THE RESULTS OF CROSSES BETWEEN INBRED STRAINS OF GUINEA PIGS, DIFFERING IN NUMBER OF DIGITS

SEWALL WRIGHT

University of Chicago, Chicago, Illinois

INTRODUCTION

Guinea pigs normally have only 3 toes on the hind feet. This is the condition in all of the wild species of the family Caviidae. Atavistic return of the little toe is not, however, especially uncommon. CASTLE (1906) noticed an animal with an imperfect little toe and by inbreeding and selection developed a strain in which every animal had 4 perfect digits on the hind feet. Strain D, in my possession, traces exclusively to 3 animals of this strain, kindly presented by Professor CASTLE in 1915. It has bred true to the 4-toed condition to the present time. As there have seldom been more than 2 or 3 breeding males at a time, there has been much inbreeding. It may safely be assumed to be homozygous in most respects.

CROSSES BETWEEN STRAINS 2 AND D

Family 2 is a strain tracing by exclusive brother-sister mating to a single pair mated in 1906 in an inbreeding experiment of the U. S. Bureau of Animal Industry (WRIGHT 1922a). Two 4-toed animals were recorded from it in its early history among about 3,500 young. All of the animals used in the crossbreeding experiments described here traced to a single mating in the sixth generation, which has had only 3-toed descendants. Those used in the Chicago series of experiments all traced to a single mating in the 15th generation. This strain may safely be assumed to be homozygous or nearly so in some combination of genes which determines the normal 3-toed condition of the hind feet.

Reciprocal crosses were made between strains D and 2 at Beltsville, Maryland. (U.S. Bureau of Animal Industry) in 1923–25. Female D ×male 2 produced 11 young, all normal. Female 2 by male D produced 76 young, also all normal. In experiments in Chicago, 1926–30, matings of female 2 by male D produced 59 young, again all normal. Thus F_1 included a total of 146 young, all of which were 3-toed. The results in F_2 were as follows. No separation is made by sex in this and later tables. Separate tabulations of males and females have been made but in no case do they show any significant difference. In these tables good 4-toe means that the little toes of both hind feet were of maximum size and too firm to be bent easily back to the foot.

TABLE 1

Results of F_2 from matings of the pure 3-toed stock 2 with the pure 4-toed stock D.

$F_1(2 \times D)$	PERCENTAGE			TOTAL NUMBER
	3-TOE	POOR 4-TOE	GOOD 4-TOE	
Beltsville	81.6	9.2	9.2	207
Chicago	73.1	23.1	3.8	26
Total	80.7	10.7	8.6	233

If all polydactyls be combined the proportion, 19.3 percent, differs from 25 percent by only 2.0 times the standard error, an amount which is hardly significant. The first suggestion from the results in F_1 and F_2 is thus that polydactyly depends on one major recessive factor, supplemented by modifiers necessary for perfect development of the little toe and occasionally, perhaps, for expression of the digit at all.

The results of backcrosses of F_1 females to males of the pure 4-toed stock D, appear to confirm this interpretation.

TABLE 2

Results of backcross, female 3-toe from (2×D) with males of pure-toed stock D. Young 3/4 blood D.

	FEMALE (2×D)	MALE (D)	PERCENTAGE			TOTAL NUMBER
			3-TOE	POOR 4-TOE	GOOD 4-TOE	
Beltsville	3-toe	good 4-toe	45.1	20.7	34.2	82
Chicago	3-toe	good 4-toe	44.4	23.7	31.9	207
Total	3-toe	good 4-toe	44.6	22.8	32.5	289

The proportion of 3-toed young does not differ significantly from 50 percent (1.8 times standard error).

There are many cases in slow-breeding animals in which a gene has been designated on no more basis than dominance in F_1 of a cross between true breeding strains, a 3:1 ratio in F_2 and a 1:1 ratio in the backcross to the recessive strain. There is, however, no conclusive evidence for or against its existence until breeding tests have been made of the segregating generation. In the present case such tests were made by mating all types which came from the backcross matings (Chicago series) to the pure 4-toed strain, D. Only females were tested in this and later generations because of the very low fertility of the D females, which made it desirable to use all that were reared in maintaining the pure D stock.

The supposed dominants (3-toed) produced only 22.6 percent 3-toed young, significantly less than the expected 50 percent on the basis of one major factor.

