CHAPTER 2

HISTORICAL PERSPECTIVE OF PEMPHIGOID DISEASES IN THE NETHERLANDS: FROM BLISTERHEAD COW TO NONBULLOUS PEMPHIGOID

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The official birth of bullous pemphigoid took place in February 1953 with its description in an analytical review by Walter Lever in the journal Medicine, in which he separated bullous pemphigoid from the pemphigus group and dermatitis herpetiformis. In this chapter we will focus on the historical milestones of autoimmune bullous diseases and illustrate historical research from The Netherlands. ‘Pemphigoid’ means ‘pemphigus-like’ and to review the history of pemphigoid, it starts with pemphigus. Before the introduction of the name bullous pemphigoid, the disease entity was termed ‘pemphigus vulgaris chronicus’ or ‘benign bullous pemphigus’, and considered a more benign form of pemphigus vulgaris. Moreover, until 1953 the term ‘pemphigus’ was used for all noncontagious bullous diseases, with the only exception of dermatitis herpetiformis of Duhring.

Hippocrates used the term ‘pemphigodes pyretoi’ to describe various feverish diseases, not necessarily related to bullous diseases. Pemphigus is derived from pemphix in Greek, meaning ‘blister’. Until early 1700’s the term pemphigus was used as synonym for symptoms of vesicles and blisters and not to describe a specific group of entities. François Boissier de Sauvages introduced the term ‘pemphigus’ in 1768 in his nosology for the description of bullous diseases. De Sauvages described five forms of pemphigus (major, castrensis, helveticus, indicus and brasiliensis) that were also based on the origin of reported patients and cannot be related to current classifications. In retrospect, König reported the first clinical description of a patient with pemphigus vulgaris, unaware of the disease at that time. It was Wichmann who described a patient with pemphigus vulgaris in 1791 in his ‘Beytrag zur Kenntnis des Pemphigus’ and used ‘pemphigus’ as name of the chronic bullous disease. He described remarkable details of ‘presence of flaccid blisters, and loosening of the epidermis without blister formation when pressure applied, resulting in eroded areas of the skin’. In 1896 this phenomenon was described by Nikolsky as a diagnostic feature in pemphigus, and still used nowadays. Between 1780 and 1850 dermatology started to branch of medicine. In that period there were two leading schools in Europe, the French school led by Alibert, Brocq and Darier, and the German-Austrian school with names as Auspitz, Hebra and Kohn-Kaposi. The schools initiated a stream of publications and descriptions of dermatological disorders, of which classification completely depended on these clinical-morphological reports. Here we describe the publications on bullous diseases in The Netherlands during that time.

Groningen 1810, Christoffel Wilhelm Eekhout - Dissertatio Medica Inauguralis de Pemphigo

During this period, the first professor at the medical faculty of the University of Groningen in the north of The Netherlands, Thomassen à Thuessink (Fig. 1), described patients with pemphigus at the Academic Hospital in Groningen around 1800 in his ‘Medical Observations 1804-1805’. In his opinion pemphigus deserved more study, because it was a rare and devastating disease with no reports yet in The Netherlands. He encouraged his apprentice Christoffel Willem Eekhout to study pemphigus in his thesis. Eekhout described the observed patients since 1800 and reviewed the earliest scientific reports of the disease. He found no evidence of a description of pemphigus before Hippocrates in Greek, Latin or Arabic. The disease, which was then reported as pemphigus, consisted of vesicles and blisters present on all body parts and of different sizes, which broke and left serous crusts. They reported an acute benign form, and a chronic lethal form with fever. According to their understanding, pemphigus was not contagious, but caused by blockage of the intestinal organs, disturbance of body fluids and consequently skin blistering as a replacement of renal excretion. However, they also raised doubts
about this well accepted hypothesis at that time of pemphigus due to renal failure, because one reported male patient urinated very well while having the skin blistering. In the name of science, Gaitskell had injected himself and others with blister fluid, which did not lead to provocation of pemphigus.

