Commentary: Kristian Feyer Andvord's studies on the epidemiology of tuberculosis and the origin of generation cohort analysis

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Accepted 3 April 2008

The Norwegian physician Kristian Feyer Andvord (1855–1934) who had no training in epidemiology, observed differences in mortality rates from tuberculosis between counties in Norway late 19th century and started in the 1890s to speculate on why the rates differed between counties and had fallen for infants but not adults. This triggered him to spend his career on the natural history of tuberculosis by means of population data and made him suggest that primary infection with tuberculosis mainly takes place in childhood and that falling mortality rates at the time of observation was a reflection of exposure early in life.1 Wade Hampton Frost later published a similar idea citing Andvord, and in 1939 he introduced the concept of ‘cohort’.2 This seminal paper by Frost is widely known in epidemiology as it marks the birth of the concept vital to the discipline’s self-identification.3–6 Less attention has been paid to Andvord predating Frost in introducing a means to elucidate the natural history of diseases, which has had such a major impact on epidemiology as an analytical discipline (Figure 1).

The scientific community in the inter-war period when these papers were published took a keen interest in how factors early in life could result in a weakened ‘constitution’ and give rise to increased risk of ill health later in life, which has been described elsewhere in an Anglo-American context.7 A few references have been made to Andvord’s 1930 publication that due to its German translation has given it some international attention as one of the first of its kind.5,6,8,9 Rather than attempting to contribute in a contest of ‘who was the first to do a cohort analysis’, it appears as if scientific progress of this method took place in different contexts. All the way through his work, Andvord’s main objective was to identify the age dependent susceptibility of primary infection and explain later life clinical manifestation of the disease by relating patho-anatomical evidence and clinical accounts to macro-level patterns of mortality statistics.

By drawing a line from the very start of his scientific career in 1889,10 it becomes apparent that the method itself evolved from a context much earlier than the 1930 publication alone suggests.11 More than 40 years of his working life he spent on studying the natural history of tuberculosis, in the first place by means of comparing first geographic pattern and later birth cohorts. This period coincided with major changes in the scientific conceptions of tuberculosis and diseases in general and with political and ideological notions of prevention. Here, we would like to follow the origin of this method in the work of Andvord and the causal inferences he made in this process.

Who was Kristian Feyer Andvord?

Andvord was born in the Southern part of Norway in 1855. His parents, brother and sister died from tuberculosis. At the age of 24, Andvord contracted tuberculosis while he was studying medicine and was admitted to the Tonsåsen sanatorium in 1879 located in the mountains in Valdres, Eastern Norway. After graduating in medicine in 1882 he worked as a general practitioner in Valdres for several years and junior doctor at The National Hospital for some months. He then moved to Kristiania (Oslo) to work as a general practitioner until his death in 1934. Every summer until 1916 he worked as a head physician at Gausdal sanatorium (Figure 2).

Andvord went on study trips to several countries in continental Europe and Great Britain. In 1903, he went to Lille (Institut Pasteur) and London.
Brompton Hospital) to study serum therapy and modern tuberculosis surgery. From early 1900, he participated at international conferences on tuberculosis, and in 1902 he was elected as one of the vice presidents in the International Union against Tuberculosis and Lung Disease.

From geography to generations

Andvord was an author of 24 publications in Norwegian on tuberculosis, the first one published in 1889. Around 1890, he speculated on the various health effects of climate on risk of tuberculosis and therapeutic effect of placing patients in sanatoriums in the mountains. He brought this aspect into another publication ‘On the prevalence of tuberculosis’ (1895), where he proposed several potential explanations to the geographical variability of tuberculosis mortality. He gradually excluded the possible effect of climate because even if mortality rates were high in the far north, in counties like Finnmark with rough weather conditions, they were also high in the more pleasant counties in the south, Agder and Rogaland (Figure 3). Rather, he suggested that the observed differences might have their origin early during the life course. In later reference to his early work he stated that:

