THE RESIDUAL VARIABILITY IN INTENSITY OF COAT COLOR AT BIRTH IN A GUINEA PIG COLONY^{1,2}

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A NUMBER of previous papers have been devoted to describing quantitatively the interaction effects of the major and certain minor color factors of the guinea pig (WRIGHT 1949, 1959b). We will consider here what can be said of the residual variability in intensity at birth in the guinea pig colony on which these studies have been based.

It will be convenient to repeat here the genotypes of the seven major series of uniform colors that have been recognized.

1. Dark-eyed dark sepia	$E aa B P —$
2. Pink-eyed pale sepia	$E aa B pp F$
3. Brown-eyed dark brown	$E aa bb P —$
4. Pink-eyed pale brown	$E aa bb pp F$
5. Pink-eyed pale brownish cream	$E aa — pp ff$
6. Stable yellow	$ee — — F$
7. Fading yellow	$ee — — ff$

Blanks in the succession of loci above imply that replacements make no appreciable difference in quality or intensity of coat color at birth. Eye color in the yellows (6,7) depends on the B and P loci (and others) in the same way as in the genotypes with E .

Each of these series varies continuously from a color of considerable intensity (especially in 1, 3 and 6) down to white. The principal genes concerned with these variations are in all cases those of the c series of alleles (C , c^k , c^d , c^r , c^a) in which C (dominant) determines the highest intensity with one important exception to be discussed here. With $c^a c^a$, $ee c^r c^a$, $ee c^r c^r$ and $E c^x c^x ppff$ (where c^x is any c allele except C) the coat is pure white at birth, irrespective of anything else (eyes pink with $c^a c^a$ or pp , otherwise black (B) or brown (bb), slightly reduced in intensity with $c^r c^r$, much reduced with $c^r c^a$). Most other combinations of the c series give intermediate intensities, but in different orders in different cases. Heterozygotes among c^k , c^d , c^r , c^a are in general intermediate.

Replacement of aa by A (dominant) in the genotypes with E results in the presence of a subterminal phaeomelanin (yellow) band in otherwise eumelanin (sepia or brown) hair, the agouti pattern. The intensities of the two colors are the

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same as those due to ee and E respectively. The width of this band is subject to genetic variability but this has not been analyzed (except for an intermediate allele A' , introduced into the guinea pig from the Brazilian cavy, *Cavia refescens* (DETLEFSEN 1914; WRIGHT in CASTLE and WRIGHT 1916)).

Replacement of E by $e^p e^p$ or $e^p e$, results in the tortoise-shell pattern with a mixture of eumelanic and phaeomelanic areas in the coat, similar in color to those due to E and ee respectively. Gene e^p is incompletely dominant over e (CHASE 1939).

Another well-established pair of alleles is S, s . With ss and to a lesser extent Ss , there is a mosaic consisting of areas of color, usually of the quality and intensity determined by the rest of the genotype, and of pure white. There may also, however, be mosaicism in quality or intensity within the colored areas in certain cases (discussed in this paper).

There were second order variations in intensity at birth in the most intensively studied series, the dark-eyed sepias (1) and the stable yellows (6), that have been shown to be due largely to two additional loci— Si, si ; Dm, dm (WRIGHT 1959a,b). The effects are cumulative with heterozygotes intermediate. The combination $sisidmdm$ is pure white with reduced eye color even with C present, except for occasional small spots of pale color on the head. The combination $sisiDm-$ tends to produce a nonprogressive sprinkling with white (silvering) especially with C . Gene si produces some dilution (in nonsilvered areas) in the presence of C but dm produces none. Both loci have similar but less thoroughly studied effects in the other series of colors. In the pp eumelanics (2,4,5) their effects are overshadowed by independent causes of variability, the analysis of which was not complete at the time at which the project had to be discontinued.

It is desirable to round out the analysis of the genetics of color in the colony in question as far as the data permit. The present paper is restricted to color intensity at birth and largely to the variation in the presence of $Si C$.

Grades of intensity

Three methods of grading have been described in previous papers. All animals have been assigned *visual grades* at birth, and often later, on the basis of standard squares of skin, chosen so that each grade is barely distinguishable from the adjacent ones (sepias: 1 to 21, browns; the same scale but rarely reaching 18, yellows: 1 to 13). Grade 0 is white (WRIGHT 1949).

Colorimetric determinations have been made of pigment from weighed hair samples from young animals of many genotypes (RUSSELL 1939; HEIDENTHAL 1940; WRIGHT and BRADDOCK 1949). These permitted quantitative scaling of the visual grades.

Finally galvanometer readings of intensity near the middle of the back have been obtained from animals of many genotypes by means of a reflectionmeter, using variously colored filters (amber, green, blue) (WOLFF 1955; WRIGHT 1959b). Separate indices were obtained for each filter by the formula $I_x = 10 [\log R_w - \log R_x]$, in which R_x is the reading on the live animal in question and

$\overline{\log R_w}$ is the average logarithm of the readings of pure whites. These indices have been added to give a single index of intensity. This varies almost linearly with visual grade and can be transformed to give estimates of the latter and of relative amount of pigment (WRIGHT 1959b).

Analysis of variance

An analysis of variance will be made of the indices of the SiC genotypes of each major series of colors. This is of the following type in the simpler cases, letting I , M and T represent individuals, matings and total, respectively; n_I number of individuals, n_M number of matings, $\hat{n}_{I \cdot M}$ harmonic mean of numbers of individuals per mating etc. $\sigma^2_{I \cdot M}$ variance of individuals within matings etc.

	Degrees of freedom	Mean square	Variance component
I within M	$n_I - n_M$	$\bar{s}_{I \cdot M} = \sigma^2_{I \cdot M}$	$\sigma^2_{I \cdot M}$
M within T	$n_M - 1$	$\bar{s}_M = \sigma^2_{I \cdot M} + \hat{n}_{I \cdot M} \sigma^2_M$	σ^2_M
I within T	$n_I - 1$	$\bar{s}_I$	$\sigma^2_I = \sigma^2_{I \cdot M} + \sigma^2_M$

The variance within matings includes not only that due to genetic segregation but also any nongenetic variance within or between litters. The significance of differentiation among matings is tested in the usual way from the ratio of mean squares, $\bar{s}_M/\bar{s}_{I \cdot M}$. Significance would imply genetic differentiation if the numbers of individuals per litter and of litters per mating were uniform. Unfortunately, uniformity was not practicable. There were many litters in which only one individual of the genotype in question was graded, and many matings that were represented by only one litter. Matings represented by only one individual were, however, excluded.

It is necessary for interpretation to include litters (L) in the analysis. The following pattern is used.

	Dif.	Mean square	Variance component
I within L	$n_I - n_L$	$\bar{s}_{I \cdot L} = \sigma^2_{I \cdot L}$	$\sigma^2_{I \cdot L}$
L within M	$n_L - n_M$	$\bar{s}_{L \cdot M} = \sigma^2_{I \cdot L} + \hat{n}_{I \cdot L} \sigma^2_{L \cdot M}$	$\sigma^2_{L \cdot M}$
I within M	$n_I - n_M$	$\bar{s}_{I \cdot M}$	
M within T	$n_M - 1$	$\bar{s}_M = \sigma^2_{I \cdot L} + \hat{n}_{I \cdot L} \sigma^2_{L \cdot M} + \hat{n}_{I \cdot M} \sigma^2_M$	σ^2_M
I within T	$n_I - 1$	$\bar{s}_I$	σ^2_I

The differentiation of litters is tested by using the ratio $\bar{s}_{L \cdot M}/\bar{s}_{I \cdot L}$ and that of matings by using the ratio $\bar{s}_M/\bar{s}_{I \cdot M}$ except where $\bar{s}_{L \cdot M}$ is less than $\bar{s}_{I \cdot L}$ in which case $\bar{s}_M/\bar{s}_{I \cdot M}$ is used.

The nature of the population sampled is of great importance in interpreting the results. The color experiments did not consist of inbred lines (though brother-sister matings were often made) or even of closed strains. There were many variously designated strains within most of which several loci were allowed to segregate simultaneously, subject to the restriction that recombinations of interest be classifiable without question. The greatest cleavage of strains at the time at which the reflectionmeter readings were made was between a group in which segregation of c alleles (and only certain ones in any one strain) occurred in animals known to be all FF , and a group in which f (as well as F) was maintained in animals all with C .

Since animals were frequently introduced from one strain to another, within the above groups, all unselected modifiers must have been rather well distributed among them. In one heterogeneous strain, SH (genotype $(S,s)(E,e^p)bbCCPPFF$), there was, however, selection of medium to strong dinginess of brown. This strain undoubtedly came to differ somewhat from most of the colony in modifiers of dinginess. In the many strains that carried p , the pp sepias and browns that were mated were, with rare exceptions, relatively intense after a period in which there was considerable confusion of classification from modifiers that could bring about overlapping of most of the c genotypes.

In a random breeding population, the genetic variance for a pair of alleles with intermediate heterozygotes is equally divided between that within and among matings. The arrays considered here, though drawn in most cases from several "strains", were much more like samples from a panmictic population than like an array from different inbred lines.

Some differentiation of litters was not unexpected because of the occurrence of differences in hair length and in condition of the fur that applied to all littermates. While individuals and often whole litters were not graded in cases in which poor condition was obvious, it is clear from the results that there were often small differences in condition among those that were graded.

