Frank E. Correll, 61; professor of horticultural science, North Carolina State University; 20 February.

Roland P. Davis, 90; dean emeritus, College of Engineering, West Virginia University; 11 December.

Robert R. Gatts, 49; professor of mechanical engineering, University of Kansas; 8 December.

David T. Griggs, 63; professor of geophysics, Institute of Geophysics, University of California, Los Angeles; 31 December.

K. Albert Harden, 69; former dean, College of Medicine, Howard University; 24 December.

Leo E. Melchers, 87; professor emeritus of plant pathology, Kansas State University; 29 December.

John E. Nordskog, 81; professor emeritus of sociology, University of Southern California; 21 November.

Masaru Ogawa, 55; professor of physics, University of Southern California; 23 December.

John F. O'Rourke, 43; associate professor of sociology, University of Massachusetts; 6 December.

Marion Ownbey, 64; professor of botany and genetics, Washington State University; 7 December.

Melissa L. Richter, 54; professor of psychology and biology, Sarah Lawrence College; 28 November.

Lila Sands, 86; former professor of chemistry, University of Arizona; 18 November.

Ernst Simonson, 75; professor emeritus of physiology, University of Minnesota; 7 December.

Henry W. Thurston, Jr., 81; professor emeritus of plant pathology, Pennsylvania State University; 19 December.

Arthur J. Vorwald, 70; professor emeritus of medicine, Wayne State University; 29 November.

Everett P. Wheeler II, 74; senior research associate, geological sciences department, Cornell University; 30 October.

RESEARCH NEWS

Diabetes: Epidemiology Suggests a Viral Connection

Diabetes is a rapidly increasing health problem. The number of diabetics in the United States has burgeoned from 1.2 million in 1950 to an estimated 5 million now, an increase of more than 300 percent while the population has grown only about 50 percent. Treatment with insulin has markedly increased the life expectancy of diabetics. But in spite of treatment with insulin, strict diets, and oral antidiabetic agents, diabetes is still the fifth leading cause of death by disease in this country and the second leading cause of blindness. Progress in research on diabetes seemed to tail off in the 1950's and early 1960's, but there has been a marked resurgence during the last few years. Epidemiologists have produced much evidence that there is a link between viral infection and the onset of diabetes. Virologists have developed several model systems in which viruses appear to produce diabetes in animals. Geneticists have collected evidence suggesting that there are two different forms of diabetes with different methods of initiation. Endorcrinologists have shown that a second hormone, glucagon, is involved in the pathology of diabetes, suggesting that much better control of diabetic symptoms can be accomplished by regulation of the concentrations of both insulin and glucagon. And clinicians and technologists have developed new methods with the potential for providing a more natural regulation of insulin concentration, such as transplantation of pancreases or the islets of Langerhans and implantation of artificial pancreases or cultured beta cells. None of these developments have yet met with any significant clinical application, but they offer much promise for future use. In the next few weeks Research News will present several articles assessing the status of research in diabetes and examining some of the areas where progress has been most apparent.

As long ago as 1864, the Norwegian physician J. Stang reported that diabetes developed in one of his patients shortly after a mumps infection and hypothesized there might be a link between the two events. Since then, there have been many scattered reports of temporal associations between viral infections and the onset of diabetes. The agents thus implicated have included mumps, hepatitis, rubella, coxsackie, and influenza viruses, adenoviruses, enteroviruses, and cytomegalovirus. The presumed links to diabetes seem logical because many of the viruses are known to replicate in the pancreas, but they have often been dismissed as coincidence because of the relatively high incidence of both the viral infections and diabetes.