It was the frequency of the disease in Kristiansand [Agder county] which first gave me evidence that my impression was correct. Even back to the end of the 80s it appeared to be a substantial and increasing fall in childhood tuberculosis even though – despite increasing levels of prevention/prophylaxis, the mortality of pulmonary tuberculosis among adults remain high.
In the paper from 1895, he aimed at comparing prevalence of tuberculosis between areas of Norway. He further asked:

In which forms and frequency does tuberculosis occur through different periods of life? In terms of frequency, how is the disease in adult age related to the disease in childhood? ... Which influence do certain acute and chronic ailments have on the processes of tuberculosis and their development in various age classes? ... When – within which life period – and through which pathway does the infection with tuberculosis usually take place? (p. 2)
In this article, which in fact reads more like a thesis with 96 pages including 46 tables, he compared percentage mortality rates of tuberculosis from total mortality in different counties. He also compared mortality rates for different forms, such as pulmonary, scrophulous/glandular and miliary tuberculosis. The ratio between these was strikingly similar even though the base line rate between different areas differed widely. He also noted the constancy in mortality rate from year-to-year in specific areas in all forms except during the first year of infancy in contrast to the great fluctuations in mortality from childhood respiratory infections, like laryngitis. This made him think of tuberculosis more like a chronic disease.

Tuberculosis seems to appear in a different way than the epidemic diseases, as it within the same area kills similar number of individuals each year – all forms included – and when there is an increase or a decrease under all circumstances this appears to follow very smooth curves; it is as if the number of deaths one year proportionally follows that in previous years. (p. 19)\textsuperscript{15}

The various forms of tuberculosis seemed to be related in such a way that even when mortality rates differed, such as Stavanger Amt (Rogaland county) having the double of that in Kristians Amt (Oppland county), the ratio between pulmonary and the other forms was the same: 3.5. It was also puzzling to find that tuberculosis mortality followed all cause mortality when areas were compared. He ended this extensive publication by providing a genealogical account of a family heavily affected by tuberculosis through generations supporting a growing idea in him that the disease is strongly mediated by families.

In this article he also presented rates in different age groups and showed how these rates dropped in childhood and started to increase later in adulthood— which he repeatedly through his work characterizes as the rolling movement of the disease. This pattern was similar even if the rates differed when he compared Norwegian and European cities (Figure 4). From these early observations at population level he concluded that: ‘...as the disease is more or less common in childhood this will be followed similarly with the disease in adult age’. He was particularly convinced of this relationship at that stage because of the proportional relationship between pulmonary tuberculosis mortality in adult age and total mortality in infancy. Based on these mortality data, clinical observations and patho-anatomical findings from autopsies he then proposed (1908) that a decisive immunological defence probably starts early in life making various clinical trajectories more or less likely: a fulminant deadly one in infancy, a benign glandular
Andvord and the concept of cohort

Writing for a Norwegian speaking audience of physicians, Andvord did not use the term ‘cohort’. He rather referred to generation and ‘brood’ or ‘generation’ when he analysed mortality rates from tuberculosis in different age groups and stated that:

...the frequency of infection in infancy seems to indicate the mortality death rate in later years of life, a fall in mortality in infancy being invariably followed by a similar fall 20-25 years later among adults.11 (p. 660)

Andvord proposed in 1908 what he called a population frame which based on the age composition of the population he interpolated mortality from tuberculosis and numbers infected in different age groups (Figure 5).17 This population frame was conceptually similar to a closed population. As the mortality rates in the early decades on the 20th century eventually had started falling in Norway too he was able to present the parallel curves of successive birth cohorts and conduct what Sir Richard Doll later has referred to as a generation cohort analysis designated by the component of the population born during a particular period and identified by period of birth.5 This is in contrast to the modern use of cohort as when used to describe any designated group of persons followed or traced over a period of time. And correspondingly, according to Doll, cohort studies traditionally referred to the disease experience of people born at different periods are compared, properly named a generation cohort study. The more common and modern type of cohort study consists in defining groups of individuals by some variable (such as place of residence) and follow them up to see if incidence rates differ by this variable.18

Figure 5 A ‘population frame’ based on a population of 200 000 individuals with a yearly tuberculosis mortality of 3/4% (750 individuals)
Source: Reference 17.

