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

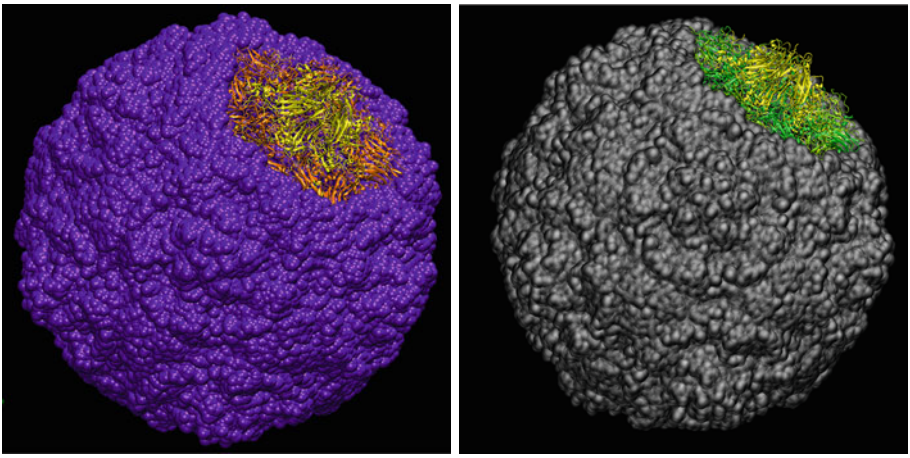
While the term "the global epidemic of diabetes" is used frequently both by the popular media and in the medical literature, it is not used in the context of infection. The late Keith Taylor reflects on the historical background of the relationship between viruses and diabetes noting that the association 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.

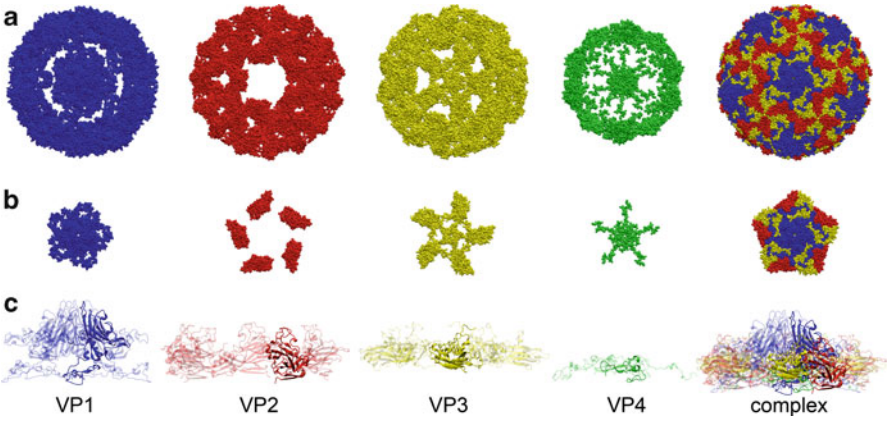
The Editors recruited a galaxy of leading researchers and physicians from many countries including, in alphabetical order, Australia, Cuba, Finland, France, Italy, Japan, Sweden, the UK and the USA, who accepted the challenge to produce rapidly an authoritative account of the current knowledge and research 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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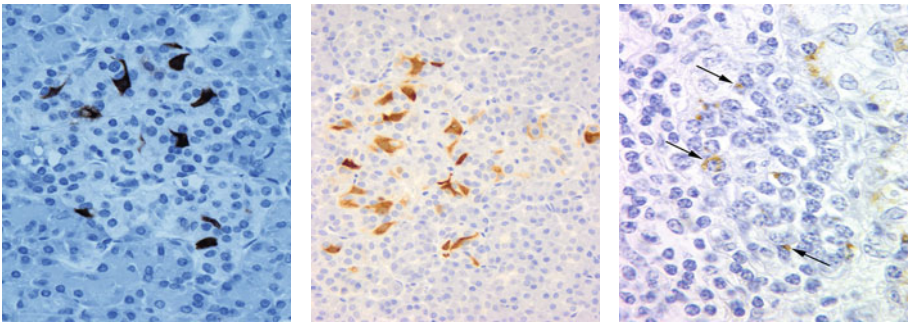

