

# THE EFFECTS IN COMBINATION OF THE MAJOR COLOR-FACTORS OF THE GUINEA PIG\*

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## INTRODUCTION

The major color variations which have been reported in the guineapig are due to seven series of allelomorphic factors. The possible combinations among these factors account for 43,740 genetically distinct sorts of guinea pigs. The effects of any given factor can thus be studied on a great variety of genetic backgrounds. The primary purpose of the present paper is to present a survey of the effects of factor differences on the appearance of coat color.

## THE COLOR FACTORS OF THE GUINEA PIG

The golden agouti variety of guinea pig is a convenient starting point for consideration of the color varieties, as having the highest dominant factor in all seven of the series of factors, and also as agreeing with the wild Peruvian cavy (*Cavia cutleri* Bennett) in this respect.<sup>1</sup> It has two kinds of pigmentation in its coat, each hair being black with an intense

\* The data for this paper were in the main obtained in experiments carried on by the author in the Bureau of Animal Industry, U. S. DEPARTMENT OF AGRICULTURE.

<sup>1</sup> The color of the wild cavy is much paler than that of the golden agouti guinea pig owing to residual heredity independent of the main color factors (WRIGHT 1916).

yellow or "red" (ochraceous tawny) subterminal band. This band is wider and lighter in color on the belly which thus appears nearly or quite self yellow.

The major color factors<sup>2</sup> may be divided into three groups according to their effect on the pattern. In the first group are those factors whose effect is a restriction of the colored areas to spots on a white ground. The factor *s* is the primary factor for bringing out a piebald pattern of this sort. The extent and localization of the white areas is affected by minor genetic factors, age of dam, and sex, but to the greatest extent by nongenetic developmental irregularities of a sort not common even to litter mates (WRIGHT 1920, 1926).

In the second group are those factors which have to do with what seems to be the primary qualitative differentiation of pigment, that of a black or sepia series and a yellow series. With factor *e* in place of *E* (CASTLE 1905), the entire coat is of some color of the yellow series, except for more or less "sootiness" which usually develops with age. The eyes and the skin in exposed parts, however, develop black pigment. There is an intermediate allelomorph, *e<sup>p</sup>* (IBSEN 1916), responsible for a mosaic coat pattern, in which spots of a dark color, like that due to *E*, are found on a ground color of the same sort of yellow as that brought out by *e*. As in the case of the piebald pattern, this "tortoise-shell" pattern is affected by minor genetic factors, sex, and nongenetic developmental irregularities.

Another factor which may be placed in this group is *a* (CASTLE 1905) which in place of *A* causes the pigmentation of the dark areas of the fur to be wholly of the black series instead of agouti. There is an intermediate allelomorph *a<sup>r</sup>* (DETLEFSEN 1914) derived from crosses with the Brazilian cavy (*C. rufescens* Lund) which has an intermediate effect. The animal has an agouti pattern as with *A* but a pattern in which the width of the yellow subterminal band is reduced.

The appearance of guineapigs with the various combinations of factors considered above, omitting *a<sup>r</sup>*, is as follows, assuming that the remaining four series are represented by the dominant allelomorphs (*CFPB*).

<sup>2</sup> The seven series of color factors discussed in this paper (*S, E, A, C, F, P, B*) are the same as those designated by the same symbols in previous papers by the author and agree with CASTLE's symbolism except in certain of the superscripts used for multiple allelomorphs (cf. CASTLE's review of the literature in *Bibliographia Genetica* 1925). The symbolism given in KOSSWIG's recent review (1925) may be homologized by equating his *S, B, G, A, E* and *C* to *S, E, A, C, P* and *B*, respectively, of the present paper.

|                       | <i>S</i>   | <i>s</i>         |
|-----------------------|------------|------------------|
| <i>EA</i>             | Agouti     | Agouti—white     |
| <i>Ea</i>             | Black      | Black—white      |
| <i>e<sup>p</sup>A</i> | Agouti—red | Agouti—red—white |
| <i>e<sup>p</sup>a</i> | Black—red  | Black—red—white  |
| <i>eA</i>             | Red        | Red—white        |
| <i>ea</i>             | Red        | Red—white        |

The third group includes four series of factors which modify the quality or intensity of the colors of the black or yellow series without disturbing their distributions as determined by the first two groups of factors.

The effects of the 15 compounds in one of these series (the albino series *C*, *c<sup>k</sup>*, *c<sup>d</sup>*, *c<sup>r</sup>*, *c<sup>a</sup>*) on black and yellow in the presence of the dominant factors of the other three series (*FPB*) was the subject of a preceding paper (WRIGHT 1925).

The most favorable combination among factors of the first two groups for study of the third is that of the black-red tortoise-shells (*Se<sup>p</sup>a*) since in these the entire coat is colored and it is possible to grade both black and yellow. Agoutis, self blacks and self reds have also been produced in many combinations and have given valuable supplementary information.

#### THE GRADES OF COLORS

The colors of the guineapigs used in the present study were graded within a week of birth, with the help of three series of skins. As described in the paper referred to above, the sepia series runs from grade 3, a light "sepia," to 14, intense black. The yellow series runs from grade 1, a very pale "cream" barely distinguishable from white, to 13, an intense "red." The "pale sepia" series runs from grade 1, a pale slate color, barely distinguishable from white, to 12, a light sepia, practically identical with grade 5 of the "sepia" series.

The sepia series has been used for grading both sepias (*PB*) and browns (*Pb*). There is a slight difference in quality, but not so great as to make it difficult to use the same set of skins for both. As a matter of fact, the sepia skins have been used as standards only after considerable seasoning, a process in which they have faded somewhat and become slightly browner than at first. The skin has been used for a lower grade than that originally assigned the animal. The final quality is about as close to brown as sepia.

The yellow series has been used for grading the yellow areas of tortoise-shells and for the cream which appears in place of black in the combination

*fp*. There is, of course, a great qualitative difference between this series and the other two.

The "pale sepia" series has been used for grading the pale sepia and pale brown found in combinations  $FpB$  and  $Fpb$ , respectively. The standard series of skins (all  $FpB$ ) grades continuously into the sepia series as noted above. For the purpose of the present paper it will be convenient to combine these into one series running from white (0) to grade 21, intense black, by adding 7 to all grades with the first series of skins. The averages for the albino series, previously published (WRIGHT 1923, 1925) are here modified in this way.

Qualitative differences were most troublesome in grading the classes of animals for which the pale sepia series of skins was used. The grading of the pale browns ( $Fpb$ ) was probably the least satisfactory. As with the sepia series, however, the standard skins had become somewhat browner than at first before being used as standards.

Even among the pale sepias ( $FpB$ ) there was difficulty in comparing all of the albino series compounds. Those with the light dilution factor ( $c^dFpB$ ) were yellowish slate in color even approaching yellow in extreme cases in contrast with the more neutral slate color of combinations of  $C$ ,  $c^k$  or  $c^r$  with  $FpB$ . The standards were taken from this latter group, but animals with the combination  $c^dFpB$  were graded by the same series.

#### GRADES ON COLOR WHEEL

In spite of the difficulties outlined above, the use of standard skins probably gives the most rapid and reliable means of obtaining the order of intensity of fur colors graded at different times. The color of the standard skins and also of a considerable number of previously graded live animals have been matched on a color wheel (Milton Bradley Co.), as suggested by DAVENPORT (1904), using mixtures of white, yellow, orange and black. The small color wheel was spun directly on the skins to be matched or beside the live animal in a room with diffuse daylight (north illumination only). The proportion of the colors necessary for matching the skins varies somewhat, depending on the illumination, more black and less white becoming necessary as the illumination increases.

Table 1 shows the combination of colors which matched the sepia series after averaging and slightly smoothing the results of a number of determinations. The browns (not pink-eyed) appear to differ from the sepias in having slightly more yellow and orange at a given grade. The difference is very slight, however. The animals themselves have a different appearance from sepias, more because of the difference in the color of the skin

in exposed parts (light brown in place of black) than because of any difference in the color of the fur.

TABLE 1

*The proportions of white (W) yellow (Y), orange (O) and black (B) on the Milton Bradley color wheel which match the standard grades of sepia.*

| GRADE | W  | Y  | O | B  | $\frac{O}{Y+O}$ | GRADE | W   | Y   | O   | B  | $\frac{O}{Y+O}$ |
|-------|----|----|---|----|-----------------|-------|-----|-----|-----|----|-----------------|
| 0     | 85 | 10 | 0 | 5  | 0               | 11    | 6   | 7   | 6   | 81 | .46             |
| 1     | 63 | 11 | 6 | 20 | .35             | 12    | 5   | 6   | 5   | 84 | .45             |
| 2     | 50 | 12 | 8 | 30 | .40             | 13    | 4   | 5   | 4   | 87 | .44             |
| 3     | 40 | 12 | 8 | 40 | .40             | 14    | 3   | 4   | 3   | 90 | .43             |
| 4     | 32 | 12 | 8 | 48 | .40             | 15    | 2   | 3   | 3   | 92 | .50             |
| 5     | 26 | 12 | 8 | 54 | .40             | 16    | 1.4 | 2.3 | 2.3 | 94 | .50             |
| 6     | 21 | 11 | 8 | 60 | .42             | 17    | 1   | 2   | 2   | 95 | .50             |
| 7     | 16 | 11 | 8 | 65 | .42             | 18    | 0.4 | 1.8 | 1.8 | 96 | .50             |
| 8     | 13 | 10 | 7 | 70 | .41             | 19    | 0   | 1.5 | 1.5 | 97 | .50             |
| 9     | 10 | 9  | 7 | 74 | .44             | 20    | 0   | 1   | 1   | 98 | .50             |
| 10    | 8  | 8  | 6 | 78 | .43             | 21    | 0   | 0.5 | 0.5 | 99 | .50             |

Table 2 shows the color combinations which matched the standard yellow series after averaging and smoothing the separate determinations. An interesting feature is the increase in the proportion of orange relative to yellow with rising intensity of color. This change is indicated but much

TABLE 2

*The proportions of white (W), yellow (Y), orange (O) and black (B) on the Milton Bradley color wheel which match the standard grades of yellow.*

|    | W  | Y  | O  | B  | $\frac{O}{Y+O}$ |
|----|----|----|----|----|-----------------|
| 0  | 85 | 10 | 0  | 5  | 0               |
| 1  | 62 | 24 | 5  | 9  | .17             |
| 2  | 46 | 31 | 9  | 14 | .22             |
| 3  | 34 | 34 | 12 | 20 | .26             |
| 4  | 25 | 34 | 15 | 26 | .31             |
| 5  | 18 | 32 | 18 | 32 | .36             |
| 6  | 13 | 29 | 20 | 38 | .41             |
| 7  | 10 | 25 | 21 | 44 | .46             |
| 8  | 7  | 21 | 22 | 50 | .51             |
| 9  | 5  | 17 | 21 | 57 | .55             |
| 10 | 3  | 14 | 20 | 63 | .59             |
| 11 | 2  | 12 | 17 | 69 | .59             |
| 12 | 2  | 10 | 14 | 74 | .58             |
| 13 | 2  | 8  | 11 | 79 | .58             |

exaggerated in the popular terms "yellow" and "red." All grades are in fact intermediate between yellow and orange.

The nature of the qualitative differences among the colors is shown in figure 1, in which those grades in the various series, which require the same amount of black and orange combined, are compared.

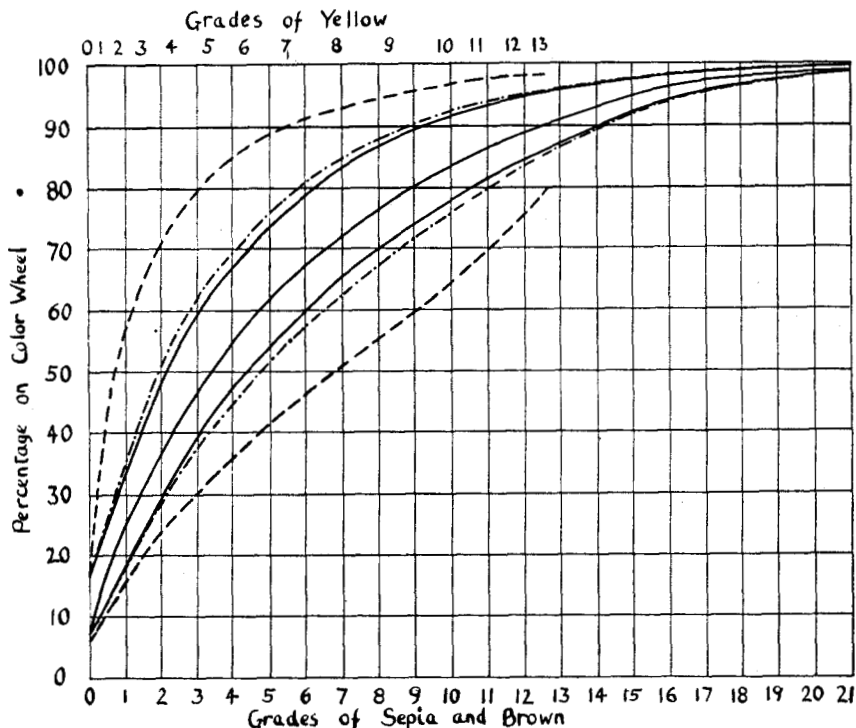


FIGURE 1.—The percentage composition of the standard grades of sepia (solid), brown (dot and dash) and yellow (dash) in terms of black, orange, yellow and white (reading from the bottom) on the Milton Bradley color wheel. The yellow scale is distorted in such a way that the total black and orange agrees with the grades on the sepia (and brown) scale. Note that these scales differ principally in the proportions of neutral gray (black and white) mixed with the spectral hues (yellow and orange).