Although the concepts of immunology and autoimmune disease were still distant, around that time the local farmer Geert Reinders from Groningen performed breakthrough immunological experiments, that make him one of the founders of immunology. He conducted extensive experiments with vaccination in his cattle, the characteristic Groningen blisterhead cows. The name blisterhead was derived of the solitary coloured blisters surrounding the eyes (Fig. 2). At that time, rinderpest was a highly infectious disease with major outbreaks that decimated entire herds of livestock in the rural areas of Europe. Despite religious opposition, research was conducted to fight rinderpest by vaccination, with little success. Farmer Geert Reinders noticed that calves that were born of cows that had recovered from the disease, were immune. However, this immunity was only temporary, and he experimented with repeated vaccination until complete immunity was achieved. He was the first to make immunological experiments on a large scale and one of the first examples of maternally derived immunity and booster vaccination. The results of Geert Reinders were published in 1774 and 1776, years before Edward Jenner used the cowpox vaccine as an immunization for smallpox in humans.\textsuperscript{9}

\begin{figure}
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\caption{1807 Thomassen à Thuessink the first professor of the medical faculty of the University of Groningen. University Museum Groningen.}
\end{figure}
Following Eekhout, Arend Evertsz evaluated the classification and treatment of various types of pemphigus based on reported symptoms and complications. He described the inflammatory character of pemphigus with blisters on erythematous skin and with dolor, calor, tumor, rubor and sometimes unbearable itch. Often an adjective was used to describe different types of pemphigus. Hence, in 1829 Von Martius described 97 different types of pemphigus, bringing together many diseases of various etiology. Instead of pemphigus with or without fever, acute and chronic or benign and malignant, Evertsz and his promotor Thomassen à Thuessink abridged the classification to simple and complicated pemphigus. Thus far, the etiology of pemphigus was still unknown. Osiander described neonates with pemphigus, in whom the mother remarkably ate much herring during pregnancy, and hypothesized high concentrations of phosphoric acid in herring could lead to pemphigus. However, his experiments in persons with added high concentrations of phosphoric acid to herring did not provoke pemphigus. Pemphigus was considered to be a very dangerous disease. With longer duration of the disease, the imbalance of internal organs and body fluids could be fatal. Evertsz concluded pemphigus had three causes: 1) most commonly an abnormal urine excretion, 2) pemphigus following other skin diseases, or 3) excessive use of phosphoric acid. For the first cause, the pharmacist Evertsz advised treatment with alkali and water with calcium, soda and sulphur against kidney stones. Additionally, digitalis or belladonna could be used and he recommended an acid-free pemphigus diet.

Fig. 2 Groningen blisterhead cows, with coloured blisters surrounding the eyes. Painting by Karel Buskes, courtesy of M.F. Jonkman.
In the period following the thesis of Evertsz, the classification and differentiation of dermatoses became more clear and the number of diseases classified as pemphigus declined. The term pemphigus, originally describing a symptom of skin blistering, developed into a disease entity. However, the disease entity was not strictly defined and the etiology was still unknown. In 1844 Cazenave recognized a specific variant of pemphigus and thereby appended pemphigus foliaceus. Following this development, Hebra stated in 1860 that pemphigus was a chronic blistering disease, without an acute form of the disease. He introduced the term pemphigus vulgaris and distinguished pemphigus foliaceus based on the clinical symptoms. In 1886 Neumann described another new variant of pemphigus; pemphigus vegetans. In the following period also other bullous dermatoses were identified within the pemphigus group and subclassified, such as dermatitis herpetiformis by Duhring in 1884, lichen ruber pemphigoides in 1892 by Kaposi and pemphigus erythematosus in 1926 by Senear and Usher.

In 1915 Macleod was invited to open the discussion on pemphigoid eruptions in the Journal of the Royal Society of Medicine. Pemphigoid eruptions included dermatitis herpetiformis of Duhring and Dermatite polymorphe douloureuse of Brocq and was distinct from the pemphigus group. The main point of diagnosis was the differentiation of pemphigoids from chronic pemphigus, and the important question whether they represented a distinct entity or simply a variant of common disease. He argues the term ‘pemphigoids’, introduced by Besnier in the literature, was a somewhat unfortunate one. Pemphigoids signified an eruption that char-
acterised only a phase of bullae during the disease course. Another descriptive term used by Hebra was pemphigus pruriginosus, indicating the importance of the symptom of pruritus. Macleod analysed more than one hundred cases of pemphigoid eruptions, and was struck by the small advances in their knowledge of the pemphigoids that were made in the last decades. He described a multiformity in eruptions, such as prurigo-like papules, papulo-vesicles and bullae. The intensity of pruritus was an essential feature of the diseases. In his experience, the pruritus was so intense that the pain of digging out a papule with the fingernail was preferable to it. When the pemphigoid eruption was profuse with intense pruritus, some patients may had benefit from local antipruritic applications containing menthol or lead, or a vegetarian diet.

