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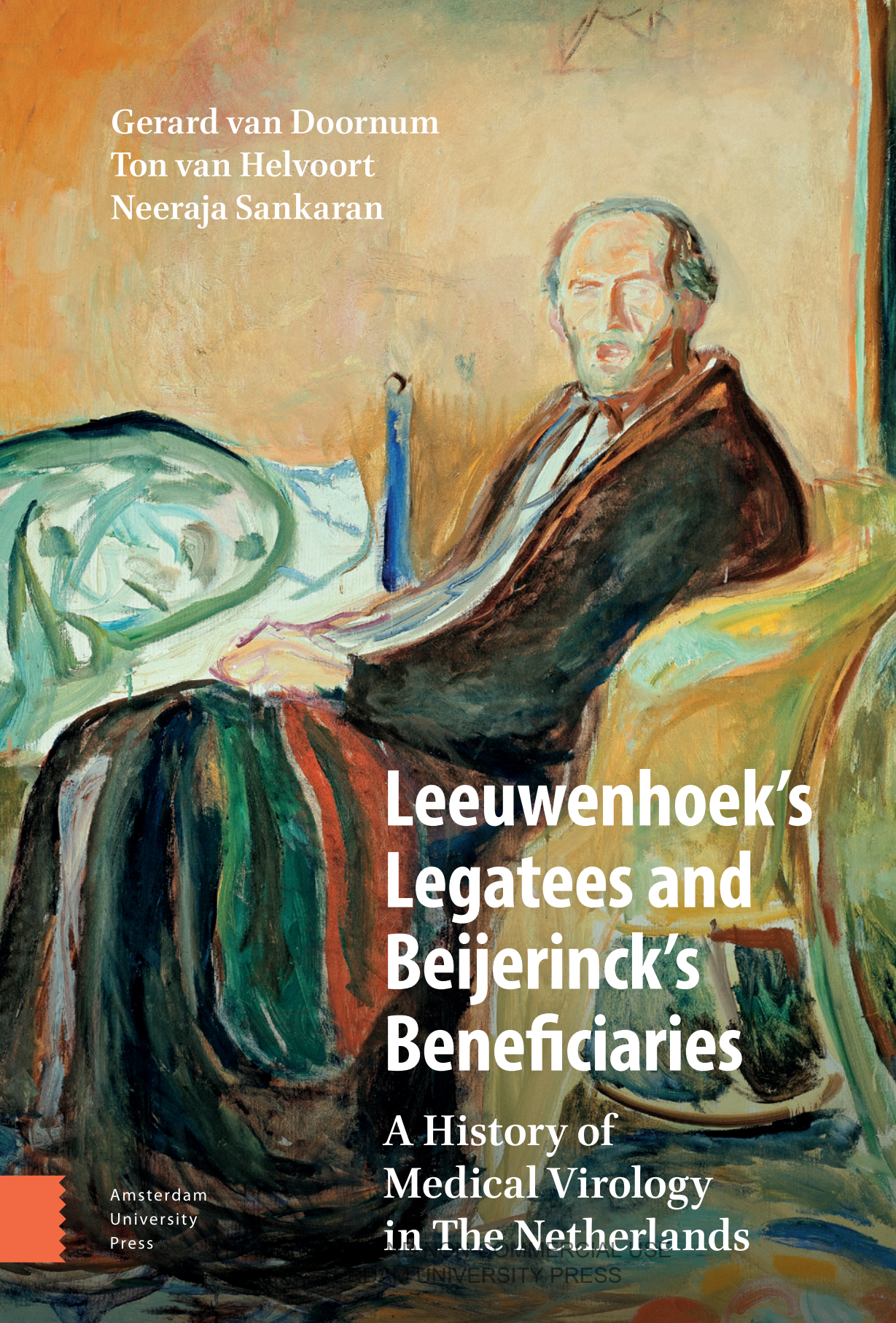

