Letters to the Editor

Am. J. Hum. Genet. 65:1195–1197, 1999

SPERMSEG: Analysis of Segregation Distortion in Single-Sperm Data

To the Editor:

Single-sperm typing has proved to be a valuable tool for detection of segregation distortion at a variety of loci in males (Williams et al. 1993; Leeflang et al. 1996; Takiyama et al. 1997; Girardet et al. 1998; Grewal et al. 1999; Takiyama et al. 1999). Sperm typing can provide the large sample sizes needed to detect even small deviations from 50:50 segregation that might arise during meiosis or that are due to differential sperm viability during or immediately after spermiogenesis (Leeflang et al. 1996). Furthermore, the problem of ascertainment bias, a serious concern in family-based studies of segregation distortion, is circumvented by sperm typing. However, in order to analyze such sperm data, one must model experimental errors—such as failure of alleles to amplify to a detectable level, deposit of 0 or >1 sperm in a sample, and contamination by exogenous DNA (Cui et al. 1989). Here I describe SPERMSEG, software programmed in C to analyze segregation in single-sperm data. This likelihood-based software is very flexible, allowing for any number of one- and two-marker data sets from one or more donors, with the capabilities to fit virtually any identifiable submodel of interest, to provide confidence intervals for all parameters, and to perform a wide range of hypothesis tests, including simulation-based goodness-of-fit tests.

For a likelihood analysis of segregation distortion using single-sperm data, the basic study design involves one or more two-marker data sets from each of several donors. By a two-marker data set, I mean that, for a given donor, two markers, for which the donor is heterozygous and which are linked to the locus of interest, are typed on each of a number of sperm. The reason two markers are typed is that if only one marker were typed on each sperm, it would not be possible to estimate the error parameters in the sperm-typing model. However, with additional assumptions, one-marker data sets can be included in the analysis, in addition to two-marker data sets. Such additional assumptions could include equality, between one-marker and two-marker data sets, of some of the error parameters. Only markers for which the donor is heterozygous can be included in the SPERMSEG analysis. Data from markers for which the donor is homozygous contain no information on segregation distortion (although they may contain a very small amount of information on the error parameters). Thus, it is assumed that each donor's sperm are typed only for markers for which the donor is heterozygous, with those markers allowed to differ among donors, and with possibly different pairs of markers typed for different subsets of sperm from the same donor.

Let G be the locus of interest, with alleles *G* and *g* in a given donor. Each two-marker data set involves sperm typed at a pair of markers A and B, at which a given donor has alleles *A*/*a* and *B*/*b*, respectively, linked to G. Assume that the donor haplotypes are known, say *GAB*/*gab*, and assume that the three recombination probabilities θ_{GA}, θ_{GB}, and θ_{AB}, between G and A, G and B, and A and B, respectively, are known. This parametrization of the recombination probabilities is completely general, to allow for interference. Special cases in which one or both of A and B are completely linked to G are allowed and lead to simplified calculations. The observed data for a given donor and pair of markers are assumed to be multinomial, with 16 possible outcomes: ––––, –––*b*, ––*B*–, ––*Bb*, ––*a*–, –*a*–*b*, –*aB*–, –*aBb*, *A*–––, *A*––*b*, *A*–*B*–, *A*–*Bb*, *Aa*––, *Aa*–*b*, *AaB*–, and *AaBb*, where, for example, –––– means that no allele was amplified to a detectable level, and, for example, –aBb means that alleles *a*, *B*, and *b* were detected, but *A* was not. For each donor, there may be several such two-marker data sets, with one or both of the linked markers differing among data sets. Different donors may be typed at different markers and, in general, will have alleles different from each other. In SPERMSEG, there is no limit on the overall number of markers or number of alleles, except that each sperm is assumed to be typed at no more than two markers.

Consider a single two-marker data set. The segregation-distortion model for the two-marker data set was described by Leeflang et al. (1996) for the special case when G, A, and B are completely linked, and it is also a good approximation when there is very tight linkage. This model includes segregation parameter $s = P$(sperm has allele *G*), with $1 - s = P$(sperm has allele *g*). It includes sperm-deposit parameters γ_i, which allow for the

possibility that, instead of one sperm being present in a given sample, either zero or two sperm are present, where $\gamma_i = P(i$ sperm present in a given sample), i = 0,1,2, with the assumption $\gamma_0 + \gamma_1 + \gamma_2 = 1$. The model includes amplification parameters α_A, α_a, α_B, and α_b, where, for example, α_A is the probability that allele *A* is amplified to a detectable level by PCR, given that it is present on a single sperm. If two sperm are deposited, both with allele *A*, then the two *A* alleles are assumed to amplify independently of one another, each with probability α_A. The contamination parameters are β_A, β_a, β_B, and β_b, where, for example, β_A is the probability that allele *A* is falsely detected because of contamination by exogenous DNA. This model is very close to the original model developed by Cui et al. (1989) for estimation of a recombination fraction, which was extended to three loci by Goradia et al. (1991). Both of these models include deposit parameters γ_i, i = 0,1,2,3,4, assumed to sum to 1, and amplification and contamination parameters as given above. Cui et al. (1989) have an unknown recombination fraction in their model, whereas Goradia et al. (1991) have two unknown recombination fractions with an unknown interference coefficient, a parametrization that is equivalent to our trio of recombination probabilities. Both models assume $s = .5$. The segregation-distortion model described here is a three-locus model, as in the article by Goradia et al. (1991), but s is allowed to vary, the amplification and contamination parameters for locus G are effectively set to 0, and the recombination probabilities are assumed to be known instead of estimated. Furthermore, since the parameters γ_3 and γ_4 are always estimated as 0 in the articles by Cui et al. (1989) and Goradia et al. (1991), I follow the lead of Lazzeroni et al. (1994), in setting them to 0. Cui et al. (1989) and Goradia et al. (1991) have not shown that their model including γ_3 and γ_4 is actually identifiable. If it is assumed that it is identifiable, there is certainly very little information, in a reasonably sized data set, with which to estimate γ_3 and γ_4, and the fact that γ_2 is typically estimated at just a few percent suggests that these values are close to 0 in any case.