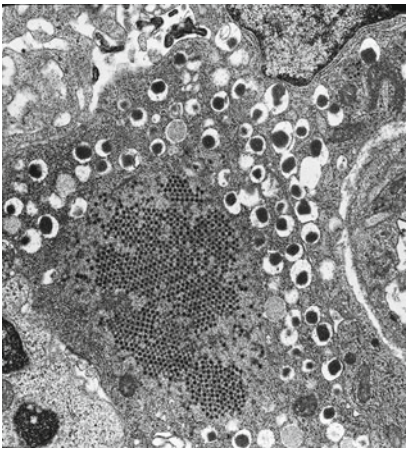

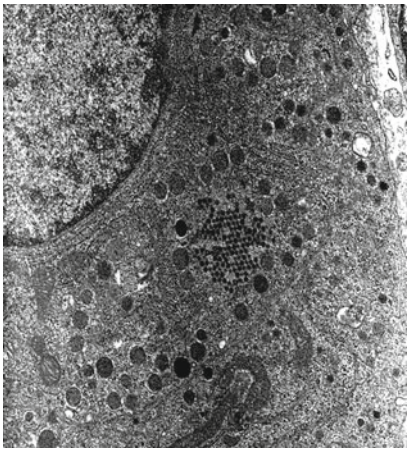

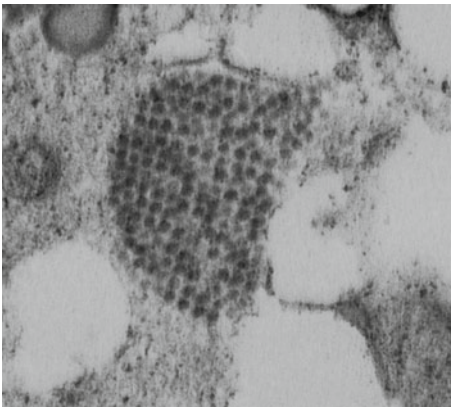

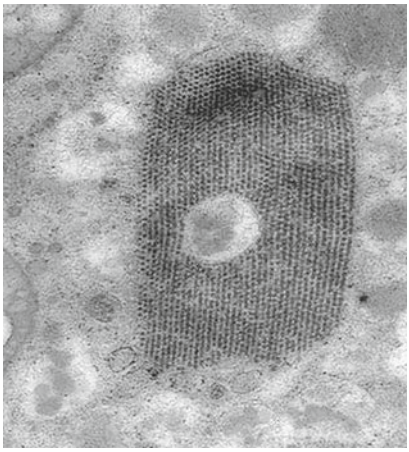

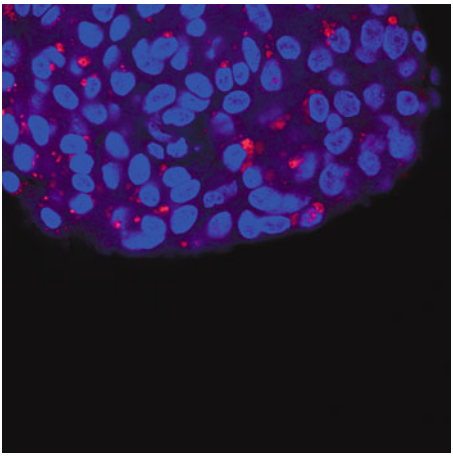

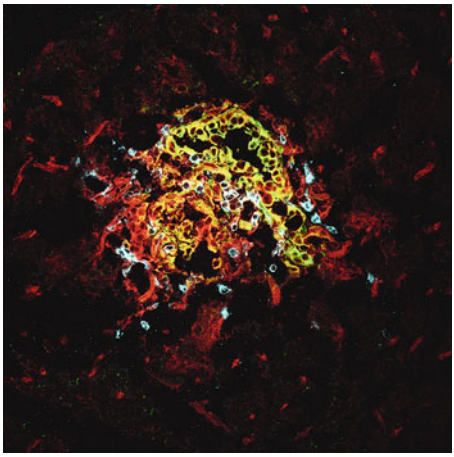

Figure Legends

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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Other Viruses and Diabetes

With improvements in virological techniques, however, in the 1950s and 1960s it became evident that diabetes might be associated with infection by a number of other viruses in addition to mumps in man as well as in animals. An outbreak of foot and mouth disease in cattle in Italy was accompanied by ketotic diabetes (Barboni and Manocchio 1962) with pancreatic lesions. In mice, strains of encephalomyocarditis virus caused diabetes with damage to the islets of Langerhans (Craighead and Mclane 1968). Parallel work also showed that coxsackieviruses might produce a pancreatitis in mice although without diabetes (Pappenheimer et al. 1951).

