The Danish Twin Registry: Past and Present

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The Danish Twin Registry was established formally in 1954 and thus celebrates its 50th anniversary in 2004. Here we give an account of its founding and the early years, and a brief summary of more recent progress.

Early History

Tage Kemp and the Institute of Human Genetics and Eugenics

The creation of the Danish Twin Registry was part of a general build-up in Danish human genetics research. The Rockefeller Foundation had a great impact, especially economically, on this development in Denmark. In 1929 the head of the Rockefeller Foundation’s science department, Warren Weaver, introduced “A New Science of Man” to coordinate the social, medical, and natural sciences. As part of this program, the foundation gave very considerable grants, among other things, to psychiatric and genetic research, such as Lionel Penrose’s Colchester studies of oligophrenia. The foundation’s link to Danish genetics research was the vice-managing director of the foundation’s European branch in Paris, Daniel O’Brien. In 1930 he visited the professor of general pathology, Oluf Thomsen (1878–1940), in Copenhagen to discuss research plans for genetics and took an interest in Oluf Thomsen’s young assistant, Tage Kemp (1896–1964), whose main area of interest was genetics. This resulted in some very generous research grants to Kemp, including a long stay at the Cold Spring Harbor Record Office of Eugenics, whose registry held information on approximately 750,000 persons. Kemp was inspired to some extent by this huge register, but was also rather critical of the research at the registry.

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Danish human genetics research gained momentum after the establishment of an Institute of Human Genetics and Eugenics (usually called the Institute of Human Genetics) in 1938 at the University of Copenhagen, with Tage Kemp as director and then from 1948 as professor. The financing of the Institute was based on funds provided by the Rockefeller Foundation on condition that the University of Copenhagen contributed to the running costs. The Rockefeller Foundation’s sponsorship must be seen in the light of the personal respect in which Tage Kemp was held in the American research community.

It was clear to Tage Kemp that Denmark could fill a niche in human genetics research by virtue of the high degree of demographic stability of the Danish population, its high educational level and the intensive public registration in various registries: parish records since ca. 1650; census papers since 1769; national registers since 1924; conscription registers since 1701; and criminal registers since 1896.

A special register of various, mostly hereditary, diseases and defects had been established by the anthropologist Søren Hansen (1857–1946), who in 1904 was a founding member of the Anthropological Committee. This committee had among its members a number of influential and outstanding researchers. The register of this committee received reports from the Danish psychiatric reception centres. In connection with the establishment of the Institute of Genetics the register and its secretary, Annelise Betke, of the Anthropological Committee were transferred to the Institute, and the committee closed down.

This register was the basis for the registration of genetic diseases that Tage Kemp built up in the following decades, drawing on reports from a majority of the country’s psychiatric wards and reception centres (Kemp, 1951). The register was run on a daily basis by a staff of 30 unemployed office workers who...
had been referred to the Institute as part of an employment program. During the course of the 1950s the register covered 100,000 persons, but the reports were very inhomogeneous. It was most likely Kemp’s vision that the registration of the total Danish population would become an important and unique research resource. The information on individuals and families was of considerable importance to the clinical genetic counselling function and also to some of the scientific projects of the Institute, but it was not until the psychiatric part of the register had been transferred to Psychiatric Hospital in Aarhus that this part of the register became the core of psychiatric epidemiological and demographic research activities in Denmark.

Psychiatric Epidemiology

Two psychiatrists influenced the initiation of the Danish Twin Registry, Erik Strømgren (1909–93) and Kurt Fremming (1908–2003), through their population-based studies. During World War II, Fremming carried out a so-called catamnestic investigation of the prevalence and incidence of the major psychiatric diseases in some well-defined, almost complete birth cohorts (1885–89) (Fremming, 1947). Throughout a period of 50 years, Fremming’s results stood the test of time as valid values of reference; only the change in psychiatric diagnostics of recent years has necessitated a revision. Fremming demonstrated how the existing Danish patient registers could be utilized in follow-up studies “from the cradle to the grave”.

