

Establishing a Clinical Trial Unit in Dermato-Venereology at Odense University Hospital, Denmark

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The Department of Dermatology and Allergy Centre, Odense University Hospital (OUH) is one of 5 dermatology departments in Denmark. It was established in 1968, when the clinical part of the curriculum at the medical school opened at the University of Southern Denmark (SDU), founded in 1966. Situated in the heart of Denmark, the department serves the Region of Southern Denmark with a catchment area of 1.2 million people. In the region we have 14 dermatologists in private practice.

The department has 2 research units comprising dermato-venereology and type I allergy, and this article refers to the former. Head of research at the allergy unit is professor, PhD, DMSc Carsten Bindslev-Jensen. The website of the research unit can be found on SDU's website and the department's allergy elite research centre at the ORCA website.

The first professor at the department was Henning Schmidt, who had a broad clinical interest and research focus on venereology, especially syphilis. He studied the symbolics of tattoos and had a huge photo collection of these. He was succeeded by professor Klaus Ejner Andersen in 1989, who worked as a clinical professor until May 2015. Dr Andersen is a renowned international researcher within contact dermatitis, contact allergy, plant dermatitis and skin toxicology. He established the Allergen Bank in 1992.

In October 2015, Anette Bygum was appointed Clinical Professor and became responsible for medical teaching and research. The focus areas of Dr Bygum are genodermatoses and paediatric dermatology.

Research is a core task for a university hospital and contributes to an inspiring and stimulating working environment. Through all the years, the research tradition has been mostly clinical and application-oriented, often in collaboration with other departments and university institutes. Research and education strengthen the collaboration between OUH and the Department of Clinical Research at SDU.

Within recent years, we have been aware of the value of nurse research and development projects, as an important part of our specialty. All staff at the department has a joint responsibility for research, development and teaching activities as part of

daily clinical life. Patients' thoughts and inputs are important in the research process, and they pave the way for more collaboration with patients and patient associations, also in the planning phase of the research projects. The new found knowledge must be made visible and implemented, so that patients can be offered the best treatment as fast as possible.

Our research unit comprises one Clinical Professor Anette Bygum, one 5% Professor Klaus E. Andersen, 6 Associate Professors: Flemming Andersen, Sigurd Broesby-Olsen, Tine Vestergaard, Rasmus Bach, Lone Hvid and Sumangali Prasad, 3 clinical nursing specialists: Jeanette Møller Hansen, Julie Hansen and Nadja Trier Munk, 1 Research Fellow Evy Paulsen, two Adjunct Professors Steven Feldman and Julia Reichelt together with one Adjunct Associate Professor Maja Hofmann. Several medical students are affiliated performing pregraduate projects and helping with databases and clinical studies.

The department collaborates with other research units in Denmark and abroad in relation to translational research, as we do not have our own laboratory facilities. This does not only apply to translation from basic research to clinic, but also vice versa. The aim for the department and hospital is to have an international research profile. At the same time we strive to have a close collaboration with general practitioners and dermatologists in private practice also with potential collaborative research projects in mind.

Research activities

Our research unit is involved in 9 PhD projects:

- Mathias Tiedemann Svendsen: *Adherence to topically prescribed corticosteroids and corticosteroid/calcipotriol combinations.*
- Bettina Trettin: *Improving management of psoriasis patients: a teledermatology approach.*
- Eva Rye Rasmussen: *Non-histaminergic Angioedema Patients: Identification, Characterization And Treatment (NAPICAT).*
- Mads Gustaf Jørgensen: *Prevention of Lymphedema with Tacrolimus.*
- Laura Barrett Ryø: *Unravelling molecular disease mechanisms in Hereditary Angioedema with normal and abnormal C1 inhibitor.*
- Didde Haslund: *Identification and modeling of hereditary*

angioedema disease mechanisms by genetic engineering in patient-derived cells.

- Anne Lindegaard Christiansen: *Porphyria cutanea tarda: Relations to iron overload, metabolic and cardiovascular diseases and mortality.*
- Stine Bjørn Gram: *Improved genetic characterization and diagnostics in hereditary palmoplantar keratoderma: A cohort study.*
- Azmi Al-Jubury. *Schistosome dermatitis in Denmark - Clinical features, occurrence and diagnostics.*

Research Committee, Strategy and Clinical Trial Unit

A Research Committee was established in November 2015 to strengthen the research and strategic priorities at the department. The committee prepares the department's research strategy and contributes to implementing the department's and hospital's research strategy.

