentioned, to be very poorly placed; here the total tuberculosis mortality still remains twice as high as for the southernmost part of the country, and, according to the recruit investigations of 1924-1925, the same was also the case with regard to the tuberculosis morbidity amongst the 20-21 year olds. A native Finnmark man of 20-25 years old, with a negative Pirquet reaction, can, therefore, not be compared with a negatively Pirquet-reacting Dane of the same age; as they are approximately opposites, as we find within the same generation group 5-6 times higher tuberculosis mortality in Finnmark than in Denmark, a mortality of which probably 20-30% in the north can be attributed to the primary infection in adulthood. We would, of course, find an even greater contrast if we went further and took the coloured races into the comparison.

Just as the positive Pirquet reaction can be considered as a benign sign for a very large part of the growing population, it can, on the other hand, for a very limited number, let me say 5-7%, be one of the many, although often vague, symptoms of the person in question carrying a tuberculosis process of a very serious nature, a suffering which, in my opinion, is normally started in the first 3-5 years of life, which in the majority of cases will result, sooner or later, in death. To distinguish these two prognostically so different forms from each other, before the suffering as manifested itself, is yet not within our power; anamnesis, x-ray, blood pressure, obsonin index and blood picture helps us on the way and clinically no-one skilled in the art has described these partially latent forms better than Grancher; but in spite of this, we are still left fumbling in this area.

And when it comes to the negative Pirquet, it is, as we have just seen, also the soil, the reaction modus of the organism and the receptivity which play the main roles for the formation for the start of the primary suffering and its course in adulthood; for if it was the negative Pirquet as such that was decisive, how can we explain that, for example, in Norway the tuberculosis mortality between the 15 and 30 year olds has fallen so remarkably in the last decade at the same time as the inhabitants with a negative Pirquet reaction seem to have increased in the very same time period. Does not the proven decline of tuberculosis mortality from generation to generation just as the so different receptivity for the primary infections in adulthood indicate that there must be biological factors that play a role, factors that we still do not

know but which cannot be ignored? The Pirquet reaction only tells us about whether an individual has been infected with tuberculosis or not, but it tells us little or nothing about the receptivity, the prognosis and the clinical course, as we can encounter the largest contrasts with the same Pirquet reaction with regard to the course of the disease and the prognosis. See, for example, the difference there is in tuberculosis mortality among the positively reacting children for the first three to four years of life and the corresponding numbers for another child age; I should think the difference is at least 20 to 1, and we know that as many children die of tuberculosis in the first five years of life as in the next ten; and we must not forget that even if 5–7% positively reacting children for the first 3–4 years of life constitute a rather large number infected to cover the whole of the total tuberculosis mortality for all age groups; I think particularly here about the morality which exists with us at the moment of about 1.5 per million. From this point of view, there is therefore in reality nothing to prevent one from assuming that the largest part, let me say 75–80% of all individuals who later die from tuberculosis have got their primary infection at this stage in their lives.

Within the three different Nordic countries there was a large difference regarding the death values for tuberculosis with, as said, Denmark having 14.9 per 10,000, Sweden 27.1 per 10,000, and Norway 42.8 per 10,000 for the age group 20–25, there also seems to be the same relative situation between the countries regarding the living population's receptivity and reaction modus as for the primary infections in adulthood.

The Danish population seems, in this regard, to be in the most favourable position, the best immunised; clinical symptoms are given as a rare, indeed a very rare, occurrence within the primary infected groups and the prognosis is set to be completely benign. The Norwegian population probably shows a more changing situation for the different parts of the country, but it is for certain, regarded as a whole, in the worst position, poorest immunised, as Sweden also here seems to take up a middle ground, with clinical symptoms for very few (about 4%) of the infected, relatively good prognosis and a morality which only seems to make up a smaller part (10–15%) of the total tuberculosis mortality. As previously mentioned, we lack, in this area, exact values for a direct and thorough comparison between the three countries and

I have, therefore, as we can see, had to express myself in rather general terms.

To have a well-founded opinion about the clinical course of tuberculosis and its prognosis, it will, therefore, be in many cases very important to find out to what extent the local population, as well as the generation in particular, shows itself to have been infected by tuberculosis, not least during the first years of life. The same is true for a comparison of clinical observations from different time periods and different countries and different regions. The obtained scientific results may well be correct and well-founded, but as absolute values they cannot always be used in a comparison without further explanation; in this context, as we have seen, the tuberculosis picture is far from always being the same. On the contrary it is, in certain cases, subjected to the law of change – and also for these reasons – it is therefore of great significance that tuberculosis is examined generation by generation. I mention this to generate understanding for all parties as the different opinions in this area are often unnecessarily contrary or critical of each other.

In my opinion, the scientific experiences of the last years also seem to support the opinion I have expressed earlier that tuberculosis behaves as an infectious illness closely tied to one family and one generation which gradually changes character and becomes more and more benign as the resistance of the generation seems to increase through a certain adaptation, or if one wants, through a probable innate immunity.

It could also be the case that the increasing benignity which the illness gradually shows could stem from the virulence of the tuberculosis bacteria itself which gradually, in one way or another, becomes more weakened, thus it was not the organism itself, the soil as such, which here played the main role; an opinion which does not find much support in the experiences made so far in this and similar fields; in spite of this, we ought to include this important factor in the equation too.

All in all, because of certain undisputed facts which the later years have brought us, each and everyone of us will find, sooner or later, that we have to change certain aspects of our understanding of the etiological condition of tuberculosis.

Time will tell.