COMBINATIONS OF THE ALBINO SERIES WITH FACTORS *b* AND *p*

The methods by which the 15 compounds of the albino series were produced and tested (*FPB* present) have been described in some detail in the 1925 paper. It does not seem necessary to go into the details of the matings by which these same 15 compounds were combined with the pink-eyed factor (*p*) (CASTLE 1914) the brown factor (*b*) (CASTLE 1907) and with both combined (*pb*) as the general effects and the simple recessive nature of these factors have long been established.

One set of matings (L) was largely devoted to combining the pink eye factor with compounds of the albino series. The matings here considered

were practically free from factor  $b$  and wholly free from factor  $f$ . Another set of matings (N) was similarly devoted to combining the brown factor ( $b$ ) with the albino series and was also wholly free from  $f$ . A few pink-eyed browns ( $ppbb$ ) appeared, however. In a third set of matings (UR) the primary purpose was the production of a multiple recessive stock ( $sse^pe^paac^kc^kppbb$ ). This was started before the distinction between the dilution factors  $c^k$  and  $c^d$  had been made but on study of the pedigrees it was found that the dilution factor involved in a considerable number of matings traced back exclusively to sources of  $c^k$  and in a few to sources of  $c^d$ . Dilutes which trace to both sources are omitted. As factors  $C$ ,  $c^r$  and  $c^a$  were also present in the foundation stock, all of the 15 compounds were produced although with rather scanty numbers in some cases. Because of the possibility of confusing pink browns ( $ppbb$ ) with pink-eyed sepias ( $ppBB$ ) care was taken that the pink-eyed browns used in mating should be derived by segregation from brown-eyed browns ( $PPbb$ ) which are unmistakable. Throughout experiments L and N (and UR after checking up the early matings) care was taken to make the matings in such a way that there should be no doubt from the ancestry as to which dilution factor ( $c^k$  or  $c^d$ ), if either, was present. This does not mean that two distinct strains were kept in each case since albinos ( $c^a$ ) and red-eyed dilutes ( $c^r$ ) from parents carrying either of the dilution factors,  $c^k$  or  $c^d$ , were freely crossed with animals tracing their dilution to the other source. The factors  $c^k$  and  $c^d$  themselves were brought together only in crosses especially intended to produce the compound  $c^kc^d$ .

In case of matings producing more than one class of young, use was made of the grade of yellow in assigning genetic constitutions. Neither  $p$  nor  $b$  have any recognizable effect on grades of yellow in any combination which the writer has made. It has seemed safe from the results described previously (WRIGHT 1925) to assume that pink-eyed or brown animals (factor  $F$  present) showing red of grade 9 or more were intense ( $C^-$ ) that those showing a yellow of grade 7 or 8 were dilutes of one of the compounds indicated by the symbols  $c^{kd}c^{kd}$ , that those showing cream of grades 3 to 5 were dilutes of one of the four types included in the symbol  $c^{kd}c^{ra}$  and finally that those showing white in a pattern resembling tortoise-shell were either  $c^rc^r$  or  $c^rc^a$ . There is some overlapping of the above limits but such cases are so uncommon as to introduce no important error. Yellows of grade 6, however, are frequently either  $c^{kd}c^{kd}$  or  $c^{kd}c^{ra}$ . Assignment has been made, if at all, on the basis of contrast with litter mates, where not certain from ancestry or descendants.

By taking into account ancestry, descendants and grade of yellow, nearly all of the animals produced in experiments L and N could be assigned to one of the 15 albino series compounds with reasonable certainty. A number of pink-eyed and brown animals which segregated from the experiments (J and K) discussed in the previous study were also available. It may be added that much use has been made of true breeding

TABLE 3  
Distribution of grades of brown in animals of constitutions FFP-bb and different known constitutions relative to the albino series.

| GENETIC CONSTITUTION          | WHITE |    | GRADE OF BROWN FFP-bb |    |    |    |    |    |    |    | NUMBER | MEAN  | σ    |
|-------------------------------|-------|----|-----------------------|----|----|----|----|----|----|----|--------|-------|------|
|                               | 0     | 10 | 11                    | 12 | 13 | 14 | 15 | 16 | 17 | 18 |        |       |      |
| C-                            |       |    |                       |    | 4  | 12 | 17 | 43 | 15 | 2  | 93     | 15.63 | 1.11 |
| c <sup>k</sup> c <sup>k</sup> |       |    |                       | 3  | 5  | 40 | 25 | 20 | 1  |    | 94     | 14.61 | 1.00 |
| c <sup>k</sup> c <sup>d</sup> |       |    |                       |    | 1  | 7  | 8  | 8  | 6  |    | 30     | 15.37 | 1.13 |
| c <sup>k</sup> c <sup>r</sup> |       |    | 1                     | 1  | 1  | 19 | 12 | 5  | 6  |    | 45     | 14.76 | 1.27 |
| c <sup>k</sup> c <sup>a</sup> |       |    |                       | 5  | 27 | 37 | 5  | 1  |    |    | 75     | 13.60 | 0.77 |
| c <sup>d</sup> c <sup>d</sup> |       |    |                       | 2  | 15 | 30 | 22 | 5  |    |    | 74     | 14.18 | 0.91 |
| c <sup>d</sup> c <sup>r</sup> |       |    |                       | 1  | 3  | 6  | 16 | 11 | 2  |    | 39     | 15.00 | 1.09 |
| c <sup>d</sup> c <sup>a</sup> |       | 4  | 3                     | 1  | 13 | 5  |    |    |    |    | 26     | 12.46 | 1.34 |
| c <sup>r</sup> c <sup>r</sup> |       |    |                       |    | 1  | 2  | 5  | 4  | 2  | 1  | 15     | 15.47 | 1.25 |
| c <sup>r</sup> c <sup>a</sup> |       |    | 3                     | 7  | 24 | 12 | 2  |    |    |    | 48     | 13.06 | 0.00 |
| c <sup>a</sup> c <sup>a</sup> | X     |    |                       |    |    |    |    |    |    | -  | -      | 0.00  | -    |

TABLE 4  
Distribution of grades of pale sepia in animals of constitution FFppB and of different known constitutions relative to the albino series.

| GENETIC CONSTITUTION          | WHITE |   | GRADE OF PALE SEPIA FFppB- |    |    |    |    |    |   |   |    |    |    |   | NUMBER | MEAN | σ    |
|-------------------------------|-------|---|----------------------------|----|----|----|----|----|---|---|----|----|----|---|--------|------|------|
|                               | 0     | 1 | 2                          | 3  | 4  | 5  | 6  | 7  | 8 | 9 | 10 | 11 | 12 |   |        |      |      |
| C-                            |       |   |                            |    |    |    |    | 1  | 1 | 6 | 4  | 22 | 8  | 1 | 43     | 9.70 | 1.18 |
| c <sup>k</sup> c <sup>k</sup> |       |   |                            |    |    |    |    | 1  | 5 | 9 | 38 | 16 | 6  |   | 75     | 9.08 | 1.02 |
| c <sup>k</sup> c <sup>d</sup> |       |   |                            |    |    |    |    | 1  | 4 | 4 | 2  |    |    |   | 11     | 7.64 | 0.87 |
| c <sup>k</sup> c <sup>r</sup> |       |   |                            |    |    | 2  | 2  | 2  | 2 | 2 |    |    |    |   | 10     | 7.00 | 1.41 |
| c <sup>k</sup> c <sup>a</sup> |       |   |                            |    |    | 9  | 5  | 1  |   |   |    |    |    |   | 15     | 5.47 | 0.61 |
| c <sup>d</sup> c <sup>d</sup> |       |   |                            | 1  | 10 | 30 | 53 | 21 | 7 | 1 |    |    |    |   | 123    | 4.88 | 1.04 |
| c <sup>d</sup> c <sup>r</sup> |       |   |                            | 3  | 15 | 12 | 16 | 1  | 1 |   |    |    |    |   | 48     | 4.00 | 1.08 |
| c <sup>d</sup> c <sup>a</sup> |       |   | 5                          | 9  | 17 | 4  |    |    |   |   |    |    |    |   | 35     | 2.57 | 0.87 |
| c <sup>r</sup> c <sup>r</sup> |       |   |                            | 12 | 10 | 2  |    |    |   |   |    |    |    |   | 24     | 2.58 | 0.64 |
| c <sup>r</sup> c <sup>a</sup> |       | 6 | 7                          | 2  |    |    |    |    |   |   |    |    |    |   | 15     | 0.73 | 0.68 |
| c <sup>a</sup> c <sup>a</sup> | X     |   |                            |    |    |    |    |    |   |   |    |    |    |   | -      | 0    | -    |



TABLE 5

Distribution of grades of pale brown in animals of constitution  $FFppbb$  and of different known constitutions relative to the albino series.

| GENETIC CONSTITUTION | GRADE OF PALE BROWN $FFppbb$ |    |   |   |   |    |    |     |    |    |   | NUMBER | MEAN | $\sigma$ |      |
|----------------------|------------------------------|----|---|---|---|----|----|-----|----|----|---|--------|------|----------|------|
|                      | WHITE                        | 0  | 1 | 2 | 3 | 4  | 5  | 6   | 7  | 8  | 9 |        |      |          | 10   |
| $C-$                 |                              |    |   |   |   |    |    |     | 1  | 4  | 1 | 1      | 7    | 8.29     | 0.87 |
| $c^k c^k$            |                              |    |   |   |   | 5  | 29 | 110 | 64 | 12 |   |        | 220  | 7.22     | 0.83 |
| $c^k c^d$            |                              |    |   |   |   | 2  | 6  | 2   |    |    |   |        | 10   | 6.00     | 0.63 |
| $c^k c^r$            |                              |    |   | 1 | 1 | 13 | 32 | 25  | 1  |    |   |        | 73   | 6.12     | 0.87 |
| $c^k c^a$            |                              |    |   |   |   | 15 | 10 | 3   |    |    |   |        | 28   | 5.57     | 0.68 |
| $c^d c^d$            |                              |    |   | 1 |   | 3  | 12 |     |    |    |   |        | 7    | 5.43     | 1.29 |
| $c^d c^r$            |                              |    |   | 1 | 2 |    |    |     |    |    |   |        | 3    | 3.67     | 0.47 |
| $c^d c^a$            |                              |    |   | 5 | 1 |    |    |     |    |    |   |        | 6    | 3.17     | 0.37 |
| $c^r c^r$            |                              | 2  | 4 | 6 | 5 |    |    |     |    |    |   |        | 17   | 2.82     | 0.99 |
| $c^r c^a$            | 4                            | 17 | 7 |   |   |    |    |     |    |    |   |        | 28   | 1.11     | 0.61 |
| $c^a c^a$            | X                            |    |   |   |   |    |    |     |    |    |   |        | —    | 0.00     | —    |

stocks (included in L, N and UR) of types  $c^k c^k ppBB$ ,  $c^k c^k PPbb$ ,  $c^d c^d ppBB$  and  $c^d c^d PPbb$  in producing the various compounds. Tables 3, 4 and 5 show the distribution of grades of sepia and brown in the combinations of  $pp$ ,  $bb$ , and  $ppbb$ , with the albino series compounds. The averages are brought together in table 17. The significance of the differences in the averages within each group are discussed later.

#### THE DILUTION FACTOR $f$

In the case of combinations involving factor  $f$  it is desirable to go into greater detail, since only scanty data have previously been published on this factor (WRIGHT 1923).