Afterwards, there were reports of coxsackieviruses inducing pancreatitis in new born infants (Kibrick and Benirschke 1958). It became clear that a number of other viruses in addition to mumps might be involved in pancreatic damage and perhaps the precipitation of diabetes in man.

A more general association of enteroviruses with the onset of diabetes in type 1 diabetes was first suggested by the work conducted in London and Birmingham in the UK during the late 1960s (Gamble et al. 1969). In preliminary work, it had been noticed that there was a marked seasonal incidence for type 1 diabetes, with autumnal and winter peaks (Gamble and Taylor 1969). It was suggested that the autumnal peak might be due to an enterovirus infection, and that the winter peak represented intercurrent non-specific infection which had worsened carbohydrate tolerance following earlier pancreatic damage.

This led to a much larger scale investigation to determine in detail whether enteroviral infection might be involved with the onset of type 1 diabetes.

The investigation involved 123 patients, all with diabetes of sudden onset. Most required insulin treatment and were ketotic. Those investigated covered a broad age range from early childhood to over 60 years of age, although with the 0–40 years group age predominating.

Using a neutralising antibody technique, higher titres of antibodies to coxsackieviruses were found than in controls than in those diabetics tested soon after onset. In these first studies, coxsackievirus B4 was the virus most commonly detected, even though it is now clear that several other enteroviruses seem to be involved.

Similar studies using classical immunological techniques to detect viruses were repeated by many other investigators during the next 30 years, with most, though not all, showing comparable results. Since the choice of patients investigated, the methods of handling blood and subsequent virus identification varied very widely, it is not surprising that results were not always clear cut. Some of these problems are discussed in Chaps. 13, 15, 17, 23, and 32. The use, however, of the polymerase chain reaction (PCR) has generally confirmed the original suggestions.

The seasonal incidence of type 1 diabetes in temperate countries was also confirmed (see Chap. 11). This supported the idea that an infective process could be associated with the precipitation of diabetes.

Rubella and Diabetes

At about the time of the first studies on enteroviruses and diabetes, interest was focussed on a long-term study of children with congenital rubella following severe rubella epidemics in Australia in the 1940s. In a 25-year follow-up of 50 such patients, one case of undiagnosed diabetes was reported (Forrest et al. 1967). By 1974, 8 of 45 patients had acquired diabetes, 4 of whom were on insulin (Menser et al. 1974). It was clear that foetal infection with this virus could be linked with diabetes in the long term.

Isolation of Viruses from Patients with Type 1 Diabetes

In an important study on of a single case of ketotic diabetes in a child who died, coxsackievirus B4 virus was isolated from the pancreas and the strain shown to produce diabetes in mice (Yoon et al. 1979). Lymphocytic infiltration of the islets of Langerhans in this case was observed. In this instance, Koch's postulates appear to have been fulfilled. A similar case was reported a year later (Champsaur et al. 1980), in an infant, this time involving coxsackievirus B5. Other isolated cases where severe enterovirus infection was associated with diabetes continued to be reported (Szopa et al. 1993).

In summary, therefore, not long after the middle of the last century a number of viruses were beginning to be clearly linked with the onset of diabetes in man and animals. The latter are reviewed elsewhere (Yoon 1991).

In humans, the most important viruses were mumps virus, rubella virus and especially enteroviruses. In a few instances, enteroviruses appeared to be directly causative, but doubts remained as to the proportion of patients with type 1 diabetes who were infected with these viruses before onset. Many of these doubts have been removed by the use of molecular methods for virus detection (Yeung et al. 2011).

