Dutch contributions to dermatology

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Colophon

ISBN/EAN: 978-9073459-46-5

This book is an initiative of the History Working Group of the Dutch Society for Dermatology and Venereology (NVDV), on the occasion of the 23rd congress of the EADV - European Academy of Dermatology and Venereology (Amsterdam 8-12 october 2014). Its publication has been made possible through an eductional grant from the Teljer-foundation of the NVDV.

Published by Belvédère Publishers Limited, Bloemendaalseweg 244, 2051 GN Overveen, The Netherlands, in close cooperation with the NVDV, Mercatorlaan 1200, 3528 BL Utrecht.

Cover
"Jupiter and Antiope", etching by Rembrandt van Rijn, 1659, 140 x 205 mm.
In Greek mythology, Antiope was the daughter of the Boeotian river god Asopus.
Her skin attracted Zeus, who, assuming the form of a "dermatologist", took notice of her.

Bridges
The Dutch bridges depicted in this book are meant as a visualization of the slogan of the 23rd congress of the EADV: "Building Bridges".

Linguistic consultancy
Sophie van Everdingen & Simon Hudson, Cambridge.

Design
Grafitext, Velp.

Print
SMG-Groep, Hasselt.

Figure and tables (page 24-25)
Evangeline Ip Vai Ching, Rotterdam.

Photography
Dreamstime: page 4, 6, 26, 48, 78, 79, 94, 112, 127, 141, 142, 152.
Wikimedia Commons: page 62 (photographer Arjan den Boer), 95 (photographer Havang).
Rotterdam Image Bank: page 126 (photographer Ossip van Duivenbode).
Tamar Nijsten: page 5 (photographer Levien Willemse).
Dermatology department staff at the VUmc in 2014: page 125 (photographer Paul Starink).
Suzanne Pasmans: page 139 (photographer Kees Wollenstein).
Clinical medical photos, portraits and buildings Medical Centers: archives of contributing centers.

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Zeeland Bridge.
The Zeeland Bridge, built between 1963 and 1965, is, with its 5 kilometer span the longest bridge in the Netherlands. It is part of the Delta Works, a series of civil engineering projects in the southwest of the Netherlands made to protect a large area of land around the Rhine-Meuse-Scheldt delta from the sea.

1 Introduction

Tamar Nijsten, chairman Dutch Society for Dermatology and Venereology

Hosting the 2014 European Academy of Dermatology and Venereology (EADV) in Amsterdam is a privilege for the Dutch dermatologists. This event gives us the opportunity to present our clinical, scientific and organizational skills to our European colleagues. As in every relationship, knowing the past of your counter part is increasing the chances of developing a better and deeper understanding. With this book, we set out to give our international guests an introduction to Dutch dermatology and its scientific contributions. In writing this book and reading it we got to know each other better as well.
Søren Aabye Kierkegaard (1813-1855) said 'life can only be understood backwards, but it must be lived forward'. Most of us are so busy living our lives forward with full clinics, administration, science, family live and our smart phones that we forget to look back. Although I recognized most focus areas and their main investigators and clinicians of the different university departments, I have to confess that I felt like getting acquaintaned with the past of my colleagues and their centers. We all share a common background as dermatologists and have picked the clinical and research topics that are close to our hearts and often in line with our predecessors. It is fascinating to see how the evolution of dermatology from infectious diseases (venereal diseases) to inflammatory and oncological diseases is reflected in history of most dermatology departments in the Netherlands.
I congratulate the editors and authors of this marvelous document on past and present of Dutch dermatology, and strongly recommend it to all dermatologists.

View of the river IJssel in Deventer, with the Wilhelmina Bridge in the foreground.
This bridge doubled for the eponymous structure at Arnhem in the film 'A Bridge Too Far' (1977).
The landscape beyond features some water meadows typical of this part of the country.

2 Dermatology in the Netherlands, past and present

Henk Menke
with contributions by Jannes van Everdingen, William Faber, Johan Toonstra and Willem van Vloten

This introductory chapter is about the origin and development of Dutch dermatology. It is intended to give the following chapters a broader context and a historical perspective. It is simply a starting point, presenting developments through the eyes of the recently established history working group of the Dutch Society for Dermatology and Venereology (NVDV). Hopefully this preliminary analysis will serve as an incentive for dermatologists and others to unravel matters within the wider framework of the history of science and the social history of medicine.

Trailblazing scientific contributions from the past

Dermatology emerged as a separate discipline of medicine in Europe in the nineteenth century. The Netherlands was not a forerunner in this specific development. However, from the so called Dutch golden age (the 17th century) onwards, important views, discoveries and developments had already been developed by Dutch pioneers, which laid the early foundations and created the research tools that contributed to human biology and medicine with a spin-off for what we now know as dermatology. So, while celebrating the achievements of today's dermatologists, some mention should be given of these pioneers who indirectly contributed to the establishment of this field. To rephrase Newton, it is by standing on their shoulders that we have been able to see that much further.

Sufferers of syphilis being treated with mercury (John Sintelaer, 1709).

Theatrum anatomicum, Museum Boerhaave, Leiden.

Herman Boerhaave

Professor of medicine, botany and chemistry in Leiden, Herman Boerhaave (1668-1738), was a famous teacher of medicine, attracting students from all over Europe, including for instance Carl Linnaeus (1707-1778). He also was a world famous clinician and scientist. He promoted mechanistic disease explanations with a corpuscularian matter theory, seeing health in terms of hydrostatic equilibrium, a balance of internal fluid pressures.[1] Boerhaave attached great importance to autopsy, as a means through which the consistency between anatomical abnormalities and clinical symptoms could be established. Regarding the Great Pox (syphilis), ravaging European countries in those days, he argued that it had arisen as a result of African sexual promiscuity, but that in Europe it could be spread in a number of ways, and not only by genital contact.[2] One of Boerhaave's pupils was the Dutchman Gerard van Swieten (1700-1772), who later became professor of medicine in Vienna and personal physician to Queen Maria Theresia of Austria. He questioned the utility of the conventional mercury salivation therapy and developed and studied the use of mercury water therapy for syphilis. His formula (the so-called Van Swieten's liquor) was listed in the pharmacopeia of many countries, including Japan, up to 1930.[3]


HERMANNI
BOERHAAVE
OPERA OMNIA
MEDICA
COMPLECTENTIA
VENETIIS MDCCLI.
Apud Laurentium Basilium.

Opera Omnia Medica: an anthology of works by Herman Boerhaave.

Antoni van Leeuwenhoek

The birth of microbiology is usually dated to 1675, when Antoni van Leeuwenhoek (1632-1723) first came to mention “wee beasties” in a series of letters to the Royal Society of London for Improving Natural Knowledge. A Delft textile merchant by trade, Van Leeuwenhoek used magnifying glasses to inspect the weaving of sheets. Encouraged by doctors including his fellow townsman Reinier de Graaf, himself a correspondent of the Royal Society, he improved his lenses and manufactured his first microscope around 1670. The lens enlarged five hundred times and, more importantly, gave a high resolution. His technique for the manufacture of small glass beads was probably based on a combination of grinding and blowing, but sadly he took his secret with him to the grave. It was another century before scientists were able to improve on his version of the microscope, and some further 50 years after that before micro-organisms were first identified as pathogens. Without the original light microscope and the later development of specific techniques such as dark field microscopy and immunofluorescence microscopy, the development of modern medicine, including microbiology and dermatology, would not have been possible.[4]

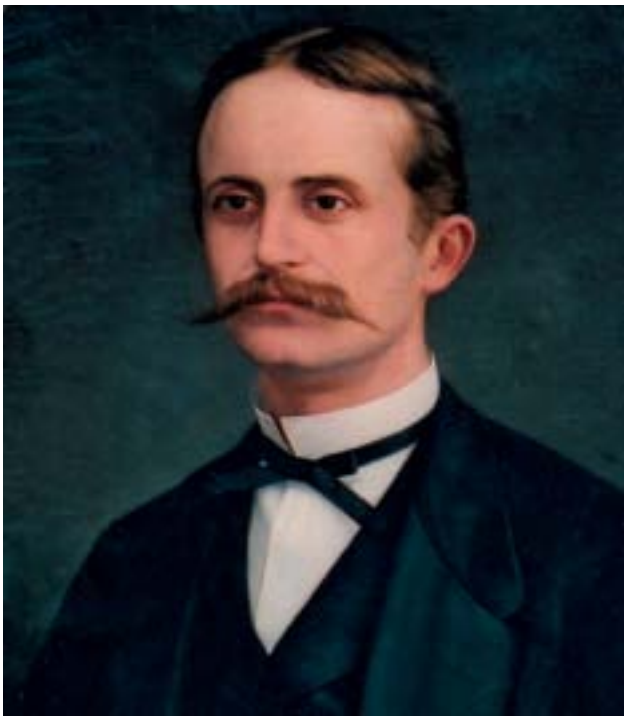
Replica of a Van Leeuwenhoek microscope, latter half of the 17th century.
Museum Boerhaave, Leiden.

Reinier de Graaf

Reinier de Graaf (1641-1673) became famous for his research in the male (1668) and female reproductive organs (1672), in which he relegated to the realm of fiction the old Aristotelian notion that females play a passive role in reproduction. His "De mulierum organis generationi inservientibus" provided an remarkable description of the ovaries - at the time still referred to as "female testes" - together with observations on vesicles which are still known today as Graafian follicles. Besides these, he also studied rabbits' ovaries after mating and found yellow bodies, or what we now call corpora lutea. According to de Graaf, humans, like other mammals, originate from the egg. He soon entered into a vitriolic battle with his friend Jan Swammerdam (1637-1680), who had published his research on the same subject that same year. They both claimed to be the first to describe the follicle, but ultimately the battle was cut short by de Graaf's untimely death in 1673, at the age of 32, from galloping consumption.[5] Through his findings de Graaf became one of the pioneers of genital anatomy.

Petrus Camper

Petrus Camper (1722-1789) was a Dutch physician and anthropologist born in Leiden. He studied philosophy and medicine at the University of Leiden and was appointed professor first in Franeker and subsequently in Amsterdam and Groningen. His contribution to dermatology is mainly related to his view on human pigmentation. His significance to this area is best understood when placed in the context of the work of other Dutch scientists from that period. From the European perspective, black skin was evidently different from white skin and merited investigation. Frederik Ruysch (1638-1731), an anatomist from Amsterdam and a pioneer in techniques of preserving organs and tissue, described two black African foetuses in his 'Thesaurus Anatomicus' (1716). Some 20 years later, Bernard Siegfried Albinus (1697-1770) a student of Boerhaave from Leiden, was the first to publish in a scientific paper (1737) an illustration of the dissected skin of a black subject. It was Petrus Camper who described the location of the human skin pigment during his inaugural lecture 'On the Origin and Colour of Blacks', on 14 November 1764 in the Anatomy Lecture Theatre of the University of Groningen. He showed that the skin (dermis), whether of a black or a white person, is white and that the second or middle layer, which is called the reticulum, can be black, brown, red-copperish or tanned, depending on the skin type. He further demonstrated that this layer does not contain blood vessels, and that the upper layer, the so-called cuticula, is transparent, so that it appears more or less coloured by the underlying layer.[6]



Charles Louis Drognat Landré

Leprosy occurred in overseas European colonies, but also appeared to be highly prevalent in the western part of Norway in the 19th century. The debate on its cause was confused by a diversity of ideas, but by around the middle of the 19th century both Norwegians and British alike vigorously defended the idea that the disease was hereditary, with no role for infectivity. The Dutch Charles Louis Drognat Landré (1844-1917) entered the debate in 1867 with the dissident opinion, defended in his thesis at Utrecht University (title: "On the contagiosity of lepra arabum, proven by the history of this disease in Suriname"), that leprosy was a contagious disease. Two years later he published his ideas in a French monography.[7] At the core of his argument was the observation of 12 white settlers in Suriname, suffering from leprosy, for whom contact with non-white leprosy patients - African slaves or their descendants - could be demonstrated in all cases. Drognat Landré's French publication was read by the Norwegian Armauer Hansen. The latter concludes that it was Drognat Landré's book which made him aware that Norwegian research had paid insufficient attention to the question of infection. Hansen continued his research in this new direction and discovered the culpable micro-organism in 1873. In an obituary after Hansen's death in 1912, H. P. Lie, his closest collaborator and successor as leprosy medical officer in Norway, commented that: "All of Hansen's investigations fitted completely those results, which Drognat Landré had arrived at through investigations in Surinam."[8]

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Ehlers-Danlos Syndrome diagnosed in George Albes, a Spanish sailor famed for being able to stretch the skin of his chest out to arm's length. Albes was presented by the Dutch surgeon Job van Meekeren to a group of senior physicians at the Academy of Leiden in 1657.

The birth of dermatology in the Netherlands

In his historical essay on the origin of the specialism of Dermatology in the Netherlands, Berend Mesander (1926-2000) points out that, until the 19th century, patients with skin and venereal diseases were treated by barber-surgeons and quacks.[1] Doctores medicinae, professionals with a university education, focused on internal medicine. They might have been interested in theoretical aspects of skin and venereal diseases, but generally considered these ailments far beneath them, particularly disdaining the crude practice of treatment with ointments, bandages and fumigation. Qualified doctors entered the scene if the barber surgeon requested their assistance to prescribe internal medication.

Starting at the end of the 19th century, the origin of medical specialisms is on the one hand related to the emergence of new knowledge (e.g. microbiology) and new techniques (e.g. the use of anaesthetics), and on the other to the increase of wealth, prosperity and life expectancy. Dermatology, or to be more precise Dermato-venereology, was one of the first specialisms to emerge. The first chair in dermatology was established at the University of Amsterdam in 1867. It took a further 50 years before another university, Groningen, found room for another. Chairs at Utrecht and at Leiden were soon to follow. Early interest in dermatology focused on patients with infectious diseases of the skin, such as scabies, favus, syphilis and erysipelas.

The first Dutch dermatologists were mostly autodidacts: general practitioners and health officers who had gleaned knowledge of skin and venereal diseases through self-study, practical experience and visits to well-known dermatological centers outside the Netherlands, such as the Unna clinic in Hamburg. Some dermatologists were trained in Amsterdam, the only Dutch academic dermatology center in those days. By 1900 dermatology had been established as a specialism in all major cities of the Netherlands: Amsterdam, Rotterdam, the Hague, Groningen and Utrecht. Nevertheless, setting up a dermatological practice remained a challenge. General practitioners did not easily surrender their position to newcomers. Many believed they had sufficient knowledge to treat patients themselves, perhaps taking this view as much for financial as for professional reasons. Dermatologist-urologist (!) Lucas Maillette de Buy Wenniger (1875-1934) accentuated the tension between traditional practitioners and the new specialists, when he wrote to his fiancée in 1902: “I’m beginning to understand what having a specialism essentially means: it means doing just one thing and knowing something about that thing, of which colleagues shamefully know absolutely nothing.”

Ultimately, the universities played only a marginal role in the rise of dermatology as a separate specialism. According to Jan Roelof Prakken (1897-1982), the same could not be said for the NVDV, established in 1896[2]. Interestingly, the society’s 1896 memorandum of association does not explicitly describe venereology. The proposed line was the study of dermatology and venereology, but originally substantial attention was paid to diseases of the urogenital system. Urology was thus specifically considered part of the society’s field of study. This was confirmed by P.H. Schoonheid’s demonstration held in 1905 on modern diagnostics with new cystoscopes and separators, and by a thesis on the urine of those suffering from dermatoses, published in 1908 by M.E. Polano, father to the later dermatology professor M.K. Polano. The situation changed in 1910, when the urologists left the society en masse to establish their own. At the society’s general meeting, the president announced

that urology had been dropped as a field of study: “We apply ourselves to dermatology and venereology, and will leave urology to the urological society.”
In the early years of dermatology only a few dermatologists had the courage to confidently proclaim their specialism. The NVDV’s archive holds a relatively large amount of letters and prescriptions. Among these are letters dated between 1896 and 1900, in which two physicians have “dermatologist” printed by their name and four others, more cautiously, have “practitioner, consults for skin diseases etc.” After 1900, however, nearly all letters are signed “dermatologist”, sometimes with “etc.”, combined with bladder specialist or, after 1915, X-ray or radiation specialist.

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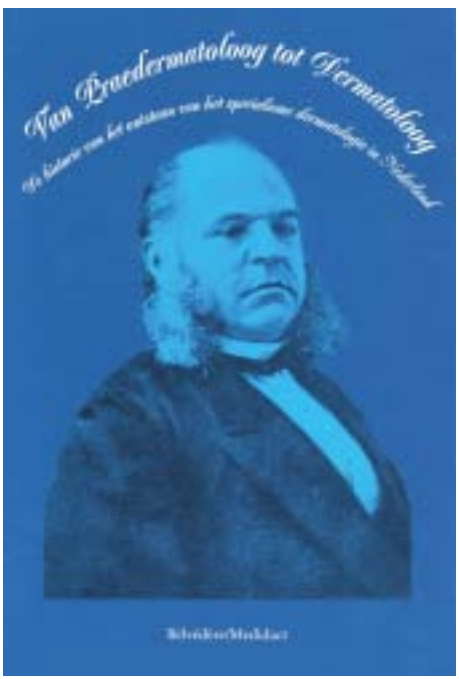


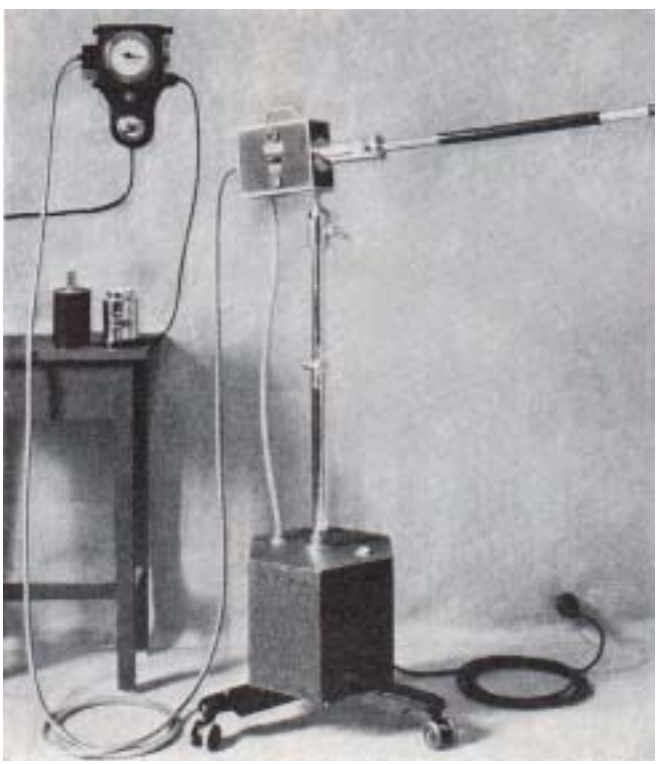
Book by B. Mesander on the history of dermatology in the Netherlands.

Dutch dermatologists and their working place

Up until the 1960s, almost all dermatologists worked independently in extramural practices and less than 10% of them were women. Today, most work intramurally (often in a partnership), and in 2013 half of the 474 active dermatologists in the Netherlands were women. The field has also changed significantly in terms of content, which can be ascribed to the major economic, social, cultural and medical technological changes of the last 50 years.

Since the emergence of the specialism in the second half of the 19th century, and well into the 20th century, it was not uncommon for dermatologists to run clinics in a separate part of their own home. The field was particularly suitable for this approach because the most important diagnostic measure was inspection with the naked eye, sometimes aided by a magnifying glass. For most patients, therapy consisted of nothing more than receiving a prescription, usually for a local treatment. Surgical procedures were kept to a minimum, including the diagnostic biopsy and excochleation and/or electrocoagulation of benign skin tumours and precancerous lesions. Basal cell carcinomas were treated with radiotherapy, also known as contact X-ray therapy, and almost any self-respecting dermatologist owned such a device which, incidentally, was also used for a variety of benign skin conditions.

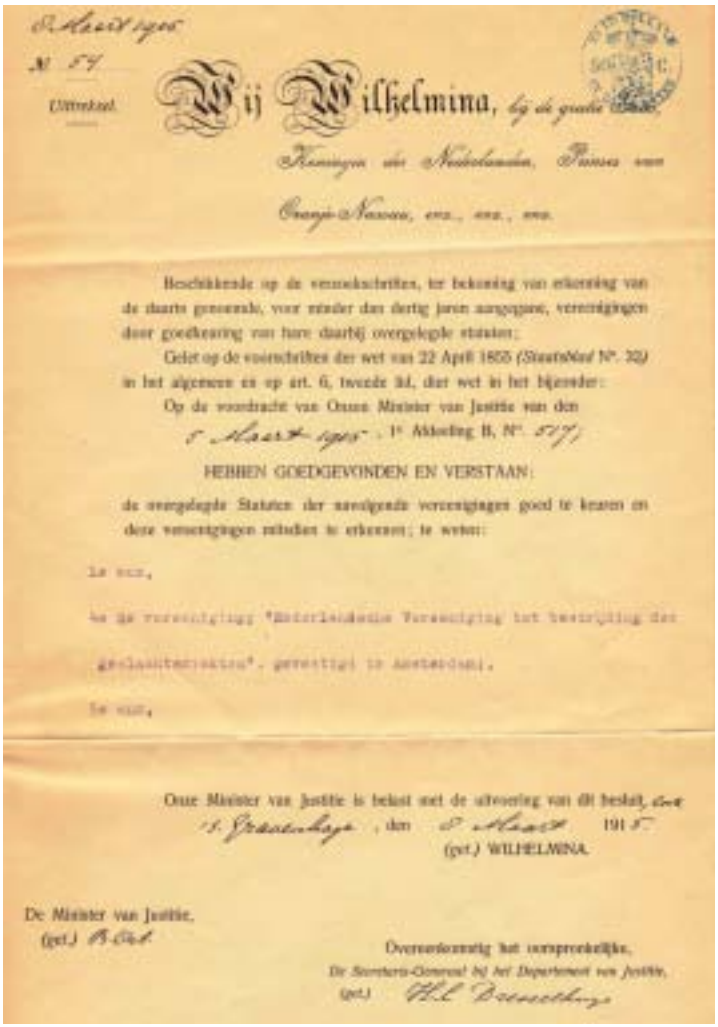
In the 1980s the use of contact X-ray therapy was fiercely debated with regard to therapy-resistant plantar warts. In the 1950s, liquid nitrogen treatment became popular, partly as an alternative to electrocoagulation. Patients with severe, extensive skin disorders such as generalised eczema or psoriasis could be hospitalised for weeks. Many dermatologists therefore had agreements with nearby hospitals, where beds were available. These patients were visited once or more times per week by the dermatologist in order to adjust the local therapy. The shift from solitary practice to hospital began in the 1960s, and continued towards the end of the 20th century. Dermatology had gradually become more complicated, not only through a deeper knowledge of the cause of disease which opened up new diagnostic possibilities, but also through the development of systemic therapies for chronic inflammatory skin diseases, the emergence of dermatosurgery, associated with the cancer epidemic and the development of phlebology and cosmetic dermatology. Moreover, dermatologists



Röntgen treatment from the early 20th century.

wanted to take advantage of the support services of a hospital and the availability of other specialisms. At the same time, patients had become more critical and outspoken, united in patient organizations and supported by new healthcare legislation, so that the old authoritarian doctor-patient relationship gradually gave way to a more consultative model with an emphasis on participation, dialogue and choice. Because healthcare now took up an increasing share of total government expenditure, political entities, health insurers and hospitals started playing a more explicit role in judging eligibility for reimbursement.

In this changing climate, dermatologists could no longer hold their own and opted to work within the precincts of the hospital, in partnership with their colleagues. Such cooperation could also be extended to other specialisms: for example, with gynaecologists in cases of vulvar pathology and surgeons with regard to phlebology. Thanks to increased regulation, peer review, the delegation of tasks to other health professionals, and through collaboration with specialists from other disciplines, a new formula for good quality dermatological care could begin to take shape.



Wij Wilhelmina, bij de gratie

Koningin der Nederlanden, Prinses van

Oranje-Nassau, enz., enz., enz.

Beschikkende op de verzoekschriften, ter bekoming van erkenning van de daarin genoemde, voor minder dan dertig jaren aangegane, verenigingen door goedkeuring van hare daarbij overgelegde statuten;

Gelet op de voorschriften der wet van 22 April 1855 (Staatsblad N°. 32) in het algemeen en op art. 6, tweede lid, dier wet in het bijzonder;

Op de voordracht van Onzen Minister van Justitie van den 5 Maart 1915, 1e Afdeeling B, N°. 517;

HEBBEN GOEDGEVONDEN EN VERSTAAN:

de overgelegde Statuten der navolgende verenigingen goed te keuren en deze verenigingen middelen te erkennen; te weten:

1e een,

de vereeniging "Nederlandsche Vereeniging tot bestrijding der Geslachtsziekten", gevestigd te Amsterdam,

2e een,

Onze Minister van Justitie is belast met de uitvoering van dit besluit, dat 's Gravenhage, den 5 Maart 1915.

(get.) WILHELMINA.

De Minister van Justitie,
(get.) A. Ort

Overeenkomstig het oorspronkelijke,
De Secretaris-Generaal bij het Departement van Justitie,
(get.) Ch. L. Bauduin

Fading of attention for venereal diseases

The first Professor of Dermatology in the Netherlands, Chanfleury van IJsselstein was appointed in 1867 in Amsterdam in response to the venereal problem. Combating venereal diseases (VD's), and scientific research of this group of disorders remained high on the agenda for decades, not only in Amsterdam, but also at the three academic departments of dermatology (Groningen, Utrecht and Leiden) that were established at the beginning of the twentieth century. This can be illustrated by the research agenda of the Department of Dermatology at the University of Utrecht, for example.

Document establishing the founding of the Dutch Society for the Fight against Venereal Diseases (1915).

The importance of venereology was noticeable in the academic output in the early days of the department. During the professorship (1919-1943) of the first ordinarius, professor dr. van Leeuwen, thirteen PhD theses were published. Six of them dealt with VD's. And from the 126 scientificpublications in this period, 51 dealt with VD's. In the second half of the last century, we observe a steady growth in attention to inflammatory disorders and oncology, while the interest in VD's declines.
The output of VD research is greatly diminished. Venereal diseases, nowadays in a broader concept referred to as Sexually Transmitted Infections (STIs) have also almost entirely disappeared out of sight of the practical working dermatologist. What happened? With the emergence of antimicrobial therapy it was thought in earnest that STIs would disappear - worldwide. The interest of dermatologists in venereal diseases diminished and their attention was increasingly taken up by the impressive developments in the diagnosis and treatment of skin diseases. Moreover, the government began to see STIs explicitly as a task for general practitioners (GPs) and as public health issue. Today, some 70% of all STIs in the Netherlands are diagnosed and treated by general GPs and around 30% are dealt with in special - government supported - STI outpatient clinics. In these specialized STI clinics patients can make an appointment without a referral from their GP and the diagnosis and treatment are offered anonymously and free of charge. To make an appointment at these clinics the patients have to meet certain criteria, like a high number of sexual partners and/or being part of a known risk group like males who have sex with males (MSM), or having symptoms.
There were specialized STI clinics in the Netherlands' larger cities: one in Amsterdam, two in the Hague, one in Rotterdam and one in Utrecht. All of these were operated by dermatologists in academic and community hospitals in close collaboration with the municipal health services. Amsterdam's clinic has always been run by the city's municipal health services while, today, the same city bodies carry out STI care all over the country with finance direct from government and varying degrees of involvement by dermatologists. In summary, academic medical centers have little interest in STI research anymore, and the diagnosis and treatment of STIs in the Netherlands - no longer in the hands of the average dermatologist - comes under the purview of municipal health services.

Education

Around the turn of the 19th century it was common practice in most specialisms, including dermatology, to train for two years as a volunteer or assistant with a professor and private lecturer in their relevant area. When residents were considered able to practice independently, they received a certificate of competence, enabling them to start working as a medical specialist. Specialists establishing themselves without sufficient experience could not count on support from their colleagues or the referring general practitioner (GP). Training in dermatology initially involved additional internships with professors and private lecturers abroad such as Ricord, Cazenave, Besnier and Vidal in Paris, Köbner and Jadassohn in Breslau, Hebra and Kaposi in Vienna and, most famous of all, Unna in Hamburg.
As more chairs were established in the Netherlands, one could train to become a dermatologist not only in Amsterdam, but also in Utrecht, Groningen and Leiden.
Because they laid down their own conditions for membership, it made sense for the NVDV to develop some initiative to legitimize the dermatology qualification. Some fifteen to twenty years after the turn

1990s poster featuring the Top 10 Sexually Transmitted Diseases in the Netherlands.

of the century the NVDV began using the two-year training period as an unconditional criterion for society membership. What this training entailed was of less concern. This situation did not change until 1931, when specialist registration was introduced nationwide. A year on, the Specialist Registration Committee asked the NVDV for advice on the expected duration of dermatological training and on other requirements. While the NVDV did not exactly leap into action, it was eventually determined that the training programme should last three years. The drift towards specialization continued after the Second World War. In 1949, calls were made for a four-year course, which was eventually implemented in 1954. A special arrangement was made with the Radiological Society regarding radiotherapy, which dermatologists had become used to carrying out themselves. Dermatology, together with internal medicine areas, was traditionally considered a more theoretical, rather than a hands-on specialism. For this reason, little attention was paid to the surgical aspect of the profession for many years. This outlook has changed significantly over the last 20 years. With the development of - among others - dermato-oncology and phlebology, another year was added to the four-year training in the year 2000.
For the last fifty years, the demands laid out for dermatological training have become clearer and more concrete in a dermatology training charter. In order to gain first-hand experience, the resident has training practices in key subjects. These consist of clinical internships with the resident caring for patients on the ward, as well as various outpatient internships. In the eighties special hands-on courses were started, organized for the first time by Willem van Vloten (Utrecht), in dermatosurgery and dermatopathology. During the outpatient internships, additional courses are taken, such as photodermatology, allergology, phlebology and sexually transmitted infections (STIs). At present, the five-year period of training is once again under discussion. Scientific and technological progress in dermatology have made knowledge and experience so complex, that it is not any longer possible for an individual to gain familiarity with the entire field, let alone keep track of new developments. It has become a challenge for a dermatologist to keep up with the developments. Hence it has been decided to maintain a four-and-a-half year training programme with the option of further specialization in particular areas. Nowadays dermatology is one of the 29 recognized specialisms in the Netherlands. Access to specialist training is limited to prevent a sudden influx of medical specialists.

Knowledge exchange

Knowledge exchange is essential for the development of science. Dermatology in the Netherlands has evolved and continues to do so as a process of knowledge exchange with neighbouring European countries and beyond. The basis for modern dermatology was laid in Western Europe in the 18th- and 19th centuries, the main branches being the English, French and German schools with Willan, Alibert and Von Hebra as leading figures, respectively. These have all had their impact on the development and evolution of Dutch dermatology. In terms of academic dermatology, the German school in particular has been of influence on the early development of Dutch dermatology.
Several German physicians held the post of dermatology professor at Dutch universities in academic dermatology's early years: Siemens was professor in Leiden from 1929 to 1962, Zurhelle in Groningen from 1931 to 1945, and Happle in Nijmegen from 1986 to 1991. The Dutch Kerkhof, dermatology

lecturer in Leiden from 1911 to 1928 prior to Siemens' appointment in 1929, had trained with Unna in Hamburg, and Carol (Professor of Dermatology in Amsterdam from 1930 to 1945) was educated in Hamburg and Berlin.
Knowledge exchange reaches beyond the developed world to include countries in Africa, Asia and South America. The centuries-old interest of Dutch physicians and adventurer-researchers in tropical diseases can partly be ascribed to its colonial history, which developed from its seafaring traditions. Further, the interest in "exotic diseases" may also be related to the immigration of various groups to the Netherlands. The interest in tropical skin diseases is evident from the "tropical dermatology" chair, recently changed to "infections of the skin with special attention to leprosy" at the University of Amsterdam, that was established in 1995.

Changes in dermatological research

To get a picture of dermatological research in the Netherlands, we have carried out a brief survey of the topics covered in dissertations over the period 1800-2014. This analysis includes all universities. The dissertations have been categorised into 13 scientific domains: the 11 domains used by the NVDV, with the addition of "biology of the skin" and "other". A total of 655 dissertations were published during the study period (Table 1, see page 25). Of these, 202 were categorized under two domains (Table 2, see page 25). The first dermatological dissertations appeared before dermatology was established as a separate academic discipline in the Netherlands. In this pre-academic phase, 63 academic theses were published. Table 1 shows that numbers increased gradually until 1980, and then exponentially between 1980 and 2014. The five largest areas were: inflammatory dermatoses, therapy, oncology, infectious disease and allergy/eczema. If we divide the study period into 11 periods of 20 years each, it becomes clear how the interest in these domains has shifted over the past two centuries (Figure 1, see page 24). Much attention has been paid over the entire period to inflammatory diseases. From the titles of the theses it is evident that the focus in the last 35 years has moved from clinical/histological research to fundamental scientific research, aimed at unravelling causes.
The number of therapy studies has increased significantly since 1980, a figure which correlates with the advent of systemic therapies including biologics. The decline in attention given to infectious diseases is spectacular. Even greater is the decrease in attention to STIs, such as syphilis and gonorrhoea, the group of diseases which effectively defined dermatology when the discipline was first established in 1867: 14 to 21% of the total number of dissertations between 1821 and 1969 dealt with STIs; after 1960, this dropped to just 1% from 2001. Finally, something that is not reflected in the diagrams, is the recent increase in attention to phlebology. The specific areas of research by universities are discussed in chapters 3 to 10 and research from non academic centers is presented in chapter 11.

Closing comment

The idea to write this book was conceived by the History working group of the NVDV, whilst discussing how to deliver a lasting contribution to the EADV meeting in October 2014 in Amsterdam.
In order to get to know each other better, the message we would like to extend to fellow dermatologists

from other countries is simply to tell them who we are and what we do. The spirit of this book is therefore in keeping with the motto of the EADV congress, "building bridges" - bridges between dermatologists in European countries and beyond, bridges that make dermatology stronger the world over, in the interest of our patients.
This book also seeks to build bridges between Dutch dermatologists. It has, too, another meaning for ourselves. Everything is constantly changing, and so is dermatology. This introductory chapter is a testimony to these changes. As knowledge increases and changes, so the way we practice and teach our profession changes. Such change - the connecting thread of this introduction - can be taken to be improvement. But it is a thorough analysis of these changes, something that the authors have not fully attempted here, which in the end leads to increased understanding. It is only with this increased understanding, that we can rightfully speak of improvement, which is our ultimate goal.

