Am J Hum Gent 30:180–189, 1978

Effects of Reproductive Compensation and Genetic Drift on X-Linked Lethals

K. LANGE,[1] K. GLADSTIEN,[1,2] AND M. ZATZ[3]

INTRODUCTION

The introduction of accurate tests for the detection of female heterozygotes in Lesch-Nyhan disease has stimulated a revival of interest in Haldane's equilibrium theory for X-linked lethals [1]. Francke et al. [2] applied these tests to 47 pedigrees ascertained through male probands. Only four of their probands appear to represent new mutations. Assuming an equal mutation rate in males and females and no selective advantage or disadvantage of normal over carrier females, one would expect ⅓ of their probands to be new mutations. Francke et al. [2, 3] argue that the data suggest a mutation rate in males that increases with age and is on the average higher than the mutation rate in females. Morton and Lalouel [4] contend that the excess of familial cases is probably due to biased ascertainment. While agreeing with Morton and Lalouel about the possibility of biased ascertainment, Vogel [5] emphasizes replication dependent mutation as a biological explanation for a higher average mutation rate in males.

None of these authors seriously entertains the idea of a selective advantage of carrier females over normal females. In the present paper we wish to discuss this hypothesis in some detail as well as comment on the possibility of genetic drift. We do not wish to imply that either a higher mutation rate in males or biased ascertainment is an unrealistic hypothesis. It may be that a combination of forces has produced the Lesch-Nyhan pedigrees of Francke et al. [2].

REPRODUCTIVE COMPENSATION

Women have practiced various forms of contraception and induced abortion since

Received August 10, 1977; revised October 14, 1977.

This work was supported in part by the University of California at Los Angeles; a National Institutes of Health Special Resource Grant (RR-3); grant 6-55 from the National Foundation–March of Dimes; Conselho Nacional de Desenvolvimento Cientifico e Technologico (CNPq); and a Birth Defects Center Grant, National Foundation–March of Dimes.

[1] Department of Biomathematics, University of California, Los Angeles, California 90024.

[2] Department of Psychiatry, University of California, Los Angeles.

[3] Division of Medical Genetics, Harbor General Hospital, University of California, Los Angeles, Torrance, California 90509

classical Greek times. For instance, the medieval Islamic world governed coitus interruptus by explicit law, and in the 17th century, birth control was common among the bourgeoisie of Geneva and the peers of France [6]. But effective birth control has probably not been widely used in industrial cultures for more than a few generations. We will argue, however, that even a few generations of contraception and induced abortion may be enough to shift the balance between selection and mutation for X-linked lethals.

To be specific, if heterozygous women are willing to compensate for the birth of defective sons, then they will inadvertently overproduce carrier daughters who can further propagate the defective gene. Reproductive compensation will be particularly effective in increasing the proportion of familial cases if selection against the affected sons occurs in utero or affected sons show symptoms at an early age. In either case a mother is more likely to have time during her childbearing years to reproductively compensate. Thus one would expect reproductive compensation to have a greater effect in Lesch-Nyhan disease than in, say, Duchenne muscular dystrophy.

There are two plausible family planning models that lead to reproductive compensation. The first model postulates that parents desire n phenotypically normal children. Holloway and Smith [7] show that under this scheme normal females have a fitness f about ¾ that of carrier females. This holds for all n. (See Appendix A for a different derivation.)

The second family planning model postulates that parents desire at least b normal boys and at least g girls. In Appendix A we explain how to compute fitness values according to this second model. Table 1 records the fitness f of normal females relative to carrier females for various values of b and g. (We assume in our computations that 106 boys are born for every 100 girls.) Table 1 shows that f is very sensitive to how highly sons are valued compared to daughters.

The X-linked trait, testicular feminization (*tf*) syndrome, presents an interesting contrast to our conclusions so far. Affected boys are sterile and are perceived as outwardly normal girls. Under the first family planning model, normal females will be just as fit as *tf* carrier females. But under the second family planning model, affected boys are counted as girls. This leads to the fitness values given in table 2. Note that normals can actually be more fit than *tf* carriers when g is greater than b.

TABLE 1

FITNESS VALUES OF NORMAL FEMALES RELATIVE TO CARRIER FEMALES

b \ g	0	1	2	3	4
0	· · ·	1.00	1.00	1.00	1.00
1	.50	.65	.79	.88	.93
2	.50	.55	.64	.74	.82
3	.50	.52	.57	.63	.70
4	.50	.51	.53	.57	.63

NOTE. —The minimum number b of normal boys desired is listed in the first column and the minimum number g of girls desired in the first row. Without reproductive compensation the fitness would be 1.