In interpreting the variabilities that are considered here it should be recalled that it requires an index difference of about 2.3 units in most cases (1.5 in the case of black) for the difference in intensity to be barely recognizable to the eye. In no case was the standard deviation due to differentiation of litters as great as the minimum difference perceptible to the eye and in only two cases (pink-eyed pale browns, FF and Ff) was it more than half of this.

Residual variability of black

The blacks of genotype $Si(E,e^p)BCP$ show little variability to the eye (60 of grade 21, six of grade 20). This seems to be due to visual saturation at grade 21 since the relative variability of the amounts of pigment extracted per unit weight of hair (standard deviation of logarithms .067) is not much less than the average for the dark-eyed sepias of all of the various genotypes (.086) (WRIGHT and BRADDOCK 1949). The reflectionmeter readings of blacks are naturally very low and less reliable than for any other color. An analysis of variance was, however, carried through for the 66 indices of blacks of the above genotype after excluding

all with more than a trace of silvering and excluding matings from which only one offspring was graded. The harmonic means of numbers per litter and per mating were 1.393 and 2.678, respectively.

Black *Si(E,e^p) B C P*. Mean 41.50

	DF	Mean square	F	Prob.	Variance components
<i>I</i> within <i>L</i>	27	.452			$\sigma^2_{I \cdot L} = .45$
<i>L</i> within <i>M</i>	18	1.501	3.32	<.01	$\sigma^2_{L \cdot M} = .75$
<i>I</i> within <i>M</i>	45	.871			
<i>M</i> within <i>T</i>	20	3.569	2.38	<.05	$\sigma^2_{M \cdot T} = .77$
<i>I</i> within <i>T</i>	65	1.701			$\sigma^2_I = 1.97$

There is significant differentiation of litters within matings, and only somewhat doubtful differentiation of matings on allowing for differentiation among litters. All components and the total are small.

More than half (35) of those graded came from matings in which one or both parents carried *si*. There were ten graded young (mean 40.35) that were excluded because of having more than a trace of silvering and, thus, probably *sisi*. The mean grades of six tortoise-shells (*e^pe^p*) and 29 self-colored blacks (*E*) in the above group were 40.75 and 41.32, respectively. The means of 17 of genotype *EBCPFF* and 14 of genotype *EBCPff* from the other matings were 41.72 and 42.13, respectively. Thus, there are indications that *Sisi* (or even unrecognized *sisi*) and *e^pe^p* tended to reduce the index slightly. The *ff* blacks came from the same strain that produced the most intense browns and probably were affected by the same intensity modifiers.

Residual variability of nondingy dark brown

The browns of genotype *Si(E,e^p)bbCP* present a more interesting situation than do the blacks. There is clear evidence for two kinds of genetic modifiers: (1) ones concerned with the upper limit of intensity, and (2) ones concerned with the peculiar sort of dilution known as dinginess. Silvering was not involved in the present data.

Table 1 excluding the bottom row shows the distribution of indices in a number of groups in which dinginess was absent, at least on the back. These include two groups of genotype *EbbCPpff* separated according to whether the mean index of the mating was above or below 35.00, one group consisting of those of genotype *EbbCPpF* and one consisting of the corresponding tortoise-shells, *e^pe^pCPpF*. Three groups with lower *c* combinations of approximately the same intensity as those with *C* are given for comparison.

The average index with *E* is higher than with *e^pe^p*, both in association with *CPpF* (difference $.87 \pm .53$) and with *c^kc^{kdr}* (i.e., *c^kc^k*, *c^kc^d*, *c^kc^r*) (difference 1.47

TABLE 1

Distribution of reflectionmeter indices of nondingy, intense brown, various genotypes and of dingy browns from strain SH

Genotype (all <i>bb</i>)	No. matings	Reflectionmeter index																Index <i>I</i>		Transformed from <i>I</i> Visual grade pig- ment		
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39		Total	Mean
Nondingy																						
<i>ECp⁺p⁺</i>	7	..	..	..	..	..	..	..	..	..	1	..	..	3	6	10	1	1	22	36.78	.28	16.3 113.8
<i>ECp⁺p⁺</i>	5	..	..	..	..	..	..	..	1	2	1	2	7	1	1	..	..	..	15	33.81	.41	15.0 93.7
<i>ECp⁺p⁺</i>	10	..	..	..	..	..	..	..	..	2	..	5	12	15	8	1	..	..	43	34.94	.19	15.5 100.9
<i>e⁺e⁺CP⁺p⁺</i>	6	..	..	..	..	..	..	..	..	2	1	3	1	3	2	..	..	..	12	34.07	.50	15.1 95.3
<i>Ec⁺ck⁺dr⁺PFF</i>	3	..	..	..	..	..	..	..	..	..	..	..	1	2	2	..	..	..	5	35.48	.39	15.7 104.6
<i>e⁺e⁺ck⁺ck⁺dr⁺PFF</i>	8	..	..	..	..	..	..	..	..	..	3	3	3	3	..	..	..	..	12	34.01	.31	15.1 94.9
<i>Ec⁺cr⁺PFF</i>	6	..	..	..	..	..	..	..	1	..	2	2	3	4	8	4	2	..	26	34.66	.37	15.3 99.1
<i>E</i> nondingy	31	..	..	..	..	..	..	..	1	1	6	4	10	24	29	21	13	1	111	35.11	.16	15.5 102.1
<i>e⁺e⁺</i> nondingy	14	..	..	..	..	..	..	..	..	2	4	6	4	6	2	..	..	..	24	34.04	.29	15.1 95.1
Dingy (SH)																						
<i>ECCPPFF</i>	8	2	3	2	..	3	3	5	3	2	3	2	1	..	..	..	..	..	29	27.88	.59	12.3 62.3

The mean indices and the corresponding visual grades and relative amounts of pigment of 198 nondingy browns (*Ec⁺bb⁺CP*) with mean index 34.8 are taken as 100 as in a previous paper (Wright 1959b).

$\pm .50$). The grand average for nondingy browns with E exceeds that for those with $e^p e^p$ by $1.07 \pm .33$.

An analysis of variance was made of the 76 indices in the first three rows (*EbbCPp*) after excluding matings from each of which only one animal was graded. The harmonic means for individuals per litter and per mating were 1.774 and 3.130, respectively.

Nondingy brown *SiEbbCPp*. Mean 35.24

	DF	Mean square	F	Prob.	Variance components
<i>I</i> within <i>L</i>	42	1.038			$\sigma^2_{I \cdot L} = 1.04$
<i>L</i> within <i>M</i>	16	2.423	2.33	<.05	$\sigma^2_{L \cdot M} = .78$
<i>I</i> within <i>M</i>	58	1.420			
<i>M</i> within <i>T</i>	17	8.409	3.47	<.01	$\sigma^2_M = 1.91$
<i>I</i> within <i>T</i>	75	3.004			$\sigma^2_I = 3.73$

The estimated variance of litters within matings is small and about the same as in blacks but is less certainly significant because of the more than doubled variance of individuals within litters. The estimated variance among matings is highly significant and nearly 2.5 times that estimated for blacks.

Intense brown has only about half as much eumelanin as intense black. There is a general parallelism in the effects of the lower c combinations on the two colors but relatively (as well as absolutely) much less spread among the browns. Thus, $c^r c^a$ and $c^d c^a$ browns (with *SiSiDmDm*) have about 75 percent as much pigment as nondingy C browns in contrast with 46 percent in the corresponding comparison in sepias. Similarly, $c^r c^r$, $c^k c^{kdr}$ and nondingy C browns are indistinguishable in coat color, while $c^r c^r$ dark sepias are obviously lighter than C blacks, and $c^k c^{kdr}$ can usually be distinguished from the latter on comparison of live animals. These comparisons indicate, as noted in previous papers, that the reduction to about 50 percent of the quantity of eumelanin from black to brown is associated with imposition of a more drastic limit on the amount of pigment that can be produced by excess tyrosinase (the effectiveness of which is determined primarily by the C alleles) (RUSSELL 1939; GINSBURG 1944; FOSTER 1956). Thus, there is more damping of the effects of the lower c alleles by approach to a ceiling in the browns than in the sepias. The replacement of P by pp reduces the amount of eumelanin of blacks much more than does replacement of B by bb , but there is no indication of imposition of a limiting factor on the effects of the lower c alleles. These, on the contrary, show a much greater relative spread than in dark sepias. The replacement of B of *BppF* sepias by bb changes the quality to pale brown but reduces the amount of pigment only slightly. The relative spread among the effects of the lower c alleles is almost as great as in the pale sepias. It has been concluded that with ppF there is greatly reduced efficiency of the tyrosinase due to a given c combination instead of imposition of a lower ceiling on its activity as with bb .

The data of Table 1, and the analysis of variance, indicate that the height of the ceiling varies considerably, and that this is to a large extent under genetic control. The seven matings in the first row of Table 1 produced only one offspring in 22 with index below 35.00, while the five matings of the second row (of the same genotype in all major factors) produced only two offspring in 15 with index above 35.00. The former group produced on the average 21 percent more pigment than the latter. There is, however, no clear evidence of segregation of a major modifier within matings.

The most plausible interpretation of this aspect of the residual genetic variability of browns is that there are multiple loci that affect the level of the physiological limiting factor for intensity. This can have nothing to do with the limiting factor responsible for dominance of *C* since this is found whether brown (or any other color) is near its ceiling or not (e.g., in pale brown *EbbC⁺ppF*). Dominance must be due to a physiological limit that applies directly to the *C* product.

