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Review

Inflammatory responses to infection: The Dutch contribution

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This paper is dedicated to Professor Joep Lange, a Dutch pioneer in AIDS research and a great protagonist of access to effective antiretroviral therapy for all. On July 17 this year, Joep died in the plane crash in Ukraine on his way to the AIDS conference in Australia.

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A B S T R A C T

At any given moment, our body is under attack by a large variety of pathogens, which aim to enter and use our body to propagate and disseminate. The extensive cellular and molecular complexity of our immune system enables us to efficiently eliminate invading pathogens or at least develop a condition in which propagation of the microorganism is reduced to a minimum. Yet, the evolutionary pressure on pathogens to circumvent our immune defense mechanisms is immense, which continuously leads to the development of novel pathogenic strains that challenge the health of mankind. Understanding this battle between pathogen and the immune system has been a fruitful area of immunological research over the last century and will continue to do so for many years.

In this review, which has been written on the occasion of the 50th anniversary of the Dutch Society for Immunology, we provide an overview of the major contributions that Dutch immunologists and infection biologists have made in the last decades on the inflammatory response to viral, bacterial, fungal or parasitic infections. We focus on those studies that have addressed both the host and the pathogen, as these are most interesting from an immunological point of view. Although it is not possible to completely cover this comprehensive research field, this review does provide an interesting overview of Dutch research on inflammatory responses to infection.

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1. Introduction

Originally, the immune system of multicellular organisms evolved for the defence against microorganisms. During their evolution, vertebrates and especially mammals developed a very sophisticated immune system consisting of an innate and an adaptive arm. Despite this sophistication, pathogenic microorganisms may win the battle, in the worst case leading to death of the mammalian host.

The insight of scientists in the pathophysiology of infection and in host defence emerged slowly over the past centuries. Although the Dutch inventor of the microscope, Antoni van Leeuwenhoek, had discovered microbes around 1675, and the visionary scholar Girolamo Frascoro had postulated seminaria (small seeds or “germs”) as causes of communicable diseases already in 1546, the microbial discoveries of Pasteur and Koch were needed to establish the microbial pathogenesis of infectious diseases. Dutch scientists, especially those of the “Delft school” (Beijerinck, Kuyper, Van Niel), delivered important contributions in the early days of microbiology, i.e. during the end of the 19th century and the first decades of the 20th century [1]. In fact, it was Martinus Beijerinck who introduced the term “virus” in 1898, for the filterable agent infecting tobacco plants, which he called ‘contagium vivum fluidum’ and which is now known as tobacco mosaic virus [2].

Relevant discoveries in especially parasitology were made by scientists (Swellengrebel, Schüffner) in The Netherlands East Indies (Indonesia) in the first half of the twentieth century [3]. However, significant research dealing with the host immune response to infection, following the work of Ehrlich, Metchnikoff and von Behring, was not performed in The Netherlands. Vaccine development and antiserum production, “applied immunology”, had started in 1919 in The Netherlands, coming to full bloom after 1953 under the leadership of Hans Cohen.

In this paper, which was written on the occasion of the 50th anniversary of the Dutch Society for Immunology, we describe the major research activities and accomplishments of research dealing with the immunology of infectious diseases in The Netherlands, during that era. Although separating this area of immunological research from other areas is artificial, we had to be rather strict in our selection, i.e., to be included in this overview, research had to
deal with both host and pathogen for a paper to be included. To
develop the lists of major contributions to immunological progress
(depicted in Tables 1-4), we had several brainstorm meetings, inter-
views, and performed searches in PubMed. This led to a long list of Dutch
scientists that were felt to have significantly contributed to the under-
standing of the immunology of infection, thereby focusing on research
that was also performed in The Netherlands. Our next step was to contact these people and ask them to provide us with
no more than 3 of their most contributory publications. With this
information, using the premises formulated above, we were able
to construct the tables below. We chose not to go for a bibliomet-
ric approach for a number of reasons. First of all, the bibliometrics
in this field appears to be flawed by rather arbitrary listing in one
of the following fields: immunology, microbiology, infectious dis-
ees, public health, and medicine. Secondly, the real impact of
articles is often difficult to assess. A certain idea or concept may not
be readily taken up, or even may be captured by others. Also the
publication habits have profoundly changed over the past decades.

