b. Practical inadequacies
   * creation and inability to cope with "difficult cases";
   * risk of misunderstanding of the expert's role in paternity investigation.

The only way to avoid these problems is to stick to the time honoured methodology introduced by ESSEN-MÖLLER and not to use, at least when dealing with non-experts, the exclusion concept.

In practice that means a generalization of the proposal of GÜRTLER (1977) to the cases where non-conformity of the genealogical hypothesis with the genetic model cannot be alleviated by the presence of a silent gene but only by mutation. That is to say: L or W can be calculated in any cases and they are the only statistics that can deal in a uniform, unbiased manner with all kinds of genetic results.

Another corollary of this proposition is that a coherent efficiency criterion of genetic analysis for paternity investigation can no longer rely on the exclusion probability, but on the difference between the means of paternity probabilities among fathers and non-fathers. The description of the derivation of the algorithm is deferred to another paper.

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The Avuncular Index and the Incest Index

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INTRODUCTION

From time to time in the paternity laboratory evidence for non-paternity is obtained in one or more genetic systems, while the remaining systems strongly suggest paternity. While this can occur by chance, such cases should be pursued further. Such a situation can be an important clue that silent alleles are present, if the evidence for non-paternity is limited to conditions of apparent opposite homozygousity (so-called "second order exclusions"). Rarely, such a situation can be a clue that the evidence for non-paternity is based on serologic irregularities; confirmation may be prudent. More commonly, especially when the evidence for non-paternity is incontrovertable, the situation provides a clue that a man related to the tested man is the father. We derive the theoretical framework for such an evaluation and review our experience with case material, which demonstrates that undisclosed unclehood is by no means rare.

DERIVATION OF THE AVUNCULAR INDEX

Suppose in a disputed paternity matter the results in a particular genetic system are such that the probability that a mating of a man of the phenotype of the tested man and a woman of the phenotype of the mother would result in a child of the observed phenotype is X, while the probability that a mating of an unknown (i.e. genetically random) man and a woman of the phenotype of the mother would result in a child of the observed phenotype is Y. This standard formulation yields a likelihood ratio (paternity index) of X/Y.

It is of interest to ask: what is the probability that an unphenotyped brother of such a man would produce such a child with such a woman? An unphenotyped brother of such a man has two sets of genes (haplotypes). One set is to be called "common" genes. Each "common" gene was inherited by both the tested man and his unphenotyped brother as part of the same chromosome segment from the same parent. The other set, to be called "random" genes, were inherited by the unphenotyped brother but not by the tested man.

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It is clear that each gene in a zygote produced by the unphenotyped brother is "common" with probability 1/2 and "random" with probability 1/2. If a "common" gene is contributed, the probability that an unphenotyped mother would produce such a child with such a woman is X, while if a "random" gene is contributed, the probability that an unphenotyped mother would produce such a child with such a woman is Y. Since each of these situations occurs with equal probability, it follows that the probability that an unphenotyped brother of the tested man would produce such a child with such a woman is equal to (X+Y)/2.

The avuncular index (AI) is defined as the likelihood ratio which tests the hypothesis that the tested man is a paternal uncle of the child versus the hypothesis that the tested man is unrelated to the child, so that AI = (X+Y)/2Y = (PI+1)/2. The AI also tests the hypothesis that the tested man is a paternal half brother of the child (i.e. that the unphenotyped father of the tested man is the father of the child). By arguments similar to the above the likelihood ratio for an unphenotyped second degree relative (half brother, uncle, double first cousin) of the tested man can be shown to be equal to (X+3Y)/4Y = (PI+3)/4. This can easily be extrapolated to any degree of kinship.

While for a single genetic system the AI is a simple function of the PI, the cumulative AI is not a simple function of the cumulative PI. This point is of some practical importance and will be discussed later.

EXPERIMENTAL RESULTS

The AI was calculated in a prospective study of 1500 consecutive paternity cases. In 37 of these cases the mother named two men; 3 of these pairs of men were brothers, so that the prevalence of alleged unclehood in this material is one in 500. A total of 360 men were excluded, including at least one of each of the 37 pairs. The cumulative distribution of the AI for the 360 excluded men is shown in Fig. 1. The cumulative distribution is approximately sigmoidal, suggesting that this population of mostly random (with respect to their mother-child pairs) men have AI that are approximately log normally distributed. The median AI for the population is 0.26 - for the typical excluded man, his phenotypes occur four times more frequently among random men than among uncles of the respective children. Two inflection points are present, at AI ∽ 1 and AI ∽ 4. This suggests that the population of excluded men may not be homogenous; the distribution of random excluded men might well be represented by the dotted line, with the excess of excluded men with high AI's due in part to undisclosed uncles.

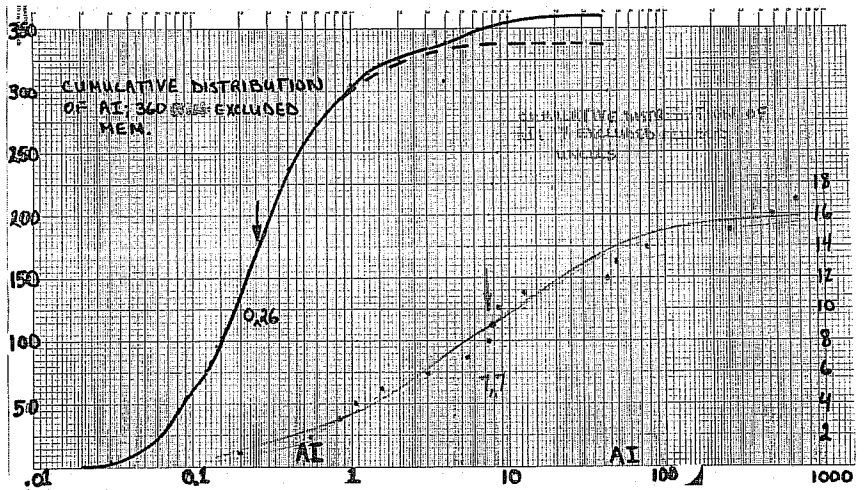

Fig. 1. Cumulative distribution of AI (logarithmic scale) for 360 excluded men and for 17 uncles excluded as the father.