Leeuwenhoek's Legatees and Beijerinck's Beneficiaries

A History of Medical Virology in The Netherlands

Amsterdam University Press

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Cover illustration: Edvard Munch, *Self-Portrait with the Spanish Flu*, 1919
It is a sick and enfeebled artist who meets our gaze in *Self-Portrait with the Spanish Flu*. Edvard Munch became ill at the turn of the year 1918-1919, having apparently contracted the Spanish flu, which became a serious worldwide epidemic, taking the lives of many millions of people in the years from 1917 to 1920. In a series of studies, sketches and paintings, Munch followed the various stages of the illness, illustrating how close death came to life.
The painting was donated to the National Gallery by Charlotte and Christian Mustad in 1937.
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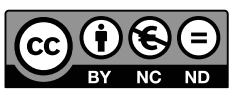

To the memory of Jan van der Noordaa
A true legatee and beneficiary of Leeuwenhoek and Beijerinck
Nestor of Dutch medical virology

Jan van der Noordaa (1934-2015)

By courtesy of E. van der Noordaa

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The British historian M. Worboys worked on the field of the history of tropical medicine and acknowledged that he was drawing almost entirely on the work of other historians. Likewise, in the event of scarcity of original sources we had to do the same. Of course, we apologize for any misinterpretations of the work of our forebears.

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Ton van Helvoort
Neeraja Sankaran

Abbreviations

AAI	Accelerating Access Initiative
ACS	Amsterdam Cohort Studies on HIV infection and AIDS
AFP	Acute flaccid paralysis
AIDS	Acquired immunodeficiency syndrome
AMC	Amsterdam Medical Center (Academisch Medisch Centrum), since 2018 location AMC of Amsterdam UMC
Amsterdam UMC	Amsterdam University Medical Center, locations AMC and VUmc
ASM	American Society for Microbiology
AvL	Antoni van Leeuwenhoek Hospital (Antoni van Leeuwenhoek Ziekenhuis)
AZL	Academisch Ziekenhuis Leiden
AZR	Academisch Ziekenhuis Rotterdam
AZU	Academisch Ziekenhuis Utrecht
CLB/Sanquin	Central Laboratory of the Blood Transfusion Service of the Netherlands Red Cross, since 1998 Sanquin (Centraal Laboratorium van de Bloedtransfusiedienst van het Nederlandse Rode Kruis)
CMV	Cytomegalovirus
COTG	Central Organ Tariffs Healthcare (Centraal Orgaan Tarieven Gezondheidszorg)
CPE	Cytopathic effect
CVI Lelystad	Central Veterinary Institute, Lelystad
DAVS	Dutch Annual Virology Symposium
DDL	Delft Diagnostic Laboratories, moved to Rijswijk in 2003
DTA	Direction of Technical Assistance of the Ministry of Foreign Affairs
DTaP/IPV	Diphtheria, tetanus, acellular pertussis, inactivated poliovirus
DTaP/IPV/Hib	Diphtheria, tetanus, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type B
DTP	Diphtheria, tetanus, pertussis
EAVRI	East African Virus Research Institute
EBV	Epstein-Barr virus
EGRVD	European Group for Rapid Viral Diagnosis
EIA	Enzyme immunoassays
ELISA	Enzyme-linked immunosorbent assay
EMBO	European Molecular Biology Organization
ERL	Epidemiological Research Laboratory, London
EHNRI	Ethiopian Health and Nutrition Research Institute
ENARP	Ethiopian-Netherlands HIV/AIDS Research Project

