the most significant finding from the segregation analysis is the evidence it provides that a small proportion of the cases are nongenetic in etiology.

In conclusion, genetic registries, such as the one described in this article, could have a nationwide impact on the diagnosis of hereditary disease and on genetic counseling for affected individuals and their families. Our research applies an innovative technique for the diagnosis of genetic diseases that could serve as a prototype to demonstrate the practical value of categoric genetic registries. This research will almost certainly lead to the recognition of new forms of hereditary deafness and retinitis pigmentosa which could be the first step in the development of specific therapies.

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The Genetic and Environmental Effects on Diabetes in Humans and Animals: An Overview

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LINDA A. COREY, PH.D., Assistant Professor of Human Genetics

Despite intense scrutiny the precise etiology of diabetes mellitus remains unclear. There appear to be two major forms of diabetes: juvenile-onset or insulin-dependent diabetes, and late-onset or insulin-independent diabetes1,2; the late-onset form, in itself, may be etiologically heterogeneous.3 Either form may occur at any age, with a clear distinction between the two often being difficult to make. Juvenile-onset diabetes, representing 5% to 10% of all cases, is charac-
terized by abrupt onset, clinical manifestation of hyperglycemia and ketoacidosis, and generally by a requirement for exogenous insulin; in maturity-onset diabetes plasma levels of insulin are usually normal or elevated and the abnormality in glucose metabolism results from a decrease in the number of insulin receptors rather than a deficiency of the hormone itself.

**Genetics of Diabetes in Man**

It is generally accepted that there is an hereditary predisposition to diabetes, but there is little agreement as to its mode of inheritance. Early investigators concluded that diabetes was inherited in a simple Mendelian fashion, probably as an autosomal recessive trait. Subsequent studies, however, suggest that diabetes may be controlled by a number of genes whose final expression is influenced to varying degrees by the environment. It is still impossible to resolve the multifactorial versus monogenic controversy from the data and analytical methodologies now available. Diabetes is undoubtedly heterogeneous and this fact, as well as the late age of onset in many cases, greatly complicates genetic analysis. For example, striking differences in concordance rate among identical twin pairs who have late-onset diabetes (92%) compared with identical twins with early-onset diabetes (52%) provide strong evidence that the two forms are etiologically distinct. Concordant juvenile-onset pairs also had a positive family history of diabetes more frequently than discordant pairs, suggesting that some cases are predominantly genetic, and others environmental, in etiology.

**Genetics of Spontaneous Diabetes Mellitus in Animal Models**

A variety of animal models with spontaneous diabetes mellitus have been reported in the literature (Table I). Apparently many different mutations can lead to spontaneous diabetes. Simple autosomal recessive inheritance is displayed in db/db, ob/ob,

<table>
<thead>
<tr>
<th>Animal Name</th>
<th>Mutation &amp; Chromosome number</th>
<th>Inheritance</th>
<th>Obesity</th>
<th>Hyperglycemia</th>
<th>Elevated Serum Insulin</th>
<th>Ketosis</th>
<th>Changes in Islet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>db/db</td>
<td>Autosomal recessive</td>
<td>++</td>
<td>+++</td>
<td>transient</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>C57Bl/Ks</td>
<td>ob/ob</td>
<td>Autosomal recessive</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Yellow</td>
<td>A/a</td>
<td>Autosomal dominant</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>KK mouse</td>
<td>-</td>
<td>Polygenic</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NZO</td>
<td>-</td>
<td>Polygenic</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PBB/Ld</td>
<td>-</td>
<td>Polygenic (?)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>C57Bl/6</td>
<td>-</td>
<td>Polygenic</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spiny mouse</td>
<td>-</td>
<td>Polygenic</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Sand rat</td>
<td>-</td>
<td>Polygenic</td>
<td>+</td>
<td>+++</td>
<td>transient</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Zucker rat</td>
<td>fa/fa</td>
<td>Autosomal recessive</td>
<td>+</td>
<td>+</td>
<td>transient</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Chinese hamster</td>
<td>Polygenic (4 genes)</td>
<td>+</td>
<td>+++</td>
<td>transient</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>S. African hamster</td>
<td>Polygenic</td>
<td>-</td>
<td>+++</td>
<td>(?)</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
and fa/fa rodents; autosomal dominant A'y inheritance is apparent in the yellow mouse; and finally, polygenic inheritance has been invoked for the KK, NZO, PBB/Ld mice strains, rats, and hamsters.

The clinical syndromes expressed by these rodent models will in most cases involve obesity and/or hyperglycemia as seen in the db/db, ob/ob mice, and the fa/fa rat with or without ketosis; hyperglycemia without obesity is evident in the Chinese and South African hamster; while marked obesity without overt diabetes was displayed in ob/ob, A'y, NZO, PBB/Ld mice, and the Zucker rat. This wide range of symptoms illustrates the difficulty in determining whether genetic, environmental or maternal factors are the primary determinants in this disease.