Since Hebra in 1860, not many new insights were known about the etiology of pemphigus of pemphigoids and the lack of knowledge was a problem for treatment. Pemphigus and dermatitis herpetiformis were considered to be strongly related, because of the clinical similarities. In contrast to this theory of the German-Austrian school, the dermatologists of the French school preferred to distinct both entities, mainly based on the histological findings of Civatte and cytologic studies of Tzanck. In 1943 Civatte reported histological studies in which he concluded that dermatitis herpetiformis and pemphigus vulgaris could be separated, based on the observation of acantholysis. Civatte described intra-epidermal separation in pemphigus vulgaris, by loss of intercellular connections in epidermal cells. Acantholysis was solely present in pemphigus, in dermatitis herpetiformis he found a subepidermal localisation of the blister without acantholysis. The French school followed the view expressed by Brocq, and recognized only two chronic blistering diseases: pemphigus with acantholysis and dermatitis herpetiformis with subepidermal blisters without the acantholysis. Brocq emphasized the polymorphous spectrum of dermatitis herpetiformis beyond the definition by Duhring, including presence of disseminated bullae. Therefore, he proposed the term ‘dermatite polymorphe prurigineuse chronique à pousées successives’ instead of dermatitis herpetiformis. Therefore, for a long time in France dermatitis herpetiformis was called ‘dermatite polymorphe douloureuse Duhring-Brocq’. In line with the French view, the fundamental publication by Civatte describing acantholysis in pemphigus was entitled ‘Diagnostique de la dermatite polymorphe douloureuse ou maladie de Duhring-Brocq’ and not mainly focused on the important aspect of differentiation of pemphigus. Acantholysis was previously mentioned by Auspitz in 1881, but at that time not recognized as an important clue for diagnosis of pemphigus and not further studied within the German school. In The Netherlands, Theodorus Nelemans studied pemphigus and dermatitis herpetiformis in his thesis, mainly focused on histopathology and with attention to the theories of a viral etiology.

GRONINGEN 1951, TH.G. NELEMANS - PEMPHIGUS VULGARIS AND DERMATITIS HERPETIFORMIS DUHRING. A ETIOLOGICAL, HISTOLOGICAL AND CYTOLOGICAL STUDY.

At this time, three clinical variants of pemphigus were distinguished; pemphigus vulgaris, pemphigus foliaceus and pemphigus vegetans. Of more rare clinical variants the inclusion in the pemphigus group was not certain, however, criteria for the disease were not established yet. The developments in microbiology gave researchers opportunities to prove micro-organisms as a cause of dermatoses, and in other dermatoses a viral etiology. It was known that pemphigus was not contagious, nor hereditary. Nelemans described in his own histopathological studies in pemphigus vulgaris both intra-epidermal blistering with local acantholysis, as well as subepidermal blistering without acantholysis. Therefore, he recommended to separate both forms,
because they might have different etiology. He thought acantholysis was not ‘la lésion élémentaire histologique’ as described by Civatte, but secondary to intercellular spongiosis. He recommended more research to acantholysis and the alterations of tonofibrils, and whether subepidermal blistering with acantholysis could also occur. After reviewing the literature, replication of other studies and performing his experiments with blister fluid, blood and urine samples, Nelemans concluded that there were no indications of a viral etiology of pemphigus vulgaris and dermatitis herpetiformis.