When we had gathered the articles that we wanted to include in
this review, an important dilemma was how to order these

| Virus | Year | Findings | Reference |
|-------|------|----------|-----------|
| HIV   | 1988 | Experimental induction of early-type specific antibodies against HIV-1 | [5] |
|      | 1992 | Deletion of antigen-reactive T cells in HIV-1 infection is driven by aspecific T cell activation | [8] |
|      | 1995 | HIV-1-specific CD8 T cells do not protect against the progression of HIV-infection to AIDS | [7] |
|      | 1996 | Initial viral rebounds during HIV-1 suppression caused by treatment-induced CD4 T cell increase | [12] |
|      | 1996 | CD4 T cell loss in HIV-1 infection is not due to proliferation-induced exhaustion | [4] |
|      | 1998 | Extracellular granzymes A and B present in plasma and increases upon HIV-1 and EBV infection | [126] |
|      | 2000 | Identification of DC-SIGN and molecular mechanism how HIV-1 transmission by DCs occurs | [13, 127] |
|      | 2000 | HIV-1 varients using coreceptor CXCR4 accelerate CD4 T cell loss by infecting naive T cells | [6] |
|      | 2000 | T-cell proliferation and deletion in HIV-1 is a consequence of generalized T cell activation | [9] |
|      | 2007 | Langerhans cells are protected from HIV-1 infection by the C-type lectin receptor langerin | [14] |
|      | 2009 | Sugar-specific signaling through DC-SIGN shapes immunity to viruses and bacteria | [15] |
|      | 2010 | HIV-1 variants with long variable loops in envelope escape antibody neutralization | [10] |
|      | 2010 | Cross-reactive neutralizing antibodies do not protect against disease progression in HIV-1 | [31] |

Influenza 1999 | Polyclonal memory T cell populations to influenza provide protection against a range of viral variants | [16] |
| 2005 | Innate immune response during Influenza A infection is associated with disease severity | [27] |
| 2008 | Development of human antibodies with broadly neutralizing capacity against influenza | [22] |
| 2009 | CD200-CD200R interactions attenuate T cell-mediated immune pathology upon influenza infection | [25] |
| 2009 | Constitutive costimulation through CD27 impairs CD8 T cell memory to influenza | [24] |
| 2011 | Discovery of functional intraepithelial CD8 T cells against influenza in human lung | [17] |
| 2011 | Recall T cell responses peak within 1 week after the start of influenza | [18] |
| 2011 | Costimulation through CD27 regulates T cell cross-reactivity against influenza variants | [19] |
| 2011 | Development of human antibodies with broadly neutralizing capacity against influenza | [23] |
| 2012 | CD200R ligation inhibits TLR7 signaling and IFN production, without affecting influenza infection | [26] |
| 2013 | Low pathogenic influenza strains induce NK cell responses, but high pathogenic strains do not | [20] |
| 2014 | Nasal vaccination to influenza with bacterium-like particles induces TLR2-dependent immunity | [21] |

CMV 1992/95 | Virus-specific T cell responses in blood correlates with clinical responsiveness to CMV | [28, 29] |
| 2003 | Importance of CD4 T cells in primary response to human CMV | [30] |

EBV 2003 | EBV gp42 contributes to immune evasion by blocking TCR-MHCII interactions | [32] |
| 2007 | Early EBV lytic cycle gene BNLF2a prevents CTL-mediated lysis by interfering with the TAP complex | [33] |
| 2007 | EBV impairs protein synthesis in infected cells through BGLF5-induced mRNA degradation | [34] |
| 2012 | CD27 deficiency is a combined immunodeficiency with persistent symptomatic EBV viremia | [31] |
| 2014 | EBV attenuates TLR signaling through the deubiquinatase activity of BPLF1 | [35] |

HPV 1995 | Eradication of HPV-induced tumors in mice by vaccination with a subdominant CTL epitope from HPV | [36] |
| 1995 | Identification of immunogenic peptides from HPV16 E6 and E7 that can be used for vaccination | [37] |
| 1996 | Evidence for natural immunity against HPV16 epitopes in patients with HPV16+ cervical lesions | [38] |
| 1999 | Only cervical precursor lesions with a persistent HPV infection show progression to cancer | [39] |
| 2009 | Vaccination with long peptides from HPV16 can induce remission of HPV-induced lesions | [40] |