Figure 1:
Number of theses in the Netherlands between 1800 and 2014, regarding the 5 most common research domains. Each bar represents the number of theses about the research domain in the indicated period, depicted as percentage of the total number of theses in that same period.

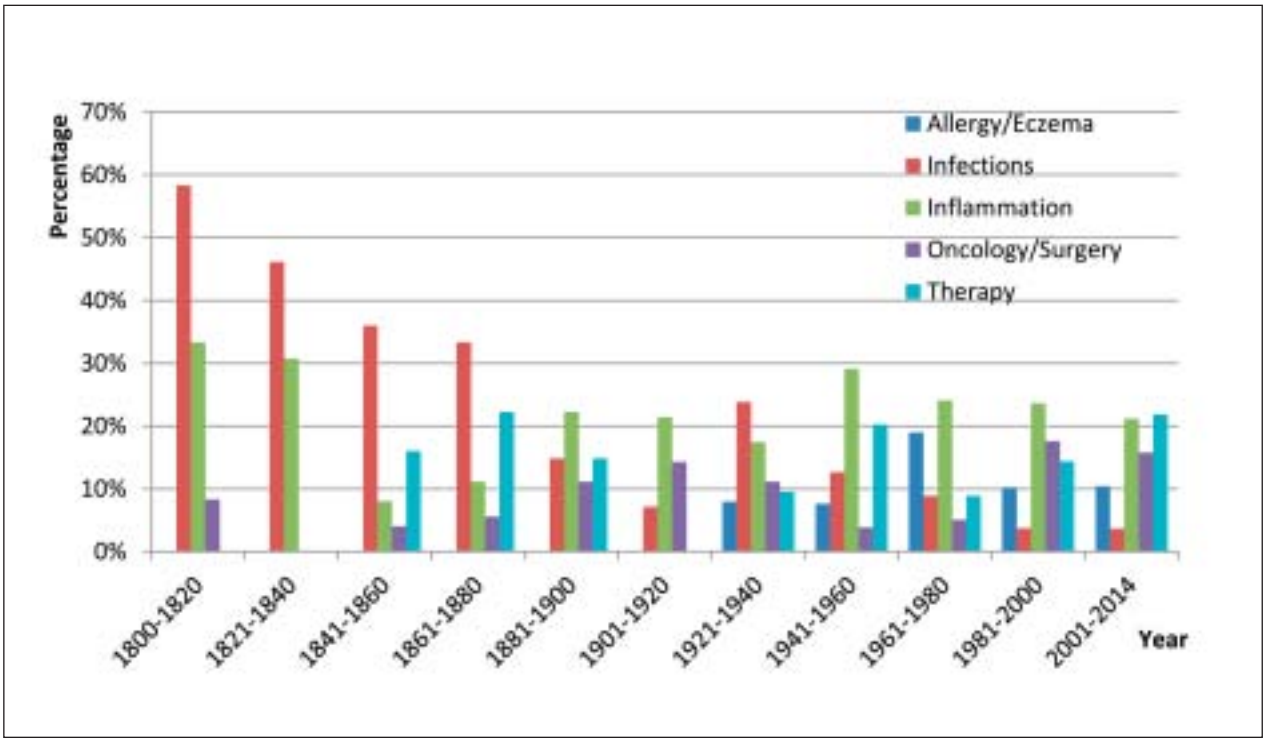


Table 1:
Number of dermatological theses in The Netherlands between 1800 and 2014, per period of twenty years.

Period	Number of these
1800 - 1820	12
1821 - 1840	25
1841 - 1860	22
1861 - 1880	14
1881 - 1900	20
1901 - 1920	11
1921 - 1940	53
1941 - 1960	64
1961 - 1980	67
1981 - 2000	173
2001 - 2014	194
Total	**655**

Table 2:
Number of dermatological theses in The Netherlands between 1800 and 2014, by research domain; 202 of the 655 theses were classified in two research domains.

Research domain	Number of theses
Inflammatory diseases	192
Therapy	137
Oncology/surgery	107
Infectious diseases	90
Allergy/eczema	79
Biology of the skin	67
Sexually transmitted infections	64
Pediatric dermatology	31
Other	29
Blood vessels (phlebology)	25
Pigment abnormalities	20
Hair and other skin adnexa	12
Proctology/vulvar pathology	4
Total	**857**

The Skinny Bridge, Amsterdam.
The yellow box contains salt.
In the Netherlands it is a custom
to sprinkle salt on the bridges when it's icy.

3 Academic Medical Center University of Amsterdam

Menno A. de Rie
with contributions by Jan D. Bos, William R. Faber, Henry J.C. de Vries, John de Korte, Rosalie M. Luiten, Jan R. Mekkes, Phyllis I. Spuls and J.P. Wietze van der Veen

Introduction

In 1813 King Willem I decreed Amsterdam as capital city of the newly established Kingdom of the Netherlands. At that time, Amsterdam had no university, but it did have a comparable institution called the "Athenaeum Illustre". Founded in 1632, it was not until 1865 that the Athenaeum received full authority for academic medical education. Before 1865 surgeon students and midwives were educated in the out-buildings and lazar houses that surrounded the municipal hospital.
The conversion of the Athenaeum Illustre into the Municipal University of Amsterdam was celebrated with due ceremony on the 15th of October, 1877.

History

Jan Leonardus Chanfleury van IJsselsteijn

Jan Leonardus Chanfleury van IJsselsteijn (1819-1905) was named professor of skin and venereal diseases in Amsterdam in 1867, the first such appointment to be made in the Netherlands. Chanfleury studied medicine in Groningen and completed his Ph.D. to Doctor medicinae, chirurgiae et artis obstetriciae in 1844. Initially, he worked in the Municipal Hospital (Stadsziekenhuis) of The Hague, treating patients with syphilis and skin diseases. Later he became the hospital's medical director. After some years his career took him to the Binnengasthuis, the academic clinic of the University of Amsterdam. He was among the founders of the Dutch weekly medical periodical now known as the Nederlands Tijdschrift voor Geneeskunde.
The recognition that venereal diseases required a specific approach, was probably the basis for his appointment. His inaugural address was titled "On the special clinics" and mainly concerned the question of how to stem the spread of venereal diseases, whose destructive impact could be felt across all levels of society at the time. It was in his day that the Dutch expression "going under the clock" (a euphemism for visiting a VD clinic) was first coined, referring to the large clock at the entrance of the Binnengasthuis' outpatient clinic where syphilis

A 19th-century view of the Binnengasthuis, Amsterdam, with the Department of Dermatology occupying the left-hand side of the building.

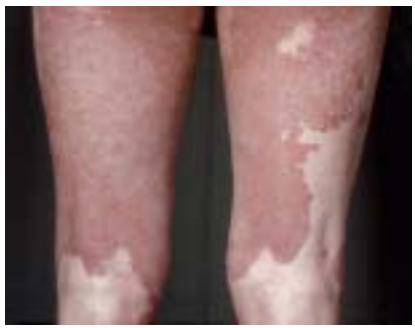
and other venereal diseases were treated. A syllabus was preserved from the lectures presented by Prof. Chanfleury. This manual, written by a student named Mart Kleyer, can be considered the first textbook on dermatology and venereology in the Dutch language.
Chanfleury was one of the early members of the 'Nederlandsche Vereeniging van Dermatologen' (Dutch Society of Dermatologists), founded in 1896 and he later on became honorary member of that Society. After the resignation of Chanfleury in 1883, the Department of Dermatology and Venereology was temporarily transferred to the surgical clinic.

Dirk van Haren Noman

Dirk van Haren Noman (1854-1896) succeeded Chanfleury in 1886. He accepted his position with a lecture entitled "The concept of disease in the doctrine of Dermatology". He had a comprehensive knowledge of histopathology and bacteriology and dedicated his laboratory to their study. Developments in the relatively new medium of photography allowed him to publish a collection of dermatological images in 1889 that ultimately resulted in a standard work "Casuistique et diagnose photographique des maladies de la peau" - French still being the European language of science at the time. By this period, dermatology had increasingly become a discipline of external etiological factors and external therapeutic modalities. This is an important co-factor in explaining the rather eccentric position of dermatology, resulting in a certain distance from other medical specialisms still felt to this day. After Van Haren Noman's death in 1896 the Department of Skin and Venereal Diseases was temporarily transferred to the Wilhelmina Gasthuis due to a lack of space at the Binnengasthuis.

Samuel Mendes da Costa

Samuel Mendes da Costa (1862-1943) was appointed Van Haren Noman's successor in 1898 and took office with a lecture entitled "Some aspects of fighting dermatoses". Initially, Mendes da Costa also focused on the control of infectious diseases. He used epidemiological techniques and helped to start special clinics. He also introduced new therapeutic techniques such as Finsen rays and X-rays. The latter (applied as so-called röntgen epilation) was successful in special favus-patient clinics, ending the endemic presence of trichophytic tinea capitis. Mendes da Costa wrote the first handbook of dermatology in the Dutch language, initially collaborating with Dr. Alexander Nathan van Praag. Later, he also wrote a monograph on venereology. He enjoyed a great international reputation and his name still lives on as an eponym for several - albeit rare - dermatological diseases.



Erythrokeratoderma variabilis.

Willem Lambertus Leonard Carol

Willem Lambertus Leonard Carol (1879-1951), appointed in 1930, was a highly productive dermatologist who had received his training in Berlin and Hamburg. During the First World War he worked at a private dermatological practice in Amsterdam, while also working part-time in the university's pathology laboratory. He was a highly-regarded clinician and an excellent pathologist. Carol replaced with his own textbook the by then outdated work of Mendes da Costa.
He accepted his appointment with a lecture entitled "Views and trends in the doctrine of eczema". Controversially, Carol continued his work during the German occupation of the Second World War, perhaps partly as a consequence of his German background and training. Rather than resigning, as many of his colleagues did, Carol remained in office and even contributed to German medical literature. That the first edition of his Textbook of Dermatology (1944) was published in a period of paper shortage, has blemished his reputation almost as much as his willingness to continue working under the Nazis. In any case, immediately after the war, he was forced to resign and was replaced by Reijer Kooij until a new professor was appointed. Kooij, who had a special interest in leprosy, later became head at the Municipal Hospital of The Hague's dermatology clinic, the only non-academic training facility of its type at the time.

Jan Roelof Prakken

Jan Roelof Prakken (1897-1982) appointed in 1946 was, like Carol, an example of a dermatologist whose excellent diagnostic skills led him to be mainly clinically orientated. Nevertheless, he also saw that greater attention to the physiology of the skin could be the basis for an improved understanding of dermatological diseases. At his inaugural address he spoke on "Functional disturbances in skin diseases". Continuing with tradition, Prakken published his dermatological textbook in 1963, having already published a venereological textbook in 1948. Typical of his management style, Prakken preferred staff members who held part-time positions in non-academic city outpatient clinics, alongside their part-time position at the University Clinic. Less concerned with research in familiar areas, he promoted diversity and the individual interests of his staff members. On his appointment, the clinic was in a particularly poor and outdated condition, with beds numbering to 100, divided into wards of sometimes more than 20. Although Prakken complained about this in his inaugural address, it was not until 1966 that the clinic was relocated to the Binnengasthuis, where the former obstetrician department was completely renovated to suit its new purpose. Shortly after this move, Prakken retired.

Rudi Harold Cormane

Rudi Harold Cormane (1925-1987) was born in Bandung, Indonesia, and studied medicine in Leiden. During an academic vacation period, Cormane became one of the victims of an epidemic of poliomyelitis. After partial recovery, he resumed his studies and began specialization in internal medicine. His chief interest was in mycotic infections, and he gained his PhD on a thesis about Candida albicans. After training as an internist, he became the medical director of a small nursing home in Limburg. Attracted by academia, he specialized in dermatology at Utrecht. During his training he began research on the application of immunofluorescence techniques in dermato-pathology. Cormane accepted his appointment in 1968 with the inaugural address "Tradition and imagination in dermatology". Being an internist as well as a dermatologist, Cormane was often more interested in underlying pathogenic processes than in the sometimes extreme morphological-oriented differential diagnostics preferred by dermatologists. As a result, a creeping crisis of confidence emerged between the established dermatological staff and the relatively young Cormane. Prakken's policy, allowing combined academic and peripheral activities of staff, was put to a stop. Cormane also had very different ideas about the organization of science-based research. The new sub-discipline of immunodermatology, in which he was indisputably an international pioneer, was the central theme of his professorial career.

Breaking with tradition, Cormane did not write a textbook and, after his early death in 1987, there was no evidence that he had ever intended to do so. His preferred ambition clearly had been to strengthen the scientific signature of the discipline of dermatology. This is substantiated by the fact that he, together with several other European dermatologists, established the European Society of Dermatological Research (ESDR). His discovery of skin-bound complement and immunoglobulin in patients with chronic discoid lupus erythematosus and systemic lupus erythematosus, resulted in probably two of the most cited publications by a Dutch dermatologist.[1,2]
Cormane's value is indisputable and his influence on Dutch dermatology is demonstrated by the fact that several of his pupils became professors themselves. H.A. Martino Neumann was appointed at the University of Limburg and William R. Faber succeeded Dick L. Leiker at the University of Amsterdam. Furthermore, Theo van Joost was appointed at the Erasmus University of Rotterdam, and Jan D. Bos became Cormane's successor at the University of Amsterdam.

Johannes Dositheus Bos

Johannes Dositheus Bos (1951) accepted his appointment with an inaugural address in 1991, entitled "Skin and defence". In turn, immunodermatology would remain the main line of his research. Attention was to be given to the immunopathogenesis, immunodiagnosis and immunotherapy of dermatological diseases. A solid foundation to this new emphasis was provided by the introduction of research management. Research was concentrated around the following themes: psoriasis, dermato-allergology, scleroderma, infection and immunity, wound healing, and pigmentation diseases. The new research theme of photo-immunology was also added.
The focus on biomedical research was maintained, while significant investments were made in medical research with a more epidemiological accent, with an emphasis on developing protocols, guidelines and the introduction of principles of evidence-based medicine in research, education and patient care.
A partnership was established with the Outpatient Clinic for Venereal Diseases of the Public Health Service in Amsterdam.
Further, major changes in the department were introduced, with attention to the quality of patient care, training, research and education. In addition to maintaining a good international reputation, a policy was implemented to improve the clinic's standing within the Academic Medical Center (AMC) itself. The Department of Dermatology was elected the best department of the AMC in 1993, by a jury headed by professor Els Borst-Eilers who, not long afterwards, would become the Dutch government's Minister of Health.

Menno Alexander de Rie

While Menno Alexander de Rie (1956) was working on his PhD thesis in immunology at the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB, currently Sanquin), Rudi Cormane suggested him to study immunodermatology and offered him a position as a resident. De Rie finished his PhD thesis entitled "Studies on in-vitro activation of human B cells" in 1988 and started his training in dermatology in 1989 at the AMC's department of dermatology, under the supervision of Jan Bos. After his training, De Rie stayed on as a staff member at the AMC and later became senior director for translational medicine with Novartis in Basel, Switzerland. In 2011 he was appointed Professor of Dermatology at the University of Amsterdam. Since January 2012 the dermatology departments of the University of Amsterdam and the Free University Medical Center in Amsterdam have been merged.

The oldest dermatology clinic in the Netherlands has evolved over the course of nearly 130 years from a clinically-oriented unit into a modern department with a small inpatient clinic, a busy outpatient clinic, a day care center, and a research laboratory. In addition to Cormane's insistent focus on a more medical-biological approach ("biomedicine") towards the wide variety of dermatological diseases, attention was also paid to clinical epidemiological aspects of the discipline. The strong emphasis on clinical experience ("experience-based medicine") in determining diagnostic and therapeutic policy has become increasingly criticized in all medical specialisms, by the government and insurance companies especially. The development of good scientific research methods to strengthen the application of therapeutic modalities should provide a better policy in future towards treatment choices for dermatological and venereological diseases.

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Research

From leprosy clinic to skin infections clinic

An outpatient leprosy clinic was established in the 1960s by Dick L. Leiker at the AMC's Department of Dermatology. Among former dermatology residents, the clinic was also known as the "Hansen poli", after the discoverer of the leprosy bacterium.

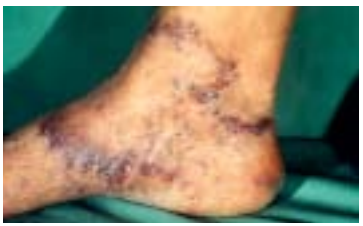
Derk Luitjen Leiker

Derk Luitjen Leiker (1919-1995) finished his medical studies in Groningen in 1948 and left as a medical missionary to former Dutch New Guinea. In 1953 he was appointed by the Dutch government as head of the local leprosy control programme. Influenced by the American leprosy expert Norman R. Sloan, he broadened his knowledge of leprosy. Little was known about the epidemiology of leprosy in New Guinea, and Leiker initiated large-scale house-to-house population surveys. He later specialized in dermatology in Rotterdam. Having completed his specialization, he accepted an appointment as head of the leprosy programme of Northern Nigeria in 1961, which involved the care of 360,000 registered leprosy patients. In 1965 Leiker received the Albert Schweitzer Prize for Medicine recognising his achievements in the field of leprosy. In the same year, he returned to the Netherlands to devote himself to leprosy research as a senior lecturer at the Royal Dutch Institute for the Tropics in Amsterdam. In 1964 he described a new disease entity "Granuloma multiforme" presenting as atypical tuberculoid leprosy in patients in Nigeria.[1] Together with Ciska Anten-Mengelers, he founded the Dutch Leprosy Foundation (NSL) in 1967. He was also a visiting consultant for leprosy at the Rotterdam University clinic. At the time, the number of leprosy patients from the former colonies was significant and reached a peak after Suriname gained independence in 1975.[2] As a consultant for the WHO, Leiker was a pioneer in the evaluation and implementation of Multi Drug Therapy (MDT), still the mainstay in the current treatment and eradication programme of leprosy.[3] In 1981 he was awarded an honorary doctorate by the University of Amsterdam. After Leiker's retirement, William R. Faber succeeded him as head of the leprosy clinic in 1981.

William Richard Faber

William Richard Faber (1940) dedicated much of his career to the fight against leprosy. After obtaining his medical degree, he was employed in Uganda from 1967 to 1969 as a medical officer for the Ugandan government. In 1971 he began his training in dermatology with Professor Cormane in Amsterdam, where he first met Leiker. His study of the immunological aspects of leprosy culminated in his 1978 PhD thesis "Leprosy. Clinical and Immunological Studies". In subsequent years, the number of new cases of leprosy decreased. Still, leprosy care comprises of more than just a proper diagnosis and treatment of the infection. Because neuropathic complications often call for life-long medical care, Faber set about organising multidisciplinary care, in close cooperation with the departments of Radiology, Rehabilitation, Traumatology and Surgery. From 1981 onwards, Faber divided his time between a part-time position at the AMC and a new role as dermatologist at Amersfoort hospital De Lichtenberg.

Over the course of time, the leprosy clinic's focus shifted from leprosy care to a wider range of tropical skin diseases. Tropical skin conditions, such as cutaneous leishmaniasis in travellers, expats and military personnel returning from tropical regions were diagnosed in increasing numbers.[4,5,6] In 1987, the leprosy clinic was transformed into an outpatient clinic for Tropical Dermatology.



Borderline tuberculoid leprosy.

In 1995 Faber was appointed Professor of Tropical Dermatology. This gave him the opportunity to share his knowledge with medical students, doctors preparing for deployment in the tropics and dermatology residents. Faber has been involved in many organizations such as the NLR (Netherlands Leprosy Relief). He has also been a supporter of the Bethesda Foundation's fight against leprosy in Suriname and the Gastmann-Wichers Foundation's efforts to stimulate leprosy research. The latter's research has dealt with the immunology of leprosy, rehabilitation and neuropathic foot complications, epidemiology and history, and led to many publications and PhD theses.[7-10]

Henry John Christiaan de Vries

After Faber's retirement, Henry John Christiaan de Vries (1967) took over his professorship. His research topics are: STI in men who have sex with men (MSM), lymphogranuloma venereum, HPV related anal dysplasia, cutaneous leishmaniasis, and leprosy. The clinic for tropical dermatology became known as the skin infections clinic in 2011 with his inaugural lecture about "Skin infections, in particular leprosy", thus accentuating the department's expertise in skin infections, both with and without a tropical association.

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Staff of the AMC Department of Dermatology with (from left to right) Henk Sillevis Smitt, William Faber, Jan Bos, Hendrik-Jan Hulsebosch, Marcus Meinardi, Menno de Rie, Shafi Ashgar, Marcel Teunissen, Jan Mekkes and Henry de Vries (2002).

The Skin Immune System

The first immunohistological studies in psoriatic skin demonstrated the importance of T lymphocytes and their subsets in psoriasis.[1] This understanding coincided with the discovery of monoclonal antibodies for detection of new T-cell subsets. At the same time, the T-cell selective immunosuppressant cyclosporine was successfully introduced for the treatment of psoriasis, underlining the pivotal role of activated T cells in this skin disease. All these developments led to the concept of the skin immune system that was published in 1986.[2]

The term "skin immune system - SIS" was introduced to underline the complexity of cells and mediators present in normal human skin (resident) and those that invade it during different inflammatory and immune-mediated skin diseases (recruited). Thereby, a more complete approach to normal human skin and its inflammatory and autoimmune diseases was promoted. For example, in psoriasis, which was regarded as a disease of keratinocyte hyperproliferation and granulocyte infiltration, it was found that different subsets of T cells might also play a role. The subsequent findings that T-cell inhibitors such as cyclosporin and the biologics directed against T cells were very effective, further endorsed the view that psoriasis might well be an autoimmune, T-cell-mediated disease.

A similar situation occurred in understanding atopic dermatitis. The received idea was that it was a disease related to the other manifestations of atopy, rhinitis and asthma. A primary role was given to mast cells and their mediators, as well as to the IgE molecules on their membranes. By carefully immunophenotyping the subpopulation of inflammatory cells, it could not be denied that T cells were prominent in the superficial layers of atopic skin. And again, the T-cell inhibitor cyclosporin proved to be very effective, also in severe cases.[2,3,4]

In the late nineties, the "millennium criteria" for atopic dermatitis were introduced, distinguishing between atopic dermatitis and so-called atopiform dermatitis.[5] This discussion and the criteria for atopic dermatitis have yet to be concluded.

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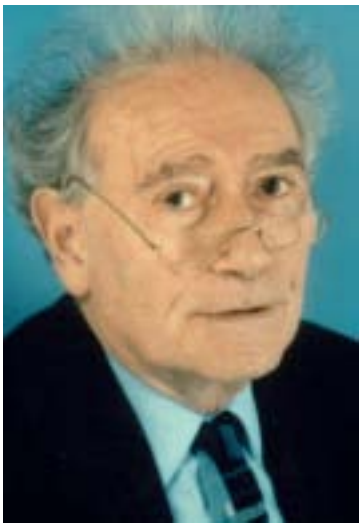
Herman Musaph



Herman Musaph (1915-1992), psychiatrist, was born in Amsterdam, studied medicine at the University of Amsterdam, and started as a general practitioner in 1940. After the war he specialized in psychiatry and psychoanalysis.
He made valuable contributions to the understanding of the long-term psychosocial implications of World War II, elucidating how that nightmare of oppression and terror affected daily life in contemporary society. From 1953 onwards Musaph was a consulting psychiatrist at the University of Amsterdam's Department of Dermatology, where he later started research in psychodermatology. In 1977, he was appointed Professor in Medical Sexology at the University of Utrecht. That same year, he published a Handbook of Sexology, which was subsequently translated into many different languages.[1]
Musaph's psychoanalytic background enabled him to develop a thorough understanding of emotional factors in skin diseases. He published on the role of aggression in self-induced conditions, such as dermatitis artefacta, and on emotional conflicts in patients with psychogenic pruritis. Whereas others used the terms "psychosomatic dermatology" or "psychocutaneous medicine", Musaph deliberately used the word "psychodermatology". In a study on its history, he described psychodermatology as the study of psychological variables related to the onset, course and treatment of skin diseases.[2]
Musaph was particularly interested in itching and scratching behavior.[3] Itching and scratching may occur when an anger or anxiety impulse is signalled and warded off, eventually resulting in skin lesions.

He also described patients with repetitive scratch behaviour: obsessive-compulsive scratching aiming at a reduction of tension, anxiety or aggression or aiming (unsuccessfully) at a resolution of an emotional conflict.
Although Musaph primarily studied psychopathological aspects of skin disease, he always emphasized the psychological meaning of the skin in normal personal development. He focused on the meaning of skin contact, touching, and intimate behaviour in mother-childhood relationships, and he considered skin contact between parent and child as essential for a healthy emotional life. He also promoted strategies resulting in closer skin contact, such as breast-feeding rather than bottle-feeding. Skin contact, touching and intimate behaviour contribute to feelings of trust, belonging and acceptance, in children and adults alike. In 1987, the city of Vienna hosted the first International Congress on Dermatology and Psychiatry. As a result of this congress, many countries including The Netherlands founded societies for psychodermatological research.

Itching and Scratching (1964).

Later, in 1993, Vienna was also the venue for the establishment of The European Society for Dermatology and Psychiatry (ESDaP).
In 1995 the Herman Musaph Foundation for Psychodermatology was established in Amsterdam to commemorate his role as a founding father of psychodermatology. Biannually, the Foundation presents the Herman Musaph Award to a scientist who has made an outstanding contribution to the advancement of psychodermatology.
In recent years the research group led by John de Korte has developed into an internationally recognized center of excellence.[4] Focus of research is on measurement of quality of life in patients suffering from chronic inflammatory skin diseases such as psoriasis and vitiligo.[5,6,7,8,9] This group validated the Skindex for The Netherlands and this scoring system is now widely used. In addition to quality of life, patient compliance and patient reported outcomes are now also studied.[10]

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The Netherlands Institute for Pigment Disorders (SNIP)

In 1994 Wiete Westerhof started the SNIP as an independent foundation based at the University of Amsterdam's Academic Medical Center. The institute developed into a unique center of expertise, attracting patients from all over The Netherlands and beyond.

In 1997 Narrowband UVB (311nm) phototherapy was introduced for the treatment of vitiligo.[1] This modality is now widely accepted as the most effective treatment for this disease. It has largely replaced PUVA therapy, which is less effective and has more side-effects.

Progressive macular hypomelanosis (PMH) is a skin condition characterised by the development of multiple round hypopigmented maculae, especially on the trunk. Here the lesions have the tendency to coalesce around the midline. Westerhof discovered the presence of red follicular fluorescence under Woods lamp illumination in these lesions and, together with his group, linked this to a pathogenetic role of a subtype of Propionibacterium acnes and subsequently demonstrated the efficacy of topical therapy with benzoylperoxide and clindamycin together with UVA as a treatment for this condition.[2,3]

After his retirement, Westerhof initiated studies to develop a melanoma vaccine, which was based on his haptenation theory of vitiligo.[4,5]

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Vitiligo on the hands in a symmetrical pattern.

Vitiligo and melanoma

The research group of Rosalie M. Luiten demonstrated that the depigmentation in vitiligo is mediated by cytotoxic T lymphocytes. They showed that the lesional skin of active vitiligo patients contains cytotoxic T lymphocytes that react with melanocyte antigens, and induce melanocyte apoptosis.[1] These findings contributed to the consensus of vitiligo as an autoimmune disease at the Global Vitiligo Consensus Meeting in Bordeaux in 2011. Vitiligo research of the department has further continued on the occurrence of chemical-induced vitiligo, the correlation with thyroid autoimmunity, quality of life and the development of new treatment modalities and outcome measures.[2-4]
Melanoma patients who develop vitiligo-like depigmentation, referred to as melanoma-associated leukoderma (MAL), have more chance to survive longer. Advanced melanoma patients generally have low levels anti-melanoma immunity that may not be functional to eradicate the melanoma.[5]
In melanoma patients with MAL, dr. Luiten's group found immunity against antigens that are expressed on melanocytes and melanoma cells.[6] This immunity may explain the potential positive effect of depigmentation on the survival of melanoma patients. Intriguingly, their epidemiological research on the reversed case, the occurrence of melanoma and skin cancer in vitiligo patients, has shown that vitiligo patients have a three times decreased risk of developing melanoma or basal cell carcinoma.[7] This highlights vitiligo as a favorable sign for melanoma patients and the important of its mechanism of action in the treatment of melanoma.
A new concept for the treatment of melanoma, based on the immunising potential of some skin-bleaching agents was proposed. It was demonstrated that the skin-bleaching agent monobenzone induces immunity against melanocytes and melanoma cells.[8,9] Preclinical proof of concept was obtained for monobenzone combined with immunostimulation as an innovative therapeutic strategy for melanoma[10], which is currently investigated in melanoma patients.

Vitiligo-like depigmentation in a stage IV melanoma patient with mestatases in cerebrum and axillary lymph nodes; skin lesions and favourable disease course are probably related to antimelanoma immune response, enhanced by radiotherapy (Teulings HE et al, reference 6).

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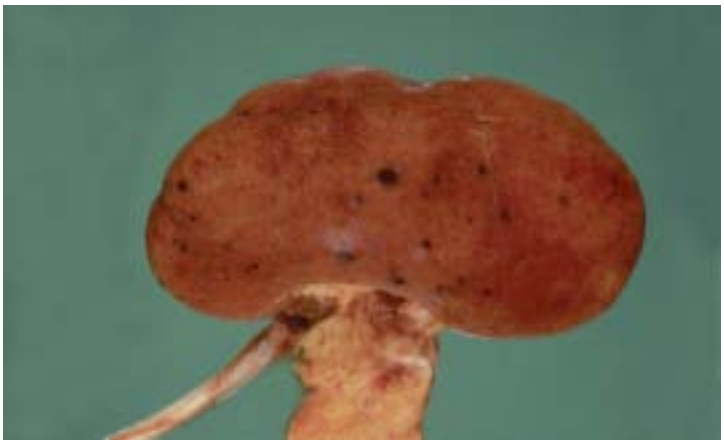
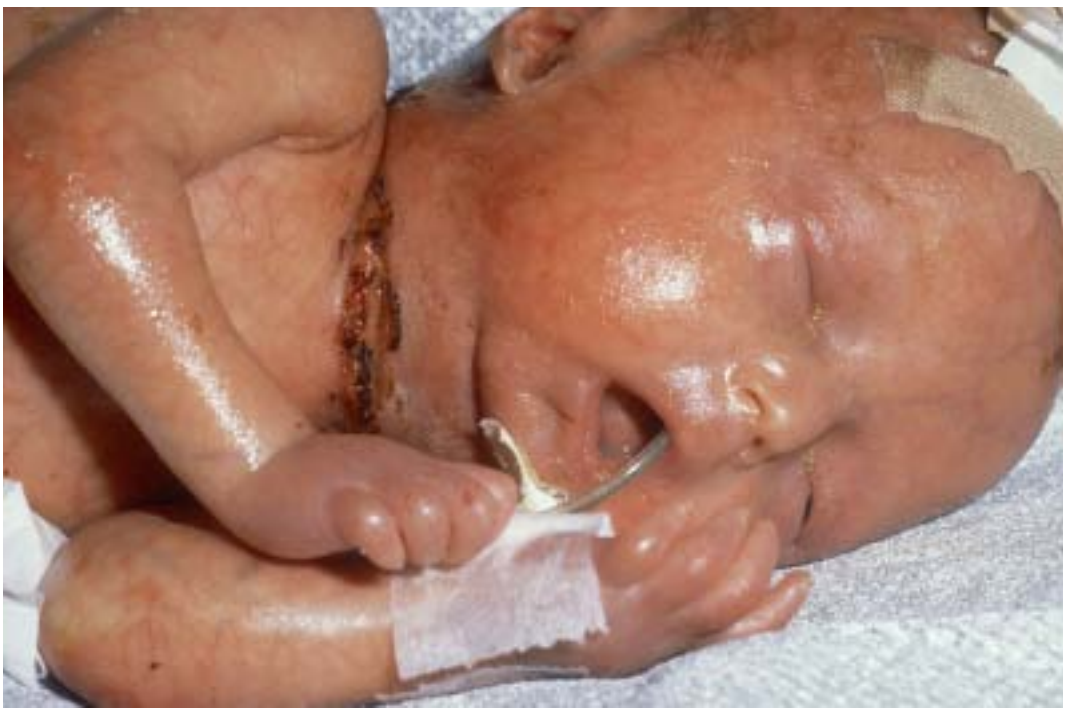
Kidney with melanoma metastases.



Pediatric Dermatology

From 1983 onwards J. Henk Sillevis Smitt was responsible for pediatric dermatology (PD) at the Academic Medical Center (AMC) and the outpatient clinic PD of the Emma Children Hospital which joined the AMC. The number of out-patient clinics in PD grew from one clinic a week in 1986 to 7 in 2014 including one at the Free University Amsterdam and day-care facilities for children.
A second pediatric dermatologist, Pina M.A. Middelkamp Hup was appointed in 2008.
Research is concentrated on immunology and allergology (primary immunodeficiencies or PID, atopic dermatitis), genodermatoses, and congenital/neonatal vascular lesions.
In cooperation with the pediatric immunologists of the department of pediatrics and Sanquin Blood Supply, skin problems in PIDs were analyzed. It was shown that 31% of 16 X-linked Chronic Granulomatous Disease (CGD) carriers as well as two autosomal recessive patients with CGD displayed discoid lupus erythematosus-like lesions.[1,2] The histopathology was not typical and the immunofluorescence findings were negative, but the immunophenotype of the infiltrating cells resembled that found in discoid lupus erythematosus. A review of skin symptoms in PIDs helps the dermatologists to be aware of skin problems in immunodeficient children.[3]

Restrictive dermopathy in a newborn, a rare genodermatosis.