In the period of 1943 to 1953 the important separation in the pemphigus group was made by Civatte and Lever. With the discovery of acantholysis Civatte had separated the pemphigus group from subepidermal bullous dermatoses.20 Already in 1940 Lever emphasize the existence of an acute and a chronic form of pemphigus. He stated ‘Acute pemphigus may be distinguished from chronic pemphigus clinically by the early development of lesions in the mouth, a rapid fulminating course, and a high racial susceptibility. Chronic pemphigus, on the other hand, progresses slowly and may have prolonged asymptomatic periods. Death usually occurs from a complication due to high age or lowered resistance.1 After the reports of Civatte, Lever found acantholysis exclusively in these distinct patients with pemphigus vulgaris acutus. Moreover, the subepidermal blisters were only present in the patients with pemphigus vulgaris chronicus. However, the clinical features of these patients with pemphigus vulgaris chronicus were different than dermatitis herpetiformis. Therefore, he identified the disease as an independent entity termed ‘benign bullous pemphigus’, or later ‘bullous pemphigoid’. He separated bullous pemphigoid from the pemphigus group and dermatitis herpetiformis, based on clinical and histological findings.1 Lever stated that pemphigus vulgaris was a lethal dermatosis with intra-epidermal blistering and acantholysis, while bullous pemphigoid had a better prognosis and was accompanied by subepidermal blistering. Because of the high morbidity, pemphigus belonged to the ‘grandes dermatoses’ and various treatments were tested, without substantial improvement. After reports in the literature about surprising results of adrenocorticotropic hormone (ACTH) and cortison in patients with rheumatoid arthritis and other diseases, this was studied by Pieter van Aken in 14 patients with pemphigus in Utrecht.

**Utrecht 1954, Pieter van Aken - Treatment of pemphigus with ACTH and cortison.**

Up till now, no effective treatment for pemphigus was available and the disease course left patients in agony. The most commonly used drugs was germanine, besides arsenicum, sulphur and antibiotics. The introduction of adenocorticotropic hormone (ACTH) and cortison in 1950 was a revolution in treatment of pemphigus. The first studies reported spectacular improvement of pemphigus, but also the considerable side effects. Van Aken reported improvement as soon as one to two days, disease control in four to seven days and remission before four weeks and with a negative Nikolsky sign.23 However, patients with pemphigus could not be cured and Van Aken recommended to titrate the dosage of ACTH and cortisone to have the minimal and effective dosage to reduce side effects.

The differentiation of bullous pemphigoid from pemphigus and dermatitis herpetiformis led to a new scientific discussion of the existence and nomenclature for the group of subepidermal autoimmune bullous diseases. Different views were expressed, a series of 20 patients from the United States published in 1953 supported the existence of bullous pemphigoid.24 Others opposed the idea and suggested nonacantholytic subepidermal bullae in pemphigus.25,26 In Great Britain Rook and Waddington published 38 cases of bullous pemphigoid in 1953. They
favored the plain term ‘pemphigoid’ already meaning ‘pemphigus-like’, and pointed out bullous pemphigoid was a tautology; saying the same thing twice. Following these publications, Prakken and Woerdeman reported 16 adults and three children from The Netherlands with bullous pemphigoid. However, they suggested the term ‘parapemphigus’ instead of bullous pemphigoid, since the latter was an adjective and not a noun. The term parapemphigus was only used in The Netherlands and Germany, and still used by some. Within the German-Austrian school, uncertainty prevailed of the differentiation of bullous pemphigoid. Authors referred to bullous pemphigoid as ‘old age pemphigus’, or ‘pemphigus vulgaris of the dermatitis herpetiformis type’ as a bullous variant of dermatitis herpetiformis located between dermatitis herpetiformis and pemphigus.

A few years later, in the discussion on bullous dermatoses at the 11th International Congress of Dermatology in Stockholm in 1957, the French group stated that bullous pemphigoid represented a bullous variant of dermatitis herpetiformis. They referred to the histologic findings of Civatte and retained in line with Brocq’s views of the polymorphous disease. Others accepted the existence of bullous pemphigoid and concluded that the division of dermatitis herpetiformis of Duhring from bullous pemphigoid of Lever was justified. Another discussion took place regarding the term herpes gestationis, that was used for a subepidermal autoimmune bullous disease exclusively found in pregnant women and post-partum. The clinical observation of herpes gestationis was earlier described by others, such as Hebra describing ‘pemphigus hystericus’ with the occurrence of the eruption during pregnancy, and remission within short time after delivery. The disease is nowadays termed pemphigoid gestationis, and may persists to a chronic form of bullous pemphigoid. In the time following, bullous pemphigoid became generally accepted as being different from pemphigus vulgaris because of the absence of acantholysis. With the breakthrough of immunofluorescence microscopy for diagnostic classification, the diseases were classified as autoimmune diseases and confirmed to have different types of antibodies, with intercellular bound antibodies in pemphigus first described by Beutner and Jordon in 1964 and subepidermal bound antibodies in bullous pemphigoid discovered by Jordon in 1967. Subsequently autoimmune bullous diseases were further classified and specified using immunofluorescence microscopy, and the previously reported clinical and histopathological findings of certain bullous diseases were confirmed to be specific entities.