TABLE 3

Results of 3 top crosses of pure 4-toed stock (D) on strain 2. Young 7/8 blood D.

FEMALE ((2×D)×D)	MALE (D)	PERCENTAGE			TOTAL NUMBER
		3-TOE	POOR 4-TOE	GOOD 4-TOE	
3-toe	Good 4-toe	22.6	32.2	45.2	186
Poor 4-toe	Good 4-toe	34.5	13.8	51.7	29
Good 4-toe	Good 4-toe	10.0	24.4	65.6	90

Even more disconcerting was the result from the supposed recessives (good and poor 4-toed combined) which mated with pure 4-toed produced as many as 16.0 percent 3-toed. There is indeed no significant difference (1.4 standard error) between this 16.0 percent normals from 4-toed mothers and the 22.6 percent from 3-toed mothers. It may be added that matings between perfect polydactyls of the backcross generation produced 2 3-toed, 3 poor 4-toed and 5 good 4-toed young.

Clearly there is no one major factor distinguishing strains D and 2. Perhaps there are two factors of about equal importance. In this case 25 percent of the backcross progeny should be homozygous in both. Most of the good polydactyls of this progeny should be of this type since these made up only a slightly larger percentage (32.5 percent). Yet even these when tested by mating with the pure 4-toed strain produced 10 percent 3-toed young as well as 24 percent with rudimentary little toes. Ten females were tested in this way. Nine of them produced 3-toed or poor 4-toed young and the other had only two young altogether. There is thus no evidence that any of the *good* 4-toed animals of the backcross progeny bred like the animals of the pure 4-toed stock which they resembled phenotypically. There must be more than two equally important factors distinguishing strains 2 and D.

With three factors, 12.5 percent of the backcross progeny and thus nearly half of those with well-developed little toes, should be homozygous for all three. The fact that 9 out of 10 were proved to be genetically different from strain D (the other inadequately tested) practically rules out this hypothesis. It may be concluded that strain D and 2 differ in at least 4 factors of comparable importance.

There is indeed very little evidence of any genetic differentiation in the entire backcross progeny. There is a remarkable approach to completely blending inheritance of a character which approaches alternative expression. On the other hand, the appearance of polydactyls in F_2 after their complete absence in F_1 indicates that there really is segregation and that the number of genes is not indefinitely large.

An attempt to obtain further evidence of segregation was made by testing females of the second backcross progeny by yet another backcross to the pure 4-toed stock.

TABLE 4

Results from four top crosses of pure 4-toed stock (D) on strain 2. Young 15/16 blood stock D.

FEMALES (((2×D)×D)×D)	MALE (D)	PERCENTAGE			TOTAL NUMBER
		3-TOE	POOR 4-TOE	GOOD 4-TOE	
3-toe from 3-toe	Good 4-toe	16.7	43.3	40.0	60
Good 4-toe from 3-toe	Good 4-toe	0	8.7	91.3	69
Good 4-toe from good 4-toe	Good 4-toe	0	0	100.0	28

There are real enough differences here. Two successive selections of perfect polydactyly are enough to give females which breed like those of the pure 4-toed strain as far as this test goes. But perfect polydactyls selected from the progeny of 3-toed mothers produced 9 percent imperfect polydactyls even though their offspring were 15/16 blood of strain D. Three-toed females from 3-toed mothers produced almost the same results from the mating with strain D as did their mothers. The percentage of perfect polydactyls is actually less (40 percent instead of 45 percent) though not to a significant extent. It appears that a point has been reached at which the swamping effect of repeated backcrossing to the pure 4-toed stock can be neutralized by counter selection.

Another generation of such backcrossing was attempted. Unfortunately, the very low fertility of the females of the D stock had come to be characteristic of these later backcross generations. No young were obtained from the 3-toed females of this generation and only a few from the others.

TABLE 5

Results of 5 top crosses of pure 4-toed stock (D) on strain 2. Young 31/32 blood stock D.