Kurt Fremming’s investigations had an indirect impact on the establishment of the Danish Twin Registry in two ways. They demonstrated the possibilities of following a person through various registers, developing the most appropriate methods for this purpose, and indicated the lowest boundary for the birth cohorts for which such a follow-up was profitable.

Cancer and Genes

From his early years Tage Kemp had been interested in the study of human chromosomes. He had attempted to count the chromosomes in tissue culture studies, but arrived at the wrong number: 48 instead of 46. Kemp was able to confirm the frequently very deviant chromosome numbers in malignant cells, and he was among the first to point out the probability that cancer is caused by somatic mutations.

Kemp’s interest in cancer resulted in a number of studies of chromosomes in irradiated cells, as well as the series of epidemiological cancer studies of a very high quality coming from the Institute in the first decade after its start: breast cancer, cervical cancer and leukaemia. The studies came to a common conclusion of sorts: compared to the general population there was a slightly increased cancer incidence among relatives of cancer patients, both in the same type of tumour and in the number of malignant tumours as such. Apart from a few families it was not possible, however, to detect any obvious Mendelian inheritance pattern. The financing of the investigations in the post-war years was based chiefly on the generous grants of the National Cancer Institutes in Bethesda, Maryland. Tage Kemp had the trust of these institutes as a consequence of his former wide-ranging contact with the American research community.

A later addition to these cancer studies was a study of the well-known connection between gastric cancer and pernicious anaemia carried out by Aage Videbæk (1914–90), later professor of haematology, and Johannes Mosbech (1922–), later a consultant. These studies were completed in the fall of 1953, placing Tage Kemp in the rather exceptional situation where the Institute was financed for another two years by the National Cancer Institutes, but had no major cancer project on which to spend the money.

Cancer in Twins — the Establishment of a Twin Register

Kemp now called for proposals for a cancer-related project. In this connection Bent Harvald (1924–) and Mogens Hauge (1922–1988), who at this time were both on the staff of the Institute as research assistants, put forward a plan to investigate cancer in twins in order to throw light on the relative aetiological importance of genes and environment on the occurrence of cancer. Johannes Clemmesen (1908–), who in 1942 had been the leader in initiating the Cancer Register under the Danish Cancer Society, noticing new incidences of cancer, made enquiries into whether the patients were twins. The material collected in this way had been published in 1948 by Busk, Clemmesen, and Nielsen. The material revealed a significantly higher concordance in identical than in
fraternal twins, but it had to be taken into account that the process of data collection involved a considerable risk of over representation of concordant pairs, especially among the identical twins. Therefore, it was reasonable to collect a more representative twin sample.

Kemp was immediately in favour of the idea. A twin register which considered all theoretical demands of representativeness would be a valuable research tool as well as constituting a logical supplement to the eugenics register of the Institute. Furthermore, the project’s relevance to cancer research was indisputable.

The American sponsors, the National Cancer Institutes, accepted the project, which they subsequently supported until 1960 with a very substantial donation that covered the salary of two secretaries, three part-time physicians plus very considerable costs for travel and equipment. Almost from the beginning of the project Gudrun Hauge (1931–) occupied one of the secretarial positions. With a few brief interruptions, she held this position for more than 45 years, which was of great importance to the continuity of the Danish Twin Registry.

The start of the Danish Twin Registry can thus be seen as a result of several lucky coincidences:

1. A “ripe” scientific problem. So many former twin studies had shown remarkably high concordance rates compared to what was expected from family studies. At the same time the twin series in question did not fulfil basic methodological requirements.

2. The research model the Institute had used up until then, proband-wise family studies of several cancer forms, had “run out of steam”. It was not expected that further use of the model would yield surprising results apart from those already demonstrated — increased familiar occurrence of cancer with the same or another localization.

3. An economic basis for the start and provisional running of the registry. The money was earmarked for cancer alone, but it was possible to extract information on other diseases from the material collected as an inexpensive “spin-off”.

