Historical Perspectives: Perinatal Profiles: Bent Friis-Hansen: A Danish Pioneer of Neonatology
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NeoReviews 2010;11:e613-e618
DOI: 10.1542/neoreviews.11-11-e613

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Perinatal Profiles: Bent Friis-Hansen: A Danish Pioneer of Neonatology

Gorm Greisen, MD*

Introduction

Bent Julius Friis-Hansen was the prime mover in developing neonatology as a pediatric field in Denmark starting in 1964. He had been a co-founder of the European Club of Pediatric Research in 1959, which evolved into the European Society for Pediatric Research. He and his American colleagues Leo Stern and later William Oh led the International Perinatal Collegium, an informal group of pioneers from both sides of the Atlantic, through a series of biannual meetings from 1971 until he retired in 1990. (1)

An Immature and Rebellious Boy

Friis-Hansen was born in 1920 in Svendborg, a small town in Southern Funen. The primary income of the town came from shipping, and all families had fathers and brothers on the high seas. When the young Bent and his older brother were in kindergarten, the woman who taught them to write decided that they should be in primary school, in grades 2 and 3, respectively. At that time, Bent was only 5 years old. He later wrote that he probably was too immature for his class, which was the reason why he had frequent conflicts with teachers. His dyslexia and problems with reading also may have contributed. He often shirked school, preferring the free life of a young boy to schoolwork. When he started high school, staying quiet in class still was a problem for him. His father died when he was 16, and his mother and elder brother moved to Copenhagen. He remained in Svendborg, living with friends of the family for the last year of his high school. He wrote that the conflicts with teachers persisted. Although the head master often threatened to expel him from school, he got his certificate, joined his mother in Copenhagen, and started the study of medicine.

To make it to his last examination in January 1945, he missed a meeting of the resistance group of which he was a member. Leaving the examination room, he received a message that the Gestapo of the German occupation forces had been informed about the group and had taken them to prison. Four of them were later executed. Friis-Hansen lived under cover until the liberation of Denmark in May 1945.

Rapidly Into Research

The first year of clinical practice was spent in Kolding, Western Denmark, doing internal medicine and surgery. Friis-Hansen already was engaged in research, publishing first on glucose tolerance of partially hepatectomized rabbits, then on glucose tolerance in artificial diphtheria toxemia. One evening, a newborn was brought in who had been found on the railway track, presumably having been delivered on the toilet of the train and fallen directly onto the tracks. The mother was found and reunited with her child. Friis-Hansen cited this event as one of the sources for his life’s work in neonatology.

Back in Copenhagen and working in the medical department of Frederiksberg Hospital, he published on gastric acid production after hist-
mine stimulation in 12 febrile adult patients in the ward. Perhaps because of his talent and energy and perhaps because of his service in the resistance during the war, the professor of surgery at Rigshospitalet, Erik Husfeldt, who himself had played a central role in the resistance movement, mediated a contact with a blood bank in Boston. While Friis-Hansen prepared himself by reading everything he could find on blood transfusions, he was informed that they had found an American who, as Friis-Hansen writes in his autobiography, hopefully was a better qualified physician. As an alternative he was invited to join the team of the newly appointed professor in surgery at the Peter Bent Brigham Hospital in Boston, the 32-year-old Francis D. Moore. Friis-Hansen borrowed money and left Denmark. On his arrival in Boston, he obtained a fellowship from the American-Scandinavian Foundation and worked from 1948 to 1950 as a research fellow in surgery at Harvard in Dr Moore’s laboratory.

Happy Postwar Days in Boston

Moore was a pioneer, using the new advances of the physical sciences that had produced radioactive isotopes of hydrogen, sodium, and potassium. These achievements had made it possible to study the fluid spaces of the human body in health and disease. Moore was particularly interested in burns, but his laboratory hosted young researchers from many countries who used this new methodology in other applications. Moore was an extraordinary leader. He had reported measurement of total body water using the indicator dilution principle and intravenous administration of the nonradioactive isotope of deuterium in the form of heavy water in Science in 1946. Moore had shown that equilibrium takes place within 1 hour. Moore also was a good host to a young and somewhat miserable stranger from postwar Denmark. It became a happy time.

