THE GENETICS OF THE DUTCH RABBIT—A REPLY.

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PROFESSOR Punnett has honoured me by reviewing in this Journal[1] my paper on the inheritance of white spotting in Dutch rabbits. His own studies of the same subject have led him to suggest an interpretation of the results, which I have reported, somewhat different from my own. I wish to point out that the two interpretations differ less in substance than the casual reader might suppose, and to indicate what are the essential differences and why preference should be given to one interpretation rather than the other.

Professor Punnett has described accurately the essential facts observed. Three races of Dutch rabbits were found to breed true (within limits), each to a different modal condition of the same general type of white spotting. Punnett himself has observed three similar races, though they were perhaps not identical with mine. Upon crossing the races one with another, or with unspotted rabbits, F_1 individuals were obtained which were either intermediate in amount of white spotting or more nearly resembled the darker parent. In F_2, segregation of the original types occurred, but with evidences of modification, the recovered types been less divergent than those which entered the cross. So much as to the facts agreed upon. Now as to the interpretation, I have assumed that the segregation is of a monohybrid sort involving in each cross one principal pair of allelomorphic factors and that the "mutual modification" of types seen in F_2 is due to "residual heredity." Punnett objects to the assumption of modification and to the term residual heredity, unless it is understood in both cases that factorial recombination is meant rather than factorial modification. I am quite ready to concede the point. I used the expression "residual heredity" to cover the unanalyzed genetic agencies responsible for the observed modification in the extracted types. If Professor Punnett prefers to employ the term "genetic factors" I am quite willing to use that phraseology. Punnett

[1] Vol. IX, p. 303.

and I are agreed in supposing that the "residual heredity," when analyzed, will probably be found to be factorial. He refuses to consider any other possibility; I have preferred to use a non-committal term, until a fuller experimental analysis has been made.

The chief difference between Punnett's views and mine lies in the *number* of factors assumed to be in operation in the various crosses and the relative importance of these factors. I have assumed that *one* Dutch factor was present in each race and that the slight genetic variation seen in each uncrossed race, and also the modifications resulting from crossing, were due to minor or modifying factors (collectively "residual heredity"). Punnett ignores genetic variation in uncrossed types and the possibility of modification through minor genetic factors. He assumes that three independent major factors are concerned in the production of Dutch patterns. I have assumed the existence of three allelomorphic conditions of one and the same factor (one in each race), whereas Punnett assumes the existence of three independent factors which in different combinations produce the three races. It should not be difficult to test the relative merits of these assumptions by experiment, for on my view, when two races of Dutch are crossed, monohybrid inheritance ratios are to be expected (3 : 1 in F_2, 1 : 1 in back-crosses), but on Punnett's view dihybrid or trihybrid ratios are often to be expected. If with this point in mind the reader will examine my Text-figure 1[1], in which are summarized the data on crosses between two of the Dutch races studied (viz. Dark and White), I think he will be convinced that the inheritance is unmistakably monohybrid. Punnett does not attempt to apply in detail to this cross his three-factor hypothesis. If he did, I think that hypothesis would be found to fail completely. This cross is, of all those made, least affected by minor genetic factors ("residual heredity"), since the two races crossed were originally isolated from the same stock and may thus be supposed to have had most minor genetic factors in common.

Punnett offers three specific objections to the interpretation of this case as involving a single pair of (major) allelomorphic factors. Each of these objections rests on a misapprehension of the facts.

1. The first objection is that the "Dark" race is not homozygous (in major factors) because too variable. In reality the variation curve for the uncrossed Dark race is steep, monomodal, and nearly symmetrical. It is based on 172 carefully graded progeny all by the same sire. It is the smoothest variation figure of those obtained for any of the Dutch

[1] Carnegie Inst. Wash., Publ. No. 288.

races studied. If there were two major factors involved in this group and part of the mothers were, as Punnett suggests, heterozygous, the variation curve should show two distinct peaks, which it does not. Punnett admits the genetic purity of the White Dutch race with which Dark was crossed, although the total number of individuals is smaller and the variation figure is one-sided. The evidence for the genetic purity of the Dark race is even stronger.

2. The second objection is that my one-factor hypothesis calls for the recurrence in F_2 of the same types as occurred in P_1 and F_1 but not for darker animals, whereas Punnett's hypothesis calls for the occurrence through factorial recombination of darker animals ("a small proportion of animals tending towards complete pigmentation"). Now the actual result here confirms my view and disproves Punnett's. Not a single animal in F_2 was *darker* than animals of the uncrossed Dark race, and the proportion of low-grade Dark animals was less among the extracted than among the uncrossed Darks. I think Punnett must have had in mind the F_2 of a different cross when he raised this point, which is really decisive in favour of my view.