Only within the past few years has there appeared more substantive evidence linking viruses and diabetes. This new material includes more extensive epidemiological evidence, the identification of high concentrations of antibodies to viral antigens in newly diagnosed diabetics, and several demonstrations that viral infections can produce diabetes-like conditions in animals. Some of this evidence is contradictory and inconclusive, but it is nonetheless becoming clear that viruses may play some role in the initiation of the type of diabetes known as acute-onset or juvenile-onset diabetes. It is equally clear, however, that genetic predisposition to diabetes may play a large role in juvenile diabetes and may be the predominant factor in the maturity-onset form. The virus-initiated development of diabetes in animals will be discussed in a subsequent article.

Mumps virus has been most consistently associated with diabetes in scattered reports, but there has been little concrete epidemiological evidence to support the association. The most notable exception was the 1958 report by Kerstin Melin and Bo Ursing of the Hygiea Sverige in Lasarettet, Umeå, Sweden, who studied an outbreak of mumps in an isolated Swedish community. Of 40 children who contracted mumps during the episode, four developed diabetes during the following year. This proportion is much higher than would be predicted from the normal incidence of juvenile diabetes and is suggestive of a link to the mumps infection.

Somewhat stronger evidence was presented last year by Harry A. Sultz and his associates at the State University of New York at Buffalo. They studied

medical records in Erie County, New York, for the 25-year period 1946 to 1971 and found that the incidence of mumps varied through three cycles of high and low incidence, with the peaks occurring approximately every 7 years. The incidence of juvenile diabetes, they found, paralleled the incidence of mumps, but with an average lag period of 3.8 years. This lag period, Sultz argues, may reflect the time required for the virus to produce permanent damage to the pancreas.

Sultz and his associates then located 118 Erie County children who were diagnosed during that period to have juvenile diabetes. Of the 118, 59 either had had mumps or had been exposed to mumps prior to the onset of diabetes and 29 more had been vaccinated against mumps prior to its onset. Eight had been exposed to mumps at an unknown time, and the remaining 22 had apparently never been exposed.

Some scientists have criticized Sultz's findings on the grounds that mumps is a nearly universal disease of childhood; but Sultz counters that the cyclical relationship between mumps and diabetes strongly supports the association. In the light of his findings, Sultz speculates that the sharp increase in the incidence of diabetes among young boys during the 1950's may have been related to the then-common practice of exposing preadolescent boys to mumps to prevent the possible sterility that can result from contracting the disease after puberty. He also notes the apparent link between diabetes and vaccination for mumps, but argues for continued vaccination on the grounds that the damage resulting from a high frequency of mumps would be much more severe than that produced by the present frequency of diabetes.

Another viral infection that has frequently been linked to diabetes is rubella (German measles). Many physicians have reported incidents similar to that described by George M. Johnson of the Fargo Clinic in Fargo, North Dakota, and Robert B. Tudor of the Quain and Ramstad Clinic in Fargo. They delivered two unrelated infants with congenital rubella and observed that both had diabetes at birth, a very uncommon occurrence among healthy infants. The only organized study of such a link, however, has been performed by Jill M. Forrest and her colleagues at the Children's Medical Research Foundation in Sydney, Australia.

In 1967, Forrest's group located 50

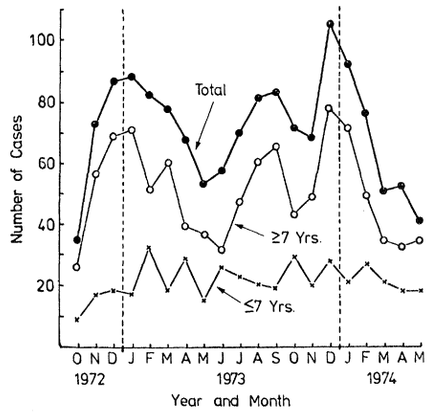

Fig. 1. Seasonal incidence of new cases of juvenile diabetes among children less than 16 years old, as reported to the British Diabetic Association register. [Source: D. Robert Gamble]

young adults who had suffered congenital rubella—a rather large number considering the low incidence of the affliction. One of the 50 had diabetes. Four years later, Forrest had lost track of six of the patients. By this time, however, five of the remaining 44 were diabetic and four others had an abnormal glucose tolerance and abnormal insulin release characteristic of the early stages of diabetes. This proportion—9 out of 44, or 20 percent—is nearly ten times the normal incidence of diabetes in the population.

