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Review

Historic overview of allergy research in the Netherlands

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ABSTRACT

Research in allergy has a long history in the Netherlands, although the relation with immunology has not always been appreciated. In many aspects Dutch researchers have made major contribution in allergy research. This ranges from the first characterization of house dust mite as an important allergen, the first characterization of human Th2 and Th1 T cell clones, to the development of diagnostic test systems. In this overview Aalberse and Knol have made an overview of the major contributions of Dutch immunologists in allergy.

1. Introduction. Linking allergology and immunology. The pre-IgE era

The relation between allergology and immunology has had its ups and downs. In the first two decades of the 20th century, when the concept of allergy was established, a relation with immunity and antibodies was generally assumed. This was to a large degree due to the fact that many allergic reactions were a side effect of the therapeutic use of animal antiserum, a condition in which precipitating antibodies were easily demonstrable. This situation changed when Coca and Cooke wrote in 1920 in The J Immunology an influential paper on the distinction between anaphylactic allergy and atopic allergy. One of the main points was that in atopic allergy (with hay fever as the prototype) no antibody was involved, but a mysterious heat labile substance, which they named the "atopic reagin". This created a demarcation between atopic allergy and immunology. It took 45 years before the link between allergy and immunology was reestablished.

For an extensive overview of the early history of Allergy worldwide, with all the references, see [1]. The most prominent Dutch pioneers in the pre-IgE era of allergology were Storm van Leeuwen, Voorhorst and Berrens. Their focus of research (with skin tests as their major tool) was mostly on indoor allergens, i.e. house dust.

Storm van Leeuwen was famous for his studies with allergen-free rooms. In his critical and informative state-of-the-art paper of 1932 (regrettably written in Dutch) he promotes the 10% rule for ideal allergen extracts: no more than 10% false-negatives, no more than 10% false-positives [2]. It is a sobering thought that many extracts currently in use do not achieve this (seemingly modest, but possibly unrealistic) ideal.

Voorhorst and his coworkers M. and F Spieksma became famous by their identification of the house dust mite. For an historical overview, see [3]. Voorhorst was also much interested in the skin test reactivity in human dander extracts, which he considered to be a prototypic form of auto-allergy, reviewed in [4]. It took many years before another contributor to the skin test reactivity of human skin scales became established: proteins derived from a lipophilic yeast currently usually referred to as the Malassezia family [5,6]. Because IgE to this yeast is almost exclusively found in patients with atopic dermatitis, whereas in Voorhorst's studies skin test reactivity to human dander is often also found in atopic patients without dermatitis, it is still open whether this skin test reactivity is partially due to auto-allergy. This issue is also relevant in relation to the IgE-dependent histamine-releasing factor, discussed below.

Berrens, a chemist by training, had a very different view on allergens. Based on his work with Bleumink on the skin test reactivity of the cow's milk protein beta-lactoglobulin (published in 1966 in Nature [7]) he proposed that allergenicity of all allergenic proteins was due to a modification of the protein structure by a non-enzymatic glycation reaction known as the Maillard-reaction. According to the Berrens hypothesis "the house dust allergen" was allergologically indistinguishable from the cat allergen or any other allergen. The relevance of mites was a matter of fierce discussions between Berrens and Voorhorst. The achievements of Storm van Leeuwen and Voorhorst have been described elsewhere

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[1,3,8]. History has been less kind to Berrens. This was mainly because of his innate tendency to attack scientific orthodoxy and the urge to formulate highly original alternative views in an eloquent and scientific, but also dismissive to anyone unconvinced, way. Unfortunately, the Maillard hypothesis became untenable upon the appearance of monoclonal anti-allergen antibodies and recombinant allergens. There is still a possibility that the Maillard-modification (now known as Advanced Glycation Endproducts, AGE, with a corresponding family of receptor proteins cold RAGEs) may be a relevant factor of allergenicity, but this is unlikely to be a major contributor in the initiation phase and is certainly not required for the elicitation phase. Berrens also postulated a unique mode of complement activation by atopic allergens, with a potent house dust fraction as the prototypic complement activator [9–12]. One hallmark of this process was that only human (but not guinea pig) complement was active. This house dust effect was confirmed by Van der Zee [13], but was found to be due to soluble polysaccharides from house dust rather than by allergenic proteins. This property was shared with soluble bacterial polysaccharides, with IgM as an important factor [14]. A recent study in food allergy indicated that complement plays a role in the binding of allergen on B cells via IgG [15] indicating that the role of complement in allergy might be more widely implicated than anticipated before.

With the discovery of IgE in 1966 by Ishizaka and by Johansson, and the development of the RadioAllergoSorbent Test (RAST) by Wide, Bennich and Johansson in 1967, (for references see [1]), tools became available to investigate the allergenicity of house dust from a different perspective. Using sera selectively positive for mites or cats and performing inhibition of IgE binding to house dust extract by cat and mite extracts, it was found that both mite and cat allergens were found in all Dutch dust extracts, albeit in different ratios [16]. Neither Voorhorst nor Berrens accepted these results as relevant for clinical allergy. Berrens because at that time (early seventies) he did not accept that IgE was relevant, Voorhorst because he did not accept the finding that cat allergens were found in almost all dust samples, including in dust from houses without cats.