The millennium diagnostic criteria for atopic dermatitis (AD) were developed for both children and adults.[4] In cooperation with the department of pediatrics (psychosocial care), the course of life and the disease-related consequences in young adult patients with childhood AD was evaluated. Patients with severe AD in childhood were found to be significantly delayed in their social development later in life.[5] It was shown that AD lesions contain increased levels of IL-31-producing T cells, suggesting that a substantial part of previously reported increased IL-31 mRNA levels in AD skin is T cell-derived and that these cells may be involved in the pathogenesis of AD.[6]
The Dutch task force on genodermatoses, with Henk Sillevis Smitt as its secretary and later chairman, described restrictive dermopathy in more detail, based on 12 cases in the Netherlands.[7]
Blood and/or tissue DNA of some of these cases was used to unravel the cause of the disease.[8]
In a cross-center team, terminology was developed to describe patients showing vascular malformations not only in the face, and combined with growth disturbances. This terminology was used to differentiate the nature, localization and timing of growth disturbances; the nature of co-localization of the vascular malformations and growth disturbances; and the presence or absence of other features.
Six subgroups were defined within the group of entities with vascular malformation-deregulated growth. Subsequently a mixed group of both experienced and non-experienced observers evaluated 146 patients (106 from the Netherlands; 40 from the UK) with vascular malformations and disturbed growth. Scoring the patients using the proposed classification yielded a high inter-observer reproducibility.[9]

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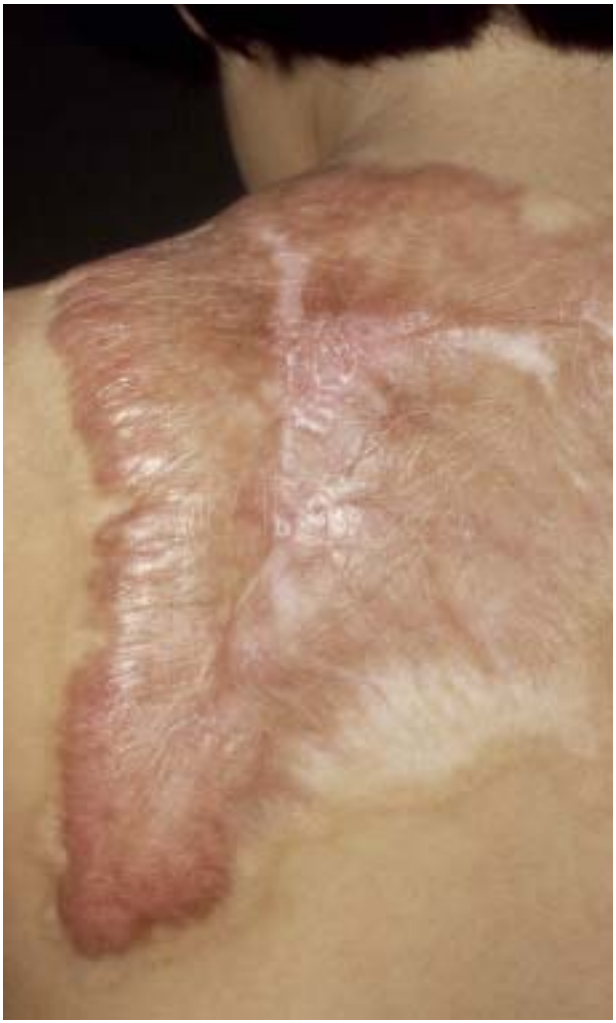
Wound Healing Research

In 1986, Wiete Westerhof started a research group on the topic of wound healing. Many researchers started their career in wound healing research; in total 8 academic theses were written on this subject. The research projects were financed entirely from external sources, including some large and prestigious grants from the government.

That same year, the punch graft technique for venous leg ulcers was developed. By 1989, Wiete Westerhof and Bart Nanninga, in cooperation with TNO (Dutch Organization for Applied Scientific Research), had developed a sophisticated cultured skin equivalent consisting of autologous keratinocytes on a layer of fibroblasts. These grafts were successfully used in venous leg ulcers. Their efficacy was compared to the punch grafting method in a clinical study.[1]



Enzymatic debridement was another research subject. Jan Mekkes and Caroline Le Poole investigated various proteolytic enzymes such as fibrinolysin/DNAse, collagenase, papaine, and peptidases, derived from Antarctic krill, in vitro, in animal studies, and in randomized controlled clinical trials in venous leg ulcers.[2,3] The enzymes were effective in vitro and in animal studies, but not in venous leg ulcers, due to the excessive amount of proteolytic enzymes that are already present in chronic wounds. As a result of these negative clinical results, several commercial enzymes for wound debridement were withdrawn from the European market. Growth factors such as the epidermal growth factor and platelet-derived growth factor were investigated in clinical studies, and were shown to be ineffective in chronic wounds, because of the same aggressive proteolytic wound environment.

Animal wound models, cell cultures and tissue culture wound models, were developed and used to investigate enzymes, growth factors and other products. A novel computer-image analysis system was designed objectively to measure the wound size and percentage of granulation tissue for clinical trials. Henry de Vries and Dory Enomoto used laboratory methods such as the Fournier analysis of laser scatter images and skin

Large hypertrophic burn scar illustrating the need for better wound healing techniques.

elasticity meters to quantify fibrosis in wound healing and in systemic sclerosis.[4,5] In patients with severe scleroderma treated with extracorporal photopheresis, this expertise was used to quantify fibrosis.[5]
One of the main research goals was the development of an epidermal and dermal skin substitute, a cultured multilayer skin equivalent to be used in chronic ulcers, and especially in burn wounds. Many dermal substitutes covered with autologous keratinocytes were evaluated in tissue cultures, animal studies and in humans.[6,7,8] The skin equivalent research line was developed in close collaboration with Dutch burns units. Related subjects were scar formation, keloïd, hypertrophic scars and wound contraction in burns.
Delayed wound healing in diabetic ulcers was investigated and the distribution of extracellular matrix proteins in diabetic ulcers in various stages of healing was assessed.[9,10] Fibroblasts from non-healing diabetic ulcers and controls were cultured and their proliferative response to growth factors were measured. The fibroblasts of diabetic patients showed a reduced response to growth factors.[10]

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Evidence Based Dermatology (EBD)

Shortly after Gordon Guyatt's introduction of Evidence Based Medicine (EBM) in 1992, many departments of dermatology began performing systematic reviews (SRs). Our department initiated a close relationship with the Department of Epidemiology and Biostatistics to improve its skills in methodology. The first evidence based systematic review in dermatology, written in 2003 on the treatments of psoriasis, was the basis for the first national evidence based guideline for the Dutch Society of Dermatology and Venereology and the first European guideline.[1,2,3]

Summarizing and grading the existing evidence help clinicians when making decisions for diagnostic and therapeutic interventions. SRs expose what evidence is missing and what's on the agenda for future research. A good example of this is the guideline for off-label azathioprine and randomized controlled trials comparing azathioprine and methotrexate for atopic dermatitis.[4]

Another aspect which becomes visible due to the systematic approach of EBD is the huge variety in diagnostic criteria and outcome parameters.[5] The harmonisation (www.comet-initiative.org) and improvement of outcome parameters (www.cosmin.nl), besides focusing more and more on patient reported outcomes, is now a new field of research in the department, with a view to better patient care. In addition the department got involved in the ongoing quality of life research.[6] In 2010 the harmonizing outcome measures for eczema (HOME) initiative (www.homeforeczema.org) was initiated.[7,8] Recently the Grading Recommendations Assessment, Development and Evaluation, GRADE (www.gradeworkinggroup.org) methodology was introduced and is now incorporated in the department's research.

Phyllis Ira Spuls

In 2013 Phyllis Spuls (1964) was appointed as professor in Evidence based Dermatology at the University of Amsterdam (AMC). The department continues to play a role in EBD education with, for example, critical appraisal of topics (CAT), high-quality clinical research, guideline development, the harmonization of outcome parameters and patient registries.

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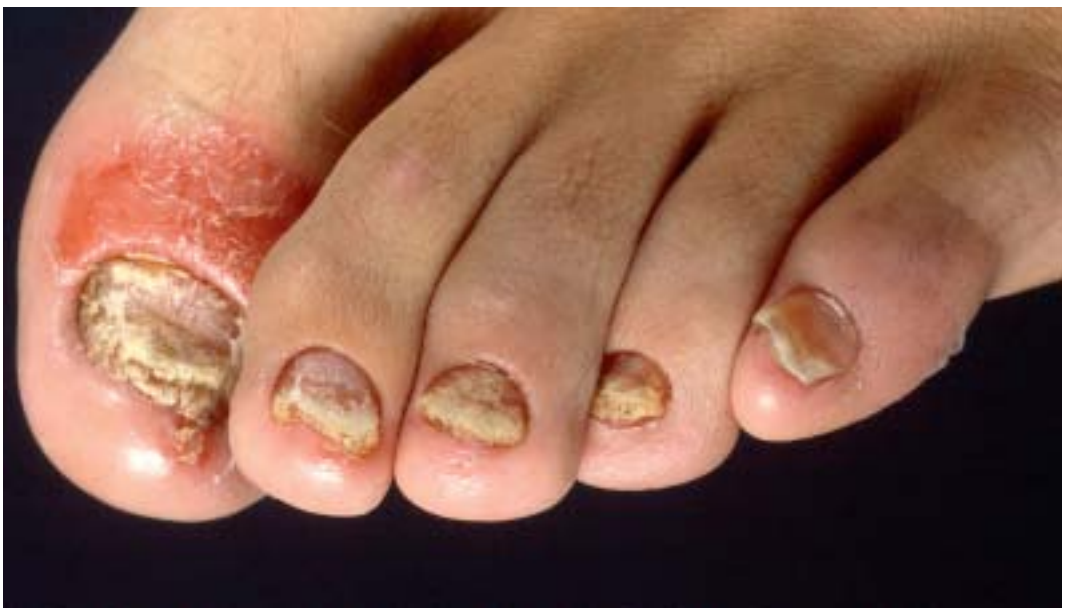
Psoriasis of the toenails.



Museum Bridge, Groningen.
Many bridge operator houses in the Netherlands today serve no function.
This one is now a museum piece maintained by the nearby Groninger Museum.

4 University Medical Center Groningen

Marcel F. Jonkman
with contributions by Sylvia H. Kardaun, Pieter-Jan Coenraads, Henri H. Pas and A. Marjon G. Pasmooij

Introduction

The University of Groningen was established in 1614, the second oldest in the Netherlands. In 2014, the year this book is published, the university celebrates its 400th anniversary. The university hospital, the Nosocomium Academicum, was built in 1797. Medical education was provided from the outset. Responding to pressure from the student body in the early 20th century, the hospital board introduced dermato-venereological education and appointed an ordinarius for dermatology and venereology.
The University Medical Center Groningen serves 2 million people in the north-east of the Netherlands comprising 18.2% of the Dutch population. Annually 7000 new patients visit the academic out-patient department. In addition, 800 STD patients in Groningen are seen annually. The department has two approved national Centers of Expertise: 1) blistering diseases (epidermolysis bullosa and autoimmune bullous diseases), and 2) eczemas / occupational dermatology.
An additional focus of research will be dermato-oncology.

Entrance to the University Medical Center, Groningen.

History

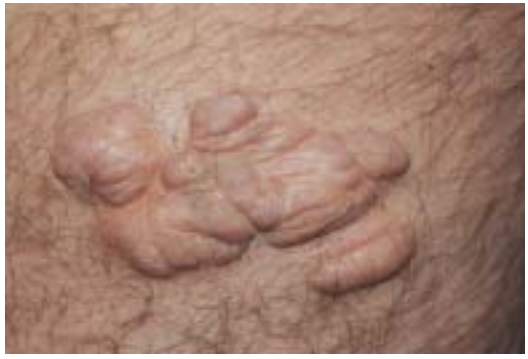
Rutger Adolf Reddingius

Professor of pathology and previous Rector Magnificus, Prof. Dr. Rutger Adolf Reddingius (1857-1923) was appointed in 1913. He lectured to the appreciation of the students and started a dermatological polyclinic in the pathologic anatomy laboratory. As a pre-clinical professor, Reddingius was not supported by the clinical professors who took the dermatology and venereology patients in their wards. Reddingius stood down in 1921, and dermatological education remained untaught in the medical faculty until 1924, when Prof. Johan Willem van der Valk from the Amsterdam school was appointed.

Johan Wilhelm van der Valk (1877-1929) was an eloquent clinician and teacher, and devoted his inaugural speech to "Skin diseases and internal medicine". His dermato-venereological clinic in Groningen opened in 1925 with 26 beds and 12 cradles. By the time he died unexpectedly in 1929, the number of out-patient consultations was 18,962. Venereological diseases were treated for free.

Emil Friedrich Zurhelle

His successor, appointed in 1931, was the German dermatologist Emil Friedrich Zurhelle (1889-1965). Zurhelle came from the famous Bonn dermatological department of Prof. Erich Hoffmann, who had discovered the *Treponema pallidum* in 1905, the microbe causing lues. In 1922 the couple reported the nevus lipomatosus superficialis Hoffmann-Zurhelle. Zurhelle was an expert in lues and wrote the chapter on syphilitic infections of the lymphatic system and spleen in Josef Jadassohn's "Handbuch der Haut- und Geschlechtskrankheiten". Zurhelle was an experimental scientist following the German tradition prevalent at that time. He was unmarried and devoted his life to dermatology, supervised five theses and oversaw the establishment of a new clinical building in 1939. After the German invasion of 1940, he continued to work with impartiality and evidenced no sympathy for the Nazis. However, in 1945, events took an unfortunate turn for Zurhelle. He was recruited into the Wehrmacht and forced to wear German military uniform. Immediately after the war, he disappeared into Germany.



Naevus lipomatosus Hoffmann-Zurhelle.

Maximiliaan Ruiter

In 1947 Maximiliaan Ruiter (1900-1974), Zurhelle's assistant, was appointed professor and chair, a position he held for 22 years until 1969. He had been born in Nijmegen and grew up in Harlingen, Friesland. He was known as a private man, who made a shy impression. He felt best in the quiet surroundings of his office and laboratory. To those who knew him better and had gained his trust, he was warm and humorous. His interests were broad and included art, history and music. In 1932 his thesis on pyodermas was awarded cum laude. As a dermatologist, he was able to collaborate with basic scientists. His scientific advancements are described elsewhere. In 1960, the NVDV honoured him as the first recipient of the golden Mendes da Costa medal, which is awarded once every five years for outstanding dermatological research carried out in the Netherlands. Ruiter used the Bucky-ray apparatus for skin diseases, dark-field microscope for diagnosis and electron microscope for research. In 1965 the Dermatology department was housed in a new three-storey building with 50 beds, three polyclinics, and diagnostic and research laboratories.

Arnoud Hendrik Klokke

The new professor, Arnoud Hendrik Klokke (1920), became installed in 1971. Klokke had trained in Rotterdam under Prof. Dr. E.H. Hermans, and from there brought along with him Johan Nater and Henk Doeglas, as well as two basic scientists Eric Bleumink and Marcelus de Jong. Klokke's heart lay in Indonesia where he gained experience in leprosy, framboesia, and fungal infections. He expanded tropical dermatology, medical mycology and histopathology in the Groningen clinic. The 80s were prodigious years in the dermatological clinic, and a successor was not easily found after Klokke's retirement in 1984.

Johannes Pieter Nater

In 1986 Johannes Pieter Nater (1927-2001) was appointed as professor for four years by the university board. Nater established a center for occupational dermatology in Groningen with a dynamic allergic contact dermatitis unit. From his stable came dermatologists such as Henk van der Walle, Pieter-Jan Coenraads, Derk Bruynzeel, Anton de Groot and Pieter Van der Valk, who all became experts in contact dermatitis. During this period, Nater, and the head of the out-patient department Pieter van Voorst Vader, taught the basics of dermatology and venereology to innumerable students and residents.

Jan Bareld van der Meer

In 1992 Jan Bareld van der Meer (1936-2003) started as the new head of department. He was trained by Prof. Jansen from Utrecht, where he discovered in 1969 granular IgA depositions in the skin of dermatitis herpetiformis. Van der Meer's expertise was in immunology. He introduced the 'Grande dermatologie' in Groningen and started treating toxic epidermal necrolysis and Fournier's gangrene with dexamethason pulse therapy. In 2001 he was succeeded for two years by Prof. Dr. Pieter Jan Coenraads, a student of Nater, who had developed an expertise center for occupational dermatology and eczemas.

Marcelinus Franciscus Jonkman

In 2003 Marcelinus Franciscus Jonkman (1957) was appointed. Before he was trained as dermatologist by Nater and Van der Meer, he had produced a thesis on wound healing and artificial skin in 1989 at the Department of Medical Electron Microscopy. Intrigued by the regeneration of the basement membrane, and invited by the immunofluorescence microscopist Marcelus De Jong, he moved into bullous diseases while collaborating with biochemist Hendri H. Pas. In 1997 he founded the Expertise Center for Blistering Diseases in Groningen. The center attracted many patients with epidermolysis bullosa, pemphigus and other bullous diseases from the Netherlands, for which a large multidisciplinary team was available. Science flourished and the quality and number of dissertations increased. In 2006 he was honoured for his research with the Mendes da Costa medal. Jonkman was also engaged in developing dermatological training since more structured training programmes were required by new Dutch laws. In 2009, he restructured Dutch resident dermatology courses. Today, the Groningen residents enjoy an additional 12 months' training in large hospitals in Leeuwarden, Zwolle and Groningen. Jonkman joined the ILDS (International League of Dermatlogical Societies) Dermatological Nomenclature working group and the board of the European Academy of Dermatology and Venerology (EADV).

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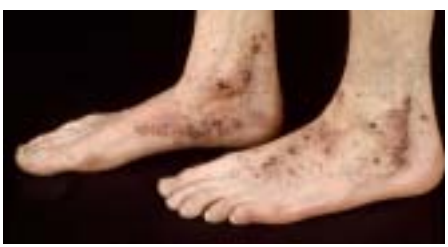
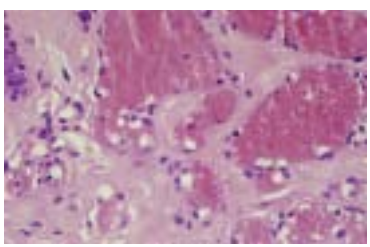
Vasculitis allergica of Ruiter and Ruiter-Pompen-Weyers thesaurismosis lipoidica

"His work was his life!" So says of Ruiter his friend and former colleague Henricus Martinus Maria Wentholt. "An outstanding and dedicated representative of dermatology; a scientist who also has great clinical skills", so adds his pupil and later chef de clinique, Frans Henderikus Oswald. Both praise the man who played such a great role in the history of dermatology, and whose name became synonymous with the terms 'vasculitis allergica' or Gougerot-Ruiter disease, and with angiokeratoma corporis diffusum or Fabry's disease, also called Ruiter-Pompen-Weyers thesaurismosis lipoidica. In Deventer in 1947 he wrote with colleagues internist Pompen and pathologist Weyers on angiokeratoma diffusum as a clinical marker for a phospholipid disease in the internal organs.[1] This publication helped him to be assigned in that same year as professor in Groningen. In 1952 he gained international recognition with the concept of vasculitis allergica.[2,3] Ruiter recognized that the disorder was an allergic reaction on various signals, such as bacteria, drugs, food additives, and insect bites. Only later it became apparent that the reaction was established by immunocomplex depositions. Normally, no treatment is necessary, and if the causing agent is identified and eliminated the symptoms largely vanish quickly. At the end of his ordinariate he was the first to use the electron microscope in collaboration with his co-worker and biologist Dr. Van Mullem. They demonstrated the human papilloma virus as cause of epidermodysplasia verruciformis, and revealed lipid inclusions in endothelial cells in angiokeratoma corporis diffusum.[4,5]



Vasculitis allergica.



Skin biopsy in Fabry's disease with vacuolization of endothelial cells.

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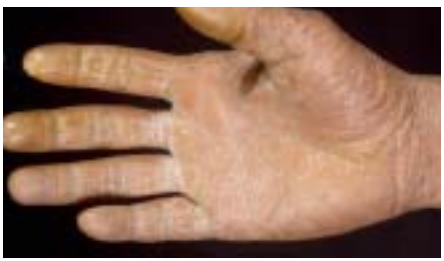
Contact allergy

Nater started a new line of research on contact allergy. He was known for his work on chromate allergy in masons. His co-worker Pieter-Jan Coenraads extended the work to eczema of the hands in the general population. There was a remarkable lack of knowledge during this time regarding the debilitating effect and costs for society of this form of hand eczema. In a broader context the work was continued on hand eczema generally, including studies on barrier function.[1,2] Their work on the role of nickel and the role of the barrier function of the skin is still a relevant issue. The development of validated photographic guidelines for clinical trials in patients with hand eczema was essential.[3] The department participated in a study on the use of a new retinoid in severe hand eczema.[4]



Chronic hand eczema.

An important contribution was made in the European Guideline Hand Eczema in a Cochrane Systematic Review.[5]

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Dexamethasone pulse therapy in TEN

Already before his appointment as a professor in Groningen in 1991, Van der Meer had a special interest in blistering diseases. His appointment coincided with an existing interest in cutaneous adverse drug reactions (cADR) by department dermatologist Sylvia Kardaun. As a consequence, a study on the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) was started. It is eminently important to restore the barrier function of the skin and mucosae as quickly as possible and in the meantime prevent the negative effects of its loss. Attempts have been made to decrease mortality by improved supportive care and several modalities of specific treatment. For most of these treatments, however, results are variable and placebo-controlled trials are difficult to accomplish because of the low incidence of SJS/TEN and the large number of patients required for a study to be statistically meaningful.

Historically, corticosteroids were advocated, but after reports with a negative outcome in the 80s of last century, they were increasingly regarded as harmful and even detrimental by some authors. Building on J.S. Pasricha's use of pulse therapy with dexamethasone/cyclophosphamide for pemphigus in 1988, the group around Van der Meer reappraised the use of corticosteroids in SJS/TEN.[1]
The assumption was that the negative general opinion was due to the fact that low-dose corticosteroids, administered for too long and too late in the process, are hardly therapeutically effective, raise the risk of infection and possibly have a negative effect on wound healing. The rationale was that a short course of high-dose corticosteroids, administered earlier in the process, might possibly influence the immune-mediated cascade, leading to massive apoptosis.
We developed an overall treatment protocol with high-dosed pulse therapy with 1.5mg/kg bodyweight dexamethasone on three consecutive days, and reported a low mortality.[2] Although the controversy on treatment modalities has not been settled, the general opinion is less negative nowadays and this protocol has become widely followed. Current opinion is that systemic corticosteroids are clearly deleterious in the late stage of SJS/TEN while in the early stage their benefits are not yet evidenced.
Derived from Van der Meer's propagation of pulse therapy, Jonkman embarked on the first randomized double-blind clinical trial in pemphigus (PEMPULS), and found that pulse therapy did not appear to have any benefit in pemphigus above standard therapy with prednisolon and azathioprine.[3]
The study on cADR in general and severe cADR such as acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms in particular, has led to the appointment of Kardaun as head of the Reference Center for Cutaneous Adverse Drug Reactions in the Netherlands.[4,5] Besides a national role in treatment, this has resulted in cooperation with a leading multinational study group (RegiSCAR), as well as multiple publications, in particular on classification problems in severe cADR and a thesis on severe cADR.[6]

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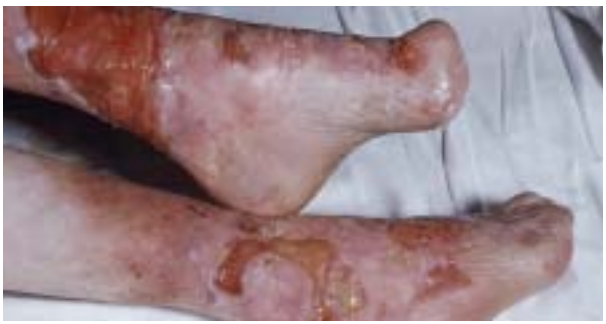
Epidermolysis bullosa

Research and management of the genetic bullous disorder epidermolysis bullosa is an important subject in the Groningen clinic. Marcel Jonkman saw his first patient in 1989 in the era that none of the genes of this devastating disease had been discovered. Now, eighteen genes are known to cause one of the more than 25 phenotypes. The Groningen clinic was reponsible for identifying two of these. In 1995 Jonkman discovered that bullous pemphigoid antigen-2 or type XVII collagen is deficient in non-Herlitz junctional epidermolysis bullosa, by that time known as generalized atrophic benign epidermolysis bullosa (GABEB).[1] In 2005 he delineated a new severe EB phenotype called lethal acantholytic epidermolysis bullosa and also demonstrated that the disease was caused by loss of desmoplakin tail.[2] And in 2011, type XVII collagen was found to be the cause of the late-onset subtype of junctional epidermolysis bullosa.[3] The multidisciplinary epidermolysis bullosa team in Groningen has been serving a large number of Dutch patients with epidermolysis bullosa since 1997.



Epidermolysis bullosa dystrophica.

The long-term follow-up has resulted in import clinical observations.[4]

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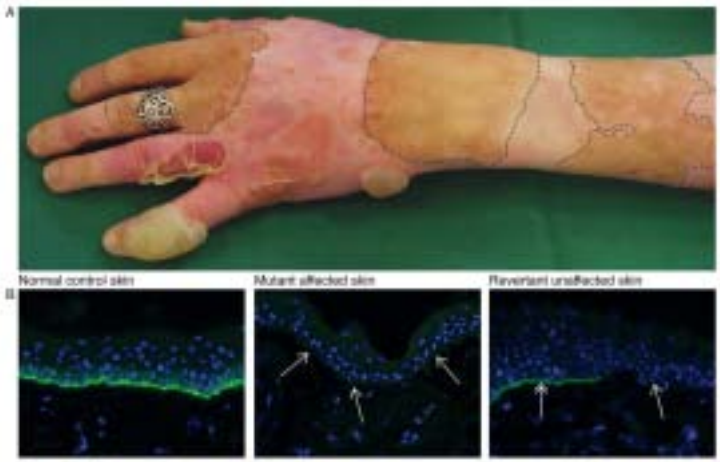
Revertant mosaicism

Revertant mosaicism is a naturally occurring phenomenon involving spontaneous correction of a pathogenic mutation in a somatic cell. In 1997 revertant mosaicism was discovered in skin for the first time by the Center for Blistering Diseases in Groningen.[1] A patient with the hereditary blistering disease epidermolysis bullosa (EB) had spontaneously healed skin areas without blister formation (i.e., revertant) where the deficient protein was re-expressed, whereas the surrounding skin was fragile. To find the underlying correction mechanism Jonkman spent three months in Prof. Jouni Uitto's laboratory in Philadelphia to study DNA/RNA from keratinocytes cultured from the patient.



(A) Patient with EB caused by germ-line mutations in the COL17A1 gene. Due to the absence of collagen XVII, her skin is fragile and blisters easily. She has, however, several areas that are clinically normal and do not blister (dashed lines).
(B) Skin biopsies taken from the affected skin show the absence of the green collagen XVII staining (arrows) compared to normal control skin. In contrast, the normal seeming revertant skin shows patchy re-expression of the deficient protein (double arrowhead). The figure is reprinted from Pasmooij et al., 2012, Discov Med, 14(76): 167-79.

In 2003 a new Laser Dissection Microscopy (LDM) technique was introduced in the Center for Blistering Diseases by cell biologist Anna Maria Gerdina (Marjon) Pasmooij. With this technique it became possible to immediately analyze frozen skin biopsies for their spontaneous correction event, thereby omitting the need for cell culturing. Although it was initially thought that only one reversion event had occurred in a patient, data obtained with LDM revealed that every single patch originated from a distinct genetic event.[2] At the time of the publication in 2005, the general opinion was that revertant mosaicism was rare. However, the identification of many more patients with EB and revertant mosaicism in the following years changed this, and led to the belief that revertant mosaicism is common.[3]
Experiments were carried out on the possibility of culturing keratinocytes from a revertant skin area, creating a skin graft and subsequently transplanting back to affected skin.[4] Although the surgical method of the transplantation was successful, the amount of revertant keratinocytes was insufficient for obtaining fully functional skin with normal integrity. A hurdle still to overcome is the improvement of graft production, such that adequate percentages of revertant stem cells are present to secure functional repair of the skin.[5]
Another exciting possibility, attracting the interest of many current researchers, is combining revertant mosaicism with induced pluripotent stem cell (iPSC) technology. Patient-specific keratinocytes from revertant mosaic patches that have been corrected spontaneously could be used as a source for patient-specific iPSCs and provide an essentially unlimited number of patient-specific cells for grafting.
As revertant mosaicism seems to be common in EB, and the possibility of using the patient's own naturally corrected keratinocytes is an appealing one, the first symposium on Natural Gene Therapy of the Skin was held in Barcelona in 2011 with financial support from the Dutch Butterfly Child Foundation (http://www.vlinderkind.nl), and prior to the 41st Annual Meeting of the European Society for Dermatological Research (ESDR).[6]

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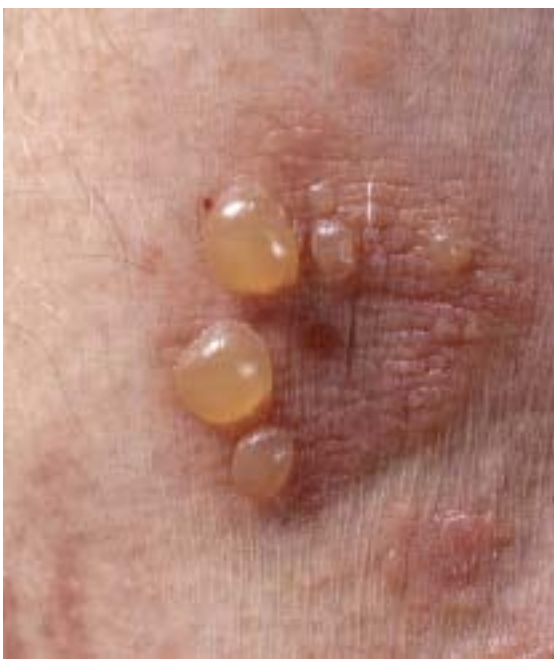
Enhancements in immunofluorescence microscopy

The breakthrough in the diagnostic classification of pemphigoid diseases came with the use of immunofluorescence microscopy in 1965 by Beutner and Jordan. In the following years several pemphigoid diseases were further unravelled and specified by using direct and indirect immunofluorescence microscopy (IF). In the Center for Blistering Diseases in Groningen new techniques were developed that increased the yield of IF diagnosis, and helped the clinician to solve the most complicated diagnostic cases. Fluorescent overlay antigen mapping, a new transport medium for IF skin biopsies, and the serration pattern analysis to differentiate epidermolysis bullosa acquisita from other pemphigoid diseases are three of the important improvements made by our immunofluorescence laboratory, and in which the immunologist-biologist De Jong played a pivotal role.
By mapping immunodeposits along the basement membrane zone it is possible to differentiate pemphigoids with high deposition (bullous pemphigoid) from those with low deposition (epidermolysis bullosa acquisita). The technique for mapping was called Fluorescent Overlay Antigen Mapping (FOAM).[1] This IF technique was developed by Siert Bruins and Marcelus De Jong in our laboratory. For instance, FOAM could differentiate between immunoreactivity to bullous pemphigoid antigens from that to type VII collagen, the epidermolysis bullosa acquisita antigen. Robert Vodegel et al extended this technique and reported the possibility of discerning immunoreactivity between intermediate depositions against laminin-332 from low depositions against type VII collagen.[2]
The work with epidermolysis bullosa provided skin tissue samples in which autoantigens in the basement membrane zone were absent. These samples could be used as knockout substrates to test the presence of specific autoantibodies by indirect IF in sera of patients with subepidermal autoimmune bullous diseases.[3]
For preservation of tissue-bound immunoreactants, biopsies were usually fresh-frozen in liquid nitrogen or transported in Michel's fixative. These transport mediums can give false negative results due to the

relatively high fluorescence background in the dermis evoked by aspecific bound circulating IgG. The value of saline as a transport medium was serendipitously found by Jonkman in the 90s when he used saline as a replacement for unavailable liquid nitrogen to transport IF biopsies during a consultation at the weekend. Vodegel systematically studied IF biopsy transport and concluded in 2004 that saline for 24 hours at room temperature (without freezing) improves the desired IF signal and therefore the diagnostic yield in routine direct IF for autoimmune skin diseases.[4] The superior results by saline incubation were explained by washing out aspecific IgG from the skin sample. The use of saline as a transport medium is easy, inexpensive and convenient, but transport time is limited to 36 h. In the early 90s, after seeing hundreds of biopsies of pemphigoid patients it appeared to De Jong that the linear pattern of immunodeposits along the epidermal basement membrane zone is serrated like the edges of leaves. As a biologist he was trained to differentiate leaves by their serration pattern. Vodegel systematically investigated the serration pattern and reported in 2004 that u-form serration is only seen in epidermolysis bullosa acquisita or bullous systemic lupus erythematosus, and that the n-form serration was only found in the other pemphigoids.[5] The u-serration pattern represents immunoglobulin depositions in upstanding arms ("grass") of the sublamina densa zone between the rootlets of basal keratinocytes. In 2013 J. Terra and co-workers created an image-based online test and instruction video available free of charge (www.nversusu.umcg.nl). The accessibility of direct IF serration pattern analysis was demonstrated among experts, dermatologists and residents using this online IF instruction and testing system.[6]



Meanwhile immunoserological diagnosis by immublot was developed by Hendri Pas. He demonstrated that a 120 kDa molecule was bound by both bullous pemphigoid IgG autoantibodies and linear IgA dermatosis IgA autoantibodies, and showed that it was identical to the ectodomain of BP180, which is the major antigen of various forms of pemphigoid.[7] The importance of this discovery was that it demonstrated that bullous pemphigoid and the lamina lucida form of linear IgA dermatosis were diseases that targeted the same antigen. Pas also suggested that the 120 kDa form of the BP180 molecule could be the proteolytically cleaved-off ectodomain of BP180, and that in this process neoepitopes might be formed which explained the observation that some patient sera only bound to the 120 kDa molecule but not to BP180.[7]

Bullous pemphigoid.

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Rituximab dose finding in pemphigus

Pemphigus is treated by long-term systemic corticosteroids, immuno-suppressive and anti-inflammatory agents, and intravenous immunoglobulins. Pemphigus was an incurable disease until the arrival of rituximab. Rituximab was developed in the late 80s and is the first therapeutic monoclonal antibody. It is a chimeric human-mouse monoclonal antibody, which binds specifically to the transmembrane antigen CD20, expressed on B-lymphocytes from the pre-B-cell stage to the pre-plasma-cell stage leading to their depletion. Rituximab is labelled for CD20+ B-cell non-Hodgkin lymphomas and rheumatoid arthritis. For years rituximab has also been used as an off-label drug for different autoimmune diseases. The first successful treatments with rituximab in patients with blistering diseases were seen in paraneoplastic pemphigus associated with B-cell non-Hodgkin lymphomas.[1] Since then, a remarkable therapeutic effect of rituximab was seen in several open case series with pemphigus.[2,3]

The common dose of rituximab was adopted from haematology, namely 375 mg/m2 once a week for four consecutive weeks. We questioned if the dosage of this expensive drug could be lower for off-label use in pemphigus.