It is probable that *e^pe^p* sometimes lowers the ceiling for brown. It will be convenient to use the symbols *Lb₁*, *Lb₂*, etc., and collectively $\Sigma(Lb)$ (limited brown) for the plus phases of the other loci (hypothetical) that affect intensity within *EbbCP*.

The variations in intensity among browns with *c^kc^{kd}r* and *c^rc^r* are presumably due to these same modifiers. Lesser damping effects would be expected with the still lower *c* combinations, but in these the effects are confounded with the increasing effects of *Si,si* and *Dm,dm* on intensity.

It is probable that the same modifiers, $\Sigma(Lb)$ also affect the limiting intensity of black.

Analysis of the variability of dingy browns

The second type of variation in browns is wholly restricted to those that carry *C*. With a low grade of dinginess (WRIGHT 1947) there are scattered hairs, restricted to the cheeks and nape, that are as light as pink-eyed pale browns either in a subterminal band or throughout their lengths, except for two or three millimeters of intense brown at the tip. In higher grades the proportion of such hairs is greater in the regions referred to and there is a sprinkling of them on the back, especially anteriorly. In the highest grades all hairs are affected over most of the coat. The rump, nose and feet are least affected.

Animals of the highest intensity in unaffected hairs may show scattered hairs of the above type. The term "dinginess" is not an appropriate one for these attractively silvered intense browns. High ceiling intensity seems, however, to be incompatible with the higher grades of dinginess. The term is most appropriate where there is a mixture of dark-tipped pale-brown and uniform dull-brown hairs. No white could be found in the affected hairs of even the palest dingy browns in this colony.

As described in a previous paper (WRIGHT 1947), a strain (S) was established in which all animals were dingy browns, most of them of high grade, by selection of such animals as parents. This strain was continued as SH into the period in which reflectionmeter indices were obtained. There was occasional introduc-

tion of strongly dingy animals from other strains. This strain came to be of constitution (*S,s*) (*E,e^p*) *bbCCPPFF*.

The reflectionmeter index from the darkest region of the back is a very imperfect measure of this character since animals with slight to medium dinginess may show no reduction of the index. Nevertheless, as shown in Table 1, bottom row, the distribution of indices for strain SH contrasts markedly with distribution for nondingy intense browns. The mean index of the former $27.88 \pm .59$ contrasts with $35.23 \pm .19$ for *EbbCCPp* in Table 1. This implies only about 60 percent as much pigment. The amount of pigment extracted from weighed samples of strongly dingy hairs was 42 percent of that in samples of nondingy intense brown hairs. (Analyses by Dr. A. S. Fox).

The analysis of variance is given below for the 74 animals of this genotype that came from matings from which at least two young were graded. The harmonic mean of individuals per mating was 3.884.

Dingy brown, *EbbCCPPFF*. Mean 25.63

	DF	Mean square	F	Prob.	Variance components
<i>I</i> within <i>L</i>	47	16.000			
<i>L</i> within <i>M</i>	11	9.275	1.72	>.05	
<i>I</i> within <i>M</i>	58	14.725			$\sigma^2_{I:M} = 14.73$
<i>M</i> within <i>T</i>	15	49.849	3.38	<.001	$\sigma^2_M = 9.04$
<i>I</i> within <i>T</i>	73	21.942			$\sigma^2_I = 23.77$

In this case the differentiation among litters within matings is less than expected by chance though not significantly. The differentiation of matings, on the other hand, is significant at the .001 level. The two components of variance are enormously larger than in the nondingy browns or blacks. There is undoubtedly a considerable nongenetic component in the variance of individuals, but the large variance among matings makes it certain that genetic modifiers played a large role in this strain.

An attempt was made to produce a weakly dingy or nondingy strain (SL) of the same major genotype (*EbbCCPPFF*) at the time of establishment of strain SH, but all such animals that were tested turned out to be *Pp*, already known to reduce dinginess greatly (WRIGHT 1947). Later, outcrosses of SH were made to animals from various sources believed to be *PP*. In two cases a few nondingy browns of genotype *EbbCCPPFF* were obtained.

In one of these, a male with very strong dinginess from strain SH (mating SH83) was mated with an unrelated black of genotype *EBbCCPPFF*. All of the five offspring that were brown showed much less dinginess than any of the nine offspring of SH83. They showed slight to medium dinginess on the head but no more than a trace on the back, too little to affect the index (average of three, 34.0). A brother-sister mating, SN39, produced an F_2 progeny of 19 individuals.

None of these showed more than the weak dinginess of F_1 . Four showed mere traces on the head, and two showed none at all. The average index for 13 was $34.45 \pm .49$. One of the two with no dinginess was mated with a pink-eyed pale-brown male ($EbbCppFF$). The 18 offspring were all nondingy dark browns (Pp) except for one with a trace of dinginess on the head. The mother was the first clear case of nondingy $EbbCPPFF$ to be observed. Two F_3 matings were made. One from very slightly dingy parents produced three offspring like themselves. The other came from parents that were the dingiest of the weak dingies of F_2 . One of the four offspring was only slightly dingy, but the other three were as strongly dingy as the average of SH83. Thus, while strong dinginess did not appear in F_1 or F_2 , it did in F_3 . These results show that genotype $EbbCPPFF$ can vary from the highest degree of dinginess to none at all, but that the difference between extremes, or even that between nondingy and dingy collectively, must have been multifactorial.

In the other outcross (SN41) a female with relatively slight dinginess for strain SH (from a brother-sister mating from SH83) was mated with an unrelated dilute brown ($e^nebbc^dc^aPPFF$). Eight of the 35 offspring in this case showed dinginess fully typical of strain SH, 22 showed no more than in the preceding F_1 and F_2 , three showed mere traces on the head and two were nondingy. The average index of 16 (including two strong dingies) showed little depression (34.35), but it is clear that this outcross was to an animal that was heterozygous in genes favoring dinginess. Two F_2 matings were made, both from parents that showed only weak dinginess restricted to the head. In both cases, the offspring covered the range from very strong dinginess to none at all. Unfortunately the nondingies were of doubtful genotype since one of the matings produced c^dc^a and the other c^dc^d segregants, neither of which ever show a trace of the character. These are not as intense as browns with C but there is overlap at least in the case of c^dc^d . The most intense of the F_2 nondingy young (index 34.8) was tested by mating with a pink-eyed pale sepia of genotype $Ebbc^dc^appFF$. All of the 27 young were dark-eyed (Pp) and seven were blacks (C) proving that this tested nondingy F_2 female was $EbbCPPFF$, and thus, the second case in which it was proved (by breeding tests) that this genotype may be nondingy.

In this second outcross, there appeared to be segregation of one or more, probably two, major modifiers. There is agreement with the first outcross, however, in the indication that no single locus controls the difference between nondingy and dingy, collectively, in browns of genotype $EbbCPPFF$. We may postulate an array of modifiers Db_1 , Db_2 , etc., collectively $\Sigma(Db)$, that vary considerably in effect.

Mosaicism of dingy brown due to gene s

A reading was taken on the lightest as well as on the darkest region of the back in most of the animals of strain SH. Table 2 shows the means of the maximum index in all animals in which a reading was taken and both the maximum and minimum for all on which both were taken. A subdivision is made according to the absence (E) or presence (e^p) of yellow spotting and according to the amount

TABLE 2

Mean maximum and minimum indices of classes of dingy browns of strain SH classified by absence (E) or presence (e^pe^p) of yellow spotting and by amount of white (none, white present but not on back, and white on the back). Mean maximum indices are given for all graded and for those with a minimum index

<i>E, e^pe^p</i>	Amount of white	No.	All graded		Maximum grade With min. grade		Minimum grade	
			$\bar{I}$	SE	$\bar{I}$	SE	$\bar{I}$	SE
<i>E</i>	no W	29(25)	27.9	0.6	(27.6	0.7)	19.9	0.8
	little W	8(6)	24.0	2.0	(22.5	2.4)	15.9	1.8
	W on back	23(18)	25.1	1.2	(26.2	1.0)	18.2	1.6
	Total <i>E</i>	60(49)	26.3	0.6	(26.5	0.6)	18.8	0.8
<i>e^pe^p</i>	no W	2(2)	26.9	..	(26.9	..)	18.5	..
	little W	3(2)	22.9	..	(22.5	..)	16.7	..
	W on back	14(8)	22.7	0.9	(22.4	1.2)	16.1	1.1
	Total <i>e^pe^p</i>	19(12)	23.2	0.8	(23.1	1.0)	16.6	0.9

TABLE 3

*Mean maximum and minimum of index, visual grade (VG) and amount of pigment (Pig.) (VG and Pig. by transformation of *I*) for the dingy browns of strain SH, classified by *E, e^pe^p* and by presence or absence of any white*

<i>E vs. e^pe^p</i>	Amount of white	No.	Maximum grade			Minimum grade			Percent pig. min. max.
			<i>I</i>	VG from <i>I</i>	Pig. from <i>I</i>	<i>I</i>	VG from <i>I</i>	Pig. from <i>I</i>	
<i>E</i>	no W	29	27.9	12.3	62.3	25	19.9	8.8	54.0
	W present	31	24.8	11.0	49.7	24	17.6	7.8	55.7
<i>e^pe^p</i>	no W	2	26.9	11.9	58.0	2	18.5	8.2	51.5
	W present	17	22.7	10.1	42.4	10	16.2	7.2	57.3

of white: "no W" if no white, "little W" if some white but none on the back and "W on back" if white on the back. There is no indication of bias from the failure to obtain a minimum index in all cases.

