Keith W. Taylor · Heikki Hyöty
Antonio Toniolo · Arie J. Zuckerman
Editors

Diabetes and Viruses

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Foreword

Every house has many builders and is never finished—Paavo Haavikko (Finnish poet, 1931–2008).

To the memory of Keith W. Taylor (Shropshire, 1930—Rye, 2012) who set a wheel in motion in diabetic research with original investigations on the possible role of viral infections. His perspective and judgement contributed greatly to this work, and his spirit pervades this volume. We also wish to recall the wonderful and continuous support given to him by his wife Margareth, his daughter Ann and especially Nick, his son.

This book is also dedicated in everlasting loving memory to Alice Zuckerman (neé Adamson; 28 January 1932 to 16 January 2011), who devoted her life, love and energy to her husband Arie, and children Mark and Jane; and who encouraged, supported and inspired them to excel in the science and art of Medicine.

Finally, we acknowledge the generous contribution of Gianni Valcavi, Attorney, and Cariplo Foundation (Milan) without which diabetes research in Varese (Italy) would have been not possible. It is also a pleasure to acknowledge the skilful help and pleasant cooperation of our secretaries Ms. Tanya Shennan, Mrs. Irene Smith and Mrs. Stefania Triballi. Lastly, we gratefully recognize the distinguished skill and patience of Arthur Smilios, Ms. Fabian Shalini and the entire Springer's staff during the preparation of this book.

The Editors

Preface

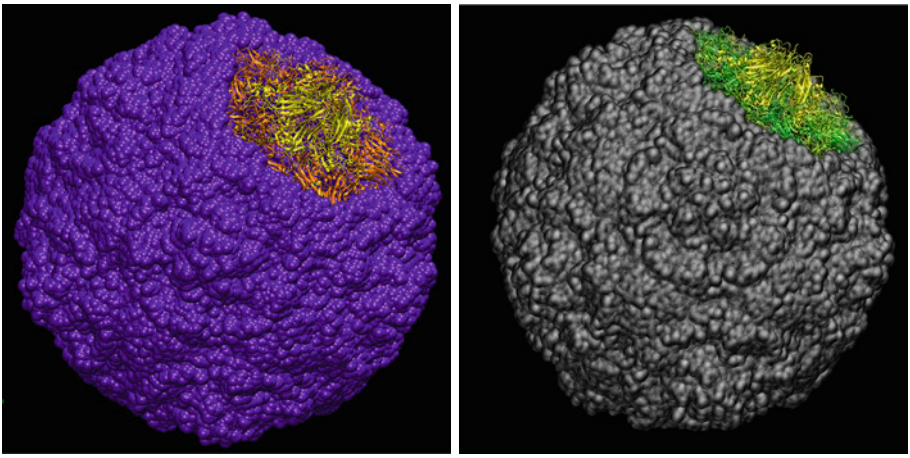
While the term "the global epidemic of diabetes" is used frequently both by the popular media and in the medical literature, it is not used in the context of infection. The late Keith Taylor reflects on the historical background of the relationship between viruses and diabetes noting that the association between mumps and diabetes was described in the middle of the nineteenth century, but it was not until 1927 that the Norwegian Army physician Edvard Gundersen published a paper in the *Journal of Infectious Diseases* entitled "Is diabetes of infectious origin?". The subsequent history of virus infection and diabetes in humans and animals is described eloquently in the Chap. 1 of this book, which contains precisely what is stated in the title; that is, information on diabetes and viruses.

