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A. H. Sturtevant, and Jack Schultz

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THE INADEQUACY OF THE SUB-GENE HYPOTHESIS OF THE NATURE OF THE SCUTE ALLELOMORPHS OF DROSOPHILA

A. H. STURTEVANT AND JACK SCHULTZ

CALIFORNIA INSTITUTE OF TECHNOLOGY AND CARNEGIE INSTITUTION OF WASHINGTON

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In a series of papers, Serebrovsky (1930), Dubinin (1929), Agol (1930) and their colleagues have described an extremely interesting group of bristle-reducing mutant genes lying at the scute locus of the X-chromosome of *Drosophila melanogaster*. As a result of their careful studies of this material, they have elaborated an interpretation of the situation. According to this hypothesis, the normal allelomorph of the scute genes is not a single unit, but is made up of a series of "sub-genes" arranged in linear order, each sub-gene being concerned with the development of one or of a few bristles on the fly. The scute mutations involve changes in blocks of these sub-genes, but of different blocks. Scute 11, for example, represents mutation of a few sub-genes at the left end of the series; scute 4, of practically all the sub-genes not affected by scute 11; scute 5 of a few sub-genes near the right end. All the known allelomorphs may be described in such terms.

Serebrovsky has arranged the bristles in a linear series, that he takes to correspond to the linear series of sub-genes. From our own data,¹ which include a few additional bristles, we have constructed a linear series, paying particular attention to variations in amount of effect. The resulting seriation of bristles is substantially the same as Serebrovsky's, though we believe it to be slightly more accurate, and to be capable of still further improvement. This seriation is: 1, p. dorsocentral; 2, a. dorsocentral; 3, p. supra-alar; 4, inner vertical; 5, "ventral;" 6, p. postalar; 7, pre-sutural; 8, p. orbital; 9, a. supra-alar; 10, outer vertical; 11, a. postalar; 12, a. notopleural; 13, middle orbital; 14, ocellar; 15, postvertical; 16, a. orbital; 17, coxals; 18, sternopleural; 19, p. scutellar; 20, a. scutellar; 21, humerals. Using this series as a base-line, we have drawn a curve for each scute allelomorph, showing its effectiveness in removing the successive bristles. Most of the allelomorphs give smooth unimodal curves. The irregularities that do exist may be due to modifying genes at other loci, or they may present real difficulties. It should be emphasized that these remarks apply to our own data, based on male flies only. In other words, Serebrovsky's seriation may be derived and further elaborated without using the data from heterozygous females, except insofar as these data are necessary to establish that the genes dealt with belong to one series of allelomorphs.

In a recent communication Agol (1930) has presented briefly what he

believes to be a striking confirmation of this theory. He has studied the behavior of scute in the presence of the deleted chromosomes induced by x-rays. If the hypothesis is correct, occasionally chromosomes should be broken within a gene, and fragments result lacking some of the sub-genes within a given locus. Such fragments should suppress the effects of the sub-genes which they themselves contain; but the characteristic effects of those to the right of the break should appear as usual. These expectations have been fulfilled, offering what may appear to be a complete verification of the guiding hypothesis.

On closer examination, certain difficulties appear. In the first place, Agol's results may be interpreted as due to the occurrence of a new scute allelomorph in the deletion at the time of breakage. Since scute is a rather mutable locus, it is by no means unlikely that out of a number of deletions tested, some should contain new allelomorphs. Even assuming, however, that no mutation to a scute allelomorph occurred, there remains the possibility that the dominance relations at the scute locus are different in the presence of the deletion. It is well known that the dominance relations between a gene and its normal allelomorph are affected by changes in the rest of the genetic system (see Bridges in Morgan, Bridges and Sturtevant, 1925). For example, in the case of the original Pale-translocation of Bridges, the included gene, *plexus*, presents a greater dominance effect in the flies carrying two doses of *plexus* and the normal allelomorph in the duplication than is seen in triploids with two doses of *plexus* and one normal allelomorph.

In the present case, the question is whether or not the dominance of scute in Agol's experiments may be a property of other portions of the X. This may be tested by studying the behavior of scute with duplications² which all include scute itself and in addition other varying portions of the X-chromosome. We have done this, and our data indicate that scute may under certain circumstances behave as a dominant, particularly for bristles in the right portion of Serebrovsky's linear map.