No clear indication of any relation of dinginess to white or to yellow spotting was found at the time of the 1947 paper on the basis of the averages from arbitrary grades of the character. The data in Table 2 suggest, however, that both tend to reduce intensity somewhat, though not wholly conclusively, because of heterogeneity and because of a possible effect of the restriction of the sites at which readings could be taken in the case of the tortoise-shells.

This probable effect of *e^pe^p* may be interpreted as a by-product of an occasional lowering of the ceiling for brown, which as noted favors dinginess.

There is no consistent difference between those with white on the back and those with white restricted to other parts of the coat. These two categories are combined in Table 3 which shows not only the mean indices for darkest and lightest areas on the back but also the mean visual grades and mean relative

amounts of pigment both estimated by transformation of the indices. The amount of pigment estimated for 198 nondingy browns, *EbbCPFF*, mean index 34.8, is taken as 100 as in the previous paper (WRIGHT 1959b).

It is interesting that the ratio of amount in the lightest area to that in the darkest is about the same (average 55 percent) in all four categories. This contrasts with the approximate uniformity of the intensity of brown on the back of nondingy browns. There was a correlation of $.81 \pm .07$ between maximum and minimum in the self-colored browns and of $.75 \pm .09$ in those with white in the coat. It may be noted that the amount of brown pigment is reduced to one third of that of intense brown in the lightest region in self-colored dingies and to about one fourth in tricolors.

While the effect of *s* on the mean index is slight at best, there is clear evidence from mere inspection of spotted dingies that there is an effect of another sort. In self-colored dingies of strain SH, there was almost always an orderly symmetrical pattern. As already noted there was usually strong dinginess on cheeks and nape but little or none on the nose. In about 25 percent a transverse line back of the shoulders sharply separated a light anterior region from a darker posterior one. In most of the others, there was a gradual transition from light to dark in this region, but in a few there was little change. In about a third, gradual darkening continued posteriorly culminating in brown of almost full intensity at the extreme posterior end where readings were never taken. The belly showed considerable dinginess as a rule but not the legs.

Among 43 self browns of this strain in which the pattern was carefully described in a rubber stamped outline, there was appreciable asymmetry in only one (strong dinginess in an area on the left side of the back opposite moderate dinginess on the right side).

The contrast between these self browns and those with any white in the coat is brought out in Table 4 (which is restricted to browns with no yellow spotting). About 40 percent of the 81 with a little white but none on the back and 48 percent of the 102 with some white on the back showed marked bilateral asymmetry with respect to degree of dinginess.

A second relation to white is also conspicuous. In 27 percent of those with some white but none on the back, and in 53 percent of those with white on the back,

TABLE 4

Pattern of dingy browns of strain SH classified according to amount of white as in Table 2 and according to whether differences in grade of dinginess show a relation to white, if present, and according to bilateral symmetry or asymmetry

	Amount of white	No relation to white		Relation to white		Total	Percent asym.	Percent relation to white
		Sym.	Asym.	Sym.	Asym.			
<i>E</i>	none	42	1	..	..	43	2.3	..
	little W	47	12	2	20	81	39.5	27.2
	W on back	43	5	10	44	102	48.0	52.9
	Total <i>E</i>	132	18	12	64	226	36.3	33.6

there were abrupt intensity boundaries that were clearly related to the pattern of color and white. The commonest relation was a pronounced difference in grade of dinginess on opposite sides of the head, separated wholly or in part by a narrow white nose streak. In other cases two adjoining areas of markedly different degrees of dinginess on the back were separated in part by a sharp boundary which ran into the point of a wedge of white which continued the separation of grades of dinginess. In some cases such a boundary, continued as a white streak, might lie transversely across the back so as to give a symmetrical pattern, but more frequently it lay diagonally or longitudinally, giving asymmetry. In Table 4, each animal is entered only once although some showed such peculiarities, as described, in more than one part of the coat. Thus, gene *s* clearly brings about a tendency toward mosaicism within the colored areas, and it is clear that this is related developmentally to the mosaic pattern of color and white that is its most obvious effect. In spotted nondingy browns there is, on the other hand, no indication that *s* brings about any tendency toward mosaicism of intensity.

This modification of the dingy pattern by *s* is much like that which *s* causes in the tortoise-shell pattern (WRIGHT 1917, 1923; ILJIN 1928; CHASE 1939). In tortoise-shells that have no white (*SSe^ve^v*) there is usually a mere sprinkling of yellow hairs on a eumelanic ground. In tricolors (*sse^ve^v*), the pattern of irregular blocks of color on a white ground is the same as in piebald bicolors (*ssE*, *ssee*), but, instead of these blocks being all tortoise-shell, some tend to be largely or wholly eumelanic and others largely or wholly phaeomelanin. Such blocks may be wholly separated by a white streak or by a sharp boundary that runs into a white streak or at least into the point of a wedge of white.

While eumelanin and phaeomelanin are distributed in the main as equal alternatives in the tricolor pattern, there are many cases in which eumelanic head spots on a phaeomelanin ground simulate the typical relations of color to white on the head in piebalds. There are also moderately frequent cases in which a narrow streak between two eumelanic blocks is white at one end, yellow at the other. There are few, if any, cases of the reverse relation between the two colors. Thus, eumelanin is related to phaeomelanin within the colored areas somewhat as color, collectively, is related to white.

This raises the question whether there is a similar relation between grades of dinginess. An examination of the recorded patterns of strain SH revealed nine cases in which a narrow streak of dark brown separated, at least in part, two large blocks of light (strongly dingy) brown. In two of these the dark brown streak was a continuation of a white streak, and in two others it was a continuation of a yellow streak. There were also two cases (not included above) in which a double streak (dark brown along one side, white on the other) separated light brown areas. There were eight cases in which a large light-brown area had a narrow dark-brown border next to a large yellow area. In only one doubtful case was a reverse situation to any of these found: white continued by light brown between dark-brown areas.

There were many cases in which light-brown cheek spots were set off sharply from a dark ground, but this differs from the situation in unspotted slightly dingy

animals only in the sharpness of the boundaries. Related to this was a large number of cases in which a white nose streak was continued on the nape by a small area of dark brown (instead of the more usual white spot) both surrounded by light brown. It seems clear that in mosaics due to *s*, the *light*-brown areas are related to the *dark* ones in the way that eumelanin, collectively, is to yellow or as color, collectively, is to white.

It may be added that mosaicism due to *s* is much less frequently manifested in other colors. It is occasionally responsible for blocks of sharply different intensity of pale sepia or pale brown, separated wholly or in part by white streaks. As noted in the previous paper, it seems to be responsible in some cases for blocks of different grades of silvering in animals with *sisi*. Still more rare are cases of apparent somatic mutation of major color factors in which the "mutant" spots are related to white in a similar way to those above. Such a relation has been noted in other mammals (cf. CASTLE 1929; DUNN 1934 on such cases in rabbits and mice respectively). It should be said that a few apparent somatic mutations have been observed in which *s* was absent.

Relation of genes C, P and F to dinginess of brown

Earlier studies of dinginess (WRIGHT 1947) were based on outcrosses of the dingy strain S (genotype (*S,s*) (*E,e^p*) *bbCCPPFF*). A systematic attempt to introduce the character into brown-dilute yellow tortoise-shells carrying *c^kc^k* instead of *C* was made by repeated backcrossing to tortoise-shells of strain S followed by inbreeding in order to extract ones with dilute yellow spotting. The resulting strain (SK) was maintained by crosses of *Cc^k × c^kc^k* and *Cc^k × Cc^k*. The brown-*red* segregants (*C*—) showed moderate to strong dinginess as in strain S while no trace of dinginess was ever observed in the brown-*yellow* segregants (*c^kc^k*). Less systematic observations of lower *c*-combinations indicated that *C* is necessary for any dinginess whatever. This conclusion has been fully substantiated by all later observations.

An attempt to introduce dinginess into pale browns (*bbCCppFF*) also completely failed. These experiments (strain SP) showed moreover that *PP* is necessary for more than a trace of dinginess on the back or for strong dinginess on the head. Matings of *PP × pp* or of *Pp × pp* have never produced young with strong dinginess in spite of high concentration of dingy ancestry of strains S or SH, while matings between *Pp* offspring of such matings produced strong dinginess in the proportion expected of *PP*. Numerous breeding tests of strong and weak dingies from *Pp × Pp* have shown the former to be *PP* and the latter *Pp*.

An attempt to introduce dinginess of strain S into brown-dilute yellow tricolors of genotype *sse^pe^pbbCCPPff* was more successful, but among 203 of this genotype with high concentration of S ancestry, only three showed dinginess of the highest grade. In a strain (SF) maintained by matings *Ff × ff* and *Ff × Ff* (as well as *ff × ff*), the brown-*red* segregants (*F*—) showed significantly stronger dinginess than the brown-*yellow* ones (*ff*). This strain continued into the period in which reflectionmeter indices were obtained. The average for 13 brown-reds (all *Ff*) was 26.9 ± 1.5 and for 31 brown-yellows (*ff*) was 30.9 ± 0.6 . The difference is

significant. No clear evidence has been obtained, however, of a difference between *FF* and *Ff*.

The combination *ECPpff* has been produced in considerable numbers (Table 1). These have shown no dinginess at all except for mere traces on the head in two cases.