Now, suppose that several two-marker data sets are to be analyzed simultaneously. For instance, one might have two two-marker data sets from donor 1 (perhaps with different markers; i.e., some sperm are typed at markers A and B, and other sperm are typed at markers C and D), a two-marker data set from donor 2, and a two-marker data set from donor 3. One might wish to analyze the data by using a model with, say, donor-specific segregation parameters, experiment-specific deposit parameters, allele-specific amplification parameters, and locus-specific contamination parameters. SPERMSEG is designed to be very flexible in allowing the user to specify such models and will maximize the likelihood subject to these constraints. Any segregation parameters may be set equal to each other or to fixed values—similarly for deposit, amplification, and contamination parameters. This is especially useful for testing hypotheses of interest, such as whether there is segregation distortion at all in a collection of data sets; whether, among donors within a phenotypic class, there is heterogeneity in the segregation ratio; and whether, among phenotypic classes, there is heterogeneity in the segregation ratio. Parameter estimates and the maximized log-likelihood are output for each model that the user selects. SPERMSEG allows the user to calculate confidence intervals for all estimated parameters under any of these models as well.

In addition to two-marker data sets, there may be one or more single-marker data sets. Each single-marker data set involves sperm typed at a single marker C, at which a given donor has alleles *C* and *c*, linked to G with known recombination fraction (possibly 0). The four possible multinomial observations are then –, -*c*, C-, *Cc*. There are only three freely varying observed counts, so the segregation, deposit, amplification, and contamination parameters (seven parameters in all, in this case) cannot be estimated from such a data set alone. However, either in combination with two-marker data sets from which these parameters can be estimated, or with some of the error parameters assumed to be known, the single-marker data sets provide additional information. Thus, of the seven parameters in a one-locus data set, most of them either must be set equal to comparable parameters in some two-locus data set that is also included in the analysis or must be set equal to fixed values, if appropriate values are known. SPERMSEG allows for any number of one-marker data sets to be included in the analysis, in addition to the two-marker data sets, with the user specifying which parameters are to be set equal to each other or to fixed values, so that the model is identifiable.

SPERMSEG uses the expectation-maximization (EM) algorithm of Dempster et al. (1977) to maximize the likelihood. For a single one- or two-marker data set, the complete-data likelihood is simply a product of binomials and multinomials. For the published and simulated sperm-typing data sets so far analyzed for segregation distortion, the EM algorithm has quickly converged to the global maximum of the likelihood, even from starting points relatively far from the maximum. SPERMSEG allows the user to specify different starting points, if desired, to help determine that a global maximum has been reached.

In maximum-likelihood analysis of sperm-typing data, it is common to have some parameters estimated on the boundary of the parameter space. These are either contamination parameters (β) or probabilities of two sperm deposited (γ_2) that are estimated to be 0. When this occurs, the gradient of the log-likelihood of the data at

the maximum-likelihood estimate is not necessarily 0, and it is not appropriate to estimate the standard errors of the parameter estimates by calculating the Fisher information. Instead, the SPERMSEG software inverts the likelihood-ratio test to obtain confidence intervals for the parameter estimates. Confidence intervals obtained by inverting the likelihood-ratio test are generally more accurate than those obtained from the Fisher information, even when the maximum-likelihood estimate is in the interior of the parameter space.

One can perform a χ^2 goodness-of-fit test to make sure that the model used to analyze the sperm-typing data actually fits the data. However, when some parameters are estimated on the boundary of the parameter space, the appropriate number of df for the χ^2 test is no longer clear. SPERMSEG has a built-in simulation routine to calculate a *P* value, for the goodness-of-fit test, that will be valid even when some parameters are estimated on the boundary.

In order to make full use of single-sperm typing as a valuable tool for the study of segregation distortion, flexible software must be available to analyze the resulting data. SPERMSEG allows for any number of one- and two-marker data sets from one or more donors. It performs full likelihood analysis of the data, using models of the user's choice. Log-likelihoods are output for use in hypothesis testing, and confidence intervals based on inverting the likelihood-ratio test and simulation-based goodness-of-fit tests are calculated, both of which are reliable even when parameters are estimated on the boundary.

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Electronic-Database Information

The URL for data in this article is as follows:

SPERMSEG, http://galton.uchicago.edu/~mcpeek/software/spermseg (for SPERMSEG software and documentation)

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Cultural Difference and the Eugenics Law

To the Editor:

Mao recently reported results of a survey of Chinese geneticists' views on ethical issues in genetic testing and screening, which are quite different from those of their Western counterparts (Mao 1998). Although this report provides a welcome opportunity to further illuminate the East-West controversy that surrounds the Chinese

eugenics law, unfortunately the report suffers from some gross factual errors, such as the statement that "sickle cell disease is very common in China" (Mao 1998, p. 690). In addition, Mao's argument that social, economic, and cultural differences "most likely will give rise to a disagreement between China and the West, on the issue of eugenics" (p. 693) is not quite convincing.

Granted, sociocultural differences may indeed account for the difference in views on eugenics, but differences in knowledge may also contribute. In fact, differences in knowledge can confound the explanation, making it extremely difficult to infer which factor is primarily involved, especially when, like Mao, one makes no attempt to assess the magnitude of difference in genetic knowledge between the East and the West.

For various reasons, human genetics research in China lags far behind that in Western nations. This gap unavoidably permeates Chinese geneticists' views on eugenics. No mention is made, in Mao's article, of the credentials of the survey respondents, although the survey does contain ample information of this kind. In fact, there is a noticeable gap in genetic knowledge.

For example, almost all respondents agreed that "an important goal of genetic counseling is to reduce the number of deleterious genes in the population" (Mao 1997, p. 20) and that "carriers of the same defective gene should not marry each other" (Mao 1998, p. 693). In truth, it is well known that discouraging carriers of the same defective gene from mating is not an effective way to reduce the number of deleterious genes responsible for rare recessive diseases (see, for example, Li 1955). Another example: although the issue of whether there is a susceptibility gene for alcoholism is far from settled, 69% of the respondents agreed that genetic tests for predisposition to alcoholism should be done in children.

Mao argues that the eugenics concept in China is somewhat different from the concept in Western nations and portrays the Chinese eugenics law as benign. It may be benign, but the languages of several controversial articles in the Chinese eugenics law are uncomfortably similar to those of, say, the 1920s Idaho eugenics law, which allowed sterilization of "mentally defectives, epileptics, habitual criminals, moral degenerates, and sex perverts" (Russell 1929, p. 259). This is all the more serious given the lack of legal recourse for Chinese couples diagnosed with or suspected to carry a genetic disease, as the law stipulates. There is a clear and real danger that the law can be abused.

