normal value, a finding that supports the likelihood of heterozygosity. These studies suggest that prenatal diagnosis of transcobalamin II deficiency may be possible by means of measuring transcobalamin II production in amniotic-fluid cells.

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LIKELIHOODS IN PEDIGREE ANALYSIS UNDER SEQUENTIAL SAMPLING

To the Editor: In a recent paper, Hodge and Boehnke (1986) claim to find error in a sequential sampling result of Cannings and Thompson (1977). However, the supposed "error" is the result of misunderstanding of the context of the probability statements involved. For brevity we shall refer to the recent paper as H&B and to that presenting the original result as C&T. Although H&B admits the validity of the general conclusions of C&T and points to important practical applications of sequential sampling in genetic epidemiology, it claims to produce a counterexample of the precise equation that expresses that validity. Some clarification of this confusion is therefore necessary.

What is the source of the misunderstanding and of the supposed counterexample presented in H&B? All probability statements must presuppose a wealth of background context, which, since it is impossible to specify the universe within the page limitations of a journal, must be taken as understood. The proof

in C&T, as the immediately following sentence makes clear, is of the fact that the likelihood obtained under sequential sampling is proportional to that on a predetermined fixed structure, the constant of proportionality being independent of the genetic model. Thus, clearly, the initial statements of the proof must be understood in the context of the rule g, whereas the concluding statement concerns the fixed sample structure. Unfortunately, the point at which the sequential sampling rule g disappears from the probability statements was not made explicit. The proof shows that the likelihood for parameters θ based on data $X^{(N)} = (X_1, X_2, \ldots, X_N)$ obtained on (sets of) individuals $C^{(N)} = (C_1, C_2, \ldots, C_N)$ obtained under sequential sampling rule g is proportional to

$$\prod_1^N P(X_n|X^{(n-1)}, C^{(n)}, \theta, g) ,$$

with the natural null-data interpretation being given to $X^{(0)}$. However, each probability of this expression is independent of the rule g, and thus the sequential rule may be replaced by the fixed structure $C^{(n)}$—or, for data on $C^{(n)}$, by any fixed structure containing $C^{(n)}$; that is, each term in the product may be replaced by the fixed-structure conditional probability

$$P(X_n|X^{(n-1)}, C^{(n)}, \theta) , \tag{1}$$

which, since $C^{(N)}$ contains $C^{(n)}$, is

$$P(X_n|X^{(n-1)}, C^{(N)}, \theta) ; \tag{2}$$

and the product reduces to the fixed-structure likelihood

$$P(X^{(N)}|C^{(N)}, \theta) .$$

Thus, the likelihood under sequential sampling is proportional to the likelihood on the fixed structure; this is the form in which researchers use the result, and it is correct.

The "counter-example" of H&B shows that the assumption

$$P(X_n|X^{(n-1)}, C^{(n)}, \theta, g) = P(X_n|X^{(n-1)}, C^{(N)}, \theta, g)$$

would be incorrect, but the proof in C&T does not claim otherwise. In addition to being incorrect, it would not aid in the proof of the sequential likelihood result, for the whole point of that result is the removal of g from the probability statements involved. The statement in H&B that the sequential sampling result as used in equation (1) is correct but that equation (2) is incorrect is confusing and misguided, for they are the same equation and neither involves the sampling rule g.

Although it is useful that H&B has pinpointed the lack of clarity in C&T, it would be unfortunate if its criticisms should lead applied researchers to have

more general doubts concerning the validity of likelihood inference under sequential sampling procedures. Such procedures are well known in many fields (see, e.g., Barnard 1946; Hawkins 1964). In the area of genetic epidemiology, they have been employed (Goldstein et al. 1973) and validated (Ott 1979) both previous and subsequent to C&T. H&B also expresses doubts about the properties of sequential estimators and tests of composite hypotheses. Although it is true that such properties require investigation, they have been widely studied. Wetherill and Glazebrook (1986) provide a thorough review of the general theory, and Van Eerdewegh (1987) discusses the pedigree-sampling case. All likelihood inference is within the context of an assumed class of models. Within such a prespecified class, sequential sampling techniques can substantially enhance the efficiency of estimation procedures in the genetic epidemiological context (Thompson 1986).

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MERGING AUTOSOMAL DOMINANCE AND RECESSIVITY

To the Editor: In the December 1986 issue of the *American Journal of Human Genetics* (vol. 39, pp. 811–816), Couch et al. report an interesting family with autosomal dominant multinodular goiter. In the discussion the authors suggest a defect in thyroglobulin (Tg), the 660-kd dimeric precursor protein of the thyroid hormones. In the course of our DNA studies of the human and goat Tg genes, we have reported the mapping of the human Tg gene to chromosome