FEMALES ((((2×D)×D)×D)×D)	MALES (D)	PERCENTAGE			TOTAL NUMBER
		3-TOE	POOR 4-TOE	GOOD 4-TOE	
Poor 4-toe from 3-toe from 3-toe	Good 4-toe	0	25.0	75.0	12
Good 4-toe from 3-toe from 3-toe	Good 4-toe	0	0	100.0	6
Good 4-toe from good 4-toe from good 4-toe	Good 4-toe	0	0	100.0	7

The young here are 31/32 blood of pure 4-toed stock, yet it has been possible to maintain rudimentary development of the little toe by counter selection. This confirms the results from F_2 and the preceding backcross generation that there is segregation of a not indefinitely large number of factors.

CROSSES BETWEEN STRAINS 32 AND D

Before attempting further interpretation of the results of this cross, it will be well to present data from crosses between strain D and other inbred

strains. Family 32, like 2, was started in 1906 from a single pair and maintained by exclusive brother-sister mating by the U.S. Bureau of Animal Industry. All of the recorded young were 3-toed. Females descended from a single mating in the 11th generation were mated with males of strain D and the young were mated *inter se* or backcrossed to strain D. The results were remarkably similar to those from the experiments with strain 2, with one exception. In F_1, there was a single imperfect polydactyl (one feeble extra toe on one foot) to 25 3-toed young. The similarity of the results in F_2 and the backcross progeny makes it probable that the F_1 from $2 \times D$ was also not far below the threshold for polydactyly in spite of the failure of any to appear among 146 young.

TABLE 6

Results of cross between 3-toed strain 32 and pure 4-toed strain D, of F_2 and of backcross of F_1 to strain D.

	FEMALE	MALE	PERCENTAGE			TOTAL NUMBER
			3-TOE	POOR 4-TOE	GOOD 4-TOE	
F_1	3-toe (Fam. 32)	4-toe (D)	96.2	3.8	0	26
F_2	3-toe (32×D)	3-toe* (32×D)	80.0	6.0	14.0	50
BX	3-toe (32×D)	4-toe D	45.8	25.0	29.2	24

* The single poor 4-toed F_1, a male, is included. He produced 2 3-toed and 1 good 4-toed.

CROSSES BETWEEN STRAINS 13 AND D

Family 13 also was started in 1906 from a pair and maintained by brother-sister mating in the experiments of the U.S. Bureau of Animal Industry. One polydactyl has been recorded among some 6,000 young. This was otherwise abnormal, being clubfooted, a very uncommon condition in family 13.

The cross breeding experiments were made with animals descended from a single mating in the 9th generation. They may be assumed to be homozygous in most factors.

The results are very different from those obtained by mating the same 4-toed strain with the other two 3-toed strains (2 and 32). About one-third of F_1 were polydactyls. The reciprocal crosses are tabulated separately, but there is no significant difference, giving further evidence that there is equal transmission by males and females. That the appearance of polydactyls in F_1 is not a result of segregation is clearly shown by the results in F_2 and in the backcrosses to the pure 4-toed strain. Thus, F_2 from 3-toed ×3-toed actually included fewer 3-toed and more good 4-toed young than did F_2 from matings between 4-toed F_1's, although the differences are not significant. In the backcross tests the 3-toed F_1's produced somewhat fewer good 4-toed (but more poor 4-toed) than did the 4-toed F_1's tested

TABLE 7

Results of crosses between 3-toed strain 13 and 4-toed strain D, of F₂ and of backcross of F₁ to strain D.

	FEMALE	MALE	PERCENTAGE			TOTAL NUMBER
			3-TOE	POOR 4-TOE	GOOD 4-TOE	
F_1	3-toe (13)	4-toe (D)	63.6	36.4	0.0	44
	4-toe (D)	3-toe (13)	73.9	26.1	0.0	23
F_2	3-toe (F_1)	3-toe (F_1)	42.9	19.0	38.1	84
	4-toe (F_1)	4-toe (F_1)	53.1	18.8	28.1	32
BX	3-toe (F_1)	4-toe (D)	16.7	33.3	50.0	12
	4-toe (F_1)	4-toe (D)	13.2	25.0	61.8	68
Total F_1			67.2	32.8	0.0	67
Total F_2			45.7	19.0	35.3	116
Total Backcross			13.8	26.2	60.0	80

in the same way, but again the differences are not significant. The variability in F_1 must therefore be attributed to non-genetic factors similar to those demonstrated within another inbred strain (35) in the preceding paper of this series.