Erasmus MC	Erasmus Medical Center, Rotterdam
ESAVD	European Association against Virus Diseases
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESCV	European Society for Clinical Virology
ESV	European Society for Virology
FUNGO	Fundamental Medical Research
GG&GD Amsterdam	Municipal Health Service, Amsterdam
GGD Amsterdam	Municipal Health Service Amsterdam, since 2005
GHI	Health Inspectorate, until 1995
GNGH	Society for the Advancement of Science, Medicine and Surgery (Genootschap ter bevordering van Natuur- Genees- en Heelkunde)
GPLN	Global Polio Laboratory Network
GR	Health Council of the Netherlands (Gezondheidsraad Nederland)
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMPV	Human metapneumovirus
HPV	Human papillomavirus
IGZ	Health Inspectorate, since 1995 (Inspectie voor de Gezondheidszorg)
IPV	Inactivated polio virus vaccine (Salk)
KEMRI/KMRI	Kenyan Medical Research Institute
KIT	Royal Tropical Institute (Koninklijk Instituut voor de Tropen)
KNAW	Royal Netherlands Academy of Arts and Sciences
KNMG	Royal Netherlands Medical Association (Koninklijke Nederlandsche Maatschappij tot Bevordering der Geneeskunst)
KNMP	Royal Dutch Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie)
KNVM	Royal Netherlands Society for Microbiology (Koninklijke Nederlandse Vereniging voor Microbiologie)
KWF	Queen Wilhelmina Fund (Netherlands Cancer Society)
LCI	National Coordination Structure for Infectious Diseases (Landelijke Coördinatiestructuur Infectieziekten)
LHV	National Association of General Practitioners (Landelijke Huisartsen Vereniging)
LUMC	Leiden University Medical Centre
Maastricht UMC	Maastricht University Medical Center
MTI	Mammary tumour inciter
MMTV	Mouse mammary tumour virus

MRC	Medical Research Council, London
MSM	Men having sex with men
NASBA	Nucleic acid sequence-based amplification
NATEC	National Antiviral Therapy Evaluation Centre, at AMC
NHI	Netherlands Institute of General Practitioners (Nederlands Huisartsen Instituut)
NIH	National Institutes of Health, USA
NIPG	Netherlands Institute for Preventive Medicine, Leiden
NKI-AVL	Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (Nederlands Kanker Instituut-Antoni van Leeuwenhoek Ziekenhuis)
NMG	Nederlandse Maatschappij tot Bevordering der Geneeskunst
NTvG	Netherlands Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde)
NVTG	Netherlands Society for Tropical Medicine (Nederlandse Vereniging voor Tropische Geneeskunde)
NWO	Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek)
NVI	Netherlands Vaccine Institute, RIVM, Bilthoven
NVLA	Netherlands Society of Laboratory Medical Doctors (Vereniging van Laboratorium Artsen)
NVMM	Netherlands Society for Medical Microbiology
NVvB	Netherlands Society for Biochemistry
NVvM	Netherlands Society for Microbiology, since 2011 designation Royal
NWKV	Dutch Working Group for Clinical Virology (Nederlandse Werkgroep Klinische Virologie)
OPV	Oral poliovaccine (Sabin)
PAGRVD	Pan American Group for Rapid Viral Diagnosis
PCR	Polymerase chain reaction
PHLS	Public Health Laboratory Service, UK
QCMD	Quality Control for Molecular Diagnostics
Radboudumc	Radboud University Medical Centre
R.I.T.	Recherche et Industrie Therapeutique, Rixensart, Belgium
RIV	National Institute of Public Health (Rijks Instituut voor de Volksgezondheid), relocated from Utrecht through 1953-1965 to Bilthoven
RIVM	National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu), since 1984
RVP	National immunization programme (Rijksvaccinatieprogramma)
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome

SAZU	Stads- en Academisch Ziekenhuis Utrecht, since 1971 AZU, and since 1999 UMC Utrecht
SGM	Society for General Microbiology
SIIL	Serum Institute of India Ltd
SIV	Simian immunodeficiency virus
SKML	Foundation for the Quality Control of Medical Laboratory Diagnostics (Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek)
SKMM	Foundation for the Quality Control of Medical Microbiology (Stichting Kwaliteit Medische Microbiologie)
SSDZ	Foundation of Collaborating Delft Hospitals (Stichting Samenwerkende Delftse Ziekenhuizen)
SVM	Foundation for the Advancement of Public Health and the Environment (Stichting tot Bevordering van de Volksgezondheid en Milieuhygiëne)
SVOI	State Veterinary Research Institute (Staatsveterinair Onderzoekingsinstituut)
TMD	Tobacco mosaic disease
TMV	Tobacco mosaic virus
TNO	Netherlands Organisation for Applied Scientific Research (Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek)
TNO-NGO	Netherlands Organisation for Applied Scientific Research: Health Organisation, or Dutch Health Organisation
TNO-RVO	Netherlands Organisation for Applied Scientific Research: Defence, Safety and Security
UICC	Union Internationale contre le Cancer
UMC	University Medical Centre
UMCG	University Medical Center Groningen
UMC Utrecht	University Medical Centre of the University of Utrecht
UVRI	Uganda Virus Research Institute
VOC	Dutch East India Company (Vereenigde Oostindische Compagnie)
VRL	Virus Reference Laboratory, PHLS, London
VUmc	VU University Medical Center, Amsterdam
WHO	World Health Organization
WIC	Dutch West India Company (West-Indische Compagnie)
WMDI	Working Group for Molecular Diagnosis of Infectious Diseases (Werkgroep Moleculaire Diagnostiek van Infectieziekten)
ZWO	Netherlands Organisation for Pure Scientific Research (Nederlandse Organisatie voor Zuiver-Wetenschappelijk Onderzoek)

Preface

> To me it seems most desirable that the collaborative character of these investigations should be understood, not solely for personal reasons but because much of all modern medical research is conducted in this way.
> – *John F. Enders (1961)*

The title of the book pays tribute to two Dutch scientists without whom virology would arguably not exist today, at least not in its present guise. The first is Antony van Leeuwenhoek, whose reports of microscopic discoveries in the early eighteenth century aroused interest in the world of invisible creatures. His findings laid the basis for a theory of a particulate cause of infectious diseases, but, as George Rosen wrote, without any tangible results in support of the theory (1993/1958, pp. 84-85). Some 250 years later Martinus Willem Beijerinck launched the discipline of virology with his idea that tobacco mosaic disease (TMD) was caused by a living contagious fluid or filterable living pathogen.

When asked why he wanted to climb Mount Everest, George Mallory famously replied, ''Because it's there'' (New York Times. 1923. Climbing Mount Everest is work for supermen. New York Times, 18 March). Our answer to the question of why we decided to write a book about the history of medical virology in the Netherlands is : Because there isn't one. Although there are a fair number of books about the history of medical, experimental, animal, or plant virology in the Western world more generally (Booss and August, 2013; Calisher and Horzinek, 1999; Chastel, 1992; Grafe, 1991; Waterson and Wilkinson, 1978), only a few talk about virology in the Netherlands. A lacuna surely, considering that it was the birthplace for the discipline; the place where Beijerinck first characterized the principle '*contagium vivum fluidum*'. Even with the publication of Bos's and Thung's histories of plant virology in the Netherlands (Bos, 2000; Thung, 1957) and Offringa's history of the veterinary faculty of the University of Utrecht (1971, 1981), a history of Dutch medical virology is still lacking. This is why we decided to make it our focus in this book.

Travelling through Dutch virology we compared the developments in the Netherlands with other Western countries; this voyage may also give insight in the connections and communication between scientists in former days. Travelling companions were medical doctors, self-taught

Figure 2 Antoni van Leeuwenhoek (1632-1723)

Portrait by Jan Verkolje, c. 1680-1686
Reproduction by courtesy of Rijks Museum, Amsterdam

scientists, biologists, graduate engineers, veterinarians, biochemists, physicists, epidemiologists, and molecular biologists. As the Nobel Prize winner John F. Enders (1961) wrote in a commentary on a for him very laudatory editorial about his accomplishment in developing a vaccine against measles: 'To us it seems most desirable that the collaborative character of these investigations should be understood, not solely for personal reasons but because much of all modern medical research is conducted in this way.'

