Virus Isolated from Juvenile Diabetic

Epidemiology and animal studies had suggested a viral role in juvenile-onset diabetes, but conclusive evidence was elusive

The first solid evidence that juvenile-onset diabetes in humans can be caused by a virus has been reported by investigators from the National Institute of Dental Research (NIDR) and the National Naval Medical Center (NNMC). They isolated a virus known as coxsackie B4 from a child who developed diabetes and died within days after the onset of a viral infection, then demonstrated that the virus infects and damages cultured animal and human pancreas cells and induces diabetes in susceptible mice.

Juvenile-onset diabetes normally begins abruptly, most often in young people, and the full range of symptoms is generally exhibited almost immediately. It is the most difficult form of diabetes to control, and individuals afflicted with it almost always require insulin. Insulin manufacturers estimate that 12 to 15 percent of the 10 million diabetics in the United States suffer from the juvenile-onset form. Epidemiological studies by many investigators (*Science*, 25 April 1975, p. 347) have shown both a seasonal incidence of juvenile-onset diabetes and a temporal relation between certain viral infections and the subsequent development of diabetes, suggesting that viruses are involved in the etiology of the disease. The most likely candidates include the mumps virus, the rubella virus, and members of the coxsackie virus family. The last are common, small, RNA-containing viruses that can produce upper respiratory infections, muscle pain, and infections of the heart and brain. D. Robert Gamble of West Park Hospital in Epsom, Surrey, England, and his colleagues, in particular, have observed high concentrations of antibodies to the coxsackie B4 virus in the blood of many victims of juvenile-onset diabetes.

Until about a year ago, the epidemiological studies were only partially supported by laboratory work with animal models (*Science*, 2 May 1975, p. 436). John E. Craighead of the University of Vermont and Abner L. Notkins and his colleagues at NIDR had both shown that diabetes could be induced in certain strains of mice by encephalomyocarditis virus, which was first isolated from a pig dying of inflammation of the muscular walls of the heart. Eliot Rayfield of the Mt. Sinai School of Medicine had also demonstrated diabetic symptoms in hamsters inoculated with Venezuelan equine encephalomyelitis virus. Neither of these viruses infects humans, however, so the significance of these findings to the human condition was questionable. Gamble had demonstrated the induction of diabetes in mice with a strain of coxsackie B4 virus, but no one had been able to reproduce his results, even using a virus sample obtained from him.

Within the past year, however, Notkins and his colleagues have reported that they have been able to demonstrate damage to cultured β cells—those cells in the pancreas that produce insulin—by infection with the mumps and coxsackie B3 viruses. They have also been able to induce diabetes in susceptible mice with reovirus type 3 and coxsackie B4 virus. All four are common infectious agents in humans. They achieved this result by passaging each virus many times through cultured β cells. This repeated passaging selects for variants of the virus that replicate readily in the cells and damage them. They also examined many different types of mice until they found strains that were susceptible to the viral effects. These results provided a very strong suggestion that viruses play a role in the induction of juvenile-onset diabetes. The most recent findings provide proof.

The new virus specimen was obtained from a previously healthy 10-year-old boy who was admitted to NNMC in a diabetic coma within 3 days after the onset of symptoms of a flu-like illness. The boy died 7 days later and a postmortem examination showed destruction of β cells. Marshall Austin of NNMC contacted Notkins and his colleagues, Ji-Won Yoon and Takashi Onodera, and provided them with tissue specimens and blood samples from the youth. Inoculation of ground pancreas tissue from the youth into cultures of mouse, monkey, and human cells led to isolation of a virus identified as a variant of coxsackie B4. Injection of the new virus into susceptible mice produced diabetes, and the investigators were subsequently able to recover the virus from the diabetic mice. The NIDR group was thus able to fulfill the four Koch's postulates that are commonly accepted as proof that an infectious agent is the cause of a disease.

Many questions remain to be answered about the nature of the disease process. Gamble and others have shown, for example, that antibodies to coxsackie B4 are present in about half of the population. Antibodies to mumps, rubella, and reoviruses are also quite common. It thus seems clear that initiation of juvenile-onset diabetes requires more than a single virus infection. Similarly, many juvenile-onset diabetics show no evidence of ever having been infected with coxsackie B4, so there are apparently a multiplicity of causes for the disease. Some investigators speculate that infections by each of the viruses may produce some damage to β cells in susceptible individuals, but that diabetes is initiated only when a sufficient degree of damage is achieved; its onset would then correlate with the last infection.

It is also clear that not everyone is susceptible to the effects of viruses on β cells, just as only selected strains of mice are susceptible. In fact, several studies have shown that juvenile-onset diabetics have a higher than normal incidence of certain histocompatibility antigens, which implies that a particular genetic makeup is necessary. Notkins suggests that the genetic effect involves the presence of specific receptors on the surfaces of β cells that permit infection by viruses. Only persons with the receptors would be able to contract juvenile-onset diabetes as the result of an infection. Craighead, though, argues that there is no evidence for the presence of such a receptor on β cells. He suggests instead that differences in metabolism of β cells are responsible for differences in susceptibility to cellular damage. No matter which is the correct explanation, though, both investigators hope that it will eventually be possible to identify those individuals who are most susceptible to β cell damage and find some way to protect them. And if it turns out that coxsackie B4 alone, or in conjunction with one or more other viruses, plays a key role in initiation of diabetes, it may well be possible to develop a vaccine against one or more of them and sharply reduce the number of individuals who might contract the disease in the future.

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