quent (depending on the severity of the retinopathy) (3). Our data relate to patients <20 years old and cannot be generalized to the adult population. Stefánsson states that in Iceland, no patient progressed from "no retinopathy" to "vision-threatening retinopathy" within 2 years. However, since collecting the original data (1990–2002), we have been informed of two former patients who had rapid progression from level 31 and level 45 retinopathy to blindness in <2 years. These patients were 21 and 23 years old when blindness occurred (therefore outside of our study group), and both had significant risk factors for retinopathy (persistently high HbA_{1c} and diabetes duration 17 years).

Stefánsson describes a decrease in legal blindness due to retinopathy in the Icelandic population. Although this may be due to improved management of retinopathy, it may also indicate a reduction in retinopathy due to intensive insulin therapy. This would be in keeping with the trend in our population, in which the incidence of retinopathy has decreased over the last decade from 49 to 24% in patients of 8 years' diabetes duration (4). However, despite the declining incidence of retinopathy in our population, adolescents should be advised of the serious and real risk of blindness due to diabetic retinopathy. Indeed, blindness occurred in the two patients mentioned above in 2003 and 2004. Clinicians must not underestimate the risk of future blindness from retinopathy for adolescents.

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Of Genes and Men: The Alternative View of Sex Differences in Cystic Fibrosis

Response to Sims et al. and Milla et al.

Female subjects with cystic fibrosis–related diabetes have a worse prognosis than male subjects according to two independent studies recently published in *Diabetes Care* (1,2). It has been known for some time that females with cystic fibrosis generally have a significantly higher mortality than males from age 1 to 20 years (3), a sex difference that remains despite radical improvement in survival rates through the years (4). Are these differences a result of evolutionary, sex-specific selective pressures? We propose an evolutionary explanation for the observed sex differences in cystic fibrosis.

Congenital bilateral absence of the vas deferens (CBAVD), a cause of infertility in 1–2% of European men, is a clinical sign of cystic fibrosis. Conversely, mutations in the cystic fibrosis transmembrane regulator (*CFTR*), the cause of cystic fibrosis, are also found in 80% of patients with isolated CBAVD (5,6). Indeed, the observation that the vas deferens is abnormal in almost all male cystic fibrosis patients led to the suggestion that CBAVD is an incomplete form of cystic fibrosis (7).

To account for the high incidence of *CFTR* mutations in the population, it is generally assumed that there are selective advantages in being a heterozygous carrier, perhaps in the form of resistance against typhoid fever (8); such *CFTR* mutations must, however, simultaneously place an enormous selective pressure against men carrying these same "infertility" alleles even in heterozygosity. This selective pressure is much less pronounced in female carriers.

We postulate that compensatory mutations in the Y chromosome have arisen to ensure that *CFTR* mutations do not lead to sterility in men; such mutations will preserve the selective advantage of *CFTR* mutations. As an evolutionary consequence, the phenotype of cystic fibrosis will be skewed toward less severe manifestations of the disease in men. Furthermore, these protective effects of alleles in the Y chromosome may be reflected in the extreme cases of CBAVD patients lacking clinical evidence of cystic fibrosis who harbor "serious," homozygous *CFTR* mutations (5).

Our postulate could help explain epidemiological findings such as unequal sex distribution among diagnosed cystic fibrosis patients and prevalence of women diagnosed later in life (9). What is our suggested explanation for this observation? Simply, females homozygous for mutations in the CFTR gene diagnosed as adults still have penetrant cystic fibrosis, whereas age-matched males do not, and are therefore never diagnosed, except, perhaps, if these males have CBAVD or pancreatitis (10).

In view of the recent findings reported by Sims et al. and Milla et al., we believe that searching for alleles in the Y chromosome that confer resistance to CBAVD, cystic fibrosis, and cystic fibrosis–related diabetes may be of considerable scientific value. In conclusion, rather than decreased lung function and survival in women, we should view the published results as better survival and lung function in men.

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Of Genes and Men: The Alternative View of Sex Differences in Cystic Fibrosis

Response to Creus et al.

Creus et al. (1) offer an intriguing hypothesis, namely that protective genes on the Y chromosome confer a survival advantage to men with cystic fibrosis. While there are aspects of this theory that are attractive, its does not explain the fact that in our series of >1,000 patients, survival was only decreased in women with both cystic fibrosis and diabetes (2). Survival in women without diabetes did not significantly differ from that of men with or without diabetes. While this does not preclude a genetic explanation, it suggests that excessive mortality in cystic fibrosis is related to the relationship between diabetes and sex rather than sex per se. Perhaps this is a direct negative interaction between diabetes and some factor associated with female physiology. Alternatively, there may be negative effects of diabetes that men but not women are able to overcome. These might be due to hormonal or other differences found in all men, but one could speculate that there may be protective genetic factors specific to men with cystic fibrosis. While diabetes affects men and women differently in the general population, the sex difference in cystic fibrosis is certainly more dramatic, and it is possible that genes on the Y chromosome may modify survival in men with cystic fibrosis–related diabetes.

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Of Genes and Men: The Alternative View of Sex Differences in Cystic Fibrosis

Response to Creus et al.

We thank Creus et al. (1) for their interesting comments on our proposal that female subjects with cystic fibrosis–related diabetes develop worse lung function compared with age- and genotype-matched male peers. They ask whether these differences are a result of "evolutionary, sex-specific selective pressures." They then make the assertion that cystic fibrosis heterozygosity must "simultaneously place an enormous selective pressure against men carrying these same 'infertility' alleles even in heterozygosity." The difficulty we face in accepting this notion of selective negative pressure on the Y chromosome is that most heterozygote males are perfectly fertile, but for reasons unknown, more males are diagnosed with cystic fibrosis than females (1.1 to 1.0). The latter ratio is higher than the accepted male preponderance at birth in the population as a whole (1.05 to 1.0), which is offset back toward unity by a higher male mortality in childhood (2).

We accept that it is not fully understood why some patients with apparently "severe genotypes" do not develop classical cystic fibrosis, although intronic/exonic boundary structure, modifier genes, and environmental factors have all been implicated (3). However, although Rodman et al. (3) reported that females outnumbered males by three to one in their late-diagnosed cohort, females formed a smaller proportion of their early-diagnosed cohort. But, Rodman et al.'s results contradict the recognized excess of female cystic fibrosis mortality (4). Indeed, we have recently submitted a manuscript responding to Rodman et al.'s findings and report that for a national population of 135 patients aged >40 years, comparable male-to-female ratios were found in pediatric- and adult-diagnosed cohorts (J.M., personal communication). The different findings between our work and that of Rodman et al. could indicate a possible unknown bias in a single-center approach (3).

Finally, Creus et al. (1) also suggest that "rather than decreased lung function and survival in women, we should view the published results as better survival and lung function in men." We suggest that the imminent imposition of neonatal screening across the U.K. and France provides an opportunity to test the ideas proposed by the correspondents, but we feel it is premature to envisage a change in the title of our report (5).

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