All yellows and creams which the writer has tested have proved to owe their dilution of color to an intermediate allelomorph of albinism ( $c^k$  or  $c^d$ ) with the exception of descendants of three animals, two sisters and the very remotely related mate of one of these (matings B205 and B211) in a stock (B) which had been maintained for many years without out-cross, as a control in the inbreeding experiments of the Bureau of Animal Industry. The factor was probably present in the stock from the first as many black-yellows and yellow-agoutis were recorded but it was not recognized as new, since factor  $c^k$ , with closely similar effects, was also present. In mating B211 an albino male was mated with an intense agouti female. The progeny consisted of 11 intense and 5 dilute. While it seemed probable that the mating was of type  $c^a c^a \times Cc^k$ , attention was attracted

to it by the grade of intensity of the yellow in the dilute young which was distinctly higher than encountered, except very rarely in dilutes of formula  $c^k c^a$ . The dilutes from this mating were of grade 7 or 8, while  $c^k c^a$  is typically of grade 4 or 5. The black associated with the yellow moreover showed no dilution whatever. Two of the dilute young were mated with each other, producing 6 dilutes (yellow-agouti) and 2 albinos. Four matings were made between these dilutes and albinos of the stock used in studying the effects of the albino series compounds. In previous experiments albino by dilute, regardless of ancestry on either side, had never given intense young. These four matings, however, produced 17 unmistakably intense young (black-red, or golden-agouti), in addition to 5 intense blacks and 26 albinos. This result practically demonstrated that a new recessive dilution factor ( $f$ ) was present which was independent of the albino series. These intense young were backcrossed with albinos from the same stock as in the previous generation. Again, only intense and albinos appeared (9 with red in the fur, 10 intense black and 24 albinos). It is thus clear that albinos can transmit the intense allelomorph of the new dilution factor. As a complement to this experiment, two of the albinos from the first of the above crosses were mated with ordinary dilutes. The young were all ordinary dilutes (2 cream agouti,  $c^k c^a$ , and 3 medium sephia,  $c^d c^a$ ). The albinos from this source thus do *not* transmit the intense allelomorph of ordinary dilution nor any intense modifier. Similarly, dilutes tracing to mating B211 were mated with ordinary dilutes ( $c^k c^k$  and  $c^d c^d$ ). The four matings produced 21 intense (red in fur) and 21 dilute (yellow or cream in fur). The occurrence of intense young proves that each of the two kinds of dilution supplies the dominant intensity factor lacking in the other. The dilute young were expected from matings of type  $Cc^{da}ff \times c^{kd}c^{kd}FF$ . Four matings of intense from the first cross of  $ff$  dilutes with ordinary albinos, and thus necessarily  $Cc^aFf$  were made with albinos from the same type of mating and thus necessarily  $c^a c^a Ff$ . The young consisted of 20 intense with red in the fur, 4 dilutes with yellow in the fur, 11 blacks which might belong with either of the foregoing classes and 35 albinos. This result is reasonably in accord with expectation. A mating between two double heterozygotes ( $Cc^aFf \times Cc^aFf$ ) produced 14 intense with red in the fur, 5 dilutes with yellow in the fur, 1 black (intense or dilute) and 10 albinos, also in good agreement with the hypothesis of a dilution factor independent of albinism, but impossible for a dilution factor allelomorphous with albinism.

It was next of interest to find the combined effect of the two series of dilution factors. An intense (black-red) from a mating  $c^d c^d FF \times Cc^a ff$

was mated with an intense (black-red) from a mating  $Cc^{aff} \times CCFF$ . As ordinary dilutes were produced, this mating was of the type  $Cc^dFf \times Cc^aFf$ . Black reds ( $C-F-$ ), black-yellows ( $C-ff$ ) and a light sepia-cream ( $c^dc^aF-$ ) were produced in the earlier litters. There appeared some blacks with cream spotting. It was at first thought likely that these were the desired combination  $c^dc^{aff}$ , but one which was tested by mating with an ordinary dilute ( $c^dc^dFF$ ) gave intense young, proving that it was  $C-ff$ , although with more dilution of yellow than had been encountered up to that time. The effect of factor  $f$  has in fact proved to be rather variable, as may be seen from table 6. Meanwhile, this mating gave 3 light or medium sepias, which were brindled with *white*, giving them the appearance of red-eyed dilute tortoise-shells ( $c^rc^a$ ) except for their black eyes. One of these was tested with an  $ff$  dilute ( $CCff$ ). It produced 14 black-yellow or black-cream young ( $C-ff$ ) proving it to have been of the desired combination. The mating which we have been discussing ( $Cc^dFf \times Cc^aFf$ ) produced altogether 10 black-red ( $C-F-$ ), 6 black-yellow or black-cream ( $C-ff$ ), 1 sepia-cream ( $c^dc^aF-$ ) and 4 sepia-white (3 brindled with white,  $c^dc^{aff}$ , but 1 with merely piebald white and proved by breeding test to be  $c^dc^aF-$ ).

A large number of black-eyed sepias brindled with white have since been produced where  $c^dc^{aff}$  was expected. Black-eyed silver agoutis (each hair sepia with a white instead of red or yellow band) have also been produced in cases where the agouti factor was present. It thus appears that  $ff$  in combination with  $c^dc^a$  reduces cream to white. There have been a few cases, however, in which this reduction was not complete. A white brindled sepia mated with an albino, homozygous in the new dilution factor ( $c^dc^{aff} \times c^ac^{aff}$ ) produced 6 albino young, 6 light sepia-white, 3 silver agoutis of the kind described above, but also 2 light sepias with brindling in which there was clearly a slight creamy tint (grade 1) and 1 silver agouti with a slight creaminess on the nose. The creamy white of these animals was much paler than the cream of ordinary heterozygous dilutes ( $c^dc^aF$ ), which are seldom graded less than 4. As shown in table 6, 69 out of 74 known to be  $c^dc^{aff}$  had white in place of cream, 3 had cream of grade 1, one of grade 2, and one of grade 3. The grade of sepia in these animals (tables 7, 17) was not significantly different from that of  $c^dc^dFF$  (13.9 in place of 14.0). Comparison of  $c^dc^{aff}$  and  $c^dc^aF-$  from the same litter has revealed no consistent difference. These results suggest that factor  $f$  is a diluter of yellow only, a conclusion which, however, it will be seen must be modified in dealing with combination with factor  $p$ .

A number of guineapigs of formula  $c^dc^dFf$  were produced from a mating  $c^dc^dFF \times Cc^dff$ . These were indistinguishable from ordinary homozygous

dilutes  $c^d c^d FF$ . Two of them were mated with each other to produce the combination  $c^d c^d ff$ . The young consisted of 11 medium sepia-yellow like  $c^d c^d F-$  (sepia grade 14 to 17, yellow grade 6 or 7), and 4 medium sepia-pale cream (sepia grade 15 or 16, cream grade 2 or 3). The assumption that the latter were  $c^d c^d ff$  attributes a similar effect to  $ff$  in this combination, as in  $c^d c^d ff$ , that is, further dilution of yellow but no further dilution of sepia. As a breeding test two of those believed to be  $c^d c^d ff$  were mated with an albino, known to be  $c^a c^a ff$  (a segregate from a mating  $Cc^a ff \times Cc^a ff$ ). They produced 23 young, all light to medium sepia and with the white or, in a few cases, the creamy white brindling, characteristic of  $c^d c^d ff$ . The combination  $c^d c^d ff$  has also been produced from mating  $c^d c^d ff \times c^d c^d ff$ . Four such matings produced 6 medium sepia-pale cream ( $c^d c^d ff$ ), 23 light sepia-white ( $c^d c^d ff$ ) and 12 albinos ( $c^a c^a ff$ ). These matings have given a rather curious illustration of the vagaries of dominance. One litter, for example, contained a black-eyed medium sepia (17)—cream (1), a black-eyed light sepia (13)—white (0), and an albino. In this litter, containing the types  $c^d c^d ff$ ,  $c^d c^d ff$  and  $c^a c^a ff$ , respectively, there was complete dominance (at least superficially) of the dark eye color of  $c^d$ , imperfect dominance of  $c^d$  in the sepia parts of the coat and apparently complete dominance of the albino factor  $c^a$  in the cream parts. By a suitable combination of factors ( $ecc^d c^a ff pp$ ) one could produce a strain in which pink-eyed cream would appear as a recessive to albinism, the latter due to a factor  $c^a$ , often cited as the type of a recessive factor.

A stock of medium sepia-pale cream ( $c^d c^d ff$ ) has been developed. These do not differ from  $c^d c^d FF$  in grade of sepia (16.8 in place of 16.9) but are consistently graded 0 to 3 in the cream parts of the fur in place of 6 or 7. The combination  $ecc^d c^d ff$  has been produced in two animals. One was a self colored black-eyed cream, grade 3, while the other was called black-eyed white. As it was born dead and was disposed of before grading it is possible that it was really a very pale cream.

The combination  $c^d c^r ff$  has been bred from a number of matings. Thus, 3 matings of type  $c^d c^r ff \times Cc^r Ff$  have produced 5 black-red ( $Cc^d Ff$ ), 4 black-yellow ( $Cc^d ff$ ), 3 dark sepia-cream ( $c^d c^r Ff$ ) and 6 dark sepia with white or pale cream brindling ( $c^d c^r ff$ ). In all of these dilutes the grades of sepia (18 or 19) have been the same as those most characteristic of  $c^d c^r FF$  but the cream in the latter has been reduced in  $c^d c^r ff$  to white or occasionally very pale cream below the limit of  $c^d c^r FF$ .

Sixteen red-eyed sepia-whites or silver agoutis have been produced from matings which should produce equal numbers of  $c^r c^a ff$  and  $c^r c^a Ff$ . It is reasonably certain that some of these are of the desired combination

$c^r c^a f f$  but this has not yet been proved by an adequate breeding test. From the appearance of these 16 animals and on analogy with the lack of effect of  $f f$  on the sepia of  $c^d c^d$ ,  $c^d c^r$ , and  $c^d c^a$  it is probable that the combination with red-eyed dilution will have no visible effect whatever, since the red-eye factor by itself reduces yellow to white.

The combinations  $c^k c^k f f$  and  $c^k c^a f f$  have been made in a few animals, nearly all silver (or very pale cream) agoutis. Here again factor  $f$  appears to have no effect on intensity of sepia but to reduce yellow ( $c^k c^k$ ) and cream ( $c^k c^a$ ) to very pale cream and white, respectively. The interpretation of the crosses involving  $c^k$  and  $f$  is complicated by the fact that the two types of dilutes  $c^k c^k F F$  and  $C C f f$  are both black-yellows and virtually indistinguishable in appearance.<sup>3</sup> In the former there is undoubtedly a slight tendency to dilution of black, absent in the latter, but the difference is not enough to give a safe criterion for distinguishing animals which may be of either type.

TABLE 6

Distribution of grades of yellow in animals of constitution  $f f$  and of different known constitution relative to the albino series.

| GENETIC<br>CONSTITUTION | GRADE OF YELLOW $f f$ |            |    |       |   |    |        |     |    |     | NUMBER | MEAN | $\sigma$ |
|-------------------------|-----------------------|------------|----|-------|---|----|--------|-----|----|-----|--------|------|----------|
|                         | WHITE                 | Pale cream |    | Cream |   |    | Yellow |     |    | Red |        |      |          |
|                         |                       | 0          | 1  | 2     | 3 | 4  | 5      | 6   | 7  |     |        |      |          |
| $C -$                   |                       |            |    | 1     | 2 | 20 | 33     | 186 | 18 | 2   | 262    | 6.77 | 0.76     |
| $c^k c^k$               |                       | 4          | 1  |       |   |    |        |     |    |     | 5      | 1.20 | 0.40     |
| $c^k c^a$               | 21                    |            |    |       |   |    |        |     |    |     | 21     | 0.00 | 0.00     |
| $c^d c^d$               | 9                     | 34         | 30 | 16    |   |    |        |     |    |     | 89     | 1.60 | 0.89     |
| $c^d c^r$               | 8                     |            | 1  |       |   |    |        |     |    |     | 9      | 0.22 | 0.63     |
| $c^d c^a$               | 69                    | 3          | 1  | 1     |   |    |        |     |    |     | 74     | 0.11 | 0.45     |
| $c^r c^r$               | 1                     |            |    |       |   |    |        |     |    |     | 1      | 0.00 | 0.00     |
| $c^r c^a$               | X                     |            |    |       |   |    |        |     |    |     | X      | 0.00 | 0.00     |
| $c^a c^a$               | X                     |            |    |       |   |    |        |     |    |     | X      | 0.00 | 0.00     |

The effects of  $f f$  on the albino series compounds in graded animals is given in tables 6 and 7 with averages in the appropriate columns in tables 17 and 18. The general conclusion already suggested, that  $f f$  has no visible effect on grades of sepia but greatly reduces yellow pigmentation is

<sup>3</sup> The appearance at birth and up to 2 or 3 months of age is here referred to. Later in life the two varieties may readily be distinguished by the persistence of the yellow color of  $c^k c^k F F$ , but fading of that of  $C C f f$  to a cream or even white.



combinations made are a brown-yellow,  $C\text{-}ffbb$ , and a brown-pale cream,  $c^d c^d ffbb$ . The brown parts showed ordinary brown grades, 16 and 15, respectively, which are typical of browns  $C\text{-}FFbb$  and  $c^d c^d FFbb$ . A number of less certain cases tend to confirm the view indicated by these two cases that factor  $f$  has no effect on the intensity or quality of brown in albino series compounds.

#### COMBINATIONS OF FACTORS $f$ AND $p$

Matings between black-yellows ( $CCffPP$  and  $Cc^d ffPP$ ) and animals from a pink-eyed, pale sepia-yellow stock ( $c^d c^d FFpp$ ) resulted in black-eyed, black-reds ( $Cc^d FfPp$ ) and black-eyed medium sepia-yellows ( $c^d c^d FfPp$ ). A rather extensive 3-factor  $F_2$  generation was bred ( $Cc^d FfPp \times Cc^d FfPp$ ) and also a considerable number from 4 matings of type ( $Cc^d FfPp \times c^d c^d FfPp$ ) (table 8). Two new color varieties appeared, namely, a mosaic of pale cream and yellow with pink eyes, and a pink-eyed nearly self white variety usually with small amounts of pale cream in the fur. Breeding tests demonstrated that these were the desired combinations  $C\text{-}ffpp$  and  $c^d c^d ffpp$ . As neither showed any trace of sepia in the fur it becomes necessary to suppose that  $ff$  in combination with  $pp$  has an effect on black, contrary to the expectation based on the combinations of  $ff$  discussed earlier. This effect seems to be one of complete elimination, permitting an underlying pale cream (in  $C\text{-}ffpp$ ) to reveal itself. The latter seems to be as pure a cream as that in  $ecc^d c^d ffPP$ , from which indeed it is virtually indistinguishable in grade of intensity.

