Dermatological Research at Gentofte Hospital, University of Copenhagen

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The Department of Dermato-Allergology, Gentofte Hospital, is part of the University of Copenhagen. Established in 1970, as the Department of Dermato-Venereology, *Professor Niels Hjorth* was department chairman for the first 20 years, followed by *Torkil Menné* for the next 20 years, until his retirement in February 2011. From a department with only two doctors the department has grown steadily over the last 20 years. There are currently more than 165 employees in a large clinical unit and an extensive research section. In 2007 the department merged with the Allergologic Clinic, Rigshospitalet, and Copenhagen Studies on Asthma in Childhood (COPSAC), into the Department of Dermato-Allergology, Gentofte Hospital. *Claus Zachariae* is the current chairman, and *Jeanne Duus Johansen* and *Lone Skov* are professors of dermatology, *Lars K. Poulsen* is professor in the Allergologic clinic, and *Hans Bisgaard* is the professor in COPSAC.

In 2010, the Department of Dermato-Allergology was awarded a prize by the "Global Excellence in Health" programme in the Capital Region of Denmark for one of the ten most outstanding departments for research and treatment.

The main research areas at the Dermato-Venereological Clinic are contact dermatitis, atopic dermatitis and psoriasis, as described below.

Contact dermatitis

Since the establishment of the department, one of the main areas of research has been contact dermatitis. Over the last 10 years this has primarily been performed within the frame of the National Allergy Research Centre, led by *Jeanne Duus Johansen* in collaboration with *Torkil Menné*.

The research strategy has concentrated on epidemiology, gene-environment interactions and prevention of contact dermatitis. Selected highlights of the research programme are mentioned below.

Contact allergy

A series of population-based studies of contact allergy has been performed in the Region of Copenhagen. The most recent study, in 2006, comprising a random sample of adult individuals, showed that nickel allergy decreased significantly from 20% to 10% in young females after regulations were introduced in 1990 reducing nickel. This strongly indicates that the regulations limiting nickel release from consumer items, have been effective.

A network of dermatologists has been established, all of whom are members of the Danish Contact Dermatitis Group. The network members are widely distributed in Denmark, and report all results on patch-tested patients to The National Allergy Research Centre. These results have been the basis of a series of publications on trends in different allergies and risk factors for disease, leading to European regulation of, for example, the preservative methyldibromo glutaronitrile or recommendations for safe use for, for example, the fragrance ingredient hydroxyisohexyl 3-cyclohexene carboxaldehyde. A general model for risk assessment of contact allergens has been developed and published in a PhD thesis by *Louise Arup Fischer*.

Contact allergy: immunology

Contact allergy is classically described as type IV hypersensitivity mediated by T cells, primarily Th1 cells and cytotoxic T cells. However, various other cell types from both the innate and adaptive immune system have been suggested to play a role in allergic contact dermatitis as well as in the induction of tolerance. A novel effector T-cell type has been identified recently; this T-cell subtype produces IL-17 and is named Th17 cells. In collaboration with Department of International Health, Immunology and Microbiology, Panum Institute, Copenhagen, the dermato-immunology section of the department, led by *Lone Skov*, has found that keratinocytes are able to produce IL-23 following nickel stimulation, IL-23 is required for the expansion of Th17 cells. Furthermore, nickel-specific Th17 cells were found in blood from nickel allergic patients and not in blood from healthy controls. Together, the cellular mechanisms mediating type IV hypersensitivity appear to be more complex than previously thought. Two PhD students are continuing to study the type and role of effector and regulator T cells in contact allergy.


Lone Skov, professor of Dermato-allergology.


Jeanne Duus Johansen, professor of Dermato-allergology.


Claus Zachariae, head of the Department of Dermato-allergology, Gentofte Hospital.


Torkil Menné, professor emeritus of Dermato-allergology.

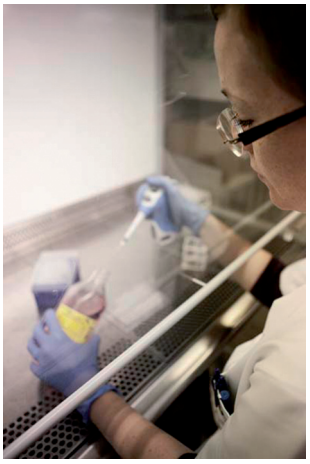


Fig. 1. Laboratory research at Gentofte Hospital.

Disease patterns

A number of studies have been performed concerning the inter-relationship between contact allergy and auto-immune diseases (diabetes type I, rheumatoid arthritis, inflammatory bowl disease) and a significant inverse relationship. This has been studied further in animal models. The results have been published as a PhD thesis by *Kåre Engkilde*.

Hand eczema

A guideline on the classification, diagnosis and treatment of hand eczema has been developed together with the Danish Contact Dermatitis Group. A focus has also been on occupational hand eczema in hairdressers and intervention, as part of the information centre for hairdressers established in the department and led by Heidi Søsted. Two PhD studies on hairdressers and occupational hand eczema have been carried out recently. One was an intervention study on hairdresser apprentices, where an educational programme was developed and tested in the technical school. The programme was successful in reducing the incidence of hand eczema among the apprentices and is now being implemented in schools educating hairdressers in Denmark. The study is published as a PhD thesis by *Anne Bregnhøj*. The other PhD is on hand eczema and reasons for leaving the trade and is in its final phase.

Hand eczema, empowerment and information

An intensive programme for the empowerment of patients with hand eczema is currently being tested in the department. The programme is based on qualitative interviews with patients with hand eczema and consists of a consultation with a specialist nurse and information based on a personal profile of the patients.