Turning to the totals for F_1, F_2 and the backcross generation, it will be seen that the simulation of one-factor Mendelian heredity completely breaks down in this case. Clearly family 13, though equally as normal as families 2 and 32, is closer to the threshold for polydactyly.

CROSSES BETWEEN STRAINS 35 AND D

Family 35 also was started from a pair in 1906 and has been maintained by brother-sister mating by the U.S. Bureau of Animal Industry. It has produced a high percentage of polydactyls in most of its branches. An analysis of its record was the subject of the first paper of this series. It was shown that a large branch descended from a single mating in the 12th generation, broke up into substrains ranging in extreme cases from 9 percent to 69 percent incidence of polydactyly but that the variability due to this cause made up only 18 percent of the total variance. The non-genetic variance (82 percent) was largely due to factors common to litter-mates (44 percent), leaving 38 percent of the total as due to separate action on individuals. Age of mother was the most important factor common to litter-mates to be demonstrated. All genetic variability appeared to have been lost in the strain maintained in Chicago descended from a single mating in the 22nd generation. In this case the variability was analyzed into 3 components, that common to whole sibships (27 percent), that common to litter-mates but not sibships (27 percent) and that which was individual in incidence (46 percent).

This analysis of variance was based on the assumptions that the alternative categories, 4-toed and 3-toed, depend on whether the combination of factors, genetic and non-genetic, is above or below a certain threshold, and that there is a normal distribution on this hypothetical scale of factor combinations.

The records of the family in Beltsville from the 12th generation and in Chicago from the 22nd generation are given below with the results of crosses with the pure 4-toed stock D made at Beltsville. Note that F_1 was backcrossed in this case to family 35 instead of to D.

TABLE 8

Records of family 35 in two periods, of its crosses with the pure 4-toed stock D, of F_2 and of back-crosses of F_1 to family 35.

		PERCENTAGE			TOTAL NUMBER
		3-TOED	POOR 4-TOE	GOOD 4-TOE	
Family 35	Beltsville	68.9	26.2	4.9	1,976
	Chicago	57.9	35.9	6.2	356
F_1	35×D	12.0	24.0	64.0	25
	D×35	0.0	0.0	100.0	22
	Total	6.4	12.8	80.8	47
F_2	$F_1 \times F_1$	25.0	19.6	55.4	56
Backcross	$F_1 \times 35$	31.5	30.1	38.4	73

There is an indication here of some matroclinous tendency in F_1 (exhibited equally by sons and daughters it may be added). Slight genetic differences between the parents from family 35 is most probable as an explanation, however, since as noted above there were demonstrable substrain differences in polydactyl tendency within the Beltsville stock. Various subdivisions of the F_2 and backcross data have been made but as nothing of significance was brought out, they are not given here.

Polydactyly is here more nearly dominant than recessive. There were 94 percent polydactyls in F_1 while F_2 showed a *smaller* percentage (75). This is the reverse of the situation in the crosses considered previously. It is suggested that dominance in the case of polydactyly (as in white spotting in guinea pigs) is a matter of character thresholds rather than of anything inherent in the genes themselves. The backcross of F_1 to family 35 gave intermediate percentages as might be expected.

MEANS AND STANDARD DEVIATIONS

In view of the great importance of non-genetic factors demonstrated in family 35, and in $F_1(13 \times D)$ it is obviously futile to attempt to assign specific genes to different phenotypes. The most instructive course would

seem to be to compare the means and variabilities on the postulated scale
of factor combinations. As the unit of measurement, it is convenient to take
the distance between the threshold for any polydactyly and that for per-
fect development of the little toe. Approximately normal distributions are
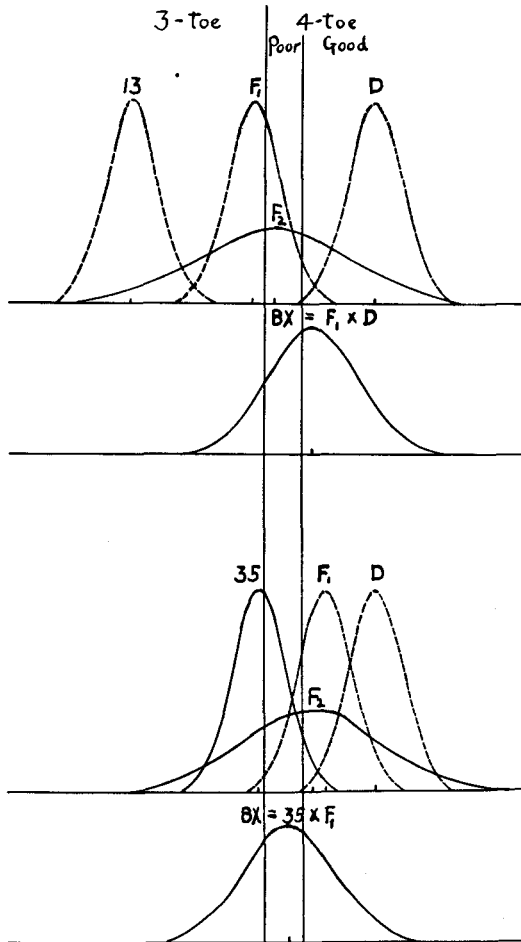expected if variability is determined by independent factors of which none