It was not clear at first whether the pale cream or the yellow areas in the mosaics were to be considered as representing the "black" portion of the tortoise-shell pattern. The production of agoutis of composition  $A\text{-}C\text{-}ffpp$  settled the matter. In these, each agouti hair was pale cream or white with a yellow subterminal band indicating that the former colors represented black and the latter red. The reduction of red merely to yellow in  $C\text{-}ffpp$  as in  $CffPP$  is in harmony with the absence of effect of  $p$  on yellow pigmentation. In the pink-eyed pale cream and white variety found to be of constitution  $c^d c^d ffpp$ , it appears that the white represents the black of the tortoise-shell pattern and the pale cream the red parts.

A stock consisting of pink-eyed cream-yellow mosaics and pink-eyed white-pale creams was produced from  $F_3$  matings. One of the  $F_2$  and two of the  $F_3$  pink-eyed cream-yellows were tested by mating with stock pink-eyed pale sepia-yellows ( $c^d c^d FFpp$ ). In each case intense young with red in the fur were produced proving that the tested animals carried factor  $C$  and were therefore of composition  $C\text{-}ffpp$ . An apparent pink-eyed white

from  $c^d c^d Ffpp \times Cc^d ffpp$  was mated with a medium sepia-pale cream ( $c^d c^d ffPP$ ) and produced 5 young all like the medium sepia-pale cream parent in harmony with the hypothesis that it was  $c^d c^d ffpp$ .

TABLE 9  
The segregation in  $F_2$  following matings of type  $CCffPP \times c^c c^c FFpp$ .

| FUR COLOR     |                | EYE COLOR | GENETIC CONSTITUTION | $C^c FfPp \times C^c FfPp$ |            |
|---------------|----------------|-----------|----------------------|----------------------------|------------|
| "Black" areas | "Yellow" areas |           |                      | Observed                   | Calculated |
| Black         | Red            | Black     | $CFP$                | 15                         | 11.0       |
| Dark Sepia    | White          | Red       | $c^c c^c FP$         | 1*                         | 3.7        |
| Black         | Yellow         | Black     | $CffP$               | 3                          | 3.7        |
| Pale Sepia    | Red            | Pink      | $CFpp$               | 1                          | 3.7        |
| Dark Sepia    | White          | Red       | $c^c c^c ffP$        | 1*                         | 1.2        |
| Pale Sepia    | White          | Pink      | $c^c c^c Fpp$        | 2                          | 1.2        |
| Pale Cream    | Yellow         | Pink      | $Cffpp$              | 2                          | 1.2        |
| White         | White          | Pink      | $c^c c^c fpp$        | 1                          | 0.4        |
|               |                |           |                      | 26                         | 26.1       |

\* As  $c^c c^c FP$  and  $c^c c^c ffP$  are indistinguishable, the two red-eyed dark sepia-white young from this mating may have been either of these types.

A mating of type  $c^r c^r FFpp \times CCffPP$  (table 9) gave the basis for three-factor  $F_2$  matings in which  $c^r$  took the place of  $c^d$  in the matings discussed above. One of these matings produced in  $F_2$  an apparent albino which, however, must have been of constitution  $c^r c^r ffpp$ , indicating that  $ff$  combined with  $pp$  eliminates black in a variety in which yellow is eliminated by  $c^r c^r$ . Two red-eyed medium sepia-whites were produced which may have been either  $c^r c^r FP$  or  $c^r c^r ffP$ . The appearance of two pink-eyed cream-yellows confirmed the view that these are of constitution  $Cffpp$ .

TABLE 10  
Distribution of grades of cream (in place of sepia) in animals of constitutions  $ffppB$  and of different known constitutions relative to the albino series.

| GENETIC CONSTITUTION | CREAM IN PLACE OF SEPIA $ffppB$ |            |   |       |   | NUMBER | MEAN | $\sigma$ |
|----------------------|---------------------------------|------------|---|-------|---|--------|------|----------|
|                      | WHITE                           | Pale cream |   | Cream |   |        |      |          |
|                      |                                 | 0          | 1 | 2     | 3 |        |      |          |
| $C-$                 |                                 | 4          | 4 | 4     | 1 | 13     | 2.15 | 0.95     |
| $c^d c^d$            | 16                              |            |   |       |   | 16     | 0.00 | 0.00     |
| $c^r c^r$            | 1                               |            |   |       |   | 1      | 0.00 | 0.00     |

The close similarity of the intensity of the pale cream ( $e^p e^p c^d c^d ffpp$ ) (grade 1.6) representing the yellow parts of the tortoise-shell pattern and



of that of  $e^{pe}C-ffpp$  (grade 2.2) representing the *black* parts indicates the possibility of a rather peculiar two factor ratio. There can be no reasonable doubt that both  $eec^dc^dffpp$  and  $EECCffpp$  would be pink-eyed pale creams of about grade 2. True breeding stocks of the two sorts should be indistinguishable. Crosses yielding pink-eyed pale creams of type  $EeCc^dffpp$  would give no indication of a genetic difference. In  $F_2$ , however, one would expect a 3:10:3 ratio of yellows ( $eeC-$ ), pale creams ( $E-C-$  and  $eec^dc^d$ ) and whites ( $E-c^dc^d$ ), all pink-eyed.

TABLE 11

*Distribution of grades of yellow in animals of constitution Ff and of different known constitutions relative to the albino series.*

| GENETIC<br>CONSTITUTION | WHITE | GRADE OF YELLOW Ff |   |       |    |   |        |    |   |     |     |    |    | NUMBER | MEAN | $\sigma$ |
|-------------------------|-------|--------------------|---|-------|----|---|--------|----|---|-----|-----|----|----|--------|------|----------|
|                         |       | Pale Cream         |   | Cream |    |   | Yellow |    |   | Red |     |    |    |        |      |          |
|                         |       | 0                  | 1 | 2     | 3  | 4 | 5      | 6  | 7 | 8   | 9   | 10 | 11 |        |      |          |
| $C-$<br>$c^kca$         |       |                    |   |       |    |   |        |    | 2 | 40  | 220 | 15 | 3  | 280    | 9.92 | 0.50     |
|                         |       |                    |   |       | 6  | 1 |        |    |   |     |     |    |    | 7      | 4.14 | 0.35     |
| $c^dc^d$                |       |                    |   |       | 2  | 1 | 9      | 14 | 2 |     |     |    |    | 28     | 6.46 | 0.96     |
| $c^dc^r$                |       |                    |   | 1     | 12 | 3 |        |    |   |     |     |    |    | 16     | 4.13 | 0.47     |
| $c^dc^a$                |       |                    |   | 1     | 13 | 7 |        |    |   |     |     |    |    | 21     | 4.29 | 0.54     |
| $c^rc^r$                | X     |                    |   |       |    |   |        |    |   |     |     |    |    | X      | 0.00 | 0.00     |
| $c^rc^a$                | X     |                    |   |       |    |   |        |    |   |     |     |    |    | X      | 0.00 | 0.00     |
| $c^ac^a$                | X     |                    |   |       |    |   |        |    |   |     |     |    |    | X      | 0.00 | 0.00     |

IMPERFECT DOMINANCE OF  $f$ 

In the majority of cases, heterozygotes ( $Ff$ ) are indistinguishable from homozygous ( $FF$ ) litter mates. This applies to all albino series compounds examined. The averages (table 11), however, indicate that dominance is not quite perfect. In the case of  $C-Ff$  the average is 9.9 compared with 10.6 for  $C-FF$  and in the case of  $c^dc^dFf$  an average of 6.5 is to be compared with one of 7.0 for  $c^dc^dFF$  (table 16). The numbers are smaller in the other cases and the differences not consistent. The stocks involved are so nearly the same that the significant difference indicated by the probable errors in these cases apparently can only be due to imperfect dominance. In the first of these cases, grade 9 is very uncommon in homozygotes, but in heterozygotes 40 out of 280 were assigned this grade while 2 others were actually assigned grade 8 a "yellow" rather than a "red." On the other hand, a number of heterozygotes were assigned grades of 11 and 12, indicating that there is no necessary dilution.

There is also evidence (table 12) for imperfect dominance in the effect on black in the presence of factor  $pp$ . The sepia of stock pink-eyed pale sepia-yellows ( $c^d c^d pp FF$ ) is always markedly distinct from yellow of any grade of intensity. The pink-eyed pale sepia yellows which appeared in the 3-factor  $F_2$  matings, discussed above, were not nevertheless always easy to distinguish from the pink-eyed cream-yellows. The sepia parts of many were of a creamy color differing from the cream of the latter only in a slight sootiness. The two varieties were, of course, easily distinguished

TABLE 12

*Distribution of grades of pale sepia in animals of constitutions  $FfppBB$  and of different known constitutions relative to the albino series.*

| GENETIC CONSTITUTION | GRADE OF PALE SEPIA (YELLOWISH) $FfppBB$ |   |   |   |   |   |   |   |   |   |    |    | NUMBER | MEAN | $\sigma$ |      |
|----------------------|--|---|---|---|---|---|---|---|---|---|----|----|--------|------|----------|------|
|                      | WHITE<br>0                               | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |        |      |          | 12   |
| $C-$                 |  |   |   |   |   | 3 | 0 | 6 | 6 | 3 | 2  |    |        | 20   | 7.60     | 1.43 |
| $c^d c^d$            |  |   | 1 | 4 | 5 |   |   |   |   |   |    |    |        | 10   | 3.40     | 0.66 |
| $c^d c^r$            |  |   | 1 |   | 1 |   |   |   |   |   |    |    |        | 2    | 3.00     | 1.00 |

by breeding tests designed to reveal the presence of factor  $C$  or of factor  $F$ . The average grade of sepia in  $c^d c^d FF pp$  is 4.9, in  $c^d c^d Ff pp$  was 3.4, still on the sepia scale but so close to cream (of slightly higher grade) as to be difficult to grade. The average grade of sepia in  $C-FF pp$  was 9.7, with a strongly slaty quality, the average grade of sepia in  $C-Ff pp$  was 7.6 and much browner in quality, the average grade of cream representing sepia in  $C-ff pp$  was 2.2.

ABSENCE OF LINKAGE

The results shown in tables 8 and 9, combined in table 13, are so close to the expected ratios that it seems reasonably certain that there is no linkage between any two of the three factors  $c^d$ ,  $f$  and  $p$ .

It may be added that fairly extensive data indicate that there is no linkage among the factors  $s$ ,  $e^p$ ,  $a$ ,  $c^k$ ,  $p$  and  $b$  and that  $f$  at least crosses over freely with  $s$ ,  $e^p$ ,  $a$  and  $b$  as well as with  $c^d$  and  $p$ .

ENVIRONMENTAL EFFECTS

In addition to the genetic factors which affect intensity and quality of color, there are environmental ones which may be considered here briefly. The sepia parts of the fur in all of the albino series compounds become darker as the animal grows older, often becoming a dark sepia or black. This effect is especially marked in red-eyed sepias. Even albinos develop

TABLE 13

Combination of data in tables 8 and 9 bringing out the approach of the observed results to those calculated, on the assumption of no linkage among factors  $c^d$ ,  $f$  and  $p$ . The probability from  $X^2(=2.56)$  is .95 of getting as poor a fit by chance.

|          | GRAND TOTAL |            |
|----------|-------------|------------|
|          | Observed    | Calculated |
| $CFP$    | 88          | 91.4       |
| $ccFP$   | $43 \pm 1$  | 44.7       |
| $CffP$   | 37          | 30.5       |
| $CFpp$   | 30          | 30.5       |
| $ccffP$  | $17 \mp 1$  | 14.9       |
| $ccFpp$  | 15          | 14.9       |
| $Cffpp$  | 8           | 10.2       |
| $ccffpp$ | 4           | 5.0        |
|          | 242         | 242.1      |

black pigmentation in the exposed parts of the skin and often enough sootiness on the back to make it possible to distinguish a piebald or white tortoise-shell pattern. Red or yellow parts of the fur, on the contrary, do not ordinarily change in intensity to any appreciable extent unless factor  $f$  is present. The only case of a change which the writer has noted, in a stock in which factor  $F$  was present, was in a particular inbred family no. 18, in which animals genetically dilutes,  $c^k c^k$ , were reddish yellow (between grades 8 and 9) at birth, and later changed to an ordinary yellow (grade 7). While the yellow itself does not ordinarily change a black sootiness usually appears in yellow spots with age, especially in the cream or white spots which represent the yellow portion of a tortoise-shell pattern.