UTRECHT 1972, JAN BARELD VAN DER MEER - DERMATITIS HERPETIFORMIS A SPECIFIC (IMMUNOPATHOLOGICAL?) ENTITY. In 1969 Jan Bareld van der Meer reported immunofluorescence microscopy findings in 59 patients with dermatitis herpetiformis and bullous pemphigoid, and discovered that different types of in-vivo bound immunoglobulines differentiated the diseases. In patients with dermatitis herpetiformis granular depositions of IgA were seen in the dermal papillae of the basement membrane zone, while a homogeneous staining pattern of IgG in the basement membrane zone was observed in pemphigoid. Later on, he was appointed head of department in Groningen and introduced the expertise in immunology and ‘grandes dermatoses’ continued nowadays at the Groningen Center for Blistering Diseases. Further differentiation followed of two bullous diseases with solely IgA staining along the basement membrane zone by direct immunofluorescence; with linear staining found in Linear IgA Disease, and with granular papillary staining in dermatitis herpetiformis described by van der Meer. A few years earlier in 1966, Marks described that many patients with dermatitis herpetiformis had concomitant intestinal malabsorption (gluten-sensitive enteropathy), which was absent in patients with bullous pemphigoid.
would take more than 30 years until this link could be further explained with the identification of epidermal transglutaminase as the autoantigen of dermatitis herpetiformis, with an isotype of tissue transglutaminase causing the associated gluten sensitive enteropathy.\textsuperscript{38,39}

In 1971 Roenigk established clinical criteria for the entity of epidermolysis bullosa acquisita (EBA), with the name of the subtype derived from the original view of EBA as a disease resembling hereditary recessive dystrophic epidermolysis bullosa.\textsuperscript{40} In addition to immunofluorescence microscopy, the technique of immuno-electron microscopy allowed to study the ultralocalisation of immunodepositions in bullous diseases. Thereby, EBA could be distinguished from bullous pemphigoid showing IgG depositions within and below the lamina densa.\textsuperscript{41,42} Subsequently, two clinical phenotypes of EBA were distinguished by Gammon in 1982 with the original description of mechanobullous EBA with scarring and milia at extensor skin surfaces, and an inflammatory form of EBA resembling bullous pemphigoid.\textsuperscript{43} Of other differentiated subtypes, Tufannelli already found that the bullous eruption in patients with systemic lupus erythematosus (SLE) could be placed within the spectrum of subepidermal autoimmune bullous diseases, and findings of direct immunofluorescence and immuno-electron microscopy revealed a deposition pattern similar to EBA in patients with bullous SLE.\textsuperscript{44-46} Similarly, the specific immunofluorescent findings in lichen planus pemphigoides were described in 1981 by Souteyrand.\textsuperscript{47}

The breakthroughs in diagnosis of autoimmune bullous progressed in identification of distinct subtypes, illustrated in Fig. 4 as the tree of autoimmune bullous diseases resembling Alibert’s L’arbre des Dermatoses. Clinical reports of patients still remained valuable for the understanding of the diseases. Various authors describe the ‘enigma of bullous pemphigoid and dermatitis herpetiformis’ and point out that the classical direct and indirect immunofluorescence findings are not always seen with typical skin blistering, but may resemble dermatitis herpetiformis.\textsuperscript{48-50} Approximately twenty-five years after the introduction of bullous pemphigoid by Lever, more patients are being reported with atypical forms of bullous pemphigoid without skin blistering, such as papular pemphigoid, pemphigoid nodularis and generalized pruritus with an eczematous rash.\textsuperscript{51-55} Barriere even described patients with pruritus ‘sine materia’ preceding the diagnosis of bullous pemphigoid. Moreover, Asbrink and Barker mention that besides the urticarial prodromal lesions, pruritus and an eczematous prodromal eruption may precede the blister development for months and may cause misinterpretation in patients with bullous pemphigoid. Barker concludes that the disorder deserves more attention related to pruritus in elderly, and that further studies are needed to the long duration of prodromal pruritus. In addition, Bingham reported eight elderly patients with prolonged pruritus preceding the diagnosis of BP with a mean of 10 months. The authors also reviewed the detection of serum IgG autoantibodies against the basement membrane zone by indirect immunofluorescence in patients with bullous pemphigoid, as a screening or diagnostic test. They reported the false-positive detection of autoantibodies in elderly with pruritus and conclude it is not indicative for diagnosis of bullous pemphigoid, and direct immunofluorescence may permit an early diagnosis in these cases.\textsuperscript{56}