Since the antibody producing B-cells in pemphigus are not malignant, and a single dose as low as 100 mg/m2 can deplete B-cells, we hypothesized that a lower dose of rituximab might be sufficient for pemphigus. Marcel Jonkman and Barbara Horváth started to give two infusions of 500 mg rituximab in an open series of 15 pemphigus patients, cutting the medicine costs to half compared to the lymphoma schedule, but also added azathioprin. All of our patients (100%) responded with clinical

improvement, while 53% of the patients achieved complete remission.[4] The treatment had an excellent safety profile and relapse rate was not significantly higher than at higher dosages.
Yearly about 20 pemphigus patients, referred from all over the Netherlands, are treated with rituximab in Groningen. Soon after our publication, a study from a group in Rome appeared using the rheumatoid arthritis dose regime of 2x1000 mg that showed a complete remission rate of 86% without the need for azathioprin or other immunosuppressive agents.[5] Omission of the immunosuppressive agent with its usual side effects, and the better remission rate, is the reason that in 2012 we changed to the higher-dose rituximab to compare it with the historical low dose series.
Rituximab might become the therapy of first choice for pemphigus if the results of a forthcoming randomized trial in France are encouraging. Moreover, there are several second and third generation fully human or higher affinity anti-CD20 mAbs (ofatumumab, ocrelizumab, veltuzumab) being developed by several companies, for which pemphigus may become a labelled indication.
These advancements may make this chronic disease curable by insured medical intervention.

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Townhall Bridge, Utrecht with the "Dom" in the background.

5 University Medical Center Utrecht

Carla A.F.M. Bruijnzeel-Koomen
with contributions by Johan Toonstra, André Knulst and Suzanne Pasmans

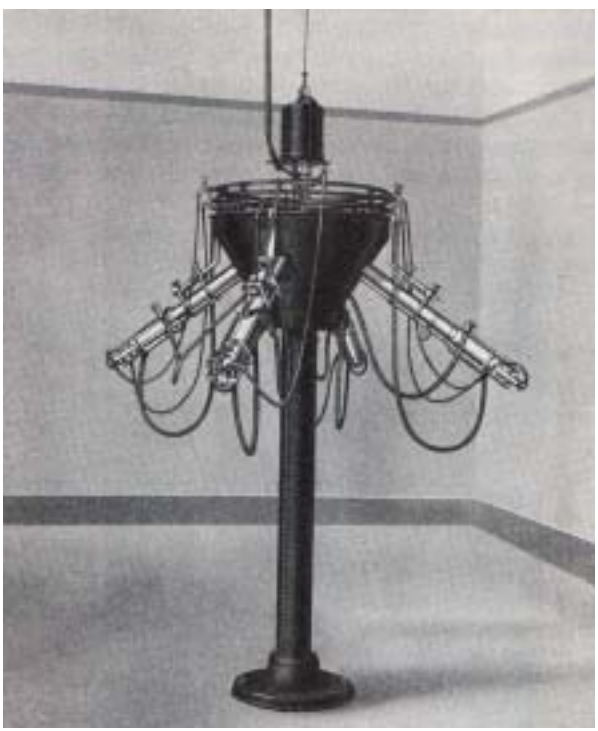
Introduction

The city of Utrecht, located in the center of the Netherlands is the fourth largest city in the country, with a population of about 330.000. It was established by the Romans in 50 BC on the border of the Rhine river, where they build a fortress, the so-called Castellum Traiectum. The 12th century brought rapid growth to the town, which was both an ecclesiastical and a commercial center. Until the Dutch Golden Age in the 17th century, Utrecht was the most important city of the Netherlands; after this, Amsterdam became the country's cultural center and most populous city. Nevertheless, Utrecht remains home to the largest university in the Netherlands, Utrecht University. Its origins go back to 1634, when the City Council founded an 'Illustrious School', which in 1636 officially became Utrecht University in order to make possible the awarding academic degrees. Its inauguration took place on 26 March 1636, a day the university continues to celebrate annually.

Aerial photograph of the University Medical Center Utrecht (2011).

Theodoor Marinus van Leeuwen

Theodoor Marinus van Leeuwen (1876-1952), began his training in pathology in 1906. Since he wanted to maintain contact with patients, he decided to do a parallel specialization in dermatology. This decision took him to the established European centers of excellence in dermatology at the time: Berlin, Hamburg and Paris. He felt particularly drawn to the French School and was tremendously impressed by the teachers he studied under there, Brocq and Darier.
In 1914 the famous Dutch surgeon professor Laméris saw the need to create a separate discipline of dermatology and asked his assistant van Leeuwen to run a clinic for patients with skin and venereal diseases. The reason for this request was the marked increase of venereal diseases during the First World War, and the fact that the rise of patients numbers could not be accommodated by the normal surgical routine.
In 1919, Van Leeuwen accepted the first ever chair in Dermatology at Utrecht University. His personal interest in the effect of sunlight on diseased and healthy skin led to the establishment of a long tradition of patient care and research in the Dermatology Department. During those years the focus was on the new treatment of tuberculosis of the skin using the Finsen-Lomholt lamp. Following the principles of Willem Storm van Leeuwen of Leiden University, the clinic started with an allergen-free room in 1934, thus establishing a further strand to the department's tradition of patient care and research.
Until the end of Van Leeuwen's tenure - he retired in 1945 - dermatology remained a mainly descriptive medical discipline. During this time, more than 25 physicians qualified as certified dermatologists. In 1938 the first female resident was admitted to the programme. Among the 126 publications of this period, 50% was on venereal diseases. Out of the 13 theses produced, 6 were on venereal diseases, 2 on allergic skin diseases and 2 on Röntgen therapy.

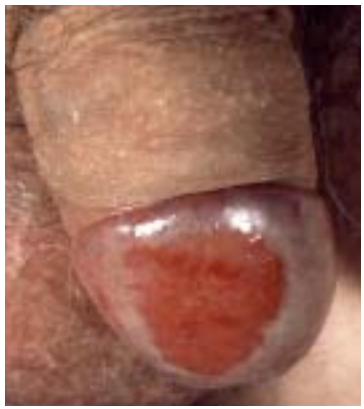


The Finsen-Lomholt lamp.

Johannes Jacobus Zoon

Johannes Jacobus Zoon (1902-1958), Van Leeuwen's successor, became aware of the necessity to develop insight into pathophysiology. He was in charge of the department from 1945 till 1957. During this period, attention to venereal diseases decreased: only 17 of 97 articles published related to this topic. The Finsen lamp was used for the last time in 1955. In a 1949 landmark demonstration before a meeting of Dutch dermatologists, Zoon presented 3 patients with a well-demarcated red skin lesion on the glans penis and foreskin, and with many plasma cells in the upper dermis revealed microscopically.

Balanoposthitis circumscripta benigna plasmocellularis.



He concluded that this was a benign condition with no relationship to syphilis and different from a similar-looking premalignant condition called erythroplasia of Queyrat. In 1952, Zoon proceeded to describe this condition in 8 patients under the name "Balanoposthitis circumscripta benigna plasmocellularis".[1] Since then his name has become synonymous with this condition. Zoon promoted research activities by physicists and chemists. Many non-medical scientists, usually already holding a PhD degree, were enlisted to consolidate the staff.

Like Van Leeuwen before him, Zoon too had to work under relatively primitive conditions. Only after many years did Zoon succeed in obtaining facilities adequate for an in-patient department. Such facilities were needed at a time when some 1000 patients were admitted annually. Today, by contrast, only 200 patients are admitted per year . Being a passionate teacher, his lectures were always overcrowded with students. His management style was autocratic, limiting the number of topical therapies to no more than ten. Hydrocortison acetate could only be prescribed with the permission of the professor. At that time, Roentgen therapy was popular for treating many benign skin diseases. Zoon set up laboratories for dermatopathology, mycology, physics and chemistry. Paul Bastiaan Rottier focused on the diagnostic equipment for UV sensitive skin while Jan Cornelis van der Leun concentrated on UV-induced erythema. Van der Leun discovered the phenomenon of UV desensitization, which was further developed by Huib van Weelden and made Utrecht the national center for the diagnosis and treatment of photodermatoses.

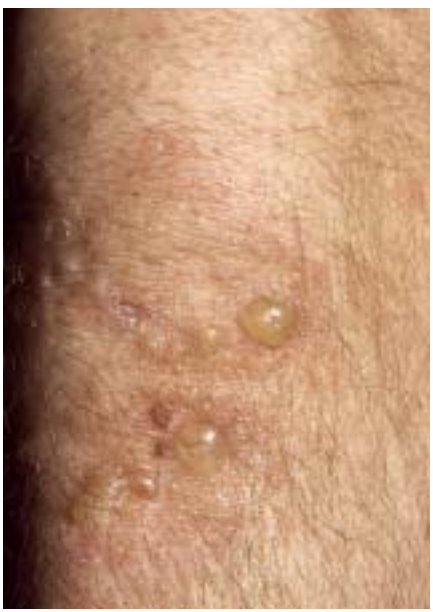
Leendert Hendrikus Jansen

Zoon's successor, Leendert Hendrikus Jansen (1916-1977), presided over a busy period of scientific development and expansion of the Utrecht Dermatology Institute. Unlike his predecessor, Jansen preferred to give his staff more free rein. In 1955, Jansen described the abnormal structure of the dermal collagen fibers in Ehlers-Danlos syndrome.[2] Along with his Utrecht colleague, Jan B. van der Meer, who published on dermatitis herpetiformis, Jansen was the only other Dutch dermatologist who was included in the Citation Classics from dermatological journals between 1945 and 1990.

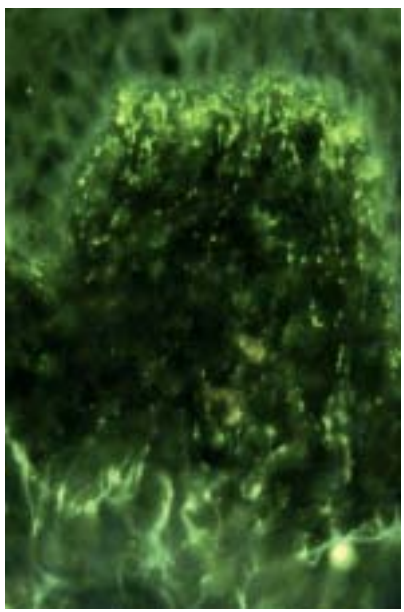
Cormane was the first to describe bound globulin in the skin of patients with chronic discoid lupus erythematosus (CDLE) and systemic lupus erythematosus (SLE). This method was also useful for cases in which the clinical and histological diagnoses were questionable.[3,4]

In those days, immunofluorescence studies were popular in Utrecht. In 1969 van der Meer used direct immunofluorescence to describe granular deposits of IgA in the dermal papillae of perilesional and uninvolved skin in dermatitis herpetiformis.[5] In 1973 Eva Baart de la Faille-Kuyper et al. demonstrated that there were IgA deposits not only in renal glomeruli but also in skin vessels in patients with Henoch-Schönlein vasculitis.[6]

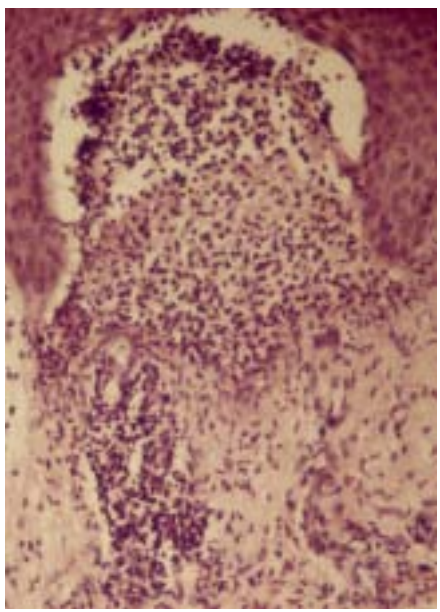
Clinical picture of dermatitis herpetiformis on the knee.



Granular IgA in the papillary dermis in dermatitis herpetiformis.



Dermatitis herpetiformis with infiltrate of mainly neutrophils in the papillary dermis.



Many of Jansen's co-workers became professor at dermatology departments in the Netherlands: Lubertus Berrens, Eric Bleumink, Annelies van Bronswijk, Rudi Cormane, Eise van Dijk, Götze Kalsbeek, Arnoud Klokke, Jan van der Meer and Edward Young. A highlight of this period was the newly built dermatology department, designed by Zoon but only completed in 1959, a year after his death. Room was made for many different laboratories, notably experimental allergy, histopathology, immunofluorescence , mycology and "mini-biology". Another new development was the start of an out-patient department for auto-immune diseases which eventually merged with the multidisciplinary Department of Immunology.

Meanwhile, the allergy department continued to expand, with a multidisciplinary out-patient clinic for allergic diseases opening in 1960. Encompassing pediatrics, lung diseases, ENT, ophthalmology, bacteriology/immunology, this clinic was headed by Edward Young. Together with Lubertus Berrens, Young was particularly keen to lead the study of immediate-type allergy. A sizeable number of PhDs was awarded to non-medical researchers on the subject of characterization of allergens. Berrens received the Robert Koch Medal for his work on the reactivity of allergens by means of complement activation.

Lubertus Berrens and Leendert Hendrikus Jansen.

Götze Lucas Kalsbeek

Three years after Jansen's death in 1977, Götze Lucas Kalsbeek (1927-1982) was appointed professor of dermatology in Utrecht. Earlier, Kalsbeek had identified together with Rudi Cormane, immunoglubulins in the skin of patients with lupus erythematosus.[4] Sadly, Kalsbeek died unexpectedly within 2 years of his appointment.

Lupus band in CDLE with granular IgG along the basal membrane.

Willem Anton van Vloten

Willem Anton van Vloten (1941), was appointed in 1985. Having trained in Leiden, he was the first professor from outside Utrecht. Due to economic restraints, the department's budget was repeatedly reduced, prompting a reorganisation of staff. The chairs of Berrens and van der Leun were lost and JEMH (Annelies) van Bronswijk, who had been appointed endowed professor in environmental hygiene in 1990, left for Eindhoven's Technical University in 1995.

The move of the University Hospital to a new building outside Utrecht's city center in 1989 ushered in new management structures and centralizations. The department lost its laboratories, library and photography unit, leaving only a small research facility, and became subsumed under the Division of Internal Medicine and Dermatology. Van Vloten initiated a Utrecht-based working group on psychodermatology which after several years grew into a national working group, which is still currently active.[7,8] This led to the establishment of the Netherlands Society of Psychodermatology in 2006.

Dermatology Department Staff, Utrecht 1983.
From left to right, front row: Jan van der Leun, Edward Young, Fré de Maat-Bleeker and Harold Baart de la Faille;
Back row: Frederik de Wit, Willem Koers, Annelies van Bronswijk, Rob Roberti, Ben Martens, Huib van Weelden,
Carla Bruijnzeel-Koomen and Johan Toonstra.

Catharina Ansfrieda Francisca Maria Bruijnzeel-Koomen

In 1991 Catharina Ansfrieda Francisca Maria Bruijnzeel-Koomen (1954) succeeded Young as professor in dermato-allergology, having returned to Utrecht after a 3-year stay in Davos at the Swiss Institute of Asthma and Allergy Research. That same year, the department decided to restrict its research to two main topics: allergy and photodermatology including photocarcinogenesis. These were incorporated into the mainstream of research in the medical faculty as well as the university hospital. The staff was successful in attracting external grants, notably for allergy (atopic eczema) and physics (genotoxic and immunosuppressive effects of UV light).
In 2001 Van Vloten was succeeded by Bruijnzeel-Koomen. Again the department was hit by a round of financial constraints, which led De Gruijl to leave for Leiden, where he could continue his work on photobiology. The department's research focused on eczema and food allergy.
A fruitful collaboration on food allergy was started with TNO Quality of Life in Zeist, the department of pharmaceutical sciences and the veterinary faculty: the Utrecht Center for Food Allergy. In the meantime, the department was able to attract funding, while young researchers working on both adult and child

eczema, took the lead in formulating the national guideline improving care for patients with atopic eczema. The department also initiated funding for the first patient portals for eczema and food allergy. The eczema portal was praised by the Ministry of Health as one of the most innovative new information technology projects. Patients files were digitized, making the outpatient clinic for venereal diseases the first paper-free clinic at UMC Utrecht. In 2010 Vigfús Sigurdsson took over from Carla Bruijnzeel-Koomen the responsibility of training dermatologists. Van Weelden retired in 2011 and with his departure a long era of research in photodermatology ended.

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Research

Cutaneous lymphomas

Van Vloten continued his work in the Dutch cutaneous lymphoma group (chapter 6, page 86). This group, consisting of dermatologists and pathologists, discusses all new patients with (suspected) cutaneaus lymphoma from the whole country on a quarterly cycle. Diagnosis is finalized and advice given on therapy. All data are stored and made available for follow-up studies. More than 3000 patients are included in this lymphoma group.[1,2] The group plays an important role in the European Organization for Research and Therapy of Cancer (EORTC) and in 1997 proposed a classification for primary cutaneous lymphomas, which is still being used today.[3] The Dutch group is very active and participates in exentsive international studies on different subclasses of cutaneous lymphoma. This collaboration is essential since cutaneous lymphomas are rare diseases.[4]

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Allergens, atopens and reagins

Allergens are a complex mixture of proteins and carbohydrates. At the department, a common structure present in many allergens - the lysine-sugar structure - was identified and denoted as the atopen.[1] For allergens containing a lot of protein, such as pollen allergens, this appeared to be less valid. However, regarding house dust allergen, this theory seemed to be quite sound. An in-vitro test was developed, based on the complement binding assay resulting in the lysis of erythrocytes, which could be used to test the potency of the allergenic extract before testing it on humans. The stronger the complement activation, the stronger the skin reactivity of the allergenic extract.[2,3]

Once allergens have passed the epithelial barrier they will encounter reagins to elicit an allergic response. In the concept of Berrens, allergens are not single entities, they form a complex mixture of antigens and atopens. This evokes the theoretical question whether reagins interact with the antigen or with the atopen structure of the allergen. Regular exposure to allergens would elicit an antigen-antibody response and in addition an atopen-reagin response. In this concept, the antibody was IgE and the reagin remained a structure to be elucidated. All attempts to identify a component of an acute phase system as the responsible factor have failed. Arguments for this theory were that the interaction between an atopen and a reagin would be much faster than one between an antigen and an antibody. Moreover, UV light would be capable of destroying the atopen reagin interaction by deactivating the lysine-sugar residues (Maillard reaction), whereas the antigen-antibody interaction would not be influenced, supporting the view that allergen-free environments found at high altitude are beneficial. It was however demonstrated that UV also deactivated the binding of antigen to IgE.

In the 1980s it became evident that Der p1 was the most important allergen in house dust and that it was generated by the house dust mite. The IgE antibodies that were specifically directed towards epitopes in Der p1 were called reagins. Being lysine sugar residues, the atopens have since been neglected by researchers, although they are still present in the allergen.

However, a revival of the atopen concept may occur, since recently attention has been paid to the role of common sugar structures (mannose) in allergens of plants, insects and parasites. They are considered to increase the allergic response by interfering with mannose receptors on innate immune cells like dendritic cells.[4]

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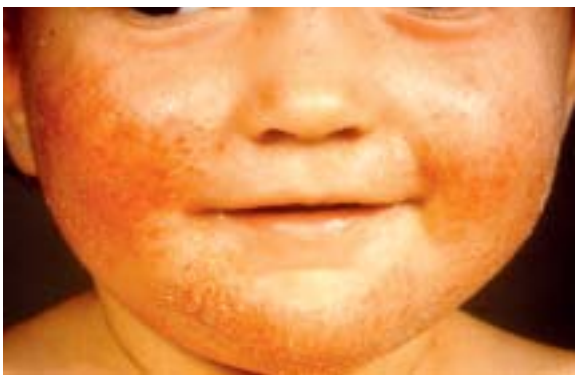
Atopic dermatitis

Research on atopic dermatitis has a longstanding tradition in Utrecht. In 1933 patients with eczema and prurigo were treated in an allergen-free room. Further, a special interest was taken in the cutaneous reactivity to human dander, since all atopic eczema patients showed positive immediate type skin responses to this product.[1] A breakthrough in the pathogenetic model of atopic dermatitis occurred in 1986 with the publication of a paper on the presence of IgE molecules on epidermal Langerhans cells in the lesional skin of patients with atopic dermatitis.[2] This linked the sensitization to allergens and the induction of eczema via allergen specific Th2 cells.[3] The induction of eczema by inhalant allergens, the atopy patch test, was internationally accepted as an in-vivo model for atopic dermatitis. In this model the phenotype of antigen specific T cells was studied, leading to the observation that, in the acute phase of eczema, the pattern was dominated by a Th2 type of inflammation and in the late or chronic phase by a Th1 type of inflammation.[4] The role of eosinophils and macrophages was also elucidated. In the meantime, clinical research was initiated to show the effect of house dust mite elimination on the clinical activity of eczema. This was carried out as a multicenter project in collaboration with the allergy departments of Rotterdam and Groningen.[5] Together with the department of pulmonary diseases, it could be shown that inhalation of allergens gave flare reactions especially in patients who also suffered from asthma.[6]



Atopic dermatitis.

In the meantime, the first patients with severe eczema were treated with ciclosporin, leading to an increased referral of patients from outside Utrecht and improved experience in treating severe eczema patients with oral immunosuppressants.[7,8] Patient education and information, preferably by trained nurses, became an important quality indicator in the national eczema guideline. In order to make eczema care more efficient, a digital project was started, showing that the provision of care via a protected, dedicated portal was cost-effective and much appreciated by the patients.[9] Translational research using the gene array technique showed a stable down regulation and up regulation of genes involved in T cell proliferation and apoptosis, independent from the effect of therapy.[10] New biomarkers were explored from which thymocyte and activation-regulated chemokine (TARC) turned out to be significantly correlated to disease activity, providing an objective parameter. Gene array techniques were developed and applied to lesional and non-lesional skin and allergen-induced eczema skin, suggesting interesting new possible leads for therapy. Translational research is facilitated by the recent establishment of the central eczema biobank, as well as the eczema database, which contains data of more than 500 well-characterized eczema patients and their sera. The focus for the future will be on further characterizing eczema patients by defining the different phenotypes.

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Food allergy

Food allergy is a disease that for a long time was neglected and even disregarded, probably due to the difficulties in diagnosis. Many eczema patients are sensitized to foods, but do not have symptoms related to food exposure. Even in patients who are clearly allergic to food, no more than 50% of the sensitizations found are clinically relevant.

Fré de Maat-Bleeker was one of the first clinicians to recognize the problem and discover cross-reactivity between inhalant allergens and food allergens, such as latex, buckwheat and birds' eggs.[1] Research was focused on improvement of diagnosis by implementing double-blind placebo-controlled food challenges (DBPCFCs), which became the gold standard. Low doses of allergens appeared to be able to elicit allergic reactions.[2] Challenge protocols were developed, starting with low doses and progressing to the dose causing clear symptoms. Thus, it was possible to establish thresholds for clinical reactivity for several different foods in large patient groups, consisting of both adults and children.[3,4] Knowledge of thresholds for clinical reactivity is used in new strategies to improve food labeling on a European level and even world-wide, supported by expert groups of the International Life Sciences Institute (ILSI), in which we participate actively.[5]

We have been involved in two major European studies, both coordinated from our center. Firstly, the SAFE project on plant food allergies, involving field-to-table strategies for reducing their incidence in Europe.[6]. Secondly, the Europrevall study on the prevalence, cost and basis of food allergy across Europe.[7] These studies have strongly improved our insight into allergens involved in food allergy, and into the differences between the food allergens involved in different geographical regions.

This approach, also called component-resolved diagnostics (CRD), was further developed and makes it possible to standardize diagnostic procedures.[8,9] Data so far indicate that at least for a number of foods, CRD allows better prediction of allergy and/or the severity of the reaction.

Curative treatment is just in its infancy. New, potentially safer and more effective routes of allergen administration are currently being investigated. Participation has begun in the VIPES (Viaskin Peanut's Efficacy and Safety) study, the largest peanut vaccination study to date, using the transcutaneous route of peanut allergen administration. This study is aimed at at assessing the efficacy and safety of administration of several doses of Viaskin peanut in adults and children with peanut allergy.

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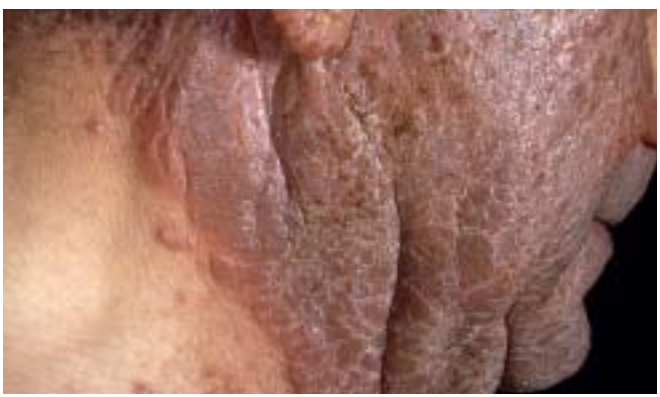
Photodermatology

The Department of Dermatology in Utrecht has a long tradition in research on photodermatology. The first professor in dermatology, van Leeuwen, accepted his chair with a speech entitled: "On the influence of sunlight on healthy and disesased skin". He used light for the treatment of certain skin diseases. His successor, Zoon, studied patients with xeroderma pigmentosum. Rottier received the Finsen medal for photobiology in 1960 "for fundamental studies of the basic phenomena underlying the formation of erythema of the human skin by UV radiation". In 1972 Van der Leun became head of the department of physics in dermatology. The phenomenon of light-induced tolerance to light was detected and developed for the treatment of several photodermatoses.
Since 1974 it has become clear that the depletion of the ozon layer may be dangerous and could lead to an increase of skin cancer. Van der Leun became more and more involved in this area and was awarded the 1996 Finsen medal for photobiology for his contributions on this subject.[1]
Huib van Weelden focused on the clinical aspects of photodermatology, more particularly on normal and abnormal reactions to light and the application of phototherapy for several skin diseases.[2,3]
He also studied the risks of photocarcinogenesis in relation to the use of sun tanning beds. In 1988 he introduced the small spectrum UVB lamp (TL-01), nowadays the preferred treatment in phototherapy worldwide over PUVA and broad band UVB.[4]
Furthermore, he investigated several photodermatoses: polymorphous light eruption, actinic reticuloid, lupus erythematosus and erythropoietic protoporphyria.[5-8] The treatment with light of several (skin) disorders, such as atopic dermatitis, psoriasis, acne and the Crigler-Najjar syndrome, also came under his attention.



Severe chronic actinic dermatitis in elderly male patient.

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Pediatric Dermatology

Children with skin diseases were treated in the past in the Department of Dermatology of the University Hospital (AZU) in a specialized ward for children. In the 1970s this ward was dissolved and children were subsequently hospitalized in the Wilhelmina Children's Hospital (WKZ).
In 1999 the WKZ became part of the University Medical Center and the following year Suzanne G.A.M. Pasmans took the lead on pediatric dermatology and allergology.[1-3] A Pediatric Provocation Unit was started for children with food allergy. In 2005 the first Group Medical Consultation (GMC) took place in the WKZ for patients with atopic dermatitis. In a GMC, headed by a dermatologist and a dermatology nurse, about 6 children have a medical consultation together with their parents. The communication principle is that the question of the patient is foremost. At the end of 2012 a randomized clinical trial was finished to investigate the effects of GMCs on children with atopic dermatitis compared with face-to-face consultations.
To improve the care for children with severe atopic dermatitis, a national study was carried out comparing new multidisciplinary care in the Dutch Asthma Center in Davos with new care in the WKZ.[4] For improved communication, the digital Eczema Center was developed together with Harmieke van Os-Medendorp, nurse researcher (including information, a multidisciplinary electronic patient file, e-consultation and e-coaching) to take care of transmural communication between the children, their caregivers and the involved professionals.[5] In 2007 the Center for Congenital Vascular Anomalies was initiated. A further well-received initiative was the introduction of atenolol

for the treatment of hemangiomas instead of propranolol.[6] An e-learning tool for parents of children with a suspected hemangioma was also succesfully introduced (www.aardbeivlek.nl).[7,8]
Difficult cases were discussed in the Task Force Group on Genodermatology with members from all university hospitals. In 2009 this body became the Dutch Task Force Group on Pediatric Dermatology, as part of the Dutch Society of Dermatology and Venereology. To make the care for children with skin diseases more accessible and efficient, the National Skin House (www.huidhuis.nl) was developed in 2012 for children, their care givers and involved professionals. This digital platform involves patient information, professional guidelines, a patient platform, e-consultations and e-care, as well as a research database. Pilots have been successful. This project has been singled out by the Dutch Council for Quality of Healthcare as an example of transmural care innovation, crossing and opening borders in national care.

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The 17th-century Koorn Bridge (Koornbeursbrug) straddling the New Rhine in the centre of Leiden, with the city hall pictured in the background. At this point, the Old and the New Rhine converge. Combining "Lug", the name of the Celtic sun god, and "dunum", or "dune", the city founded here first became known as Lugdunum and later Leiden.

6 Leiden University Medical Center

Rein Willemze
with contributions by Maarten H. Vermeer, Jan Gerrit van der Schroeff, Wilma Bergman, Nelleke A. Gruis, Jan Nico Bouwes Bavinck, Frank R. de Gruijl, Abdoel El Ghalbzouri and Sjan P.M. Lavrijsen

Introduction

Leiden has historically been associated with the Roman outpost Lugdunum Batavorum. Leiden was founded on an artificial hill (today called "the Burcht van Leiden") at the confluence of the rivers Oude and Nieuwe Rijn (Old and New Rhine). In the oldest reference to this, from circa 860, the settlement was called Leithon.

The municipality of Leiden has a population of about 120,000, but the city forms one densely connected urban area with a few suburbs. The larger Leiden agglomeration counts 332,000 inhabitants which makes it the sixth major agglomeration in the Netherlands.

In 1572, the city sided with the Dutch revolt against Spanish rule and played an important role in the Eighty Years' War. Besieged from May until October 1574 by the Spanish, Leiden was relieved by the cutting of the dikes, thus enabling ships to carry provisions to the inhabitants of the flooded town. As a reward for the heroic defence of the previous year, the University of Leiden was founded by William I of Orange in 1575.

Main building of the Leiden University Medical Center (LUmc).

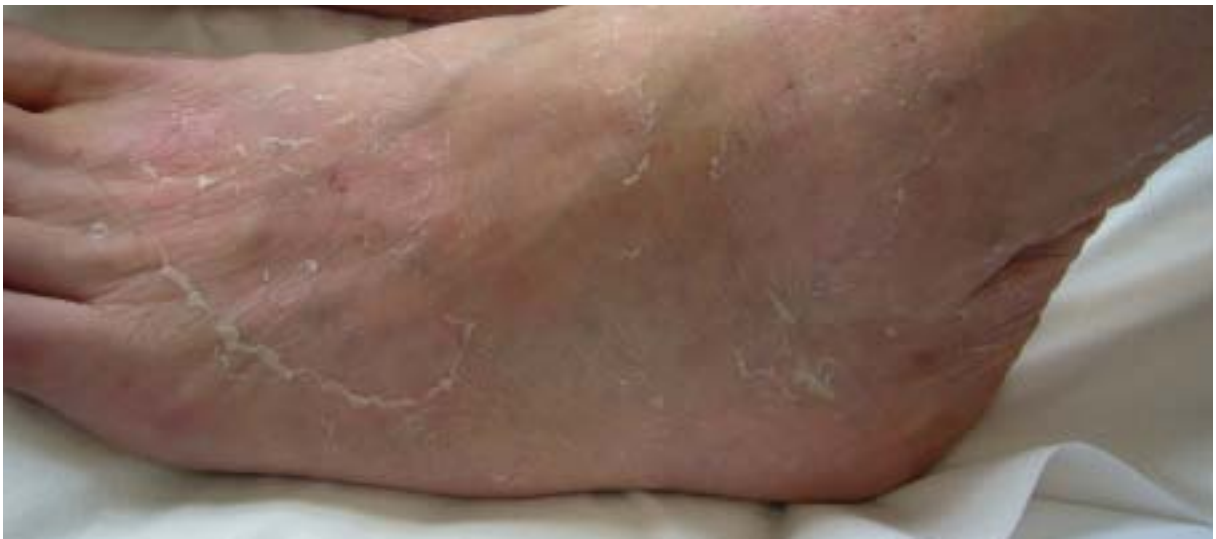
History

It was not until 1929 that dermatovenereology was recognized as an independent specialism within Leiden University. Before 1911 dermatovenereology was included within the department of medicine and afterwards in the department of surgery. In 1911 a lectureship for dermatology and venereal diseases was instituted within the department of surgery, and Dr. J.H.P. Kerkhoff (1863-1937), who had received his dermatological training in Unna's department in Hamburg, was appointed. He accepted this position, which he held until his retirement in 1928, with the inaugural speech 'Syphilis as disease of tropical descent'. In 1929 dermatovenereology finally became a separate specialism.

Hermann Werner Siemens

In 1929 Hermann Werner Siemens (1891-1969) was appointed the first professor in dermatology and venereology at Leiden University, and became chair of the new dermatology department within the Academic Hospital Leiden. Siemens was born in 1891 in Berlin-Charlottenberg and received his dermatological training in Breslau (Jadassohn) and Munich (von Zumbusch). In 1923 he was appointed as private tutor and in 1927 as extraordinary professor in dermatology and venereal diseases at the University of Munich. In 1924 he published a book on Twin Pathology ('Zwillingspathologie') and became considered one of the pioneers in twin studies. In Leiden he continued his research on genodermatoses including congenital ichthyosiform dermatoses and incontinentia pigmenti, and several of these conditions were named after him.[1] In addition, he introduced controlled clinical trials comparing therapeutic efficacy of topical agents versus controls applied at different body sides (method of paired comparisons).[2] He retired in 1962.

Ichthyosis bullosa of Siemens.



Machiel Karel Polano

Siemens was succeeded by Machiel Karel Polano (1907-1997). Polano came from a family of longstanding medical tradition. His great-grandfather had been professor of surgery in Leiden, his grandfather a general practitioner and his father a prominent dermatologist in The Hague. Polano studied medicine in Leiden and received his dermatological training in Siemens's department. In 1934 he defended his PhD thesis entitled 'The quotient cholesterol/phospholipoid in skin diseases'. In 1935 he joined his father's private practice at the Municipal Hospital in The Hague. When Polano took over Siemens's position patient care, research and education were modernized. While his predecessor had typically run a one-man practice and had never incorporated basic scientists in his department, Polano created new staff positions both for dermatologists and for basic scientists. The department was completely renovated and a new outward department and research laboratory were built. He introduced audio-visual teaching programmes for medical students and started postgraduate courses for dermatologists. Polano was an excellent clinician and a widely respected teacher both for his students and his residents. He continued his previous research on xanthomas in relationship to hyperlipoproteinemias, in close collaboration with other departments. The importance of collaboration with other clinical as well as basic disciplines is illustrated by the title of his inaugural speech: "Interchange between dermatologists and other disciplines". He stimulated other staff members to develop their own lines of research, which focused on cutaneous lymphomas (Willem van Vloten), photobiology (Dick Suurmond), drug penetration into the skin and skin cultures (Maja Ponec) and electron microscopy of xanthomas (Bert Jan Vermeer). After his retirement in 1978 he continued publishing manuscripts and books including a new edition of Topical Skin Therapeutics and - together with Thomas B. Fitzpatrick and Dick Suurmond - the successful Color Atlas and Synopsis of Clinical Dermatology.[3,4]

Five Leiden professors of dermatology. From left to right: Rein Willemze, Bert Jan Vermeer, Machiel Polano, Dick Suurmond and Willem van Vloten (1992).

