Dermatological Research at Herlev and Gentofte Hospital, University of Copenhagen

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The Department of Dermatology and Allergy, Herlev and Gentofte Hospital is part of the University of Copenhagen. It was established as the Department of Dermato-Venereology in 1970, with Professor Niels Hjorth as the department chair for the first 20 years. He was followed for the next 20 years by Professor Torkil Menné, until his retirement in February 2011. From its beginnings, with only two doctors, the department has grown steadily over the last 40 years. In 2007, the department merged with the Allergy Clinic, Rigshospitalet into the Department of Dermatology and Allergy, Herlev and Gentofte Hospital. By 2017 the department had more than 182 employees, constituting a large clinical unit and research section. In 2016 the department produced more than 160 publications and 5 PhD theses were defended.

Claus Zachariae is the head of the department, Jeanne Duus Johansen and Lone Skov are professors in the dermatological section, and Jacob Thyssen is professor from December 2017. Lars K. Poulsen is professor in the allergy section.

The department has two research units in connection with the dermatological section (the National Allergy Research Centre and the Copenhagen Research Group for Inflammatory Skin (CORGIS)) and one in connection with the allergy section. The main research areas in the dermatological section are contact dermatitis, the skin barrier, atopic dermatitis, and psoriasis. The main research areas in the allergy section are immunoglobulin E (IgE)-mediated allergy, allergen immunotherapy and drug allergy.

The research areas with focus on the dermatological section are described below.

Research units, dermatology

Since its beginning, one of the main focuses of research in the department has been contact dermatitis.

Over the last 15 years, contact dermatitis research has primarily been performed within the frame of The National Allergy Research Centre, led by Professor Jeanne Duus Johansen formerly in collaboration with Professor Torkil Menné. At present, 11 PhD studies on contact dermatitis are ongoing. Information about former as well as current studies and publications can be found at www.videncenterforallergi.dk.

For the last 20 years, research at the department has also focused on other inflammatory skin diseases, especially psoriasis and atopic dermatitis. The research has primarily been performed within the CORGIS, led by Professor Lone Skov in collaboration with head of department Claus Zachariae and new professor Jacob Thyssen. At present, 9 PhD studies on atopic dermatitis and psoriasis are ongoing. A large unit for clinical trials is connected to this research unit, with specially trained staff, including study coordinator, nurses and a laboratory technician.

There is a high degree of collaboration between the two units.

Selected highlights of the research programme for the last few years are mentioned below.

Contact allergy and prevention

In recent years, the focus has been on the rapidly increasing frequency of contact allergy to methylisothiazolinone (MI), following permission to use it in cosmetic products in 2005

in the European Union (EU). This has been the subject of several PhD studies from our department, demonstrating the increase, risk factors, important consumer and occupational exposures. The latest PhD thesis on this subject is from 2017 by Jakob Schwensen. Based on these data and similar from other European countries, MI has been banned from use in leave-on cosmetics, restricted in rinse-off cosmetics, and requirements have been enforced for labelling and warnings on chemical products, including paints.

In May 2015, a REACH (Registration, Evaluation, Authorisation and restriction of Chemicals) regulation on chromium VI in leather products intended for skin contact was introduced in the EU on the initiative of the Danish Government. In a series of studies, the epidemiology of chromium allergy and risk factors in Danish patients with dermatitis were elucidated as a basis for a future evaluation of the REACH regulation. Furthermore, the efficacy of a spot test for chromium VI detection was evaluated and found valid when used on leather and metal articles. The results are reported in a PhD thesis by David Bregnbak.

Occupational contact dermatitis

Occupational contact dermatitis is a frequent problem and exposure assessment is challenging. A systematic stepwise exposure assessment, consisting of 6 steps, was developed. Using this tool, we found additional, relevant allergies in one-third of patients. In total, 132 different allergens were present in the work environment and were relevant for the patients' dermatitis. Of these, 103 allergens were not included in the European baseline series. These findings have been published in a PhD thesis by Ulrik Fischer Friis.

A prospective questionnaire study was conducted among hairdressing apprentices and young adults from the general population. The incidence of contact dermatitis, urticarial and rhinitis symptoms occurring over a 3-year period was significantly increased in the hairdressing apprentices. A total of 21.8% of the hairdressing apprentices had left the trade after 3 years, and more than 70.4% of those who left reported doing so because of disease. These results have been published in a PhD thesis by Majken Hougaard Foss-Skiftesvik.