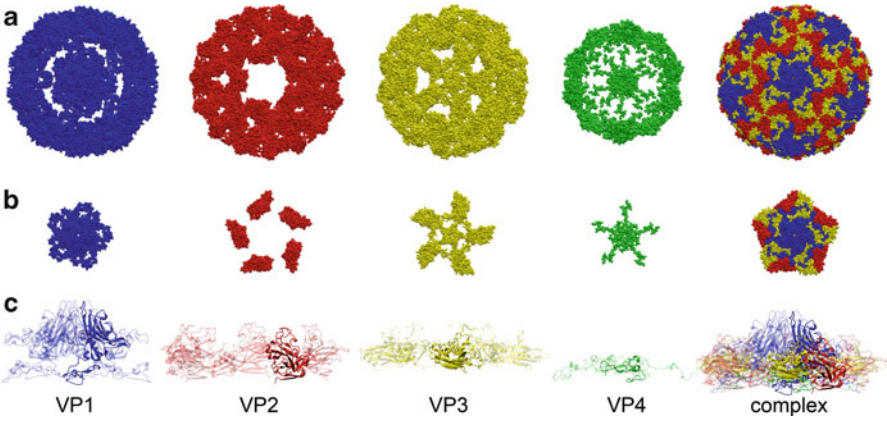
The Editors recruited a galaxy of leading researchers and physicians from many countries including, in alphabetical order, Australia, Cuba, Finland, France, Italy, Japan, Sweden, the UK and the USA, who accepted the challenge to produce rapidly an authoritative account of the current knowledge and research in progress on this important topic, for which the Editors are most grateful.

Many topics are reviewed expertly including the role of autoimmunity, molecular mimicry, genetic factors, immune mechanisms, environmental factors (an ever popular topic on virtually every aspect of human activity), and with a particular emphasis on a number of viruses affecting the pancreas in animals and humans. The text is written in a way that we hope will be understood by general physicians, clinical specialists in diabetes, researchers—especially those involved in immunology and virology—senior nurses, public health workers and medical students. We also hope that the pharmaceutical industry is listening. Throughout we attempted to avoid the description of excessively complex techniques and molecular porn, and simplify technical jargon.

Finally, there is an old military maxim "never attack a revolution", and—in the context of this book—we should not ignore the direct or indirect role of viruses in the aetiology of diabetes mellitus, but rather continue to explore this intriguing association.

London, UK — Arie J. Zuckerman

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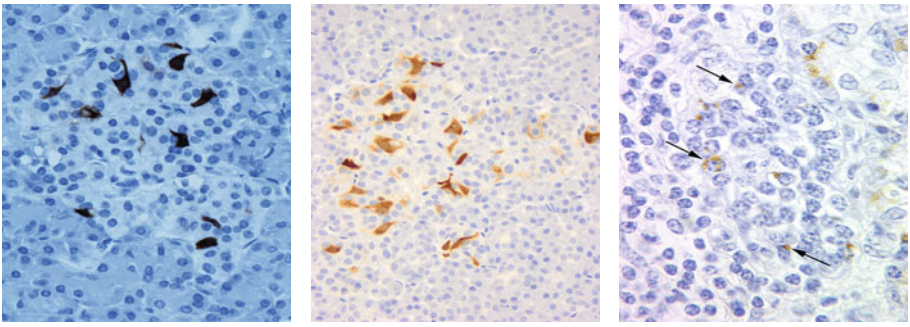