Mao (1998) points out, correctly, that the motivation of the law is underscored by the lack of a universal health care program that covers genetic services. This seems to imply that the law, when rigorously enforced, will help to reduce the economic burdens on many people inflicted with diseases perceived to be hereditary. However, this may prove to be wishful thinking. The truth is, our knowledge base is so minuscule that there is no evidence to support the notion that the law would effectively serve that purpose, especially given that the documentation of genetic diseases is scant in China.

Lastly, the notion that sociocultural differences can justify the eugenics law also is seriously flawed. The traditional Chinese culture favors boys over girls. Does this justify selective abortion and female infanticide? The culture also encourages large families, which is directly at odds with China's one-child policy. If Mao's logic is correct, does that mean that policy should be abandoned altogether?

So far, most defenders of the law in China have been, conspicuously, social scientists and molecular biologists, whose distinctive insight may reflect their vantage points. What seems to have been disregarded completely is that we are dealing here with much more than cultural or social differences. It is imperative that a law concerning genetic aspects of health and population is based on principles of population genetics and genetic epidemiology.

Different people may have various ways to interpret the difference in views on the Chinese eugenics law. The point, however, is to change the grave reality: that there are>50 million disabled people in China. But this will require hard science and solid data. It is simply counterproductive to defend post hoc an ill-conceived law that apparently was not drafted with the best knowledge and utmost care.

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Chinese Geneticists Are Far from Eugenics Movement

To the Editor:

The article by Dr. Xin Mao (1998), published in the September 1998 issue of the *Journal,* came to our attention just recently. Unfortunately, it misrepresented in many ways the real attitudes of many of the medical geneticists in China. We feel that it is necessary to speak out for ourselves. For instance, sickle cell anemia is as rare among Chinese as it is among whites. The statement that "sickle cell disease is very common in China" (Mao 1998, p. 690) is incorrect. Hence, there is no reason to require newborn screening for sickle cell disease in China (Mao 1998, table 1). Cystic fibrosis is also very rare in China. Hence, there is also no need to perform newborn screening for this disease (Mao 1998, p. 690). Population screening for defective alleles of the α-antitrypsin gene (i.e., the PiZ and PiS alleles) has revealed none in China, with the exception of one case with the genotype of M1S. Therefore, it will be meaningless to conduct genetic testing for α-antitrypsin deficiency among workers in very dirty workplaces (Mao 1998, p. 689). Actually, it will be very difficult to define "very dirty workplace." Mao also stated that "almost all respondents said that the goal of human genetics was 'improvement of the population quality, decrease of the population quantity, and furtherance of eugenic principles' and agreed that 'an important goal of genetic counseling is to reduce the number of deleterious genes in the population'" (pp. 692–693). We wonder whether any knowledgeable human geneticists will believe that human genetics can decrease the population quantity. We also doubt that the number of deleterious genes—especially "recessive genes"—in the population can be readily reduced. As for the term "eugenics," one should be very careful not to equate it with "you sheng" in Chinese, which means "to give birth to a healthy baby." There are many other controversial points in Mao's article. For example, his table 4 asks whether the country should have laws to prohibit disability discrimination. The original questionnaire, however, asked whether the country has or does not have laws to prohibit disability discrimination. The percentage given in table 4 will lead readers to the conclusion that Chinese medical geneticists do not favor the enactment of such laws! This letter will be too long if we try to list all of the controversial points in Mao's article. We are fully aware that, because of differences in culture, value systems, customs, religion, and demographic and economic situations, our viewpoints on many ethical issues may be different than those of our Western colleagues. This stresses the importance of dialogues between us to promote mutual understanding. All constructive suggestions will be heartily welcome, and we will be most grateful for all of them.

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Reply to Guo and to Chen et al.

To the Editor:

Ethical, legal, and social issues in human genetics are hot—but also complicated—topics in developed countries. Since my article (Mao 1998*a*) about Chinese geneticists' views on ethical issues in genetic testing and screening was published, it has attracted attention from the international scientific community and the media. Many gave positive comments on the article (Mao 1998*b*, 1998*c*; Coghlan 1998; Knoppers 1998), but others, such as Guo (1999 [in this issue]) and Chen et al. (1999 [in this issue]), expressed different views.

Ethical, legal, and social issues in human genetics are very sensitive inside China (as well as elsewhere), and there have been few Chinese scientists, either in genetics or in the social sciences, willing to investigate these subjects. For example, Chinese geneticists were invited to

take part in the first international survey on ethics and genetics, conducted in 1984, but none responded (Wertz and Fletcher 1989). The report on ethics and genetics in China presented in the September issue of the *Journal* last year (Mao 1998*a*) came from the second international survey on ethics and genetics, which was conducted in 37 nations, including China, in 1993 (Wertz and Fletcher 1993). In this survey, a total of 402 Chinese geneticists, in 30 provinces and autonomous regions, were targeted with the Chinese version of an anonymous questionnaire that included 50 questions on ethical issues. All of these geneticists were registered members of the Chinese Association of Medical Genetics, the Human and Medical Genetics Branch of the Chinese Society of Genetics, and the Chinese Society of Family Planning. In all, 255 (63%) Chinese geneticists responded. Although some of the situations described in the questionnaire might be remote from Chinese geneticists' own practices in 1993, the survey results definitely helped to define the geneticists' attitudes toward ethical, legal, and social issues in genetics at that time and provided, for the first time, a scientific basis for international discussion of ethical issues in genetics in China (Mao and Wertz 1997; Wertz 1997, 1999; Mao 1998*a*; Wertz and Fletcher 1998).

Eugenics and laws related to it are the most contentious ethical issues in the world of genetics. On the basis of the first comprehensive national survey data and the actual situation in China, my article provided well-informed evidence of the balanced opinions on eugenics and genetics ethics in China, which aimed to promote constructive dialogues between Chinese geneticists and their Western counterparts on these issues. I agree with Chen et al. (1999) in their desire for more-comprehensive scientific reporting and more unbiased international discussions on genetics ethics in China. Perhaps this is the proper approach to exploring the cross-cultural eugenics and genetic ethics in developing nations.