The corporate vision is: *Clinical research makes life easier for patients with skin diseases and allergies.*

The strategic research areas include:

- Adherence, response to treatment, quality of life
- Bradykinin mediated Angioedema
- Contact dermatitis and contact allergy
- Cutaneous lupus erythematosus
- Genodermatoses
- Hyperhidrosis
- Pyoderma gangrenosum
- Skin cancer
- Teledermoscopy

In 2016 a Clinical Trial Unit (CTU) was formerly established, initially as "a part time study nurse with a trolley" (Fig. 1) and since 2017 with a separate room for clinical studies, two part time study nurses, a physician one day per week together with



Fig. 1. Study nurse with her trolley and binders.



Fig. 2. Head of department inspecting Clinical Trial Unit.

the Clinical Professor and head of the department (Fig. 2).

The CTU performs investigator and sponsor-initiated clinical research in accordance with responsible conduct of research. With support from the National Experimental Therapy Partnership NEXT (see below), a focus on early phase clinical studies has been made involving physicians and nurses in describing standard operating procedures (SOPs). Until now we have performed 3 sponsored clinical trials within the field of hereditary angioedema and one clinical trial within psoriasis. We are preparing another 3 trials within the areas of angioedema and skin cancer. For many of us, it has been a learning experience but also a huge work coordinating the protocols, contracts and economy with sponsor and the collaboration with pharmacy, clinical chemistry and other departments such as nuclear medicine and cardiology. Due to lack of manpower, we have used medical students in the study team, which seemed to be a very good solution.

Our first clinical study was a phase IIA randomized, double-blind, placebo-controlled study to evaluate a small oral molecule BCX7353 as long-term prophylaxis to reduce attacks in patients with hereditary angioedema (HAE). With 8 recruited patients we happened to be the top recruiter among 26 sites in Europe, Canada and Australia and we are very much looking forward to the publication of study results in NEJM (paper accepted).

The Research Committee and CTU now serve as a platform and knowledge base also for investigator initiated projects. Since November 2015 a total of 27 different research protocols have been approved by the Research Committee. The committee seeks to have a high information level in the department and publishes quarterly newsletters to inform all staff about the activities, new rules and funding possibilities (Fig. 3).

Research should be part of the culture of a university hospital and all employees should take a responsibility for research. Some contribute to the framework and logistics, while oth-



Fig. 3. Site initiation visit in the Clinical Trial Unit with sponsor, CRO-representative, physicians, nurses, medical students and laboratory staff.

ers are more directly involved in research. This is brilliantly illustrated by the following story:

President John F. Kennedy was visiting NASA headquarters for the first time. While touring the facility, he introduced himself to a janitor who was mopping the floor and asked him what he did at NASA. *"I'm helping put a man on the moon!"*. It is important to strive to attain a vision of the larger whole.

Databases

Patient consents and databases form part of the foundation for research and the professional development of the department and can also be seen as a strategy for the department to maintain the assigned regional and highly specialized functions. The department has initiated and participates in established clinical research databases containing patients with various skin diseases:

- Allergen Bank
- Cutaneous Lupus Erythematosus + biobank
- Danish Genodermatosis Database (upcoming)
- Danish Melanoma Group
- Dermbio (National Quality Assurance Database of psoriasis)
- European Society for Cutaneous Lupus Erythematosus
- Genodermatoses – regional research database and biobank
- Hereditary Angioedema + biobank
- Hereditary palmoplantar keratoderma and ichthyosis + biobank
- Hyperhidrosis
- National Database of Contact Allergy
- NEXT Derma
- Non histaminergic Angioedema + biobank
- Porphyria cutanea tarda
- Scabies
- Teledermoscopy

Most of our databases are hosted at OPEN Odense Patient data Explorative Network, which is a research infrastructure with a mission to increase and strengthen clinical research in the Region of Southern Denmark.