Damage to Embryonic Organs

Subsequently, Forrest located four other youths with both congenital rubella and diabetes. Her findings are a strong indication of a link between congenital rubella and diabetes, and the nature of the link seems obvious. Congenital rubella is known to damage many different embryonic organs, so it is reasonable, Forrest suggests, that it might damage the pancreas; nearly all the subjects examined by Forrest also had other birth defects. There is, however, little evidence regarding the speculation that postnatal rubella might also be linked to diabetes.

The suggested link between diabetes and viral infections is further supported by the seasonal pattern of the onset of diabetes. As early as 1926, S. Franklin Adams of the Mayo Clinic reported that the onset of juvenile diabetes in Minnesota showed a peak incidence in September and the lowest incidence in May and June. He attributed this pattern to the sedentary life and respiratory infections of winter. In 1957, Thaddeus S. Danowski of the University of Pittsburgh Medical School reported a series of 409 cases of juvenile diabetes which showed a slight increase in incidence during winter.

Perhaps the best epidemiological data on the link between viruses and diabetes has been produced by D. Robert Gamble of the Public Health Laboratory at West Park Hospital in Epsom, Surrey, England, and K. W. Taylor, now at the University of Sussex in Brighton. They examined the records of 2816 diabetics treated at King's College Hospital in London from 1955 to 1968. Among 174 insulin-dependent (or juvenile) diabetics below the age of 20, the lowest incidence of onset occurred in June; the incidence was about seven times higher at the peak in October. Similar results were obtained when they combined their data with that of Adams and Danowski.

Among the 184 insulin-dependent diabetics who were 20 or older, there was much less seasonal variation, but there was a broad peak in autumn. The incidence of onset among a much larger number of insulin-independent or maturity-onset diabetics over the age of 40 also showed little seasonal variation. There was a sharp minimum in December (attributable, Gamble speculates, to hesitancy in consulting a doctor during the holidays), but in general there was only a slightly higher incidence of onset in the winter months than in summer. These results thus reflect the growing consensus that there is an association of viral infections with the juvenile form of diabetes, but perhaps not with the maturity-onset form.

In December 1972, the British Diabetic Association began a registry of all newly diagnosed cases of juvenile diabetes in England. To date, according to Gamble, the registry has accumulated data on nearly 3000 new cases. Among patients aged 7 to 15, he says, there are peaks in incidence in October and December with a marked minimum in May and June. Patients less than 7 years old, however, show no obvious seasonal incidence, suggesting that they may contract diabetes through a different mechanism. Data from the survey also show that the incidence is lowest in the first year of life and increases to a maximum at 11 years of age, with a smaller peak at age 5.

The seasonal incidence of diabetes, Gamble says, is similar to that of the total incidence of viral infections of childhood, which shows an autumn peak due to enteroviral infections and a win-

ter peak due to respiratory viruses. The peaks of incidence with increasing age, he argues, correspond with entry to school at age 5 and transfer to secondary school at age 11. It is conceivable that these milestones of school life may represent periods of exposure to new viruses. This correlation is supported, Gamble points out, by the observation that children who enter school at a younger age than normal also develop diabetes at a younger age.

Gamble suggests two possible explanations for his observations. It may be, for example, that certain viruses may immediately provoke sufficient pancreatic damage to produce diabetes. The peaks of incidence that occur in autumn and winter might then be associated with viral infections that are prevalent at, or just before, these times. This possibility is inconsistent with Sultz's suggestion of a lag period between infection and the onset of diabetes. An alternative and more likely possibility, Gamble says, is that the pancreatic damage caused by many different viral infections may be cumulative. The onset of diabetes would thus be correlated only with the most recent infection—even though most of the pancreatic damage might have been caused by a nearlier infection. There would thus be little lag between the final infection and the onset of diabetes.