Other 1977 | Cellular immune response to vaccinia virus in humans is associated with HLA | [41] |
| 1978 | Measles virus can enter and be activated inside resting lymphocytes | [42] |
| 1988 | Sensitivity to lymphomas by murine leukemia virus is determined by MHCII-regulated immunity | [128] |
| 1995 | Successful immunotherapy with CD8 T cells directed against an epitope in an adenosar protein | [129] |
| 2010 | SARS in aged macaques show exacerbated innate response; type I IFN as potential intervention | [43] |
| 2010–13 | IFN-y-production upon LCMV infection dramatically alters hematopoiesis in bone marrow | [48–50] |
| 2012 | Double-stranded RNA upon cellular infection with picornavirus is recognized by MDA5 | [45] |
| 2013 | Antibodies in camels to Middle East respiratory syndrome coronavirus indicate widespread infection | [44] |
| 2013 | The deubiquinatase activity of PLP2 from arterivirus inhibits innate immune signaling | [47] |
| 2014 | Enteroviruses repress transcription of IFN genes through cleavage of MDA5 and MAVS | [46] |

2. Viral infections

In Table 1, contributions to host and virus interactions are pre-
Table 1. The effects of antigenic variation, the non-protective anti-
Table 1. Viral infections

In Table 1, contributions to host and virus interactions are pre-
studies. Other important contributions have been made at the level of receptors that mediate HIV transmission to either dendritic cells (DCs) or T cells [13–15].
| Table 2 | Host/bacterium interaction. |
|---------|-----------------------------|
| Bacterium | Year | Findings | Reference |
| Staphylococcus | 1979 | Intracellular killing of bacteria by monocytes requires extracellular Igs and complement | [51] |
| | 1983 | Differential role of monocytes and granulocytes during course of Staphylococcus endocarditis | [52] |
| | 1990 | Bacterial iron contributes to oxidative killing of S. aureus | [53] |
| | 1996 | The complex clinical course of S. aureus bacteremia is not due to a relative lack of specific opsonins | [54] |
| | 2005 | Staphylococcal complement inhibitor decreases bacterial phagocytosis and killing by neutrophils | [55] |
| | 2009 | Staphylococcal SSL is immunomodulatory by targeting several stages of leukocyte extravasation | [56] |
| | 2013 | Staphylococcal toxin leukocidin targets C5a receptors, thereby regulating bacterial virulence | [57] |
| Neisseria | 1992 | The T cell repertoire against meningococcal OMP is more diverse than assumed | [58] |
| | 1994 | Fulminant meningococcal sepsis is associated with downregulated ex vivo cytokine production | [59] |
| | 1997 | The cytokine response in meningococcal sepsis soon turns into an anti-inflammatory repertoire | [60] |
| | 1998 | Descriptive of a Neisseria meningitidis mutant that can survive without lipopolysaccharide | [60] |
| | 1999 | Genetic predisposition to produce high PAI-1 levels impairs outcome of meningococcal sepsis | [61] |
| | 2009 | Functional mutation of Neisseria meningitidis with altered LPS form has low TLR4-activating capacity | [62] |
| | 2010 | Susceptibility to meningococcal disease depends on genetic variation in complement regulators | [63] |
| Mycobacterium | 1976 | Host response to Mycobacterium leprae is controlled by at least two HLA-linked genes | [64] |
| | 1986 | First identification of protein antigens from M. leprae that can activate specific CD4 T cells | [65] |
| | 1993 | Major antigenic epitopes from M. leprae are differentially expressed in leprosy lesions | [66] |
| | 1997 | Role of M. leprae-specific Th1 cells in driving tissue damage during reversal reactions in leprosy patients | [67] |
| | 1998 | IL-12R deficiency increases sensitivity to mycobacterial and Salmonella infections in humans | [68] |
| | 2003 | Mannose caps on glycolipid of M. tuberculosis targets enable binding to DC-SIGN | [69] |
| | 2007 | siRNA screening identifies AKT signaling network that controls intracellular bacterial growth | [70] |
| | 2009 | Antisense-mediated exon skipping can be used to correct the IL-12R gene defect in vitro | [71] |
| | 2009 | Sugar-specific signaling through DC-SIGN shapes immunity to viruses and bacteria | [72] |
| | 2013 | Lower induction of pro-inflammatory cytokines parallels evolutionary success of modern Beijing strain | [73] |
| Salmonella | 1987 | Genetic background determines the capacity of phagocytes to kill Salmonella | [74] |
| | 1998 | IL-12R deficiency increases sensitivity to mycobacterial and Salmonella infections in humans | [75] |
| | 2009 | BCR-mediated internalization of Salmonella by B cells efficiently induces humoral immunity | [76] |
| | 2012 | Salmonella-specific B cells can act as a survival niche and a reservoir for reinfection | [77] |
| Bordetella | 2001 | Clearance of Bordetella pertussis is driven by Fcgamma receptors rather than by CR3 | [78] |
| | 2003 | Antibodies to pertactin are crucial to phagocytosis of Bordetella pertussis | [79] |
| Helicobacter | 1996 | Molecular mimicry between Lewis blood group antigens and LPS of H. pylori | [80] |
| | 2004 | Mutation in fuscosyltransferase of H. pylori alters Th1/Th2 balance through DC-SIGN | [81] |
| | 2009 | Sugar-specific signaling through DC-SIGN shapes immunity to viruses and bacteria | [82] |
| Gut flora | 1974 | Intestinal microflora has a strong impact on allogeneic lymphocyte responses in GVHD | [83] |
| | 1977/88 | Resident intestinal microflora plays a role in the occurrence of GVHD | [84] |
| | 2001 | Immune status of mother and pup controls bacterial colonization in neonates | [85] |
| | 2010 | Microbiota composition in the gut is highly dependent on presence of enteric defenses | [86] |
| Sepsis/endotoxins | 1988 | Circulating endotoxins as good predictors of septicaemia in patients with bacterial infection | [87] |
| | 1989 | Low dose IL-1 enhances survival of Pseudomonas infection in neutrophic mice | [88] |
| | 1989 | IL-6 levels are increased in septic patients and correlate with disease severity | [89] |
| | 1990 | Single injection of recombinant TNFs is sufficient to cause activation of the coagulation system | [90] |
| | 1990 | Thorough analysis of innate immune responses upon experimental endotoxemia in humans | [91] |
| | 1993 | BPI is expressed on the surface of the granulocyte | [92] |
| | 1996 | Reconstituted high-density lipoprotein has anti-inflammatory effects during endotoxemia | [93] |
| | 1996 | Epinephrine inhibits TNFα release and enhances IL-10 production upon endotoxin challenge | [94] |
| | 1998 | High IL-10/TNF ratio is associated with mortality in community acquired infection | [95] |
| | 2007 | TLR2 rather than TLR4 plays important role in Burkholderia-induced sepsis | [96] |
| | 2012 | IFN-γ partially reverses endotoxin-induced immunosuppression in vivo in humans | [97] |
| | 2012 | Endotoxin challenge in humans induces a subset of neutrophils that inhibit T cell responses | [98] |
| | 2012 | Extracellular granzyme K enhances endotoxin-induced cytokine responses by human monocytes | [99] |
| | 2014 | Voluntary activation of the sympathetic nervous system can attenuate response to endotoxin | [100] |
| Other | 1979 | Epidemic with typhoid and yellow fever has induced natural selection of certain HLA types | [101] |
| | 2006 | Fc receptor polymorphisms influence the response to pneumococcal polysaccharides | [102] |
| | 2007 | TLR4 polymorphisms were under evolutionary pressure during human migration | [103] |
| | 2007 | Enzymatic cleavage of CXCR1 on lung neutrophils in CF patients reduces bacterial killing | [104] |
| | 2011 | Avian TLR15 is a sensor for secreted microbial proteases | [105] |