No clear evidence has been found of a difference at birth between *Cc⁺PPFF*, which has frequently been of the highest grade of dinginess, and *CCPPFF*. It was found, however, that the former darken significantly more with age (WRIGHT 1947). There is some indication that *Cc⁺PPFf* tends to have less dinginess than comparable *CCPPFF*, but one clear case of strong dinginess (index 26.7) has been obtained. Genotype *Cc⁺PpFF*, on the other hand, has never shown more than a trace of dinginess and, thus, less than *CCPpFF*.

It is clear that the system of major genes that control the intensity of brown pigmentation (*Ebb* present) is one that has an optimum. The combination *c^kc^k-ppff* is pure white. *Cppff* has a trace of brown; *c^kc^kppFF* and *CppF* are pale browns with the latter more intense, and *c^kc^kP-* is of full intensity. The observed maximum is with *CpPff*. With a given array of modifiers, $\Sigma(Db)$, *CPpFf*, *CPPff* and *CCPPFF* are progressively lighter, the last becoming as pale as *CppF* except at the tip of the hair, with sufficient minus modifiers.

IBSEN (1932) and IBSEN and GOERTZEN (1951) have described a color variation (called "white tipped" in the former reference; "whitish" in the latter reference) that is clearly related physiologically to dinginess. In whitish browns, a few to most of the hairs are affected. The tip is always intense (according to the later paper), but below the tip the hair may be pure white, or there may be one or more bands of pure white separated by dilute brown. Other hairs are merely of the dingy type, dilute with dark tip. The data clearly indicated the presence of a gene *W* which causes many of the hairs of intense browns (*EbbC*) to be whitish in homozygotes (*WW*) but only a few in heterozygotes (*Ww*) and none with *ww*, which, however, usually is dingy brown. Like dinginess, the character was shown to require the presence of *C*. No mention was made of a relation to *P*, *p* or *F*, *f*, but *f* was probably wholly absent from the colony, and as no mention was made of segregation of *p*, this was probably absent in the experiments on whitish. The whitish character disappeared with age in some two thirds of the females and one third of the males which agrees with the behavior of dinginess to the extent that females darken with age more than do males (WRIGHT 1947). It differed from dinginess in that it could be transferred to blacks, but only in homozygotes (*WW*) and in these only in a few hairs on the head which were soon replaced by wholly black hairs.

It appears that *W* is a modifier of dinginess that was wholly absent from the colony discussed here, since even the strongest dingies never showed any white in the lightest brown hairs.

The peculiar genetics of brown may be interpreted in various ways. The following scheme was suggested in a previous paper (WRIGHT 1949). "With regard to dinginess of brown, the simplest interpretation—is that the product of the *C*, *P* and *F* series combine with some other factor to produce the eumelanin enzyme

system and that this reaction is practically quantitative up to the limit determined by the amount of this factor. It is supposed that this limit is reached in genotype *Cc^aPpff* and that the excess of *CPF* product in higher genotypes gives rise to an inhibitor which tends to transform the brown (but not the sepia) substrate in a way that does not lead to pigment. It is further supposed that this diversion takes precedence almost quantitatively over the competing process of transformation to brown pigment”.

In the light of IBSEN and GOERTZEN's evidence that the gene *W* when homozygous and associated with *CCPPFF* may produce a slight inhibition even in black, it may be postulated that in addition to a qualitative difference gene *B* doubles the amount of the limiting factor found with *bb* and so prevents excess *CPF* product and production of inhibition in blacks except under the most extreme conditions.

With respect to the competition postulated between inhibitor and the brown enzyme system, it cannot be maintained that pigment substrate (tyrosine) is a sharply limiting factor since its rate of production is great enough to maintain the formation of black pigment in twice the amount of the most intense brown. Under the above view it must be supposed that the inhibitor (present only with excess *CPF* product) is so much more effective in competition with the brown enzyme system that the amount of tyrosine available for formation of brown pigment may be reduced far below half of that in the absence of the inhibitor. This is a rather extreme requirement.

There is no necessity that the second competitive phase be in the reaction with tyrosine. It may occur within the formation of the enzyme system itself. This possibility is represented diagrammatically in Figure 3. It is supposed that the *CPF* products interact with the limiting factor (high in amount with *B*, only half as high with *bb*) to produce the corresponding enzyme system. If, however, the *CPF* products are still in excess as the limiting factor approaches exhaustion, they proceed to modify the enzyme system in such a way that it is no longer effective *in vivo*, with dinginess as the consequence.

FIGURE 1.—Key to Figures 2 and 3: (a) process controlled by gene *X*; (b) process (due to *X*) modified by another (due to *Y*); (c) additive processes; (d) a joint reaction; (e) nonalternative effects; (f) alternative effects; (g) an inactive gene; (h) an inactive reaction product. The relative extents of reactions are indicated in Figures 2 and 3 by the heaviness of the lines and by numerals.

FIGURE 2.—Hypothetical processes leading to the formation of the yellow producing enzyme system in melanocytes with phaeomelanin differentiation. These include all in hair follicles (at birth) in genotype *ee*, many in *e^pe^p*, relatively few in *e^pe^p*, subject to modifiers, especially *S,s*. Also included are the melanocytes in an intermediate phase of the follicle cycle in EA etc. Presence or absence of *P,p* $\Sigma(Mp)$ or *B,b* are without effect. The occurrence of thresholds is shown especially by the absence of dorsal pigment in *ee^{kd}c^{ra}ff*, presence in *ee^{kd}c^{ka}ff*. The limiting capacity to form yellow is enormously higher in guinea pigs than in wild *Cavia cutleri*, because of unanalyzed modifiers $\Sigma(Lph)$.

The qualification "*in vivo*" seems to be required by studies of the dopaoxidase activity of colorless extracts from skins of new born guinea pigs of various genotypes by GINSBURG (1944) and the tyrosinase and dopaoxidase activity of homogenates of fetal guinea pig skin of various genotypes by FOSTER (1956). GINSBURG found somewhat higher activity in forming melanin in extracts from browns (*EbbCPPFF*) than in extracts from any other genotype including black. Nearly all of his browns were strong dingies of strain S. Similarly FOSTER found higher oxygen consumption and melanin formation from both tyrosine and dopa by homogenates from browns than from blacks or any other genotype. Half of his browns were strong dingies from strain SH (*EbbCCPPFF*), others were very intense browns of genotype *EbbCCPpff*. There was no consistent difference. Thus, whatever the basis for the inhibition manifested in dingy browns, it does not affect tyrosinase or dopaoxidase activity *in vitro*.

The residual variability of stable yellow

Following is the analysis of variance of the indices from intense yellows ("reds") of genotype *Si(e,e^p)CFF*. All matings from which *sisi* might segregate are excluded. The harmonic means of individuals per litter and of individuals per mating were 1.486 and 3.240 respectively.

There is very little variability within litters and no significant differentiation of matings on taking account of the small but highly significant differentiation of litters within those matings that were represented by more than one litter. There is clearly no residual genetic variability of importance.

This does not mean that such variability may not occur in other colonies. In fact at a much earlier period, the present colony included an inbred strain (No. 32) of genotype *SiSie^pe^pCCFF* that was of so intense a brownish red that visual

FIGURE 3.—Hypothetical processes leading to the formation of pigment producing enzyme systems in melanocytes with eumelanic differentiation. These include all in hair follicles in genotype *Eaa*, most in *e^pe^paa*, relatively few in *e^paaa*, subject to the effects of modifiers, especially *S_s*. Also included are the melanocytes in early and late phases but not an intermediate phase of the follicle cycle in EA, etc. All melanocytes in skin and eyes (in which $c^d > c^r$) are included. A feeble underlying potentiality for producing yellow becomes manifested in follicles in genotype *ECppff* and in genotypes with c^d (especially *Ec^dc^dppF*). The occurrence of both eumelanin and phaeomelanin thresholds is shown by the complete absence of any pigment in *Ec^kc^kppff* in comparison with the presence of both sorts in *ECppff*, and in other cases. Inactivation of the brown enzyme system occurs only in *E(e^p)CP* and is greatest in *E(e^p)CCPPFF* with favorable modifiers $\Sigma(Db)$ and *W*. Inactivation of the sepia enzyme system occurs only under the most extreme conditions (including presence of *WW* (which was absent from the colony discussed here, but present in IBSEN's colony).

Intense yellow, *Si(e, e^p)CFF*. Mean 22.90

	DF	Mean square	F	Prob.	Variance components
<i>I</i> within <i>L</i>	21	.410			$\sigma^2_{I \cdot L} = .41$
<i>L</i> within <i>M</i>	17	2.241	5.47	<.001	$\sigma^2_{L \cdot M} = 1.23$
<i>I</i> within <i>M</i>	38	1.229			
<i>M</i> within <i>T</i>	9	3.062	1.34	>.05	$\sigma^2_M = .25$
<i>I</i> within <i>T</i>	47	1.580			$\sigma^2_I = 1.89$

grade 13 was regularly assigned to individuals in contrast with grade 10 in other strains of the same genotype in known major genes (e.g., inbred strain No. 2). This implies about twice as much phaeomelanin in strain 32 as in strain 2. Crosses between these strains produced young of intermediate intensity. There

was no recognizable segregation in F_2 which indicates that the difference was due to multiple minor factors.