Dick Suurmond

In 1978 Polano was succeeded as head of the department by Dick Suurmond (1926-2011). He was born in 1926, studied medicine in Leiden, and received his dermatological training at Polano's department in The Hague. In 1962 he accompanied Polano to Leiden. A year later he defended his PhD thesis entitled: "Lichen sclerosus et atrophicus and kraurosis vulvae", before being made associate professor in 1966. In Leiden his research focused on erythropoietic porphyrias, photobiology and phototherapy. Already in 1979 he warned against the deleterious effects of unlimited use of sunbeds and suggested that sales of these tanning devices should be strictly regulated. Not surprisingly, the title of his inaugural speech in 1979, with which he accepted his professorship was "Light on the skin". In 1980 Willem van Vloten (1941; photograph on page 68) was appointed professor. He had initiated multidisciplinary studies not only on cutaneous lymphomas, but also on dysplastic nevi and melanoma, which formed the basis of two long-standing and very successful lines of research. In 1985 Willem van Vloten left Leiden to become head of the dermatology department in Utrecht. In 1987 the department of dermatology moved to the new hospital buildings of the Academic Hospital Leiden, currently known as the Leiden University Medical Center (LUMC).

Bert Jan Vermeer

Shortly afterwards, in 1988, Suurmond stepped down as head of the department and was succeeded by Bert Jan Vermeer (1942-2004). Vermeer studied medicine in Groningen and followed his residency in dermatology in Leiden. His father was a well-known dermatologist in Amsterdam, and also his son would become a dermatologist. He successfully expanded the research line of Polano and studied the ultrastructure of xanthomas and hyperlipoproteinemias (PhD thesis, 1979). The results of these studies contributed significantly to the understanding of atherosclerosis and cardiovascular disease, topics far away from everyday dermatology. For this reason a successful line of research was discontinued and Vermeer's interest shifted to photoimmunology. His enthusiasm and creativity, generally in a very non-conformist way, stimulated others, and dermatologic research flourished in the late 80s and 90s as never before. Bert Jan Vermeer served in the board of the European Society of Dermatological Research as treasurer and in 1988 as president. In 1998 he became dean and member of the board of directors of the LUMC. Between 1998 and 2000 Wilma Bergman served as acting head of the department. In 2002 Bert Jan Vermeer stepped down as dean and retired. Plans to continue photoimmunologic research were never accomplished because of his untimely death in 2004.

Rein Willemze

In 2000 Rein Willemze (1951) became head of the department. He had studied medicine and received his dermatological training from Polano and Suurmond in Leiden, where he defended his PhD thesis “Diagnostic and basic aspects of cutaneous lymphomas”. In 1985 he moved to the department of dermatology of the VU University Amsterdam and was appointed professor in 1988 together with Theo Starink. With his return to Leiden new staff members were appointed bringing in expertise in molecular biology (Kees Tensen), melanoma genetics (Nelleke Gruis), photo-carcinogenesis (Frank de Gruijl) and cutaneous lymphoma (Maarten Vermeer), further strengthening the skin cancer research programme of the department. This programme is focused on cutaneous lymphomas, familial melanoma and skin carcinoma in organ transplant recipients, all three patient groups for which the department serves as a tertiary referral center. In addition, cultured human skin equivalents are continued to be used as useful models for a wide variety of skin diseases.
In 2004 the whole research group of over 30 researchers, technicians and fellows moved to a brand-new research building. In the last ten years educational efforts of the department increased significantly. In that period the number of medical students increased from 12 to 24 every four weeks, while the number of residents in dermatology increased from 6 in 2000 to 16 in 2013. The number of professors also increased. In 2008 Wilma Bergman (1953) was appointed professor of dermatology, focusing on education and public information regarding melanoma, while in 2012 Maarten Herman Vermeer (1967) was appointed professor in clinical dermatology.
In 2014 the LUMC department of dermatology will celebrate its 85th anniversary. Much has changed, but what continues is the integration of clinical care with basic research, as illustrated by the following paragraphs. In the past the subjects of these studies have changed from genodermatoses to metabolic disorders and then to dermato-oncology. Similarly, research techniques have evolved from clinical observations to (electron) microscopy and recently to whole genomic approaches, but a constant factor has been the strong embedding of our research into the clinic. These studies not only increased our understanding of dermatological diseases, but also improved the diagnostic and therapeutic management of our patients. We look forward to continuing this tradition of fruitful interplay between research and patient care at our department.

Wilma Bergman

Maarten Herman Vermeer

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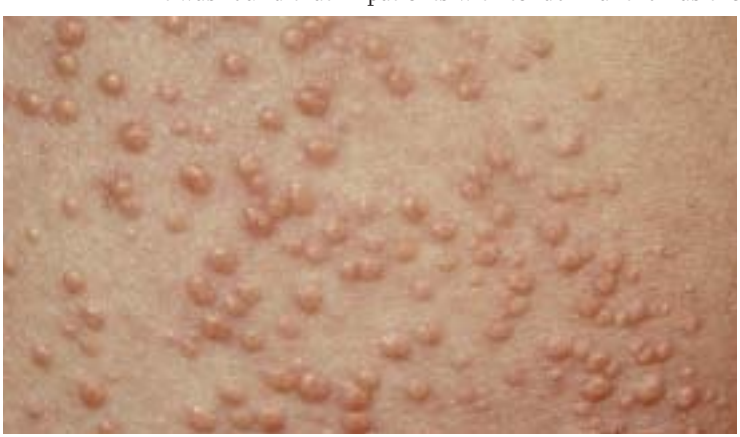
Research

Xanthomatosis, hyperlipoproteinaemia and atherosclerotic cardiovascular disease

One of the fields of scientific research at the department of dermatology in Leiden was the study of the relationship between elevated blood lipids, xanthomatosis and atherosclerotic cardiovascular disease. These studies were initiated by Polano. He became interested in this topic during his dermatological training, when he examined a family in which xanthomatosis and early cardiac death occurred frequently. Probably this family suffered from familial hypercholesterolemia, a disease which was not yet described at that time. In 1964, after his appointment as head of the department, the Leiden Lipoproteinosis Working Group was founded, in which the departments of dermatology and metabolic diseases of the University Hospital cooperated with the Gaubius Institute of TNO (Netherlands Organisation for Applied Scientific Research).[1]

In patients with different types of xanthomas the lipoprotein profiles were determined, seeking to establish a correlation between specific types of xanthomas and separate classes of lipoproteins.[2] It was found that in patients with tendon xanthomas the level of low density lipoproteins (LDL) was elevated, combined with normal levels of very low density lipoproteins (VLDL). In these patients the highest rate of cardiovascular disease was found. Tuberous xanthomas and papulo-eruptive xanthomas were found predominantly in patients with normal levels of LDL and elevated levels of VLDL. Patients with palmar xanthomas (xanthoma striata palmaris) were characterized by the presence of intermediate density lipoproteins.[3]



Papulo-eruptive xanthomas.

These studies were continued by Vermeer. He investigated the relationship between xanthomatosis, atherosclerosis and hyperlipoproteinemia in biochemical and

ultrastructural studies. He demonstrated the binding of LDL by cultured fibroblasts using an immunoperoxidase technique. On the ultrastructural level, he was able to show that LDL is bound and internalized by cultured fibroblasts at specific areas of the cell membrane, the so-called coated pits.[4] LDL binding sites were absent in cells derived from a patient who was homozygous for familial hypercholesterolemia. This finding demonstrates the deficient binding of LDL to its receptors in patients with familial hypercholesterolemia, which is caused by mutations in the LDL-receptor gene. The investigations were extended to cultured monocyte-derived macrophages. By using immunofluorescence microscopy and electron microscopy Jan Gerrit van der Schroeff showed that monocyte-derived macrophages exhibited LDL binding in a similar way as fibroblasts.[5] With these techniques, no binding sites could be found for acetylated LDL, which is a modified form of LDL that induces cholesterylester accumulation within the cells. Mieke Mommaas-Kienhuis demonstrated, however, that colloidal gold conjugates with LDL and acetylated LDL were internalized by the coated pit/coated vesicle system in monocyte-derived macrophages.[6] She also studied the binding and uptake of LDL and acetylated LDL in other cell types, such as endothelial cells, liver cells and keratinocytes. Further studies on intracellular cholesterylester accumulation in cultured monocyte-derived macrophages revealed that the process of foam cell formation could be suppressed by a HMGCoA reductase inhibitor and by lipoxygenase inhibitors.[7] The results of these studies have contributed significantly to the understanding of atherosclerosis and cardiovascular disease, but at the same time shifted too far away from everyday dermatology. For that reason this successful line of research was discontinued in the early 80s.

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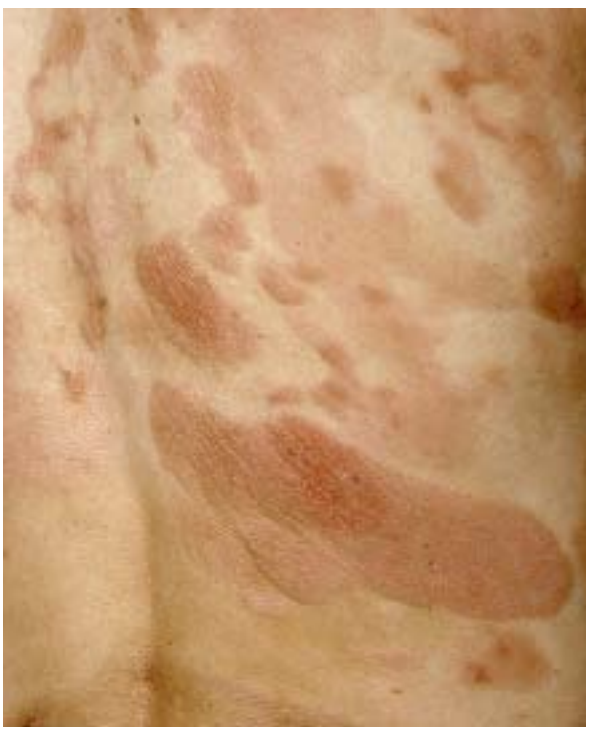
Cutaneous Lymphoma

Willem van Vloten may be considered the founding father of this longstanding and highly successful line of research. Almost from the very beginning a multidisciplinary approach was followed, both in patient care and research in close collaboration between the departments of dermatology (Willem van Vloten, Rein Willemze), pathology (Chris Meijer, Erik Scheffer) and radiation oncology (Ed Noordijk). In the 70s and early 80s research was focused on new diagnostic techniques including DNA cytophotometry, morphometry (nuclear countour measurements) and immunohistochemistry facilitating differentiation between early stages of mycosis fungoides from benign inflammatory dermatoses.[1,2,3] In the mid 80s the Leiden cutaneous lymphoma group split apart, when Willem van Vloten moved to Utrecht and Rein Willemze and Chris Meijer left for the VU University Amsterdam. To prevent counteractive competition and to continue successful multidisciplinary collaboration the Dutch Cutaneous Lymphoma Group was constituted. The main goals of this group, which consisted of dermatologists, pathologists and a radiation oncologist from all eight university centers was to provide diagnostic and therapeutic advice for individual patients, to develop uniform criteria for diagnosis, management and treatment, to constitute a classification for cutaneous lymphomas, to start a national registry, to stimulate clinical and basic research, and to organize postgraduate courses for dermatologists, pathologists, radiation oncologists and hematologists.



Mycosis fungoides.

To this end, each year four to five meetings are organized, in which clinical and histological data of all new patients with a (suspected) cutaneous lymphoma are reviewed by a multidisciplinary panel, a final diagnosis is made and therapeutic options are discussed. All patients submitted to the group are included in the national database and follow-up data are collected annually. Between October 1985 and April 2013 this number has reached more than 3500 patients. In recent years this Dutch model has also been introduced in many other European countries. Because of the availability of relatively large groups of patients with uncommon types of cutaneous lymphoma, the Dutch group played a key role in the definition of new types of cutaneous T-cell lymphoma and cutaneous B-cell lymphoma, the formulation of new classification systems for cutaneous lymphomas (EORTC classification, 1997; WHO-EORTC classification, 2005; WHO 2008 classification, 2008) and the development of international guidelines for the diagnosis and management of these diseases.[4-7]

In 2000 the Dutch Cutaneous Lymphoma Group and the national cutaneous lymphoma registry came home and Leiden once again became the national referral center for

cutaneous lymphomas. Clinical activities include weekly consultations for cutaneous lymphoma patients (headed by Maarten Vermeer) and weekly pathology panel meetings. Clinicopathologic correlation is essential in the diagnosis of cutaneous lymphomas and is guaranteed by the input of both a hematopathologist (Patty Jansen) and a dermatologist (Rein Willemze). Aided by the excellent research facilities in the LUMC, recent studies coordinated by Kees Tensen have focused on the molecular genetics of the different types of cutaneous lymphomas. Using micro-array based technology (gene expression profiling, comparative genomic hybridization, microRNA profiling) clear-cut differences in molecular alterations between different types of cutaneous lymphomas have been demonstrated and new diagnostic and prognostic markers identified.[8-10] These findings have resulted in functional studies on signalling pathways involved in the pathogenesis of some types of cutaneous lymphoma, which should contribute to novel therapeutic strategies.

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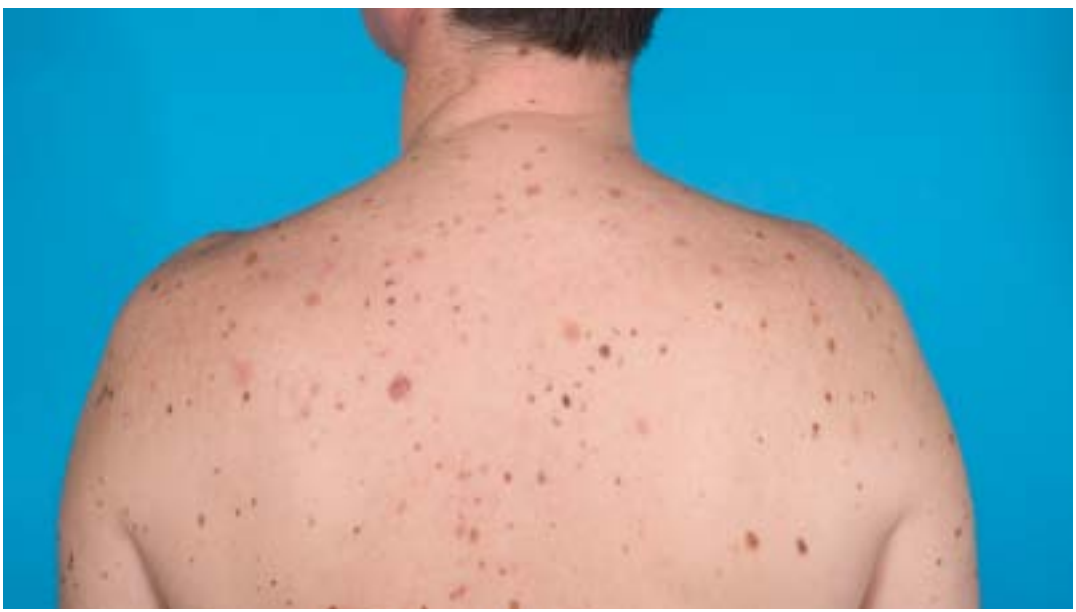
Familial melanoma

Around 1980 clinicians at the LUMC noticed that in some families from a nearby fishing village community several members had developed melanoma and sometimes showed a remarkable moliness. This combination of hereditary melanoma and dysplastic moles was named B-K Mole syndrome. Based on large pedigrees drawn by Lou Went and his co-workers at the department of Human Genetics a founder population of familial melanoma patients was suspected around the city of Leiden.[1] After a teaching visit of Arthur Sober from Harvard (Boston, USA) in 1982 the Pigmented Lesion clinic (PLC) at the LUMC department of dermatology was founded according to the Boston PLC model. Wilma Bergman, then a young resident, dedicated herself to the surveillance of the members of these families and continues to do so today. In 1987 she defended her thesis entitled "The dysplastic Nevus syndrome". In close collaboration with professor Rune Frantz, the new head of the department of human genetics, in 1989 Nelleke Gruis started her PhD studies aimed at finding the genetic basis of this hereditary cancer syndrome, now called FAMMM (Familial Atypical Multiple Mole Melanoma) syndrome. In 1994, collaboration between the Leiden group and Mark Skolnick from Salt Lake City resulted in the identification of a melanoma-associated gene, called multiple tumour suppressor gene 1 (MTS1, later renamed as CDKN2A). One specific deletion of 19 basepairs in the CDKN2A gene appeared to be present in several Dutch melanoma pedigrees from the Leiden area, and was therefore called the P16-Leiden mutation.[2] In 1994 Nelleke Gruis was awarded her PhD degree for a thesis entitled 'Genetics of the Familial Atypical Multiple Mole Melanoma syndrome'.



Patient with FAMMM syndrome at the LUMC Pigmented Lesion Clinic.

From old population registers, she also proved that the families around Leiden indeed had a common ancestor around 1700. More recently, Femke de Snoo defined the whole tumour spectrum of the FAMMM syndrome, including a strong association with pancreatic cancer.[3] The Leiden melanoma group plays a key role in the International Melanoma Genetics Consortium (GenoMEL; www.genomel.org), which was founded in 1997, and was formalized as an EU network of excellence in 2005. This group, of which Nelleke Gruis is also vice-coordinator, participates in many collaborative projects on penetrance, susceptibility and modifying genes and gene-environment interactions in melanoma.[4,5] Recent studies of the Leiden group focused on (epi)genetic alterations that drive the subsequent stages of melanoma progression, and on optimal screening and management of familial melanoma patients.[6-9] Besides research, the department has a longstanding tradition in postgraduate education. Recently a series of courses on dermoscopy was awarded the Boerhaave Penning for teaching excellence. The course was considered an outstanding example of blended learning aimed both at general practitioners and advanced dermoscopists. To underline the aspirations of the department in early diagnosis and prevention of melanoma, Wilma Bergman was appointed teaching professor by the Melanoma Patient Society in 2008. The efforts of our melanoma group will certainly continue to revolve around these themes in the years to come.

LUMC Melanoma Group. From left to right: Remco van Doorn, Nicole Kukutsch, Nelleke Gruis, Wilma Bergman.

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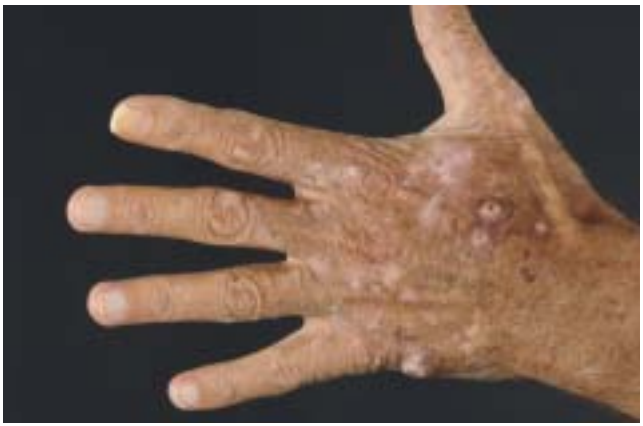
Skin cancer in organ transplant recipients

The Department of Dermatology in Leiden has a long tradition of research into non-melanoma skin cancer. In the 70s and 80s Dick Suurmond and Ab Schothorst started this line of research studying photobiology and phototherapy, while Bert Jan Vermeer continued this line with photoimmunology. In 1985 Jan Nico Bouwes Bavinck started research in organ transplant among recipients, who frequently develop skin cancers.[1] Several studies report a cumulative incidence of 10% at 10 years up to 40% at 20 years after transplantation.[2] Clinical and epidemiological studies were focused particularly on risk factors for skin cancer in organ transplant recipients, and in 1992 Jan Nico Bouwes Bavinck defended his PhD thesis on this topic. In the last two decades these studies, which were performed in close collaboration with other departments within the LUMC, across the Netherlands and world-wide (http://www.scopenetwork.org/ and http://www.itscc.org/), identified many risk factors including the immunosuppressive therapy, exposure to UV light, smoking, human papilloma virus (HPV) infection, and genetic factors, such as HLA phenotype and polymorphisms in the melanocortin 1 receptor (MC1R) gene.[3,4,5] Several clinical trials were performed. It was shown that acitretin was effective in reducing the number of skin cancers, but photodynamic therapy and switching the immunosuppressive regimen to rapamycine were less effective.[6] Curettage followed by electrocoagulation was shown to be an effective treatment of selected squamous-cell carcinomas. In 2001 Frank de Gruijl joined the Leiden group and clinical and epidemiological studies were supplemented with fundamental studies in mice, cell cultures and in vitro skin models. These studies focused on early UV-driven carcinogenic events (DNA damage and mutations in the P53 tumour-suppressor gene) and modulation thereof by immunosuppressants and by HPV.[7,8,9] Additionally, patient material was analyzed to retrace the putative pathogenic steps of tumour formation, and tumour explants and cell lines were introduced into in vitro skin models to study tumour growth and invasion. Recent studies supported by grants from the Dutch Cancer Foundation focused on the role of stem cells.[10] It was found that quiescent stem cells can accumulate DNA damage at low UV dosages and thus run an increased mutation risk (e.g., in the p53 gene); at high dosages newly identified actively proliferating stem cells are more likely mutational targets. Their potential conversion to tumour-initiating cells would make them prime targets for preventive and therapeutic intervention.



Multiple squamous cell carcinomas in a renal transplant patient.

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Reconstructed Human Skin Equivalents; development and applications

Maja Ponec, who was appointed 1969 by Polano to study penetration of corticosteroids through the skin in vitro, started a research line on cultured human keratinocytes to study antiproliferative effects of corticosteroids. Studies with cultured fibroblasts and keratinocytes revealed that glucocorticosteroids inhibit both the cell proliferation and collagen synthesis.[1]

Cultured keratinocytes also found clinical applications. In 1985 the first severely burned patients were successfully treated with cultured epidermal sheets.[2] In further studies research focused on generation of a skin substitute with a biodegradable matrix that should provide a support for the epidermal cell cultures and function as a scaffold for neodermal regeneration in full-thickness skin loss. More than 25 years ago human skin equivalents (HSEs) were introduced in the research laboratory of the department of dermatology.[3] Such HSEs were generated by seeding human keratinocytes onto a dermal substrate populated with or without fibroblasts. Lifting of the HSEs to the air-liquid interface results in keratinocyte proliferation, differentiation and migration, after which a reconstructed epidermis is formed, closely mimicking the native tissue.

As stratum corneum lipids and organization play an important role in the formation of a proper barrier function, extensive studies with advanced techniques in collaboration with Joke Bouwstra at the Leiden/Amsterdam Center for Drug Research (LACDR) have, and are still being performed on this topic. These studies revealed that all lipid classes present in native tissue are also present in HSEs and the supplementation of vitamin C to the culture medium markedly improved barrier function.[4] Studying the barrier function parameters in various keratinization disorders by Sjan Lavrijsen resulted in collaboration with Professor D. Hohl (Lausanne, Switzerland) and contributed to the identification of mutations in lamellar ichthyosis.[5,6]

In 2009 Kees Tensen, Abdoel El Ghalbzouri and Suzan Commandeur received the "ZonMw Pearl" of the Netherlands Organisation for Health Research and Development, for their in vitro three-dimensional model of primary human cutaneous squamous cell carcinoma.

After Maja Ponec's retirement in 2005 this pioneering line of research was continued by Abdoelwaheb El Ghalbzouri. Currently, various HSEs are available composed either of the epidermal compartment like the Leiden Epidermal Model (LEM) or of both the epidermal and dermal compartments like the Full-Thickness collagen Model (FTM) and the Fibroblast Derived Matrix (FDM) model.[7] In recent years HSEs have been used to construct in vitro models of various skin diseases and conditions including recessive epidermolysis bullosa simplex, melanoma, squamous cell carcinoma, wound healing, skin aging and atopic dermatitis.[8,9] In addition, as an alternative to animal testing, these skin models are perfectly suited for prediction of irritants, corrosive and toxic compounds.[10] In January 2013 a spin-off company (Biomimiq, division of Aeon Astron Europe B.V.) was launched for that purpose.

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The new Nijmegen city bridge (2013) over the river Waal is named "The Crossing" in honour of the military operation carried out by American soldiers in September 1944. Liberating Nijmegen from the Nazis, the American army achieved this heroic task at the cost of 48 of their own lives.

7 University Medical Center Nijmegen Sint Radboud

Peter C.M. van de Kerkhof
with contributions by Joost Schalkwijk

Introduction

Nijmegen is a large city in the east of the Netherlands, near the German border. It is considered to be the oldest city in The Netherlands, founded on a hill at the River Waal and celebrated its 2000th anniversary in 2005.

The location had great strategic value because of the surrounding hills, which gave (and continue to give) a good view over the Waal and Rhine valley. In 104 AD Emperor Marcus Ulpius Trajanus named the town Ulpia Noviomagus Batavorum, or Noviomagus for short, from which the modern name Nijmegen is derived. The name comes from the Celtic words novio = new and magus = market. It has been contended that in the 8th century Emperor Charlemagne (Carolus Magnus) maintained his palatium in Nijmegen on at least four occasions.

The Radboud University of Nijmegen was founded on May 15, 1923. It was named after Radboud, a bishop, scientist and poet who lived from 850 to 917 AD.

Heyendael, the gatehouse of Radboud University Medical Center.

History

The town's spirit of innovation and market orientation has inspired the department of dermatology since its beginning more than 56 years ago. During the first three decades allergology and phlebology were important areas of clinical care and research. Non-invasive methods to measure the skin barrier, sweating and vascular functioning were important innovations which were recognized internationally as 'Nijmegen made'. Since the 1980s research on pathogenetic and clinical aspects of psoriasis has achieved international recognition. From 1985 onwards the department has developed an interest in genetics, at first related to genodermatoses and subsequently related to the molecular genetics of psoriasis. More recently, innovations in pathogenesis and treatment of psoriasis have included real clinical practice research in children and adults, evaluation of experimental treatments, quality-of-life research, studies on immunopathogenesis and molecular biology and development of biomarkers. In the meantime, innovations in skin cancer management have included the development of non-invasive diagnostic tools, clinical characterization, as well as epidemiological studies of skin cancers in special populations and cooperative projects with general practitioners to improve quality of care for skin cancer patients.

Johannes Wilhelmus Henricus Mali

Johannes Wilhelmus Henricus Mali (1918-1996) was the founding chairman of the Department of Dermatology at the Radboud University Nijmegen Medical Center, which was opened on the 18th of June, 1957. Established in a centrally located villa, the site accommodated both an out-patient unit and an in-patient department. Mali created a multidisciplinary research group consisting of pharmacologists, an organic chemist and a physical chemist. This group developed non-invasive methods to measure skin barrier functions, and performed extensive analyses on the composition of allergens and irritants. Non-invasive methods for measuring the venous system and microcirculation were developed by a group of medical physicists. Already, in the very first years of the department, medical psychologists made an active contribution to patient care. There was an important unmet medical need with respect to allergic contact dermatitis and leg ulcers in the region of Nijmegen.

Nijmegen dermatology clinic (1958-1992).

Klaus Malten and (left) Johan Kuiper

These areas of expertise were developed respectively by Klaus E. Malten (1920-2009) and by Johan P. Kuiper (1931-2013). Mali inspired the development of clinical expertise together with translational research.

After Mali's retirement in 1984, the transition of the department was facilitated by the interim leadership of Johan P. Kuiper.

Rudolf Happle

Rudolf Happle (1938) became chairman in 1986 and initiated important new developments. He introduced to the department genodermatology, dermato-surgery, topical immunotherapy for alopecia areata, and pediatric dermatology. His clinical leadership was well-respected throughout his tenure at Nijmegen. In May 1991 he accepted nomination as chairman of the dermatology department at the university hospital of Marburg, Germany.

Petrus Cornelis Maria van de Kerkhof

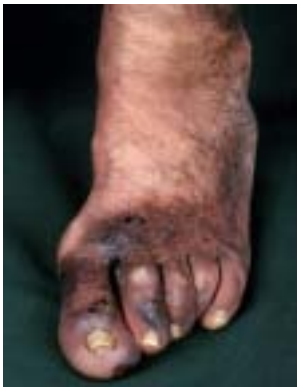
Petrus Cornelis Maria van de Kerkhof (1952) became chairman of the department in 1992, placing at the heart of the department a vision of clinical expertise areas aligned with research. He continued with his work on pathogenesis and the treatment of psoriasis. In the meantime, genodermatology patient care and research was continued by P.M. Steijlen as part of a collaborative working group on hemangioma and vascular malformations. In 2003 Steijlen accepted the chair of the department of dermatology at the University Medical Center in Maastricht. The department of dermatology was comprised of around 70 co-workers at this time. With a relatively small patient care capacity of about 2000 new patients per year and 24 patient beds, a substantial scientific output was nevertheless realized. In 1992 the department was ready for the next step: moving to a brand new building at the Radboud Campus, which was opened on the 1st of May, 1992 by the mayor of Nijmegen (see page 98).

New dermatology building at the Radboud Campus.

Other transitions were also underway. Pieter G.M. van der Valk entered the department as an allergologist, starting the new day care unit and the in-patient department, while Elke G.J.M. de Jong took on the role of out-patient department head and developed a unit for skin and systemic diseases. In the seventies the concept of psoriasis had developed from a skin disease to a systemic disease involving the skin. Systemic treatments such as methotrexate, ciclosporin and etretinate were introduced. Photochemotherapy (PUVA) and high-dose phototherapy (UVB) were added in the treatment of psoriasis during the eighties. Research on the pathogenesis and therapeutic targets of psoriasis was initiated at the department at that time.
Carine J.M. van der Vleuten took over the leadership of the working group on hemangioma and vascular malformations and consolidated a multidisciplinary team on the treatment of hemangiomas and vascular malformations. From 2004 onwards, Michelle M. van Rossum contributed by developing high standards of care and research for melanoma and lymphoma.
Over the years the number of training positions for residents increased from 5 to 18. De Jong oversaw resident teaching for 15 years. Overseen by Prof. Dr. Joost Schalkwijk and Dr. Piet E.J. van Erp, the laboratories have always been located in close vicinity to the clinical care units. Such proximity between clinical and research units has allowed for ongoing translational collaborations. In 2012 a total of 10,262 new patients visited the out-patient department, while 2323 patients were treated in day care. Over the last decade, the number of in-patients has dropped, with only 135 recorded in 2012.

Research

Phlebology



In 1965 Mali and Kuiper described acro-angiodermatitis or pseudo Kaposi. From a pathogenic point of view, the authors describe pseudo Kaposi as a long-term complication of chronic venous insufficiency. Mali and Kuiper have studied pseudo Kaposi with mercury gauge plethysmography. Patients with pseudo Kaposi present an insufficiency not only of the muscular pump of the calf but also of the venous pump of the foot.[1] Kuiper and his colleagues studied venous insufficiency in dermatology.[2,3,4] Over the years they carried out assessments of the functioning of the venous system in parallel with clinical characterization of the signs and symptoms of venous insufficiency. Indirect venous resistance and capacity measurements were developed and standardized by the group.

Acro-angiodermatitis or pseudo-Kaposi of Mali.

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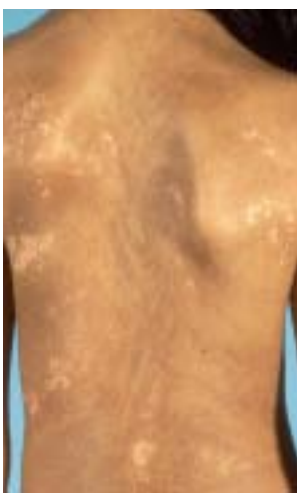
Genetics



Happle had the vision that the distribution pattern of some skin disorders approaches the distribution of the lines as described by Blaschko. The typical dorsal V-shape and the abdominal S-figure of these lines are highly characteristic and not compatible with the distribution of dermatomes.[1] Blaschko's lines represent a non-random developmental pattern of the skin. He described in several reports that these lines become manifest in the heterozygous state of various X-linked gene defects such as incontinentia pigmenti, focal dermal hypoplasia, X-linked dominant chondrodysplasia punctata, X-linked hypohidrotic ectodermal dysplasia, and Menkes syndrome. He hypothesised a causal relationship between lyonization and Blaschko's lines, and suggested that in women affected with X-linked skin disorders, Blaschko's lines visualize the clonal proliferation of two functionally different populations of cells during early embryogenesis of the skin. He described several new and existing skin conditions, arranged following the distribution pattern of Blaschko's lines.[2,3]

Lines of Blaschko in focal dermal hypoplasia.

