Furthermore, COI studies generally use average costs of activities to estimate total costs. Because several elements of the cost of activities, such as hospital days, will remain fixed when such activities are reduced (say, by prevention), total disease costs are likely to be gross overestimates of potential cost savings. To aid policy making, marginal analysis is the key, starting with estimates of current uses of resources (but not full COI studies), identification of possible changes in how these resources could be used, and enumeration of the costs and benefits of these proposed changes.

A third criticism of COI studies is their reliance on the "human capital" method to value time lost from productive activity through absenteeism, premature mortality, and premature retirement. The human capital method involves the use of earnings data, which may bias resource allocation toward diseases affecting white middle-class males. Furthermore, the use of such an approach in most studies may lead to overestimation of the costs of diabetes. Early retirement and loss of life will result in less lost production for society than is estimated if those who retire or die can be replaced from the pool of unemployed labor that exists in most countries (6). This methodological development does not appear to have been taken into account by recent COI studies on diabetes.

A final, and more trivial, criticism is that the use of results of COI studies in resource allocation would seem to provide strange incentive signals to health care providers; the more costly your disease, the more resources you will be allocated! Whether this may encourage inefficiency is not clear, but such a theoretical possibility exists.

We do not deny that good epidemiological data are required on the health and social consequences of diabetes and its complications. These data inform us that diabetes presents a major challenge to society, something that is already recognized, as evidenced by the recent substantial increase in federal funding for diabetes treatment and research (7). Why add a (very rough) monetary value to fairly accurate epidemiological estimates? Research monies may be better spent on estimating potentially preventable and treatable fractions associated with diabetes and the costs and benefits of specific activities aimed at prevention and treatment. One potential start to this process is to promote economic evaluations alongside existing randomized trials, as was done with the DCCT (5).

Of course, one often needs to go beyond the lifetime of a trial to establish the magnitude of future costs saved (or incurred) by an intervention. To model the future, a set of reference costs is required to permit estimation of the lifetime costs saved by preventing diabetes and its associated conditions. Some aspects of existing cost studies may be useful in this regard (8). A combination of economic evaluation alongside trials and data on reference costs is needed to provide the information that will lead to improved value for health care dollars spent on diabetes, a disease already estimated to cost $98 billion annually (1).

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Mutations in HFE, the Hemochromatosis Candidate Gene, in Patients With NIDDM

Genetic hemochromatosis (GH) is a frequent autosomic recessive disorder of iron metabolism characterized by excess iron deposition in various organs. In patients with GH, the frequency of diabetes ranges from 10 to 60%. Increased blood glucose levels and insulinemia have been recently reported in middle-aged men with high serum ferritin concentrations (1). Because iron metabolism is abnormal in some subjects heterozygous for GH, such individuals might be at increased risk for the occurrence of diabetes. The characterization of HFE, a strong candidate gene for GH, allows for the investigation of this hypothesis. HFE is a major histocompatibility complex class I–like gene in which two mutations have been described: a G/A transition at nucleotide 845, responsible for a Cys-to-Tyr substitution at position 282, and a C/G transition at nucleotide 187, resulting in a His-to-Asp substitution at position 63. The Cys282Tyr mutation is closely associated with GH, since 80–100% of GH patients are homozygous for this mutation, compared with 0.2% of control subjects (2). The role of the His63Asp mutation is less clearly defined.