Filaggrin, atopic dermatitis and skin barrier research

The skin barrier and individual susceptibility to eczema (atopic dermatitis and contact eczema) has been studied by analysis of the 3 common filaggrin gene (FLG) mutations (*R501X*, *2282del4*, and *R3247X*). At the department, it was shown that FLG mutations were strongly associated with dermatitis on the hands and feet in individuals with atopic dermatitis. A history of atopic dermatitis predicted both incident and persistent hand eczema in the general population. Self-reported dermatitis, particularly in individuals with FLG mutations, was significantly associated with receiving disability pension in the general population. These results have been published in a PhD thesis by Nina Glasser Ulrich. Kristiane Aasen Engebretsen has finalized her PhD thesis on the effects of environmental stressors on the skin in the context of atopic dermatitis. She has shown how domestic exposure to hard water as well as winter weather significantly increased the risk of paediatric atopic dermatitis. Moreover, by using non-invasive tape strips methods she has been able to identify molecular changes in the skin following exposure to hard water, house dust mites, *Staphylococcus aureus* toxins,

ultraviolet irradiation and other stressors. Stine Simonsen has in her PhD thesis studied the effect of acute and chronic ultraviolet B exposure on immune cells and filaggrin in healthy and atopic skin. Along that line, an ambitious birth cohort is now being established that attempts to examine cutaneous predictors of atopic dermatitis by using tape strips in premature and mature newborns. Moreover, a large study will be initiated in Greenland, in which the genotype, immunotype and phenotype of atopic dermatitis in Greenlanders will be examined. This is foreseen to be of particular value as it may identify new genetic and environmental risk factors for atopic dermatitis. In her PdH thesis, Yuki Andersen has carefully studied major non-atopic co-morbidities of atopic dermatitis in adults and among other shown that patients have increased risk of autoimmune diseases, but not cardiovascular diseases.

Psoriasis – epidemiology and co-morbidity

Patients with psoriasis have an increased risk of several co-morbidities. The department has, in collaboration with the Department of Cardiology at the hospital, used the nationwide Danish registers to study the associations between psoriasis and other inflammatory diseases. Alexander Egeberg has defended his PhD thesis on certain central nervous system (CNS) diseases, including multiple sclerosis and the association with psoriasis, and has subsequently continued in the department with epidemiological studies on prevalence and co-morbidities related to psoriasis, rosacea and atopic dermatitis. The prevalence and metabolic risk factors as diabetes in patients with psoriasis is supported by epidemiological studies in twins, as reported in a PhD thesis by Ann Sofie Lønnberg. Findings that support the notion that psoriasis is a pre-diabetic condition and suggest that gastrointestinal-related mechanisms are involved in the increased susceptibility to type 2 diabetes in patients with psoriasis is reported in the PhD thesis by Mette Gyldenløve.

Psoriasis – immunology and biomarkers

Psoriasis is a chronic inflammatory disease in which Th17 T cells are important; however, other lymphocytes also play a role, including innate lymphoid cells, gamma delta T cells and neutrophils. These results have been reported in the PhD thesis by Beatrice Dyring-Andersen. Biomarkers for identifying subgroups of patients and biomarkers 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. We, and others, have previously described a specific miRNA profile in psoriasis. miRNA as robust biomarkers in skin and blood was reported in the PhD thesis by Marianne Løvendorf.

IgE-mediated allergy

The research unit in the allergy section covers all kind of IgE-mediated allergy, clinical and basic and patients with suspected drug allergy. The research in the section is led by Professor Lars K. Poulsen and Associated Professor Lene Heise Garvey in collaboration with head of department Claus Zachariae. A main research area is the optimization of diagnostics in penicillin allergy and other drug allergy, including the use of drug provocation. The Allergy Clinic also has a National Reference Centre for the investigation of perioperative hypersensitivity (the Danish Anaesthesia Allergy Centre). The main research areas are specific causes, including allergy towards chlorhexidine and other hidden and rare allergens such as excipients, mechanisms and treatment of perioperative hypersensitivity and the use of drug provocation in perioperative hypersensitivity. Doctors from the clinic are represented in national and international working groups on both penicillin allergy and perioperative hypersensitivity.