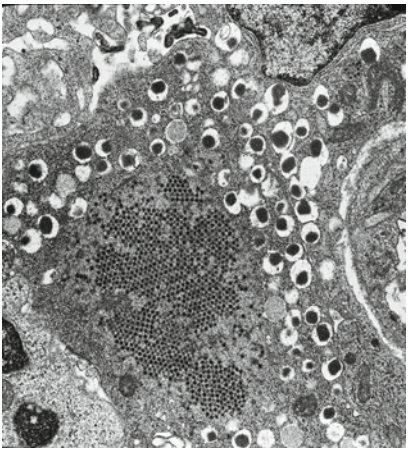

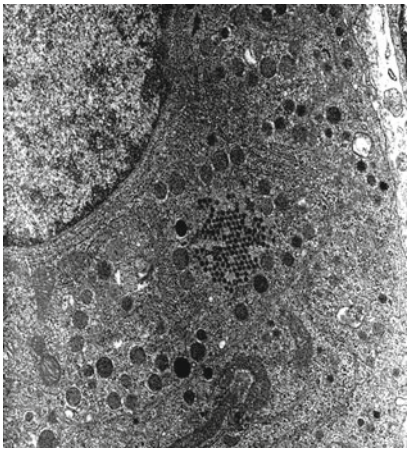

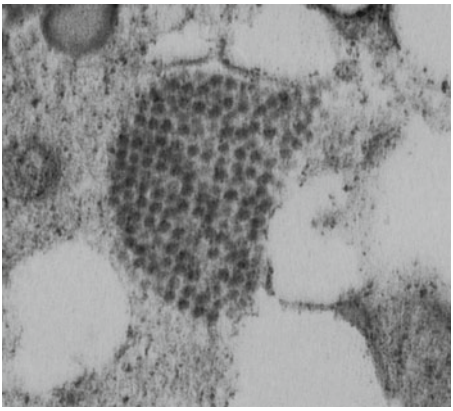

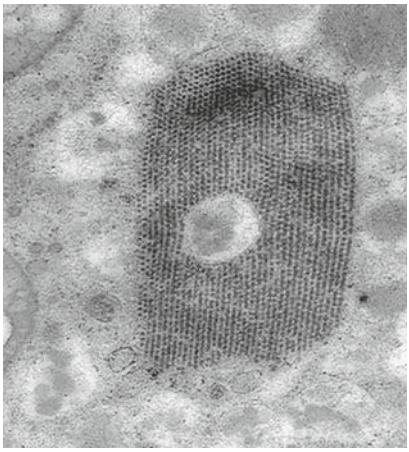

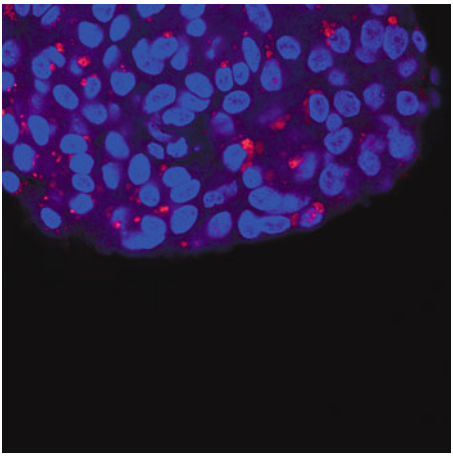

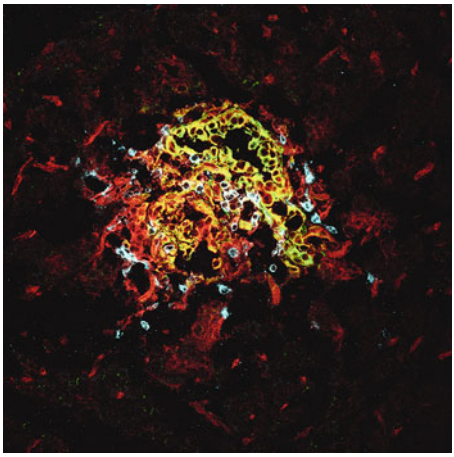

Figure Legends

Figs. 1 and 2 Three-dimensional model of an enterovirus. One pentamer of capsid proteins is shown in detail (two different orientations of the virus particle). The remaining part of the capsid surface is shown as Van der Waals spheres. Reconstruction based on the X-ray analysis of coxsackievirus A9 at 1.2 Å resolution has been performed using the VMD 1.8.7 program (Protein Data Bank access code 1D4M). Courtesy of Vesa Hytönen, University of Tampere, Finland.