We have analyzed the frequency of these two HFE mutations in 184 unselected patients with NIDDM and in 87 healthy blood donors of the same ethnic origin. The two regions of the HFE gene containing the mutations were amplified by polymerase chain reaction. The Cys282Tyr mutation creates a new *Rsa*I site, which was identified by enzyme digestion of the amplification products. The His63Asp mutation was detected by allele-specific oligonucleotide hybridization assay (2). The mutations were present at the same frequencies in NIDDM patients and in the control population: 9.2 and 8% of the NIDDM patients and the control subjects, respectively, expressed the Cys282Tyr mutation, and 25.5 and 26.1% the His63Asp mutation. There was no significant difference in the distribution of the various phenotypic and genotypic combinations at the two loci between the two populations. Altogether, allelic frequencies for the Cys282Tyr mutation were

4.9 and 4% in NIDDM patients and control subjects, respectively, and 14.4 and 18.4% for the His63Asp mutation. Only one NIDDM patient was found homozygous for the Cys282Tyr mutation. When the NIDDM patients were analyzed according to the presence of either HFE mutation, no difference between the patient groups was observed with regard to the frequency of family history of NIDDM, age at diagnosis, presence of obesity, presence of liver enzyme abnormalities or hyperlipidemia, or requirement for insulin therapy. The same results were observed when the patients were analyzed according to phenotypic combinations of the two mutations. Serum iron and transferrin saturation and ferritin concentration were significantly increased (by an average of 22, 30, and 15%, respectively) in patients expressing HFE mutations compared with those without any mutation.

Our results first show that two mutations in the HFE gene, the Cys282Tyr mutation, which has been closely associated with GH, and the His63Asp mutation, are not more frequent in NIDDM patients than in the control population. In one study, the prevalence of GH among diabetic patients was 1.34%, higher than in the general population (3). However, other studies addressing this issue did not demonstrate an increased prevalence of GH in diabetic subjects (4,5). Our study confirms, by direct analysis of the candidate gene for GH, that GH is not more frequent in NIDDM patients than in the general population. This is probably due to the fact that diabetes, although frequent in GH, is not a usual presenting clinical feature of this disease (6). A role for heterozygosity for GH in the occurrence of diabetes has been suggested. One large study of heterozygous subjects from GH families showed that in males, the relative risk for diabetes was marginally elevated (1.16) (7). Our results do not show an increase in the frequency of heterozygous subjects for HFE mutations in the NIDDM patients compared with the control subjects. This suggests that if HFE mutations are involved in the pathogenesis of NIDDM, this is not a frequent phenomenon. However, indexes of iron metabolism were higher in patients carrying at least one HFE mutation than in those with no mutation. This observation is in keeping with GH family studies showing that a fraction of subjects heterozygous for the GH gene have abnormal indexes of iron metabolism (8). Studies performed in subjects with liver iron overload (9) and in subjects from the general population (1) showed that increased iron stores are associated with abnormal glucose tolerance or insulin resistance. Thus, in those subjects in whom it is associated with increased iron stores, heterozygosity for HFE mutations may play a role in the pathogenesis of diabetes.

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Low Incidence of IDDM in Children of Veracruz-Boca del Rio, Veracruz

Results of the first validated IDDM registry in Mexico

By evaluating the incidence of IDDM in Spanish heritage populations, important insight into the etiology of IDDM may be gained. The available data have shown that there is at least a 10-fold difference in risk between individuals of Hispanic ancestry in the U.S. and, for example, Peruvians in Peru (1,2). A large number of the Hispanic population in the U.S. is of Mexican descendant. Up to now, no population-based information was available on the incidence of IDDM in Mexicans living in Mexico. We conducted a study to determine the incidence of IDDM in children <15 years of age, residents of Veracruz-Boca del Rio, Mexico, using standard methodology as proposed by the World Health Organization DIAMOND Project (3). Veracruz-Boca del Rio, the largest port in the country, is located on the Gulf of Mexico and is considered an urban area. According to the 1990 census (4), the total population was 447,202, with 144,640 (32.3%) aged <15 years.

Cases were included in the registry if they had a diagnosis of diabetes between 1 January 1978 and 31 December 1992, were put on insulin at discharge, were <15 years old, and were residents of the city of Veracruz-Boca del Rio. Eligible cases were identified by review of medical records from all nine hospitals in the public sector of the national health system, which covers >85% of the population (5). Reports from all seven endocrinologists,