Guo (1999) suggests that the article supports the "eugenics" section of China's Maternal and Infant Health Care Law. As I stated in the article, my purpose was to present the survey data and to discuss the likely basis of eugenics in China (Mao 1998*a*). Accomplishing this aim does not mean I have to support or oppose the law.

The history of eugenics in Western society has shown that socioeconomic and cultural factors contributed considerably to the development of the movement in industrial nations (Paul 1992). Dikötter analyzed the many dimensions of the history of eugenics in China. In his book, Dikötter concluded that Chinese eugenics law reflects an articulation of Chinese knowledge of heredity and disease and demonstrates how Chinese assumptions about the relationship of the individual to the society form the core of their attitudes toward procreation and their cultural, social, and economic views of population and disability, as well as the trend of nationalism generated from late imperial China to the People's Republic (Dikötter 1998). Dikötter's studies provide evidence that sociocultural differences are most likely to give rise to a disagreement between China and the West on the ethical, legal, and social issues that surround genetics, including the issue of eugenics.

The aims of the International Survey on Ethics and Genetics were to investigate the attitudes of genetics service providers toward ethical, legal, and social issues in their practice and research. The first section of the international questionnaire collected the participants' sociodemographic data and made a particular effort to check the credentials of the survey respondents. These data have been presented elsewhere (Mao and Wertz 1997).

Guo (1999) suggests that better knowledge of genetics will alter beliefs about reducing the number of deleterious genes in the population. China has made genetic research the top priority of its basic science research program and also has made a large-scale investment in the Chinese Human Genome Project (CHGP) (Lei 1998). If Guo is correct, then Chinese beliefs about eugenics will probably disappear in the future, when China catches up to the West in genetics. Views have been expressed in the West that, if genetic knowledge is not used properly or ethically, then it is likely to do more harm than good. My article (Mao 1998*a*) showed that, in 1993, most Chinese geneticists thought that ethical guidelines were necessary to improve genetics services in China. So far, however, very few Chinese geneticists and ethicists have been interested in the ethical, legal, and social issues of CHGP, although enhancement of research in this area has been listed as a subproject of phase II of CHGP (Chen and Zhang 1998). Ethical guidelines for genetics research and practice have not been drafted, nor has there been any public debate on these issues in China. All of these facts indicate that it is imperative that the international genetics community should export advanced genetics technologies to China and should help the Chinese people learn how to use genetic knowledge ethically to avoid any potential harm. One approach to altering beliefs about eugenics depends on facilitating public debate on these issues and establishing an evidence-based policy-making system worldwide. Perhaps these will be the toughest issues in genetics in the new millennium.

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The Duty to Recontact: Benefit and Harm

To The Editor:

The survey by Fitzpatrick et al. (1999), "The Duty to Recontact: Attitudes of Genetics Services Providers," represents a significant contribution to, and an important step forward in, the resolution of a complex and troubling issue. But, in both their Introduction and their Discussion, the authors refer to statements of mine (Sharpe 1994*b*) that have been taken out of context and therefore misrepresent my position on this issue. More critically, Fitzpatrick et al. have failed to take note of medical principles and legal obligations that are fundamental to discussion about whether a duty to recontact exists within the context of medical genetics and genetic counseling.

For example, the authors wrote that I stated "a physician's duty of care toward patients is considered to include the obligation to advise them of any developments in management and treatment that would be beneficial or detrimental" (Sharpe 1994*b*). This statement, in the context in which it is presented, is incorrect. My article (Sharpe 1994*b*) focused on the psychological aspects of presymptomatic testing for Huntington disease and, in particular, on whether a geneticist would have a continuing obligation to provide psychological support after disclosure of the test results. This issue was examined within the context of a physician's traditional postoperative duties of care to a patient, including the duties to monitor a patient's condition, to provide appropriate aftercare, to refer, and not to abandon the patient. As cited in my article, such obligations have long been recognized in the various codes and principles of ethics of organizations such as the American Medical Association and the Canadian Medical Association.

With respect to Huntington disease, because of the potential for and the nature of the psychological and psychiatric responses associated with risk clarification or a clinical diagnosis, I suggested that, in the same manner in which a physician may have a duty to continue treatment until recovery is complete, a geneticist may have a continuing duty of care until appropriate psychological or psychiatric counseling has been arranged. Once such counseling has been secured, however, the geneticist's obligation would come to an end.

In the same article, with respect to phenylketonuria, I also speculated—as evidenced by my explicit use of the term "theoretically"—that, because of the necessity of maintaining a low-phenylalanine diet and the fact that the gene technically has been expressed, a geneticist might have a duty to monitor a patient's condition over

a prolonged period of time (assuming that an appropriate referral could not be arranged).

Both of these clinical scenarios concern situations in which the patient may require *immediate* and continuing treatment and management. Strictly within this context, I wrote, "This duty to monitor may include the obligation to advise of any developments in management and treatment that would prove of benefit or detriment to the patient" (Sharpe 1994*b*). At no time did I suggest that either of these scenarios were examples of, or would support the concept of, a duty to recontact *former* patients. Indeed, the duty to recontact was never mentioned in my article.

With respect to a physician's continuing duty of care, as cited (Sharpe 1994*b*), American and Canadian courts of law have created a number of *distinct* categories in which to interpret a physician's duty to monitor, to refer, not to abandon, and to provide appropriate care. Generally speaking, these categories include: (1) advising a patient of the nature of her or his medical status; (2) providing a proper follow-up, which may include an obligation to instruct a patient about all appropriate precautions that must be carried out subsequent to treatment and/or an obligation to carry out regular medical examinations to monitor the patient's medical condition; and (3) a continuing duty of care, recognized by a number of American jurisdictions, when a risk of future injury arises from the original patient-physician relationship (Tresemer v. Barke 1978).

What these categories have in common, however, is the fundamental medical issue—not cited by Fitzpatrick et al.—of whether a patient is in continued need of a physician's *expert care* (Sharpe 1994*b*). In the past, the term "expert care" has been resolved within the traditional context of treatment and cure. In phenylketonuria and Huntington disease, because a patient may require immediate treatment and management, the geneticist or physician arguably will have a continuing obligation to provide such expert care until an appropriate referral has been arranged.