FIGURE 1.—Estimated distributions of strains 35 and D, and of F_1, F_2 and the backcross of
F_1 to 35, relative to a scale on which the distribution curves are normal and the thresholds for
any development of the little toe and for perfect development are separated by one unit (below).
Estimated distributions of strains 13 and D, and of F_1, F_2 and the backcross of F_1 to D on the same
scale (above).

are of major importance and whose effects combine additively (no domi-
nance or epistasis). These assumptions will be shown to be at least in har-
mony with the data (figure 1).

Given a scale with two thresholds at a unit distance apart, a normal dis-
tribution is uniquely determined by the three percentages cut off by the

thresholds (in a population including all three types). To describe the distribution we find the inverse probability functions of the frequencies between each threshold and the median (that is, prf^{-1} (q − .50) where q is the proportion below the threshold). These locate the thresholds relative to the mean of the population but on a scale on which the standard deviation is the unit of measurement. The reciprocal of the distance between the thresholds on this scale gives the standard deviation on the postulated scale on which the thresholds are separated by a unit distance. The thresholds can now be located by multiplying the previous expressions by the value for the standard deviation.

These calculations are shown below for the Beltsville and Chicago branches of family 35.

	S.D. = 1	S.D. = .861
Family 35 Beltsville		
Threshold for good 4-toe, prf^{-1} (.951–.500) =	1.655	1.424
Threshold for poor 4-toe, prf^{-1} (.689–.500) =	.493	.424
Distance between thresholds	1.162	1.000
Family 35 Chicago	S.D. = 1	S.D. = .747
Threshold for good 4-toe prf^{-1} (.938–.500) =	1.538	1.149
Threshold for poor 4-toe prf^{-1} (.579–.500) =	.199	.149
Distance between thresholds	1.339	1.000

No such construction is possible, of course, unless all 3 categories are present. The method is not satisfactory if the proportions in one of the extreme classes is small (unless the total number is very large) since a slight change in percentage makes a large difference in the inverse probability function in this region.

Fortunately the extensive data from family 35 make it possible to estimate the standard deviation in an inbred strain. This comes out .861 as indicated above for the Beltsville branch descended from one mating in the 12th generation. As already noted, the genetic variance was about 18 percent of the total. The standard deviation due to non-genetic factors can be obtained by multiplying by .90 ($= \sqrt{1.00 - .18}$) giving .775. This is close to the estimate of the standard deviation (.747) in the Chicago stock, from one mating in the 22nd generation, in which analysis indicated no residual genetic variability.

The value .80 will be assumed as that characteristic of a genetically homogeneous stock and of the first cross between two such stocks. No high degree of refinement is of course possible.

F_1 from 35×D includes all three categories but the numbers are too small for a satisfactory calculation of the standard deviation from them. It is best to adopt .80 as the standard deviation, and locate the mean from

this and the proportion of *good* polydactyls. This puts the mean at 1.70 above the threshold for any polydactyly.