Gamble and Taylor have also examined the blood serums of diabetics for antibodies to antigens from common viruses. In one series of tests, they examined serums from 123 patients with juvenile diabetes of recent onset and from 250 controls. For most of the viruses studied, including mumps virus and several common respiratory viruses, the percentage of diabetics with a high concentration of antibodies was little different from that of controls. The only exception was with coxsackie viruses, a family of common, small, RNA-containing viruses (picornaviruses) that produce upper respiratory infections and a pattern of symptoms much like poliomyelitis except that there is no paralysis.

Antibodies to one coxsackie type known as B4 were present at high concentrations in 65 percent of 79 youths examined within 3 months after the onset of diabetes, but in only 41 percent of the controls. Among another group of patients who had had diabetes for more than 2 years, however, the percentage with high concentrations of antibodies to any viral antigen was little

What Is Diabetes? What Does It Do?

Diabetes mellitus, generally called simply diabetes, is a disease in which the metabolism of carbohydrates is impaired and that of proteins and fats is enhanced. Ingested glucose or glucose mobilized from the body's reserves cannot be assimilated into fat and muscle cells for use, and thus builds up to high levels in the blood (hyperglycemia) and is excreted in the urine (glucosuria). Both hyperglycemia and glucosuria persist even when the diabetic individual is fasting.

Breakdown of tissue proteins is sharply accelerated in diabetics, with a concomitant increase in the excretion of nitrogen in the urine. Breakdown of lipids and fatty acids is also accelerated, leading to the production of large quantities of the so-called ketone bodies, such as acetoacetic acid, β-hydroxybutyric acid, and acetone. Excretion of glucose and these ketone bodies causes loss of water and salt from the body, producing dehydration and severe thirst. In severe cases, buildup of the ketone bodies can produce a condition known as ketoacidosis; the accumulation of these acids in the blood pushes its *p*H below the critical level of 7.4, thereby producing coma and, if the condition is not corrected by the administration of insulin, eventually death.

Many tissues, however, do not require insulin to assimilate glucose so that, during hyperglycemia, the concentration of glucose within these cells approaches that in the blood. Much of this glucose is oxidized to sorbitol and to fructose, both of which are retained in the cell even when the concentration of glucose in the blood is returned to normal. The high concentrations thus created produce electrolyte imbalance, water retention, and other ill effects. Accumulation of sorbitol in the lens of the eye, for example, may result in formation of cataracts, while its accumulation in peripheral nerve cells may damage those cells and produce numbness. Effects on blood vessels may result in atherosclerosis and retinopathy, a form of blindness. Diabetes is the second leading cause of blindness in the United States.

Two Major Forms of Diabetes

There are two major forms of diabetes: juvenile-onset diabetes and maturity-onset diabetes. Despite their names, either type can strike individuals of all ages. The chief differences between the two types are the speed of onset of the symptoms and the severity of those symptoms. The juvenile-onset form (also called acute-onset diabetes) begins abruptly, and the full range of symptoms is often exhibited almost immediately. It is the most difficult form of diabetes to control and individuals afflicted with it almost always require insulin. Hence, the terms insulin-dependent diabetes and juvenile-onset diabetes are often considered to be synonymous. Manufacturers of insulin estimate that there are about 1.25 million insulin-dependent diabetics in the United States.

Maturity-onset diabetes, in contrast, begins slowly and generally produces milder symptoms. Individuals with this form of diabetes can generally control the disease by dietary regulation or with oral drugs that stimulate the release of insulin, but they nevertheless often develop many of the side effects of diabetes. There are an estimated 3.75 million maturity-onset diabetics in the United States. The total number of new cases of diabetes in this country, moreover, is growing at the rate of about 1 million every 3 years.