4. Bent Harvald and Mogens Hauge, at the time in question, both had the opportunity to involve themselves in the project. Both were engaged in genetic research and together they had completed several quite extensive projects. With regard to expertise they complemented each other. Bent Harvald was taking his clinical education in internal medicine, while Mogens Hauge worked with linkage analyses of serological markers, thus having special qualifications for zygosity diagnostics that are central to twin studies.
The Work Begins

Based on Fremming’s experiences, the starting point for the twin registry was the parish registers. The registers for the past fifty years were in the hands of the vicars, while the older registers were kept in the regional archives. To begin with we chose the cohorts 1870–1910. We were interested in cohorts old enough to show a fairly high cancer frequency, but we could not go further back than 1870, due to difficulties in tracking down the twins. Jutland south of the Kongeaa border (the border between Denmark and Germany 1864–1920) had to be left out, as the older parish registers from these parts could not be found in the parish or local Danish archives.

Over the course of the first couple of years contact was made with all Danish vicars north of the Kongeaa border, a total of 800. What we asked the vicars to do was not a little:

We kindly ask you to help us by copying out the twins from your parish for the period 1870–1910. We are interested in the following information for each pair of twins (whether they are of the same or opposite sexes):

- full name and date of birth of the twins
- name and address of the parents

If it appears that one or both twins died immediately after they were born, you don’t have to inform us of them, as we are only investigating twins where both reached at least 5 years of age.

We are fully aware that what we ask may cause you much inconvenience and can only be regarded as a very great favour that you are doing us. However, we have a limited grant at our disposal, which enables us to give you some compensation. We therefore ask you to enclose your charge.

Yours sincerely
M. Hauge B. Harvald
Physicians

The response rate was very high indeed. We only met with two refusals to participate: a rural dean in Lolland and the parish clerk for the Danish National Hospital (for reasons of discretion). A characteristic answer from a North Jutland rural parish, which was accompanied by information on a total of six pairs of twins, read as follows:

This is the meagre harvest from two parishes. There were many twin pairs, but babies died like flies in the period you are investigating. The pairs copied out here did all reach the age of five years at least.

As we all have to cut down our expenses — and we have not seen the end of that — I appreciate that I have to limit myself to a microscopic hourly rate: send me 10 Dkr. for my parish magazine. That will not ruin your budget, I hope.

Yours sincerely
— —
Vicar

The First Results

Right from the start of the project it was clear that it would be a long time before we could begin reaping the results from the register. After two years it was possible to publish some preliminary results concerning a few, very frequently occurring conditions. After the twins had been traced we sent them a questionnaire if they were still alive, or, if they had died, to their closest living relative. All information about hospitalizations was followed up by the loan and examination of medical records — all in all a rather time-consuming process that provided very comprehensive information on each twin.
A substantial obstacle to the feasibility of the entire project was the large loss of twin pairs as a consequence of the high rate of infant mortality in the early days. It was especially high for twins because of their low birthweight. Twin pairs in which one or both had died before the age of five were considered unimportant to the planned analyses. More than half of the total number of twins registered in the parish registers were left out of the material for this reason. In addition there was the loss of pairs that it had not been possible to trace.

In 1956, the first proper summing up gave just under 2000 finished pairs, concluding that genetic factors play a very modest role in connection with cancer and myocardial infarction, while a significantly higher concordance rate in identical than in same-sexed, fraternal twins was found for hypertension, apoplexy, intelligence defects, epilepsy, manic-depressive psychosis, tuberculosis, rheumatic fever, rheumatoid arthritis, asthma and diabetes (Harvald and Hauge, 1956).

These very early results were confirmed in essence in later analyses: in 1958, of 3000 fully finished pairs; and in 1963 of just under 7000 pairs. In a count in 1964 of pairs in which both twins in a pair had died after the age of five, we were able to demonstrate that the difference in age at death was significantly less for identical than for same-sexed fraternal twin pairs. The heritability factor for life expectancy was found to be .29.

It is amazing how these early results agree with later results, which had the benefit of a growing twin sample and more sophisticated statistical methods. The results were published in the Journal of the American Medical Association (Harvald and Hauge, 1963) and in the US Public Health Service Publication No. 1163 “Genetics and the Epidemiology of Chronic Diseases” (Harvald and Hauge, 1965). Despite their deficiencies these publications served in those days as publicity for the international propagation of the Danish Twin Registry.