Fig. 3 Assembly of the enterovirus capsid. A) The four capsid proteins represented as Van der Waals spheres (VP1, blue; VP2, red; VP3, yellow; VP4, green) are shown as assembled in the capsid. B) The four capsid proteins are shown as assembled in a pentamer. C) Side view of capsid proteins assembled in a single pentamer. As in Figures 1 and 2, the models are based on the X-ray structure of coxsackievirus A9 (courtesy of Vesa Hytönen, University of Tampere, Finland).

Fig. 4 Immunohistochemical detection of a capsid protein of an undefined type of enterovirus in the cytoplasm of islet cells of a recent case of type 1 diabetes (courtesy of S. Richardson and A. Foulis).

Fig. 5 Immunohistochemical detection of a capsid protein of an undefined type of enterovirus in the cytoplasm of islet cells of a case of type 1 diabetes of short duration (courtesy of H. Hyoty and S. Oikarinen).

Fig. 6 Expression of bovine diarrhea virus (BDV) antigen in the cytoplasm of pancreatic islet cells of a cattle with type 1 diabetes (courtesy of K. Matsuda and H. Taniyama).

Fig. 7 Crystalline array of 70 nm virus particles in a beta cell (note insulin-containing granules) of a mouse neonatally infected with reovirus type 1 (courtesy of T. Onodera, A. Toniolo, A.L. Notkins).

Fig. 8 Crystalline array of 70 nm virus particles in a alpha cell (note glucagon-containing granules) of a mouse neonatally infected with reovirus type 1 (courtesy of T. Onodera, A. Toniolo, A.L. Notkins).

Fig. 9 Crystalline array of enterovirus particles (approximately 30 nm) in a cultured human pancreatic islet that had been infected in vitro with coxsackievirus B5 (courtesy of G. Frisk).

Fig. 10 Crystalline array of enterovirus particles (approximately 30 nm) in the cytoplasm of a beta cell of cultured human pancreatic islets that had been infected in vitro with coxsackievirus B5 (courtesy of G. Frisk).

Fig. 11 Enterovirus capsid antigen (red) in the cytoplasm of cultured human pancreatic islets infected in vitro with coxsackievirus B3 (nuclei in blue; courtesy of M. Craig and M. Poon).

Fig. 12 Pancreatic islet from a patient with type 1 diabetes of 3 years duration. Frozen pancreas section stained for insulin (green), HLA class I (red), and CD8 (cyan blue). Note the infiltration of CD8(+) T cells and the hyperexpression of HLA class I molecules (confocal microscopy; courtesy of K. Coppieters, T. Kay, M. von Herrath).

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Part I
Background and Pathogenesis

Chapter 1
Historical Background: Earlier Studies on the Connexion Between Viruses and Diabetes

Keith W. Taylor

Although there are references to the possible relationships between mumps and diabetes in the mid-nineteenth century (Stang 1864), it was not until much later that Harris (1899), described in detail a likely association between the two diseases. In the case discussed by Harris, glycosuria in a young American farmer quickly followed the initial mumps attack, but full blown diabetes with ketosis developed over a 3-year period. It was assumed that the mumps produced pancreatitis which involved the islets. In the ensuing 30 years, sporadic cases where there was an association between mumps and diabetes were reported (Patrick 1924), but it was generally assumed that mumps was a rare cause of diabetes. Gundersen (1927), however, published a paper with the intriguing title "Is Diabetes of Infectious Origin?", in which it was suggested that what he termed infectious parotitis or mumps produced pancreatic disease leading to diabetes in the young some 3 years after the initial infection. His figures were based on death rates due to diabetes in Norway in the pre-insulin period. At that time diabetes in the young with ketosis was usually fatal, and death rates from the disease bore a relationship to its incidence.

It is now known that several other viruses can produce a parotitis, as well as pancreatic disease, including enteroviruses. Since methods for the accurate identification of viruses did not then exist, viruses other than the mumps virus could well have been involved on occasions.

The association of mumps with subsequent diabetes has been reported in isolated cases ever since.

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