Many subspecies of diabetes are also recognized. Perhaps the most important of these is latent diabetes, a mild form in which the patient displays no overt symptoms, but exhibits characteristic responses to diagnostic procedures, such as above-normal concentrations of glucose in the blood after fasting and an abnormal response to the administration of glucose. Latent diabetes generally progresses to maturity-onset diabetes.—T.H.M.

different from that among the controls.

In a more recent study of another 162 patients with juvenile diabetes of recent onset, Gamble and Taylor found somewhat lower concentrations of antibodies in a higher percentage of patients. Among diabetics aged 10 to 19 years, 87 percent showed antibodies to coxsackie B4 compared to 65 percent of the controls. Among those more than 20 years old, 63 percent showed antibodies to coxsackie B4 compared to 55 percent of controls; this difference was not statistically significant. The sum of this evidence, Gamble argues, is that coxsackie viruses appear to be in some way linked to the initiation of juvenile diabetes.

Gamble and Taylor's findings have not been fully supported by other investigators. J. A. Weaver and his associates at the Royal Victoria Hospital in Belfast, Ireland, have reported that they could not find a statistically significant difference between the percentages of diabetics and controls with antibodies to coxsackie B4 antigens. Gamble argues, however, that their sample was not large enough either to prove or to disprove an association.

Peter H. Bennett and his associates at the Epidemiology and Field Studies Branch of the National Institute of Arthritis, Metabolism, and Digestive Diseases, Phoenix, studied an epidemic of coxsackie B4 infections that struck the relatively isolated Pribiloff Islands during the winter of 1967–1968. Before the epidemic, Bennett says, less than 2 percent of the islands' population showed antibodies to coxsackie B4 antigens; afterward, 77 percent showed antibodies.

Five years after the epidemic, Bennett's group measured the glucose tolerance of 335 islanders. They found that there was no difference between the incidence of diabetes in those who were infected and those who were not. Furthermore, they found no cases of diabetes among islanders under the age of 20, even though the incidence of infection among this group was exceptionally high. It is possible, he notes, either that the sample was not large enough to detect an association or that the Aleut population might not be susceptible to pancreatic damage resulting from viral infection. In contrast, Bennett has obtained some preliminary evidence among Pima Indians in Arizona —a population with an abnormally high incidence of diabetes—suggesting a higher prevalence of coxsackie B4 antibodies among newly diagnosed diabetics.

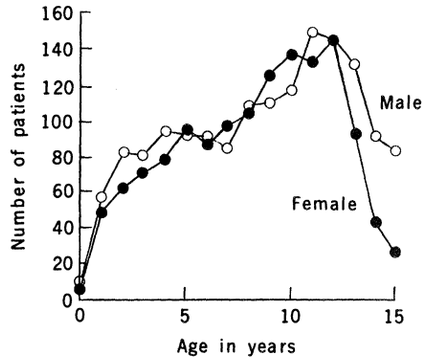

Fig. 2. Age incidence of new cases of juvenile diabetes, as reported to the British Diabetic Association register. [Source: D. Robert Gamble]

A similar study was that of John C. Hierholzer and his associates at the Center for Disease Control, Atlanta, who studied an outbreak of coxsackie B3 and B4 infections in a children's home during 1968. Four years later, they located 64 youths who had been infected with either or both viruses during the outbreak and 24 who had been infected with either or both prior to the outbreak. None of these youths had any abnormalities of glucose metabolism, suggesting that there is no link between coxsackie viruses and diabetes. It is possible, though, that this sample is also too small for any definite conclusions to be drawn.

A Geographic Cluster

Hierholzer and his associates also studied an unusual geographic and temporal cluster of 12 cases of juvenile diabetes that occurred in Pinellas County, Florida, in early 1972. They were able to obtain serum samples from 9 of the 12 patients. Eight of the nine patients had experienced recent viral infections, predominantly respiratory, but the illnesses bore no uniform temporal relation to the onset of diabetes. Immunological study of the serum samples showed that there was no viral infection common to all. Three of the nine diabetics showed high concentrations of antibodies to antigens from coxsackie B3 virus, compared to only 6 percent of the controls. The mean concentration of antibodies to a group of 26 viruses, however, was no higher among the diabetics than among the controls. These results, Hierholzer argues, neither support nor negate a link between viral infections and diabetes.

