

## Viruses and the Etiology of Diabetes

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The purpose of this review is to summarize the current evidence for a possible role of viruses in the pathogenesis of diabetes mellitus. The evidence has accumulated along a number of lines: (A) The evidence that diabetes always or even usually has a genetic basis is far from satisfactory, particularly in light of the recent studies on identical twins of diabetic patients;<sup>1</sup> (B) A more direct line of evidence derives from the observation that viruses have been isolated which will produce a specific lesion in the pancreatic islets of animals, particularly in mice; (C) A study of the seasonal incidence of young, insulin-requiring diabetes has been reported which suggests that it coincides with a rise in antibodies to Coxsackie virus group B, type 4. It is, however, only fair to state that up to this moment no virus has been cultured from either human blood, pancreatic tissue or excreted by newly diagnosed diabetic patients.

Craighead and collaborators have established that a strain of the encephalomyocarditis virus will produce direct insular lesions.<sup>2-4</sup> This virus belongs to the group of picornavirus. As the name indicates, it is a small type virus of the RNA variety measuring 15 to 30 microns. To the picornavirus belong the poliovirus, Coxsackie A and B and the echo viruses, the rhinovirus of the common cold, and finally a group containing the encephalomyocarditis virus and that of foot-and-mouth disease. For some time the encephalomyocarditis virus has been known to be pathogenic for mice in which it produces myocarditis or encephalitis or both. Until recently, it has been thought not to be pathogenic for man although antibodies to this virus have been found to be widely

distributed, particularly in subtropical areas. The "M" variant of this virus may also produce inflammation of the islets of Langerhans, an isletitis, the extent of which will depend on the virus; it can produce chemical diabetes or ketoacidosis. There is also a marked endogenous variability. Some strains of mice are more susceptible than others, possibly pointing toward genetic factors. This virus is not only pathogenic for mice but also for marmosets and rhesus monkeys. Of interest is that some of the mice surviving after three to six months develop PAS-positive (Kimmelstiel-Wilson-like) lesions in their kidneys.<sup>5</sup>

On the other hand, workers from England have rediscovered that the onset of insulin-dependent, juvenile diabetes is somewhat more frequent in the fall and winter.<sup>6</sup> Retrospectively, they tested for various viral antibodies but found an elevation only for those against Coxsackie B<sub>4</sub> when compared to nondiabetic controls or diabetes of long duration.<sup>7,8</sup> This must, however, await further confirmation.

Whereas Craighead's studies in mice have recently been corroborated by Volk,<sup>9</sup> the studies in man of the British workers could be confirmed in animals; Coxsackie B type 4 virus will produce diabetes-like changes in islets of mice.<sup>10</sup> Finally, we have the evidence described by Le Compte, Gepts and others<sup>11,12</sup> that in some juvenile diabetes there is a marked lymphocytic infiltration of the islets, which could be ascribed to either virus or autoimmune disease.<sup>13</sup> Thus it seems feasible that occasionally diabetes may be attributed to a viral etiology. This would be relevant for those patients with a rather explosive onset of diabetes if it follows a general virus infection. In table 1 are listed viruses which over the last years have been found to affect the pancreas. Among them one has to distinguish between agents which produce a general pancreatitis with maybe secondary islet involvement (example mumps) and those which produce only a specific isletitis (encephalomyocarditis virus).

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TABLE 1  
Types of Viruses Known to Affect the Pancreas

Virus	Animal Affected	Reference
Coxsackie B	mice	Pappenheimer et al., 1951 <sup>13</sup> Burch et al., 1971 <sup>10</sup>
	man	Kibrick et al., 1956 <sup>14</sup>
encephalomyocarditis	mice marmosets	Craighead et al., 1966, 1971. 1972 <sup>2-5</sup>
mumps	man	Kremer 1947 <sup>15b</sup> Hinden 1962 <sup>16a</sup> McCrae 1963 <sup>16b</sup>
Infectious mononucleosis	man	Wislocki 1966 <sup>17</sup>
rubella	man	Forrest et al., 1969, 1971 <sup>18,19</sup>
reovirus	mice	Stanley et al., 1953 <sup>20</sup>
infectious pancreatic necrosis virus	trout	Wood et al., 1955 <sup>21</sup>
foot and mouth	cattle	Pedini et al., 1962 <sup>22</sup>

Does a viral etiology of diabetes negate its genetic aspects? Both are compatible with each other. Whether there is a genetic basis for diabetes of the kind proposed by Cerasi and Luft<sup>23</sup> or not, it is clear that such defects might render individuals more susceptible to toxic or viral agents. In addition, it is obvious from many clinical observations that factors other than heredity, such as pregnancy, obesity and infection, play an important role. It is conceivable that the defect in diabetes is the inability to regenerate or expand the beta cell mass. If for example the islets are damaged by a virus in a normal person and if destruction is not complete, they may undergo total regeneration, whereas in a person predisposed to diabetes, the beta cells could be partially or drastically reduced in an irreversible manner resulting in the development of beta cell failure and thus diabetes. The idea that there is a "variable penetrance" of the diabetic gene could be explained in this way.

As no genetic marker for diabetes has been discovered, it has been proposed that what is inherited is a receptor site for a betatropic virus.<sup>24</sup> Such a difference in susceptibility probably due to genetic factors has been reported for viral hepatitis.<sup>25</sup> Another possibility to be considered is that the viral infection initiates an autoimmune mechanism. This may be precipitated by a direct effect of the virus on the beta cell resulting in damage with release of host antigens. They, in turn, either by themselves or together with the virus, may induce the production of antibodies. The work of

Nerup<sup>26</sup> suggesting that newly diagnosed diabetes may exhibit cellular hypersensitivity to pancreatic components may be important in this connection. However, antibodies to insulin have not unequivocally been detected in untreated diabetic patients.

To establish more definite proof that viruses play a role in the development of clinical diabetes, the following *prospective* studies may be needed: serial blood cultures, pharyngeal washings and stool cultures, associated with measurement of serum antibodies. As it is always difficult to define diabetes, it would be best if only insulin-requiring diabetic subjects whose diabetes was of recent onset were studied. It is of paramount importance that adequate controls be selected not only from nondiabetic patients, but also from family members of patients with diabetes of recent onset. The importance of adequate selection of controls cannot be overemphasized. They must be matched, not only by age and sex, but also by geographic areas. For example, antibodies to encephalomyocarditis virus are more common in city ghettos than in suburban areas. Of course, patients and controls have to be examined during the same season of the year. Finally, during an autopsy of juvenile diabetic patients whose diabetes was of recent onset, every attempt should be made to obtain pancreatic tissues for virus culture.

If the viral etiology of diabetes is a reality, a number of intriguing questions pose themselves. For example, how frequently can a viral etiology be incriminated as precipitating the disease. We are fully aware that no definite answer can be given at the present time. However, from some published data it may be inferred that as many as 15 per cent of newly diagnosed, juvenile, insulin-requiring diabetics might fall into this category. Again, is one virus involved, or as seems quite likely, more than one?

Naturally enough, caution must be exercised at this stage in delineating the function of viruses in the etiology of diabetes. Nevertheless it is clearly of great importance that studies on the possible viral cause of diabetes now be pursued vigorously.

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