Information is also provided more generally. A film on hand eczema has been developed and, based on the results of a survey, is well-accepted by patients with hand eczema. The film is shown to all patients in the department with hand eczema. It is available at: www.handeksem.dk.

Filaggrin, atopic dermatitis and skin barrier research

The skin barrier and individual susceptibility to eczema (atopic dermatitis and contact eczema) have been studied by analysis of the two major filaggrin mutations (R501X and 2282del4), which may lead to a disrupted stratum corneum. It is already known that these mutations correlate with atopic dermatitis, where it is found in up to 40% of patients. Analysis for filaggrin mutations was established at the Department of Clinical Biochemistry at Gentofte Hospital as part of a joint project. This means that the analysis is offered to relevant patients in the clinic and that typing has been performed on different populations, patients and the general population, in order to describe the possible effects of a disrupted skin barrier on the risk of allergy and eczema.

Genotyping has so far been performed in our department on 6,000 individuals from the general population and 900 patients with eczema. We have established that 8% of the general Danish population carries one of the two filaggrin mutations. Also, a positive and significant relationship between filaggrin gene defect and nickel allergy was found among those who had never been pierced and had a lower age of onset of nickel dermatitis. While no relationship was found with other frequent allergens, or with multiple allergies in eczema patients (by *Berit Carlsen*), which supports the theory that the major risk factors for contact allergy are environmental. Filaggrin mutations and atopic dermatitis were positively associated with neomycin and ethylenediamine sensitization, probably due to intensive topical treatments. Work is currently being carried out to extend the genetic analysis to more mutations and to extract filaggrin from the stratum corneum to establish a relationship between phenoand genotypes, both in patients with atopic dermatitis and in those without. Studies on children with atopic dermatitis, filaggrin mutations and risk factors are being performed in collaboration with the COPSAC section of the department and led by *Hans Bisgaard*.

Studies exploring other genes associated with atopic dermatitis are being performed in an international co-operation and immunological mechanism in atopic dermatitis in collaboration with the allergy clinic led by *Lars K. Poulsen*.

Psoriasis: biomarkers

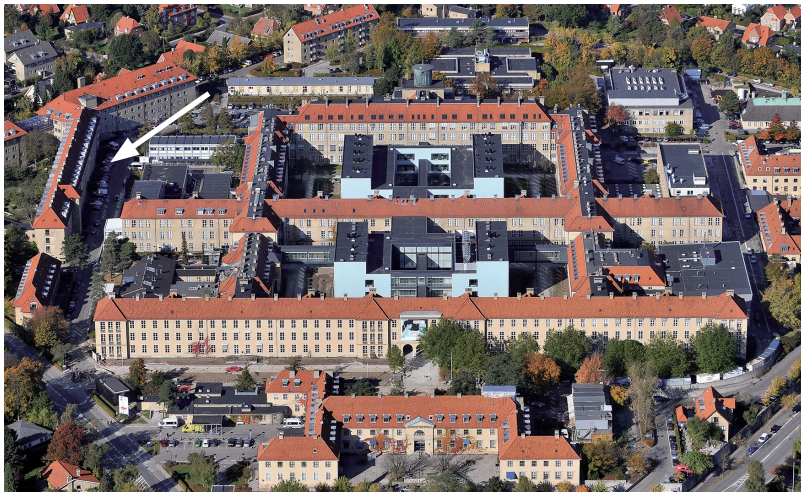
Biomarkers for identifying subgroups of patients and for identifying patients with different response to treatment among patients with psoriasis are missing. MicroRNAs (miRNAs) are endogenous, non protein-coding oligo-RNAs of 18–24 nucleotides. miRNAs are hallmarks in a broad range of biological

processes, including development, cellular differentiation, proliferation and apoptosis. Moreover, several publications implicate that miRNAs are important players in the pathogenesis of human diseases such as cancer and metabolic disorders, and that miRNAs are key regulators of gene translation in the immune system. We and others have described a specific miRNA profile in psoriasis. The results have been published as a PhD thesis by *John R. Zibert*. Our goal is to substantiate this finding in skin and blood, and to compare the miRNA with identified known mRNA profiles. *Lone Skov*'s group are also looking for other biomarkers in psoriasis useful in the monitoring of the disease activity, and as possible targets for new treatment. The studies are being performed in co-operation with the Department of International Health, Immunology and Microbiology, Panum Institute, Copenhagen and the industry.

Psoriasis: co-morbidity

Patients with psoriasis have an increased risk of arterial hypertension, coronary heart disease, hyperlipidaemia, obesity and type II diabetes, and severe psoriasis is associated with increased risk of death. Activated inflammatory cells and pro-inflammatory cytokines contribute to the development of psoriasis and also play important roles in the development and stability of atherosclerotic plaques. For the last 3 years the focus of the group, which is led by *Lone Skov* and *Claus Zachariae*, has been on epidemiological evidence for an association between psoriasis and cardiovascular disease, and treatment of co-morbidity and psoriasis severity. For example, whether weight reduction leads to decreased severity of psoriasis and whether treatment of psoriasis has a positive effect on the risk of cardiovascular co-morbidity.

Gentofte Hospital.
White arrow indicates the position of Department of Dermato-Allergology.



Facts

The University of Copenhagen was founded in 1479. Gentofte Hospital was built 1927. The Department of Dermatology and Venereology was opened in 1970, where also its first Professor was appointed. The department was in 2007 changed to The Department of Dermato-Allergology and have now more than 165 employees.

The group of researchers at the Department of Dermato-Allergology at Gentofte University hospital consists of:
4 professors
1 professor emeritus
8 post-doctoral researchers
26 PhD students

The research at the department has in the period 2008–2010 lead to publication of 233 original articles and 17 theses have been defended in the period.