Wild Peruvian cavy (*Cavia cutleri*), which produce fertile hybrids with the guinea pig and are believed to be ancestral, have a cream color in their agouti pattern which can hardly have more than one fourth as much phaeomelanin as in a typical golden agouti guinea pig (*CCFF*). Yet they have the same genotype with respect to major known genes. They have been shown to possess *C* rather than a lower allele by crosses with albino guinea pigs ($c^a c^a$). Gene *f* was not known at the time but the absence of unifactorial segregation indicates *F*, (CASTLE in CASTLE and WRIGHT 1916). It is possible that they were *dmdm* (WRIGHT 1959b), but *Dm,dm* have no visible effect in intense yellow guinea pigs. Thus, there must be multiple modifying factors $\Sigma(L\ ph)$ that can cause at least an eightfold difference in the amount of yellow pigment within genotype *SiSiccCCFF* but these were absent in the strains analyzed here.

A separate analysis of variance was made of the light reds with *Ff* instead of *FF*. The harmonic means of individuals per litter and per mating were 1.635 and 2.797, respectively.

Light red, *SiSiccCCFf*. Mean 20.71

	DF	Mean square	F	P	Variance components	
<i>I</i> within <i>L</i>	20	1.119			$\sigma^2_{I \cdot L} = 1.12$	
<i>L</i> within <i>M</i>	6	1.628	1.46	>.05	$\sigma^2_{L \cdot M} = .31$	
<i>I</i> within <i>M</i>	26	1.237				$\sigma^2_{I \cdot M} = 1.24$
<i>M</i> within <i>T</i>	9	7.331	4.50	<.05	$\sigma^2_M = 2.04$	$\sigma^2_M = 2.18$
<i>I</i> within <i>T</i>	35	2.804			$\sigma^2_I = 3.47$	$\sigma^2_I = 3.42$

The situation is very different from that with the *FF* reds. There was clearly appreciable residual genetic variability. It is possible that the same genes were present but ineffective with *FF* in the strains from which the *FF* reds were drawn, but this is not certain because of the separation of the strains for several years. The data do not permit any analysis in terms of specific genes.

The variability of yellows with various combinations of lower *c* alleles has been analyzed in previous papers (WRIGHT 1959a,b) as due largely to *Si,si*; *Dm,dm* of which the former pair also affects the intensity of *C* yellows while the latter pair does not. The identification of the genotypes of individuals in these terms is too uncertain to permit analysis of residual variability which in any case was slight.

It may be noted here, however, that there was one small cluster of matings in which there was segregation of abnormally high intensity of *eec^dc^aFF* (visual grade 6 as opposed to grade 4 or 5 of littermates) for several generations after an outcross to another color. This shows that additional modifiers exist.

The residual variability of fading yellow

The analysis of variance of yellows of genotype *SiSieeCCff* is based on animals from the same strains as those from which *Ff* light reds were taken. The harmonic means of individuals per litter and per mating were 1.300 and 2.509, respectively.

Fading yellow, *SiSieeCCff*. Mean 13.51

	DF	Mean square	F	P	Variance components	
<i>I</i> within <i>L</i>	16	1.008			$\sigma^2_{I \cdot L} = 1.01$	
<i>L</i> within <i>M</i>	13	1.078	1.07	>.05	$\sigma^2_{L \cdot M} = .05$	
<i>I</i> within <i>M</i>	29	1.039				$\sigma^2_{I \cdot M} = 1.04$
<i>M</i> within <i>T</i>	12	5.432	5.04	<.001	$\sigma^2_M = 1.74$	$\sigma^2_M = 1.75$
<i>I</i> within <i>T</i>	41	2.325			$\sigma^2_I = 2.80$	$\sigma^2_I = 2.79$

As with the *Ff* light reds, there is slight but appreciable variability within litters, no significant differentiation of litters within matings but significant differentiation of matings. The estimated variance components (whether litters are ignored or not) are remarkably similar to those for *Ff*. It is probable that the same array of modifiers is involved.

There was not much residual variability of the pale creams with *ee* ($c^k c^k$, $c^k c^d$ or $c^d c^d$) *ff* judging from the visual grades of many that were produced in the earlier years of the project. Animals of genotypes *ee* ($c^k c^r$, $c^k c^a$, $c^d c^r$, $c^d c^a$) *ff* were nearly always pure white on the back although differing in the presence or absence of a tinge of very pale cream on the head.

Residual variability of pink-eyed pale sepia

Following are the analyses of variance of pale sepias of genotypes *Si(E, e^p)BCppFF* and the same except for *Ff*. The harmonic means of individuals per litter and per mating were 1.470 and 3.002 respectively in the former, 1.398 and 3.964 respectively in the latter. As in the other cases, *FF* and *Ff* came from strains that had been separated for several years.

Pale sepia, *Si(E, e^p)BCppFF*. Mean 22.79

	DF	Mean square	F	P	Variance components	
<i>I</i> within <i>L</i>	27	6.897			$\sigma^2_{I \cdot L} = 6.90$	
<i>L</i> within <i>M</i>	19	7.324	1.06	>.05	$\sigma^2_{L \cdot M} = .29$	
<i>I</i> within <i>M</i>	46	7.074				$\sigma^2_{I \cdot M} = 7.07$
<i>M</i> within <i>T</i>	13	42.564	5.81	<.001	$\sigma^2_M = 11.74$	$\sigma^2_M = 11.82$
<i>I</i> within <i>T</i>	59	14.893			$\sigma^2_I = 18.93$	$\sigma^2_I = 18.89$

Pale sepia, $Si(E,e^p)$ $BCppFf$. Mean 20.39

	DF	Mean square	F	P	Variance components
<i>I</i> within <i>L</i>	28	10.684	1.24	>.05	
<i>L</i> within <i>M</i>	25	8.651			
<i>I</i> within <i>M</i>	53	9.725			$\sigma^2_{I \cdot M} = 9.73$
<i>M</i> within <i>T</i>	10	20.240	2.08	<.05	$\sigma^2_M = 2.65$
<i>I</i> within <i>T</i>	63	11.394			$\sigma^2_I = 12.38$

There is much more variability than in any of the other cases considered except the dingy browns. There is much variability within litters but very little or none among litters within matings in both cases. There is much differentiation among matings with FF but relatively little with Ff . There had been much more with Ff before separation of these strains judging from visual grades.

Space was not available for systematic genetic analysis of the large segregating differences that were apparent. No complete analysis is now possible from pedigrees since only 333 of the 1817 of these genotypes were from matings in which both parents were pale sepias, $BCppF$. Nevertheless, such analysis as can be made leaves little doubt that most of the residual variability in the late strains was due to segregation of a single pair of alleles with intermediate effect in heterozygotes. It will be convenient to designate this hypothetical pair Mp , mp (plus and minus modifiers of pp eumelanic colors). There is evidence, however, that in the early period, when the most extreme dilutes were appearing, there was at least one additional pair, Mp_2 , mp_2 .

The first row of Table 5 shows the distribution of visual grades of all nonsilvered pale sepias carrying C recorded from 1933 to 1954, except for those from a few matings in which there was possible confusion with lower c combinations, and for certain special experiments. Row 2 gives the distribution from the later strains in which f had been eliminated. There is still much variability but no individuals of grades 2 to 6 and only two of grade 7. A search of the earlier records revealed only one FF of lower grade, and this was a silvered grade 6, expected to be diluted by $sisi$. This combination was not observed otherwise except in special experiments which are not included here. The range of $Si(E,e^p)$ $BCppFF$ may be taken as very rarely exceeding visual grades 8 to 13.

Row 3 in Table 5 shows the progeny of a single rather early (1943) mating (Zp79) of the late strains (row 2). The distribution covers the range from grades 8 to 13 (mean 10.11) in spite of coming from rather high grade parents (11.12). Both parents are interpreted as $FFMpmp$. Two brother-sister matings (parental average 10.0) gave the array of row 4, with a higher average (10.85). Five matings in the next two generations (rows 5 and 6) from high grade parents (11.59) produced an array with mean $11.49 \pm .10$ and standard deviation

TABLE 5

Distribution of visual grades and their means among offspring of certain matings and strains

Mating	Par. mat.	Colors and grades of parents			Genotypes of parents		Visual grades of offspring														No.	Mean
		male	female	$\bar{p}$	male	female	2	3	4	5	6	7	8	9	10	11	12	13	14			
1. (1933-54)	Total				FF	FF	5	6	14	41	61	103	219	330	479	338	197	21	3	1817	9.51	
2. Late strains																				505	10.40	
3. Zp79		S ₁₁	S ₁₂	11.5	FFMpmp	FFMpmp							3	2	7	5	1	1		19	10.11	
4. Zp107,108	(3) (3)	S _{10,11}	S _{10,9}	10.0	MpMp	Mpmp								5	4	2	7	2		20	10.85	
5. Zp118,119,123	(4) (4)	S _{10,11,11}	S _{13,9,11}	11.3	MpMp	MpMp									3	16	14	3		36	11.47	
6. Zp126,137	(5) (5)	S _{13,13}	S _{11,12}	12.2	MpMp	MpMp											8	9		17	11.53	
7. Zpb65		S ₁₂	Br ₉		FFMpmp	FFMpmp							1	2						8	9.50	
8. Zpb69	(7) (7)	S ₁₁	S ₇		MpMp	mpmp									6					6	10.00	
9. Zpb79,80	(8) (8)	S ₁₀	Br ₉		Mpmp	Mpmp							1	5	2	14	1	1		24	9.50	
10. (1933-54)	Total				F-	ff		2	3	10	13	33	70	85	66	25	10			317	8.70	
11. Late strains					F-	ff				3	1	5	39	36	31	19	8			142	9.26	
12. Zfp268		S ₁₂	pCr		FFMpmp	ffMpmp				2	1			6	1	7	4			21	8.90	
13. Zfp286		pCr	S ₁₀		ffMpmp	FfMpMp							1	6	2	1				10	9.30	
14. Zfp302		pCr	S ₁₀		ffMpMp	FfMpMp									1	4	3	1		9	10.44	
15. RP60		S ₉	pCr		FfMpMp	ffMpMp									3	5	5	1		14	10.29	
16. EA113		S ₄	S ₈		Ffmpmp	FFmpmp	3	2	1			2	2							10	4.60	
17. ZpCa4	(16)	S ₈	W		FFmpmp	Ffmpmp	1			3	1									5	4.80	
18. ZpCa1	(16)	S ₈	W		FFmpmp	FfMpmp		1	1				2	1		1				6	7.17	
19. ED172	(16)	Y ₈ (P)	S ₄		FFMpMp	Ffmpmp				3	3		1							7	5.86	
20. ED173	(16)	Y ₈ (P)	S ₇		FFMpMp	FFmpmp										1	1			2	10.50	
21. Zpb1		S ₅	S ₅		Ffmpmp	Ffmpmp			1	2	2									5	5.20	
22. Zfp6	(21)	pCr	W(P)		ffmpmp	FFMpmp		2	1	2		1	1							7	5.00	
23. Zfp11	(22) (22)	S ₃	S ₃		Ffmpmp	Ffmpmp	1		1		2	1		1	2					8	6.75	

