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Effect of Artificial Insemination on Frequency of Undesirable Recessive Genes

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Abstract

Reduction in the frequency of undesirable recessive genes is examined for several combinations of initial gene frequencies and number of offspring obtained by random mating of young sires to the population. Only sires not having affected offspring are then returned to heavy use. Such selection can very rapidly reduce the number of affected offspring, if the initial gene frequency is high or if the number of tested offspring is 200–500 for lower gene frequencies. For some combinations, frequency of affected offspring in the population is higher after two or three generations of selection than in the first generation of selection. With high initial gene frequencies, practically all heterozygous males are detected and culled during the test period, resulting in practically no affected offspring in the first generation. The population gene frequency remains relatively high, due to the influence of the unselected females. In the next generation the heterozygous males are not detected with high probability and the frequency of affected offspring increases above that of the first generation. After the new peak of affected offspring is reached in a few generations, frequency drops, as expected.

One criticism of the artificial insemination (AI) industry has been that the frequency of deleterious recessive genes could be increased very rapidly by unknowing use of carrier males. Various methods of testing sires for heterozygosity have been proposed—mating to known carriers, mating to own daughters, etc. Another proposal has been to mate sires at random in the population. Such a test would parallel a production proof made on a limited number of progeny. If the frequency of a recessive gene were high in the population, a carrier of the recessive gene would be detected with high probability and few affected offspring would result when tested bulls were used heavily. If the gene frequency were low, carriers would not be detected with very high probability, but the frequency of affected offspring would not be high because of the low frequency of the gene in the female and male populations. Gene frequency might be increased temporarily, but in the next generation carriers would be detected with higher probability and no damage would be done. This concept of balance seems reasonable enough, but has never been formally presented.

The purpose of this paper is to describe in terms of population genetics the effects of an A.I. testing program on the frequency of undesirable recessive genes. None of the concepts described is original, since the basis of the entire discussion is the Hardy-Weinberg law and the properties of random union of gametes from populations of males and of females. Hopefully, however, this development will make some practical application of these genetic principles to a problem of the A.I. industry.

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Method

Let p_0 be the frequency of the normal allele and $q_0 = 1 - p_0$ be the frequency of the undesirable recessive allele in the gametes which will combine randomly to form the initial generation. Frequencies of the zygotes in the initial generation are, as is well known by the Hardy-Weinberg law:

Genotype	Frequency
AA	p_0^2
Aa	$2p_0q_0$
aa	q_0^2

If all the aa individuals fail to reproduce (recessive lethal), the AA and Aa genotypes have equal fitness, and the surviving animals mate randomly, frequencies of the genotypes in the next generation are p_1^2, $2p_1q_1$, and q_1^2, where $q_1 = \frac{q_0}{1 + q_0}$ and $p_1 = 1 - q_1$. After t generations the frequencies will be p_t^2, $2p_tq_t$, and q_t^2, where $q_t = \frac{q_0}{1 + tq_0}$ *and* $p_t = 1 - q_t$. This is the well-known situation in a random mating population with complete selection against homozygous recessives.

Suppose, in addition, that a fraction of the heterozygous males can be detected as carriers and that none of the heterozygous females can be detected. Frequencies of males and females in the i^{th} generation are described in the following table where $j = i - 1$:

	Males		Females	
Genotype	Frequency	Survivor's Frequency	Frequency	Survivor's Frequency
AA	$p_j x_j$	$p_j x_j$	$p_j r_j$	$p_j r_j$
Aa	$p_j y_j + q_j r_j$	$\alpha_i(p_j y_j + q_j r_j)$	$p_j y_j + q_j r_j$	$p_j y_j + q_j r_j$
aa	$q_j y_j$	0	$q_j y_j$	0
Total	1	$p_j x_j + \alpha_i(p_j y_j + q_j r_j)$	1	$p_j x_j + p_j y_j + q_j x_j$

Note that (x_j, y_j) are the frequencies of the two alleles in the females of the j^{th} generation surviving to produce the i^{th} generation and (p_j, q_j) are the corresponding frequencies of the selected males which produce the i^{th} generation.