*Graph No. 1 (———) illustrates latent tuberculosis. Graph No. 2 (-x-x-) illustrates more or less latent and benign glandular tuberculosis. Graph No. 3 (-----) illustrates frequency of latent tuberculosis bacillae detected after inoculation on animals. Graph No. 4 (-xx-xx-) illustrates according to Sophus Bang ‘undoubtedly healthy, macroscopically verified tuberculosis’ as secondary finding in 6006 autopsies. Graph No. 5 (-o-o-) illustrates according to Prof. Grancher clinically detected early stages of tuberculosis among Parisian infants and adolescents. Graph No. 6 (-.-.-) Glandular tuberculosis clinically detected. Graph No. 7 (-..-..-) Positive tuberculin reaction in healthy individuals
Andvord’s causal models

There was a dramatic decline in tuberculosis in developed countries during the 20th century (prior to the introduction of effective drugs).19,20 This decline has been attributed to many factors, such as improvements in housing conditions and nutrition, reduced crowding and segregation of infectious cases. The extent to which the reduced morbidity was attributable to a reduction in infection transmission per case, as opposed to a reduced risk of developing disease among infected individuals, is unknown.19 All these factors (crowding, segregation, susceptibility) are potentially mediating the strong social pattern of tuberculosis morbidity and mortality observed across populations.21 For this reason, it is remarkable how little attention Andvord paid to the social environment for the evolution of the disease through time and its’ natural history in individuals, although he recognized poor people’s suffering and the potentially contributing factors of ‘spiritual elasticity for the life energy’ grounded in climate and living conditions in his early works.13,22 But in his last paper, published post-mortem in 1935 (p. 607), the emphasis was much clearer:

If we want to make up our opinion about the deeper regularities which seem to be governing the course of tuberculosis, it seems to me as if nature aims to increase the body’s defensiveness – its resistance for the microbe, partly inborn and partly acquired through the life-course by benign processes... As second main explanation I would put the increasingly more effective prophylaxis, particularly for the children. Hygiene, therapy and the social conditions of course have some influence on the mortality – but the effects appear NB! according to my generation tables – to be of limited temporary importance, and they do not seem to any substantial degree to shift the ‘regularity’ of the generation curve. These temporary deviations might be of interest, as they point at ‘extraordinary condition’ which could have been of importance in ameliorating or deteriorating direction.23

Andvord’s main attention was on the regularity of the mortality rates in different age groups as a reflection of how susceptibility (possibly through raised immunity in the population) changes throughout life. These changes, which he from hindsight inference denoted the two maxima and minima of the disease, were effectively ‘increasing resisting power to primary infection of tuberculosis’ after the age of 3–4 years. When he compared mortality rates in Norway with Sweden, Denmark and England/Wales the similarity of the age distribution is mainly seen as confirmatory and indicating how the disease risk runs through the life course in individuals. After rejecting that differences in mortality rates between areas were due to differences literally in the soil or climate, he eventually metaphorically moved to seeing these population differences as properties—a process of immunization—as the soil within the population. The fact that Denmark England/Wales and Sweden in decreasing order had arrived at lower mortality rates than Norway, Andvord considered a consequence of nothing less than the larger size (England/Wales and Sweden) and concentration (England/Wales and Denmark) of these populations. He acknowledged that this new method of following generations could provide distinct interpretations at both individual level (the age dependent susceptibility of tuberculosis) and population level (the differential mortality rates across historical time and geographical areas). The immunological change he thought was responsible for these population level contrasts, could be seen as what is later known as herd immunity or the average level of immunological resistance to a given microbe in the population—well known for childhood viral infections where thresholds of susceptibility might be decisive for epidemics to occur but with uncertain role for tuberculosis.24,25 But Andvord was more in favour of seeing the decline, and the fact that the disease seemed to run in families, as evidence of acquired and inborn immunity.

In the author’s opinion the scientific experience of the later years are in support of my opinion, also maintained by me in earlier years, that tuberculosis has turned out an infectious disease decidedly belonging to the family and the generation, becoming constantly more benign, in proportion as the resistance of the generation seem to increase as a result of a certain adaptation or, as it may be expressed – a probably inherent immunity,26 (p. 495).