Strain D may also be assigned the same standard deviation as an inbred strain. It must be assigned a mean sufficiently above the threshold for perfect polydactyly that only a negligible portion of the frequencies fall below. This means at least 2.5 times the standard deviation or about 2.0 units above this threshold (3.0 units above the threshold for any poly-dactyly). Since the perfect polydactyly of strain D was reached by selec-tion it is not likely that its mean is much higher. Thus we reach an esti-mate of $+1.70$ for the mean of F_1, intermediate between that of $-.42$ for family 35 and of $+3.0$ for strain D, all relative to the threshold for any polydactyly. An estimation from F_2 (which shows fairly high frequencies in all three categories (3-toe, poor 4-toe and good 4-toe) yields a mean of $+1.25$ (also intermediate) and a standard deviation of 1.86 which is very much larger than in family 35. The backcross data $(35 \times D) \times 35$ give a mean at $+.62$ which is intermediate between F_1 and family 35. The stand-ard deviation comes out 1.29, less than that of F_2 but greater than that of family 35, as should be the case if Mendelian factors are responsible for the genetic differences.

<center>ESTIMATION OF NUMBER OF FACTORS</center>

If α is the effect of a single gene and there are n such genes (with equal effect and no dominance or epistasis) the difference (Δ) between *extreme* plus and minus types is $2n\alpha$. The F_2 variance due to each pair of genes is $\frac{1}{2}\alpha^2$ and hence to n genes is $\dfrac{n\alpha^2}{2}$. The observed variance in F_2 is com-pounded of this genetic variance and the non-genetic variance which may be taken as measured by the variance of F_1 or of the parental strains (P). Thus $(\sigma_{F_2}^2 - \sigma_P^2)$ gives the genetic variance of F_2. Eliminating α and solving for n gives $n = \dfrac{\Delta^2}{8(\sigma_{F_2}^2 - \sigma_P^2)}$. In the backcross progeny the variance due to each pair of genes is $(1/4)\alpha^2$ so that the genetic variance should be just half as great as in F_2. A *minimum* estimate of the number of genes (ignoring chance variation) can be obtained from either of these formulae if Δ is taken as the difference between the parental strains (that is, these are assumed to be *extreme* plus and minus respectively). Any degree of dominance or of epistasis increases the estimate (WRIGHT in CASTLE 1921, SEREBROVSKY 1928, BERNSTEIN 1929).

Applied to the present, admittedly rather rough, data, the minimum number of factors differentiating strains 35 and D comes out *one* whether based on the variance of F_2 or that of the backcross data, or on Δ as the difference between 35 and D or as twice that between 35 and F_1. There is

therefore enough segregation to make it possible to assume that these strains are differentiated by only one major factor. It is also possible however that 35 has some plus factors not present in D and that the number of major factors is larger.

Figure 1 (lower half) shows a construction of the distribution of 35, D, F_1, F_2 and the backcross on the assumptions made above. The two thresholds divide the distributions of 35, F_2 and the backcross into the observed percentages while F_1 is assigned the same standard deviation as 35 and located so as to give the observed percentage below the threshold for perfect polydactyly. Strain D is also assigned the standard deviation of 35 and located so that no appreciable percentage falls below perfect polydactyly (mean at 2.0 above this threshold). It will be seen that with this construction, the variability of F_2 is shown as transgressing slightly both grandparental ranges. The backcross data are, however, in close accord with segregation of one factor.

Consider next the crosses involving family 13. In F_1 assume that the variability is wholly non-genetic (as indicated by the tests of F_1 3-toed and 4-toed), and that the resulting standard deviation is .80 as deduced for non-genetic variability from family 35. The mean can be located from the proportion of polydactyls and comes out at $-.56$ relative to the threshold for any polydactyly. The numbers and percentages in the 3 categories in F_2 are adequate for determination of mean and standard deviation. They yield a mean only a little higher than that reached for F_1, namely, $+.22$ but a much larger standard deviation, namely, 2.06.

In the upper part of figure 1, strain D is located as before, while strain 13 is assigned such a mean that F_1 is exactly intermediate between it and D. This locates 13 so far below the threshold that polydactyly is to be expected from it only as a rare anomaly (assuming the same standard deviation as in 35). The distribution for F_2 and the backcross are located strictly by the percentages of 3-toed, poor 4-toed and good 4-toed.

The mean of the backcross progeny $(+1.30)$ falls about half way between the mean of F_1 $(-.56)$ and that assigned to strain D $(+3.00)$, giving a further check on the latter. The standard deviation of the backcross progeny (1.20) is greater than that of the inbred strain 35 but less than that of F_2.