With factor  $f$  present, sepia darkens as described above, but yellow becomes markedly paler. Yellow of grade 7 or 8 ( $Cff$ ) fades to cream of grade 3 or 4, or even to sooty white. Pale creams of grade 1 to 3 ( $c^{kd} c^{kd} ff$ ), fade to sooty white. Browns ( $bb$ ) darken slightly with age but much less conspicuously than sepias. The pale sepias found with factor  $p$  on the other hand usually become distinctly paler and in some cases creamier with age.

These effects are accentuated by pulling or cutting the hair and thus exposing the skin to cold. The results of a considerable number of experiments in which a patch of hair was plucked from animals, in most cases a few days after birth, are summarized in tables 14 and 15. In the case of sepias and even blacks, the spot of new hair stood out distinctly after two or three weeks because of its darker color. The greatest effect was obtained

in 4 red-eyed medium sepias in which the new hair came out nearly 5 grades darker, practically intense black. The effect was marked, however, in all cases in which the hair was not nearly black to begin with. A spot of grade 5 was brought out in one albino and a slight tinge of sepia in

TABLE 14  
Summary of experiments on the change of color of sepia hair following the plucking of an area.

|                        | FORMULA                              | COLOR OF NEW HAIR |                |                | AVERAGE GRADE |          | CHANGE IN GRADE |
|------------------------|--------------------------------------|-------------------|----------------|----------------|---------------|----------|-----------------|
|                        |                                      | Lighter           | No change      | Darker         | Unplucked     | New hair |                 |
| Black                  | <i>C</i>                             | ..                | ..             | 2              | 21.0          | 21+      | +               |
| Dark sepia             | <i>c<sup>k</sup>c<sup>a</sup></i>    | ..                | ..             | 2              | 18.0          | 20.5     | +2.5            |
| Medium sepia           | <i>c<sup>d</sup>c<sup>a</sup></i>    | ..                | ..             | 9              | 15.8          | 18.7     | +2.9            |
| Light sepia            | <i>c<sup>d</sup>c<sup>a</sup></i>    | ..                | ..             | 11             | 13.9          | 16.8     | +2.9            |
| Dark sepia (red eye)   | <i>c<sup>c</sup>c<sup>r</sup></i>    | ..                | ..             | 2              | 20.5          | 21.0     | +0.5            |
| Medium sepia (red eye) | <i>c<sup>c</sup>c<sup>a</sup></i>    | ..                | ..             | 4              | 16.0          | 20.7     | +4.7            |
| White (albino)         | <i>c<sup>c</sup>c<sup>a</sup></i>    | ..                | 4              | 2 <sup>1</sup> | 0.0           |          | +               |
| Pale sepia (pink eye)  | <i>C pp</i>                          | 1                 | 2 <sup>2</sup> | ..             | 7.0           | 6.0      | -0.0            |
| " " " "                | <i>c<sup>k</sup>c<sup>k</sup> pp</i> | 6                 | ..             | ..             | 8.7           | 4.3      | -4.4            |
| " " " "                | <i>c<sup>k</sup>c<sup>d</sup> pp</i> | 3                 | ..             | ..             | 7.3           | 5.7      | -1.6            |
| " " " "                | <i>c<sup>k</sup>c<sup>r</sup> pp</i> | 1                 | ..             | 1              | 7.0           | 7.0      | 0.0             |
| " " " "                | <i>c<sup>d</sup>c<sup>d</sup> pp</i> | 6                 | ..             | ..             | 5.2           | 1.3      | -3.9            |
| " " " "                | <i>c<sup>d</sup>c<sup>a</sup> pp</i> | 2 <sup>3</sup>    | ..             | ..             | ..            | ..       | ..              |
| " " " "                | <i>c<sup>c</sup>c<sup>r</sup> pp</i> | ..                | ..             | 1              | ..            | ..       | +               |
| Brown                  | <i>bb</i>                            | ..                | 3              | 5              | 14.0          | 15.0     | +1.0            |
| Pale brown (pink eye)  | <i>bbpp</i>                          | 2                 | 4              | ..             | 5.5           | 5.0      | -0.5            |

<sup>1</sup> One became Grade 5, the other Grade 1.  
<sup>2</sup> Includes an old animal already faded to Grade 2.  
<sup>3</sup> In these, pale sepia was replaced by a nearly pure cream.

another. No sepia appeared in 4 other albinos but the plucked hair may have come from a piebald area in which cold never brings out pigmentation.

Plucked areas in browns of various sorts developed hair which was in general darker than the surrounding hair. The difference was barely perceptible, however.

In pink-eyed pale sepias, the new hair was distinctly lighter than the surrounding hair in 19 cases, showed no contrast in 2 cases and seemed slightly darker in 2 cases. In a few cases it had a distinctly creamy hue.

In experiments on yellow and agouti areas, there was a lightening of the color where any change was perceptible. The effect was much more distinct with agouti than with clear yellow. Ten red agoutis had sharply

distinct yellow agouti (or light red agouti) spots after the new hair had grown. The effect was less marked in yellow agoutis and noticed in only one of three cream agoutis. Plucking did not bring out any yellow in the white brindles spots of red-eyed sepias, but did bring out sepia sootiness in two of three animals tested.

TABLE 15

Summary of experiments on the change of color of agouti and yellow hair following the plucking of an area.

|                   | Formula         | COLOR OF NEW HAIR |                |        | AVERAGE GRADE |          | CHANGE<br>IN<br>GRADE |
|-------------------|-----------------|-------------------|----------------|--------|---------------|----------|-----------------------|
|                   |                 | Lighter           | No<br>change   | Darker | Unplucked     | New hair |                       |
| Agouti (red band) | $C$             | 10                | ..             | ..     | 11.0          | 7.7      | -2.3                  |
| Yellow agouti     | $c^k c^k$       | 5                 | 2              | ..     | 7.0           | 5.6      | -1.4                  |
| Cream agouti      | $c^k c^a$       | 1                 | 2              | ..     | ..            | ..       | ..                    |
| Red               | $C$             | 4                 | 2              | ..     | 11.0          | 10.0     | -1.0                  |
| Yellow            | $c^{kd} c^{kd}$ | 2                 | 4              | ..     | 7.0           | 6.3      | -0.7                  |
| Cream             | $c^{kd} c^a$    | ..                | 2              | ..     | 5.0           | 5.0      | 0.0                   |
| White (tortoise)  | $c^r c^r a$     | ..                | 3 <sup>1</sup> | ..     | 0.0           | 0.0      | 0.0                   |
| Yellow agouti     | $C_{ff}$        | 2                 | ..             | ..     | ..            | ..       | ..                    |
| Yellow            | $C_{ff}$        | 3 <sup>2</sup>    | 1              | ..     | ..            | ..       | ..                    |

<sup>1</sup> No yellow appeared, but in two cases marked sootiness developed.

<sup>2</sup> Whole fur changed to cream with spot leaving no contrast.

In yellow agoutis and yellows in which the dilution of color is due to  $ff$ , the whole fur fades in about two months. Plucking, however, usually brings out a contrasting spot.

In all of these cases the contrasting spot disappears after several months when all of the fur has been replaced.

The experiments described above were carried on throughout most of a year (January to October). Marked effects were obtained in summer months as well as in winter months, indicating that no great fall in skin temperature is necessary.

That the pigmentation which develops in the naturally exposed parts of the skin of albino guineapigs and in parts from which the hair has been removed are due to cold rather than to some other stimulus is probable from the experiments of SCHULTZ (1922) and ILJIN (1926a) with albino guineapigs as well as from the experiments of SCHULTZ (1918), LENZ (1923), KAUFMAN (1925) and ILJIN (1926b) in the similar case of the Himalayan rabbit. It is also probable that the development of black sootiness in tortoise-shell spots in guineapigs is comparable to the blackening of the sooty yellow (or Thuringian) rabbit which SCHULTZ (1922) has also shown to be due to cold.

The variation in grade of color at birth among animals of the same factorial composition, as far as known, seems to be largely non-genetic in origin. A portion must be attributed to variations in judgment of colors, but this can only rarely account for differences of more than one grade among individuals. The standard deviations are given in the last columns of the tables which present the distributions, and are averaged by groups in table 16.

It will be noticed that the effects of the environmental factor cold (to which the ordinary age effect is probably due) are more complex than

TABLE 16

*Averages of standard deviations of classes whose distributions are given in tables 3 to 7 and 10 to 12 of this paper and tables 11 and 12 of the preceding (Wright, 1925). The groupings by mean grade and constitution are those which seem of most significance. These averages have been used in calculating probable errors.*

| CLASSES (BY MEAN GRADE AND CONSTITUTION) |         |   | NUMBER CLASSES | NUMBER ANIMALS | AVERAGE |
|--|---------|---|----------------|----------------|---------|
| Black                                    | (21)    | (C-ffP)   | 1              | 151            | 0.32    |
| Dark sepia                               | (18-20) | (P)   | 7              | 605            | 0.80    |
| Medium sepia                             | (11-18) | (P)   | 5              | 634            | 1.26    |
| Pale sepia                               | (4-11)  | (pp)  | 8              | 345            | 1.07    |
| Very pale sepia                          | (0-4)   | (pp)  | 4              | 84             | 0.75    |
| Brown                                    | (11-18) | (P)   | 10             | 539            | 1.03    |
| Pale brown                               | (4-11)  | (pp)  | 6              | 345            | 0.83    |
| Very pale brown                          | (0-4)   | (pp)  | 4              | 54             | 0.70    |
| Red                                      | (9-13)  |   | 2              | 519            | 0.57    |
| Yellow                                   | (6-8)   | FF  | 3              | 176            | 0.50    |
| "  | "       | C-ff, c <sup>d</sup> c <sup>d</sup> Ff          | 2              | 290            | 0.78    |
| Cream                                    | (3-6)   | c <sup>k</sup> c <sup>r</sup> a FF              | 2              | 251            | 0.71    |
| "  | "       | c <sup>d</sup> c <sup>r</sup> a FF              | 2              | 383            | 0.44    |
| "  | "       | c <sup>k</sup> d <sup>c</sup> r <sup>a</sup> Ff | 3              | 44             | 0.48    |
| Pale cream                               | (1-3)   | ff  | 3              | 107            | 0.87    |
| Creamy white                             | (0-1)   | ff  | 3              | 104            | 0.38    |

those of any genetic factor, even *f*, which we have considered. It affects the sepias with *P* present and those with *p* in opposite directions. It accentuates the dilution effect of *f* on yellow. It dilutes yellow markedly in agouti hairs but only slightly if at all in non-agouti hairs. The indication is that temperature affects in one way or another many independent processes which have to do with pigment production, while the genetic factors are more specific, each affecting only one or at most only a very few processes.

## DISCUSSION

In attempting to analyze the physiological workings of genetic factors, we must distinguish between primary and secondary effects. It must be supposed that there are one or more conditions in the cells of a developing organism under which each gene has some immediate physiological action. The smallness of genes and their persistence has suggested to many (MOORE 1910, GOLDSCHMIDT 1916, TROLLAND 1917, and others) that in this action the genes must behave as enzymes. The primary products themselves become factors in later developmental processes and so on in ever widening circles. Through the mediation of the circulatory system, nervous system, as well as through mechanical influences, a single primary gene action may ultimately have effects on the most diverse characters. It is to be expected that the relation between factor and character will ordinarily be found to involve a great many steps. There is some reason to believe, however, that the relation is relatively close in the case of melanin pigmentation.

The melanin pigments are amorphous, organic compounds containing nitrogen, the exact chemical constitutions of which are as yet unknown. The generally accepted theory as to their origin traces to the work of BERTRAND in 1896, who was able to extract an oxidizing enzyme from plant tissues which converted tyrosin into a substance resembling the natural melanins in its properties. Tyrosinase has since been demonstrated in the tissues of many invertebrates by a considerable number of investigators. As to vertebrates, DURHAM (1904) obtained indication of tyrosinase in the skin of colored guinea pigs. H. ONSLOW (1915) was unable to confirm her results by the same method but obtained a dark melanin-like substance by adding tyrosin and hydrogen peroxide to a colorless extract from the skin of young black rabbits. He was unable to extract such a peroxidase from white skin, whether from albinos or white spotted animals, or from the skins of yellow rabbits. The extracts in these three cases did not prevent the reaction when added to extracts from black rabbits. The reaction was, however, inhibited by extracts from the skin of dominant whites (English rabbits) or from the white belly of rabbits with the dominant agouti pattern. KAUFMANN (1925) has confirmed ONSLOW to the extent of never being able to extract tyrosinase from albino rabbits while usually obtaining positive, although slight reactions, from extracts from black rabbits.

SCHULTZ (1925) has also obtained evidence of enzyme differences in skins of rabbits of various colors. He obtained a marked blackening of "dopa" (dioxypheynylalanin), a substance more easily blackened than

tyrosin (p-monoxyphenylalanin) in frozen sections of the skin of black rabbits, a weaker *blackening* in the case of brown rabbits, a still weaker blackening in the case of yellow rabbits, whether recessive or dominant (agouti), and no reaction in the case of either recessive white (albinos, white Viennas, white parts of Dutch rabbits, or Himalayans) or dominant whites (English). The skin of Himalayans stimulated to the production of black pigment by cold, on the other hand, gave strong blackening with dopa and the same was true of sooty yellow stimulated to black production by cold. Because of the *blackening* of brown skin, he believes that dopa cannot be the actual chromogen in these cases but merely that its blackening indicates the degree of activity of enzymes which in nature oxidize a closely related chromogen.