Selective survival of population groups with inborn resistance to tuberculosis has been proposed as one of the potential explanations of the historic decline, but has been evaluated as unlikely given the rapidity of the decline. Genetic mutations are not likely to change sufficiently to alter host resistance for tuberculosis over the scope of a few generations.27 Today Andvord probably would have been accused of committing what is known as an atomistic fallacy: inferring a causal relationship at the individual level (acquired and inborn immunity) what is more appropriately located at the ecological level (population differences in exposures).28 After all, the generation cohort analysis is essentially an ecological approach, and Andvord was never explicit about this distinction.

Tuberculosis—research and public health in Norway: Andvord’s contributions

The Norwegian population was heavily struck by tuberculosis. Reasonably reliable statistics show that adult mortality overall in the country increased from late 1860s reaching a peak around 1900 and then declined substantially.29,30 As Newsholme noted in
1908 Norway, Ireland and France were exceptions to the general decline that had started in many other countries half a century earlier.31 In 1885 mortality was highest in the most southern counties of Norway. The increase and subsequent decrease in mortality took place in different counties in different periods. There was an increase until 1906–10 in Sør-Trøndelag and Finnmark, until 1911–15 in Sogn og Fjordane and until 1916–20 in Nordland.

Even if Andvord’s scientific findings and theories were controversial, he steadily gained support.32 Already in the 1890s, he became influential as parts of his statistical evidence were used as foundation for the new tuberculosis act of 1900. It was solely based on a bacteriological approach where isolation and disinfecion were the primary tools for combating the disease.33 He was very active in the public debate on how to combat tuberculosis, and he inspired both private and public actors in setting up tuberculosis sanatoriums. Earlier on in his career he introduced mountain climate as medication.10 However, as Hans Jacob Ustvedt noted in 1955, Andvord never became an ‘authority’ or a ‘pope’, but his independency might also ultimately have been his advantage.34 He worked long hours as a family physician during day time and on his research in the evening. Without any influenential position in the academic field, his effects on policy had to be somewhat limited.

Andvord’s theory on the importance of tuberculosis transmission in childhood gained increasing recognition in 1910–15.34 The theory was also supported by another colleague, Dr Frølich, who conducted a school health survey in 1913 among 3000 school children in Kristiania (now Oslo). He was able to show that 80% of the pupils at the age of 7 had a positive tuberculintest. Among working class pupils this was 90%. After 2 years follow-up this had increased to 85% in the whole sample. Transmission among the working class children had a more malign course than in other social classes. For this reason it came as a huge surprise when the two doctors Johannes Heimbeck and Olaf Scheel in the 1920s documented that primary infection in childhood might not be as important after all.35 They investigated nursing school students in their 20s at Ullevål hospital in Oslo, and found that 46% were probably carriers. After finishing their training 100% of these students were Pirquet positive. The students were mostly recruited from the middle-class.

The conception of tuberculosis changed during the inter-war period. By the beginning of the 1930s when social and radical movements became stronger, the concept of disease aetiology became increasingly ‘socialized’. In Norway as elsewhere, influential physicians underlined the importance of disadvantaged economic and social factors on tuberculosis mortality; crowded houses, poor sanitary conditions, inadequate nutrition. ‘The social structure alone’, an anonymous commentator wrote in 1931, ‘is in reality decisive for tuberculosis as a mass disease…Bacteriological tools for prevention are powerless alone when confronted with these laws’. But medical doctors, including socialist doctors, were also inspired by more genetic explanations and eugenics in this period.36,37 In 1934 gypsies, alcoholics, criminals, prostitutes and mentally disabled persons were included in the national programme for sterilization, which was passed by the Parliament (Storting) against one vote.