Patient involvement and collaboration with patient organizations

OUH puts patients first, also in terms of research. Two patient representatives participate in our Research Committee with the purpose of emphasizing the patient perspective and increase research quality and relevance. Patients and relatives should be involved in the planning phase of clinical studies, which until now has been practiced in projects concerning psoriasis, hyperhidrosis and pyoderma gangrenosum wounds.

Collaboration with Patient Organizations is an integral part of our work, and especially we have had collaboration with the following organizations: Hyperhidrose foreningen, Iktyosis foreningen Danmark, HAE Scandinavia, Danish Lupus Association, Psoriasisforeningen, Ehlers-Danlosforeningen and Ectodermal Dysplasia Patientforening Danmark.

As an example, we have had a close collaboration with the Danish Patient Organization for hereditary angioedema (HAE) since 2001, with yearly meetings, collaborative written patient informations and webpages, questionnaires, development of swelling calendars and later a smartphone application (app). The patient association is now a Scandinavian organization, and we are represented in the medical advisory board. After initiating clinical studies, we have had meetings in Denmark and abroad discussing clinical studies, and the genuine interest of patients supporting and participating in these (Fig. 4).

Visibility on different platforms, including social media

The department is visible on the hospital and university platforms. The department's clinic for sexually transmitted diseases is active on Facebook. The collaboration with some of the patient associations is also visible on social media.

OUH Talks is a recent initiative, where different themes are livestreamed and later will be available on Youtube. OUH



Fig. 4. Photo taking in June 2018, where the board of HAE Scandinavia met with staff from the HAE Centre and our head nurse to discuss patient database, future meetings and upcoming research projects.

Talks about The European Reference Networks and Precision Medicine are relevant in this context.

National Experimental Therapy Partnership, NEXT

NEXT is a national public-private partnership working to strengthen Denmark as a preferred country for early clinical research sponsored by the pharmaceutical industry. With support from Innovation Fund Denmark and medical companies, all departments of dermatology in Denmark participate in NEXT Derma performing early clinical trials. A key issue has been establishment of a prospective database with patients suffering from atopic dermatitis and psoriasis. The patients are given written information about NEXT and access to a web-based platform, where they can have further information and decide, whether they would be interested in participating in clinical research trials. In case a clinical trial is planned, the responsible dermatologist will contact selected patients fulfilling inclusion criteria and ask whether they want to participate. At any time the patient can withdraw consent and be deleted from the database.

PREmedico and CAKS

The department participates in a local collaborative network on Precision medicine, PREmedico, with the purpose of integrating precision medicine in all hospital units. Also research is part of the PREmedico collaboration focusing on cancer and rare diseases. Recently a Centre was established for inherited and complex diseases CAKS, defining follow-up programs and responsible clinicians for selected disorders. The department participates in a Danish multidisciplinary collaboration on prognostic factors and personalised medicine among patients with chronic inflammatory diseases including psoriasis.

A yearly PREmedico symposium is being held, where data from our regional genodermatoses database is presented. Dr. Habil. Julia Reichelt from Epidermolysis Bullosa House, Salzburg in Austria, was a keynote speaker this year and gave a presentation with the title: Gene therapy for epidermolysis bullosa

as a model of curative treatment of inherited skin diseases. Recently Julia Reichelt has become an Adjunct Professor at our department, and we are looking forward to explore this new collaboration on genodermatoses. In September 2 physicians and 2 nurses from our department will go to Salzburg and visit the dermatology clinics and research lab.

Reference

1. Hirsch T, Rothoef T, Teig N, Bauer JW, Pellegrini G, De Rosa L, et al. Regeneration of the entire human epidermis using transgenic stem cells. *Nature* 2017; 551: 327–332.

Adherence and E-Health in psoriasis

In collaboration with our Adjunct Professor Steven Feldman, Department of Dermatology, Wake Forest Medical Center, North Carolina and Centre for Innovative Medical Technology, clinical studies are performed to increase patient satisfaction and adherence using E-Health.