**Separated Twins**

An important collaborator in these early years of the registry was the psychiatrist, Niels Juel-Nielsen (1920–1986), who from 1970 was professor of psychiatry at Odense University. He was engaged as a research assistant at the Institute of Human Genetics in 1955. He came from a position with the Psychiatric Hospital in Aarhus, where he had initiated a tracing of identical twins who had been parted at birth or in the first year of life and had been reared apart. Unfortunately twins reared apart are “as rare as hens’ teeth”.

Juel-Nielsen found 12 such pairs; 8 pairs through the Danish Twin Registry and 4 pairs more or less by chance. Juel-Nielsen told a story of a twin pair who had contacted him. One of the twins was spoken to in the streets of Sonderborg, where she had never been before, by persons unknown to her who took her to be her twin sister, whom she did not know and who happened to live in Sonderborg. In this way the twins were brought together for the first time.

Every one of the 12 pairs who had been reared apart was put through a thorough psychiatric evaluation and a psychological investigation including various psychometric tests. In a measurement using non-verbal methods, level of intelligence showed a high degree of concordance between the twins of each pair. Personality structures also showed considerable similarities with regard to character and emotions, but the twin partners displayed large differences in their attitude towards and interaction with their environment, as well as differing in the form their interaction took and their level of need for contact.


**Cooperation with the Criminological Institute**

In 1955 the Institute of Human Genetics started collaboration with Doctor of Laws Karl O. Christiansen (1908–1976) from the Criminological Institute at the University of Copenhagen. Through Karl O. Christiansen the Danish Twin Registry also started collaborating with Professor Irving I. Gottesman from the Behavioral Genetics Center at the University of Minnesota. After Karl O. Christiansen’s death in 1976, the contact between the Danish Twin Registry and the Criminological Institute drew to a close, while the collaboration with the American partners, especially Gottesman, continued. In the long term, this collaboration became a stimulus to the modernization of the Danish Twin Registry. At the Institute in Minnesota the Danish data had been computerized and put through various advanced analyses that demonstrated the clear superiority of using computers in data processing. At that time in the mid-1970s, the Danish Twin Registry still used manual sorting of data.

**Tobacco and Twins**

From the beginning of the 1960s, the status of the Danish Twin Registry gradually declined in line with Tage Kemp’s failing health. The generous sponsorship of the National Cancer Institutes was reduced gradually as it became clear that the main conclusion of the study of cancer in twins would hardly change; that genetic factors normally have a very limited impact on the development of cancer.
Alongside the classic twin method, which relies on a comparison of the concordance between identical and fraternal twins, a new perspective began to emerge: the application of the so-called discordance analyses on twin data. In discordant identical twin pairs the environmental differences between affected and non-affected twin partners were investigated, as well as differences in morbidity and mortality between partners of identical pairs who have been subjected to different environmental exposures such as smoking.

At the end of the 1950s, Elisabeth Raaschou-Nielsen MD (1924–) made a thorough mapping of the former and present tobacco consumption of the twins (Raaschou-Nielsen, 1960). She clearly demonstrated the impact of genetic factors on smoking habits. In the 1960s, collaboration with Donald D. Reid, professor at the London School of Hygiene and Tropical Medicine, began. He was also advisor to WHO on prevention of heart and lung diseases. In a comparison of the most smoking partner of each pair with the least smoking partner he demonstrated an increase in mortality from lung cancer, reduced lung function, and myocardial infarct in the group of the most smoking partners. However, the total mortality was close to being the same in the two groups. These studies, which were financed by the English tobacco industry, were unfortunately never followed up.

Intensive studies of twins with peptic ulcer revealed that the affected identical twins had been exposed to more “stress” than their unaffected partners. In a similar study of identical twins with schizophrenia it was not possible to find any specific environmental factor in any of the affected twins compared with the unaffected. Other discordance analyses of the material have not been informative either, maybe because the analyses can normally only take into account such environmental factors that are suspected beforehand.