The work of Dutch researchers during the last decades of the twentieth century, such as that of R.A. (Roel) Coutinho, J. (Jaap) Goudsmit, F. (Frank) Miedema, S.A. (Sven) Danner, and J.M.A. (Joep) Lange in the Amsterdam Cohort Studies on HIV infection and AIDS, was made possible by building on the tradition of J.J. van Loghem and A. Charlotte Ruys from the first half of the century. R. (Roel) Nusse, a biologist at the NKI, could use the laboratory mice which were introduced in the Netherlands by R. Korteweg in 1931. Nusse continued his career in the USA, when he joined the laboratory of Harold Varmus at the University of California. A.D.M.E (Albert) Osterhaus could proceed in Rotterdam on the influenza track beaten earlier by J. Mulder in

Groningen, who moved to Leiden in 1946, and by N. Masurel from the late 1950s in Leiden and since 1967 in Rotterdam.

Of course, we are aware that connections between the various fields of virology, which persist to this day, mean that we will often have to cross the borders between them. For instance, Martinus W. Beijerinck, the father of the virus concept, made his seminal discoveries through his experiments on tobacco plants and not on any human disease. About a hundred years later, vectors that were developed towards the end of the twentieth century for delivering genes to mammalian cells were derived from the work of among others investigators at the Wageningen University, such as R.W. Goldbach, J.M. Vlak and A. van Kammen on recombinant baculoviruses from invertebrate hosts during the last decades of the twentieth century. In the 1930s the veterinarian H.M. Frenkel worked together with medical doctor H.W. Julius to improve the continuous flow cell culture instrument of J. de Haan; later, after 1945 Frenkel initiated among others the medical doctors J. Huisman and J.G. (Cootje) Kapsenberg into the secrets of virology. The veterinarian J.D. Verlinde was head of the Department for Medical Microbiology of the Netherlands Institute for Preventive Medicine and professor at the Medical Faculty in Leiden, and likewise his student H.A.E. van Tongeren who was also a veterinarian became professor at the Free University in Amsterdam. Several of the scientific students or co-workers of the veterinarian M. Horzinek were appointed at medical faculties in the Netherlands: A.D.M.E. Osterhaus, W.J.M. Spaan, H.G.M. Niesters, B.A.M. van der Zeijst, M.P.G. Koopmans. Not only do virologists cross borders, but as we know, viral pathogens in humans can be transmitted by animals without causing disease in the intermediary reservoirs or vice versa. The interspecies transmission plays an important role in emerging viral diseases.

According to the medical historian Michael Worboys, the case for a Bacteriological Revolution in late-nineteenth-century medicine in Britain remains unproven (Worboys, 2000, 2007). Although Worboys restricted his argument to Britain on the grounds that the rate and extent of change might have been different in other countries, we believe that similar forces were operative for development of virology as scientific discipline and medical specialism in the Netherlands as well. When was the start of medical virology? Was it a revolution or an evolution? Which people were involved in medical virology?

We should note that although the terms 'human', 'medical' or 'clinical virology' are often used interchangeably in the wider medical literature, in this book we have used the term 'clinical virology' more specifically to represent that part of virology directly involved in patient care, namely the

fields of diagnostic and therapeutic virology. Medical virology encompasses the study of human virus infections in a much broader sense and includes basic research, vaccine technology, tumour virology, research on antiviral drugs, and epidemiology, in addition to clinical virology.