An interdisciplinary research team comprising dermatologists, pharmacists, antropologists and medical device engineers has been established to study psoriasis patients' use of prescribed antipsoriatic drugs. We have conducted drug utilization studies using the national health data registries to report psoriasis patients' real-life use of antipsoriatic drugs. A focus group study provided insights into psoriasis patients' experiences with use of topical drugs, where patients reported forgetfulness and lack of motivation as main reasons for low adherence. In collaboration with the pharmaceutical industry, smartphone app was developed to study the effect on psoriasis patients' adherence to topical therapy with calcipotriol/betamethasone dipropionate cutaneous foam. The app was tested in a single-center randomized controlled trial, which showed that the app improved psoriasis patients' adherence to use of the topical drug as well as reduced severity of psoriasis. This promising outcome gives support to initiatives to develop E-Health technologies to support patients' adherence to topical treatment for other more chronic skin diseases like

atopic dermatitis, acne and hand eczema.

Using teledermatology and patient-reported outcomes, it may be possible to tailor individual care. Patients will have more influence and the caregiver is able to respond quickly to signs of aggravation or side effects, while minimizing the use of office visits and other healthcare resources. Teledermatology allows patients to get in contact with healthcare staff when needed instead of predetermined scheduled visits. In an ongoing PhD-study we seek to improve the management of psoriasis patients using participatory design, involving both patients and healthcare professionals in the design and development of a future technology. The overall aim of the study is to identify E-Health approaches to provide health care for psoriasis patients receiving biological treatment. The theoretical framework of this study is based on empowerment, with the intention to improve patient's ability to develop, control and manage healthcare resources.

References

1. Feldman SR. Disease burden and treatment adherence in psoriasis patients. *Cutis* 2013; 92: 258–263.
2. Svendsen MT, Andersen KE, Andersen F, Hansen J, Pottgård A, Johannessen H. Psoriasis patients' experiences concerning medical adherence to treatment with topical corticosteroids. *Psoriasis* 2016; 6: 113–119.
3. Svendsen MT, Andersen F, Andersen KE. eHealth technologies as an intervention to improve adherence to topical antipsoriatics: a systematic review. *J Dermatolog Treat* 2018; 29: 123–128.
4. Svendsen MT, Andersen F, Andersen KH, Pottgård A, Johannessen H, Möller S, et al. A smartphone application supporting patients with psoriasis improves adherence to topical treatment: a randomized controlled trial. *Br J Dermatol* 2018 Apr 14 [Epub ahead of print].

Bradykinin-mediated angioedema

The National HAE Centre is a highly specialized unit seeing children and adults from all over the country for diagnostics, treatment and possible research. We welcome colleagues to visit

our Comprehensive Care Centre. A HAE database was established in 2001 and is now gradually integrated in our genodermatosis database. The phenotypes of hereditary angioedema are expanding these years and other kinds of bradykinin-mediated angioedema are recognized. The HAE Centre collaborates nationally with the Department of Molecular Medicine, Research Unit for Thrombosis Research, ENT department at Rigshospitalet in Copenhagen and Department of Biomedicine in Aarhus with regard to different research projects.

In November 2017, Anne Åbom defended her PhD thesis on Hereditary angioedema – biochemical and pediatric aspects. Three PhD projects related to the field of angioedema are ongoing, as well as several master students projects. At the last C1-INH Deficiency Workshop in Budapest, medical student Kristian Kreiberg received a prize for his presentation: *Smartphone application to record data on attack and treatment patterns in patients with hereditary and acquired angioedema: findings from a Danish cohort* (Fig. 5).

At the moment, we are planning a qualitative study in migrant patients with HAE in collaboration with a nurse from the migrant health clinic at OUH (Fig. 6). We would like to visit patients in their own homes, if they allow us to do so.

References

1. Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. *Front Med (Lausanne)* 2017; 4: 212.
2. Rasmussen ER, von Buchwald C, Wadelius M, Prasad SC, Kamaleswaran S, Ajgeiy KK, et al. Assessment of 105 patients with angiotensin converting enzyme-inhibitor induced angioedema. *Clin Otolaryngol* 2017; 2017: 1476402.
3. Aabom A, Andersen KE, Fagerberg C, Fisker N, Jakobsen MA, Bygum A. Clinical characteristics and real-life diagnostic approaches in all Danish children with hereditary angioedema. *Orphanet J Rare Dis* 2017; 12: 55.
4. Aabom A, Bygum A, Koch C. Complement factor C4 activation in patients with hereditary angioedema. *Clin Biochem* 2017; 50: 816–821.



Fig. 5. Medical student giving his prize-winning presentation.