While tyrosin has long been considered the most probable chromogen in the vertebrate skin, the question is still open. Its presence has been demonstrated in invertebrates (v. FÜRTH in PRZIBRAM, DEMBOWSKI and BRECHER 1921). An attempt to demonstrate it in vertebrate skin by SATO and BRECHER (1925) gave negative but inconclusive results. Dopa was suggested as a probable chromogen by BLOCH in 1917. PRZIBRAM (1924 and earlier) has succeeded in demonstrating its presence in the cocoons of certain insects but extensive experiments with fish scales, feathers, hair and skin of many vertebrates by SATO and BRECHER (1925) and BRECHER and WINKLER (1925) seem definitely to rule it out as the vertebrate chromogen. Other substances, more or less related to tyrosin such as adrenalin and tryptophan have been suggested as possible natural chromogens.

There is no agreement as yet as to the details of the enzyme-chromogen reaction even in those cases in which the chromogen is known. MURIEL WHELDAL ONSLOW (1923) finds reason for the suggestion that tyrosinase from plants is a mixture of enzymes including a reductase, a carboxylase, an oxygenase and a peroxidase. Suggestions have been made that the extent to which the reaction proceeds in different cases may be controlled by differences in  $p_H$  (inhibition by acid, PRZIBRAM, DEMBOWSKI and BRECHER 1921) which may in turn be affected by temperature (KAUFMANN 1925) and also that temperature may affect pigment production through the thermolability of certain of the enzyme components (LENZ 1923).

GORTNER (1911, 1912) distinguished between a diffuse pigment characteristic of red or reddish brown hair, soluble in dilute acid and containing no ash, and granular pigment from black hair (rabbit, etc.) insoluble in dilute acid and leaving 2 or 3 percent ash, chiefly iron oxide. The



relation between the enzyme differences of ONSLOW and SCHULTZ and this presence or absence of iron is an interesting question.

Most of the earlier authors believed that melanin pigment was formed in the nucleus of cells and extruded into the cytoplasm. According to HOOKER (1915) pigment is formed in the cytoplasm, especially in the immediate vicinity of the nucleus and presumably under the influence of oxidases from the latter. That the surface of contact between nucleus and cytoplasm is the chief region of intracellular oxidation had previously been demonstrated for a variety of types of living cells by R. S. LILLIE (1902). RÉNYI (1924) strongly confirms the view that pigment is formed in special bodies in the cytoplasm and finds that these bodies (Pigmentbildner) have all the staining properties of mitochondria and can be traced step by step from undoubted mitochondria. It is interesting to note that he finds Pigmentbildner in white as well as colored skin. This is in harmony with the view that the essential difference in this case is in the nuclear rather than the cytoplasmic component.

Experiments on the transplantation of skin have in general indicated autonomy in the pigment producing cells (CARNOT and DEFLANDRE 1896, LEO LOEB 1897). That there may also be diffusible components is, however, suggested by KOPPÁNYI'S (1923) experiments in which he found a development of pigmentation in the eyes of albino axolotls transplanted to pigmented hosts. Cell autonomy with regard to the effects of factors *A*, *C*, *F* and *P* in the guinea pig is indicated by the persistence of mutant spots (WRIGHT and EATON 1926). There is, of course, no necessary contradiction between cell autonomy with respect to the effects of some factors and diffusion of the effects of other factors.

On the whole, the various lines of evidence seem to be converging toward a fairly simple interpretation of the mode of action of the major genetic color factors. The most plausible hypothesis as to the genes themselves seems to be that they are to be looked upon as chemical units not much if at all beyond the size of protein molecules (MORGAN 1922, 1926), arranged in a definite linear order in the chromosomes, and characterized especially by the power of somehow duplicating themselves from the building stones in their medium, following mitosis; of simultaneously separating from these duplicates under the cell condition of mitosis; and of simultaneously attracting their homologues under the conditions of the maturation prophase. As factors in development, the genes apparently behave as catalysts in not being used up themselves by the reaction for which they are responsible. In the case of color production, the effects seem to take place through the mediation of enzymes produced by the

genes in the nucleus but acting upon protein decomposition products related to tyrosin in special bodies (mitochondria) in the cytoplasm of the appropriate cells. These enzymes, actually extractable from the skin of pigmented animals, are not, of course, to be identified with the genes themselves. Their production may or may not be related to the process by which the genes duplicate themselves between cell divisions.

Much must be learned before any such hypothesis ceases to be of a highly speculative nature. In any case, it appears probable that the relation between the major color factors of mammals and the visible color differences is exceptionally simple and worthy of thorough study from the physiological and chemical sides. The effects of the factors in the various combinations reveal a body of facts which must be taken into account in any attempt to trace the steps.<sup>1</sup>

#### RELATIONS OF FACTOR EFFECTS

On the principle of Occam's razor it is desirable to attempt analysis of factor effects by attributing as few primary effects to genes as possible and preferably only a single one. The following suggestions are essentially an analysis of the consequences of the assignment of a single graded series of primary effects as back of the apparently nonlinear effects of the albino series of factors. It will be seen that on this basis each of the factors dealt with here need have only a single point of action on color production with the exception of the gene *F* and the factors sex and temperature.

The first step in analyzing the character melanin pigmentation is the recognition of the two main series of colors, the yellow series and the sepia or black series probably corresponding to GORTNER's two types of melanin. The processes of production clearly have some degree of physiological independence, but not complete independence. Factors with a single primary effect may act (1) on yellow production alone or (2) on sepia production alone (possible examples *B*, *P*) or (3) may determine between yellow and sepia production (possible examples *E*, *A*) or (4) may act upon both sepia and yellow production through a single process antecedent to both (possible examples *C*, *S*).

The peculiar effects of the albino series (*C*, *c<sup>k</sup>*, *c<sup>d</sup>*, *c<sup>r</sup>*, *c<sup>a</sup>*) in the presence of factors *FPB* have been discussed previously. In a general way the series determines differences in quantity, irrespective of quality of pigment, and thus appears to fall in the last of the above classes. The effects of the 5 allelomorphs are not the same, however, for yellow and sepia, or

<sup>1</sup> Since the above was written the writer has had the opportunity of reading *Goldschmidt's* highly illuminating "Physiologische Theorie der Vererbung" (1927). As may readily be seen the present discussion is in harmony with his general viewpoint.

even for sepia in eye and hair. The differences in order of effect on yellow and sepia is brought out here in figures 2 and 6. The average grades of color in these and other combinations are summarized in tables 17, 18 and 19. Factor *C* is a condition for the most intense colors of both series (red and black), factors *c<sup>k</sup>* and *c<sup>d</sup>* determine very nearly the same grade of dilute yellow but widely different intensities of sepia. With factors *c<sup>r</sup>* and *c<sup>a</sup>* no yellow whatever develops but with *c<sup>r</sup>* there is an even more intense sepia than with *c<sup>d</sup>* in the fur (less intense in the eyes), while with

TABLE 17

Average grades of sepia and brown in the indicated combinations of factors from tables 3, 4, 5, and 7, of this paper and table 11 of preceding. Probable errors (.6745  $\sigma/n$ ) based on average standard deviations of table 16.

|                                   | FPB<br>SEPIA | FPbb<br>BROWN | FppB<br>PALE SEPIA | Fppbb<br>PALE BROWN | fPB<br>SEPIA | fPbb<br>BROWN |
|-----------------------------------|--------------|---------------|--------------------|---------------------|--------------|---------------|
| <i>C</i> —                        | 21.00        | 15.63 ± .07   | 9.70 ± .11         | 8.29 ± .21          | 20.91 ± .02  | 16.00 ± .68*  |
| <i>c<sup>k</sup>c<sup>k</sup></i> | 20.10 ± .08  | 14.61 ± .07   | 9.08 ± .08         | 7.22 ± .04          | 19.00 ± .54* |               |
| <i>c<sup>k</sup>c<sup>d</sup></i> | 19.43 ± .10  | 15.37 ± .13   | 7.64 ± .22         | 6.00 ± .18          | ..           |               |
| <i>c<sup>r</sup>c<sup>r</sup></i> | 20.46 ± .06  | 14.76 ± .10   | 7.00 ± .23         | 6.12 ± .07          | ..           |               |
| <i>c<sup>k</sup>c<sup>a</sup></i> | 18.53 ± .03  | 13.60 ± .08   | 5.47 ± .19         | 5.57 ± .11          | 18.00 ± .38  |               |
| <i>c<sup>d</sup>c<sup>d</sup></i> | 16.88 ± .09  | 14.18 ± .08   | 4.88 ± .07         | 5.43 ± .21          | 16.79 ± .12  | 15.00 ± .68*  |
| <i>c<sup>d</sup>c<sup>r</sup></i> | 19.09 ± .05  | 15.00 ± .11   | 4.00 ± .10         | 3.67 ± .27          | 18.56 ± .18  | ..            |
| <i>c<sup>d</sup>c<sup>a</sup></i> | 14.02 ± .05  | 12.46 ± .14   | 2.57 ± .09         | 3.17 ± .19          | 13.91 ± .10  | ..            |
| <i>c<sup>r</sup>c<sup>r</sup></i> | 20.09 ± .07  | 15.47 ± .18   | 2.58 ± .10         | 2.82 ± .12          | ..           |               |
| <i>c<sup>r</sup>c<sup>a</sup></i> | 15.49 ± .07  | 13.06 ± .10   | 0.73 ± .13         | 1.11 ± .09          | ..           |               |
| <i>c<sup>a</sup>c<sup>a</sup></i> | 0.00         | 0.00          | 0.00               | 0.00                | 0.00         | 0.00          |

\* Grade of one individual. Probable error is quartile distance (.6745 $\sigma$ ) for groups of similar average grade.

*c<sup>a</sup>* there is no visible sepia at birth though a small amount develops later in the skin and fur under the influence of cold. It was shown that these irregularities in order could be harmonized with the hypothesis that the albino series determines a graded series of effects in the order *c<sup>a</sup>*, *c<sup>r</sup>*, *c<sup>d</sup>*, *c<sup>k</sup>*, *C* on a *single* process essential to all pigmentation by means of two subsidiary hypotheses.

(1) That there is a different *threshold* of effectiveness of the immediate product of the genes of this series depending on whether the process is to go in the direction of sepia or yellow (as determined by other factors). It was shown that this threshold effect must be considered as applying to the immediate products of the two genes in the zygote *separately* instead of jointly. The difference between the order of intensity of sepia in fur and eyes requires the assumption of different regional thresholds.

TABLE 18

Average grades of yellow in the indicated combination of factors. From tables 6 and 11 of this paper and 12 of preceding. Probable errors based on average standard deviation of table 16.

|                               | FF<br>YELLOW | Fj<br>YELLOW | ff<br>YELLOW |
|-------------------------------|--------------|--------------|--------------|
| C—                            | 10.57 ± .03  | 9.92 ± .02   | 6.77 ± .03   |
| c <sup>k</sup> c <sup>k</sup> | 7.10 ± .05   | ..           | 1.20 ± .26   |
| c <sup>k</sup> c <sup>d</sup> | 7.17 ± .06   | ..           | ..           |
| c <sup>k</sup> c <sup>r</sup> | 4.63 ± .06   | ..           | ..           |
| c <sup>k</sup> c <sup>a</sup> | 4.59 ± .03   | 4.14 ± .12   | 0.00         |
| c <sup>d</sup> c <sup>d</sup> | 6.97 ± .04   | 6.46 ± .10   | 1.60 ± .06   |
| c <sup>d</sup> c <sup>r</sup> | 4.08 ± .03   | 4.13 ± .08   | 0.22 ± .09   |
| c <sup>d</sup> c <sup>a</sup> | 4.16 ± .02   | 4.29 ± .07   | 0.11 ± .03   |
| c <sup>r</sup> c <sup>r</sup> | 0.00         | 0.00         | 0.00         |
| c <sup>r</sup> c <sup>a</sup> | 0.00         | 0.00         | 0.00         |
| c <sup>a</sup> c <sup>a</sup> | 0.00         | 0.00         | 0.00         |

TABLE 19

Average grades of pale sepia or of yellow in the indicated combinations of factors. From tables 4, 12, and 10. Probable error based on average standard deviation of table 16.

|                               | FFppBB<br>PALE SEPIA | FfppBB<br>PALE YELLOW SEPIA | ffppBB<br>CREAM |
|-------------------------------|----------------------|-----------------------------|-----------------|
| C—                            | 9.70 ± 0.11          | 7.60 ± 0.16                 | 2.15 ± 0.16     |
| c <sup>d</sup> c <sup>d</sup> | 4.88 ± 0.07          | 3.40 ± 0.16                 | 0.00            |
| c <sup>d</sup> c <sup>r</sup> | 4.00 ± 0.10          | 3.00 ± 0.36                 | ..              |
| c <sup>r</sup> c <sup>r</sup> | 2.58 ± 0.10          | 0.00                        | 0.00            |

(2) That above this threshold there is competition between the yellow and black processes within those portions of the fur in which the black process goes on.