The objective of this book is to give a chronicle of medical virology in the Netherlands in a wider, international context. We approached the project with the idea that most chapters would give factual, chronological accounts of the environment in which medical virology developed – i.e. the main institutions and laboratories in the Netherlands – combined with short biographical notes on leading figures. Unfortunately, we came across the fact that primary sources are very scant. Luckily, that problem could be overcome by information in medical journals, obituaries, reports of conferences or meetings of learned societies, commemorative books, historical records, and annual scientific reports of the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AVL).[1] In addition, different editions of textbooks published from the late 1930s to the late 1950s provided information on the international position of Dutch virology in the first half of the twentieth century. The following textbooks were used for insight in the international developments: Van Rooyen and Rhodes, *Virus diseases of man* (1948, rev. ed.); Doerr and Hallauer, *Handbuch der Virusforschung* (1938-1950); Gildemeister, Haagen and Waldmann, *Handbuch der Viruskrankheiten* (1939); Rivers and Horsfall, *Viral and rickettsial infections of man* (1959). The *Reflections on a life in medicine and science* of Tom Rivers and prepared by Samuel Benison were also very useful. An update for the period until 1980 was provided by Frank Fenner and Adrian Gibbs who published *Portraits of viruses: A history of virology* in 1988. The author of the first mentioned textbook, Clennel Evelyn van Rooyen, is a descendent of a Dutch ancestor, who travelled in the service of the Dutch East India Company (VOC) to Ceylon (Halifax Chronicle Herald, 1989).

Some chapters are built around specific themes, such as the reception and redefinition of virus concept in Dutch medical circles, the Dutch Working Group for Clinical Virology, Dutch virology in the tropics, tumour virology, contributions from the Netherlands to technical innovations, and immunizations.

As we were interested in the circumstances under which virology in the Netherlands began, we have explored nineteenth-century notions about five infectious diseases which came later to be recognized as viral diseases: smallpox, measles, rabies, poliomyelitis, and influenza. Therefore, the first

1 Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AVL).

chapter begins in the nineteenth century – even the eighteenth century in the case of smallpox – and describes the understanding of and measures against these diseases. The pathway from the first insights into the nature of viruses at the end of the nineteenth century to medical virology was a long and protracted one. It is not surprising that the relatively recent science of virology has been considered as part of modern medicine built on foundations established in the nineteenth century. The origins of virology are various, and the discipline stems more from botany and veterinary medicine than from human medicine.

The second chapter deals with the concept of virus as put forward by M.W. Beijerinck in 1898, the reception of this concept among medical circles in the Netherlands, and also with redefinition of concepts of virus or bacteriophages by other Dutch researchers later in the twentieth century. Were they but spectators while the action took place in Germany, France, United Kingdom, or the United States?

In the third chapter we have attempted to describe the developments in the first half of the twentieth century – of institutes, research and diagnostic facilities in the laboratories – interspersed with short biographical details of the leading figures. Scientific research in the Netherlands was conducted almost exclusively in three venues: university laboratories, the laboratory of the NKI, and the institutes for tropical hygiene which were connected with the universities in Amsterdam and Leiden, respectively.

Chapter four is concerned with the general developments in virology and the organization of virologists over the latter half of the twentieth century. In common with developments in other countries, medical virology in the Netherlands really began to take off sometime in the middle of the twentieth century, with the practice of diagnostic virology gradually taking hold in general hospitals after the 1970s. There is consensus that the advance of virology in the 1950s can be ascribed to the application of the monolayer cell culture as first described by Enders, Weller and Robbins in their pivotal paper of 1949 (Enders et al., 1949; Mortimer, 2009; Booss and August, 2013). This development in cell culture technique was readily introduced into the Netherlands in the 1950s and contributed strongly to the commencement of clinical virology in the Netherlands. However, diagnostic virology remained from 1950 until 1970 of limited practical use for the patient. This chapter then pursues the development of clinical virology in the 1960s and 1970s when diagnosing virus infections started to be executed in a timely manner to benefit the management of the treatment of patients. Before the application of cell culture techniques, use of animals and tissues for virus identification was very cumbersome and in practical terms the results were

often too late to help the patient. The development of immunofluorescence techniques in the 1960s and enzyme-linked immunosorbent assay (ELISA) techniques and further fruits of immunology (such as the monoclonal antibodies) were introduced in the 1970s. This caused a rapid and decisive step forwards in the 1970s. During the 1980s and, in particular, during the 1990s the spectacular advances in molecular biology together with the rise of information technology facilitated the expansion of diagnostic virology in the last decades of the twentieth century. This growth encompassed epidemiology, diagnosis and treatment, and viro-immunology research of new emerging virus infections. With the epidemic of human immunodeficiency virus infections, the application of antiviral therapy proceeded with rapid strides from the 1980s after a hesitant start.