In absolute values, the variance of $(13 \times D)^2$ is greater than of $(35 \times D)^2$ but the variance of the backcross $(13 \times D) \times D$ is a little smaller than of $(35 \times D) \times 35$. But calculation of the minimum number of factors in the case of 13 and D indicates 2 (using F_2 variance) or 4 (using backcross variance). There are certainly at least two major factors of comparable importance and 3 would be a better estimate.

The data from the crosses involving 32 and 2 are in such close agreement

that they may be combined for the present purpose. F_1 must be located sufficiently below the threshold for polydactyly that polydactyls are rare (1 in 26 from 32×D, none in 146 from 2×D). This indicates a mean in the neighborhood of −2.0. Calculation from the frequencies of the 3 categories in F_2 gives a closely similar mean (−1.74 from family 2 alone, −1.93 from
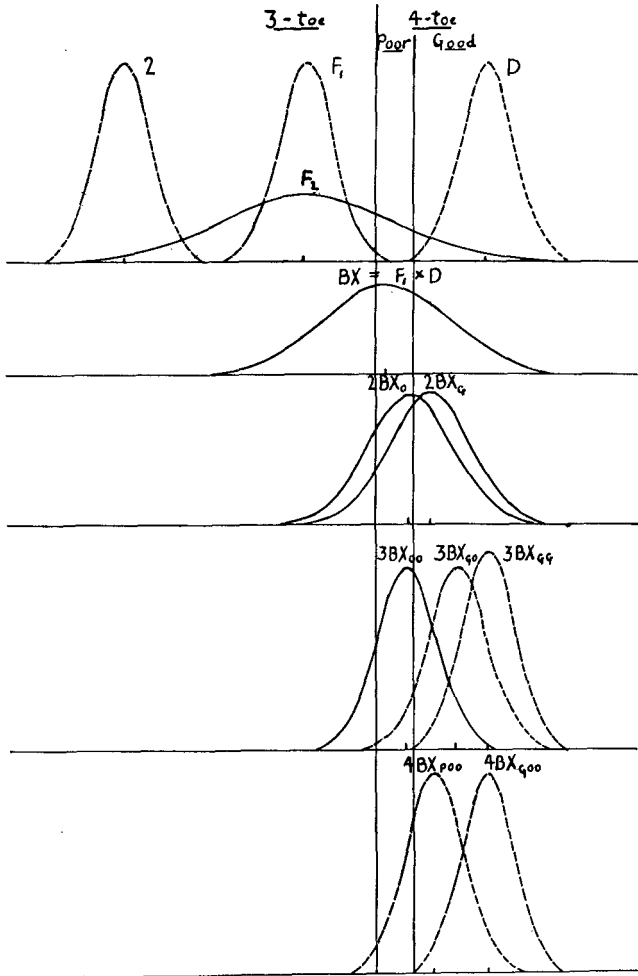

FIGURE 2.—Estimated distributions of strains 2 and D, and of F_1, F_2, and repeated backcrosses to strain D on the same scale as used in figure 1.

2 and 32 combined). The standard deviation of F_2 comes out 2.00 from strain 2 alone, 2.24 from 2 and 32 combined.

The backcross data yield a mean falling between the two thresholds (+.23 from 2 alone or combined with 32). This is about half way between the mean of F_1 (or of F_2) and that of D, as expected. The standard deviation of the backcross generation (1.70 from 2 alone, 1.69 from 2 and 32 combined) is between that of an inbred stock and of F_2.

The estimate of the minimum number of equal factors from the F_2 variance yields 4 or 3 depending on whether that of family 2 alone or that of 2 and 32 combined is used. The estimate from the backcross variance yields 3 in either case. It will be recalled that the analysis of the breeding tests of the backcross individuals indicated 3 as the least possible number of major factors and 4 as much more likely.

Figure 2 presents the results for these and later generations graphically. The close similarity of the results from the principal second backcross progenies is brought out. The progeny from 3-toed backcross individuals mated with D $(2BX_0)$ comes at $+.86$ and that from the 4-toed backcross individuals, similarly tested $(2BX_G)$ is at $+1.46$. The difference is only one-eighth of that between F_1 and D or one-fourth of that between the backcross group and D. On a one factor basis the difference should be the same as the latter. Again something like 4 equal factors are indicated. The standard deviations of both second backcross groups $(1.15, 1.14)$ show a decrease from that of the first backcross (1.70).