TABLE 2

FITNESS VALUES OF NORMAL FEMALES RELATIVE TO TESTICULAR FEMINIZATION (*tf*) SYNDROME CARRIER FEMALES

b \ g	0	1	2	3	4
0	...	1.53	1.53	1.53	1.53
1	.50	.71	.95	1.14	1.27
2	.50	.56	.68	.82	.97
3	.50	.52	.58	.66	.76
4	.50	.51	.54	.58	.65

NOTE.—The minimum number b of normal boys desired is listed in the first column and the minimum number g of girls desired in the first row. Without reproductive compensation the fitness would be 1.

BALANCE BETWEEN SELECTION AND MUTATION

It would be useful to know how rapidly reproductive compensation can shift the balance between selection and mutation to a new equilibrium. The frequency of carrier females at equilibrium is $[2f/(2f - 1)](\mu + \nu)$, where μ and ν are the female and male mutation rates, and f is the fitness of normal females relative to carrier females [7]. In Appendix B we show that equilibrium is approached at approximately the geometric rate $(2f)^{-1}$. Our explicit handling of the dynamics of approach to equilibrium supplements the approximate method of Morton [8] based on linearized systematic pressures. We also provide in equations (7) and (8) of Appendix B the necessary formulas to predict the probability that the mother of an affected boy is a carrier. These formulas can be compared to the treatment of Felsenstein [2].

Table 3 gives a specific numerical example to illustrate our mathematical development. At generation 0, the population starts at the equilibrium determined by $\mu = \nu = 10^{-5}$ and $f = 1$. However, parents at generation 0 and subsequent generations practice reproductive compensation at a level specified by $f = \frac{3}{4}$. In table 3, observe that both the probability w_n and the frequency z_n are more than halfway to their new equilibria in

TABLE 3

APPROACH TO EQUILIBRIUM UNDER REPRODUCTIVE COMPENSATION

n	z_n	w_n
0	4.00×10^{-5}	.667
1	4.67×10^{-5}	.727
2	5.11×10^{-5}	.757
3	5.41×10^{-5}	.773
4	5.60×10^{-5}	.783
5	5.74×10^{-5}	.789
6	5.82×10^{-5}	.793
7	5.88×10^{-5}	.795
8	5.92×10^{-5}	.797
9	5.95×10^{-5}	.798
10	5.97×10^{-5}	.799
∞	6.00×10^{-5}	.800

NOTE.—n is the generation number, z_n is the frequency of carrier females, and w_n is the probability that the mother of an affected boy is a carrier. The mutation rates μ and ν are 10^{-5}, and the fitness f of normal females is 3/4.

just 2 generations. The speed of approach to equilibrium is simply a consequence of the rapid turnover of lethals. In fact, the average X-linked lethal persists for fewer than 2 generations [9].

GENETIC DRIFT

Genetic drift is defined as the random fluctuation in gene frequencies caused by Mendelian segregation in a finite population. For X-linked lethals, one is interested in the frequency of carrier females. The mean of this frequency will be the equilibrium frequency. For large populations which are neither declining nor growing, we show in Appendix C that the standard deviation of the carrier frequency is

$$\frac{1}{\sqrt{n}}\left(\frac{(\mu+\nu)\left[\left(1+\frac{q}{2}\right)\left(\frac{q\sigma^2}{2}-\frac{1}{2f}\right)\right]}{\left(1-\frac{1}{2f}\right)^2\left(1+\frac{1}{2f}\right)}\right)^{1/2},$$

where n is the number of normal females, q is the probability of a female birth, and σ^2 is the variance of the number of children produced by a carrier female. When n is quite large, the carrier frequency is approximately normally distributed.

To illustrate the magnitude of the fluctuations possible, suppose $\mu = \nu = 10^{-5}, f = 1, n = 10^6, q = \frac{1}{2}$, and $\sigma^2 = 2$. Then the carrier frequency has mean 4.00×10^{-5} and standard deviation $.73 \times 10^{-5}$. For this particular example, genetic drift cannot be ignored. However, for $n = 10^8$ (i.e., about the number of females in the U.S. population), the standard deviation is only $.73 \times 10^{-6}$.