The chapter continues with the way in which virologists organized themselves. The Virology section within the Royal Netherlands Society for Microbiology[2] deals with the activities of the different branches of virology: fundamental research, medical virology, plant virology, and veterinary virology. The Section organizes the successful "Dutch Annual Virology Symposium". The Dutch Working Group for Clinical Virology of which the epidemiologist M.F. Polak of the National Institute of Public Health[3] was the initiator, is part of the Netherlands Society for Medical Microbiology. This working group played an important role in the 'devolution' of virus diagnostic work from some specialized virology, public health laboratories to general hospital microbiological laboratories. The position of medical virology within the national as well international virology and microbiology community is ascertained on the basis of the history of the Dutch Working Group for Clinical Virology, the DAVS, and the annual General Spring Meeting of both Societies.

Chapter 5 pays attention to the institutes where medical virology was practised in the second half of the twentieth century. Over the first decades of this period the leading laboratories were in Amsterdam, Leiden and Utrecht. The authors also focus on the Amsterdam Cohort Studies in the discussion on the institutes in Amsterdam. The Laboratory of Virology of the Central Public Health Laboratory of RIV in Utrecht and since 1958 in Bilthoven, the Department of Bacteriology and Experimental Pathology of the Netherlands Institute for Preventive Medicine in Leiden, and the Laboratory for Hygiene in Amsterdam played important roles in the 1950s and 1960s. This picture changed with the establishment of four new medical faculties:

2 Nederlandse Vereniging voor Microbiologie (NVVM).

3 Rijksinstituut voor de Volksgezondheid (RIV).

the new medical faculties at the existing Free University in Amsterdam and Radboud University in Nijmegen in the 1950s, and thereafter the medical faculties at the new universities in Rotterdam and Maastricht, in 1964 and 1974, respectively. In addition to the university laboratories, some municipal public health laboratories and, later, the larger general hospitals offered diagnostic virological services. At the end of the chapter attention is paid to a number of commercial companies that produce vaccines or diagnostic kits or offer other services related to medical virology.

The core theme in Chapter 6 is the Dutch contributions in a variety of technical developments. It covers the phase-contrast microscope, the electron microscope, enzyme-linked immunosorbent assays, agar gel electrophoresis, the introduction of DNA in mammalian cells, the various methods using synthetic peptides (Pepscan), and nucleic acid purification.

Chapter 7 traces the Dutch contribution to medical virology in the tropics. This chapter does not provide a comprehensive picture of medical virology in the tropics, but is rather confined to a short overview of control and public health measures as well as the laboratory facilities for diagnostics of virus infections in the former Dutch colonies. The chapter also covers Dutch activities in the field of virology in Africa from the 1960s onwards.

Chapter 8 is again thematic and deals with tumour virology and persistent virus infections. This chapter encompasses the environment of the NKI and the academic centres which played a substantial role in tumour virology throughout the twentieth century. The rise and fading of the Working Group on Persistent Virus Infections and Oncogenesis is also described. Concurrent with the vanishing of this working group was the rise of molecular biology and cell biology.

Chapter 9 explores the organization of national immunization programmes with regard to viral infections polio, rubella, measles, mumps, hepatitis B, influenza, and human papilloma virus. The role of the Central Laboratory of the National Institute of Public Health in the production of vaccines will get attention, of course.

The book ends with conclusions and short summaries. Each written history has an end, and we decided to limit ours to the close of the twentieth century. Nevertheless, as movements and developments do not always occur in synchronicity, sometimes we had to cross over into the twenty-first century. We hope that others will do further research on the revolution that is still unfolding, thanks to such developments in next-generation sequencing, immunology, vaccines, epidemiology and antiviral drugs.