Even so, thanks to the discovery of IgE and the availability of IgE tests, the link between allergology and immunology was re-established. But not always whole-heartedly, as is expressed well by the guest editorial on "Allergy and Immunology: wedding of love or marriage of convenience? (A modern medical tale)" [17].

2. Allergen characterization

The Dutch contribution to the history of allergen biochemistry was initially based primarily on RAST inhibition. This was a spin-off of the RAST, which was developed as a very efficient diagnostic test by Wide, Bennich and Johansson in Uppsala in 1967. After a very hospitable and helpful visit in 1970 to Gunnar Johansson in Uppsala, Aalberse introduced the test in Amsterdam at the Central Laboratory of the Blood Transfusion Service CLB (now Sanquin). The test required affinity purified anti-IgE for labeling with ^{125}I, and thus a source of purified IgE. In the absence of a Dutch source of monoclonal IgE, polyclonal IgE was purified (by affinity chromatography) from several liters of plasma from 2 helminth-infested patients [18]. The RAST was performed with a slight modification of the Uppsala protocol: the allergen was coated to CNBr-activated Sepharose-beads in suspension, rather than to cellulose particles or paper discs. This had two advantages. Firstly the high binding capacity of the Sepharose beads (typically 5 μg protein per test) allowed the testing of crude allergen extracts, including house dust extract. Secondly, the suspension could be titrated to optimize the reaction conditions for use in RAST inhibition.

The obvious disadvantage of the use of a suspension of beads was the need to centrifuge the test tubes (nine times). This manual procedure might seem to be incompatible with high throughput testing, but the diagnostic department at the CLB was able to run well over a 1000 test/day. This large-scale diagnostic testing resulted in a statistical analysis of 150 000 sera tested in the period 1983–1990 on a panel of five or six (for children) allergens, showing a small, but statistically significant "horoscope" effect, not only for seasonal allergens but also for perennial allergens, with sensitization to cat, dog, egg and milk being more prevalent in patients born in wintertime (possibly reflecting a protective role of vitamins A and/or D in the first half year of life, or an unfavorable role during the second half year of life) [19]. Of even more interest was the availability of a wide range of sera with interesting IgE specificities. As an alternative to the bead suspension technology a macro-bead procedure was developed in 1986 [20]. It involves the prior modification of the allergen with a hapten (or biotin). The serum is incubated with the hapten-conjugated allergen in fluid phase. The allergen (with or without antibody attached) is next extracted by added a single macro-bead (7 mm diameter polystyrene) coated with anti-hapten antibody (or streptavidin). IgE bound to the bead is detected as usual with labeled anti-IgE. Presumably because of the fluid-phase conditions, this technology was found to give much more sensitive and accurate RAST-inhibition profiles.

The allergenic activities in house dust offered interesting scientific challenges that were studied with the combined use of RAST and RAST inhibition. This resulted in the identification of food remnants, such as egg and milk proteins, as neglected contributors, even if it is still unclear how much of these settled allergens will become airborne in domestic situations [21]. A similar argument holds for allergenic activity derived from invertebrates other than mites. The common source of house dust is the content of a vacuum cleaner bag. Dead insects contain IgE-reactive substances, much of which is due to muscle proteins such as tropomyosin [22]. It is obviously relevant to take into account that these muscle proteins are often cross-reactive with IgE induced by the consumption of shrimp [23]. IgE reactivity to house dust extract is occasionally idiosyncratic, reacting preferentially with house dust of the IgE donor. The specificity of IgE of one such patient (Ka), has so far remained a mystery, despite testing hundreds of allergen sources materials and despite the help of intrigued colleagues all over the world. Observations like this indicate the ongoing need to be able to perform autologous house dust RASTs [24].

For the characterization of allergens in other source materials, the traditional physicochemical approach has been used successfully for peanut allergens by Koppelman et al. [25–27]. Even if recombinant technologies have largely replaced protein-based characterization, the need to keep a close watch on the structure of allergens and their post-translational modifications as obtained from their natural sources is illustrated by several Dutch peanut studies [28–30].

As mentioned in the introduction, Voorhorst was much interested in the skin test reactivity of extracts of human dander. This activity suggested the presence of an autoallergen, even if the presence of Malassezia derived allergens in these extracts is a complicating factor. Another potentially relevant factor was described by Susan MacDonald in 1987: the IgE-dependent Histamine-Releasing Factor (HRF) [31]. This macrophage-derived factor was described as (1) inducing basophil degranulation in an IgE-dependent way, (2) being distinct from classical allergens and (3) discriminating between two types of IgE, called IgE^{+} and IgE^{-}. A protein with some of these activities was purified, sequenced and identified as a protein known as Translationally Controlled Tumor Protein (TCTP) [32]. Studies by Pasmans [33,34] and Kleine Budde [35] confirmed the presence of IgE-dependent HRF activity of supernatants of activated monocytes, but indicated that these supernatants contain in addition variable amounts of the chemokine MCP-1, which has a potent basophil-priming activity