### Jan Mohr Succeeds Tage Kemp

Tage Kemp died in 1964 and was succeeded by the Norwegian Jan Mohr (1921–). At the beginning of the 1950s he had been a research assistant at the Institute, and he had a formal education in genetics. He had worked with Professor L. S. Penrose at the Galton Laboratory in London, and he now applied the linkage analysis method developed at the laboratory to the identification of the localization of genes on the chromosomes. The linkage analyses were used both with normal Danish families characterized by a large number of children, and with a number of families with well-known genetic diseases that had been mapped and filed in the eugenics register. In those days the chance of demonstrating a linkage was modest, primarily because of the very limited number of known markers, such as the ABO system.

In spite of these difficulties Mohr succeeded as the first ever in documenting linkage to an autosomal chromosome in human beings, namely the linkage between Lutheran (Lu[a]) and Secretor (Mohr, 1954). Jan Mohr’s finding was without doubt the largest achievement by a single researcher at the Institute of Human Genetics. It was hardly surprising, therefore, that Jan Mohr was appointed successor to Tage Kemp.

Mohr’s leadership meant a radical change to the line of research at the Institute. The classic clinical genetic studies using the register, the clinical family studies, and the twin research were all downgraded.

Since his own appointment to the Institute at the beginning of the 1950s, Mogens Hauge had cooperated closely with Mohr. When Mohr left the Institute in 1953 to continue his scientific work in Oslo in Norway, Hauge carried on the linkage analyses in Copenhagen using the method introduced by Mohr, but added an increasing number of markers and a number of genetic diseases. He did not succeed in finding any other linkage relations other than the one revealed by Mohr. Hauge finished these linkage studies at the beginning of the 1960s.

When Mohr took up his appointment as head of the Institute in 1964, Hauge concentrated his efforts on twin studies and the socio-genetic advisory function of the Institute, which did not hold Mohr’s interest. Hauge and Harvald, who had become senior lecturer in clinical genetics and assistant consultant at Bispebjerg Hospital, were both able to spend approximately half of their time on the twin registry.

### Work in Progress

Under these conditions the Danish Twin Registry made steady progress. In the course of the 1960s, same-sexed twin pairs of the 1911–30 cohorts were included, so that around 1970 the Danish Twin Registry contained a little over 11,000 same-sexed pairs ready for analysis.

Among studies completed at that time, a clinical and radiological study of twins with peptic ulcer must be mentioned. It was conducted by Kai Gotlieb Jensen (1923–84), later consultant in surgery in Ribe. The study indicated that genetic and environmental factors have almost equal aetiological weight, as well as supporting the established view in the clinic that gastric ulcer and duodenal ulcer are different diseases (Jensen, 1972).

Margit Fischer (1931–83), consultant in psychiatry in Aarhus from 1976, studied twins suffering from schizophrenia, demonstrating a substantial genetic influence (Fischer, 1973). On the other hand, the medical records also revealed how much the schizophrenic phenotype could differ in genetically identical individuals.

### An Institute of Medical Genetics in Odense

In 1969 Bent Harvald took up an appointment as professor of internal medicine at the young Odense University. At the same time a controversy about the direction of research and the twin registry was growing between Jan Mohr and Mogens Hauge.
Mogens Hauge applied for and in 1970 was appointed to the chair of medical genetics in Odense.

**The Danish Twin Registry Moves to Odense**

To whom did the twin registry belong? The original financial basis of the Danish Twin Registry had been Tage Kemp’s grants. The registry had been housed at the Institute of Human Genetics and had utilized the Institute’s common facilities, among these a considerable amount of secretarial assistance. Although by far the main part of the scientific work in connection with the registry had been made by Mogens Hauge and Bent Harvald, it was not unreasonable to claim that the twin material belonged to the Institute of Human Genetics and therefore the University of Copenhagen. It was feared that a time and resource-consuming “tug-of-war” concerning the intellectual ownership of the twin registry would ensue, but no conflict arose. Jan Mohr never disputed the right of Hauge and Harvald to the twin material. On the contrary, because of a lack of space, he wished to have the registry moved to Odense as quickly as possible. The transfer of the Danish Twin Registry to Odense in 1971 meant that the new Institute of Genetic Pathology had no lack of material, and so it got off to a flying start. From 1973 a continuous flow of publications based on the registry emanated from the Institute.