DISCUSSION

Vogel [5] has summarized the human data bearing on Haldane's theory of the balance between selection and mutation in X-linked lethals. For Duchenne muscular dystrophy, most of the empiric evidence cited by Vogel lends support to Haldane's theory. The Brazilian study of Zatz et al. [10, 11] and the Italian study of Danieli et al. [12] add further support. We agree with Vogel's suggestion that the data should be reexamined when a precise carrier detection method is perfected. Vogel does not mention testicular feminization syndrome. This X-linked genetic lethal may provide data comparable to the Lesch-Nyhan data if the carrier detection of Meyer et al. [13] proves practical.

Our discussion of reproductive compensation has been frankly speculative. It may be that some carriers are deterred from having further children by the birth of affected sons. The reproductive behavior of carriers is certainly governed in part by the perceived severity of each disease, by its duration, and by the support provided by the surrounding community. Furthermore, genetic counseling will surely influence the balance between selection and mutation for the X-linked lethals, although it may be too early to tell in which direction this influence will operate.

If more population studies on Lesch-Nyhan disease are conducted as suggested by Morton and Lalouel [4] and Vogel [5], certain cautions should be borne in mind. First, the studies should definitely be large scale. Genetic drift can be substantial in

Scandinavian size populations. Second, the population under study may not be in equilibrium due to the recent introduction of reproductive compensation or a drastic change in mutation rates. If a new equilibrium is being approached, then the frequency of carrier females should lie between the old and the new equilibria. Third, if Haldane's theory cannot account for the data, then one should follow the lead of Francke et al. [2] and pay careful attention to the proportion of carriers among grandmothers of probands. As pointed out in Appendix B, this proportion near equilibrium will be independent of the female and male mutation rates and will approach $(2f)^{-1}$. If one observes only the proportion of carriers among mothers, then fitness and differences in mutation rate will be confounded.

SUMMARY

A revival of interest in Haldane's equilibrium theory for X-linked lethals has been stimulated by the introduction of accurate tests for the detection of female heterozygotes in Lesch-Nyhan disease. Application of these tests appears to indicate an excess of familial cases. This excess can be attributed to ascertainment bias, a difference in female and male mutation rates, genetic drift, and reproductive compensation. Reproductive compensation will be particularly effective in increasing the proportion of familial cases if (1) birth control is widespread; (2) selection against affected males acts in utero; (3) affected sons show symptoms at an early age; and (4) sons are more highly valued than daughters. We demonstrate how only a few generations of reproductive compensation are sufficient to achieve an approximate equilibrium between selection and mutation showing a high proportion of familial cases. We also discuss the random fluctuations around equilibrium caused by genetic drift.

ACKNOWLEDGMENTS

We would like to thank Anne Spence and John Merriam for their helpful criticism of the text. Joseph Felsenstein suggested our use of branching processes in Appendix C; he also pointed out reference [16].

APPENDIX A

Here we derive the formulas necessary to calculate fitness values for the two family planning models discussed in the text. In the simpler model, a husband and wife desire n phenotypically normal children. If G_n is the number of girls born to such parents, and p and q are the probabilities of their getting a boy or girl at any given birth, then the expected number of girls is $EG_n = nq$ if the mother is normal. If the mother is a carrier, then the first child is an affected boy with probability $p/2$, a normal boy with probability $p/2$, and a girl with probability q. Since we count only girls,

$$EG_n = \frac{p}{2} EG_n + \frac{p}{2} EG_{n-1} + q(1 + EG_{n-1}) .$$

Rearrangement gives the recurrence relation

$$EG_n = EG_{n-1} + \frac{2q}{1+q} = \ldots = \frac{2nq}{1+q} . \tag{1}$$

The fitness f is by definition the ratio

$$\frac{nq}{\frac{2nq}{1+q}} = \frac{1+q}{2} \simeq \frac{3}{4},$$

which is the result in reference [7].

In the more complex family planning model, parents desire at least b normal boys and at least g girls. Let G_{bg} be the number of girls born to such parents. To calculate EG_{bg}, we first examine the boundary terms EG_{b0} and EG_{0g}. Writing recurrence relations similar to equation (1), one finds

$$EG_{b0} = \begin{cases} \frac{bq}{p} & \text{for normal mothers} \\ \frac{2bq}{p} & \text{for carrier mothers} \end{cases}$$

It is also clear that $EG_{0g} = g$ except for mothers carrying the *tf* gene. In this case EG_{0g} turns out to be the smaller quantity $2gq/(1+q)$ since half the sons are counted as girls.