In the 3rd backcross generation, repeated selection of 3-toed animals $(3BX_{00})$ has made it possible to keep the mean practically unchanged $(+.79)$ but the standard deviation has fallen to practically the value of an inbred strain $(.82)$. There is some indication here that the most important single gene has an effect amounting to from one-third to one-half of the difference between F_1 and D. This, however, is a maximum estimate.

These results are summarized in table 9.

TABLE 9

Estimated position of mean relative to threshold for polydactyly, and estimated standard deviation (S.D.), on scale on which threshold for perfect polydactyly is at $+1.00$. Standard deviation 0.80 in parenthesis assigned to inbred strains and first crosses on basis of results in strain 35.

	MEAN	S.D.		MEAN	S.D.
Strain D	$+3.00$	(0.80)	Strain 2	-7.00	(0.80)
Strain 35	-0.42	0.86	$F_1, (2\times D)$	-2.00	0.80
$F_1, (35\times D)$	$+1.70$	(0.80)	$F_2, (2\times D)^2$	-1.74	2.00
$F_2, (35\times D)^2$	$+1.25$	1.86	BX, $((2\times D)\times D)$	$+0.23$	1.70
BX, $((35\times D)\times 35)$	$+0.62$	1.29	$2BX_0, (((2\times D)\times D)_0\times D)$	$+0.86$	1.15
Strain 13	-4.12	(0.80)	$2BX_G, (((2\times D)\times D)_G\times D)$	$+1.46$	1.14
$F_1, (13 \ (D)$	-0.56	(0.80)	$3BX_{00}, ((((2\times D)\times D)_0\times D)_0\times D)$	$+0.79$	0.82
$F_2, (13\times D)^2$	$+0.22$	2.06	$3BX_{G0}, ((((2\times D)\times D)_0\times D)_G\times D)$	$+1.89$	(0.80)
BX, $((13\times D)\times D)$	$+1.30$	1.20	$3BX_{GG}, ((((2\times D)\times D)_G\times D)_G\times D)$	$+3.00$	(0.80)

Extensive crosses have been made between families 2, 13, 32 and 35 (WRIGHT 1922b). These have been carried to F_2 on a large scale and to F_3 in many cases. No 4-toed young have appeared from matings involving only 2, 13 and 32, or in F_1 from matings involving 35. Among 81 F_2's from 13×35, there were 2 low grade polydactyls. It is thus probable that all of these strains have some factors in common in which they differ from strain D.

The results of experiments by CASTLE, STOCKARD and PICTET (discussed in the preceding paper of this series), readily fall in line with the above interpretation.

SUMMARY

The material used consisted of strains of guinea pigs which have been closely inbred since 1906. Three of these strains (2, 13, 32) bred true to the normal 3-toed condition of the hind feet. One of them (No. 35) produces about 31 percent 4-toed young. It has been shown previously that in this family the 3-toed and 4-toed animals of the same substrain have the same genetic constitution although different substrains differ genetically to a slight extent in percentage incidence. Strain D breeds true to perfect development of the little toe and hence is regularly 4-toed.

The crosses between 2 and D simulate one factor Mendelian heredity to a remarkable extent in the dominance of 3-toe in F_1, and apparent segregation in F_2 in a fairly close approach to a $3:1$ ratio and in the backcross to strain D in a $1:1$ ratio. This interpretation breaks down completely in the tests of the supposed segregants. These tests indicate that there are in reality at least 3 factors of comparable importance and more probably 4 by which strains 2 and D differ. There is a close approach to blending inheritance in a character which approaches alternative expression, because of physiological thresholds.

The crosses between strains 32 and D gave closely similar results to those of 2 and D, indicating genetic similarity of the normal strains 2 and 32.

The crosses between 13 and D, on the other hand, gave very different results. Many polydactyls appeared in F_1. These were shown not to differ genetically from the normals from the same matings. This result indicates that strain 13, though itself as normal as 2 and 32, is much closer to the threshold for polydactyly. The F_2 and backcross data show that 13 differs from D by at least 2 and more probably 3 major factors.

The crosses between 35 and D gave results compatible with the assumption of one differential major factor, complicated by minor factors.

In no case is there any indication of dominance apart from that due to transgression of physiological thresholds.

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