These particular examples, however, do not a general rule make. And they are substantially different from the concept, incorrectly attributed to me (among others) by Fitzpatrick et al. (1999), that a geneticist or physician may have a continuing obligation "to recontact former patients about advances in research."

The duty to recontact described by Fitzpatrick et al. is not necessarily concerned with the existing medical and legal issues of whether *continuing* expert treatment is required. Rather, this duty represents a *new* "ethical" or "moral" obligation (Fitzpatrick et al. 1999) to contact patients, years after an original test was completed, in order to inform them that a new or more accurate diagnostic or risk-clarification genetic test is available.

Medical genetics and genetic counseling represent a therapeutic model of care analogous to, but distinct from, the practice of medicine. For many genetic diseases, treatment and cure are not available. Predictive genetic testing, for example, is concerned primarily with providing information about a medical condition that is likely to occur at some time in the future. Because of such limitations, the medical genetics and genetic-counseling communities have recognized that if physicians are to provide benefit and to prevent harm to the patient before, during, and after genetic testing, physicians will have to develop a more "human vision" of care, focusing on the patient's informational, communicative, emotional, and psychological needs (National Society of Genetic Counselors 1997), as opposed to a purely "medical vision" restricted to the treatment and cure of physical disease.

It must be acknowledged that the proposed duty to recontact embodies this "human vision" by advancing the principle that the clinical interpretation of "continuing expert care" can no longer be restricted to the medical treatment of disease but must be expanded to include a patient's informational needs. However, other equally compelling values and practical considerations must be taken into account.

First, if there is a lack of appropriate resources and qualified personnel, one must inquire how a geneticist or physician can reasonably and practically fulfill such a duty to recontact. This question seems especially appropriate, given that the recognition of this duty could represent a new, potentially inequitable, and onerous cause of action for medical negligence. Although a number of the suggestions proposed by Fitzpatrick et al. (1999), such as the use of Internet sites, appear to be very reasonable solutions, arguments have been voiced that a geneticist, at the risk of exposure to liability, has an obligation to ensure that not only the quality of the information, but also the manner of communication (e.g., language and terminology, taking into account cultural and socioeconomic differences) and the method of communication (e.g., telephone call or letter) (Sharpe 1994*a*; National Society of Genetic Counselors 1997) are reasonably appropriate to a patient's needs. Discussion and debate continue, for example, about how to effectively communicate health information on the Internet (Jadad and Gagliardi 1998; Kim et al. 1999).

Second, the fundamental objective and underlying rationale for the duty to recontact is that it will provide benefit and prevent harm. But is this operative assumption valid? What if recontacting a patient provokes adverse emotional and psychological responses? (Almqvist et al. 1997; Fitzpatrick et al. 1999). Aside from the fact that such responses could affect a patient's ability to appropriately understand the nature and implications of the new information (Sharpe 1994*b*), what of the impact on the patient and the family? Will the geneticist or the

physician have an obligation, and the required resources, "to provide appropriate psychological support" (Canadian College of Medical Geneticists 1997), "to help families and individuals recognize and cope with their emotional and psychological needs," and to "recognize situations that require psychiatric referral" (American Board of Medical Genetics 1997)? If the proposed duty to recontact is to become part of a geneticist's or a physician's duty of care toward a patient, it cannot operate independently of her or his other duties.

Third, the medical-genetics and genetic-counseling communities recognize that good patient care requires an individualized, patient-by-patient approach. Genetic diseases such as phenylketonuria, Huntington disease, cystic fibrosis, and neurofibromatosis represent distinct clinical problems and outcomes, with equally distinct patient needs on a short-term as well as on a long-term basis. One patient's response to a presymptomatic test result—or to the news of a new diagnostic or risk-clarification test—can be substantially different from another's. How is the duty to recontact to be applied practically, first for each of these diseases, and second on a patient-by-patient basis, given the prevailing value of nondirective counseling? More importantly, how will the duty to recontact be reconciled with a patient's fundamental right of autonomous decision making, including the right not to know (Ost D 1984; Yarborough et al. 1989; De Wert G 1992)? Will notes made at the end of a clinical record (Fitzpatrick et al. 1999) be sufficient to protect a patient's autonomy and values?

Given these concerns and risks, what practical benefit is to be gained by adding the duty to recontact to the already existing obligations to monitor, to provide appropriate aftercare, to refer, and not to abandon? Would it not be preferable—and more realistic—to resolve this issue, on a patient-by-patient basis, within the existing framework of these medical and legal obligations, especially with regard to the obligations of the geneticist or physician?

If the consensus, however, is to recognize some form of a duty to recontact, or at least an obligation to provide information to former patients, a solution may be found by returning to the underlying principles of the genetic-counseling therapeutic model of care. For nearly 25 years (Ad Hoc Committee on Genetic Counseling 1975), a fundamental objective of the genetic-counseling process has been to help patients to make the best possible adjustment, and to choose a course of action which seems most appropriate to them given their goals and ethical and religious standards. These principles recognize that the patient will play an integral role in the therapeutic process.

The patient, therefore, will have to accept a reasonable degree of responsibility, including the obligations to provide appropriate information (e.g., her or his family's medical history); to make a reasonable effort to understand the nature and implications of genetic information; and to describe his or her particular concerns, needs, expectations, and values. There appears to be no good reason why this long-standing concept of responsibility shared by the patient and the geneticist or physician should not equally apply to the duty to recontact.

The responsibility of the geneticist or physician, therefore, will be to discuss this issue with each patient, to receive instructions, and to keep reasonably up-to-date with all significant—and proven—research advances. The patient will have a corresponding obligation to contact the geneticist or the physician on a regular basis, such as once per year, for updates, and to request an appointment for clarification or for counseling, if required.

But, again, is this type of responsibility realistic and practically attainable, given the resources available to a geneticist or to a physician, especially with regard to qualified personnel? When one speaks of ethical values and moral obligations, one does not necessarily speak of absolute standards. One speaks of a choice among possible alternatives, with the knowledge that none of the available options may prove harmless. In a circumstance in which either course of action would appear to offer both benefit and harm, which course is to be given priority, and by whom?