To calculate EG_{bg} for $b, g > 0$, one can use the boundary terms and the following recurrence relations for normal mothers

$$EG_{bg} = pEG_{b-1,g} - q(1 + EG_{b,g-1});$$

for carrier mothers

$$EG_{bg} = \frac{p}{2} EG_{bg} + \frac{p}{2} EG_{b-1,g} + q(1 + EG_{b,g-1}),$$

which reduces to

$$EG_{bg} = \frac{p}{1+q} EG_{b-1,g} + \frac{2q}{1+q} EG_{b,g-1} + \frac{2q}{1+q}; \text{ and}$$

for mothers carrying the *tf* gene

$$EG_{bg} = \frac{p}{2} EG_{b,g-1} + \frac{p}{2} EG_{b-1,g} + q(1 + EG_{b,g-1}),$$

which reduces to

$$EG_{bg} = \frac{p}{2} EG_{b-1,g} + \frac{1+q}{2} EG_{b,g-1} + q.$$

The above recurrence relations lead directly to the results in tables 1 and 2. Note, however, that one can equivalently calculate fitness based on the ratio of expected number of boys. This equivalence is a consequence of the Optional Sampling Theorem ([14], Chap. 6, corollary 3.3). For a given mother, one need only observe that the ratio of her expected number of girls to her expected number of boys is q/p, regardless of the family planning model which she follows.

APPENDIX B

Let $f > \frac{1}{2}$ denote the fitness of normal females relative to carrier females, and let μ denote the female and ν the male mutation rate. If x_n and y_n are the frequencies of normal and carrier

females at generation n, then it suffices for our purposes to follow the ratio $z_n = y_n/x_n$. (In practice, y_n and z_n will be virtually the same.) We can derive a simple recurrence relation for z_n under the assumptions of (1) discrete generations; (2) infinite population size; (3) random mating of normal males with normal and carrier females; (4) no back mutation; and (5) neglect of migration effects. This recurrence relation can be written as

$$z_n = \frac{x_{n-1}f[\mu(1-\nu)+(1-\mu)\nu]+y_{n-1}\left[\frac{1}{2}(1-\nu)+\frac{\mu}{2}(1-\nu)+\frac{1-\mu}{2}\nu\right]}{x_{n-1}f(1-\mu)(1-\nu)+y_{n-1}\frac{(1-\mu)}{2}(1-\nu)}$$

$$= \frac{f(\mu+\nu-2\mu\nu)+\left(\frac{1}{2}+\frac{\mu}{2}-\mu\nu\right)z_{n-1}}{f(1-\mu)(1-\nu)+\frac{(1-\mu)(1-\nu)}{2}z_{n-1}}$$

$$= \frac{a+bz_{n-1}}{c+dz_{n-1}}, \tag{2}$$

where the constants a, b, c, and d are defined in the obvious way.

Functions of the kind $T(z) = (a+bz)/(c+dz)$ are known as linear fractional transformations [14]. Iteration of equation (2) yields $z_n = T^n(z_0)$, where T^n is the n-fold composition of T with itself. Fortunately, $T^n(z_0)$ can be explicitly expressed as

$$T^n(z_0) - s_0 = \kappa^n \frac{(s_0 - s_1)(z_0 - s_0)}{z_0 - s_1 - \kappa^n(z_0 - s_0)}, \tag{3}$$

where

$$\kappa = \frac{c+ds_1}{c+ds_0}, \tag{4}$$

and s_0 and s_1 are the roots of the quadratic $0 = dz^2 + (c-b)z - a$. We take s_0 to be the larger root, $s_0 = [(b-c) + \sqrt{(c-b)^2 + 4ad}]/2d$, and s_1 to be the smaller root.

Our aim is to show that regardless of the initial value z_0, the iterates z_n tend to s_0 at the approximate geometric rate $(2f)^{-1}$. Let us first find a good approximation to s_0. If we note that

$$\sqrt{(c-b)^2+4ad} = (c-b)\sqrt{1+4ad/(c-b)^2}$$

$$= (c-b)\left\{1+\frac{2ad}{(c-b)^2}+O\left[\left(\frac{ad}{(c-b)^2}\right)^2\right]\right\},$$

it follows that

$$s_0 = \frac{a}{c-b} + O(a^2)$$

$$= \frac{2f}{2f-1}(\mu+\nu) + O(\omega^2), \tag{5}$$

where $\omega = \max(\mu,\nu)$, and $O(t)$ means a quantity such that $O(t)/t$ remains bounded in absolute value as $t \to 0$. In a similar manner