The transfer of the Danish Twin Registry to Odense took place without any great to-do. The event is neither mentioned in any of the annual reports of Odense University nor in the book *Frugten vokser frem* (The fruits sprout up) that was published in 1991 by Odense University Press to mark the university’s 25th anniversary (Boje and Jespersen). Thus it was an unnoticed historical event which nevertheless lived quietly up to the university motto: “fructus increscit opera novo in agro” — fruits sprout up when labouring in a new field.

**Later History**

After spending productive years at the Twin Registry in Odense, Professor Mogens Hauge died unexpectedly in 1988 as the result of an accident. Niels V. Holm, now chief oncologist at Odense University Hospital, took over responsibility in conjunction with his clinical career. Thanks to Niels V. Holm and the support of Thomas Mack, professor at the University of Southern California, the registry remained in Odense, intact and productive. A computerization of the older cohorts of twins was completed in the 1980s with the purpose of linking the Danish Twin Registry with the nationwide Danish Cancer Registry. In the late 1980s and early 1990s, Niels V. Holm directed the computerization of data on the older cohorts of the twin register as part of a twin study on lifespan initiated by James W. Vaupel, professor at Duke University, and later appointed professor in Odense. This computerization was the platform for the longitudinal aging studies of all Danish twins aged 70 and older conducted by Kaare Christensen, professor of Epidemiology at the University of Southern Denmark, over the last decade in close collaboration with James W. Vaupel and Matt McGue, professor at the University of Minnesota.

In the early 1990s, the Danish Twin Registry was extended to include the 1953–1982 cohorts, thanks to Kirsten O. Kyvik, now associate professor of Epidemiology, University of Southern Denmark. This cohort was ascertained from part of her PhD project on type 1 diabetes in young twins, conducted with the support of Anders Green, now professor at the University of Aarhus, and Henning Beck-Nielsen, professor at Odense University Hospital. This twin cohort has been used especially for studies of somatic diseases with debut in young age.

As part of his PhD project on mortality in twins conducted in the mid-1990s, Axel Skytthe, now associate professor of Epidemiology, University of Southern Denmark, filled the gap in the Danish Twin Registry by ascertaining the 1931–1952 twin cohorts with the support of Kaare Christensen. This resource is now being used for both aging studies and studies of younger twins.

These two cohorts, 1931–52 and 1953–82, were both ascertained from the Danish Civil Registration System, although because of different technological possibilities, not in the same way. The possibility of linking to the Civil Registration System meant great progress with regard to completeness of the two cohorts as well as to the follow-up of the whole twin registry. At present the Danish Twin Registry receives regular updates from the Medical Birth Registry. It covers 131 birth cohorts totalling more than 67,000 pairs of twins (Skytthe et al., 2002). Furthermore, the register comprises a bio-bank established during the late 1990s.

In 1995 the Danish Twin Registry obtained permission to operate as one of the University of Southern Denmark’s registries. This has ensured especially good data security as well as support in the form of materials and tenure, and extended the possibilities for linkage with other Danish civil and health registers. The registry is a research resource of the Faculty of Health Sciences at the University of Southern Denmark with the Dean as Head and a scientific board consisting of Kaare Christensen, Kirsten O. Kyvik, Niels V. Holm, and Axel Skytthe. Kirsten O. Kyvik is the daily administrative leader, the bio-bank is headed by Lise Bathum MD, PhD, while database manager Lars Hvidberg and Jacob Mortensen PhD are responsible for data management in collaboration with Axel Skytthe, all with secretarial support from Jytte Duerlund (Bachelor of Business Language).

**Endnote**

APPENDIX
The Danish Twin Registry: Established in 1954
Complete List of Publications


Art, pp. 121-140, the Netherlands: Kluver Academic Press.


Frederiksen, H., & Christensen, K. (2003). The influence of genetic factors on physical functioning and exercise...


Ph.D. and Doctoral Theses


**Additional References**