This is particularly well shown in experiments (Table 1) with Translocation X-1, an X to III translocation discovered and analyzed by Professor H. J. Muller. In this case the break is to the right of the white locus, so that besides scute, the duplication contains a considerable section of X-chromosome. The translocation contains no scute allelomorph, since heterozygous females are substantially normal, and cross-overs for this region have been obtained, giving normal males (those carrying the translocation die). Males carrying the duplication and a normal X present certain abnormalities, similar to those described by Muller (1930). Since they are particularly sensitive to modifiers, all the stocks used were made homogeneous as far as possible, before the experiment proper. Table 1 gives some of the data. The duplication itself produces abnormalities

of bristles occasionally, particularly on the scutellars, which may be absent because of breakage in emergence from the pupa case. For this reason, the apparent effect of yellow 2 on the scutellars is spurious. These are probably unaffected in these modifiers, although in certain cases a real scute effect has been seen.

TABLE 1
MEAN BRISTLE NUMBERS¹

	POST VERTICAL	ANTERIOR SCUTELLAR	POSTERIOR SCUTELLAR	COXAL I	COXAL III	OCCIPITAL	NUMBER OF FLIES
Dupl. X-1/y ²	1.99	1.86	1.36	1.92	1.00	1.56	66
Dupl. X-1/yac	2.00	1.96	1.92	1.79	0.92	1.35	48
Dupl. X-1/ysc ¹	1.87	2.00	1.91	1.18	0.32	1.27	45
Dupl. X-1 sc ¹ pn g car	1.53	2.00	1.97	0.79	0.12	1.12	34
Del. 101/ysc ¹	2.00	2.00	2.00	1.96	1.97	1.62	50

¹ The means for the coxal III bristles are based on somewhat smaller numbers of flies than are the other values given. The occipitals, absent in the wild-type, are present in most flies that carry duplications for the scute region.

The coxal I bristles give critical evidence. It is obvious that they are strongly affected by scute,¹ and much less so by the others. Even the slight effect in the others is probably due to the admixture of non-disjunctive males which were heterozygous for scute. It is apparent that the removal from a female of a section of the X-chromosome to the right of white produces a male in which scute¹ behaves as a dominant, with respect to certain bristles.

The dominance is for bristles at the right on Serebrovsky's map. With achaete, far to the left on the map, this bristle is probably completely unaffected, as is to be expected if the dominance effect is a function of the particular scute allelomorph. Data on other scute allelomorphs, with modifiers as yet uncontrolled, support this obviously plausible view. Dominance is also a function of the modifiers in the system, as is shown by the data from Duplication X-1/sc¹ pn g car, where the indication of a post-vertical effect is strengthened, and all the other effects are more extreme.

Several other duplications for this region give similar results. If, however, the break occurs still further to the left, leaving a fragment which includes only yellow, scute and silver, different relations appear (Del. 101/y sc¹ in table 1). In this case scute is practically completely recessive. We must assume then, that there are at least three portions of the X concerned with the scute effect—a portion at the middle, tending to make scute recessive; a more distal portion (svr-w) which enhances its effect; and the normal allelomorph of scute itself. This is in complete harmony with the view that the dominance of any one gene is a function of the system as a whole. If this is granted it becomes difficult to accept the proof of the sub-gene hypothesis offered by Agol.

This view of dominance raises other difficulties for the Serebrovsky hypothesis. It implies that the developmental system is a system in which limiting factors are important, and in which, therefore, changes in the rest of the system make changes in threshold values. That thresholds are important in the all or none systems concerned with the absence of bristles is obvious, as will be shown further.

Lewit (1930) raises the question whether it may not become necessary to postulate that each scute allelomorph affects many bristles outside the region in which its action is normally detected. His own data suggest that such effects may be produced on bristles that lie (on Serebrovsky's map) adjacent to the known field of action of the given scute allelomorph. We have evidence that indicates such effects on bristles lying very remote from the known field of action. Achaete lies at the extreme left of Serebrovsky's map, scute 1 covers most of the right half. The scute 1-achaete heterozygote is completely normal; but both act as allelomorphs to scute 3, which on Serebrovsky's interpretation is to be taken as resulting from mutation of practically the entire series of sub-genes. We have studied scute 1 and achaete in flies that were also Hairless (the gene concerned is a III-chromosome dominant that removes bristles in a pattern different from that of the scutes—Plunkett (1926)).³ The table shows the results obtained for a few bristles.