α_i is the probability of not detecting a heterozygous male from n offspring in the i^{th} generation, which is equivalent to the probability of obtaining all normal offspring out of a total of n offspring. The frequency of the recessive allele among the female parents of the $i+1$st generation is $y_i = (p_j y_j + q_j r_j)/(p_j r_j + p_j y_j + q_j x_j)$. The probability of a normal offspring is $1 - \frac{1}{2}y_i$. Then, $\alpha_i = (1 - \frac{1}{2}y_i)^n$.

The frequency of the recessive allele among the selected males in the i^{th} generation is $q_i = \frac{1}{2}\alpha_i(p_j y_j + q_j x_j)/[p_j x_j + \alpha_i(p_j y_j + q_j r_j)]$. The population structure in the $i+1^{st}$ generation with random mating of the selected males and females from the i^{th} generation will be $p_i x_i$, AA; $(p_i y_i + q_i x_i)$, Aa; and $q_i y_i$, aa; for both males and females. This recursive relationship will continue through all succeeding generations.

Some idea of the effect of an A.I. young sire-testing program on frequencies of recessive lethals can be determined by calculating the frequencies of homozygous recessives for several generations. These calculations were made for various combinations of numbers of offspring expected per young sire and initial gene frequencies.

Calculations shown in the tables were made with the following assumptions: 1) that the generation interval is the same for males and females; 2) that offspring used for testing bulls do not enter the population—if they did, this would tend to increase slightly the frequency of the undesirable allele; 3) that females are not

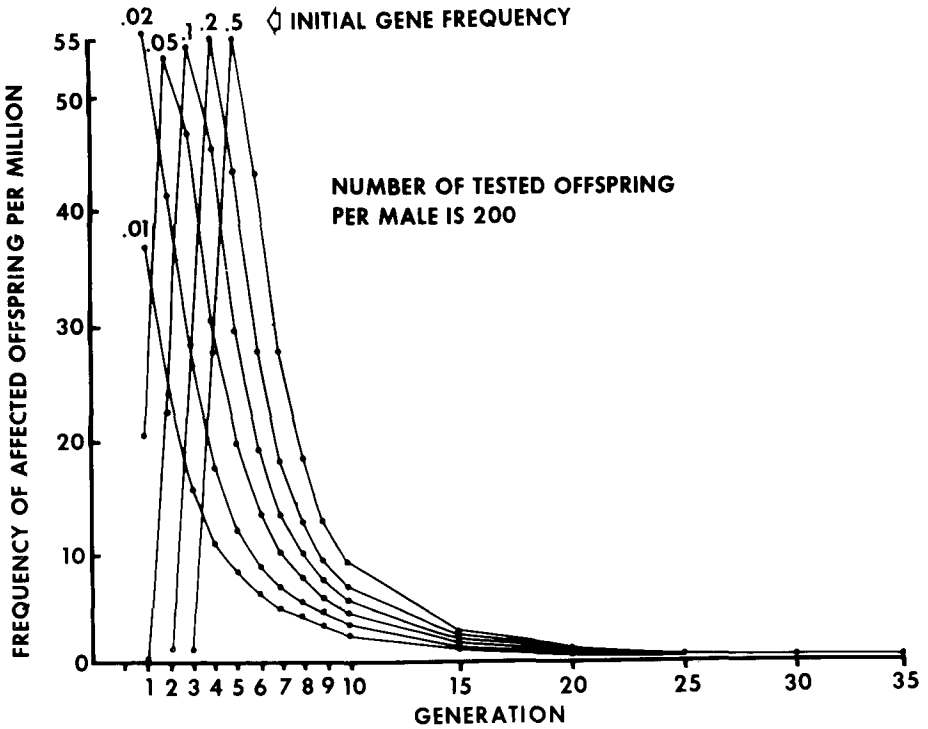

FIG. 1. Frequency of affected offspring per million by generation when males are tested for heterozygosity on 200 offspring.