Heavy Water

Friis-Hansen joined a team of young colleagues who refined the falling drop method to measure the relative abundance of heavy water. In principle, a small drop of water obtained by distillation of a sample of blood was allowed to fall through a carefully temperature-controlled column of o-fluoro-toluene (Fig. 1). The group refined the method to an astonishing precision of 0.0012 vol% deuterium/normal water in a blood sample of 150 to 200 mL. (2) Bent Friis-Hansen’s wife once told me, however, that this was not easy; one late night, the instrument was thrown through the window into the street.

Friis-Hansen studied inpatients in the Children’s Hospital in Boston, (3) and after his return to Copenhagen, he studied inpatients first at Rigshospitalet during his years as a research fellow of the professor of pediatrics at Rigshospitalet, Preben Plum, and later in Queen Louise’s Children’s Hospital as “reservelæge” with professor Oluf Andersen. The measurements of deuterium in Copenhagen were carried out at the department of biologic isotope research at the Institute of Zoophysiology headed by Professor Hans Ussing. The money for the very expensive deuterium came from many sources. This work led to six publications and a Doctor of Medical Sciences thesis.
in 1956. Before, the only data available had come from desiccation of dead human fetuses and a few dead newborns. Friis-Hansen showed that the total body water decreases from 79% on the first day after birth to 58% at puberty. These numbers fit perfectly with desiccation data from the fetus and in vivo studies in adults (Fig. 2). He also showed that the decrease in total body water is exclusively due to a decrease in extracellular water, whereas intracellular water is nearly constant from birth to puberty. These conclusions are still valid. Friis-Hansen was a tall man, and his friend and coauthor, Jørgen Vesterdal, later told me that often during those early years, Friis-Hansen’s head disappeared in clouds of heavy water.

Africa and Nutrition

In 1957, Friis-Hansen again contacted Husfeldt. Husfeldt was born in Indonesia, and after the war, he had considerable international activity based at the school of anesthesia and intensive care in Copenhagen that had been developed during the polio epidemic during which hundreds of paralyzed patients were manually ventilated until recovery. Husfeldt had become a World Health Organization (WHO) advisor. Friis-Hansen wanted to go the Far East, but Husfeldt advised him to go to Africa as an expert in nutrition. Friis-Hansen said that he was not interested in Africa and that he was not an expert in nutrition. Husfeldt told him that nutrition was easy to learn and that Africa was unknown and, therefore, twice as interesting.

Friis-Hansen spent 1 year in the Northern province of Northern Rhodesia (now Zambia) with a Scottish parasitologist, Fergus McCullough. He found widespread symptoms of vitamin A deficiency in children (4) and devised plans for interventions. He wrote that the plans were lost during the process of independence in the following years, but he remained active for WHO in childhood nutrition, and Africa stayed in his mind.

The Neonatal Intensive Care Unit at Rigshospitalet

Professor Trolle at the department of obstetrics and professor Plum at the department of pediatrics at Rigshospitalet in Copenhagen had agreed that a dedicated person was needed to develop the new field of neonatology. Thus, a department with a separate medical and nursing staff and a separate budget was established in 1964, with Friis-Hansen as the head.

Rigshospitalet at the time was state-owned and had a particular responsibility for research and developing highly specialized care for the small Danish nation (population: 5 million). At the time, it had been only 54 years since Rigshospitalet had introduced the first pediatric hospital department in the country, and it was only during the preceding 10 years that the country’s regional hospitals had developed pediatric departments of their own.

Developing neonatology required practical sense. Dr R. Cooke from South Africa helped to start intensive care of newborns and, in particular, mechanical ventilation. In 1967, the group first published the results of assisted ventilation in 14 babies of 28 to 37 weeks gestational age in