Steijlen's genodermatology working group focused on clinical characterization, genetic studies and therapeutic investigations of cornification disorders. Ichthyosis bullosa of Siemens (see figure page 80) is a blistering disorder with autosomal dominant inheritance. The disease resembles bullous congenital ichthyosiform erythroderma but is less severe.[4,5] Keratins K1 and K10 have been implicated in bullous congenital ichthyosiform erythroderma. Linkage analysis pointed to the involvement of a keratin type II gene (12q11-13) in ichthyosis bullosa of Siemens.[6] Mutations in the highly conserved regions of K1, a member of the type II gene cluster, were excluded. The gene coding for keratin 2e is also located in the type II gene cluster and the expression of the gene coincides with the occurrence of epidermolytic hyperkeratosis. Sequence analysis revealed the presence of mutations in the K2e gene in patients with ichthyosis bullosa of Siemens.[7] Three different mutations were detected, one in the 1A domain and two in the 2B domain of the rod.[8]

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Therapy studies

Alopecia areata (AA), a frequent hair disease which may cause total hair loss, was studied by Happle and his colleagues. Topical immunotherapy with diphenylcyclopropanone (DCP) was developed as a pathogenesis based therapy for AA. In untreated patients with progressive AA, the mean peribulbar T4/T8 ratio was 4: 1, whereas in untreated patients with stable AA, the ratio was 2: 1. Among treated patients with a good response to diphencyprone, the mean T4/T8 ratio was 1: 1, while in patients with poor or no response to treatment, the ratio was 0.7. Topical immunotherapy considerably alters the peribulbar T4/T8 ratio in AA.[1] Several studies have shown the efficacy of topical immunotherapy

with DCP in alopecia areata. 139 patients with severe alopecia areata (the majority with the subtotal, total, or universalis type) were treated in Nijmegen with topical immunotherapy (DCP).[2] Patients were initially treated unilaterally; the other side of the scalp served as a control. In 50% of the patients the response was either excellent (total regrowth) or satisfactory (subtotal regrowth with only a few remaining bald patches). The most frequent side effects were eczematous reactions with blistering, spreading of the induced contact eczema, and sleep disturbances.
Coal tar treatment has been a mainstay of atopic dermatitis treatment for more than 150 years. The carcinogenic effects of coal tar have been shown in animal experiments. Van der Valk and his colleagues developed two research projects on the safety of tar: 1. Biomarker development: 1-hydroxypyrene proved to be a marker for systemic availability of tar products. It was shown that this marker is highly sensitive and reproducible. In particular, during pregnancy, healthcare workers should not apply tar products to patients. 2. Epidemiology of cancer after the coal tar treatment: it was shown in the largest patient sample in the world, that there was no increased frequency of cancer in patients treated with coal tar.[3] Coal tar continues to be an important topical treatment.[4]
Infantile hemangiomas may represent major challenges in affected children. Recently, the treatment with propranolol has opened new opportunities. The Nijmegen group - the interdisciplinary working group HECOVAN (Hemangioma and Congenital Vessel malformations Nijmegen) - has studied the clinical characteristics of hemangiomas, the effect of hemangiomas on quality of life and the efficacy and safety of propranolol. From the studies it is evident that infantile hemangiomas have a major psychosocial impact.[5] The clinical characteristics differ between individual patients. It is important to realize that infantile hemangiomas may seriously impact health.[6] An impressive improvement by propranolol treatment could be shown convincingly in a large group of infants with hemangiomas.[7,8]

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Biology of the skin

Malten and his group developed and standardized new methods to study the skin barrier with non-invasive techniques. These new methods comprise transepidermal water vapour loss, electric resistance and impedance measurements.[1] The most impressive findings were the demonstration of decreased skin barrier function in atopic dermatitis and the description of chronic traumiterative eczema.[2] Malten also studied sweat gland functioning under standardized conditions comprising CO2 loss and trans-epidermal water vapor loss. Based on the measurements, a new model for thermoregulation of the sweat gland was proposed: the heat pipe principle.[3] Observations of the 'resting' sweat gland (i.e., one not secreting water onto the surface of the skin) indicate that the flow of liquid (and ions) in the sweat duct can take place from the skin surface to the gland. A model is proposed which caters for subsurface evaporation of sweat in the duct and condensation closer to the skin surface. This model is believed to be equivalent to the heat pipe, and the heat transported in each sweat duct may be quantified using the heat pipe theory. The predicted values are of the correct order of magnitude when compared with the resting human metabolism.

In inflammatory skin diseases epidermal proliferation may occur. In psoriasis the acanthotic and parakeratotic epidermis is hyperproliferative. For many decades it has been supposed that the cell cycle times were decreased. These assumptions derived from auto-radiography. Epidermal cell characterization was carried out at Nijmegen department with sequential double immunoenzymic staining procedure using the monoclonal antibody anti-BrdUrd and Ki67.[4,5] Flowcytometric analyses of percentage cells in S, G2 and M phase and in vivo labeling with BrdUrd.[6,7] This revealed that the cell cycle time in psoriatic epidermis is normal and that the growth fraction is increased by an accelerated recruitment of cycling epidermal cells from the G0 compartment.

In the early seventies, biochemistry and cytometry became important research areas. Paul D. Mier (1931-2014), who was appointed professor in 1990, and Frans W. Bauer are founders of cellular and subcellular research in dermatology, an area which gained international recognition for the Nijmegen department. Classical enzymology was applied to the skin and a wide series of enzymes were characterized. In particular, plasma membrane enzymes, enzymes involved in programmed cell death and lysosomal hydrolases were characterized. Lysosomal hydrolysis proved to be associated with the superficial layers of the epidermis, i.e. stratum granulosum.[8] Enzymes involved in phosphoinositol cycle are associated with the process of cell proliferation.

Mier showed that this mechanism is associated with the recruitment of cycling epidermal cells, which is the key process in psoriatic hyperproliferation of the epidermis.[9] Arachidonic acid release is controlled by phospholipase A2. The group of Mier has characterised this enzyme in psoriasis and showed that the enzyme activity is increased in the unaffected skin of psoriatic patients.[10]

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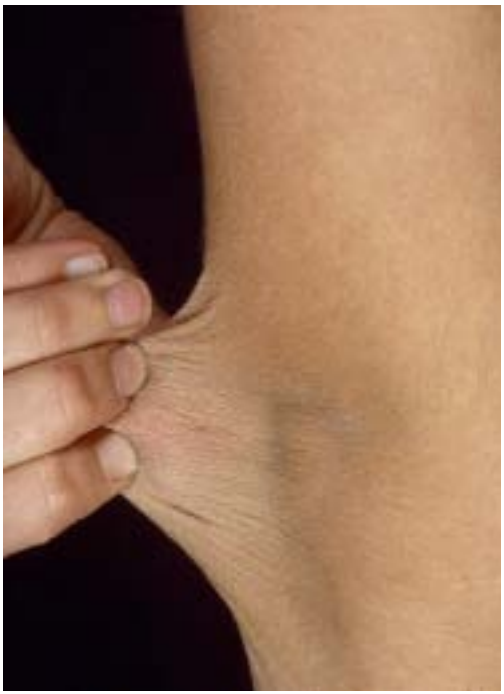
Skin barrier function

Our laboratory led by Joost Schalkwijk from 1993 onwards, was the first to describe the epithelial protease inhibitor and antimicrobial protein SKALP [1,2], which was shortly thereafter referred to in publications by others under the name 'Elafin'. The cDNA and gene were cloned and the chromosomal localization determined. We established its biochemical and biological function, which included the protection of epidermis against elastase-mediated damage. The work of Patrick L. Zeeuwen led to the identification of a new biochemical pathway that controls epidermal cornification and desquamation, centred around the cysteine protease inhibitor cystatin M/E.[3]



Hyperextensibility of the skin in Ehlers-Danlos syndrome.

The research group of our department described the role of keratinocytes in the expression of the matrix protein tenascin-C. Subsequently we demonstrated that its family member tenascin-X regulates collagen and elastin stability as witnessed by the new form of Ehlers-Danlos syndrome (tenascin-X deficiency) that we discovered. This finding was published in the New England Journal of Medicine and is a landmark paper in Ehlers-Danlos research and joint hypermobility syndromes.[4,5] The biology of tenascin-X was investigated and revealed interactions with elastin and collagen, explaining the phenotype in deficient patients.

We discovered LCE3B/C deletion as an important risk factor for psoriasis. This established psoriasis as a disease that is caused not only by immune mechanisms but also by skin barrier abnormalities. Among our Dutch research community, we were the first to find a genetic interaction between HLA-Cw6 and the LCE3B/C deletion. This finding was published in Nature Genetics, and details the first psoriasis risk gene that is associated with skin barrier function.[6,7] At the functional level, we described the expression and putative role of LCE proteins in normal human epidermis.[8]

We have invested heavily in the development of submerged and 3-D skin models. Recently we succeeded in designing a skin model that completely mimics normal epidermis, as opposed to most existing models that have an activated phenotype. This was designed to generate both a 3-D psoriasis and atopic dermatitis model and a wound healing model.[9,10] Using these models we performed drug discovery studies and found the working mechanism of coal tar in atopic dermatitis. We established the arylhydrocarbon receptor as the receptor of coal tar components that transmits a signal to the nucleus and which induces the expression of skin barrier proteins. We also found that coal tar inhibits spongiosis induction by Th2 cytokines such as IL-4 and IL-13. This finding was published in the leading periodical the Journal of Clinical Investigation and received world-wide media attention.

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Clinical dermatology

In August 1960, an explosive epidemic of an erythema multiforme-like illness affected some tens of thousands of people after the introduction in the Netherlands of a margarine containing a new emulsifier. Mali and Malten described the clinical features of this illness and designated the disease as an 'érythème du neuvième jour'. They showed antibodies against a by-product of the emulsifier ME-18.[1]

Skin and mucosal diseases of the vulva represent an important challenge for the affected patients. At the Nijmegen Center, an interdisciplinary working group led by van der Vleuten and de Hullu was created to provide optimal care for women with vulvar diseases. Vulvar discomfort is a frequent problem in patients with inflammatory skin diseases. With respect to psoriasis it was shown that more than 30% of women had vulvar discomfort, which caused a substantial impairment to quality of life.[2] Malignancies of the vulva area are easily overlooked. The occurrence of malignancies in kidney transplant recipients was investigated at the Nijmegen center.[3-6]

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Oncology

There is evidence to suggest that genetic factors play an important role in the development of basal cell carcinomas (BCCs), and that skin neoplasms might be a sign for a genetic predisposition to cancer. We investigated whether the incidence of visceral and skin malignancies among first-degree relatives of BCC patients was increased. The incidence of the following cancers was higher than expected in relatives from young BCC patients: bone and soft tissue, skin and digestive tract. In relatives of older BCC patients, only the incidence of digestive tract cancer was higher than expected. This study suggests that the risk of certain cancers, particularly that of the digestive tract, in first-degree relatives of BCC patients is increased. These findings may indicate a genetic predisposition to both skin and visceral malignancies in this patient group.[1-3]

Various new approaches in the treatment of actinic keratosis have been introduced. At the Nijmegen Center the focus of research has been on the treatment of multiple actinic keratosis, non-melanoma skin cancer and field cancerisation. Multi-center studies revealed that imiquimod is effective in the treatment of actinic keratosis.[4] A study in the Nijmegen department showed that topical methyl-aminolevulinate photodynamic therapy is effective in moderate to severe actinic keratoses of the face and scalp.[5] Photodynamic therapy is indicated in particular for the treatment of field cancerisation.[6,7]

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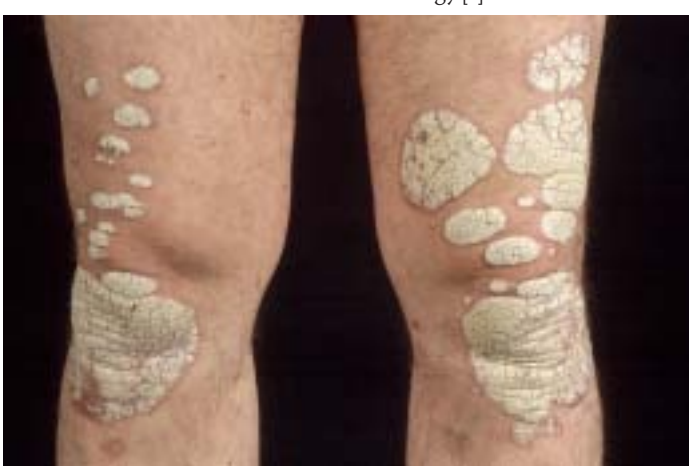
Pathogenesis of psoriasis

In the late nineties we were one of the first laboratories in dermatology to apply transcriptomics technology (microarrays and SAGE). From these studies we identified a number of new genes that were involved in skin biology.[1] We shifted our interest to the genetics of disease. We demonstrated that the epidermis-expressed beta-defensin cluster on chromosome 8 was subject to a copy number polymorphism that is associated with psoriasis This seminal finding was published in Nature Genetics.[2] We showed that the potent antimicrobial protein beta-defensin-2 is highly inducible in human skin, and is expressed at biologically relevant levels.[3] Expression of antimicrobial proteins is different between psoriasis and atopic dermatitis.[4] Recently we have turned our attention to pattern recognition receptors in skin, and reported on the expression of these molecules in human epidermis.[5] We were the first group to report the dynamics of the skin microflora (the 'microbiome') and show sex differences.[6]



Plaque type psoriasis.

Genetic studies by Marieke Seijger and her colleagues have shown that onset of psoriasis during childhood is associated with ERAP1 and IL23R loci, LCE3C_LCE3B deletion and HLA-C*06.[7] Extensive studies on the quality of life in children with psoriasis revealed that various issues have to be assessed before and during treatment. In particular, there exists in children a large discrepancy between objective assessment and quality-of-life assessment. The Nijmegen group established the world's first patient registry on juvenile psoriasis. Through long-term follow-up of patients in this registry, adequate long-term efficacy and safety data are provided on various treatments. The association between psoriasis and metabolic syndrome in children was investigated in a multi-center study. The study indicated an association in the population of this international grouping. Further studies are needed in order to scrutinise the association. The Nijmegen group has designed an evidence-based treatment, which has become the leading international paradigm.[8]
Studies by Marcel Pasch and his colleagues established the substantial impact of nail psoriasis on quality of life. The clinical manifestations of nail psoriasis were revisited: onycholysis and splinter hemorrhages were most frequently observed (both 93.9%). Leukonychia was seen more often in controls. Longitudinal ridges and Beau's lines were seen significantly more in nail psoriasis patients than in controls. Furthermore, the efficacy of the first biologic on nail psoriasis was shown in our center.

The Nijmegen center has investigated the transition between symptomless and lesional skin in order to find out sequential changes in the pathogenesis of psoriasis. Studies in the margin of spreading psoriatic lesions and studies on the relapse following successful treatment have been performed during the years and have provided some insights into the dynamics of the pathogenesis of psoriasis. Studies on enzymes involved in the pathogenesis in the 80s revealed that the marker enzyme for endothelium (alkaline phosphatase) extended in the symptomless skin of the expanding psoriatic lesions for up to 2 cm . These observations are in line with studies on the response to surface trauma. In psoriatic patients the unaffected skin showed a marked response as compared to the skin of healthy volunteers . Involvement of the endothelium early in the pathogenesis was confirmed by laser doppler follow measurements. Studies on epidermal keratinization and proliferation of the epidermis revealed that changes in the suprabasal compartment anticipated on increased epidermal proliferation.[9]
The appearance of T cells are observed after changes in the endothelium but well before epidermal proliferation. In particular, the (CD45RO+) and cytotoxic (CD8+) T cells appear in the symptomless skin before overt epidermal changes.[10] The appearance of regulatory T cells appeared to be relatively late in the pathogenesis.

Dermatology department staff, Nijmegen University Medical Center (1958).

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Therapy of psoriasis

The department has made a major contribution to the development of systemic treatments for psoriasis. With respect to the classical systemic treatments, long-term efficacy and safety has been studied for many years. In a multi-center study, designed by the department of dermatology, the addition of topical treatment with calcipotriol to methotrexate improved the efficacy.[1] Hepatotoxicity to methotrexate was studied in a large population of patients and proved to be relatively infrequent.[2]
With the introduction of biologics, a patient registry has been established with detailed information on disease characteristics, efficacy and safety outcome measures. Important new information on long-term efficacy and safety is provided from this registry created by Elke de Jong and her colleagues. Firstly it was shown that the efficacy in real clinical practice was lower when compared to clinical trials.[3] Combination treatment of etanercept and methotrexate proved to have an increased efficacy compared to etanercept monotherapy.[4] The relevance of laboratory screening during treatment with biologics was assessed.[5] The limited information retrieved from these investigations suggest that a critical appraisal is needed on the relevance of several routine screenings in real clinical practice. Studies on real clinical practice require professional epidemiological evaluation methods as long-term efficacy figures depend to a large extent on the methods of analyses used.

Dermatology department staff, Nijmegen University Medical Center (1968).

Between 1990 and the year 2000 the department has investigated efficacy and safety of topical treatments in psoriasis. With respect to dithranol treatment, short contact treatment regimens were developed. At the day care unit an innovative care instruction programme was developed which helped the patient to increase adherence to his treatment.[6] Innovative principles in systemic treatment were combinations of vitamin D-based treatments and systemic treatments. The combination of vitamin D and acitretin and methotrexate proved to be both safe and highly effective.[7] The department also participated in important registration and post-registration studies on biologics.[8,9] Currently, studies on small molecules targeting the pathogenesis of psoriasis are in progress. Of particular interest is a small molecule targeted to phospodiesterase E4. Phase 3 studies reveal efficacy and safety in a large population of patients.[10] The treatment paradigm of psoriasis has changed from an empirical to a pathogenesis-based one. Important opportunities for personalized treatment with co-diagnostics are on the horizon.

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One of the many bridges in Amsterdam.
It is customary to lock bicycles left in the street to any available secure fixture, such as lampposts and bridge railings.

8 Free University Medical Center Amsterdam

Rick Hoekzema
with contributions by Theo M. Starink, Bibi van Montfrans and Rein Willemze

Introduction

Abraham Kuyper

In 1878, protestant preacher, journalist and prime minister of the Netherlands from 1901 to 1905, Abraham Kuyper (1837-1920) founded the "Society for Higher Education on the basis of Reformed Principles" ("Vereeniging voor Hooger Onderwijs op Gereformeerden Grondslag") in Amsterdam. He did this together with a number of fellow preachers, as well as his friend Willem Hovy, who was both a wealthy entrepreneur and a politician with a social conscience. To their minds Christian faith should embrace all aspects of life - including science - and it was for this reason they established a protestant university in Amsterdam.

With a starting capital of one hundred thousand guilders, a quarter of which was donated by Hovy himself, the Vrije Universiteit, or VU University, opened it doors on the 20th of October 1880. The prefix 'vrije', meaning 'free', was introduced to underline the conviction that the institution should remain free from earthly interference by church or state, being accountable only to God.

Main building of the Free University (1918).

History

With Abraham Kuyper as its first rector magnificus, VU University initially had only 3 faculties: Theology, Law and the Arts. The Faculty of Mathematics & Physics followed in 1930, with the Faculty of Medicine established in 1950. In the preceding decades VU University had already contributed to the training of medical students from the University of Amsterdam (UvA) by providing internships and lectures at the Valeriuskiniek, a reputable, VU University-affiliated hospital for psychiatric patients. By 1955, around 150 students had been educated at VU University to become medical doctors. Originally located in the center of Amsterdam at Keizersgracht 162, as the number of students increased, the university was forced to buy further buildings throughout the city.

In 1968 the entire university - including its hospital - relocated to a campus site in the Buitenveldert district on the outskirts of Amsterdam. Today, VU University accommodates roughly 25,000 students, including 2439 medical students.

Between 1955 and 1960, VU University medical students often attended lectures on dermatology at Amsterdam's other university, the UvA. They were also lectured by two dermatologists with practices outside the university: Robert D.G.Ph. Simons (1909-1966) and Piet van Aken. Simons practiced dermatology at the Burgerziekenhuis in Amsterdam and was a private tutor at Leiden University between 1947 and 1962. Van Aken was an experienced dermatologist with a busy practice in Ede.

As VU University did not yet have its own academic hospital, students had to follow their internships elsewhere, including the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam, as well as hospitals in Haarlem and even as far afield as Rotterdam.

By the end of 1956, VU University had started the construction of its own hospital, the Academisch Ziekenhuis van de Vrije Universiteit (AZVU). As a consequence of several delays, it would take 10 years before the build was completed. In 1959, a clear need for outpatient clinics meant that temporary wooden buildings had to be set up near the construction site. Between 1960 and 1964 the dermatological outpatient clinic was housed in these same buildings.

The AZVU around 1975 with temporary outpatient buildings in the foreground.

Carel Philip Schokking

Department head Carel Philip Schokking (1906-1972) was assisted by chef de policlinique Willem Wesseldijk. Both dermatologists were appointed part-time and maintained their private practices outside Amsterdam. Although the academic hospital was not officially completed until 1966, the new buildings were put into use gradually and the department of dermatology finally moved from their temporary home to the new hospital in 1964. Schokking and Wesseldijk were asked to design the floor plan and to determine the required facilities for the new outpatient clinic, ward and laboratory. They received helpful advice from Professor Jan R. Prakken, then head of dermatology at the Binnengasthuis, the UvA's academic hospital.

In 1965 Götze Lucas Kalsbeek was appointed as a third staff member and chef de clinique. Kalsbeek had received his dermatological training in Utrecht, carrying out research on skin immunofluorescence together with Rudi Harold Cormane.[1]

After Wesseldijk left the department in 1966, Schokking asked Eise van Dijk to fill the vacancy to become the new chef de policlinique. Like Kalsbeek, Van Dijk had received his dermatological training in Utrecht. He had completed his PhD thesis on phytophotodermatitis in 1963 and had stayed on in Utrecht part-time. Even with this addition, the staff at AZVU still numbered only 3 dermatologists, each employed on a part-time basis: Schokking, Kalsbeek and Van Dijk. Because the annual number of patients visiting the outpatient clinic kept growing, from 7,840 in 1967 to 13,330 in 1970, it became necessary to recruit several junior doctors to perform outpatient consultations under senior staff supervision. Nevertheless, these junior doctors were not officially in training to become dermatologists. The department was not in fact licenced to provide dermatological training until 1970. Between 1967 and 1969 the tasks of head of department were gradually transferred from Schokking to Van Dijk. Kalsbeek, in the meantime, became increasingly involved in basic research while maintaining his role as chef de clinique for in-patients.

Eise van Dijk

In 1969 Eise van Dijk (1920-2002) was appointed professor and chair of the dermatology department. He was an excellent clinician and tutor, with an encyclopaedic knowledge of dermatology and a range of other interests. However, he felt himself to be "not built" for basic research. As a consequence, most of his publications appeared in clinically-oriented Dutch or European journals, although he also published studies in The Journal of the American Academy of Dermatology.[2,3] In 1970 the department was officially acknowledged as a training center for dermatology and venereology. With the department now fully established and the transition to Van Dijk completed, Schokking departed in 1971.

At this time, Van Dijk clearly needed new staff members for his outpatient clinic

Theo Starink, Eise van Dijk and Götze Lucas Kalsbeek circa 1979.

and to supervise the dermatological trainees. By 1972 three dermatologists had transferred from UvA and Binnengasthuis to VU University and AZVU: Martien J. Woerdeman, Wim P. de Groot and Willem G. van Ketel. Although they were again appointed part-time, thus enabling them to continue their private practices in Amsterdam, their presence amply increased the capacity to train junior doctors as dermatologists. Woerdeman, who had a special interest in electron microscopy and dermatopathology, started a structural collaboration with the department of pathology. He also initiated research in bullous diseases together with biochemist Dick M. Boorsma, who became head of the laboratory for experimental dermatology. Van Ketel started a dermato-allergology unit, which proved to be very successful in the coming decades.
In 1973 Mrs. Nel Verburgh-van der Zwan - the first dermatologist fully trained at the department - stayed on as part-time chef de policlinique. That same year Cees Nieboer moved from UvA to join the part-time staff at VU University, supervising the trainees in general dermatology and phlebology and participating in immunofluorescence research. In 1974 Kalsbeek was appointed lecturer in dermatology, specialising in immunopathology of the skin. In 1978 Theo M. Starink succeeded Verburgh-van der Zwan as chef de policlinique. As well as demonstrating his talents for clinical diagnostics and teaching, Starink also developed a passion for dermatopathology and clinicopathological correlations, inspired by his colleagues Kalsbeek and Woerdeman, and by pathologist Robert Hausman.

In 1980 Kalsbeek left the department to become professor and head of the department of dermatology in Utrecht. After Woerdeman left in 1983, Van Dijk asked Starink to take over the collaboration with the pathologists and preside over the weekly dermatopathology conference. That year Henk M. van den Hoogenband joined the staff for his expertise in phlebology. The following year Van den Hoogenband and Van Ketel left the department. They were succeeded by two former trainees: Edith de Boer, who had developed a special interest in phlebology, and Derk P. Bruynzeel, staff member since 1982 with a specific focus on allergology and occupational dermatology.

Theo Starink

Van Dijk retired in 1987 and Theo Starink (1948), who had defended his PhD thesis on Cowden Syndrome and other familial multiple hair follicle tumour syndromes in 1986, became interim head of department. In 1988 he was appointed professor and head of department, together with Rein Willemze (1951; photograph on page 83), who had joined the staff as chef de clinique 3 years earlier. Willemze had come from Leiden, where he had developed a special interest and expertise in cutaneous lymphomas. The title of their combined oration in 1989, 'the skin jointly examined' ('de huid samen bekeken') was not an empty slogan: their unique mode of dual leadership proved to be very successful. Although there was no strict separation of tasks, Starink was able to focus on management, patient care and teaching, while Willemze further developed his renowned research line on cutaneous lymphomas, yielding several PhD theses and many publications. At the same time, Starink continued to participate actively in research projects, especially in studies on familial multiple hair follicle tumour syndromes.[4-6]

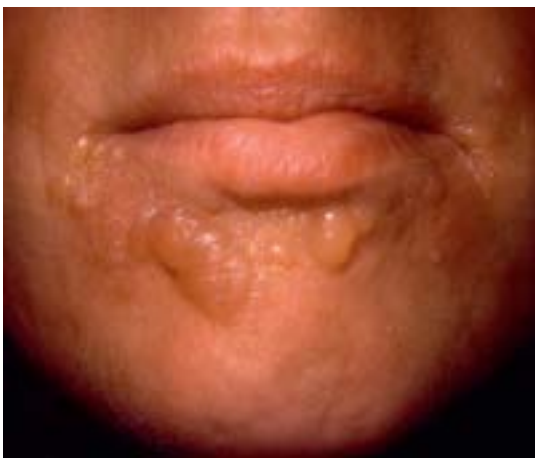
Pathology training at the Free University Medical Center, Amsterdam (2000).

Derk Pieter Bruynzeel

Thomas Rustemeyer

Derk Pieter Bruynzeel (1943) was appointed Professor in Environmental and Occupational Dermatology in 1992, confirming his important contribution to patient care and research in this field. After Bruynzeel's retirement in 2008, Thomas Rustemeyer (1967), who had joined the staff in 2001, became the new head of the dermato-allergology unit. In 2014 he was appointed as professor of dermato-allergology and occupational dermatology at VUmc. In 2000 Willemze left the department to take on the new chair of dermatology at Leiden University Medical Center (LUMC). Naturally, Willemze also moved his successful research line on cutaneous lymphomas to Leiden. In Amsterdam, the resulting vacancy for a leading investigator in experimental dermatology was filled by cell biologist Sue Gibbs, who came from Leiden where she had been involved in research on skin cultures and wound healing.

This was also the year in which the VU University Faculty of Medicine and AZVU merged on an organisational level and the academic hospital was renamed VU Medical Center (VUmc). In the following decade the department reached a stable phase, emphasising the training of good clinical and dermatopathological skills among its students, and further expanding its main research lines on wound healing and dermato-allergology, respectively.



In 2011 Starink decided to step down from his managerial role and to devote his remaining years prior to retirement to his main interests: teaching, supervising and dermatopathology. At that time, the Boards of VUmc and AMC (Academic Medical Center, the academic hospital of the UvA) had already created plans for an alliance, with a view to a potential merger of the two academic hospitals. Meanwhile, the retirement of Professor Jan Bos had created a vacancy for a new department head of dermatology at the AMC. The Boards of VUmc and AMC reached the decision to appoint two professors, entrusting them with the management of both departments.

Contact allergy for primula; plant allergy is one of the areas of interest of the department.

Rick Hoekzema

In 2012 Rick Hoekzema (1956) was appointed professor at the VU and head of both the VUmc and AMC departments of dermatology, whereas Menno A. de Rie (1956) became professor at the UvA, vice-head of both departments and coordinating head of research. The two had been friends and colleagues for many years, starting in the 1980s as young PhD students at the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (CLB, currently Sanquin). There, Hoekzema had completed his PhD thesis, 'Studies on normal and Low-Molecular-Weight C1q', after which he worked as a basic immunologist at the Interuniversity Institute of Ophthalmology, one of the research institutes of The Royal Netherlands Academy of Arts and Sciences. Following his dermatological training at the AMC, Hoekzema had been a staff member at the Academic Hospital Maastricht. In 1999 he returned to Amsterdam to build a large practice offering training qualifications in dermatology and general practice at the Onze Lieve Vrouwe Gasthuis (OLVG). He combined this with a part-time appointment at the AMC teaching trainees and supervising dermatopathology.

Since 2012 Hoekzema and De Rie have been actively engaged in integrating the departments of dermatology of VUmc and AMC. The dermato-allergology unit at the AMC was closed in October 2012 and since then patients are referred to VUmc for allergological tests. At the same time, patients from VUmc with severe skin conditions requiring hospital admission are now referred to the AMC. Staff members and trainees work in both departments for specific supervising tasks and training, and local teaching sessions for dermatology trainees are held jointly. Clinical and basic researchers and laboratory technicians from both departments increasingly collaborate under a combined research council.

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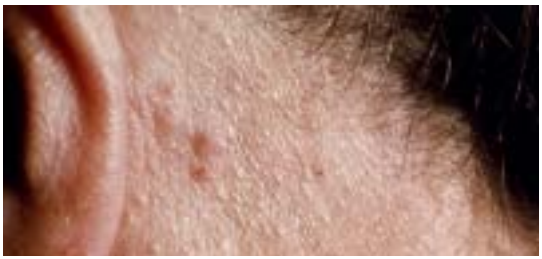

Tricholemmomas in Cowden's syndrome.

Research

The early years

Compared to other Dutch universities the history of dermatological research at VU University is relatively young. Research was introduced to the department by Godze Kalsbeek, when he joined the medical staff in 1965. Kalsbeek started a research line on immunofluorescence in viral skin disorders, in particular molluscum contagiosum. Other research subjects at that time were more clinically orientated, including studies on the immunopathogenesis of perioral dermatitis and bacterial colonization of venous leg ulcers. In 1967 biochemist Dick M. Boorsma was the first pre-clinician to join the department. He and Kalsbeek worked together on the research projects and further substantiated the laboratory for experimental dermatology. In 1970 enzyme-immunohistochemical staining (using horseradish-peroxydase conjugated antibodies) was introduced as an alternative to immuofluorescence, and in the following years this method was applied to studies on molluscum contagiosum, lupus erythematosus and bullous pemphigoid.[1,2] Other research activities included analysis of acid mucopolysaccharides in the skin and interaction between the lectin concanavalin A and stratified squamous epithelium.[3,4] Johan Vreeswijk joined the laboratory as second biochemist in 1973, followed by Peter de Haan, who started as a biochemist-in-training the next year. De Haan performed basic research on ELISA techniques and penicillin allergy, and succeeded Vreeswijk in 1981. During the 1970s dermatologists Woerdeman and Nieboer had begun to participate in research activities, which included ultrastructural studies of molluscum contagiosum and bullous disorders.[5-9]

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Contact allergy and occupational dermatology

After Van Ketel had joined the department in 1972 and started a dermato-allergology unit he initiated a new research line on contact allergy and occupational dermatology that proved to be highly success-ful.[1-3] Van Ketel's successor Bruynzeel reinforced the department's nationally recognized level of expertise in dermato-allergology and occupational dermatology and, after his appointment as professor in Environmental & Occupational Dermatology in 1992, consolidated his reputation as internationally renowned authority in this field.[4-6]

In 2001 Thomas Rustemeyer joined the staff with a remit to focus on the field of allergology and occupational dermatology. When Bruynzeel retired in 2008, Rustemeyer became the new head of the dermato-allergology and occupational dermatology unit and continued with associated research activities.[7-9] His continued efforts to supply high-quality patient care and scientific output resulted in the department's recognition as a center of expertise by the Dutch Federation of University medical centers (NFU).

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Cutaneous Lymphoma

When Rein Willemze joined the staff of the department, he continued his research on cutaneous lymphomas, which had started in Leiden. In Amsterdam, the successful collaboration with Chris Meijer, who had moved from Leiden to become department head of pathology at the VU University in 1982, was reinforced. In October 1985 the multidisciplinary Dutch Cutaneous Lymphoma Group was constituted, and with it a national database for patients with a cutaneous lymphoma, thus making the department the national referral center for this patient group. Because of the multidisciplinary approach allowing optimal clinicopathologic correlation and the availability of relatively large groups of patients with uncommon types of cutaneous lymphoma in the national database, it became possible to define new types of cutaneous T-cell lymphoma and cutaneous B-cell lymphoma, and to formulate a new classification system for primary cutaneous lymphomas (EORTC classification, 1997).[1-5] Apart from clinical and clinicopathologic studies and the development of new diagnostic techniques, basic research also focused on keratinocyte-T-cell interactions and the role of cytokines and chemokines in cutaneous T-cell lymphoma and skin inflammation.[6-10] In 2000 Rein Willemze left the department to become department head of dermatology in Leiden, where the cutaneous lymphoma research came to be continued.

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Skin tissue engineering and wound healing

One of the most advanced fields of tissue engineering is in the area of skin. In 2000 biochemist and cell biologist Sue Gibbs joined the department to become the new head of the research laboratory. Originally from the United Kingdom, she had been involved in studies on the differentiation of cultured epidermal keratinocytes and in-vitro reconstructed skin models in Leiden as a member of Maja Ponec's group since 1986. Gibbs continued this line of research after moving to Amsterdam, where she developed an autologous epidermal-dermal bilayered skin substitute for treating therapy resistant (leg) ulcers. An extended Phase I clinical study showed that this construct was safe to use and first efficacy results showed that the skin substitute stimulated wound closure and revitalized the inert wound bed.[1] This work lead to the foundation of spin-off company A-Skin and the development of Tiscover®, an autologous skin construct.[2] A multi-center Phase II study with Tiscover® is currently under way. Another construct developed by Gibbs and her co-workers in collaboration with the Association of Dutch Burns Centers, consists of proliferating keratinocytes and melanocytes in a collagen/elastin carrier, used for treating third-degree burns. Other projects include studies on the effects of dermal cells and keratinocytes on burn wounds, allergen-induced behaviour of Langerhans cells and identification of contact sensitizers in skin equivalents, an in-vitro hypertrophic scar model to identify novel drug targets and a model to study dendritic cell biology and the innate immune system.[3-7] An important advantage of the skin constructs developed by Gibbs and her co-workers lies in the fact that they provide an alternative to animal testing, which is in compliance with the '3 Rs' (Replacement, Reduction and Refinement) of animal experimentation. In recent years the laboratory has become involved in studies on the regenerative properties of oral mucosa, in collaboration with the Department of Oral Cell Biology of the Academic Center for Dentistry in Amsterdam (ACTA).
In July 2012 Sue Gibbs (1963) was appointed the Fenna Diemer Lindeboom Chair as Professor of Skin and Mucosa Regenerative Medicine at VUmc and ACTA. Currently, Gibbs and her group are addressing basic research questions, such as why oral wounds heal quickly with relatively little scar formation, whereas skin wounds heal relatively slowly, and often with adverse scar formation. The mechanisms underlying the clear differences in innate and adaptive immunology between skin and mucosa will also be studied.