$$s_1 = 1 - 2f + O(\omega) . \tag{6}$$

Substitution of equations (5) and (6) in (4) yield $\kappa = 1/(2f) + O(\omega)$. The root s_0 is the approximate equilibrium frequency of carrier females previously found by Holloway and Smith [7]. Since $0 < \kappa < 1, s_0 - s_1 > 0$, and $(z_0 - s_1) - \kappa^n(z_0 - s_0) \geq \min(s_0 - s_1, z_0 - s_1) > 0$, it can now be seen from equation (3) that z_n tends monotonically to z_0 and that the explicit estimate $|z_n - s_0| \leq \kappa^n |z_0 - s_0| \max[1,(s_0 - s_1)(z_0 - s_1)^{-1}]$ holds.

Next let us consider an affected boy and calculate the probability that his mother is a carrier. Given that the boy belongs to generation n, this conditional probability is

$$w_n = \frac{y_{n-1}\left(\frac{1}{2} + \frac{\mu}{2}\right)}{x_{n-1}f\mu + y_{n-1}\left(\frac{1}{2} + \frac{\mu}{2}\right)}$$

$$= \frac{(1 + \mu) z_{n-1}}{2f\mu + (1 + \mu) z_{n-1}} . \tag{7}$$

The sequence w_n tends monotonically to a limit w. If we assume μ and ν are of comparable size, then

$$w = \frac{\mu + \nu}{2f\mu + \nu} + O(\omega) . \tag{8}$$

In a similar vein the mother of a carrier daughter is herself a carrier with a probability that tends monotonically to $1/(2f) + O(\omega)$. Felsenstein considers the case $f = 1$ in reference [2].

APPENDIX C

Certain results from the theory of branching processes are necessary to establish our assertions about genetic drift [14, 15]. In particular, we wish to consider the equilibrium distribution for a subcritical branching process with immigration. The entities in our branching process are carrier females. Carrier females can produce further carrier females, which in turn can produce even further carrier females and so forth. Eventually, however, every line of carrier females goes extinct. This would spell the end of the branching process if the population of carrier females were not continually replenished by mutants produced by the population of normal females. Assuming that the population of normal females is large and of constant size, the number of carrier females eventually reaches an equilibrium between extinction and immigration [13, 14].

The generating function $Q_3(s)$ for the equilibrium number of carrier females satisfies the functional equation

$$Q_3[Q_2(s)]Q_1(s) = Q_3(s), \tag{9}$$

where $Q_2(s)$ and $Q_1(s)$ are the generating functions for the number of carrier females produced in a single generation by a carrier female and the whole population of normal females, respectively. Let ω_i and σ_i^2 be the mean and variance of $Q_i(s)$. We wish to find ω_3 and σ_3^2. Differentiating equation (9) and setting $s = 1$ yields

$$\omega_3 = \frac{\omega_1}{1 - \omega_2} . \tag{10}$$

Differentiating equation (9) a second time and setting $s = 1$ gives an equation for the second factorial moment of $Q_3(s)$. Straightforward algebra then shows

$$\sigma_3^2 = \frac{\sigma_1^2(1 - \omega_2) + \omega_1\sigma_2^2}{(1 - \omega_2)^2(1 + \omega_2)} . \tag{11}$$

Skellam [16] gives these formulas when $Q_1(s)$ and $Q_2(s)$ both follow Poisson distributions.

Our task now is a more careful specification of equations (10) and (11) in terms of the mutation rates μ and ν, the probability q of getting a girl at each birth, the fitness f of normal females relative to carrier females, and the number n of normal females in the underlying population. But we first need a simple result about generating functions. Suppose $Q(s)$ is a generating function with mean ω and variance σ^2. Then the generating function $Q(1 - \alpha + \alpha s)$ has mean $\alpha\omega$ and variance $\alpha^2\sigma^2 + \alpha(1 - \alpha)\omega$. For α near 0, this variance is virtually the same as the mean $\alpha\omega$.