It now seems clear that even where diabetes is associated with a specific mutation, that is, db/db in the C57Bl/7sJ mouse, other genetic and/or environmental factors, such as genetic modifiers or viral infection, may be crucial in initiating this disease. The ob/ob (obese) mutation in the C57Bl/6J inbred mouse leads to obesity without diabetes. Transfer of this mutation to the C57Bl/Ks inbred mouse strain resulted in a C57Bl/Ks ob/ob animal with a metabolic disorder strikingly similar to the diabetic mutant (db/db) itself. These results clearly indicate that two separate mutations which are known to be located on different chromosomes can give rise to indistinguishable phenotypes when placed on the appropriate genetic background.

Environmental Factors in Diabetes Mellitus

Environmental factors such as dietary intake, gross obesity, pregnancy, increased levels of estrogen in females, and other endocrine changes have been correlated with onset of diabetes mellitus. Finally, infectious agents such as congenital rubella, group B coxsackieviruses, and mumps have also been shown to be associated with this syndrome. There is good reason to believe that congenital rubella may lead to diabetes mellitus in up to 20% of children who have been infected in utero. Similarly, mumps virus has long been recognized as a cause of pancreatitis in man, and scattered reports suggest that persistent diabetes mellitus may sometimes appear one to eight weeks after infection.

Presently, three experimental models for virus-induced diabetes have been reported in the literature. The first involves infection by an unknown virus in the guinea pig; the second model involves the experimental infection of mice with encephalomyocarditis (EMC) virus which specifically destroys B cells of the pancreas. Susceptibility appears to depend on genetic factors; some inbred strains are highly susceptible and others are not. These data clearly demonstrate that a viral agent belonging to the picornavirus group, can induce diabetes mellitus in susceptible animals. The third model system involves coxsackievirus B infection of the diabetic mutant mouse. Presently the best candidate for a causative viral agent of diabetes mellitus in man is coxsackievirus B. This agent has pancreatropic properties both in mice and humans and coxsackievirus B4 has been demonstrated in both the exocrine and endocrine sections of the pancreas in human newborns with encephalohepatamyocarditis. In addition, extensive epidemiological studies have established a correlation between coxsackievirus B4 infection and acute-onset diabetes mellitus.

Recent studies carried out by one of us have shown that the db mutation in the mouse causes a significant increase in susceptibility to coxsackievirus B4, and a dose-effect correlation between the virus and the diabetes mutation was evident. These observations were well supported by histopathological findings of the pancreata of animals infected with this virus (Table 2).

These two animal models (EMC and coxsackievirus B4) involving picornavirus infection demonstrate how genetic factors can interact with the environment to cause diabetes. In the EMC virus model the nature of the genetic predisposition of the host is unknown, but is thought to be a recessive trait involving more than one gene. In contrast, the findings in the mouse demonstrate that a single mutation at the db locus is responsible for the increased susceptibility to diabetes in coxsackievirus B4 infection.

Histocompatibility and Immune Factors in Diabetes

Renewed support for the hypothesis that immune mechanisms may have an etiological role in diabetes mellitus has been provided from the association between the histocompatibility antigens HLA-B8, W15, CW3, and HLA-D with diabetes mellitus. The possibility that HLA-genes predispose the host to virus infection, resulting in B cell destruction and insulin-dependent diabetes has been suggested. Alternatively, the HLA-genes may be involved in the induction of autoimmune responses, which again may have been triggered by virus infection. The latter alternative is supported by the observation that the diabetogenic HLA-D8 marker
has also been associated with an increase in autoim­
mune diseases. Finally, the evidence for, and signifi­
cance of, autoimmunity in diabetes is still highly de­
batable and little information on the regenerative
properties or repair mechanisms of B cells is avail­
able.

In summary, the evidence presented argues for
 genetic, environmental (viral), and immunological
factors in diabetes mellitus. The complexity of the
genetic factors in this syndrome is further emphasized
by the heterogeneous nature of the disease itself,
which may represent many different genetic entities. Insulin-dependent and insulin-independent diabetes
mellitus may each be etiologically heterogeneous.
Understanding of the interaction between genetic
and environmental factors will permit the evaluation
of their respective roles in the etiology of this syndrome.

Table 1 is adapted from Renold et al and Hunt et al.

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**TABLE 2**

Coxsackievirus B4 Edwards Infection in the Inbred Diabetic and Normal C57B1Ks Mouse

<table>
<thead>
<tr>
<th>Animal Genotype</th>
<th>Virus Dose in PFU&lt;sup&gt;a&lt;/sup&gt; Animal</th>
<th>Histopathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>db/db</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>db/+</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>+/+</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> CB4E = Coxsackievirus B4 Edwards.
<sup>b</sup> PFU = plaque forming units.
<sup>c</sup> C57B1Ks inbred mice with the specific mutation were used. The db/db animals displayed only chemical diabetes; food intake was monitored and regulated.
VI. CASE REPORTS

Syndrome Identification

What's in a name? This question is often asked of a genetic counselor when a syndrome is newly delineated. The brief case reports that follow demonstrate the importance of establishing precise diagnoses. They also emphasize that many of these syndromes are recognizable only after careful physical examination of the proband and family members, consultation with other subspecialties (for example, neurology, radiology, orthopedics, dentistry, pathology), and a review of the medical literature.

While it is true that there usually is no treatment for the basic condition, complications can often be anticipated and serious consequences averted. Thus, the diagnosis of Pierre Robin anomaly forewarns...