Figure 2. Total body water and intracellular and extracellular water during childhood. Each point represents the data from clinical investigation of a child admitted to the hospital in Boston or Copenhagen. The fetal values were taken from the literature and represent averages obtained by desiccation of dead fetuses. Reprinted with permission from Friis-Hansen B. Changes in body water compartments during growth [thesis]. Acta Paediatr Suppl. 1957;46(suppl 110):1–68.
which 5 babies survived. (5) Friis-Hansen wrote: “No definite criteria were used in the selection of infants for artificial ventilation. Initially, only those infants that were clinically moribund and in gross respiratory and circulatory collapse, were subjected to this treatment.” The inspiratory pressures used ranged from 15 to 40 cm H2O, and often negative pressure was used during expiration “to overcome the resistance in the narrow naso-tracheal tube.” In an addendum, he wrote, “Since the completion of this study a further 18 infants have been treated on the respirator with 9 survivals. The lowest weight of an infant that survived the treatment being 1120 g.” The survival rate for such babies only improved slightly (Table 1), until George Gregory presented his results using continuous positive airway pressure (CPAP) delivered by endotracheal tube at the International Perinatal Collegium in August 1971. This principle was rapidly adopted at Rigshospitalet, and results improved (Table 2). Soon, a high degree of centralization of preterm deliveries to Rigshospitalet from all of Eastern Denmark was achieved. Jens Kamper worked with Friis-Hansen in this early period, (6) published several papers, and wrote his thesis on treatment of respiratory distress. Jens Kamper later moved to Odense, where he developed the “Scandinavian” approach with early nasal CPAP.

**The Family-oriented Approach**

“They pass the main entrance and through a wide door. It says ‘NEONATAL UNIT no admittance’. Then they now are in a small, warm passage. On one side is a kitchen, where a big woman is cleaning bottles, on the other side are two narrow doors, each one with a small glass window. Marie sees that one leads to the unit with cots for newborns and that the other leads to the incubators.

“Marie and the nurse face a stranger.

“Here we have a small one, three days old, dehydrated with elevated bilirubin.”

“Well yes, we will take care of that.”

“The child disappears through the door to the unit with cots. The door closes. After a moment Marie gets a receipt, a scrap of paper, a stencil that reads:

“To Mrs—the word Nansen is added in pencil—Your baby is now admitted to dept. GN, and has been given number GN 29—the number is written by hand—The children are on display for you every day from 11.30 to 12.00 AM. Furthermore the child may be seen by the next of kin the first 30 minutes of the visiting hours. Enquiries by telephone are answered every day between 8 AM and 8 PM. With kind regards.

“To Mrs Nansen it says. Her name is Hansen—well, that does not matter. The nurse makes a sign, they must hurry back, there is nothing more to do here. Marie gives her long stockings a pull and silently they move as shadows through the long white tubes back to the post-natal ward.

“Marie tells herself again and again that this is best as it happened. The responsibility had become too heavy.

“But she cannot rid herself of the thought that she carries a small certificate of death in her pocket.” (From Winter’s Children by Dea Trier Mørch, 1976—my translation).

This book was one of the roots of change. The psychologists Gretty Mirdal and Hanne Munch, both interested in parent-child interaction, became agents of change. Friis-Hansen invited them into the unit for their fieldwork and by his respectful curiosity and openness, earned their affection. The head nurse, Gerda Christensen, and later Lone Petri and Jean Paul Guilbert all took these ideas further to what is now a culture of care.

**Brain Damage**

With rapidly evolving neonatal intensive care allowing survival of ever-smaller babies, the problem of brain

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**Table 1. Mechanical Ventilation of Newborns**

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Survivors/Total Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,000</td>
<td>1/3</td>
</tr>
<tr>
<td>1,001 to 1,500</td>
<td>4/22</td>
</tr>
<tr>
<td>1,501 to 2,000</td>
<td>7/29</td>
</tr>
<tr>
<td>2,001 to 2,500</td>
<td>16/29</td>
</tr>
<tr>
<td>2,500</td>
<td>23/45</td>
</tr>
<tr>
<td>Total</td>
<td>51/128</td>
</tr>
</tbody>
</table>

*Department of Neonatology at Rigshospitalet until 1969

**Table 2. The Effect of Introducing CPAP/PEEP by Endotracheal Tube**

<table>
<thead>
<tr>
<th></th>
<th>April 1966 to August 1971</th>
<th>August 1971 to August 1972</th>
<th>August 1972 to June 1973</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>193</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>CPAP/PEEP (%)</td>
<td>0</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>61</td>
<td>51</td>
<td>23</td>
</tr>
</tbody>
</table>

CPAP=continuous positive airway pressure, PEEP=positive end-expiratory pressure.
injury and survival of handicapped children became a prime concern for Friis-Hansen.