Fig. 6. Outpatient consultation in the HAE Clinic with migrant patient from Pakistan and urdo-speaking translator.

Contact dermatitis

Children and adults with suspected contact dermatitis are examined, patch-tested, and treated at the Allergy Laboratory and the Eczema Outpatient Clinic. About 500 patients are tested each year, and among these around 25% have occupational contact dermatitis.

The Allergy Laboratory offers the service of an Allergen Bank (www.allergenbanken.dk) from which dermatologist in private practice and other dermatology departments, through subscription, can request extra allergens for patch-testing individual patients with contact allergens beyond the European baseline series.

Our clinical contact dermatitis research focuses on experimental contact dermatitis, occupational dermatoses and allergy to plants in cooperation with Dermatological Investigations Scandinavia (DIS), a joint CRO between SDU and OUH. DIS focuses on dermato-toxicological and -allergological studies on volunteers in cooperation with industry sponsors. DIS has equipment for non-invasive measuring methods related to the skin.

References

1. Andersen F, Andersen KH, Bernois A, Brault C, Bruze M, Eudes H, et al. Reduced content of chloroatranol and atranol in oak moss absolute significantly reduces the elicitation potential of this fragrance material. *Contact Dermatitis* 2015; 72: 75–83.
2. Mose KF, Burton M, Thomassen M, Andersen F, Kruse TA, Tan Q, et al. The gene expression and immunohistochemical time-course of diphenylcyclopropanone-induced contact allergy in healthy humans following repeated epicutaneous challenges. *Exp Dermatol* 2017; 26: 926–933.
3. Mose KF, Andersen F, Røpke MA, Skov L, Friedmann PS, Andersen KE. Anti-inflammatory potency testing of topical corticosteroids and calcineurin inhibitors in human volunteers sensitized to diphenylcyclopropanone. *Br J Clin Pharmacol* 2018; 84: 1719–1728.
4. Paulsen E, El-Houri RB, Andersen KE, Christensen LP. Parthenolide in Danish biodynamic and organic milk: A new source of exposure to an allergenic sesquiterpene lactone. *Contact Dermatitis* 2018 Jun 20 [Epub ahead of print].

Cutaneous lupus

Since 2007 the department has participated in a European collaboration on cutaneous lupus erythematosus (EUSCLE), collecting mostly epidemiological data. As a special interest, we have a focus on drug-induced lupus describing the changing pattern of culprit drugs during the last 20 years, finding an increase in proton pump inhibitor induced SCL. E.

We have established a research database with biobank for future clinical studies.

References

1. Laurinaviciene R, Sandholdt LH, Bygum A. Drug-induced cutaneous lupus erythematosus: 88 new cases. *Eur J Dermatol* 2017; 27: 28–33.
2. Petersen MP, Moller S, Bygum A, Voss A, Bliddal M. Epidemiology of cutaneous lupus erythematosus and the associated risk of systemic lupus erythematosus: a nationwide cohort study in Denmark. *Lupus* 2018; 27: 1424–1430.

Genodermatoses and rare diseases

Our department has a long tradition of clinical handling and research in genodermatoses, which are often rare diseases. The area is a rapidly evolving field, not only in diagnostics with next generation sequencing but also with regards to orphan drugs.

We are responsible for the national course in genodermatoses and pediatric dermatology for upcoming dermatologists. A special focus has been on hereditary hypotrichosis and severe congenital ichthyosis, with a year-long fruitful collaboration with colleagues from Bonn and Uppsala. The department is a member of the European Reference Network for rare diseases, ERN and participates in the working groups IPK (ichthyosis, palmoplantar keratoderma) and ALLOCATE (hidrosadenitis and hereditary angioedema). A European research database is planned when the legal issues have been solved.

In 2016 a grant from the Danish Dermatologic Society was donated to a National Research Database on Genodermatoses. Mostly due to legal obstacles, it is not yet up and running. Instead we made a regional database with an affiliated biobank, and as of July 2018 we have included 428 children and adults with genodermatoses.