It thus seems apparent that, even though the evidence suggests that diabetes is linked to viral infections, there is no firm evidence supporting a link to a specific virus. The identification of one or more such viruses will thus require a great deal more work, and some of it is already in progress. The British Diabetic Association register, for example, will provide the largest available base of statistical information for further study. Gamble is extending his search for viral antibodies among newly diagnosed diabetics. Sultz, in association with investigators at the Children's Hospital of Buffalo and the Rochester University School of Medicine, is beginning a similar search. And Bennett is continuing his studies among the Pimas. With all of these studies under way, it seems likely that a better understanding of the role of viral infection in diabetes will soon emerge.

The results of the epidemiological studies that have been discussed suggest that if, in fact, viruses are involved in the etiology of diabetes, they can initiate pancreatic damage only in individuals who are genetically predisposed to such damage. These studies further suggest that there are two different types of diabetes and that viruses may be closely associated with only one type. These results are supported by recent studies of the genetics of diabetes, which suggest that there are different genetic elements associated with each type. The juvenile form of diabetes appears to be linked to histocompatibility antigens that may be associated with certain genes controlling immune responses. The maturity-onset form appears to be linked to a different, as yet unknown, set of genes that are primarily responsible for familial inheritance of diabetes, although onset of this form is probably precipitated by environmental factors.

It has long been recognized that diabetes seems to occur to a greater extent in certain families. The British Diabetic Association register, for example, indicates that 12.7 percent of newly diagnosed diabetics have close relatives who are diabetic, compared to only about 2 percent of the population at large. American investigators suggest that the percentages are about the same in this country, but the nature of this familial association has never been clear.

Many of the first studies on the genetics of diabetes have focused on differences between identical and nonidentical twins—those that came from the

same egg and thus have the same genetic complement and those that do not. If there is a genetic element in diabetes, the proportion of cases in which both twins have diabetes should be much higher among identical twins. This appears to be the case.

At least four different groups of investigators have studied diabetes in twins. They include Priscilla White and her associates at the Eliot P. Joslin Research Laboratory in Boston, H. ThenBerg of Berlin, Bent Harvald of the Bispebjerg Hospital in Copenhagen, and, most recently, Marise S. Gottleib of the Joslin Laboratory and the late Howard F. Root of Harvard University.

Among the four groups, they studied 176 pairs of identical adult twins and 416 pairs of nonidentical adult twins, all chosen because at least one twin had diabetes. Collectively, they found that the second twin also had diabetes in 79 pairs of identical twins (45 percent), but in only 35 pairs of the nonidentical twins (8 percent). Furthermore, Gottleib points out, in nearly all cases in which the first twin to develop diabetes was over 40 years old at its onset—the classical type of maturity-onset diabetes—the second twin also developed it.

This observation is supported by Robert B. Tattersall and D. A. Pyke of the King's College Hospital in London, who studied 96 pairs of identical twins selected in the same fashion. They found that if the first twin was younger than 40 at the onset of diabetes, 53 percent of the 59 second twins also contracted it. If the first twin was older than 40 at its onset, however, 92 percent of the 37 second twins also contracted it. These results provide strong support for the hypothesis that the development of maturity-onset diabetes is genetically linked.

This proposition is further supported by results reported this year by Tattersall and Stefan S. Fajans of the University of Michigan. They found that 61 diabetics under the age of 25 who had been examined at the University Hospital in Ann Arbor could be divided into two distinct groups, those with classical juvenile-onset diabetes and those with maturity-onset diabetes of youth, on the basis of the severity of the abnormalities of glucose metabolism and the speed of onset of the symptoms. They found that there were strong genetic links among the patients with maturity-onset diabetes, but few links in the second group.