TABLE 2
AVERAGE NUMBER OF BRISTLES

	INNER VERTICAL	ANTERIOR DORSOCENTRAL	POSTERIOR SUPRA-ALAR	POSTERIOR ORBITAL	OSCELLARS	HUMERALS	NUMBER OF FLIES
$H \frac{+}{+}$	1.65	1.61	0.62	0.82	1.94	2.60	80
$H \frac{+}{sc^1}$	1.98	1.78	0.86	1.16	1.96	2.94	50
$H \frac{+}{ac}$	1.46	1.49	0.38	1.04	1.89	2.56	80
$H \frac{sc^1}{ac}$	0.80	0.80	0.02	0.52	1.57	2.02	60

In each series 22 different bristles were recorded for each side of each fly: in only one case did the $H \frac{sc^1}{ac}$ class have an average value higher than that of any one of the other three classes—and that difference (anterior supra-alar, 1.92 for $\frac{sc^1}{ac}$, 1.89 for $\frac{+}{ac}$) was certainly not significant. The table shows only a few of the more extreme cases; but it must be noted that these bristles are scattered throughout Serebrovsky's map: the inner vertical and the humerals are usually placed at opposite ends, and the others listed are scattered through the whole range. It should also be noted that, with this same set of modifiers (exclusive of Hairless) our data show that the inner vertical and posterior supra-alar are not affected either by achaete or by scute 1 alone. Hairless serves here only as a sensitizer,

making the effects of scute 1 and of achaete more obvious: the data given leave no alternative to the conclusion that both scute 1 and achaete are acting on bristles scattered throughout the entire length of Serebrovsky's map, though many of these effects, under ordinary conditions, are of sub-threshold degree.

This conclusion is in harmony with most recent ideas concerning the way in which genes control development. It seems to us to destroy the value, as a working hypothesis, of the extreme preformationist sub-gene hypothesis. If each scute sub-gene is affecting many or all of the bristles of the fly, the whole logical basis of the hypothesis is undermined.

The remarkable series of facts described by the Russian investigators remains. If the bristles are plotted on a picture of the fly in the order indicated above, the impression is strong that there is a real pattern present, with a single center in the median line near the level of the posterior dorso-central. Following the suggestion of Plunkett (1926), the pattern may be thought of as resulting from the diffusion of some substance from this center, not with equal speed in all directions, but more rapidly anteriorly, with occasional lateral outpushings. In any case, on this or some similar basis one may interpret the scute allelomorphs as acting at specific times during this process. This conception has already proved useful in that it led to the supposition that there might be an effect of some of the more "peripheral" scutes on the bristles of the "filter-apparatus" (Frey, 1918) in the pharynx—a supposition that we have verified for scute 3, scute 4 and scute 7.⁴

Finally, the behavior of the scute allelomorphs in heterozygous females, used by Serebrovsky as the basis of his map, raises no difficulties for the hypothesis here suggested. For these reasons and from general considerations we prefer to look for the solution of the linear series discovered by the Russian workers in some such developmental interpretation as this rather than in hypotheses as to the structure of genes.

¹ We are greatly indebted to Prof. A. S. Serebrovsky for his generosity in sending to this laboratory stocks of scute 2, scute 3, scute 4, scute 5, scute 6, scute 7 and scute 11, as well as of several other interesting new types. The other types examined were scute 1, scute B3 (the scute 3 of Morgan, Bridges and Sturtevant, 1925), achaete, and scute D (recently obtained by Prof. T. Dobzhansky in x-ray experiments, and very kindly given to us by him).

² It is a pleasure to express our indebtedness to Professor H. J. Muller, to Professor T. Dobzhansky and to L. V. Morgan, for their kindness in supplying us with stocks of the various duplications.

³ The races used in these experiments were all put through a process of inbreeding and crossing that should have made them uniform for all genes except those lying near the scute and hairless loci. We have also used most of the precautions suggested by Plunkett (1926) to insure environmental uniformity.

⁴ The wing and abdomen effect of scute 2 and scute 9 (Dubinin 1929, Lewit 1930) is probably also to be referred to the pharyngeal region, as the abdominal ab-

normality is evidently an inflation of the crop, which Eidmann (1924) has shown to be concerned in the hydrostatic mechanism of wing expansion; and the opening of the crop into the oesophagus, its only connection to the surface, is in the head.

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PROOF THAT BAR CHANGES TO NOT-BAR BY UNEQUAL
CROSSING-OVER

BY L. V. MORGAN

WILLIAM G. KERCKHOFF LABORATORIES OF THE BIOLOGICAL SCIENCES, CALIFORNIA
INSTITUTE OF TECHNOLOGY

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The hypothesis of unequal crossing-over at the bar locus in the X-chromosome of *Drosophila melanogaster*, advanced by Sturtevant to account for so-called reversion of bar, has been fully supported by his experimental evidence.¹ By use of the characters forked and fused combined with bar and a new allelomorph, infrabar, he showed that "sixteen different kinds of changes at the bar locus" occur "exclusively, or nearly so, in eggs that undergo crossing-over at or near the bar locus."

Sturtevant noted, however, in the data on the changes at the bar locus a deficit in one class of individuals, namely, double-bar. "This hypothesis makes reverted round and double-bar complementary cross-overs, and they