References

1. Ü Basmanav FB, Cau L, Tafazzoli A, Méchin MC, Wolf S, Romano MT, et al. Mutations in three genes encoding proteins involved in hair shaft formation cause uncombable hair syndrome. *Am J Hum Genet* 2016; 99: 1292–1304.
2. Mazereeuw-Hautier J, Hernandez-Martin A, O'Toole EA, Bygum A, Amaro C, Aldwin M, et al. Management of congenital ichthyoses: European guidelines of care: Part One. *Br J Dermatol* 2018 *Accepted*.
3. Mazereeuw-Hautier J, Hernandez-Martin A, O'Toole EA et al. Management of congenital ichthyoses: European guidelines of care: Part Two. *Br J Dermatol* 2018 Jun 13 [Epub ahead of print].

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Hyperhidrosis

A cohort of 400 patients with hyperhidrosis has been established and we still recruit for our hyperhidrosis database. In collaboration with the Danish Hyperhidrosis Organization, a prospective study is performed to observe symptom patterns,

health behaviour, treatment needs and quality of life in Danish patients with hyperhidrosis. Our department is until now the only public hospital offering microwave therapy for axillary hyperhidrosis. A substudy will be performed using exome sequencing to identify genes related to familial hyperhidrosis.

References

1. Hansen J. Ukontrollerbar sved – en overset sygdom. Sygeplejersken 2018, web article.
2. Kristiansen BH, Lindahl KH, Pallesen KAU, Bygum A. Two patients with localised hyperhidrosis of the hand based on functional and structural abnormalities of sweat glands. *BMJ Case Rep* 2018 Jan 31;2018. pii: bcr-2017-222530.

Pyoderma gangrenosum

Painful immunological ulcers, especially pyoderma gangrenosum, is a focus area among our nurse specialists. Two studies have been established. A qualitative study of individual interviews looks into how the lifeworld of patients with pyoderma gangrenosum is experienced. A Wound-QoL questionnaire has been translated and is planned to be used in an upcoming study of topical cannabinoids to pyoderma gangrenosum.

References

1. Knudsen JT, Hansen JM. Pyoderma gangrenosum – et smertensbarn. *SÅR*, årgang 26, nr. 3, 2017.
2. Knudsen JT. Livskvalitetsskema (Wound-QoL) i sundhedsvæsenet. *SÅR*, årgang 27, nr. 1, 2018.

Epidermal detachment

The department is treating patients with severe bullous conditions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and their overlap. A study is being conducted to test a special wound dressing for these patients.

Skin cancer and Teledermoscopy

The department has a large clinic for pigmented lesions and skin cancer with 3-4 parallel outpatient clinics daily. All kidney-transplant recipients and other solid organ transplant recipients from the Region of Southern Denmark are offered regular follow-up. Patients at high risk of developing melanoma are monitored with total body photography and sequential digital dermoscopy. In cases of hereditary disorders, such as Gorlin Goltz syndrome, the patients will be registered in a genodermatosis database.

Also, the departments cohort of mastocytosis patients are evaluated for skin cancer, as an increased risk of melanoma has been reported. A clinical study on the use of CO₂-laser



Fig. 7. Teledermoscopy using smartphone and Handyscope®

for the treatment of basal cell carcinoma is presently being undertaken in collaboration with our Adjunct Associate Professor Maja Hofmann, Department of Dermatology, Charite University Hospital, Berlin. Also the use of teledermoscopy in primary care practice for the evaluation of skin cancer is being studied (Fig. 7).

Reference

1. Broesby-Olsen S, Farkas DK, Vestergaard H, Hermann AP, Møller MB, Mortz CG, et al. Risk of solid cancer, cardiovascular disease, anaphylaxis, osteoporosis and fractures in patients with systemic mastocytosis: A nationwide population-based study. *Am J Hematol* 2016; 91: 1069–1075.

Upcoming areas

As a strategic venture and with help from our Adjunct Professor Steven Feldman and key persons at Sygehus Lillebaelt, OUH and SDU, we would like to explore the field of patient communication and narrative medicine in order to improve patients' satisfaction with care. The first ideas are born, and we are working on protocols and applications for funding.

We hope, that the readers of Nordic Forum have got an impression of our dermatologic department and research. We welcome you to visit Odense and OUH and are open for new collaborations. In order to facilitate the internationalization of clinical and research environments, we have an International Staff Office that provides help with legal, practical, social and cultural issues, if people want to relocate to Denmark.