Niels A. Lassen had measured cerebral blood flow (CBF) in adult patients with radioactive krypton in 1955 and with xenon in 1965, and Copenhagen was an international center for CBF research. Hans C. Lou had interest in pediatric neurology and was newly employed in the department of neonatology when he reported CBF data in eight newborns with Lassen and Friis-Hansen in 1977. (7) The article focused on the surprisingly low values of CBF, which were as low as 20 mL/100 g per minute, less than one third of normal adult values and much less than the values routinely obtained in newborn lambs, the most popular animal model in perinatal research at the time. A link was made to the low systolic blood pressure. In the next article, data from 19 newborns were included, (8) and the correlation between CBF and blood pressure became highly significant. The focus in this article was on the impairment of autoregulation and the risk of hypertension-induced cerebral hemorrhage. This shift in focus was due to the fact that intraventricular hemorrhage (IVH) was “put on the agenda” by the publication by Lu Ann Papile in 1978, which described detection of IVH by computed tomography scan. It had come as a great surprise to most neonatologists that 40% of all very low-birthweight infants developed IVH and that most were asymptomatic and survived.

Rigshospitalet had an obstetric ultrasonography unit where Jens Bang had performed the first intrauterine transfusions. Friis-Hansen proposed that I borrow their equipment and try it for diagnosing IVH by cranial ultrasonography. There I was in 1980, 6 months after my entry into the unit, starting a prospective study on IVH. In 1982, he took me in as his research fellow, partly because I had a bachelor’s degree in computing, useful in taking the CBF studies further.

During these years, the intention in the unit was to aim for slight hyperventilation for preterm infants to stabilize autoregulation and protect against IVH. (9) Many years later, years after Friis-Hansen was pensioned, data from the regional registry of cerebral palsy showed that this good intention had caused a local epidemic of cerebral palsy in very preterm infants, (10) another example of the risks of ambitious neonatology.

**Mentoring**

In addition to Jens Kamper, Friis-Hansen also mentored Gunnar Eg Andersen, who did his thesis work on screening for familial hypercholesterolemia; Peter Wimberley, who worked on hemoglobin F-oxygen binding; myself on cerebral blood flow; Ole Pryds also on cerebral blood flow; and Lotte Skov on cerebral near-infrared spectroscopy. Furthermore, Henrik Sardemann and May Olufson published many articles on the infants of drug-addicted mothers, Finn Ebbesen on hyperbilirubinemia, Henrik Verder on prediction of respiratory distress syndrome, and Jens Hertel on the metabolic response of diabetic mothers.

Bent Friis-Hansen had a good sense of humor and was a good mentor. Once asked how he could keep young researchers moving, he answered that he didn’t know because he found it difficult to keep moving himself. He was inspiring, not directive. He would quietly lead the way by questions.

**The Tough Piece of Toffee**

A requirement for providing up-to-date neonatal care was to be able to implement the many medical and technological advances of neonatology, which required funding. The 100% public hospital sector in Denmark was run extraordinarily restrictively during the 1970s and 1980s. This led to an overall setback in health-care spending in Denmark from being on the top in Europe to sinking to the bottom. Friis-Hansen managed to maintain and improve economic support. His wife compared his strategy toward hospital directors to chewing a tough piece of toffee: “Chew, wait, and chew.”

**A Final Word on His Portrait**

Friis-Hansen’s portrait was painted when he retired at 70 years of age (Fig. 3). At this age, he was marked by Parkinson disease and macular degeneration, two illnesses that affected him increasingly for the 12 years until his death in 2002. The painting depicts his facial expression very well: distant and respectful but curious. Friis-Hansen was not well-liked by medical students. They did
not easily understand him. His ques-
tions at examinations were feared. 
However, his younger colleagues, as 
well as other staff, were affectionate 
toward him.

Despite his illnesses, he grew old in a way that one could only respect and admire. He was cared for until he died by his wife Bente in their old house and beautiful garden north of Copenhagen. When I visited him during his last years, he would pa-
tiently, but not too attentively, listen to my explanations and then ask the central question. A long series of 
Danish pediatricians will pause when 
his name is mentioned and feel grate-
ful, and he won many friends abroad.

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