Andvord was persevering in his lifelong quest for proving that primary infection took place in childhood, despite the new evidence provided by Heimbeck and Scheel. According to Ustvedt, Andvord’s theory on the importance of childhood was probably true at the turn of the 19th century, particularly in urban areas. But increasingly, historical and geographical issues were regarded as important, and tuberculosis needed to be looked at from ‘a dynamic point of view’, as Ustvedt put it:

Not least because its occurrence varies so much between time-points of exposure to the contagion and the outer living conditions, which is so important for host resistance, the conditions may vary between countries and between regions within a country, the disease may pass different historical phases, in which time point of infection may have changed, partly because of prevention of transmission and improved living conditions. Andvord’s scientific contribution is related to one particular phase of this development.34 (p. 115)

Context

The development of epidemiology as a distinct discipline has been divided into different eras.33,38 These changes took place in Norwegian medical science as well. They did not, however, necessarily take place overnight as old paradigms of disease aetiology coincided with new ones. Epidemiology, originating from demography in the first part of 19th century, increasingly gained status as an independent discipline in the sanitary era from the 1850s to 1880s. The dominant understanding within the miasmatic paradigm was transmission of disease through contaminated air and water under the influence of telluric forces. Besides, pathology and geography were closely related. After Koch’s discovery of the Tubercle Bacillus in 1882, the year Andvord graduated medical school, epidemiological methods became important to study transmission mechanisms rather than large-scale analysis of secular trends and geographical variation. This shift signified a departure in perspective from structural causes at societal level.

Kristian Andvord represented this new epidemiology and the bacteriological understanding of disease transmission and prevention. In his concluding papers from the 1930s he referred to the ‘laws of nature governing the course of tuberculosis’. This was a rather deterministic and evolutionary way of
reasoning influenced by the eugenic explanations at that time, and which had implications for public health measures. Andvord also belonged to a distinctly Norwegian tradition. A common denominator for population health research in Norway until quite recently, has been geographic differences in health rather than individual socioeconomic position. Urbanization and industrialization took place rather late in Norway. And with the different parts of the country spread across a wide variety of climate and topographical conditions, geographical disparities have been seen as most relevant. In the 1850–60s the grounder of Norwegian sociology, Eilert Sundt, published a number of studies on different subjects, such as folklore, hygiene, nutrition and mortality. In an extensive investigation on mortality in Norway, published in 1855, he proposed a broad perspective on determinants of population health and included geographical differences and climate as important potential factors. He introduced conceptions of regularities in studies of society, much inspired by natural sciences. Sundt’s ideas had great impact on the production of statistics in Norway. When Det Statistiske Centralbureau (Statistics Norway) was established in 1876, the first appointed director, Kjær, was undoubtedly inspired by Sundt, as Andvord must have been. But among medical academics, Andvord’s use of population data and statistical analysis was considered as obscure and not proper science until late in Andvord’s career.

**Beyond tuberculosis—impact on epidemiology**

The impact of Andvord’s work beyond a Norwegian audience was likely to be limited given that only the 1930 publication was published in Germany. It was also translated in a few hand copies into English. Frost read this and criticized Andvord for extending estimates of future mortality based on present curves, which might suggest he was more in favour of looking at the generation cohort approach in a dynamic perspective than Andvord. It has been speculated that Frost had arrived at a similar idea independently of Andvord based on correspondence with Sydenstricker. Kermack et al. used a similar approach in 1934 looking at mortality concluding that ‘the health of the man is determined preponderantly by the physical constitution which the child has built up’ and countered the eugenic argument of inherited constitution. They concluded that inherited constitution was not consistent with birth cohort influences as mortality in the age groups subsequent to infancy, through the entire life course, continued the improvement generation by generation. It is interesting to note that Andvord gave another interpretation of the generation cohort approach. A similar approach was later picked up in studies of lung cancer in 1952 by Korteweg and subsequently by seminal studies on peptic ulcer and other cancers. More recently, Forsdahl’s analysis of the importance of childhood on the risk of cardiovascular disease in adulthood used geographic variations between Norwegian counties with historical data. This has been followed by a plethora of research into early life influences on adult diseases that build on the perspectives gained from the generation cohort approach.