The parental matings (par. mat.) of sire and dam are indicated if in the table. The colors (S=pale sepia, Br=pale brown, pCr=pale brownish cream, W=albino, Y=yellow) and visual grades of sire and dam and in some cases the averages are shown. The interpretation of the genotypes of the sire and dam are given. Reciprocal matings are included in rows 10,11.

$.70 \pm .07$. These may be taken as representative of *FFMpMp* on the hypothesis above.

While some lines such as the above rapidly reached a high average and low variability, a low average and high variability persisted in other cases. Row 7 shows the progeny of a late mating (1949) which produced one of the two of grade 7 in row 2. Like Zp79 of row 3 both parents, though rather intense for pale sepia (12) and for pale brown (9), are interpreted as *FFMpmP*. A brother-sister mating between offspring that were almost at opposite extremes (grades 11 and 7) produced a progeny that was uniformly sepia grade 10 except for two pale browns of grades 8 and 9. A mating of type *MpMp* $\times$ *mpmp* is suggested. The wide range, including the only other individual of grade 7 in row 2, of the offspring from two brother-sister matings (interpreted as *Mpmp* $\times$ *Mpmp*) are in harmony (row 9).

These matings in row 9 were producing young in the period in which reflectionmeter readings were being taken. Indices were obtained for 68 individuals from 23 matings of the group in which *f* had been eliminated. These matings were apportioned into three groups, interpreted as *Mpmp* $\times$ *Mpmp*, *MpMp* $\times$ *Mpmp* and *MpMp* $\times$ *MpMp* on the basis of parentage and the lowest visual grade or reflectionmeter index among their offspring. The distribution of the grades and indices are shown in Table 6. Rough estimates of the means for the various genotypes can be obtained by dividing the progeny of those called *Mpmp* $\times$ *Mpmp* as closely as possible on 1:2:1 basis, of those called *MpMp* $\times$ *Mpmp* on a 1:1 basis and treating all progeny of those called *MpMp* $\times$ *MpMp* as of this genotype. This leads to the averages shown in Table 7. The mean indices have been transformed into estimated visual grades and both visual grades and indices into relative amounts of pigment. There is fair agreement. It appears that *FFmpmp* has about half as much pigment as *FFMpMp* with the heterozygotes about half way between.

These estimates, which assume a minimum amount of overlap should tend to exaggerate the differential effects. The pedigree analysis indicates, however, that these are approximately correct.

We consider next the effects of *Mp*, *mp* in individuals known to be *Ff* because they were produced by a mating of type *F*- $\times$ *ff*. The distribution of all such individuals produced from 1933-1954 is shown in row 10 of Table 5. The upper limit reaches grade 12, only one grade less than for known *FF* (row 2), but the lower limit extends three grades lower than for known *FF*. There are 127 *Cpp* sepias of grade 6 or less in row 1. These include one *sisiFF* of grade 6 already referred to and 28 known to be *Ff* in row 10. All of the rest could have been *Ff* as far as ancestry is concerned. One or both parents of half of them were known to be *Ff*. In the other half, ancestry had to be traced one or two or, for two individuals, three generations to encounter known *Ff*. All of them were produced by six more or less connected small clusters, characterized by segregation of both *ff* and the low grade pale sepias. Moreover, among the 103 *Cpp* sepias of grade 7 in row 1,

TABLE 6

Distributions of visual grades and reflectionmeter indices of young from matings in which latter were taken. Matings classified primarily according to whether $FF \times FF$ or $F- \times f f$ (reciprocally) and secondarily according to whether interpreted as $MpMp \times MpMp$, $MpMp \times Mpmp$ (reciprocally) or $Mpmp \times Mpmp$ on the basis of distribution of grades and indices as described in the text

Parental genotypes	No. mat.	Visual grade											Reflectionmeter index											Mean	No.	Mean
		5	6	7	8	9	10	11	12	No.	Mean	12-	14-	16-	18-	20-	22-	24-	26-	28-	30-	No.	Mean			
<i>FF</i> × <i>FF</i> <i>MpMp</i> × <i>MpMp</i>	7	..	..	..	..	..	..	3	7	6	16	11.19	..	..	..	..	..	5	4	..	..	9	25.7			
<i>FF</i> × <i>FF</i> <i>MpMp</i> × <i>Mpmp</i>	9	..	..	..	..	2	14	23	7	46	10.76	..	..	..	1	3	9	5	3	1	1	23	24.2			
<i>FF</i> × <i>FF</i> <i>Mpmp</i> × <i>Mpmp</i>	7	..	..	1	8	13	42	13	9	86	9.99	..	1	6	7	7	5	6	..	3	1	36	21.6			
<i>F-</i> × <i>ff</i> <i>MpMp</i> × <i>MpMp</i>	4	..	..	..	..	3	6	7	1	17	10.35	..	..	..	1	5	5	3	1	..	..	15	22.8			
<i>F-</i> × <i>ff</i> <i>MpMp</i> × <i>Mpmp</i>	8	..	..	2	13	16	11	6	3	51	9.29	..	1	9	12	5	5	5	..	..	..	37	19.9			
<i>F-</i> × <i>ff</i> <i>Mpmp</i> × <i>Mpmp</i>	2	3	1	..	6	2	8	4	..	24	8.79	2	2	1	1	4	..	2	1	..	..	13	19.1			

TABLE 7

Mean grades of genotypes as deduced from Table 6 and relative amounts of pigment (intense black=100) as estimated by transformation of mean grades, mean indices of genotypes as deduced from Table 6 and corresponding grades and amounts of pigment as estimated by transformation of the mean indices

Genotype	No.	Mean grade	Est. pigment	No.	Mean index	Estimated Grade	Pigment
<i>FF MpMp</i>	61	11.3	23.6	29	26.2	12.0	26.8
<i>Mpmp</i>	66	10.1	19.2	30	21.6	9.9	18.6
<i>mpmp</i>	21	8.5	14.3	9	16.9	7.8	12.3
<i>Ff MpMp</i>	50	10.3	19.9	36	22.7	10.4	20.4
<i>Mpmp</i>	38	8.5	14.3	25	18.1	8.3	13.8
<i>mpmp</i>	4	5.3	7.0	4	13.7	6.3	9.0

all but six were from these same clusters. It is probable that virtually all of grades 6 or less and most of grade 7 were *Ff*.

There were only four of grades six or less, however, among the 142 *CppFf* sepias of the later strains in which *f* was carried (row 11). Three of these came from one mating, Zfp268, the distribution of which is given in row 12. In spite of the high grade of the male (12) this is interpreted as *FFMpmp* $\times$ *ffMpmp*. Row 13 gives the distribution of a more typical mating of this group, interpreted as probably *ffMpmp* $\times$ *FfMpMp*. Mating Zfp302, row 14, gave the highest average grade for *Ff* (10.44) among matings with nine or more offspring. The array in row 15 from an unrelated series is closely similar (10.29). These two matings may be taken as representative of *SiEBCppFfMpMp* (mean $10.35 \pm .18$, standard deviation $.88 \pm .13$) slightly more than a grade lower than for *FFMpMp*.

The matings in rows 12, 13 and 14 all produced young from which reflection-meter indices were obtained. Altogether 65 indices of individuals known to be *SiEBCppFf* were obtained from 14 matings of type *F-* $\times$ *ff* (92 visual grades). These matings were apportioned and mean grades and indices for genotypes were obtained in the same way as for matings of type *FF* $\times$ *FF*. There is fairly good agreement between the mean visual grades estimated from the mean indices and those estimated directly. In this case *mpmp* appears to produce somewhat less than half as much pigment as *MpMp*, with *Mpmp* again intermediate.