Table 1. Followup of 19 excluded men with AI ≥ 4

1	no followup information obtained
1	alleged uncle[a] (7.5)
3	mother denies any other man (5.9, 5.9, 6.3)
8	mother admits to unrelated man
	1 tested (4.0); PI = 203
	7 not tested (4.7, 6.5, 7.5, 7.5, 23, 39, 40)
6	mother admits to related man
	2 brothers tested
	1 not excluded (23); PI= 36,900
	1 excluded[b] (6.1)
	4 not tested
	2 brothers (4.5, 10.2)
	1 cousin (6.1)
	1 uncle (5.7)

[a] of the three pairs of brothers initially named by mothers, one member of each pair was excluded. In one of these three cases, the AI of the excluded brother ("alleged uncle") was 7.5.

[b] Identity of this excluded brother has yet to be confirmed.

To test this hypothesis, followup was requested on the 19 cases (5.3%) with AI ⩾ 4 (Table 1). The yield from this population at increased risk for undisclosed unclehood is thus 6/18 (33%); the frequency with which this limited followup resulted in disclosure of related men (6) is twice the frequency with which mothers initially alleged unclehood (3). To investigate the distribution of the AI among uncles our files were reviewed.

Of 6500 cases (including the 1500 which constitute the prospective study reported here) the mother initially named related men in fifteen. In thirteen, she named a pair of brothers; in one case both brothers were excluded and in another case neither brother was excluded. In one case the mother named three brothers, and in one case the mother named three brothers for each of two children. After testing, a total of 18 alleged uncles remained, of whom 17 were confirmed as uncles; the distribution of the AI for these 17 is shown in Figure 1. While it is hazardous to estimate the shape of the distribution from such a small sample, the median of the distribution (7.7) may be reliably estimated (range of AI: 0.2-680). Thus, the distribution of the AI for uncles appears to be shifted by a factor of 30 from the distribution of excluded men (which is comprised primarily of random men). The distribution of AI's for uncles corresponds well to the inflection in the distribution of excluded men. As a significant number of undisclosed uncles were discovered among the 19 excluded men with AI ⩾ 4, one can expect that significant numbers of undisclosed uncles remain among the excluded men with AI < 4.

The distributions of the AI for excluded men and for uncles are not strictly comparable. In our laboratory we test sequentially. All our cases are tested in HLA, ABO, Rh, and MN; the great majority are also tested in PGM, EsD, and Glo. If clearcut exclusion or a PI > 100 is obtained, no further testing is performed. Otherwise sequential testing is continued in systems selected from AcP, AK, ADA, 6-PGD, Hp, Bf, PLG, Gc, Ss, Kell, Duffy, Kidd, subtyping in PGM and Gc, and, where appropriate, CAII and Hgb. Most non-fathers are easily excluded and thus receive relatively little testing. On the other hand, uncles are rather difficult to exclude (for any genetic system, no matter how powerful for excluding random men, the exclusion probability for an uncle < 1/2) and received, on average, more testing. In fact, of the 18 uncles, only 14 (78%) were excluded by our battery of tests, which has a mean exclusion probability for random men of .997. Three were excluded by further testing in other laboratories and, as noted above, one was not excluded.

The significance of this observation is that since significant numbers of undisclosed uncles were found among excluded men with AI ⩾ 4, not only are significant numbers of undisclosed uncles expected among excluded men with AI < 4, but also among non-excluded men. Thus, while one always considers that the tested man might be the father or a random man, one should also keep in mind the possibility that he might be an uncle; this additional possibility bears on the issue of adequacy of testing. The quotient PI/AI tests the hypothesis that the tested man is the father versus the hypothesis that he is an uncle. As shown in Table 2, the distribution of the cumulative PI among the genetic systems significantly affects AI and, therefore, PI/AI.

Table 2. The effect of the distribution of evidence among genetic systems on AI and PI/AI; cumulative PI = 64 in 6 systems

Individual PI in system							
#1	#2	#3	#4	#5	#6	AI	PI/AI
2	2	2	2	2	2	11.4	5.61
4	4	4	1	1	1	15.6	4.10
64	1	1	1	1	1	32.5	1.97
256	1/2	1/2	1	1	1	72.3	0.89

Note that if the PI is distributed evenly among the genetic systems, AI is small compared to PI. However, in the limiting case in which all the evidence in favor of paternity is found in a single system, with the remaining systems on balance favoring non-paternity, AI>PI; the genetic evidence actually favors the hypothesis that the man is an uncle over the hypothesis that he is the father. In such a case the assumption that non-paternity implies that the tested man is "random" is critical.

THE INCEST INDEX

The incest index (II) tests the hypothesis that the father is a first order relative (brother, father) of the mother relative to the hypothesis that the father is unrelated to the mother. If Z is defined as the frequency with which a child of the observed phenotype is produced by a woman of the phenotype of the mother and a man of the genotype of the mother, and Y is calculated by "Method B", then for an individual genetic system II = (Z+Y)/2Y. II depends only on phenotypes of mother and child and can easily be extended for any degree of kinship. For our test battery, significant values of the II are due primarily to situations in which mother and child are HLA identical, or the child is apparently homozygous in HLA for a maternal haplotype. The use of the II in our clinical practice will be presented elsewhere.