They thus found that 85 percent of the 26 patients with maturity-onset diabetes had a diabetic parent, compared to only 11 percent of the 35 patients with juvenile diabetes. Direct transmission of diabetes through three generations was observed in 46 percent of the families of the maturity-onset diabetics, compared to only 6 percent of the families of the juvenile diabetics. And finally, 53 percent of the siblings of maturity-onset diabetics were found to have latent diabetes, compared to only 3 percent of the siblings of juvenile diabetics. These results, Tattersall and Fajans argue, indicate that there are two distinct patterns of inheritance of diabetes and suggest, but do not prove, that the maturity-onset form of the disease is transmitted by a dominant gene that is not sex-linked.

Other evidence suggests that the juvenile form of diabetes is also genetically linked, but in a somewhat different fashion. This work indicates that susceptibility to pancreatic damage resulting from viral infection is associated with certain histocompatibility antigens, immunologically defined (and genetically determined) characteristics of tissues which, among other things, determine the compatibility of organs for transplantation. Certain histocompatibility antigens have been shown to be associated with other diseases, such as Graves' disease and idiopathic Addison's disease, and the association has been particularly noted in diseases where viral infection and autoimmune processes are involved.

HL-A8 and W15 Antigens

The first investigation in this area, however, suggested that there might not be an association. Roy L. Walford and his associates at the University of California School of Medicine at Los Angeles typed the antigens of 44 juvenile diabetics of various races and compared them to a similar number of nondiabetic controls. They found no statistically significant difference between the two groups in the frequency of occurrence of any one antigen, but they did observe a difference for two of the antigens. They found that antigens HL-A8 and W15 were present in 34 and 16 percent of the diabetes, respectively, but in only 25 and 7 percent of the controls.

The significance of this difference was confirmed by D. P. Singal and M. A. Blajchman of McMaster University in Hamilton, Ontario. They typed the antigens of 50 insulin-dependent adult diabetics, 21 insulin-independent adult diabetics, and a comparable number of controls—all of the subjects were Caucasian—and found a definite increase in the incidence of the W15 antigen. They found that it was present in 36 percent of the insulin-dependent diabetics, but in only 10 percent of the controls and 9.5 percent of the insulin-independent diabetics. They found only insignificant differences in the incidence of the HL-A8 antigen, however.

The most recent and most comprehensive results have been obtained by Jørn Nerup of the Gentofte Hospital in Copenhagen, Denmark, and nine of his colleagues at other institutions in the city. They typed the antigens of 146 Caucasian diabetics, using what they contend are much better immunoreagents than those used by the earlier investigators. They found that the HL-A8 antigen was present in 42 percent of 109 insulin-dependent diabetics, compared to only 23.7 percent of 1967 controls and 24 percent of 37 insulin-independent diabetics. The W15 antigen was present in 35 percent of the first group, 17.9 percent of the second, and 22 percent of the third. Similar results, as yet unpublished, have apparently subsequently been obtained by J. C. Woodrow of the University of Liverpool, England.

Combining their results with those of Walford and of Singal and Blajchman, the Copenhagen group concluded that individuals with the HL-A8 antigen are twice as likely as other individuals to develop juvenile diabetes; those with the W15 antigen are 2.8 times as likely. In contrast, individuals with either of the two antigens are no more likely than anyone else to develop maturity-onset diabetes.

The nature of this link is unknown, but Nerup suggests that it may be immunological. Other evidence, he says, suggests that histocompatibility complexes such as HL-A8 and W15 are associated with the so-called immune response genes that control the development of cell-mediated immunity to infectious agents. It is thus possible that the genetically determined host response could fail to eliminate an infecting virus, which in turn might destroy pancreatic beta cells or trigger an autoimmune response against the infected organ. Demonstrations that such reactions can occur in laboratory animals will be the subject of a second article.

—THOMAS H. MAUGH II