Advocates of the duty to recontact argue that it should be recognized as a standard of care, because it exemplifies medicine's traditional values and objectives by providing the best opportunity for therapeutic benefit and the prevention of medical harm. This duty, however, has been given a higher priority despite the facts that (1) a former patient could suffer harm in the form of adverse psychological responses; (2) the geneticist or the physician could incur harm in the form of an inequitable and unreasonable exposure to legal liability for medical negligence; and (3) the duty may prove practically difficult, if not impossible, to fulfill. It is reasonable, therefore, to ask why the duty to recontact has been given priority, why its values have been deemed more valid, and who made this decision.

In 1994, I examined how a court of law would be likely to interpret professional accreditation standards and human/medical genetics literature with respect to a geneticist's duty of care for communication, informed consent, and psychological counseling for presymptomatic testing for Huntington disease (Sharpe 1994*a*, 1994*b*). My intent was to alert the medical-genetics and genetic-counseling communities to the implications that such standards of care could pose in terms of a physician's practical ability to provide such care in clinical- or primary-care service, as well as the potential expansion in causes of action for medical negligence.

The conclusion, which applies equally to this discus-

sion, stated that "the standard of care identified in this article has not been imposed by a court of law. It is the standard of care developed by geneticists and physicians. Debate as to its 'reasonableness' will have to be resolved by the medical genetics community" (Sharpe 1994*a*).

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Reply to Sharpe

To the Editor:
Mr. Sharpe correctly notes that in our article (Fitzpatrick et al. 1999) he was credited for considering the existence of a physician's duty of care toward patients (Sharpe 1994). His comments in this regard were indeed made in the context of Huntington disease, but, as we did not attribute to him *any* opinion on the duty to recontact, his position on this subject was not misrepresented, but simply omitted, from our discussion. We apologize to Mr. Sharpe and thank him for clarifying his position. The intention of our article was to report and discuss original research findings and not to present a detailed analysis of medical principles and legal obligations associated with a theoretical duty to recontact. It was our hope that our article would stimulate such a discourse, and we thank Mr. Sharpe for his insightful comments.

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The Choice to Have a Disabled Child

To the Editor:
What are the purposes of genetic testing, what are the principles guiding its use, and who should decide what tests should be available for what purposes? These familiar questions are raised in an unfamiliar context by a study reported recently in this journal (Middleton et al. 1998). Attitudes toward genetic testing were assessed among deaf people attending a conference in the United

Kingdom on issues concerning deaf people. About half the sample thought that genetic testing did more harm than good and that its potential use devalued deaf people. These attitudes were more negative than those previously reported in the general population (Michie et al. 1995). Attitudes were also more negative among those who identified equally with the deaf and hearing communities.

Of those who were interested in prenatal testing for deafness, a small proportion (4/14) said they would prefer to have deaf children. Out of the whole sample, 13/87 participants said they would prefer to have deaf children. This raises the possibility that some deaf people may consider using genetic technology to facilitate their having deaf children. Caution, however, is needed in interpreting these findings. The study sample was both small and likely to be unrepresentative of deaf people in that it comprised those attending an international conference. In addition, participants completed the questionnaires in a highly unusual social context: a conference auditorium, surrounded by mainly deaf delegates, at a conference about aspects of deafness entitled "The Deaf Nation." Two factors may have led to responses different from those that might have been given in the context of everyday living. The first factor is that the identity of being a deaf person may have been accentuated, temporarily, by being in a group of deaf people discussing deaf issues. Social categorization theory suggests that this is likely to increase the difference between the views of those within the group and the views of those not in the group (Turner and Oakes 1989). The second factor is social comparison, the perception of how others are likely to respond (Suls and Miller 1977). The views of individuals in a group have been found to shift in the direction of the group's views in order to gain approval and avoid disapproval. The social context within which the questionnaire was completed is illustrated here: "A Deaf chairwoman who introduced the question…[informed] delegates that they could make a difference to genetic services for deaf people, if they completed the questionnaire, or could exercise their right to refuse, by ignoring it" (Middleton et al. 1998, p. 1176).

Even if the attitudes reported are valid, attitudes should not be confused with behavior. What people say does not always indicate what they will do. For example, a majority of those at risk of Huntington disease said they would have a genetic test when it became available, yet only a small proportion underwent the test when it did become available (Bundey 1997). Similar findings have been found for predictive testing for cancers in both Europe and the United States (Lerman et al. 1996; Dudok de Wit et al. 1997).

With these caveats in mind, the finding that people affected by a condition have more-positive attitudes toward it than do others and also hold more-negative attitudes toward prenatal testing is supported by a large body of psychological literature. This literature shows that people with different experiences and perspectives (affected versus not affected, health professional versus lay) perceive the same condition differently: those with a condition very often perceive it as less serious than do those without the condition. For example, those found to have raised levels of cholesterol perceive this as less serious than do those with results in the normal range (Croyle et al. 1993). Parents of children with a chronic disease perceive that condition as less serious than do parents of children with other chronic diseases (Marteau and Johnston 1986). More than 80% of parents consider that their children with Down syndrome are well accepted by society, in contrast with 4% of physicians (Pueschel et al. 1986). Fewer offspring with cystic fibrosis (CF), when compared with their parents, perceive termination of pregnancy for CF as acceptable (Conway et al. 1994).

There are several possible explanations for this phenomenon of different experiences resulting in different perceptions. There is no evidence that these differences reflect differences in knowledge. They may, however, reflect a difference in the information available to individuals when asked to make a judgement (Tversky and Kahneman 1973): those living with a condition have available to them many more examples of the condition not being serious than do those not living with it. This phenomenon may also reflect minimization, a common and effective strategy for dealing with the emotions evoked by threat. In contrast to denial, there is evidence to suggest that such a strategy does not undermine practical attempts to solve a problem (Croyle et al. 1993).

How, then, should individuals be helped to make decisions about genetic testing, given these differing perspectives? There are several options. The authors suggest that those with a particular disability be treated by counselors who share that disability. To leave aside the practical problems that this would involve—requiring sets of counselors for every disease and disability—such a solution privileges the views of the affected over those of the unaffected. Would parents make better decisions if counseled by one of the 20% of the culturally Deaf who favors the birth of deaf children than if counseled by a genetic counselor who may hold less-positive views of deafness?