Superficially, the brown series (*B*, *b*) and the pink-eye series (*P*, *p*) seem to have closely similar effects. Neither has any visible effects whatever in yellow parts of the fur but each modifies sepia wherever it occurs in fur, skin or eyes. The combination with albino series compounds show, nevertheless, that their actions must be fundamentally different. The order of intensity in the fur of these compounds is not altered by replacing *B* by *b*, with minor exceptions which cannot be relied upon (figure 3). The same statement applies to the different order found in the eyes. The eyes of browns have brown irides in *C*, *c<sup>k</sup>*, and *c<sup>d</sup>*, have conspicuously less pigment in *c<sup>r</sup>c<sup>r</sup>* and especially *c<sup>r</sup>c<sup>a</sup>*, and are without pigment (pink) in *c<sup>a</sup>c<sup>a</sup>*. It must be concluded that *b* modifies pigmentation of the sepia series in such a way as not to affect the thresholds of sepia and yellow or the competition between them.

The replacement of  $P$  by  $p$ , on the other hand, alters the order of intensity of sepia of the fur among the different albino series compounds (figure 4). It may be seen that  $c^r$  compounds are decidedly less intense than the  $c^d$  compounds in contrast with the reverse order in the presence of  $P$ . The marked difference between the  $c^k$  and the  $c^d$  compounds and the fact that  $c^r$  produces more pigment than  $c^a$  distinguishes the order from that found in the yellow part of the fur. The different apparent orders of effectiveness of the albino series genes in different genetic backgrounds are illustrated in figure 8 by comparison of the five homozygotes of the albino series. The order found with  $p$  agreeing neither with that of sepia in the presence of  $P$  or with yellow, and only doubtfully with that of eye color in the presence of  $P$ , strengthens the view that the apparently nonlinear effects of the albino series are to be attributed to secondary physiological processes, such as the suggested threshold and competition effects instead of to primary effects of the genes themselves. Specifically, the change in position of the  $c^r$  compounds suggests that  $p$  raises the threshold of sepia from a point close to the gene level of  $c^a$  (below or above depending on temperature) nearly to  $c^r$ , besides greatly weakening the pigment producing powers of the substance involved.

It might be expected that under these conditions the yellow producing process would tend to overwhelm the reduced sepia. Actually, however, there is little difference in quality between the sepias of formula  $CFpB$  and those of formula  $c^d c^a FPB$  or even  $c^r c^a FPB$  which happen to be of the same grade (sepia 11 or 12) although red develops to full intensity in the appropriate regions of the first, only to the cream level in the second, and not all in the third. Indeed the pale slaty appearance of most of the  $p$ -sepias might suggest that there is no competition with yellow at all. The existence of a competition is best shown by the difference in quality of  $c^d p$  combinations in comparison with either  $c^k p$  or  $c^r p$  combinations. The former are, as previously noted, decidedly yellower in appearance. The actual combination of colors necessary to match a number of typical animals of these and other combinations on the color top are given in table 20. It will be seen that the  $c^d p$  combinations require an average of 17 percent yellow where the  $c^k p$  and  $c^r p$  compounds require only about 11 and 13 percent, respectively. The amount of orange is about 7 percent or 8 percent in all of them. The  $c^d p$  combinations are thus intermediate between the other  $p$ -sepias and the creams. These qualitative differences are presented graphically in figure 9. They may be explained on the same basis as the lower intensity of sepia in  $c^d P$  in comparison with  $c^r P$  and  $c^k P$ , that is, that with  $c^d$  present, there is competition with yellow which

is wholly lacking with  $c^r$  and not appreciably greater in  $c^k$  although the power of producing sepia is distinctly stronger in the latter. It must be concluded that in spite of the great reduction in pigment producing power when  $p$  is present, competition with yellow is as effective above the sepia\*

TABLE 20

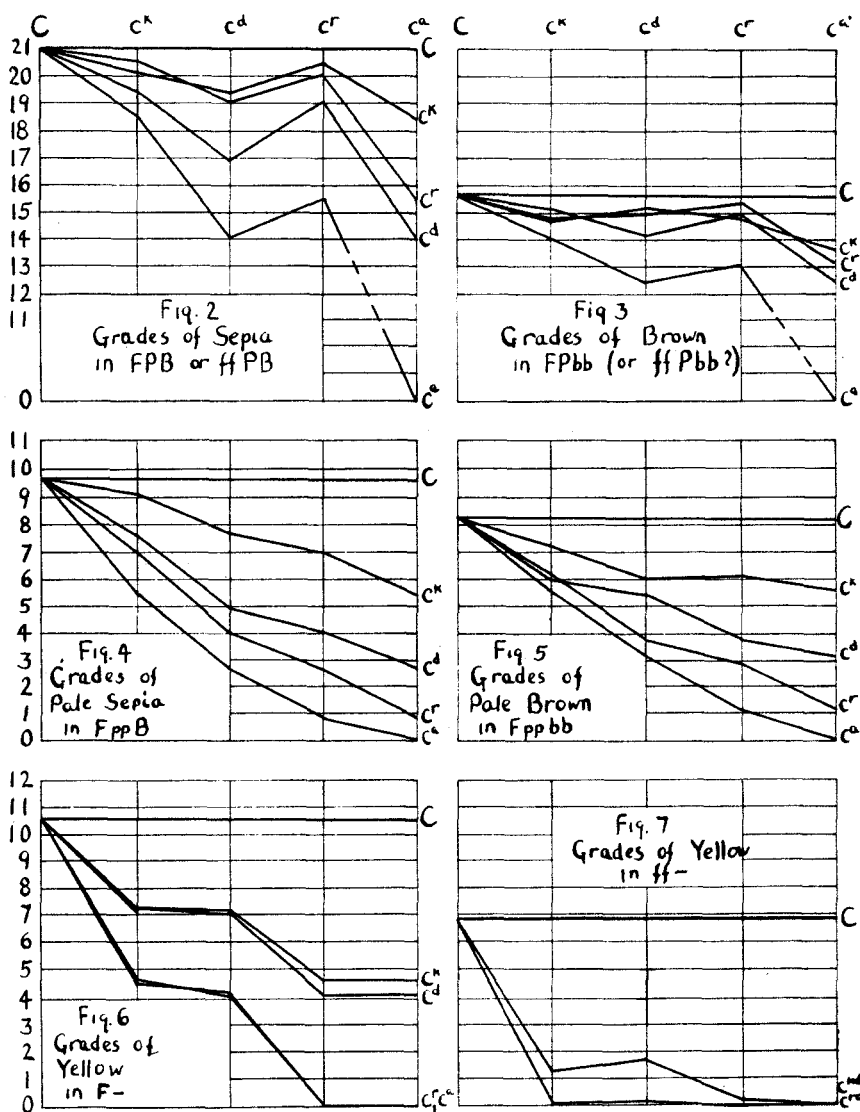
*The proportion of white (W), yellow (Y), orange (O) and black (B) on the Milton Bradley color wheel which matched the sepia or brown of animals of the genetic constitution indicated.*

| GENETIC CONSTITUTION | NUMBER | W    | Y    | O    | B    | Y+O  | $\frac{O}{Y+O}$ |
|----------------------|--------|------|------|------|------|------|-----------------|
| $C-FFp\phi B-$       | 3      | 11.3 | 10.0 | 7.7  | 71.0 | 17.7 | 43.5            |
| $C-$ “               | 5      | 7.2  | 6.4  | 5.0  | 81.4 | 11.4 | 43.9            |
| $c^k c^k$ “          | 5      | 16.6 | 9.8  | 6.6  | 67.0 | 16.4 | 40.2            |
| $c^k c^d$ “          | 2      | 21.5 | 10.5 | 8.5  | 59.5 | 19.0 | 44.7            |
| $c^k c^r$ “          | 3      | 15.0 | 10.7 | 8.0  | 66.3 | 18.7 | 42.8            |
| $c^k c^a$ “          | 6      | 25.7 | 12.3 | 8.0  | 54.0 | 20.3 | 39.4            |
| $c^d c^d$ “          | 7      | 33.3 | 17.9 | 8.1  | 40.7 | 26.0 | 31.2            |
| $c^d c^r$ “          | 5      | 31.4 | 15.8 | 6.4  | 46.4 | 22.2 | 28.8            |
| $c^d c^a$ “          | 1      | 30.0 | 18.0 | 11.0 | 41.0 | 29.0 | 37.9            |
| $c^r c^r$ “          | 3      | 37.0 | 12.0 | 7.3  | 43.7 | 19.3 | 37.8            |
| $C-Ff\phi\phi B-$    | 2      | 17.5 | 13.0 | 8.5  | 61.0 | 21.5 | 39.5            |
| $C-FFp\phi\phi b$    | 4      | 13.2 | 11.8 | 9.7  | 65.3 | 21.5 | 45.1            |
| $c^k c^k$ “          | 4      | 16.8 | 12.0 | 9.7  | 61.5 | 21.7 | 44.7            |
| $c^k c^d$ “          | 4      | 15.0 | 15.5 | 11.0 | 58.5 | 26.5 | 41.5            |
| $c^k c^r$ “          | 3      | 18.3 | 13.0 | 10.3 | 58.3 | 23.3 | 44.2            |
| $c^r c^r$ “          | 1      | 28.0 | 12.0 | 10.0 | 50.0 | 22.0 | 45.5            |

threshold as when  $P$  is present. Summing up,  $p$  has an effect on the sepia process which involves a raising of the threshold, a great reduction in pigment producing power but no reduction in the power of competing with yellow except that due to change of threshold.

It may be noted that combination of  $b$  with  $p$  (figure 5) does not change the order of sepia among the albino series compounds as found with  $Bp$  (figure 4) but in the main merely changes the quality. This confirms the view that  $b$  has a modifying influence which is independent of the threshold and competition effects.

The most conspicuous effect of factor  $f$  is the reduction of intensity of yellow. The sequence of albino series compounds is unaltered as far as



FIGURES 2-7.—The average grades of fur color found with each combination of factors of the series  $F$ ,  $P$  and  $B$  with different combinations in the albino series. Each line in each graph represents the grades found when the albino series gene at the right end of the line in question is combined successively with the albino series genes at the top of the figures.

FIGURE 2.—Grades of sepia in  $FPB$ . There is no significant difference in  $ffPB$ .

FIGURE 3.—Grades of brown in  $FPbb$ . Probably no difference in  $ffPbb$ .

FIGURE 4.—Grades of pale sepia in  $FppB$ .

FIGURE 5.—Grades of pale brown in  $Fppbb$ .

FIGURE 6.—Grades of yellow in  $FF$ .

FIGURE 7.—Grades of yellow in  $ff$ . Combinations  $c^k c^d$ ,  $c^k c^r$  not produced.

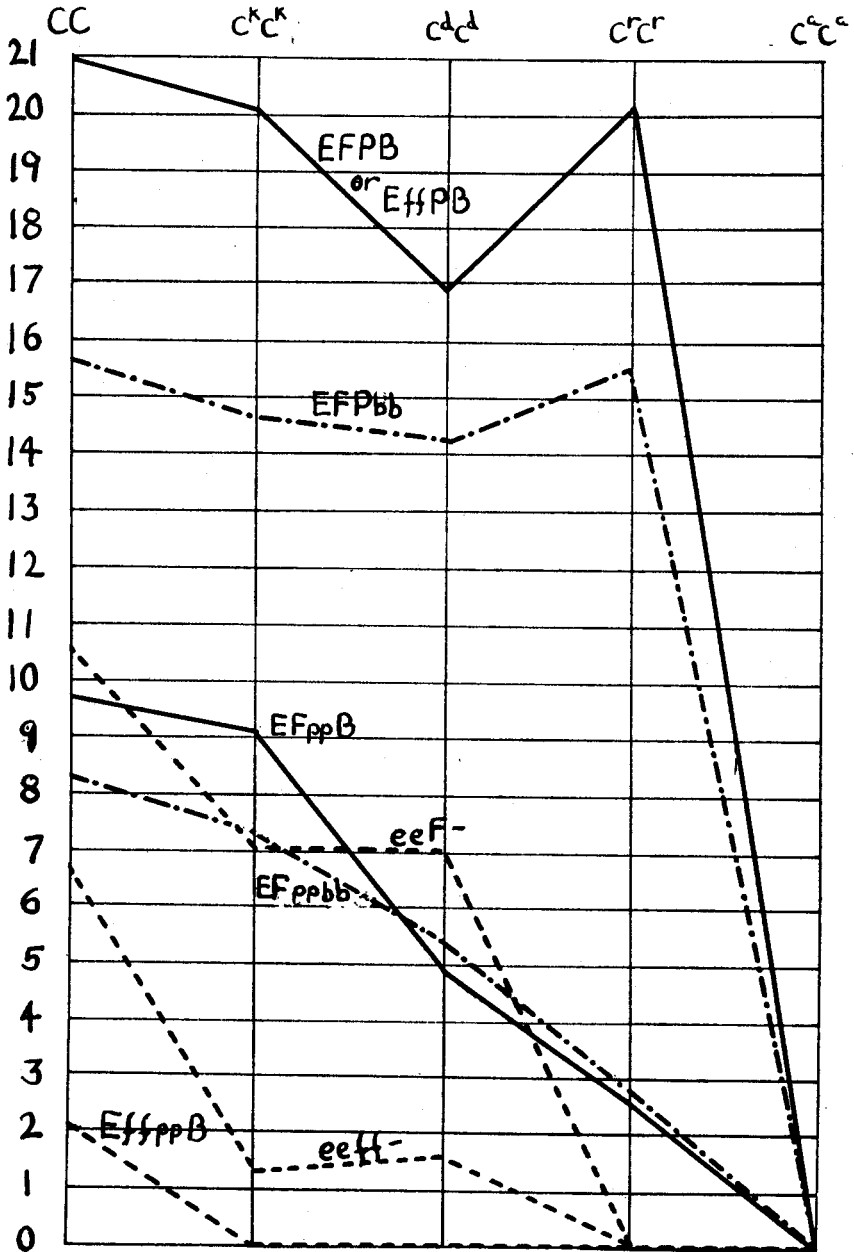


FIGURE 8.—The average grades of sepia (solid), brown (dot and dash), or yellow (dash) found with particular combinations of factors of the series *F*, *P* and *B* with the 5 homozygotes of the albino series. Factor *E* is used to indicate reference to "black" parts of the fur and *e* to "yellow" parts of the fur, although for the most part the actual grades were obtained in both cases from tortoise-shells (*e<sup>o</sup>*).