3. The third objection is that, if Dark and White are allelomorphs, when F_1 is back-crossed with White, "the two groups resulting should be sharply separated and their mean grades should be close to those of the parental stocks." Such is actually the case. Punnett apparently is under the misapprehension that the segregated groups, on my hypothesis, should be pure Dark and pure White respectively, whereas they should be (aside from modifications due to minor factors) similar to F_1 and pure White respectively. For if the heterozygote, DW, is back-crossed with WW, it is obvious that the two classes of zygotes to be expected are DW (not DD) and WW respectively. As regards the size of the two segregated groups, they number 65 and 64 respectively with one individual in doubt and not assigned to either group. Certainly this is a very good 1 : 1 ratio. As regards the point that the "mean grades should be close to those of the parental stocks," the mean grade of one group was 7·04 (as compared with 7·28 for F_1) and that of the other group was 15·56 (as compared with 16·25 for uncrossed White, and 14·40 for White extracted in F_2). These are surely very good agreements. In range the two groups agree exactly with the ranges respectively of F_1 and of White extracted in F_2. The groups moreover are monomodal as well as equal in size. In short there is no single criterion for monohybrid Mendelian segregation which is not perfectly met by this case. On the other hand if we apply a two-factor or three-factor scheme to the case,

as suggested by Punnett, we should expect segregation of more than two groups, or the formation of multimodal groups, with extended ranges resulting from recombination of factors, none of which are in evidence.

Punnett attempts a detailed application of his three-factor hypothesis to only one cross, that in which the parent races differ most widely, one race being non-Dutch and entirely devoid of white (the Self race), the other being the whitest of all the Dutch races, the so-called White race. F_1 from this cross consisted of animals bearing a very small amount of white. In F_2 the Self type reappeared in 21·4 per cent. of the young (expected on a monohybrid basis 25 per cent.). The F_1 type (of grades 1—3) was found in 46·6 per cent. of the F_2 young (expectation on a monohybrid basis 50 per cent.). The remaining 32 per cent. of the individuals are found in the range of the White race (where, on a monohybrid basis, we should expect 25 per cent. to occur, if segregation is perfect) or in the region between the ranges of F_1 and uncrossed White. The excess of 7 per cent. over expectation in this group is readily accounted for, if we explain the individuals in the intermediate region between the range of uncrossed White and of F_1, as an assemblage of modified Whites and of modified F_1's respectively. If this is so, a 1 : 2 : 1 ratio is approximated. The data present no serious difficulty to a simple monohybrid explanation, but to make sure of the soundness of such an interpretation a back-cross was made with the White race. This shows a beautiful segregation into two sharply separated groups, each of 58 individuals distributed in a monomodal and substantially symmetrical figure. The range of the lower group is exactly that of the original F_1 group plus the intermediate region in which the doubtful individuals of the F_2 distribution occurred. The range of the upper group is exactly that of uncrossed White plus two additional lower grades (13 and 14) of the intermediate region. Three unoccupied grades (10—12) separate the two groups. It would be difficult to imagine a clearer demonstration of simple monohybrid segregation, if it be granted either that the segregating factors are mutually modified (an hypothesis which I no longer entertain for reasons explained in my former paper) or if it be granted that slight modification of the extracted types has resulted from recombination of minor (modifying) genetic factors in association with the single pair of major factors.

As an alternative to this explanation Punnett has worked out in detail a three-factor hypothesis, which regards the Self race as homozygous for three dominant factors, *P*, *T*, and *S*, the White race being

homozygous for the recessive allelomorphs of these factors. If the three factors were supposed to be equivalent one with another in their whitening influence, the hypothesis would straightway break down in the face of the experimental results. But Punnett adds to the hypothesis as follows. The potency of each of the three assumed factors is supposed to be different. The recessive factor, *p*, is supposed to produce white spotting of the Dutch type either in a heterozygous or in a homozygous state. The recessive factor, *t*, by itself produces a white pattern only in a homozygous state, but in association with *p* or with *s* adds to the whitening effect, raising the grade of the pattern produced.