TABLE 1

Number of affected offspring per million in the population after one generation of testing young sires

No. of test offspring	Initial gene frequency						
	.5	.2	.1	.05	.02	.01	.001
0	111,111	27,778	8,264	2,268	384	98	1.00
10	40,691	14,432	5,567	1,819	350	93	.99
25	3,422	4,478	2,952	1,297	303	87	.99
50	37	534	966	728	239	77	.97
100	0	7	96	223	147	60	.95
200	0	0	1	20	55	37	.90
500	0	0	0	0	3	8	.78
1,000	0	0	0	0	0	1	.61

TABLE 2

Number of generations of testing young sires to reduce frequency of affected offspring in the population to various levels

Frequency of affected offspring	Initial gene frequency					
	.5	.2	.1	.05	.02	.01
	No test offspring					
.1	2	1	1	1	1	1
.01	8	5	1	1	1	1
.001	30	27	22	12	1	1
.0001	>50	>50	>50	>50	50	1
.00001	>50	>50	>50	>50	>50	>50
	10 Test offspring					
.1	1	1	1	1	1	1
.01	3	2	1	1	1	1
.001	10	9	7	4	1	1
.0001	30	29	27	24	15	1
.00001	>50	>50	>50	>50	>50	>50
	25 Test offspring					
.01	1	1	1	1	1	1
.001	6	5	4	2	1	1
.0001	16	15	14	12	8	1
.00001	46	45	44	42	38	31
.000001	>50	>50	>50	>50	>50	>50
	50 Test offspring					
.001	1	1	1	1	1	1
.0001	10	9	8	7	4	1
.00001	26	25	24	23	20	17
.000001	>50	>50	>50	>50	>50	>50
	100 Test offspring					
.001	1	1	1	1	1	1
.0001	7	6	5	4	2	1
.00001	15	14	13	13	11	9
.000001	42	41	40	39	37	35
	200 Test offspring					
.001	1	1	1	1	1	1
.00001	10	9	8	7	6	5
.000001	24	23	22	21	20	18
	500 Test offspring					
.00001	1	1	1	1	1	1
.000001	13	12	11	10	9	8
	1000 Test offspring					
.00001	1	1	1	1	1	1
.000001	10	9	8	7	6	5

culled on the basis of their affected progeny—since females with affected progeny are likely to be culled as well as most of their progeny, this would tend to reduce the frequency of the recessive gene; 4) that mutation does not occur—mutation would tend to increase very slightly the frequency of the recessive gene; and 5) that the population of cows is very large—in small populations random fluctuations could result in markedly different results.

Results and Discussion

The critical economic problem for dairymen is how many affected offspring are born. Results in Table 1 show the number of affected offspring per million after one generation of selection against carrier males.

Results are generally as expected. Frequency of affected offspring drops markedly with relatively large n (n = number of tested offspring), especially for high initial gene frequencies. An apparent paradox, however, shows up on examination of Table 1. For some n (e.g., $n = 50$) the frequency of affected offspring after one generation is lower for the high initial gene frequencies than for the lower initial gene frequencies. The reason is that with high gene frequencies the probability of detecting carrier males is very high. Thus, very few affected offspring result in the next generation. The actual gene frequency in the first generation after selection is larger than would be expected from the frequency of the affected offspring. In the following generation more affected offspring are born than in the first generation after selection. This interaction between gene frequency and the resulting probability of not detecting carriers is shown in Figure 1. Depending on the value of q_0, the frequency of affected offspring is sometimes lower in the first generation than in later generations. After the new peak of affected offspring is reached, decline in affected offspring is rapid and steady, until the point is reached

where the number of affected offspring is not important.

The somewhat surprising conclusion to be drawn from Table 1 and Figure 1 is that, although an undesirable recessive character appears to be essentially eliminated after one generation of testing males, the character may show up in greater frequency in the second generation of selection. Certainly, testing should not be stopped after only one generation. If the initial gene frequency is high, one generation of selection will dramatically lower the gene frequency. But, if selection does not continue, the gene frequency will still be at a higher than desired level—much higher than expected from the number of affected offspring after one generation of male testing. If the population is allowed to return to equilibrium according to the Hardy-Weinberg law, the frequency of affected offspring will probably be higher than expected.

The critical level for frequency of affected offspring is probably debatable. The best level would be no affected offspring. Yet, one in a million, or perhaps even one in a thousand, is not likely to be noticed or to cause much economic damage. Table 2 gives the number of generations to achieve reduction to various frequencies of affected offspring. The table shows that with either low initial gene frequencies or few tested offspring reduction in frequency of affected offspring is a slow process, even with testing in an A.I. population. Conversely, for high initial gene frequencies and large n, the reduction is very rapid.