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Dermatology department staff at the VUmc in 2014.
From left to right: Bibi van Montfrans, Sylvie M. Franken, Sue Gibbs, Theo M. Starink, Menno A. de Rie, Rick Hoekzema, Edwin J.M. van Leent, Edith M. de Boer, Thomas Rustemeyer, Marjolein Wintzen.

Erasmus Bridge, Rotterdam (1996).
This cable-stayed bridge, linking the Northern and Southern regions of the city, has a 139-metre high assymetrical pylon, earning the bridge its nickname: "The Swan". To the right of the bridge can be seen "The SkyscaperCity", a multifunctional building by Rotterdam architect Rem Koolhaas.

9 Erasmus University Medical Center Rotterdam

Martino Neumann
with contributions by Renate R. van den Bos, Ellen R.M. de Haas, Marianne G.R. De Maeseneer, Tamar E.C. Nijsten, Arnold P. Oranje, Dominic J. Robinson, Eric M. van der Snoek and H. Bing Thio

Introduction

The municipal of Rotterdam is, with a population of about 620 000, the second largest city in the Netherlands, after Amsterdam. The number of inhabitants of the city region is about 1.2 million. The harbour of Rotterdam is the biggest and most important one in Europe. Origin and development of the Erasmus University Rotterdam (EUR) are connected with the international position of this metropolis as economic, maritime and trade center. The EUR was established in 1973. It is named after the illustrious Rotterdam humanist Desiderius Erasmus (1466-1536).
The origin of the EUR goes back to 1913, the founding year of the Dutch (university) school of economics, an international distinguished institute. The Rotterdam medical faculty was created in 1966 and in fact it originated from the so called "Stichting Klinisch Hoger Onderwijs" (a foundation for university medical education), established in 1950 as an institution for the education of residents in medicine (the two final years of education of medical doctors). In 1973 these two Rotterdam schools for higher education (economics and medicine) were connected to constitute the EUR. Nowadays teaching and research at the EUR are concentrated in four fields of expertise: health (medicine), welfare (economics), administration (including law and social sciences) and culture (including history, social sciences and philosophy).

Entrance to the Erasmus University Medical Center, Rotterdam.

History

Eduard Huibertus Hermans

The Medical faculty of the Erasmus university Rotterdam (EUR) started in 1966. In the early years, the department of dermatology of this faculty, with the Rotterdam dermatologist Eduard Huibertus Hermans (1894-1981) as its first professor, resembled the dermatology departments in hospitals in other main cities in the Netherlands without a university: in those days most dermatologist generally worked solitary within the institute; radiation therapy was an important treatment option for malignant and other skin manifestations. The first dermatology department of the Rotterdam university was located in the office building of the Municipal Public Health Services. Seafarers from all over the world frequented this facility. Venereal diseases and so called import-dermatoses including leprosy were regularly diagnosed here. Research was directed at venereal diseases and several innovations in both diagnosis and therapy were introduced. Hermans was indeed interested in both venereology and tropical diseases. His PhD thesis in 1928 was on framboesia tropica, a non- venereal treponemal disease, prevalent in Indonesia and Suriname, in those days colonies of the Netherlands.

Cornelis Henri Beek

In 1967 he was succeeded by Cornelis Henri Beek (1907-1998) who was appreciated because of his inspiring clinical teaching of medical students and residents. In 1973 the dermatology department moved to the University Hospital Dijkzigt. The scientific interest and research program traditionally directed at venereal diseases was continued, but it now also shifted somewhat towards general dermatology. Close participation with Rotterdam geneticists led to the increase of research in the field of xeroderma pigmentosum, a congenital condition which is quite rare in the Netherlands. The mechanism of DNA-repair was unravelled.[1] To date, university based Rotterdam geneticists are still pioneers in the field of DNA-repair. Furthermore Beek worked closely together with the department of Medical Microbiology and so Ernst Stolz became one of the first PhD-students of the Medical faculty of the EUR, with a thesis on the diagnostic aspects on gonorrhoea.

Ernst Stolz

Theodoor van Joost

Ernst Stolz (1939) was appointed professor of dermatology in 1980, thanks to his scientific merits in venereology. He worked in association with professor Theodoor van Joost (1940) who reinforced his team from 1982 onwards. Van Joost who was interested in immunology, spent much of his work on immuno-dermatology and occupational dermatology.

Hendrik Arent Martino Neumann

In 2001, Hendrik Arent Martino Neumann (1950) succeeded Stolz and van Joost as new head of the department. He introduced microscopically controlled surgery according to Frederic Mohs for non-melanoma skin cancers in Rotterdam and furthermore enforced the interest in phlebology. The department of dermatology became a center of knowledge of diagnostics and up-to-date treatment of complex problems of venous hemodynamics such as the post-thrombotic syndrome and congenital vascular malformations in legs, pelvis and lower abdomen. The name of the Rotterdam university hospital changed in this period from Dijkzigt hospital into Erasmus University Medical Center (Erasmus MC) after an association with the Daniel den Hoed clinic (the Rotterdam cancer center) and the Sophia Children's Hospital.
To broaden the scope of the department, several new professors with specific expertise joined the team. In 2006, Arnold Pieter Oranje (1948; photograph on page 139), was appointed expert in paediatric dermatology at the Sophia Children Hospital. He had been the interim head of the department, shortly before the appointment of Neumann. In 2005, Errol Prens (1956; photograph on page 133), was appointed expert in experimental dermatology regarding inflammatory skin diseases. His current work includes research in the field of psoriasis, hidradenitis suppurativa and laser treatments.[2-4] Marianne Ghislena Renée De Maeseneer (1955; photograph on page 134), vascular surgeon with a special interest in phlebology, was appointed expert in 2010. She further developed diagnostic

strategies for patients with complicated post thrombotic obstruction, mainly by means of advanced duplex ultrasound of the deep venous system including the abdomino-pelvic veins.[5,6]
In 2012, Tamar Edmond Christoffel Nijsten (1972; photograph on page 5), was appointed expert in dermato-epidemiology and started several research projects on non-melanoma skin cancers, phlebology and quality of life of skin diseases including psoriasis.[7-10]
In 2013, Suzanne Gudule Maria Apollonia Pasmans (1963; photograph on page 139), became the new professor in paediatric dermatology at the Sophia Children Hospital.
Nowadays the situation at the Dermatology department of the Erasmus MC is entirely different from the sixties of last century, when the medical faculty started. The main expertise is now in inflammation (in particular psoriasis and eczema), dermato-oncology (in particular non-melanoma skin cancer including Mohs micrographic surgery), phlebology (in particular the diagnosis and therapy of severe problems in venous hemodynamics including congenital malformations) and paediatric dermatology. Venereology is no longer a research item, but now again field of expertise of the Rotterdam Municipal Public Health Services, the place where the department of dermatology of the Rotterdam University was born.

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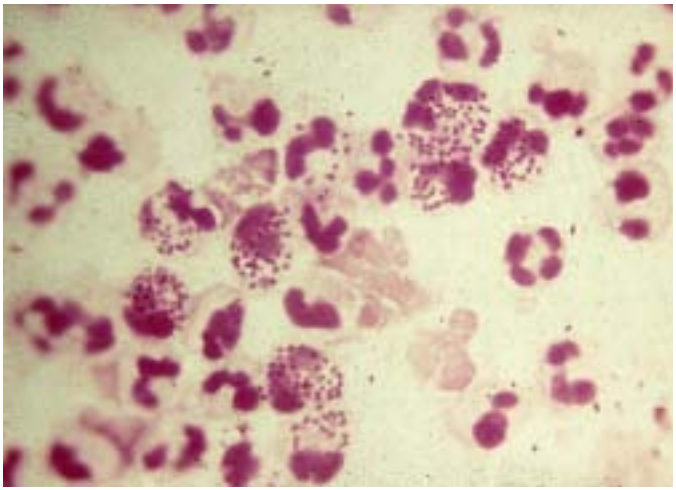
Venereology



Gram stain of gonorrhea discharge, showing gram negative diplococci intracellularly in neutrophils.

Diagnostics and treatment of venereal diseases have always been of importance in the city of Rotterdam because of its harbour and many seafarers. Even during the second World War (WWII) a paper was published in the Netherlands Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde) on the adequate treatment of venereal diseases in soldiers throughout and after times of war. While the initial interest was mainly directed at syphilis and scabies, in the years after WWII more interest arose in gonococcal and non-gonococcal urethritis. Both, diagnostics and therapy were discussed in several papers, published mainly in the Netherlands Journal of Medicine. With the start of the Medical faculty of the EUR the interest of research in the field of other STD increased, like infections caused by Chlamydia trachomatis and herpes simplex virus. One paper evaluated the use of antibodies as a test for chlamydial infections.[1] Studies on the clinical presentation, immunology and serology of syphilis and non-venereal treponematoses resulted in many papers.[2,3]

In the early nineteen eighties, more research was executed on infections due to Chlamydia trachomatis stressing - among others - the risk of infertility. Furthermore, the treatment options in genital herpes and the on-going debate about the most adequate therapy in gonorrhoea continued. Several studies were performed regarding diagnosis of bacterial vaginosis and Trichomonas vaginalis.[4]

Genital warts and the prevalence of HPV-virus infections have been intensively studied in the nineties.[5] For some years the emphasis was on venereal diseases in men having sex with men (MSM) and the influence of the risk of acquiring HIV on having unprotected sex. In later years, optimism due to hopeful results of antiretroviral therapies lead to an increase of unprotected sex and a subsequent higher incidence of STD's in MSM.[6]

In 2003, first reports on the resurgence of lymphogranuloma venereum (LGV) in Western countries were published from data in Rotterdam and caused great concern throughout the Western world. Signs and symptoms, adequate treatment and the higher prevalence of concomitant hepatitis C infections were discussed in these papers.[7,8] Later on papers were published on symptoms in patients with rectal LGV in relation to non-LGV serovars of rectal chlamydial infections in MSM.[9]

The Rotterdam department contributed to several (inter)national guidelines e.g. on the treatment of Chlamydia trachomatis and genital herpes.[10]

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Immunology & inflammation

In the early years basic and clinical research were focused on tropical infections and sexually transmitted diseases.[1,2] Stolz accommodated research in this field in cooperation with international partners such as the Department of Dermatology and Venereology, Cipto Mangunkusomo Hospital, University of Indonesia, Jakarta. The inflammatory aspects of these infections were of great interest.[3]
With the introduction of cyclosporin in the late 1980's the Department of Dermatology put more effort in the research of atopic dermatitis and type IV skin allergies.[4] Paediatric dermatology gained more and more attention. In the field of atopy / atopic dermatitis, Raman spectroscopy proved to be a high-tech methodological instrument to analyse the role of filaggrin (filament - aggregating protein).[5] This protein plays a key role in epidermal barrier function. The gene FLG is encoded within the epidermal differentiation complex on chromosome 1q21, a cluster of genes involved in the terminal differentiation of keratinocytes in the skin.

Errol Prospero Prens

At the laboratory of Immunology, Errol Prospero Prens (1956) developed with success the imiquimod mouse psoriasis model.[6] Since 2000 he and his co-investigators focused also on basic, translational and clinical aspects of hidradenitis suppurativa.[7]
In 2000 the non-registered systemic therapy with fumarates was introduced by Thio for psoriasis vulgaris and since then, this therapy is considered a relevant option on the list of systemic therapies in psoriasis vulgaris.[8]
In this modern era with several new biologics for the treatment of immune mediated inflammatory diseases (IMIDs), we started a cooperation with the Center for Human Drug Research in Leiden in order to expand our future possibilities of clinical research towards the early phase II studies.
Regarding patient care within the university hospital, the interdisciplinary consultations in cooperation with the departments of Rheumatology and Clinical Immunology lifted up the quality of the care of IMID patients, for example those with psoriasis and arthritis.

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Phlebology

Originally phlebology was not an important part of daily dermatologic care at the Erasmus MC. In 2001, the attention for this subdiscipline increased considerably; additional diagnostic and therapeutic methods were implemented rapidly. Complex problems due to altered venous hemodynamics, such as post-thrombotic syndrome, pelvic vein insufficiency and congenital vascular malformations became areas of great interest. A start was made with duplex ultrasound examination and patients were treated with ultrasound-guided foam sclerotherapy and endovenous thermal ablation from 2002 onwards.[1] The number of available treatment modalities increased rapidly: endovenous laser ablation, segmental radiofrequency ablation, and later on, around 2009, endovenous steam ablation, the latter being a novel method, were introduced. Currently the Rotterdam department is one of the few places where the latter treatment is offered.[2, 4-6] Research on compression therapy showed that stiffness plays a determining role in choosing compression stockings. A new method for calculating the dynamic stiffness index of medical elastic compression stockings was introduced.[3]
The last decade, a multidisciplinary approach has become increasingly important for the treatment of patients with complex phlebologic problems.

Marianne Ghislena Renée De Maeseneer

In view of these developments, Marianne Ghislena Renée De Maeseneer (1955), vascular surgeon with a special interest in phlebology, joined the department at the end of 2010.
She further developed diagnostic strategies for patients with complicated post thrombotic obstruction, mainly by means of advanced duplex ultrasound of the deep venous system including the abdominopelvic veins.[7] In close collaboration with the departments of interventional radiology and vascular surgery, chronic recanalization and venous stenting was performed in selected patients.
Recently the results were published of a survey performed in Belgium, the Netherlands and Luxembourg on chronic venous insufficiency in patients with atresia of the inferior caval vein.[8] On-going research in phlebology focussed on the subject of treatment and quality of life of patients with varicose vein and on ulcus cruris and venous pressure measurements.[9,10]

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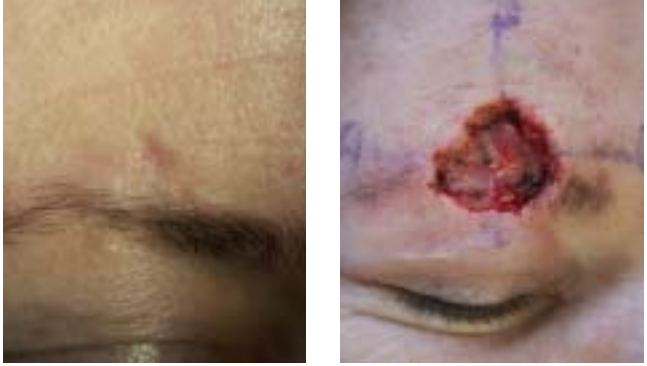
Dermato-oncology

Soon after the start in 1970 of the so-called 'Integraal kankercentrum Zuid' (Integrated Cancer Center South), the place in the Netherlands where skin cancer is epidemiological monitored, a rapid and continuous increase of non-melanoma skin cancer in the Netherlands was predicted. Worldwide, the incidence of malignant melanoma is on the rise since World War II. Less expected was the increase in non-melanoma skin cancers (NMSC), particularly basal cell carcinomas. In fact the problem appears to be worse than estimated. Probably, even the most recent predictions (that one in every 5 individuals would develop non melanoma skin cancer) underestimate the huge rise in NMSC throughout the world in generations to come.[1-3] Primary prevention has proven to be difficult, since changes in behaviour regarding sun exposure are only reluctantly accepted by the people. So early diagnosis and treatment will be of great importance.

The department of dermatology of the Erasmus MC choose dermato-oncology and in particular the treatment of complex NMSC as one of their fields of expertise. Mohs micrographic surgery, providing almost complete histological examination of the surgical margins which results in a radical excision, has been practiced in the Netherlands since 1983. A change in the patient population referred to the Mohs surgery center (at the dermatology department) of the Erasmus MC have been observed in the past years: an increase of squamous cell carcinoma, malignant adnexal tumours and dermatofibrosarcoma protuberans, and a decrease of the much more prevalent basal cell carcinomas. A multidisciplinary approach is common in the care of cancer patients. The Rotterdam working group for head and neck oncology was setup in the mid 1980's; it was the first of its kind in the Netherlands and is now the largest in this country. It served as an example for the national board of health for the development of a united national network of head and neck oncology working groups (NWHHT). The department of dermatology has participated in the NWHHT for over ten years and has covered the chair of this



Sclerosing basal cell carcinoma in the eyebrow, before (left) and after excision by Mohs micrographic surgery.

working group for the last 3 years. Multidisciplinary surgery of skin cancer at the Erasmus MC has developed in close collaboration with the plastic surgeons and the ocular surgeons. The histology is performed by dermatologist, supported by and in close collaboration with the department of pathology. An important issue in dermato-oncology at the Erasmus MC is the translational research performed in close collaboration with the Center of Optical Diagnostic and Therapy (CODT). The dermatology department has a key role in the research performed within the CODT. The use of Raman spectroscopy in the skin is being investigated. In addition to patient care a variety of research activities have been developed within the dermato-oncological domain. The use of photodynamic therapy (PDT) in dermatology was initiated in the early 1990's.[4] The Rotterdam approach for light fractionated ALA-PDT is now applied as a standard treatment for PDT in pre-malignant conditions as actinic keratosis and superficial NMSC resulting in high long term clinical response rates.[5] Pre-clinical and clinical research is continued in a variety of aspects of PDT optical spectroscopy.[6] In addition to NMSC the research in PDT has now expanded in dermatology to anal intraepithelial neoplasia (AIN) and vulvar diseases such as vulvar intraepithelial neoplasia (VIN) and lichen sclerosus, using a variety of other esterified porphyrin pre-cursors like methyl-aminolaevulinate (MAL) and hexyl-aminolevulinate (HAL), nano-formulations of ALA and pre-formed chlorin photosensitisers.[7,8]

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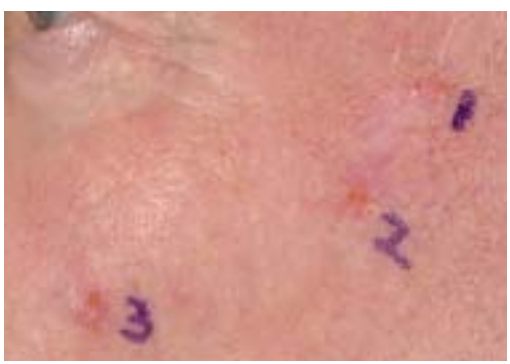
Dermato-epidemiology

The objective of most epidemiologic research is to measure the frequency of disease occurrence (and its trend in time) and/or to obtain a valid and precise estimate of the effect of a potential cause on the occurrence of disease (i.e., identification of risk factors). In addition, epidemiology is the methodological backbone for fields of public health, evidence-based medicine, and outcome research. Fundamentally, epidemiologic studies put the individual's condition in a population context.

Tamar Edmond Christoffel Nijsten

The departments of Epidemiology and Public Health of the Erasmus MC have an outstanding scientific reputation and form the back bone of the Netherlands Institute of Health Sciences (NIHES). From 2005 onwards, the relationship between these departments and the epidemiology division of the dermatology department, headed by Tamar Edmond Christoffel Nijsten (1972; photograph on page 5), intensified. Initially, collaborative projects on the epidemiology of skin cancer were started using the unique Dutch population based cancer registries that include basal cell carcinoma (BCC). In multiple studies, we showed the continuous increase of the incidence over time of BCC, squamous cell carcinoma and melanoma.[1,2] Also, the national pathology database was used for a more detailed analysis allowing us to demonstrate that approximately 30% of the people with a first BCC develop more BCC's within 5 years.[3] In addition to assess incidences and trends over time, a focus was put on gender differences in melanoma survival showing that female melanoma patients are significantly more likely to survive melanoma, independent of all known risk factors and in three of the four tumour stages. Also, we demonstrated that skin cancer is considered as a chronic disease, since patients often suffer from multiple skin cancers, it impairs their health related quality of life, and that impairment and burden of disease analyses show that people live many years with their diagnosis.[4-6] This line of research was expanded tot pharmaco-epidemiological studies by linking pharmacy database (PHARMO RLS) to pathology databases and later on to one of the four cancer registries.[7] One of the objectives was to investigate



Multiple basal cell carcinomas on the left cheek.

the association between exposure to common drugs such as aspirin and statins and the occurrence of cutaneous malignancies. Using the most advanced statistical methodology, previous observations of protective effects of these drugs on skin cancer incidence could not be confirmed. Using this pharmacy database, it was shown that psoriasis was not significantly associated with cardiovascular disease after adjusting for known confounders in Dutch patients from the general population.[8] In 2010, the department of dermatology actively engaged in 'The Rotterdam Study'. Each of the approximately 15,000 participants of this population based cohort receive a total body skin examination.[9,10] The primary outcome of interest is the incidence of cutaneous (pre)malignancies, skin aging, varicose veins and inflammatory dermatoses in the general population. However, the richness of "The Rotterdam Study" enables us to investigate the many associations between these skin diseases and available characteristics, exposures and/or phenotypes. Most importantly we are now investigating in a large population based sample, the genetic epidemiology of skin cancer.

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Paediatric dermatology

Arnold Pieter Oranje

Since 1978, Arnold Pieter Oranje (1948), later on in collaboration with Flora de Waard- van der Spek, has worked with the Sophia Children's Hospital to give special attention to paediatric dermatology. Together with representatives from other academic dermatology clinics in the Netherlands, paediatric dermatology was further disseminated with the foundation of the Dutch-Belgian Society of Paediatric Dermatology in 1993. From then on, a Paediatric Dermatology Course was annually organised in Rotterdam.
Research was initially focused on diagnostic tests in atopic eczema. As part of a European task force on atopic dermatitis, Dutch dermatologists from ErasmusMC were involved in developing a validated score system: the SCORAD index. This index was later on succeeded by the TIS and the Objective SCORAD.[1] The Skin Application Food Test (SAFT) was developed to establish food allergy in children with atopic eczema and combined with the Atopy Patch Test (APT).[2] Other clinical investigations were conducted into mastocytosis and a system comparable with the SCORAD, known as the SCORMA, was developed.[3] These investigations yielded an international guideline.

Suzanne Gudule Maria Apollonia Pasmans

Since mid-2013, under the aegis of Suzanne Gudule Maria Apollonia Pasmans (1963), a strategic plan for a broader paediatric dermatology was presented, encouraging collaboration between the departments of dermatology, paediatrics, immunology, microbiology and allergology. Main topics of clinical and research interest are the atopic syndrome, haemangioma and rare congenital diseases, such as erythroderma in newborns, and Netherton disease. Through various grants Het Huidhuis ("The Skin Home") was founded, an online portal where child patients and their parents can securely create their own patient records as well as access their own data, in an environment shared by healthcare workers. With this development a significant first step in fully integrated healthcare for children with dermatological diseases has been achieved (www.huidhuis.nl).

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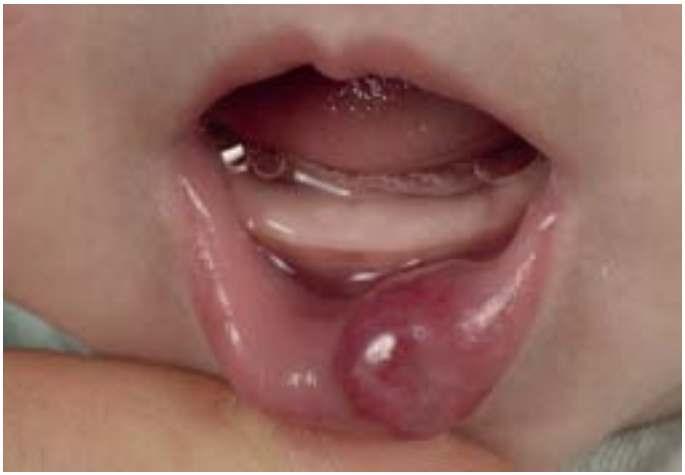
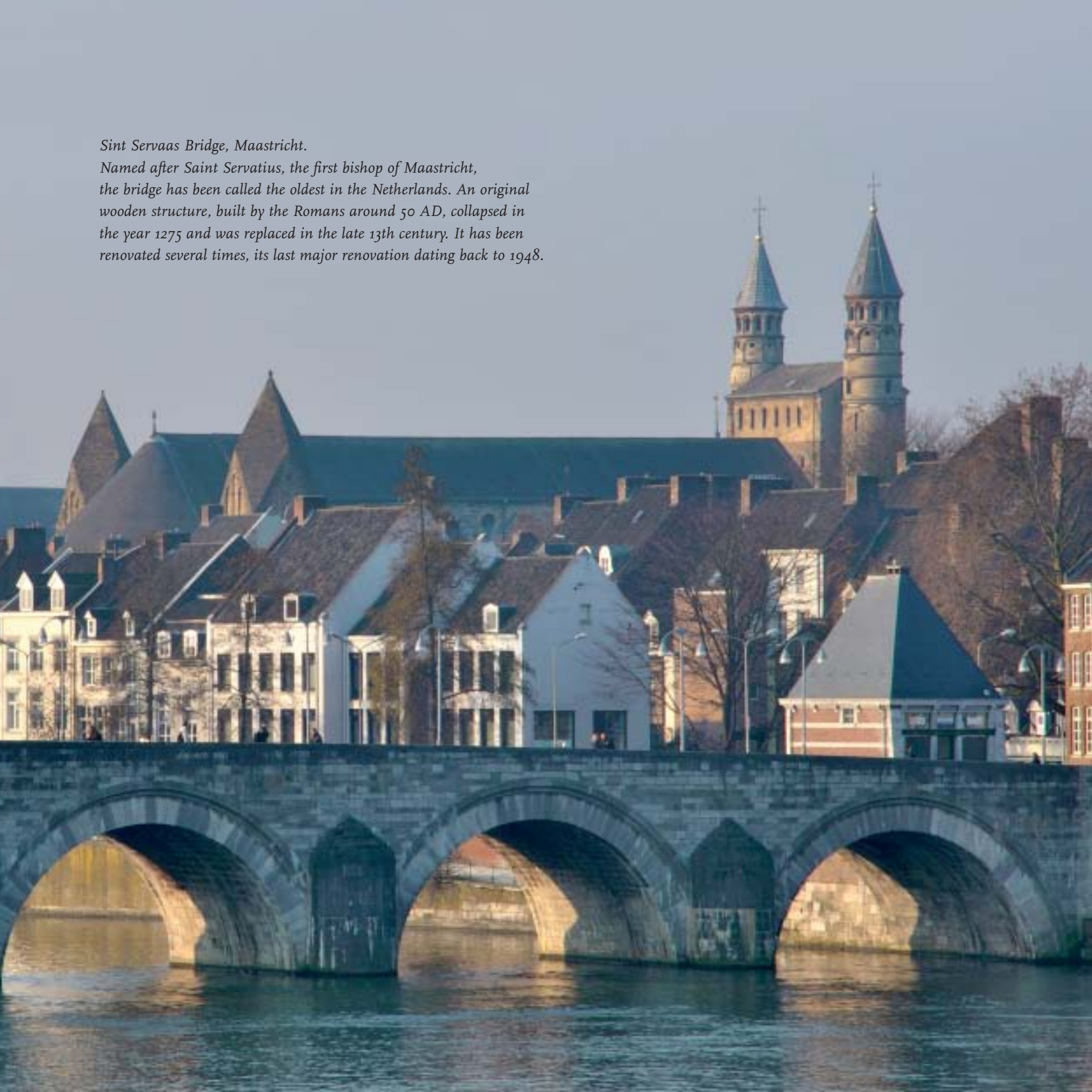


Hemangioma of the lower lip - indication for treatment.

Willemsbrug, Rotterdam.
Named after King William III of the Netherlands, this cable-stayed red bridge stands parallel to the Erasmusbrug (see page 126) and has a total span of 318 meters, joining the north and south of the port city of Rotterdam. From 2003 to 2008 an artificial beach was created on the right bank between the two bridges. Although intended as a leisure facility for Rotterdam residents, swimming was not permitted and digging sand pits - a crucial part of all Dutch children's beach activities - was limited to the 50cm depth of the sand coverage.



Sint Servaas Bridge, Maastricht.
Named after Saint Servatius, the first bishop of Maastricht, the bridge has been called the oldest in the Netherlands. An original wooden structure, built by the Romans around 50 AD, collapsed in the year 1275 and was replaced in the late 13th century. It has been renovated several times, its last major renovation dating back to 1948.

10 Maastricht University Medical Center

Peter Steijlen
with contributions by Joep C.J.M. Veraart, Maurice A.M. van Steensel and Nicole W.J. Kelleners-Smeets

Introduction

Maastricht is located in the far south of the Netherlands, in the province of Limburg, very close to the Belgian and German border. It is one of the oldest cities in the country, its history going back to Roman times. The Maastricht university was established in 1976, so it is one of the youngest institutions for higher education in the Netherlands. It is distinct from other universities in this country because of its "problem - based learning" and furthermore because of its strong international orientation, with about 50% of the students coming from abroad. In the third edition of the QS "Top 50 Under 50" ranking, Maastricht University obtained the 6th place. According to this list Maastricht University is the best performing young university in Europe.
The present university hospital is a continuation of the "Sint Annadal" hospital, which was founded on a guest house. This former monastery opened its doors in the year 1820 for the care and accommodation of the sick and infirm of the town, closely intertwined with the Roman Catholic Church.

"Sint Annadal" Hospital in Maastricht, built between 1940 and 1950, the forerunner of the University Hospital.

Aerial view of the on the University Hospital in Maastricht.

The guesthouse developed in 100 years' time into a general hospital with professional medicine and nursing for patients from all walks of life. This hospital is the direct forerunner of the University Hospital Maastricht. In the 1960s the coal mines in this most Southern province of the Netherlands closed their doors and large unemployment threatened the prosperity in this region.
The need for economic restructuring in the South of the Netherlands and the desire of the government in the Hague to spread science and education, contributed to speed up matters. Establishing a university could and should give a positive impulse to the region. In 1969 Maastricht was designated to host the eighth and youngest medical faculty of the country. In 1974, the first medical students arrived in Maastricht, two years before the official establishment of the university.

Main entrance of the University Hospital Maastricht.

History

Wim J.B.M. van der Staak

In 1982 Wim J.B.M. van der Staak (1933) was appointment as first professor of dermatology in Maastricht. Hans R.M. van Gasselt who at that time was consultant in private practice in the southern town, sold his practice to join the academic staff. The difficulties for van der Staak were manifold: in the hospital there was no room for an outpatient clinic, nor did he have beds in the hospital or an office for his secretary. In addition, the hospital faced large debts, so only the most urgent and necessary alterations were possible. Nevertheless van der Staak managed to set up a department.

In 1993 H.A. Martino Neumann (1950; photograph on page 129), who so far had been working as dermatologist in a general hospital was appointed professor of dermatology at the University of Maastricht. The Department underwent a scientific reorientation and focused on two topics for patient care and research. One was dermato-oncology including dermato-surgery. The other was dermato-phlebology with introduction of new techniques, among others Muller'ambulatory phlebectomy and Duplex sclerosing technique. The department soon achieved supraregional facilities and a top reference function for Mohs Micrographic Surgery and phlebology diagnostics and treatments. Scientifically the department joined the faculty project "Growth and Development" with regard to dermato - oncology and the research school CARIM (heart and vascular diseases) regarding the regarding dermato - phlebology. In 1994 the department appointed its first PhD student within the project "Growth and Development". To broaden the clinical support, the possibilities of clinically oriented research and the training of medical students and residents, a partnership was established with dermatology departments in general (non - university) hospitals in the cities of Heerlen, Roermond, Venlo and Eindhoven.

Peter Steijlen

In 2002 Neumann was appointed professor and head of the department of Dermatology at the University Hospital in Rotterdam. In 2003 Peter Steijlen (1958) who by then had just been appointed as extraordinary Professor for Genodermatology at the University in Nijmegen, considered it a challenge to become head of the Department in Maastricht. The Board of Directors in Maastricht right away facilitated the establishing of a laboratory for "molecular, cell biological and genetic research", like the one that had been constructed in Nijmegen. The new professor was fond of new developments, and not only those concerning research. Challenges at the outpatient department were approached by using innovative methods such as using "Lean Six Sigma programs"

to eliminate waiting lists. Furthermore open working spaces were created for staff members and residents. Teaching of medical students was modernized. The training of residents was updated. Research focused on two major topics: genodermatology and oncology. The number of staff members and residents increased significantly as well as the quality of patient care. In November 2007 the first World congress on Genodermatology was organized in Maastricht, which was the first of a number of successful conferences on this topic.

Maurice Adrianus Monique van Steensel

In 2010 the university patient department was extended with a second outpatient clinic (the so called location "West"), containing "daycare" facilities. The scientific zeal of the department culminated in the appointment of Maurice Adrianus Monique van Steensel (1969) as professor of Genodermatology in 2011.

Research

Oncology

In 1992 Mohs micrographic surgery was introduced in Maastricht. From that year on, patients were referred to Maastricht from all over the country, as it was in those days the only hospital in the Netherlands where this method was practiced. Today, our dermatologists play an important role in many multidisciplinary teams, like the head and neck oncology team and the melanoma team.
Many skin tumors are treated multidisciplinary with plastic surgeons, ENT specialists, maxilla-facial surgeons, ophthalmologists, radiotherapists and medical oncologist. The dermatology department of the Medical faculty in Maastricht was the first in the Netherlands where new targeted therapies, like Vismodegib, were offered to patients with large basal cell carcinoma (BCC) or with metastases and patients with basal cell nevus syndrome.
Research originally focused on prevention. A large screening campaign for melanoma was conducted and evaluated.[1] Later on the interest focused more on sunscreens. A lot of publicity was attracte with a study on P53 immunostaining in UV-exposed and sunscreen protected skin, in which the buttocks

The MUMC oncology research team.
From left to right: Valerie Verstraeten, Monique Thissen, Aimée Arits, Klara Mosterd and Nicole Kelleners-Smeets.

of healthy volunteers were exposed to the sun on the beach. Besides prevention, the department became interested in the epidemiology and etiology of skin cancer, especially BCC.[2] Research on the etiology of BCC still continues and now focusses on epigenetic changes.[3] Maybe with (epi-)genetics we can ultimately explain how BCC develops and find a treatment to stop this. The dermato- oncology research also covered two other common skin (pre-) malignancies: actinic keratosis and squamous cell carcinoma. Several clinical studies were executed on lasers, actinic keratosis and squamous cell carcinoma.[4,5] Although Mohs surgery was practiced more and more in Maastricht, it was still not accepted by all dermatologists worldwide, let alone by plastic surgeons. So it was time to convince the opponents with a large randomized controlled trial. Six hundred patients with high risk primary or recurrent BCC in the face were included. This study made clear that Mohs surgery is treatment of preference in recurrent BCC and large BCC of an aggressive subtype.[6,7]
At the end of the nineties of last century, dermatologists already foresaw a huge increase in skin cancer, especially BCC. So the search for effective treatments continued. And so photodynamic therapy (PDT) was introduced. In fact PDT has been a research topic at our department, from its early days onwards . It seemed promising.[8] However, years later, a large randomized controlled trial showed that it wasn't a good alternative to surgery for nodular BCC.[9] For superficial BCC, the new-comer imiquimod was superior to PDT and even the good old 5-fluorouracil showed equal effectiveness to PDT.[10] So the search goes on to find a treatment for BCC that is non-invasive, as effective as surgery and that (as an ideal) can be performed by the patient at home. But our ultimate goal is to find something that prevents skin cancer from developing and stop the enormous rise in its incidence.