Andvord’s period of acting as a professional clinician and researcher spanned between different epidemiological eras and ideologies of prevention: from remnants of the ‘miasmatic’ era in his early days via the breakthrough of the ‘bacteriological’ era and ending with the ‘social medicine’ and ‘eugenic’ conceptions dominant between the wars. His work is not exclusively positioned in any of these traditions in the sense that they represent distinct periods. As it appears what inspired Andvord in the first place was the topography of the disease in the belief that climatic factors and properties of the soil could explain the pattern. But by the end of the century he put less emphasis on this theory and gradually built a theory on the role of acquired and inborn immunity. Eventually, as tuberculosis mortality in Norway decreased or plummeted during the early decades of the 20th century, he was able to look at different generations and take advantage of a generation cohort design. Essentially, faithful to his idea of this phenomenon, he moved from a geographic approach and ended up with comparing different birth cohorts. But the underlying research question remained the same although he appeared to have been inspired by different causal models representing different epidemiological eras through this period. Even though the decline of the disease had not occurred in the 1890s in contrast with most countries, Andvord was able to raise hypothesis and make inferences on how risk was patterned by personal and historical time based on geographic contrasts within and between countries. At population level such geographic contrasts may be seen as crystallized expressions of how social and environmental conditions have shaped population risk in various places and in various periods of history even if the particular driving forces may be context specific.

Reflecting on his relation to the scientific community, Andvord said his ideas were ‘crazy’. All through his career he was considered as a ‘live wire’ in Norwegian tuberculosis discourse. His ideas were presented at the Norwegian medical society. He was ridiculed and received harsh criticism from academic authorities such as when they rejected the role of immunity. Gradually, but late in his career he received recognition and was celebrated at his 70th birthday by academics. And at the age of 75 he presented the generation approach and was characterized as ‘a grand young man’. But the method also received some criticism as Andvord had become
stubborn with his theory on age dependent susceptibility and gave the generation tables a somewhat rigorous interpretation.

Andvord's achievement was in several ways idiosyncratic. He never belonged to the inner circles of Norwegian medicine, as he neither obtained formal academic research qualifications, hospital post nor a chair at the University. The approach he developed has proven to be a powerful epidemiological tool. But the theories he built from this was contingent on the ideologies of the time he acted within as when he proposed climatic factors for the geographic distribution or genetic explanations for the decline in mortality. To Andvord there was no inherent exhaustive explanatory model within this approach.

Conflict of interest: None declared.

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Commentary: Reconciling historical epidemiological, bacteriological and immunological observations in tuberculosis

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Accepted 29 April 2008

Kristian Andvord had the remarkable insight that looking at cohort experience was by far more informative than a solely cross-sectional view of tuberculosis mortality data. A comprehensive paper by Andvord makes his thinking accessible for the English readership in this issue of the journal.

What Andvord unravelled is schematically shown in Figure 1a. A common presentation of tuberculosis surveillance data is reporting them as age-specific morbidity or mortality in a given calendar year. Any change in successive years becomes thereby apparent in sequential reports. Nevertheless, this approach hides whether early life experience may predict mortality later in life. That this is the case was unravelled by Andvord. Furthermore, as Wade Hampton Frost in the US extending on Andvord’s approach subsequently demonstrated, the cross-sectional view conceals the fact that, where tuberculosis is in decline, the commonly observed high tuberculosis rates among the elderly is just a residual of an even higher mortality that each generation had experienced when it was younger.

To explain the role of childhood experience on tuberculosis among adults, the ‘once infected, always infected’ hypothesis has been espoused. As tuberculosis has seemingly no finite incubation period, disease onset among adults could be satisfactorily explained by reactivation of an infection acquired earlier in life. Molecular epidemiology proves that recent infection can play a major role in low-incidence countries, and re-infection disease may contribute substantially to morbidity in high-incidence settings.

In the same decade Andvord and Frost furthered our epidemiological insight, Georges Canetti demonstrated that a large proportion of persons with clear evidence of prior acquisition of Mycobacterium tuberculosis had in fact eliminated all living tubercle bacilli from their old lesions. Although the annual risk of becoming infected with M. tuberculosis had been in the order of 10% among the children who were adults by the time they came under Canetti’s observation, in a large proportion it was not the primary, but a super-imposed re-infection that led to the disease (Figure 1b). Yet, Andvord’s epidemiological