Developments of new diagnostic techniques immunoblot and indirect immunofluorescence on 1.0 M NaCl split human skin enabled to further differentiate the group of subepidermal autoimmune bullous diseases. The use of 1.0 M NaCl split human skin as a substrate for indirect immunofluorescence increased the sensitivity for detection of low concentrations of autoantibodies. Moreover, the technique enabled to differentiate autoantigens in the epidermal or dermal part of the basement membrane zone.\textsuperscript{56} Using immunoblot, also the molecular
autoantigens were identified of different subtypes of pemphigoid diseases, such as the hemidesmosomal proteins BP230 (BP antigen I) and BP180 (BP antigen II) in bullous pemphigoid, in EBA type VII collagen in the anchoring fibrils and later on the extracellular part of BP180 LAD-1 in linear IgA disease by Pas from Groningen. In the following years the autoantigens of new and more rare variants of pemphigoid diseases were identified. In 1992 Domloge-Hultsch found antibodies in patients with cicatricial mucous membrane pemphigoid against laminin 5 (now termed laminin 332), within the lower lamina lucida/lamina densa and different from the sublamina densa depositions in EBA. In 1996 Zillikens and Chen described patients with a bullous eruption and with circulating autoantibodies against a 200-kDa protein located low in the epidermal basement membrane zone, termed anti-p200 pemphigoid. The sera of the majority of patients with anti-p200 pemphigoid was later found to recognize laminin γ1, with a suggested denomination to laminin γ1 pemphigoid. However, the relevance of anti-laminin γ1 autoantibodies in the pathogenesis has not yet been elucidated. Reports of autoantibodies against other antigens, such as epiplakin, p105, plectin or 168-kDa antigen, were limited or not
New serological diagnostic techniques have emerged for subtyping pemphigoid diseases, such as commercially available ELISA using recombinant forms of the proteins of target antigens BP180, BP230 and type VII collagen. Moreover, the diseases activity and risk of relapse can be indicated by measuring serum concentrations of autoantibodies. Besides the known relationship with ageing, associations have been found between bullous pemphigoid and neurodegenerative diseases, mainly dementia. The strong association could be hypothesized by an age related loss of self-tolerance of the immune system, with autoantibodies against neuronal and cutaneous antigens.

Diagnosis of pemphigoid diseases can be challenging, especially in ‘atypical’ cases when the characteristic skin blisters are absent. As discussed by Macleod in 1915, the diagnosis and classification of the polymorph pemphigoid eruptions are still matter of discussion. Recent changes in perception of the clinical spectrum of pemphigoid are exemplified by the variety of names for nonbullous clinical presentations of the same disease, such as pruritic non-bullous pemphigoid. The original name of bullous pemphigoid by Lever is a tautology, with pemphigoid derived from Greek meaning ‘form of a blister’. Therefore Rook and Waddington proposed to use the plain term ‘pemphigoid’ directly after its initiation. The more recently proposed alternative adjective ‘cutaneous’ pemphigoid by Borradori and Joly could be seen as a phenotypic description comprising various pemphigoid diseases with predominant cutaneous features at one end of the spectrum, opposing mucous membrane pemphigoid at the other end of the spectrum of the group of pemphigoid diseases. Although etymologically flawed, we simply append nonbullous pemphigoid to bullous pemphigoid to comprise the complete spectrum of pemphigoid. The new insights of today may indicate a new concept of pemphigoid in future, of a pruritic cutaneous autoimmune disease that is more than skin deep.

Back to the stable of farmer Geert Reinders from Groningen, besides the characteristic blisterhead cow also the whitehead cow could be found there. Being identical species, the only difference is the phenotype of absence of the typical 'blisters'. Based on estimations of that time the whitehead was more prevalent than the blisterhead, possibly with a similar prospect of nonbullous pemphigoid compared to the original bullous pemphigoid.
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