Another option is to give parents the choice to meet others with different experiences of, and, hence, different perspectives on, an issue. Although this latter option appears in recent guidelines in the United Kingdom on prenatal counseling (Royal College of Obstetricians and Gynaecologists and Royal College of Paediatrics and Child Health 1997), evidence is needed to determine the consequences, which may be counterintuitive. Presenting disability in a positive light may not result in more pos-

itive attitudes. In a recent study that compared the impacts of positive and negative images of children with Down syndrome, we found that presenting a photograph, regardless of whether it presented a positive or a negative image, generated more concern about the condition than presenting no photograph (Figueiras et al., in press). There is an urgent need to evaluate the cognitive, emotional, and behavioral consequences of different types of information, presented using different media and by those with different levels of experience in living with a condition.

Another important question is raised by this paper: What constitutes a legitimate request for prenatal genetic testing? Answering this raises other questions concerning the objectives of prenatal testing: Whose interests does prenatal testing serve, and what constitutes a disability? The authors state that some deaf persons may consider prenatal testing in order to have deaf children. This raises two conflicts. One concerns the objectives of prenatal testing. Is it meant to reduce disability, in which case requests for testing to ensure deaf children should not be met, or is it to offer choice, in which case such requests should be met? Views about this issue differ even among professionals in the United Kingdom. Public health specialists put more emphasis on reducing disability (e.g., Royal College of Physicians 1989), whereas the genetics community emphasizes autonomous choice (e.g., Nuffield Council on Bioethics 1993). There is also a potential conflict between the choice of parents and the opportunities and quality of life of the child in a predominantly hearing society. Parents' and children's interests may not always coincide. With the increased control provided by new genetic technologies, there is a need to ensure the widest participation of social groups in decisions about implementation. The interests of groups beyond users and providers should be incorporated, since such decisions not only reflect a society's values but, in turn, may help to shape them.

Prenatal selection for deafness has been discussed in relation to prenatal gender selection in that both are examples of using technology to "seek out and destroy" a "normal" fetus (D. C. Wertz, personal communication). Wertz reports widespread feeling among both geneticists and parents that this is a misuse of genetic technology. She suggests that it perverts the goals of medicine in order to satisfy special interests. The goals of medicine are defined as helping people to live to the fullest extent possible. This begs the question of what special interests are and why meeting them should not be a goal of medicine. Who defines what "living to the fullest extent possible" is? Some deaf parents may consider that the social advantages of sharing a Deaf culture within the family and the Deaf community outweigh the biological limitation of not hearing.

Wertz reports that the majority of 409 U.S. patients surveyed believe that a doctor should honor a parent's request for prenatal diagnosis in order to have a deaf child or a child of a specified gender (55% and 59%, respectively; D. C. Wertz, personal communication). Other surveys in the United States and Europe show that a proportion of the public is in favor of prenatal testing and selective termination for a range of conditions not considered to be diseases. For example, 25% of 147 U.S. students agreed with prenatal testing at least in some circumstances for short stature (Milner et al. 1998), and 10% of 973 citizens of the United Kingdom thought that prenatal testing with the option of termination should be available for two missing fingers (Michie et al. 1995). A 1994 U.S. survey of 1,000 members of the public and 1,084 geneticists asked whether requests for prenatal testing for gender selection should be met: just over one-third of respondees said "yes" (Wertz and Fletcher 1998). There was a belief among both geneticists and patients that withholding any service is a denial of patients' rights. However, there are considerable differences between geneticists in different countries, with only 8%–14% of U.K. geneticists agreeing that such requests should be met (a similar figure to the 16% of Middleton's sample of deaf citizens of the United Kingdom who said they would consider prenatal testing for deafness). In other countries, the figure ranged from 0% (in the Netherlands, Switzerland, and Egypt) to 90% (in Russia). Again, we should remind ourselves that these surveys only report attitudes. We do not know how such requests are actually met.

The extent to which people consider a condition to be serious depends on their culture, socioeconomic status, religion, and personal experience. These factors may differ both within a society and among different societies. In Wertz's 1994 survey, reasons given by geneticists for their views varied, with Western nations emphasizing personal autonomy and China and India emphasizing social consequences (Wertz 1995). One framework for making judgements about the use of genetic technology is not necessarily superior to another: they are different, shaped by each society's historical, cultural, and material circumstances. These circumstances determine what is beneficial and what is harmful, what is socially responsible and irresponsible, and what is autonomy. This applies to different societies as well as to different cultural and social groups within any society.

This letter started with the questions "What are the purposes of genetic testing, what are the principles guiding its use, and who should decide what tests should be available for what purposes?" Answers cannot be absolute, but must depend on the particular context within which a technology is being developed and applied. A combination of discussion, research, and developing frameworks for judgment would seem to be necessary

ingredients for the constructive development of thought and action in introducing new technologies. This is particularly the case for genetic tests used for prenatal diagnosis and selective termination of pregnancies.

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Reply to Michie and Marteau

To the Editor:

Michie and Marteau (1999 [in this issue]) make some valid points in relation to our article on attitudes toward genetic testing for deafness (Middleton et al. 1998). However, they also make some criticisms that we would like to take the opportunity to answer. Michie and Marteau point out that the study sample is likely to be unrepresentative of deaf people. It was acknowledged in our article that the study sample was biased. In fact, a culturally biased sample was chosen deliberately, since it was cultural attitudes that were of interest. Another criticism in their letter is that "participants completed the questionnaires in a highly unusual social context." Again, it was acknowledged in our article that the "responses may have been influenced by the context within which the questionnaire was distributed," and "social desirability bias" was cited as a possible confounding factor. The article was the result of a pilot study that, together with other pilot work, contributed to the design of a larger study that has ascertained the attitudes of 1,600 deaf, hard-of-hearing, or deafened adults and

hearing individuals with a family history of deafness. From the results of this larger study, it will be possible to see how the sample used in the article fits into a more general sample from the deaf community. Preliminary analysis of the results from the larger study shows that, although the attitudes expressed in our article are more negative than those based on the larger sample, the trends are the same. The results of this larger study are in the process of being written up for publication.

Michie and Marteau also say that we proposed that specialized counselors should be required for every disease and disability. This was not what we suggested. We advocated that language and cultural barriers could be kept to a minimum by the use of deaf genetic counselors to see deaf clients, in the same way that Asian counselors might counsel Asian clients in their own language, recognizing transcultural aspects in the genetic counseling process, rather than just the use of interpreters in this situation. We actually emphasized that it is unrealistic to suggest that only disabled people could counsel disabled clients.