Next let $Q(s)$ be the generating function for the number of children born to a normal female. ($Q(s)$ still has mean ω and variance σ^2.) Since the population of normal females is stable, $q\omega = 1$. (This equality and those that follow are only approximate.) One can also show that the generating function $Q_1(s)$ of equation (9) satisfies $Q_1(s) = Q^n(1 - \alpha + \alpha s)$ with $\alpha = q(\mu + \nu)$. It follows that $\omega_1 = \sigma_1^2 = n(\mu + \nu)$. Now let $Q(s)$ be the generating function for the number of children born to a carrier female. In this case, the mean number of daughters is $q\omega = f^{-1}$, and $Q_2(s) = Q(1 - a + as)$ with $a = \frac{1}{2}q$. Thus $\omega_2 = (2f)^{-1}$ and $\sigma_2^2 = (\frac{1}{2}q)^2\sigma^2 + (1 - \frac{1}{2}q)(2f)^{-1}$, where σ^2 is the variance if the number of children born to a carrier female. Substituting directly into equations (10) and (11) shows that the frequency of carrier females has mean

$$\frac{\omega_3}{n} = \frac{2f}{2f - 1}(\mu + \nu) \tag{12}$$

and standard deviation

$$\frac{\sigma_3}{n} = \frac{1}{\sqrt{n}}\left\{\frac{(\mu + \nu)\left[1 + \frac{q}{2}\left(\frac{q\sigma^2}{2} - \frac{1}{2f}\right)\right]}{\left(1 - \frac{1}{2f}\right)^2\left(1 + \frac{1}{2f}\right)}\right\}^{\frac{1}{2}} . \tag{13}$$

Equation (12) is the same as equation (5) in Appendix B.

One final remark is in order. If n and the mean number of carrier females ω_3 are both large, then the frequency of carrier females will be approximately normally distributed. This conclusion follows from the Central Limit Theorem for independent, identically distributed random variables [14] and from the following observation. Let $n = mn'$, where m is a moderately large integer. Create m blocks of n' normal females each and m independent branching processes which are fed by the mutant immigrants from each of these blocks. Then each branching process eventually reaches the same equilibrium distribution. The overall equilibrium distribution is just the sum of these m smaller distributions.

REFERENCES

1. HALDANE JBS: The rate of spontaneous mutation of a human gene. *J Genet* 31:317–326, 1935
2. FRANCKE U, FELSENSTEIN J, GARTLER SM, MIGEON BR, DANCIS J, SEEGMILLER JE, BAKAY B, NYHAN WL: The occurrence of new mutants in the X-linked recessive Lesch-Nyhan disease. *Am J Hum Genet* 28:123–137, 1976
3. FRANCKE U, FELSENSTEIN J, GARTLER SM, NYHAN WL, SEEGMILLER JE: Answer to criticism of Morton and Lalouel. *Am J Hum Genet* 29:307–310, 1977

4. MORTON JE, LALOUEL JM: Genetic epidemiology of Lesch-Nyhan disease. *Am J Hum Genet* 29:304–307, 1977
5. VOGEL F: A probable sex difference in mutation rates. *Am J Hum Genet* 29:312-319, 1977
6. COALE AJ: The history of the human population. *Sci Am* 231:40–51, 1974
7. HOLLOWAY SM, SMITH C: Equilibrium frequencies in X-linked recessive diseases. *Am J Hum Genet* 25:388–396, 1973
8. MORTON NE: Population genetics and disease control. *Soc Biol* 18:243–251, 1971
9. GLADSTIEN K, LANGE K: Number of people and number of generations affected by a single deleterious mutation. In preparation
10. ZATZ M, FROTA-PESSOA O, LEVY JA, PERES CA: Creatine-phosphokinase (CPK) activity in relatives of patients with X-linked muscular dystrophies: a Brazilian study. *J Genet Hum* 24:153–168, 1976
11. ZATZ M, LANGE K, SPENCE MA: Frequency of Duchenne muscular dystrophy carriers. *Lancet* 1:759, 1977
12. DANIELI GA, MOSTACCIUOLO ML, BONFANTE A, ANGELINI C: Duchenne muscular dystrophy: a population study. *Hum Genet* 35:225–231, 1977
13. MEYER WJ, MIGEON BR, MIGEON CJ: Locus on human X chromosome for dihydrotestosterone receptor and androgen insensitivity. *Proc Natl Acad Sci USA* 72:1469–1472, 1975
14. KARLIN S, TAYLOR HM: *A First Course in Stochastic Processes,* 2d ed. New York, Academic Press, 1975
15. JAGERS P: *Branching Processes with Biological Applications*. New York, John Wiley, 1975
16. SKELLAM JG: The probability distribution of gene-differences in relation to selection, mutation, and random extinction. *Proc Camb Phil Soc* 45:364–367, 1949