compute a low likelihood ratio, aided by which a judge or jury ultimately decides between the markedly divergent conclusions of paternity or nonpaternity. This is typical of situations in life where we have to make decisions based on incomplete information.

To touch one further point—the case is posited wherein we judged a man a priori 40% to be a *non-father*. Upon serologic testing, the man was not excluded and the likelihood ratio was 500, so by Bayes' theorem, the posterior (overall) likelihood of nonpaternity is .00133. We are advised that "we may be forgiven for wondering how our .4 belief in the father's [sic] story dwindled to .00133 just on the basis of the fact that he is not excluded from biological fatherhood." I suppose there is no harm in wondering per se, but the rhetorical meaning of this sentence seems to be that having once formed an opinion, you needn't by swayed by mere evidence. And what evidence! This man survived a veritable gauntlet of tests, such as would exclude 500 out of 501 non-fathers (and no fathers). Maintaining one's anyway rather moderate faith in his nonpaternity might be a touching show of loyalty from his friends and his mother, but is unreasonable from a juror and bad advice from an expert.

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CHROMOSOMAL IMPRINTING AND THE PARENT TRANSMISSION SPECIFIC VARIATION IN EXPRESSIVITY OF HUNTINGTON DISEASE

To the Editor: The increased severity of Huntington disease in the offspring of males compared to that of females has been of interest and comment to clinicians and human geneticists observing Huntington disease for some time [1, 2]. An old observation, now being applied to mammals by mouse geneticists, may be relevant to this difference [3, 4]. The observation is that of chromosomal imprinting. It is clear in certain insects that chromosomes transmitted through the female contain different information by being so transmitted, that is, compared to when they are transmitted through the male [5]. In this case, the imprinting results in differential elimination of the chromosomes in the male. It is now clear that such differences in chromosomal imprinting also affect the mammalian genome. The best two examples of this concern the X chromosome [6] and a chromosome 17 mutation in mice, T^{Hp}. In the former case, the mammalian male X chromosome functions differently than that of the female such that it is inactivated preferentially in extraembryonic tissues [7, 8], while X-chromosomal inactivation is random in the embryo proper. This difference in

the activity of the X chromosome might be related to the physical state of the chromosomal DNA as reflected in its different transforming ability. Although the X is thought to be inactivated during spermatogenesis [9, 10], the spermatogenic X-inactivation seems likely to be due to different mechanisms than the inactivation occurring in female somatic cells. This is demonstrated by the fact that DNA prepared from extraembryonic membranes where the paternal X is inactive [11] will readily transvect $HGPRT^-$ cells to grow in HAT media, while DNA prepared from female somatic cells when only the inactive X is $HGPRT^+$ will not. T^{Hp} is a mutation that can be transmitted through the male but not through the female [12]. When the mutation is transmitted through the female, the embryos die perinatally, whereas when transmitted by the male, the mutation survives with little fetal loss. Recent nuclear transplantation experiments demonstrate that the difference is not in the cytoplasm of the egg but is an inherent property of the mutation having been transmitted by an oocyte-derived nucleus rather than by a spermatogenesis-derived nucleus [13]. Thus, differential chromosomal imprinting provides an excellent explanation for these two situations of differential genetic effects of male and female transmission. It is probable that the failure of parthenogenesis in mammals is due to the need for nuclei with both kinds of imprinting for successful development [14–16].

It is possible that differences in degrees of methylation or other DNA modifications can explain these differences. Some repetitive elements, which are scattered on many chromosomes in the mouse, are differentially methylated in sperm and oocytes [17]. It is possible that the Huntington disease locus on chromosome 4 [18] is in an area affected differentially in male and female gametes by some such DNA modification and that the difference in modification can later lead to different times of expression of the gene. However, these DNA modifications may not be uniform among various populations—there is a suggestion that juvenile-onset Huntington disease is more frequent in offspring of female, rather than male, American blacks [19]. A search for differences in DNA methylation within and flanking the Huntington gene, when identified, between these groups (racial and sex of parent) will provide one approach to testing the hypothesis. Chromosomal imprinting may also explain maternal effects in myotonic dystrophy [20] and other disorders.

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