| Table 3 | Host/fungus interaction. |
|---------|---------------------------|
| Fungus | Year | Findings | Reference |
| Candida | 1988 | Granulocytes, not monocytes or exudate macrophages, are important in resistance against C. albicans | [106] |
| | 2003 | DC-SIGN enables DCs to bind and internalize C. albicans | [107] |
| | 2006 | Immune recognition of C. albicans is dependent on various pattern recognition receptors | [108] |
| | 2009 | CD37 regulates the immune response against C. albicans by inhibiting IgA responses | [109] |
| | 2011 | Role of STAT1 and Th17 in autosomal dominant chronic mucocutaneous candidiasis | [110] |
| | 2012 | BCG protect against Candida infection by epigenetic reprogramming of monocytes | [111] |
| | 2014 | Both ROS-dependent and ROS-independent killing mechanism of C. albicans by neutrophils | [112] |
| Cryptococcus | 2004 | VEGF produced in cryptococcal meningitis may lead to blood–brain barrier disruption | [113] |
Another virus that has been studied by several Dutch research groups is Influenza A. This work ranges from the cellular and molecular mechanisms that drive protective anti-viral immunity [16–21], to the development of human antibodies with broadly neutralizing capacity against the virus [22,23]. Investigation into the cellular anti-viral response encompassed the polyclonality of the responding T cell pool, the role of T cell co-stimulation and the formation of memory T cells, but also the involvement of innate immune cells their contribution to pathology [16,18–20,24]. Moreover, it has been shown that the inhibitory receptor CD200R plays an important role in diminishing immune pathology during influenza [25,26]. Many approaches to study the immune response to influenza relied on the mouse as experimental model [16,19,21,24–26], but several groups have also been able to perform their analysis on human cells and tissues [17,18,27].