The third assumed recessive factor, *s*, can by itself produce no white, either as a heterozygote or as a homozygote, but when associated with *p* or with *t* it adds to the whitening effect of those factors in three out of six combinations shown in Punnett's Fig. 2.

This is a rather complicated set of hypotheses to make "out of whole cloth," but no objection need be raised on that score. Any hypothesis is justifiable which will work. But the more secondary hypotheses are required to make it work, the more will the entire scheme be open to suspicion and the stronger must be the evidence that it does work, that it will in reality enable us to predict results not otherwise predictable. Let us see if this is true of Punnett's three-factor hypothesis. When applied to the F_2 generation from this cross, Punnett's scheme fits the observed results fairly well. But the real test of a scheme built up on so many arbitrary and independent assumptions is to apply it to other crosses than that which it was apparently framed to meet, the peculiar F_2 distribution. If, for example, it fits a back-cross test as well as the F_2 test, it will gain much in acceptability. Punnett makes such an application in his Table II and apparently is fairly well satisfied with the result, better at any rate than with admitting "modification" under any circumstances.

But Punnett's calculated distribution differs from the actual one in the following essential regards. The lower calculated group shows two chief modes instead of the actual one mode. The more pronounced of the two calculated modes differs widely in position from the actual mode. The upper calculated group is far from symmetrical and shows its chief mode on the wrong grade.

It appears therefore that, while Punnett's three-factor hypothesis may, with the aid of a number of carefully framed secondary hypotheses, be made to fit fairly well the observed results for the F_2 generation, it fails to agree at all well with the observed results in the more critical

back-cross. An hypothesis which works only part of the time cannot be said to work well.

Why resort to an hypothesis so complicated when a much simpler one will work better? Punnett's reasons apparently are two, (1) a distrust of explanations involving multiple allelomorphs and (2) a dislike for the idea of "modification" as implying impurity of the gametes. Now multiple allelomorphism, under whatever name one chooses to discuss it, is no longer an hypothesis but a well-established fact. Even in rabbits we have two other undoubted cases, one being the albino series of three allelomorphs (Polish, Himalayan, and coloured), the other the agouti series, likewise of three allelomorphs (grey, black-and-tan, and non-agouti). In guinea-pigs there are four allelomorphs in the albino series (Wright), and three in the extension series (Ibsen). In Drosophila there are eight or more allelomorphs in the white-eye series (Morgan), and we have conclusive proof that the linkage relations with other factors are the same throughout the series showing that all occupy the same "genetic locus." If one chooses to regard a series of allelomorphs as constructed on one and the same genetic basis, with additions or subtractions in individual cases, there can be no valid objection to such a view. Thus Himalayan albinism may be regarded as Polish albinism plus a darkening factor inseparably coupled with it, if one prefers that form of description, but the fact is not altered thereby that in crosses the two things behave as ordinary allelomorphs. So, I maintain, it is with different types of Dutch marking in rabbits. I have identified three such types. Punnett has identified positively one of the same types (White) and tentatively recognizes two other types different from any of mine. He seems to regard my two other types as dubious because they are not the same as his. My experience leads me to be more charitable. I am ready to admit the probable existence of five types of Dutch and that all will probably be found to be allelomorphs. I have even found that a very different type of white spotting which occurs in rabbits, viz. English, behaves as an apparent allelomorph of White Dutch. It may, however, only be very closely linked with Dutch, for it seems remarkable that two genes so manifestly different in their physiological properties should be variants of a single genetic locus. But in any case it is not to be inferred that white spotting in mammals generally consists of allelomorphs of one genetic locus. For Little, Detlefsen and Dunn have independently shown that piebald spotting in mice is genetically distinct from black-eyed-white spotting, the two genes manifesting no linkage (Dunn).

Punnett's second and strongest objection to the hypothesis of multiple allelomorphs seems to lie in what he characterizes as "its necessary concomitant of mutual modification." I trust that this objection will disappear with the explanatory addition which I am quite ready to make that the mutual modification is probably the result of multiple modifying factors which segregate and recombine independently of the chief factor with which they were associated in each uncrossed race. Modification, like the occurrence of multiple allelomorphs, is no longer an hypothesis but a well-established fact. The only point concerning which a reasonable doubt can exist is the correct theoretical explanation of modification. Punnett and I agree in the view that modifying factors are involved in the present case. He thinks that three factors in all will suffice to explain it. I am inclined to invoke a larger number of modifying factors, but identify positively only a single set of allelomorphs of one primary Dutch factor.