these have been produced, as may be seen by comparison of figure 6 and 7. The reduction can not, however, be attributed to a lowering of the threshold of the *immediate* gene products, since  $c^k$  and  $c^d$  in compounds with  $c^r$  and  $c^a$  ordinarily produce no yellow pigment at all while when homozygous they produce a pale cream. There is no apparent effect on *PB* sepias (table 17) or *Pb* browns. Inasmuch as competition with yellow has been assigned as one of the factors in explaining the peculiar order in these cases, the absence of change, accompanying marked reduction of yellow by  $f$ , indicates that the latter process may follow and in any case must be independent of the competition effects. The most striking instance is that of  $c^d c^a FPB$  with sepia of grade 14.0, cream of grade 4.2 which remains sepia of grade 13.9 on replacing  $F-$  by  $ff$ , although the cream is typically completely eliminated.

While factor  $f$  seems to have neither primary nor secondary effects on the intensity of  $P$ -sepias, it completely eliminates  $p$ -sepias revealing an underlying cream. The fact that the cream, in those spots of the tortoiseshell which represent black, is paler than the yellow in those of the spots which represent red (and similarly in the black and red bands of the agouti patterns) indicates two things: first, that the competition effect is present in spite of the complete absence of visible sepia and, second, that the competition effect involves a reduction of yellow as well as the reduction of black which it was previously advanced to explain. As with the effect on yellow pigmentation, it must be concluded that the effect of factor  $f$  on  $p$ -sepia either follows or at least occurs independently of the competition effect.

The fact that  $f$  leaves pale cream (grade 2.2) in place of black in animals in which red is reduced merely to yellow of grade 6.8 gives some indication of the normal extent to which the black producing process interferes with yellow in the "black" region. Factor  $f$  reduces yellow of grade 7.0 ( $c^d c^d F$ ) to a pale cream of nearly the same grade (1.6) as that referred to above. It may be inferred that black production, in the absence of  $f$ , tends to reduce red (grade 10.6) to yellow of about grade 7 and that the pale cream actually found in "black" areas when  $f$  is present represents this effect with the effect of  $f$  on yellow added to it.

Summing up,  $f$  reduces yellow pigmentation and causes complete absence of the kind of sepia determined by  $p$ . Both effects must either follow or at least occur independently of the threshold and competition effects which determine the order of intensity of the albino series compounds.

The deductions as to processes involved in color production and the points at which the known color factors have their primary effects are

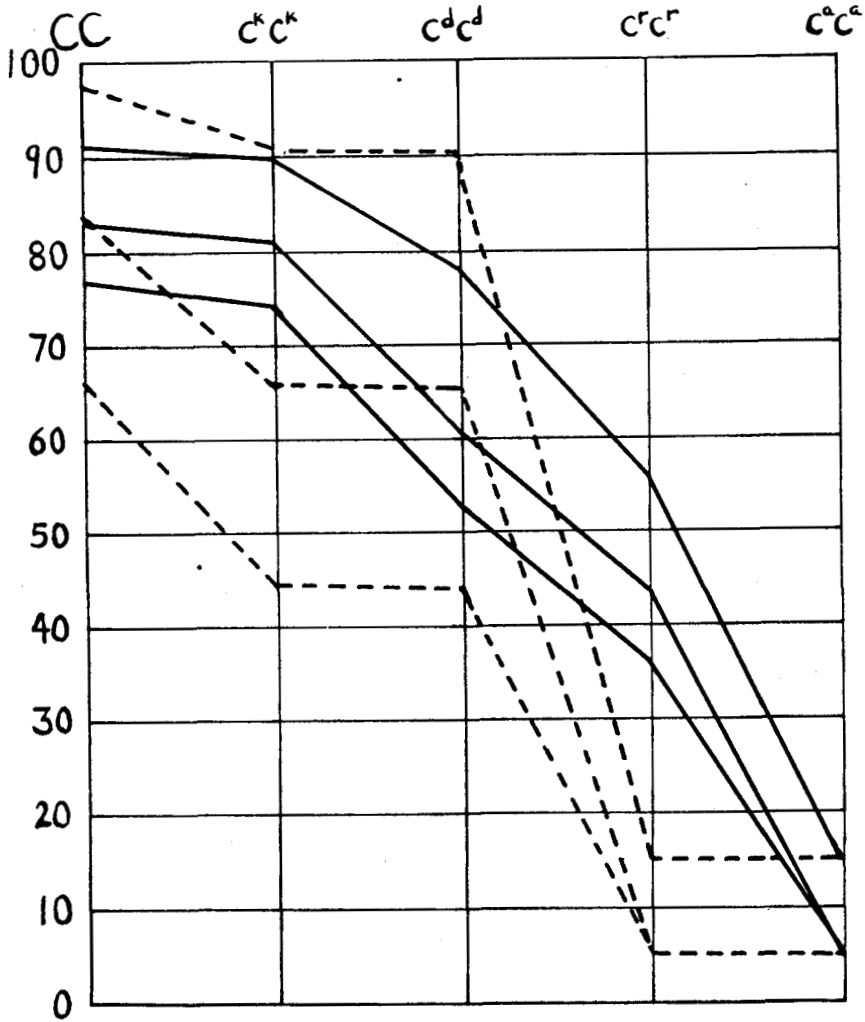


FIGURE 9.—The percentage composition of the sepia (solid) and of the yellow (dash) parts of the fur in terms of black, orange, yellow and white (reading from the bottom of the graph) in the 5 homozygotes of the albino series combined with  $FFppB-$ . Note the spread in the amount of yellow in the sepia of  $c^d c^d$  in comparison with that in  $c^r c^r$ ,  $c^k c^k$ , and  $CC$ .

presented graphically in figure 10. The albino series is represented as determining the quantity of a substance, I, called enzyme I in earlier publications (WRIGHT 1916, 1917) on the strength of ONSLOW'S determination of the presence of a tyrosinase in the skin of the black rabbit ( $C$ ), absent in the skin of albinos ( $c^a$ ). Since the "I" of the diagram is



Whatever the cause of these threshold differences, the evidence indicates that they apply to the immediate products of the two *C*-series genes in the zygotes before these products have come together in the cell (figures 2, 4 and 6, and discussion in previous paper, WRIGHT 1925). The union of I with II must of course be included among the processes which occur in the immediate vicinity of each of the *C*-bearing chromosomes.

The two substances I and I-II are represented as competing (in the regions in which II is present at all) for union with a third substance (III). It is necessary to suppose that I-II is about equally effective whether modified by *P* or *p*, except for the threshold difference. The assignment of the action of the piebald series (*S*<sub>s</sub>) and accessory modifiers (genes  $\Sigma S$ , sex, age of dam, etc.) to substance III is arbitrary. It is merely known that something essential to all pigmentation is affected in an all-or-none fashion in different parts of the skin. This may be back of I instead of III.

The brown series (*B*, *b*) appears to act upon the precursors of sepia exclusively but regardless of modifications by *P* or *p* and without influence on threshold or competition with yellow. This effect is most conveniently represented in the diagram as following these processes, although this is not a necessary conclusion.

Two distinct effects must apparently be assigned the *F* series. The threshold of yellow production is raised by *f*, but in this case without influence upon competition. The effect must be related to the zygotic combination instead of to the *C*-series genes separately. The action is thus best represented as following the competition effect. Factor *F* is also an essential for any production of sepias in the absence of factor *P*. As the action of *p* does not prevent the competition effect, action of *f* is again most conveniently represented as following. While the *f*-series like sex has been represented as affecting color production at two points, the possibility that these both rest on a single primary action of the gene is by no means ruled out.

The differences between the proportions of yellow and orange required to match intense reds, yellows and creams (table 2) suggest that more is involved than mere differences in quantity of pigment within the yellow series of colors. The close similarity in the effects of *c*<sup>k</sup> and *c*<sup>d</sup> on yellow in contrast with the differences in effects on sepia, suggest the existence of a threshold between yellow of grade 7 or 8 and red of grade 10 reached at the level of *c*<sup>d</sup> but not passed at that of *c*<sup>k</sup> (or by *C* in combination with *f*). It has not seemed desirable to introduce these complications into the diagram. Neither has it seemed desirable to indicate the apparently multiple effects of temperature.

The processes of melanin pigment production are probably essentially the same in whatever form of life they occur. The similarity of the compounds of the albino series in the mammals most studied has been discussed in previous papers (WRIGHT 1925). The evidence for a threshold difference between sepia and yellow in the rabbit, mouse, rat, dog and cat, comparable to the situation in the guinea pig, is especially noteworthy. Most of the other known color factors of mammals have effects which are similar as far as studied to the factors of the guinea pig and thus readily fall into the scheme presented here which does not differ in its essentials from that previously suggested (WRIGHT 1916-17). The most important types of color variation not found in the guinea pig are the dominant whites, such as the factor for the English pattern of rabbits, in which ONSLOW found an inhibitor of the action of tyrosinase; and the type of dilution of all color found in the blue and creams of rabbits, mice and maltese cats. These factors, however, introduce no serious difficulties.

#### SUMMARY

The distribution of sepia and yellow pigments in the fur of guinea pigs is determined by factors of the series *S*, *E* and *A* and modifying factors. The quality and intensity of these pigments is largely determined by factors of the series *C*, *F*, *P* and *B*. All combinations of the *C*, *P* and *B* series have been made with *F* present, and enough have been made with *f* present to determine the main differential effects of this pair. The sepia and yellow parts of the fur in these combinations have been graded by means of standard skins. The percentage compositions of the colors of these skins are given in terms of white, yellow, orange and black on the Milton Bradley color wheel.

The albino series compounds do not fall in the same order of intensity in different combinations with other factors. In combination *FPB* and *FPb*, the albino series genes determine increasing intensity of sepia in the fur in the order  $c^a, c^d, c^r, c^k, C$ . In the eyes of the same animals the order is  $c^a, c^r, (c^d, c^k), C$ , the latter three being indistinguishable by mere inspection. In yellow parts of the fur the order is  $(c^a, c^r), (c^d, c^k), C$ , the first two producing no yellow whatever and  $c^d$  and  $c^k$  being almost indistinguishable. Factor *b* has no effect on yellow. It replaces black by brown, but as noted above does not change the albino series order. Factor *p* also has no effect on yellow. It greatly reduces the intensity of sepia in the fur and almost eliminates all pigmentation in the eyes. The most interesting effect is another change in the order of the albino series genes in their effect on sepia  $c^a, c^r, c^d, c^k, C$  in both *FpB* and *Fpb*. Factor *f* reduces the

level of yellows in all combinations not already white with factor *F*. In contrast with the preceding cases, the effect appears to be on the products of zygotic compounds rather than on those of the separate *C*-series genes. The order of the zygotes is not changed. Factor *f* has no effect on grade of sepia in combination with *P*, but completely eliminates sepia in the presence of *p*, leaving a pale cream or white in its place. Dominance of *F* is not quite perfect. There is no genetic linkage between factors *C*, *F* and *P*.

Deductions are made as to the succession of processes involved in pigmentation of the various sorts and as to the points in this scheme at which the color factors have their primary effects.

These deductions center about two hypotheses: first, that the immediate product (I) of action of the genes of the *C*-series has different thresholds of effectiveness depending on whether an accessory substance (II) necessary for any sort of sepia or brown is present or not and whether or not II if present is modified by the *P*-series; second, that above these thresholds there is competition between the precursor of yellow (I alone) and the precursor of sepia and brown (I-II). Factors *B* and *F* must be assigned effects following or otherwise without effect upon the above threshold and competition effects.

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