Analysis of anti-viral responses directly in humans is of great value and has also been done for latent viruses such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV) by several Dutch groups, which has revealed the great importance of our adaptive immune system to keep these infections in check [28–31]. Identification of several specific strategies of EBV has provided insight into the molecular details on how this virus is able to evade the immune system and establish latency [32–35]. Moreover, important contributions have also been made at the level of persistent infection with human papillomavirus (HPV), which is key for the development of cervical cancer: human T cell epitopes from HPV have been identified and shown to be effective in peptide vaccination to HPV [36–38], which can subsequently induce remission of HPV-induced cervical lesions in patients [39,40]. This has resulted in the decision of the Dutch government in 2010 to add HPV-vaccination for 12-year-old girls to the existing national immunization program.

Other Dutch contributions to anti-viral immunity have been made with vaccinia virus [41], measles [42], SARS [43] and MERS [44], but also at the level of intracellular recognition of viruses [45], viral dysregulation of innate sensing/interferon responses [46,47] and how interferon-gamma production upon viral infection regulates hematopoiesis [48–50].

### 3. Bacterial infections

The defence of the host against bacterial pathogens has been an intensive area of investigations in The Netherlands (Table 2). At the side of the host, the function of phagocytic cells (granulocytes and mononuclear phagocytes) was investigated in different groups since the 1970s. The relevance of oxidative and non-oxidative bactericidal mechanisms, the importance of monocytes and macrophages, the activation of phagocytic cells were topics in many papers [51–54]. Since the 1980s, the role of cytokines in the inflammatory response toward bacterial pathogens also became an important topic. Looking from the site of the bacterium, *Staphylococcus aureus* and especially its serious virulence and immune evasion have been intensively studied [55–57].

Because of the high prevalence of serious meningococcal infection (especially serotype B) in The Netherlands at the end of the last century, several groups performed research to elucidate the interaction between this pathogen and the host. These studies yielded important insights in the role of the Neisseria endotoxin [58,59], the overwhelming inflammatory response and its subsequent downregulation (nowadays indicated as ‘immune paralysis’) [60,61], the genetic background of susceptibility [62–64] and in the adaptive immune response, relevant for vaccine development [65].

Much work has been done on the interaction between mycobacteria (*Mycobacterium leptae* and *Mycobacterium tuberculosis*) and the immune system [15,66–73]. The role of HLA and T-cell recognition in leprosy [66,67], the interaction of *M. tuberculosis* with DC-SIGN [15,71] and the role of cytokines and their receptors in susceptibility [70] are among the major findings. Other bacteria that have been the subject of Dutch research in immunology are *Salmonella* spp. [70,74–76], *Bordetella pertussis* [77,78] and *Helicobacter pylori* [15,79,80].

Pioneering work on the gastrointestinal flora and the induction of graft versus host disease was done by Van Bekkum and Van der Waaij in the 1970s and 1980s [81–83]. Later on, it was shown by the Bos group that bacterial colonization in neonates is controlled by the immune status of both mother and pup [84], and that enteric defensins also play a critical role in this process [85].

Parallel to the work on meningococcal sepsis, a large amount of studies was published on bacterial sepsis, the role of endotoxin and of potential interventions [86–92]. Important insights in the pathophysiology of sepsis were obtained in the experimental endotoxemia in human volunteers [93–98].

With regard to genetic susceptibility to infection, an early elegant study was done by De Vries and Van Rood; they convincingly showed that severe infections in humans causes natural selection of certain HLA types [99]. Nearly 30 years later similar effects were shown for TLR4 polymorphisms during human migration by Netea et al. [100]. Genetic susceptibility to infection was also studied for specific pathogens such as meningococci [62–64], pneumococci [101], mycobacteria [66,70] and *Salmonella* species [70,74].