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Phlebology

In 1992 Neumann started phlebology patient care and research. In the beginning only conventional therapy, such as compression therapy, was used in daily practice and also subject of research.[1] However, soon the so called Muller ambulatory phlebectomy was started, a minimal invasive technique for removing varicose veins under local anesthesia. Neumann had mastered this technique in Switzerland in the clinic of the famous doctor Muller himself. In a randomized trial the superiority of Muller's phlebectomy over compression sclerotherapy could later on be proven.[2] In 1996 the outpatient clinic was equipped with a duplex ultrasound, so the dermatologists could perform their own vascular investigation. Duplex is much more reliable in the diagnosis of (incompetent) veins that the previous used Doppler. Now vascular vessels could become visible and tested on their functionality. Besides introduction of these new procedures for daily practice, cooperation was implemented with the Cardiovascular research group of the University of Maastricht (CARIM), for more fundamental research. The intention was to focus on the microcirculation in chronic venous insufficiency and post thrombotic syndrome. It was found that Factor V Leiden mutation is more frequent present in

patients with venous leg ulcers than in the control group and the general population.[3] Another study found a synergistic pathogenic role of factor V Leiden, hyperhomocysteinemia and impaired fibrinolysis in the development of post thrombotic syndrome and its sequelae. So an increased formation of thrombi in the microcirculation of the skin in combination with ambulatory venous hypertension play a role in ulcer formation.[4] Furthermore new techniques such as laser Doppler imaging were tested on their value in micro vascular research and evaluating local treatment of the skin, like topical steroids.

Sometime after the Duplex technique had been introduced "Duplex guided sclerotherapy" was a logical next step in de armament of the dermatologist and this method was indeed introduced at the outpatient clinic in 1998. Around the turn of the century a new sclerosing technique, namely foam sclerosis, was invented by a Spanish surgeon. This method was soon introduced in Maastricht and called ultrasound guided foam sclerotherapy (UGFS). In a large randomized trial sponsored by the Dutch government, with more than 400 legs being treated, it could be shown that at 2-year follow-up, UGFS was not inferior to surgery when "reflux associated venous symptoms" was the clinical outcome of interest.[5] Also the side effects of foam echo sclerotherapy were investigated and well documented.[6] In another large study a series of patients after stripping of the long saphenous vein were included. Most of these patients were free of complaints after the surgery but more than half still had visible veins on their lower legs.[7]

Later on also lymphedema became a topic for patient care, but also as a research item, mainly from a genetic point of view. A new syndrome could be confirmed.[8] In another clinical study it could be shown that patients presenting with a first episode of erysipelas often have signs of pre-existing lymphatic impairment in the other, clinically non affected, leg. This means that subclinical lymphatic dysfunction of both legs may be an important predisposing factor.[9]

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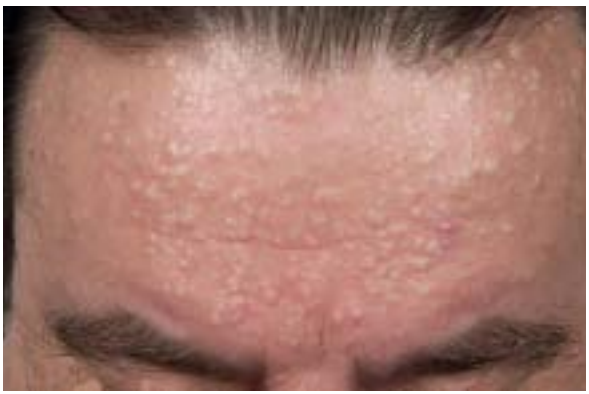
Genodermatology

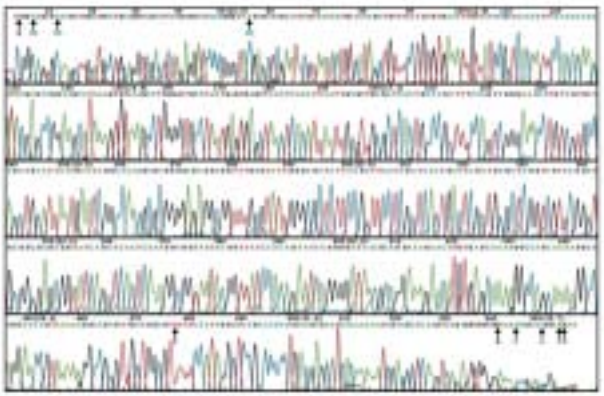
The development of the subdiscipline of genodermatology started in the year 2003. In a rather short time a laboratory for molecular genetics was created, where research was promptly started into the genetic background of several hereditary skin disorders. Moreover, experimental genetic diagnostic tests were offered to clinical working physicians. Within a year, the departments of dermatology and clinical genetics started combined multidisciplinary clinical consultations for patients with hereditary conditions. The close collaboration between dermatologist, clinical geneticist and molecular geneticist soon yielded results, and has been successfully continued till today. Highlights are publications about the genetic basis of acral peeling syndrome, about the identification of a new laminopathy, and about an important contribution to the genetic basis of atopic eczema.[1-3]

To guarantee a sustainable research policy, it was soon decided to focus not only on genetics, but also on molecular cell biology. The collaboration with the departments of Molecular Cell biology in Maastricht and with several foreign (especially British) research groups appeared to be invaluable. Research was focused on diseases of the nuclear envelope, so-called laminopathies, including for example progeria and disorders with an abnormal fat distribution. We concentrated specifically on gap junction diseases of the skin, in which anomalous keratinization and inflammation are caused by mutations in connexines, proteins controlling intercellular communication.[4,5] The change in focus facilitated the initiation of more aspiring projects. Because of the fact that Maastricht has a solid oncology research line, a connection between genodermatology and oncology was quite self-evident. Consequently, research projects regarding basal cell carcinoma and the rare Hornstein-Birt-Hogg-Dubé syndrome, the latter syndrome giving rise to benign hair follicle tumors and kidney cancer, were initiated.

For both projects grants for innovative research were received from the Dutch organizations ZonMW and KWF. Currently the laboratory of Experimental Dermatology is involved in cell biology, using a diversity of techniques including animal models. This activities resulted in investigations regarding rare hereditary diseases, in which the authors do not only focus on the genetic origin, but also on their pathophysiology.[6] About patient care it is important to note that the molecular testing for genodermatoses is now accommodated in the laboratory for DNA diagnostics. Patients with the most common inherited diseases now rapidly can get a reliable molecular diagnosis.



Multiple fibrofolliculomas on the forehead in Hornstein-Birt-Hogg-Dubé syndrome.



Example of DNA sequencing to determine the sequence of individual genes, larger genetic regions and entire genomes.

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Enclosure Dam.
A crucial part of the larger Zuiderzee Works, damming off the Zuiderzee, a salt water inlet of the North Sea, and transforming it into the fresh water lake of the IJsselmeer. The Enclosure Dam is 32 km long and symbolizes the ongoing, centuries-long struggle of the Dutch against encroaching waters.

11 Scientific contributions from non academic centers

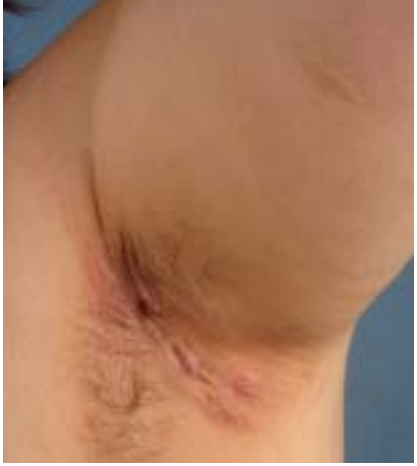
Jannes van Everdingen
with contributions by Jurr Boer, Robert J. Damstra, Anton C. de Groot, Ronald H. Houwing, Gertruud A. Krekels, Henk E. Menke, Bernard Naafs, Frans H.J. Rampen, Han J. van der Rhee and Kees-Peter de Roos

Knowledge production is not a prerogative of universities. Dermatology research is generally carried out in academic centers, but there are some dermatologists doing scientific investigations outside of universities. Their work may be an extension of the research that they started during their initial training, but it may also be related to experiences gained and observations arrived at whilst working outside the academic world. This could result in interesting complementary scientific knowledge, which could be an endpoint in itself, but could also generate new and exciting directions to academic research.
In this chapter a number of contributions are presented, highlighting the issue of "scientific contributions from non academic centers".

Research on hidradenitis suppurativa

Jurr Boer

Jurr Boer (1948) had studied medicine in Groningen and was trained as a dermatologist at the University of Leiden by Polano and Suurmond. He successfully expanded Suurmond's research line and pioneered with broadband UVB phototherapy in patients with psoriasis. He investigated, for instance, the Dead Sea circumstances in a hospital setting for his PhD thesis in 1982. In 1983 he became a dermatologist at the Deventer Hospital, Deventer, where in the beginning he continued psoriasis research, such as studying the effect of (traumatic) nerve cutting on psoriasis plaques.[1] His interest for hidradenitis suppurativa (HS) was first sparked in the mid-1980s.[2,3] At that time, despite its common occurrence among patients and the extreme discomfort it caused, interest in HS was scarce. It was not until the mid-2000s that interest in HS increased as a result of the introduction of biologicals.[4,5]
In the early 80s, it was hypothesized that HS could be a form of acne (acne triad and tetrad) and the name acne inversa (AI) was introduced.[6] At the same time, isotretinoin became the reference drug for the treatment of acne (conglobata). As with acne, isotretinoin was a mainstay of treatment for HS



Hidradenitis suppurativa of left axilla.

throughout the 1980s and 1990s. Consequently, it was a rationale step during the 80s to begin a case series with isotretinoin therapy of HS patients.[2,5] In a trial involving 68 patients over a period of almost 9 years, it was found that only 17 percent improved through oral isotretinoin, while the therapeutic benefit mostly occurred in milder forms of HS. This was in marked contrast with the highly successful use of isotretinoin in the treatment of acne. Today, it's widely accepted that isotretinoin can no longer be recommended as a primary therapy for HS.
Besides the therapeutic consequences of the study, these case series also indicated that the analogy between acne and HS is limited, at least in therapy.[2,7] This was underlined by a subsequent indirect proof, i.e. that acitretin, another retinoid, seems to be an effective treatment for HS.[5,8] There are strong arguments, therefore, that the term 'acne inversa' is a misnomer. Although HS is similarly regarded as something of a misnomer, most experts continue to use the term at the current time. Later, Boer extended his research on HS and co-supervising of PhD students in cooperation with Errol Prens, Erasmusmc, Rotterdam and Gregor Jemec, Roskilde Hospital, Denmark.[4,9,10] Jurr Boer has been founding member of the European Hidradenitis Suppurativa Foundation in 2012.

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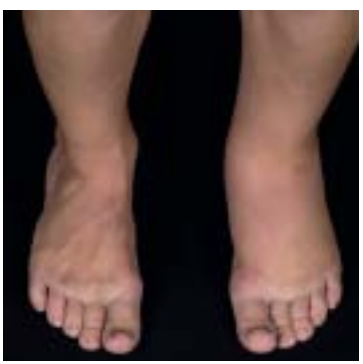
Dutch Expertise Center for lymphovascular medicine

Robert J. Damstra

In 1995, in the city of Drachten's Nij Smellinghe Hospital, an interdisciplinary working group was started, consisting of two dermatologists, a surgeon, a compression specialist, a physiotherapist, a skin therapist and a specialized oncology nurse. The working group was initially dedicated to the diagnosis and treatment of patients with cancer-related lymphedema. Later on, patients with swelling were also referred for diagnosis and conservative or surgical treatment of primary and secondary lymphedema and for a functional programme for lipedema. Until that time, lymphedema in general and specifically post-cancer lymphedema were orphan diseases in the Netherlands. In 1998 the Stichting Lymfologie Centrum Nederland (the Dutch Lymphology Foundation Center) was established to educate and inform healthcare workers. In the year 2000, this foundation published the first Dutch book on lymphology, entitled Lymfoedeem in de praktijk (Lymphedema in daily practice). Additionally, research and the development of new concepts of treatment of lymphedema and lipedema were started. In 2003 the first Dutch guideline on lymphedema was published, while by 2006 the Dutch Lymphedema Network (NLNet) had been founded. In 2009, Robert Damstra (1959) received his PhD at the University of Maastricht for his thesis "Diagnostic and therapeutical aspects of lymphedema". A rewritten edition was published commercially in 2010 and again in 2013.[1]

In 2009, the working group was officially transformed into the Dutch Expertise Center for Lymphovascular Medicine, being one of the focus areas of the Nij Smellinghe Hospital with 13 beds and over 160 in-patients, as well as some 600 patient referrals every year. In 2013, a satellite treatment center was founded in Utrecht to perform follow-up and out-patient treatment under the aegis of the expertise center. As of 2014, the center has been officially recognized by health insurance companies as a tertiary referral center in the Netherlands. Partnerships with the universities of Groningen, Maastricht, Greifswald (Germany), Malmo (Sweden), Leuven (Belgium) and universities of applied sciences (Utrecht, Groningen, the Hague) were either initiated or extended. New treatment programmes were introduced implementing the concepts of chronic care management and a functional approach according to the International Classification of Functioning, disability and health (ICF) as defined by the World Health Organization (WHO). In 2014, the second guideline on lymphedema and the first guideline on lipedema will is published in the Netherlands in collaboration with more than 17 representatives of scientific and patient organizations. Over the last 7 years, Damstra has been a member of many international guideline/consensus committees, such as the International Union of Phlebology (UIP), the ILF and the International Compression Club (ICC).



Lymphedema of the left leg and foot.

Since 1999, the research programme has developed in an organic way. Most of the research subjects were initiated in order to understand the mechanisms of compression in lymphedema, infection related to lymphedema, and to develop and improve surgical procedures. A method to measure arm lymphedema was developed and validated.[2] In close and fruitful cooperation with Prof. Dr. H. Partsch (Vienna) the mechanism of compression, which is the cornerstone in lymphedema treatment, was analyzed. New treatment programmes and compression techniques were studied.[3-5] Research in the field of primary lymphedema resulted in a better understanding of defects in the FOXC2 pathway, and also an algorithm for children with lymphedema.[6,7] In patients with unilateral erysipelas (without diabetes or chronic venous insufficiency) we found that almost 80% had bi-lateral lymphatic impairment.[8] This was a first clue as to the effectiveness of compression therapy in post-erysipelas patients. In our research programme, we studied new interventions in arm lymphedema. A study of lymph shunts showed no effectiveness in this method, but a new technique of circumferential, suction-assisted lipectomy in a multidisciplinary setting gave 100% long-lasting reduction in arm volume.[9,10]

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Research on cosmetic allergy leading to ingredient labelling in the European Union.

Anton C. de Groot

Dermatologist Anton de Groot (1951) trained in Groningen and practised in 's-Hertogenbosch from 1980-2002. He first became interested in cosmetic allergy while writing his book "Unwanted effects of cosmetics and drugs used in dermatology" (Excerpta Medica, 1983) in collaboration with his teacher Johan Nater, and drawing from their chapters on dermatological drugs and cosmetics in Meyler's series on the side-effects of drugs. In a general population survey, he found that over 12% of the participating individuals potentially had suffered from adverse reactions to cosmetics. It was demonstrated that some 10% of such reactions are caused by contact allergy.[1] Data from his own practice and from a prospective study with the Dutch Contact Dermatitis Group showed that fragrances and preservatives were the most important categories of allergens, with the preservative system methyl(chloro)isothiazolinone (Kathon® CG), the emulsifier oleamidopropyl dimethylamine and the nail polish resin tosylamide/formaldehyde as most frequent causes of cosmetic-induced allergic contact dermatitis.[2,3]
The importance of Kathon® CG as cosmetic sensitizer was soon confirmed in many studies in the Netherlands and other countries.[4] In 1988, Anton de Groot defended his PhD thesis 'Adverse reactions to cosmetics', supervised by prof. Johan Nater.

Frustrated by the lack of easily accessible information on the ingredients of cosmetic products, De Groot approached the European Society of Contact Dermatitis and became convenor of the Working Party Community Affairs. In a discussion document the Party clearly demonstrated that ingredient labelling (mandatory ingredient listing on a cosmetic product or its package) would be extremely useful with only slight and temporary disadvantages for the cosmetics industry.[5] The European Commission and its committees, elected legislators, national trade, industry and health departments and the cosmetics industries were extensively lobbied. This resulted in new legislation by the Commission of the European Communities in 1991, making ingredient labelling mandatory for all cosmetic products sold or disposed of in EC Member States by December 31, 1997.
In the mid 1990s, De Groot and his colleagues warned for a sharp rise in allergic reactions to methyldibromo glutaronitrile, which was employed on a large scale by the cosmetics industry as a substitute for Kathon® CG[6]. This new preservative was banned in the EU from all cosmetic products in 2008.
Anton de Groot recently published the 3rd edition of his book 'Patch Testing' (www.patchtesting.info).[7]

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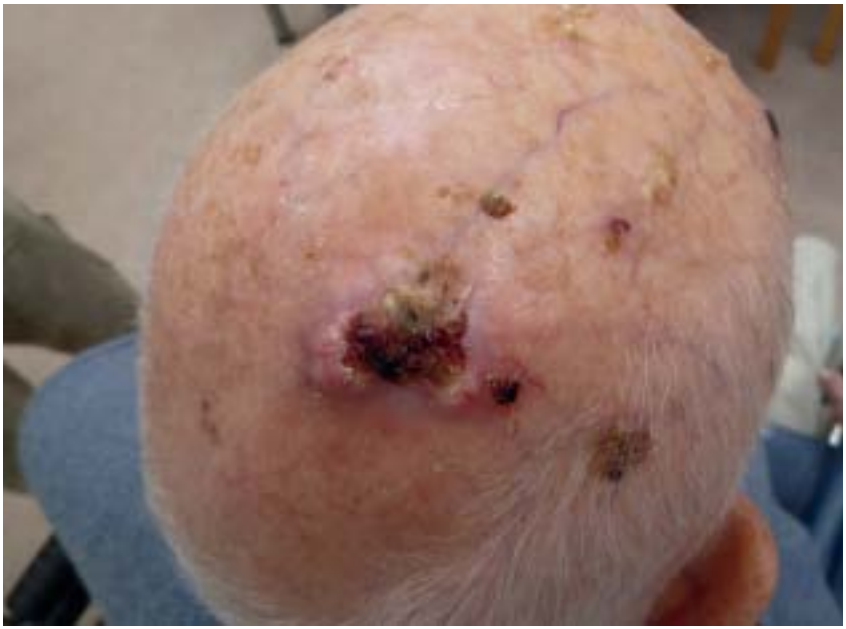
Disease Management of Non melanoma Skin Cancer

Gertruud A. Krekels

Gertruud Krekels (1965) was trained as a dermatologist in Maastricht. In Athens in 1996, she received the European Award on Photodermatology. Two years later, she received a PhD in Maastricht on Basal cell carcinoma and Mohs surgery. In 2000, as both dermatologist and one of the first Mohs surgeons in the Netherlands, she successfully applied for a grant from the Dutch Fund for Investigative Medicine (In Dutch: ZonMw Doelmatigheidsonderzoek) to perform a randomised controlled trial: Mohs Micrographic surgery versus conventional surgery for facial basal cell carcinoma, a study on the efficacy and cost-effectiveness of Mohs surgery. This randomised controlled trial was conducted under her authorship and supervision and resulted in 5 PhD theses and multiple publications.[1-3]

In 2004 she founded a Skin Cancer Center as well as a center for training dermatologists and Mohs surgeons in the Catharina Hospital Eindhoven. After another two years, she became President of the European Society for Micrographic Surgery. She was also involved in all Dutch Skin Cancer Guidelines. Krekels then started a collaboration with the University of Technology Eindhoven. The term Chronic Skin Cancer was introduced and Disease Management Models were designed.[4-8] More recently, the research focus has shifted to business process redesign in healthcare.

Previously, non melanoma skin cancer had been considered a relatively mild healthcare problem because of the low mortality rate. However, the morbidity, the burden on the healthcare system and the ever-growing financial implications of a true skin cancer epidemic, resulted in an increasing sense of urgency about how to manage this “new” chronic disease. Krekels is one of the founders of Mohs Academy (MOHSA) expert cancer centers (Eindhoven/Venray).



Large squamous cell carcinoma in sun-damaged skin.

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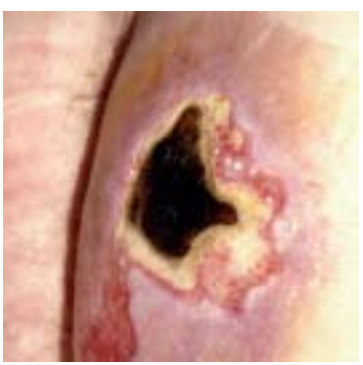
Pressure Ulcer or decubitus

Ronald H. Houwing

Throughout his medical studies, Ronald Houwing (1958) had been intrigued by pressure ulcers, or bedsores. Besides his interest in the pathophysiological mechanisms of this disease, he was taken by the lack of interest in this subject by docters, an unglamorous aspect of healthcare though it is.
During his training as a dermatologist in Utrecht under Willem A. van Vloten, he joined the "hospital pressure ulcer team". At the final stage of his specialisation he had the opportunity to start an animal study of the pathophysiology of pressure ulcers.
This study showed the role of oxidative stress in the pathophysiology of pressure ulcers and, further, a reducing tissue-damaging effect of the oxidant vitamin-E.[1,2]
He started working as a dermatologist at the hospital of Deventer in 1991 and continued there with research in the field of pressure ulcer prevention.
Contrary to the positive results found in his animal research, one human study revealed that there was no significant preventive effect by adding nutritional supplements enriched with antioxidants.[3] A study with a locally applied antioxidant (DMSO) in people at risk of pressure ulcers, even showed a detrimental effect.[4-6] More studies are necessary to establish the safety and effectiveness of antioxidant therapy.
Risk assessment tools are used to identify a person in danger of developing pressure ulcers. However, these tools have proved inadequate to determine this risk and therefore they should not be used as the only diagnostic instrument.[7] There again, a skin assessment is an indispensable method of recognising individuals at risk of developing pressure ulcers. Insight into the pathophysiology of superficial pressure ulcers in the incontinent elderly led to the adjustment of international guidelines.[8] While better-designed studies are no doubt necessary to diminish the incidence and burden of pressure ulcers, the attention and care of the nursing staff remains and continues to be an indispensable element.



Decubitus ulcer on the right buttock.

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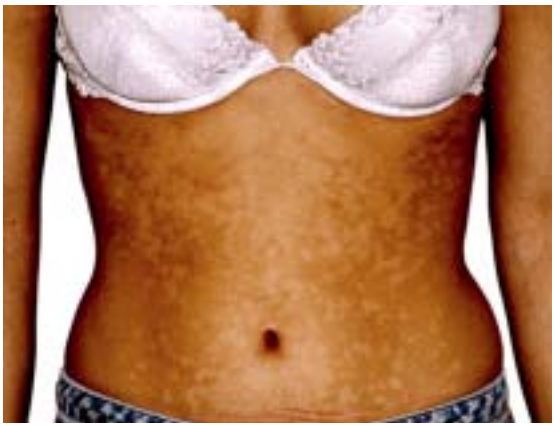
Tropical and ethnic dermatology

Henk E. Menke

Henk Menke (1942) studied medicine in the 60s at Leiden University, and specialized in dermatology at Erasmus University in Rotterdam. After his PhD thesis on aspects of the humoral immune response in syphilis patients, he worked from 1975 to 1978 as a dermatologist in his home country Suriname, where he became familiar with dermatology of the pigmented skin. He was also involved in clinical and epidemiological work regarding infectious diseases. During fieldwork in rural areas, attenuated yaws was identified as a specific type of this endemic treponematosis: a clinical/epidemiological variety with minimal symptoms, evidently emerging in the final stage of the epidemic.[1,2] Further, he mapped STDs in the country, raising awareness of regional (Caribbean) as well as transatlantic prostitution as a "social vehicle" of STD transmission between countries.[3]
Back in the Netherlands he worked as a dermatologist in the Sint Franciscus Hospital in Rotterdam from 1980 to 2003, focusing on ethnic dermatology. He pointed to the consequences of rapidly changing demographics for Dutch dermatology practice, with 10% of the population in the Netherlands having a non-white skin colour by the year 2000, and in the big cities rising even to 50%. He was the first in the Netherlands to recognize and describe patients with skin damage caused by the application of bleaching agents. This appeared



Progressive macular hypomelanosis on the trunk (courtesy Germaine Relyveld).

to be a rather common practice among certain immigrant groups, with sometimes harmful consequences, such as exogenous ochronosis, caused by hydroquinone.[4] He also recognized a distinct type of hypopigmentation, resembling yet distinct from pityriasis versicolor and pityriasis alba. Menke presented the clinical, histological and ultra-microscopical picture of this entity at the EADV congress in 1993 in Copenhagen as a poster-presentation, and won the first prize for a novel entry. This pigmentary disorder, internationally now called "progressive macular hypomelanosis", is characterized by nummular confluent non-scaly hypopigmented spots on the trunk. Research was continued in collaboration with Wiete Westerhof and Germaine Relyveld, aiming at unravelling the nature of this type of hypopigmentation. It appeared to be a frequently misdiagnosed worldwide disorder, common in adolescents and young adults, with a characteristic (but not pathognomonic) histological and electron-microscopical picture. The red fluorescence (under Wood's light) in the follicles of the hypopigmented spots - that can be considered a pathognomonic sign of this disorder - corresponds with the presence of a subtype of propionibacterium acnes, probably the causative micro-organism. The best treatment to date is application of topical antibiotics together with UV light.[5-7]

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Research on leprosy

Bernard Naafs

Reversal reaction in leprosy patient. Courtesy RDTC.

From the 1970s onwards, the Netherlands became a center for leprosy research, thanks to Dick Leiker. He recruited Ben Naafs (1943) in the early 1970s to conduct leprosy research in Africa. Naafs spent 5 years in Ethiopia at ALERT/AHRI, at that time one of the major leprosy and immunology research centers. He was trained there by John Pearson and Ross St Clair Barnetson in dermatology/leprology and immunology. He introduced proper follow-up of the treatment of leprosy reaction by graded sensory testing and Motor Nerve Conduction measurements. Naafs returned to The Netherlands in 1979 and started his training in dermato-venereology at the University of Amsterdam's Department of Dermatology under Rudi Cormane. During his residency he received his PhD degree with a thesis entitled Prevention of permanent nerve damage in leprosy. Together with William Faber, he also wrote frequently cited articles on Thalidomide in dermatology.[1,2] After completing his residency, he left again for the tropics in 1983, this time to Zimbabwe. He became head of the first leprosy programme that "eliminated" the disease. Alongside his clinical/epidemiological work, he continued with his research before returning to The Netherlands in 1986. He was appointed head of the outpatient department of dermatology at Dijkzigt, the Erasmus University Teaching Hospital in Rotterdam. There, he continued his leprosy research, particularly with Roël Chin-A-Lien, and in co-operation with Leiden University and the University of Amsterdam. The focus of research at the time was on autoimmunity in leprosy, an area which seemed to have been neglected for years, but which had recently undergone a resurgence of interest. He remained in Rotterdam for 10 years. In 1996 he published an article that is still considered the standard work for treatment of leprosy reactions.[3,4] For the past 15 years he has divided his time between The Netherlands, Tanzania, Ethiopia and Brazil. Chief among his achievements in recent years has been the writing of dermatology books for developing countries. The book written with Colette van Hees, is probably the dermatology work most referred to in Africa.[5] Ben Naafs continues to guide young dermatologists in developing countries.

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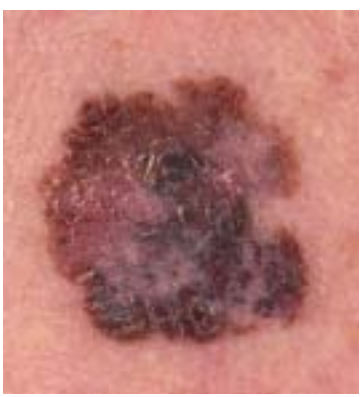
Cutaneous melanoma: risk factors, screening activities.

Frans H.J. Rampen

During his academic career (1980-87) Frans Rampen (1945) wrote many publications on naevi and melanoma. Melanoma was also the subject of his PhD thesis of 1982: "Malignant melanoma, prognostic factors". From 1987 until 2009 he practised as a dermatologist in the general hospital Sint Anna/Bernhoven in Oss. During this period he continued his research on melanoma. Special subjects he addressed were swimming as a risk factor, and screening programmes.

In the nineties, more than forty case-control studies on melanoma aetiology had been published. Sunlight was believed to be the main culprit, albeit with relative risks of only 1.5-2.0. These weak risk factors could easily be ascribed to information bias. Rampen's crusade against the sunlight hypothesis resulted in a study on water pollution and swimming behaviour as risk indicators, with sunlight exposure merely being a confounding factor.[1,2] With regard to a) regular swimming, b) the age at which swimming was learned, and c) the number of swimming certificates held, it was concluded that swimming increased the risk of melanoma. For certain subgroups risk ratios of up to 3.0 were observed. Rampen supervised Patty Nelemans' 1993 PhD thesis on this subject.[3] Rampen also organised three melanoma screening campaigns in the Netherlands. One of these formed the basis of a PhD thesis written by Michette de Rooij in 1997, studying the fundamentals, methods, advantages, and limits of secondary prevention campaigns for melanoma.[4] It was clear that melanoma screening did not fulfil all the principles of screening for disease that were generally accepted by epidemiologists, research groups and government authorities. Moreover, no definitive conclusions could be drawn as to the feasibility and the cost-effectiveness of the screenings. Therefore, according to Rampen, melanoma screening based on self-assessment of volunteers was not suitable as a national strategy. This recommendation was subsequently adopted by the Dutch Dermatology Society.



Superficial spreading melanoma.

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Melanoma and the sun

Han J. van der Rhee

Han van der Rhee (1946) had been trained as a dermatologist under Machiel Karel Polano at the Leiden University Medical Center between 1974 and 1979. During the same period he researched his thesis on blood monocytes and their differentiation into macrophages, epitheloid cells and multinucleated giant cells.[1] After qualification, he started working as a consultant dermatologist at the Municipal Hospital in The Hague, now known as The Hague Teaching Hospital, the same institution where his mentor Polano had started his dermatological career. His scientific interest then moved from electron microscopy to dermatological oncology and therapy of skin diseases, particularly psoriasis. He designed and performed one of the first randomized clinical trials (RCTs) on combination therapy in psoriasis.[2]

In 1980 he was co-founder of one of the first Dutch regional working parties on skin cancer. For more than twenty years he was a member of the Dutch National Melanoma Working Party. From 1989-1992 he launched 'de Sproetenbus' (the Freckle Bus); a series of skin cancer awareness campaigns that attracted much national and international media attention. Scientifically his interest in dermatological oncology resulted in a large number of publications on the epidemiology of melanoma. He was particularly interested in the relationship between skin cancer and sun exposure.[3,4]

In recent years this interest has extended to the effects of sunlight on health issues other than skin disease.[5,6] Although he ceased practising as a dermatologist in 2011, he remains active as a reviewer, a consultant to the Dutch Cancer Society and as a writer of both scientific and popular publications on the effects of sunlight on health.

The Freckle Bus.

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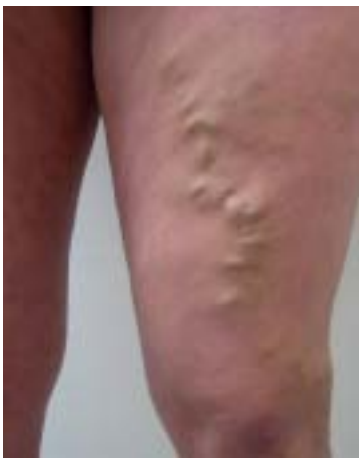
Ambulatory phlebectomy for branch varicosities

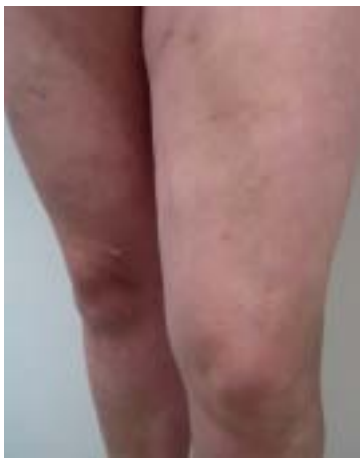
Kees-Peter de Roos

Kees-Peter de Roos (1960) studied medicine at the University of Maastricht and went on to train as a dermatologist at the University Medical Center of Maastricht. Halfway through de Roos's training in 1992, Martino Neumann became head of the dermatology department and introduced him to the art of ambulatory phlebectomy. A case report on a complication of this technique was published in 1994.[1] Before leaving Maastricht in 1994, De Roos organised several 'hands-on' workshops on this topic.

Although some phlebologists had already experimented in the ankle region, the phlebologic dogma in that period was 'never to treat varicose veins below the ankle'. Neumann and De Roos started to register the results of ambulatory phlebectomy in this particular location and found it to be a safe technique.[2,3] They additionally performed a randomized clinical trial comparing conventional sclerocompression therapy to ambulatory phlebectomy (AP).[4] It demonstrated that ambulatory phlebectomy is significantly superior to conventional sclero-compression therapy when comparing recurrences (2 vs. 37.5 % after two years) and patient satisfaction. This study formed the basis of de Roos's thesis (2003). Since then, he has broadened his field of expertise by working as a co-supervisor of several PhD candidates [5,6], but also by initiating different studies on venous disease.[7-9] After more than 15 years in a general hospital, he started a private practice in general dermatology in 2009 that specialises in varicose veins and skin cancer.



Side branch varicosis on left upper leg.



Result of ambulatory phlebectomy after 6 weeks.

From 2003 until 2013 de Roos chaired the Dutch Dermatology Society Working Party on Venous Disease. In 2011 he co-founded the Dutch College of Phlebology and currently serves as co-chair of the Dutch guideline on varicose veins and venous disease.

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