None of the very palest *Cpp* sepias (grades 2 to 4) are included in the group considered above (row 11). Row 16 gives the array from mating EA113 which produced more than any other for which grades are available. The father was a very pale sepia, born before visual grades were taken, but probably of grade 3 or 4 from his description. The female was of intermediate intensity probably 7 or 8. Both came from the cluster that was the source of nearly all extremely dilute *pp* sepias. Both parents could have been *Ff*, but, as no *ff* young were produced, the mating is interpreted as *Ffmpmp* $\times$ *FFmpmp* with segregation of *Ffmpmp* and *FFmpmp*, the former especially at a decidedly lower level than estimated above. A relatively intense son, grade 8, (presumably *FFmpmp*) was mated with two

albinos from the same cluster (rows 17 and 18). They both produced very low grade young, indicating transmission of *f* and *mp*, but, while one produced no young more intense than grade 7 (probably *FFmpmp*), the other produced young as intense as grades 9 and 11 (interpreted as *FFMmpmp*). Two other offspring of EA113 (grade 4, interpreted as *Ffmpmp*, row 19 and grade 7, interpreted as *FFmpmp*, row 20) were mated with an unrelated yellow male (*eec^ac^app*). One produced young ranging from grades 5 to 8, the lighter of which indicate *Ffmpmp* in terms of the estimates from the later matings but which may be exceptionally light *FfMmpmp*. The other produced only two rather intense offspring, grades 9 and 11, presumably *FFMmpmp*. The father of both progenies was thus probably *FFMpMp*.

Rows 21 to 23 show a chain of matings from another remotely related cluster that produced some exceptionally pale *Cpp* sepias. Both parents in Zpb-1 (brother and sister both grade 5) were *Ff* and are interpreted as *mpmp*. They seem to have produced no *FF* segregants. A mating of a pale brownish cream offspring (*ff*) with an unrelated albino (*c^ac^aFF*) produced seven pale sepias ranging from grades 3 to 8 (segregates of *Ffmpmp* and *FfMmpmp*). A mating between the two palest of these (both grade 3 and presumably *Ffmpmp*) produced an extraordinary range of intensities, grades 2 to 10. More than segregation of *Ff* and *FF* seems required.

The extremely pale *Cpp* sepias from these early clusters illustrated in rows 16 to 23 and the wide segregation in some cases seem to require an additional pair of alleles *Mp₂*, *mp₂* with differential effects comparable to those of the first pair (which may now be called *Mp₁*, *mp₁*) and cumulative with them and with *F*, *f*.

The same modifiers that affect *Cpp* sepias clearly affected those with lower *c* alleles even more on a percentage basis, but analysis is complicated by the effects of *Dm,dm* and less frequently *Si,si*. Pink-eyed pure whites and pale yellows, demonstrated by breedings tests to be *EBc^ac^appF* appeared in the early clusters in which the palest *Cpp* sepias were found. These may be interpreted as having fallen below the threshold for any eumelanic pigmentation from the effect of the minus modifiers *mp₁* and *mp₂*. Whether underlying yellow pigment is revealed or not may be interpreted as depending on whether segregation of other factors such as *Dm,dm* and *Si,si* put the yellow forming process above or below its threshold.

Residual variability of pink-eyed pale brown

The analysis of variance of the indices of pale browns of genotype *Si(E,e^p)bbCppF* is given below, again with separation of *FF* and *Ff* which came from the two separate groups of strains referred to in connection with the yellows and the pale sepias. The harmonic means for individuals per litter and per mating were 1.462 and 3.586 respectively for *FF* and 1.321 and 3.708 respectively for *Ff*.

The analyses are rather similar. There is appreciable variability within litters but so much variability of litters within matings that differentiation of matings is not significant, or doubtfully so. There is undoubtedly residual genetic variability but no factorial analysis is practicable in these data.

Pink-eyed pale brown, $Si(E,e^p)bbCpFF$. Mean 19.93

	DF	Mean square	F	P	Variance components
<i>I</i> within <i>L</i>	17	.919			$\sigma^2_{I \cdot L} = .92$
<i>L</i> within <i>M</i>	10	5.079	5.52	<.01	$\sigma^2_{L \cdot M} = 2.85$
<i>I</i> within <i>M</i>	27	2.460			
<i>M</i> within <i>T</i>	8	12.292	2.42	>.05	$\sigma^2_M = 2.01$
<i>I</i> within <i>T</i>	35	4.709			$\sigma^2_I = 5.78$

Pink-eyed pale brown, $Si(E,e^p)bbCpFf$. Mean 18.40

	DF	Mean square	F	P	Variance components
<i>I</i> within <i>L</i>	21	2.161			$\sigma^2_{I \cdot L} = 2.16$
<i>L</i> within <i>M</i>	25	8.046	3.72	<.001	$\sigma^2_{L \cdot M} = 4.45$
<i>I</i> within <i>M</i>	46	5.360			
<i>M</i> within <i>T</i>	10	18.026	2.24	ca .05	$\sigma^2_M = 2.69$
<i>I</i> within <i>T</i>	56	7.622			$\sigma^2_I = 9.90$

In the pedigree analysis of the early records, it was, however, apparent that exceptionally light *Cpp* browns (visual grade 6 or less) occurred only in the same clusters and often segregated from the same matings as those which produced the exceptionally pale *Cpp* sepias. There is no doubt that the same modifiers of type *Mp,mp* acted similarly in the pale browns and pale sepias though the differential effects seem to have been somewhat less in the pale browns.

It may be noted here that these same clusters and matings also produced genotypes of the other major series. Tabulations gave no indication of any associated effect of these modifiers on dark-eyed sepias, dark-eyed browns or yellows.

Residual variability of pale brownish creams

The analysis of variance of the indices of animals of genotype *ECppff* (in which *B* and *bb* cause no perceptible difference) gave the following results. The harmonic means of individuals per litter and per mating were 1.367 and 3.338, respectively.

The differentiation of litters within matings is not significant in spite of relatively large numbers. There is considerable differentiation within litters and a small but significant amount of differentiation of matings.

It is obvious from inspection of the animals that there is residual variability in both the very small amount of eumelanin and the larger amount of phaeomelanin. This genotype was originally described as pure pale yellow indistinguish-

Pale brownish cream, *ECppff*. Mean 4.93

	DF	Mean square	F	P	Variance components	
<i>I</i> within <i>L</i>	42	2.229			$\sigma^2_{I \cdot L} = 2.33$	
<i>L</i> within <i>M</i>	46	3.040	1.36	>.05	$\sigma^2_{L \cdot M} = .59$	
<i>I</i> within <i>M</i>	88	2.653				$\sigma^2_{I \cdot M} = 2.65$
<i>M</i> within <i>T</i>	26	6.766	2.23	<.01	$\sigma^2_M = 1.12$	$\sigma^2_M = 1.23$
<i>I</i> within <i>T</i>	114	3.591			$\sigma^2_I = 3.94$	$\sigma^2_I = 3.88$

able from *eec^dc^dff* even on direct comparison of live animals (at birth) (WRIGHT 1927). The original strain was discontinued. When reconstituted many years later, the animals usually showed a slight brownish tinge that was unmistakable on comparison with *eec^dc^dff*. As the original strain was closely related to those that gave rise to abnormally pale *Cpp* sepias, while the later one was developed after selection of the latter for higher intensity, it is probable that minus modifiers of *pp*-eumelanin (*mp₁*, *mp₂*) prevailed in the earlier strain, the plus alleles (*Mp₁*, *Mp₂*) in the later one. *Mp₁* and *Mp₂* may be considered as feeble substitutes for *F*, itself a feeble substitute for *P* in the production of eumelanin.

There was another difference, however, in that *eⁿ* prevailed in the earlier strain, *E* in the later one, and it has been apparent that the pale cream (in the pale cream-yellow tortoise-shells *eⁿeⁿCppff* that were produced in small numbers in the later strain) was of a somewhat purer cream than the self-colored brownish creams *ECppff*.

The variations in the intensity of the phaeomelanic component probably depended on *Dm, dm* and perhaps *Si, si* and on factors that affect the threshold for yellow.

Summary

The present paper is concerned with the residual variability in the intensities of the various major color varieties in a large crossbred but self-contained guinea pig colony. It is largely restricted to the genotypes carrying the highest allele (*C*) of the albino series. Analyses of variance of reflectionmeter indices are presented in each of 11 cases.

The most interesting results are those with dark-eyed dark browns (*EbbCPF*). There is slight but significant variability due to factors $\Sigma(Lb)$ that are interpreted as affecting the limiting amount of brown pigment. Enormously more variability in certain strains is interpreted as due to excess product of the genes *C*, *P* and *F* concerned with tyrosinase. The combination *c^kc^kppff* is pure white. Addition of *C*; *F* or *P* permits production of brown pigment ranging from a trace to full intensity. Maximum observed intensity is with *CPppff*. Combinations *CPpF*, *CPPff* and *CCPPFF* are progressively lighter. The last may be as pale as

CppF except at the tip of the hair. With sufficient plus modifiers, however, *CCPPFF* can be of full intensity. The spotting factor (*s*) produces mosaicism with respect to this effect in the brown parts of the coat of dilute (dingy) *CCPPFF*, related developmentally to the pattern of brown and white.

Next in importance are wide variations in the intensity of pale sepia (*EBppF*). These are shown to depend on modifiers tentatively called *Mp₁*, *mp₁*, *Mp₂*, *mp₂* interpreted as affecting the intensity of eumelanin, but appreciable only in the absence of *P*. They also affect pale brown (*EbbppF*) and probably pale brownish cream (*ECppff*) in which the plus alleles, *Mp₁*, *Mp₂*, are interpreted as functioning as very feeble substitutes for *F*, itself a feeble substitute for *P* as a cofactor of the *c* alleles in producing eumelanin.

There was residual genetic variability in other cases, but it was too slight for even tentative analysis in terms of loci.

The relations of the major factors and arrays of modifiers (identified in the text) to the processes that seem to be indicated are illustrated in Figures 2 and 3.

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