### 4. Fungal infections

Studies on host defence against the major fungal pathogen *Candida albicans* started in the 1980s, in an era when disseminated infections with this opportunistic pathogen became more

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**Table 4** Host/parasite interaction.

| Parasite | Year    | Findings                                                                 | Reference |
|----------|---------|--------------------------------------------------------------------------|-----------|
| Trypanosomes | 1980/82 | Antigenic variation of variant surface glycoproteins of trypanosomes revealed | [110,111] |
|           | 1998    | Trypanosomes prevent recognition by host species-specific usage of transferrin receptor isomers | [112]     |
| Plasmodium | 1983    | *P. berghei* sporozoites are harbored by Kupffer cells and then rapidly escape into hepatocytes | [114]     |
|          | 1985    | Identification of *P. falciparum* vaccine target proteins involved in human–mosquito transmission | [113]     |
|          | 1995/96 | Development of genetically modified malaria parasites                     | [115,116] |
|          | 2005    | Protective immunity to malaria can be induced with genetically attenuated sporozoites | [117]     |
|          | 2009/13 | Successful immunization strategies that can protect against malaria         | [118,119] |
| Schistosoma and other worms | 1998 | Schistosomiasis leads to hyporesponsive T cells | [121]     |
|          | 2000    | Schistosoma-induced IL-10 production correlates with lower occurrence of atopy in children | [122]     |
|          | 2010    | Immune responses to BCG and *P. falciparum* are suppressed by worm-induced regulatory T cells | [120]     |
|          | 2012    | Schistosoma-derived Omega-1 induces Th2-mediated responses via dendritic cells | [123]     |
| Other    | 1976    | Intestinal mast cell response following *Trichinella spiralis* infection is dependent on T cells | [124]     |
|          | 1994    | Adaptive immune responses to *Leishmania infantum* correlate with disease progression in dogs | [125]     |
5. Parasitic infections

Seminal studies on the interaction between the host and *Trypanosoma brucei* were performed by Borst and his group, demonstrating for the first time the incredible antigenic versatility of this parasite [110–112]. The parasite genome contains some 1000 genes encoding the variant surface glycoproteins, rendering vaccine development a futile undertaking.

Most of the work on parasites in Dutch immunology concerns malaria parasites. Meuwissen's group was the first to show the sequential appearance of antigens on the sexual stages of *Plasmodium falciparum*, the cause of tropical malaria [113]. This work formed the basis for development of transmission blocking vaccines. Another seminal study at that time dealt with the early liver form of the plasmodia [114]. Other Dutch research on malaria dealt with the technology to genetically modify and attenuate malaria parasites, in order to use these for immunization [115–117]. Another major advance in malaria research was obtained in the experimental malaria studies in human volunteers. Using this set up, pre-erythrocytic immunity was obtained by inoculating the volunteers with live *P. falciparum* sporozoites under chloroquine treatment, and the investigators were able to demonstrate long-lasting protection against a malaria challenge [118,119].

Intestinal helminth infestations, which are endemic in many non-western societies, appear to affect on the immune system of the host. Yazdanbaksh and her group have performed many studies to assess these immunomodulatory effects in more detail. They demonstrated that regulatory T cells induced by these worms suppress the T cell response to plasmidia-parasitised erythrocytes and to BCG [120]. This work builds on earlier work, in which T-cell hyporesponsiveness induced by schistosoma infection was shown [121]. Induction of IL-10 by the schistosomes appeared to be an important effector mechanism [122]. The major schistosoma egg antigen Omega-1 was shown to induce Th2 polarization through regulation of the mannose receptor expression [123].

Seminal work by Ruitenberg revealed that the increase of intestinal mast cells observed during the intestinal phase of infection with the nematode *Trichinella spiralis* is highly dependent on T cells, as it does not occur in athymic (nude) mice [124]. Interestingly, parasite infections were found to have even long-lasting effects on the immune system, as dogs infected with leishmania 3 years later greatly differed in the immune response according to their disease manifestations: asymptomatic dogs had a strong cellular immune response (with high IL-2 and TNFα production) while symptomatic dogs exhibited a mere antibody response [125].

6. Conclusions

In the present review we have attempted to cover nearly 50 years of Dutch immunological studies in the area of infectious diseases. Although we have tried to be complete, we are pretty sure that we have overlooked some important contributions. Moreover, because of the nature of this review, some topics and teams of scientists will have been more highlighted than others. For this we apologize. It is clear from the review that the scientists in The Netherlands that were and are active in this area have produced articles that had and still have quite an impact on the way we view host and pathogen interaction nowadays. It is interesting to see that although there are areas with quite a large number of contributions (such as those on immunity to HIV, influenza virus, *S. aureus*, *serpula*, endotoxin and malaria), there are important contributions dealing with many other infectious agents. It is also clear that the field is more active than ever before, and that we will see great future Dutch scientific contributions in this fascinating area.

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