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Chapter 2
Viruses and Autoimmune Diabetes: A History

R. David G. Leslie, Lily Ho-Le, and Huriya Beyan

Certainty: The Ascent of the Gene

The identification of an association between type 1 diabetes and certain genes transformed our understanding of this and other related diseases, including thyroid disease and multiple sclerosis. That type 1 diabetes is genetically determined and was evident from family, twin and genetic studies. The frequency of type 1 diabetes is higher in siblings of diabetic patients (e.g. in UK 6% by age 30) than in the general population (0.4% by age 30) (Field 2002). Of genes implicated in the genetic susceptibility to type 1 diabetes, the most important are in the histocompatibility (HLA) region of chromosome 6 (Kumar et al. 1993); first sought by Singal but then sought successfully by Nerup and Cudworth (Nerup et al. 1974). Such HLA genes predispose to a number of autoimmune diseases including type 1 diabetes (Kumar et al. 1993; Concannon et al. 2005), as demonstrated in both population and family studies (Redondo et al. 2001; Kumar et al. 1993; Meyer and Thomson 2001). Genes encoding HLA molecules and located within the major histocompatibility complex (MHC) on the short arm of chromosome 6 are associated with type 1 diabetes. The MHC complex is a polymorphic gene complex in which multiple alleles exist for each genetic locus. The MHC is divided into class I (HLA-A, -B and -C), class II (HLA-DR, -DQ and -DP) and class III (genes for complement components). The classes I and II proteins coded by the relevant genes are transmembrane cell surface glycoproteins which are critically involved in the presentation of both self- and foreign antigens as short peptides to T-lymphocytes.

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HLA genes are highly polymorphic with a degree of coding region diversity unequalled elsewhere in the genome. Polymorphisms of certain genes probably originated in selection pressures exerted by environmental factors including epidemics, climatic change and availability of food. A non-human somatic study of the HLA DQ beta region suggests that this region has been in balanced polymorphism for ten or more million years (Meyer and Thomson 2001). To maintain the extraordinary diversity of HLA types over this time, selection pressures must have been operating; otherwise most alleles would have been lost through genetic drift. It has been proposed that infectious pathogens are the major cause of HLA diversity. The distribution of sequence variation is clustered in nucleotides which code for amino acids composing the antigen-binding groove. This implies that natural selection must have acted at this binding site to maintain structural diversity for peptide binding. By 1990, it seemed most likely that this peptide-binding site identified an autoantigen, and that the trimolecular complex of HLA, autoantigen and T-cell receptor reflected an autoimmune disease process (Nerup et al. 1974). Such an argument was supported by the impressive technical genetic achievements, using single nucleotide polymorphisms, association studies and genome-wide association studies (GWAS), most notably by Todd and his colleagues (Nejentsev et al. 2009). Allied to which was the comparatively unimpressive ability of epidemiologists to identify any key non-genetic factor.

But the limited degree to which HLA and other non-HLA could account for all the risk of type 1 diabetes, the missing heritability, remained an issue. The term heritability reflects gene expression or penetrance in a given environment. The best estimate of heritability can be obtained by determining concordance rates of twins. Both identical and non-identical twins share the same environment in childhood but only identical twins share the same genes. In the classic twin method the difference between the concordance rates for identical and non-identical twins is doubled to give an index of heritability. Higher concordance rates, for autoimmune diseases in general and type 1 diabetes in particular, in identical compared with non-identical twins are consistent with a genetic influence on these diseases (Salvetti et al. 2000). Estimates of heritability can be obtained from studies in Finland and the University of Southern California; in both the estimates are substantially less than 100% which means the disease is unlikely to be autosomal dominant (Hyttinen et al. 2003). Age-related genetic factors also influence the risk of type 1 diabetes, as the disease risk is lower in adults than in children, and the range of incidence across European countries is also reduced in older age (Kyvick et al. 2004). Survival analysis estimated that non-diabetic identical twins of probands diagnosed with type 1 diabetes under 25 years of age had, in one study, a 38% probability of developing diabetes compared with only 6% for twins of probands diagnosed later (Salvetti et al. 2000). Such a remarkably low twin concordance rate for adult-onset type 1 diabetes implies that the genetic impact in adult-onset type 1 diabetes is limited, and certainly lower than that in childhood-onset disease (Salvetti et al. 2000; Hyttinen et al. 2003; Kyvick et al. 2004). These effects were widely attributed to a stochastic effect by geneticists, but there remained the possibility that other non-genetically determined effects (such as epigenetic effects or environmental effects) might be important. HLA associations with these diseases could, after all, operate through susceptibility to certain undefined infections.