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Using Exact *P* Values to Compare the Power between the Reconstruction-Combined Transmission/ Disequilibrium Test and the Sib Transmission/ Disequilibrium Test

To the Editor:

In a recent letter in the *Journal,* Laird et al. (1998) pointed out that Spielman and Ewens's (1998) sib transmission/disequilibrium test (S-TDT) is identical to a Mantel-Haenszel test of trend. As noted by Laird et al., it is possible by this identity to use commercial software such as StatXact to calculate exact *P* values for the S-TDT. The superiority of exact *P* values over asymptotic *P* values is evident, since it is well known (e.g., see Elston 1998) that *P* values obtained on the basis of theoretical large-sample approximations can be quite unreliable if they are much smaller than .05. An example of the need of small *P* values is the association scan proposed by Risch and Merikangas (1996), which requires that *P* values $< 5 \times 10^{-8}$ be observed in order for significance to be declared.

It does not seem to be generally known that the calculation of exact *P* values for the S-TDT does not require sophisticated algorithms at all. To the contrary, it is easily incorporated into any computer program. In essence, the test statistic of the S-TDT is the total number T of alleles A (i.e., the allele of interest) in affected children in the whole sample. The null distribution of T is the convolution of all null distributions for T_i, where T_i denotes the number of alleles A in family i. The null distribution of T_i, conditional on the observed numbers n_{ai} of affected children and n_{ui} of unaffected children and on the observed marker-genotype distribution in family i, is easily calculated from a hypergeometric distribution and is concentrated on, at most, $2n_{ai} + 1$ different values. The numerical calculation of the convolution of such distributions concentrated on a small part of the natural numbers is quite feasible, at least for sample sizes typically occurring in practice (see below). The situation is very similar for the reconstruction-combined transmission/disequilibrium test (RC-TDT [Knapp 1999]), which employs reconstruction of missing parental genotypes to enhance the power of the S-TDT. This test, which does not seem to be identical to any standard statistical procedure and, therefore, requires special software for its application, also allows the calculation of exact *P* values.

I have written an SAS (SAS Institute 1990) macro that calculates exact *P* values for the S-TDT and RC-TDT, as well as *P* values based on z scores (with and without continuity correction). In order to give an impression of the time performance of this program, it was applied to allele M7 of marker D5G23 in Genetic Analysis Workshop 9 data (Hodge 1995). When all parental genotypes in these families are assumed to be unknown, 107 families remain that can be analyzed with the S-TDT and the RC-TDT. The program required less than 3 CPU-seconds for this analysis, on a low-end IBM RS6000 workstation. If each family is multiplied 10-fold (i.e., resulting in a data set of 1,070 families, which is more than the sample sizes usually occurring in practice), the SAS macro required 24 CPU-seconds.

The implementation of the RC-TDT in this macro differs, in two points, from the description given by Knapp (1999) and from the program formerly used to compare the power of the RC-TDT versus that of the

Table 1

Simulated Power of Exact S-TDT and Exact RC-TDT, for Sibships with at Least One Affected Sib (α = .001, R = 500 Replicated Samples)

	Power							
	300 Families, Each with Two Sibs		150 Families, Each with Four Sibs			100 Families, Each with Six Sibs		
				RC-TDT			RC-TDT	
Model	S-TDT	RC-TDT: Paternal Missing[a]	S-TDT	Both Missing[b]	Paternal Missing[a]	S-TDT	Both Missing[b]	Paternal Missing[a]
D1	.63	.83	.59	.64	.67	.52	.59	.61
D2	.65	.85	.86	.88	.91	.86	.90	.90
D3	.65	.92	.97	.98	.98	.98	.98	.98
A1	.64	.79	.53	.57	.60	.40	.45	.48
A2	.61	.80	.66	.72	.75	.64	.71	.73
A3	.63	.83	.80	.85	.88	.82	.85	.86
R1	.57	.60	.52	.56	.60	.40	.44	.48
R2	.61	.66	.67	.70	.71	.64	.66	.69
R3	.59	.70	.81	.82	.84	.81	.81	.81

[a] Only the paternal genotype is missing in all families.
[b] Both parental genotypes are missing in all families.

S-TDT. Both changes are related to families with marker information available for a single parent:

1. Families in which all children possess the same genotype neither allow parental-genotype reconstruction nor are suitable for S-TDT analysis. Therefore, these families were discarded from the analysis by Knapp (1999). If only a single parental marker genotype is missing and the genotype of the typed parent is *AB*, however, Curtis and Sham (1995) have shown that affected offsprings with an allele not present in the available parent (e.g., *C*) can be used for TDT analysis. The modified RC-TDT therefore includes such families. Here, the distribution of the number of alleles *A* is concentrated on the points 0 and n_{ai}, since it is required that all children in the family have the same marker genotype. (If more than one allele that is not present in the typed parent occurs in the genotype of the sibship, the missing parental genotype can be reconstructed; and, if both alleles *A* and *B* occur in the children, the family is suitable for analysis by S-TDT.)

2. Knapp (1999, p. 864) has discussed the distinction between exact reconstruction of the missing parental genotype and the condition given in his table 2, for a *BC* × *AB* mating (with the *BC* parent being typed). Inadvertently, the program used to obtain the power estimates shown in Knapp's (1999) table 5 considered a family to be reconstructable only in the case of exact reconstruction but used the null expectation and null variance as given in Knapp's table 2. Both of these values are too large for families that allow for exact reconstruction. Therefore, this bug systematically underestimates the power of the RC-TDT.

Both to compare the power of the S-TDT with the power of the RC-TDT, when rejection of the null hypothesis is based on exact *P* values for both tests, and to assess the effect of the two changes for the RC-TDT that have been described above, the same simulated samples that had been presented by Knapp (1999) were reanalyzed. When the results shown in table 1 are compared with the power estimates given in Knapp's (1999) table 5, it can be seen that *P* values based on *z* scores with continuity correction tend to be conservative. The most pronounced increase in power for families with only one missing parental genotype is observed for two sibs, in which the first of the RC-TDT changes described above could be expected to have the largest effect. (An SAS macro that calculates the S-TDT and RC-TDT test statistics and their respective exact *P* values can be obtained, by request via e-mail, from the author.)

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