ON THE POTENCY OF MUTANT GENES AND WILD-TYPE ALLELOMORPHS

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As a starting point for the following considerations we shall use the perhaps most familiar of all Drosophila mutants, the school example of a typical recessive, vestigial wing, found by MORGAN in 1911. Most striking in vestigial is the enormous reduction of the wing, due to the trimming away of the marginal and terminal regions. This reduced wing stands out at right angles. The balancers, especially their terminal segments, are reduced in size, the posterior scutellars are erect, and the viability of the fly is somewhat below standard (BRIDGES and MORGAN 1919). Thus, vestigial is a typical representative of genes with manifold effects.

Some years ago it was noticed that both the black purple vestigial Lobe and the pure vestigial laboratory stock cultures contained some flies which failed to manifest the vestigial character. In the former stock the exceptional individuals had full-length, slightly divergent wings with large marginal incisions ("ragged" wings) and in the latter wild-type wings with a tiny terminal nick in rare cases (figure 1).

The cause of these changes was not analyzed at the time, and the stocks were propagated in the ordinary way without selection as before. Not until about one year later, when pure vestigial flies were to be used in a mating, was the case again brought to the foreground of attention. Practically all of the supposedly pure vestigial stock flies were now found to be wild-type, except for an occasional terminal nick in the wing, and when the black purple vestigial Lobe stock was reëxamined, not only the vestigial, but also the ragged wing type had disappeared entirely! All the flies had long, normal-looking wings, except for distinct terminal notches in quite a few cases.

Appropriate tests proved that these changes in the stocks were due to secondary, regressive mutations. In the multiple stock vestigial had mutated to a new allelomorph, denoted as notched (vg^{no}) which in homozygous condition produces terminal notches in about 40 percent of the cases. In compound with vestigial this gene gives the ragged wing type, encountered in this stock one year previously. Correspondingly, in the pure vestigial stock vestigial had mutated to another allelomorph, denoted as nicked (vg^{ni}). When homozygous this gene has no somatic effect, but compound nicked/vestigial flies have tiny terminal nicks in about 30 percent of the cases. In passing, it may be mentioned that from the first detection of a few exceptional flies it was not long before the new allelomorphs had entirely driven out and

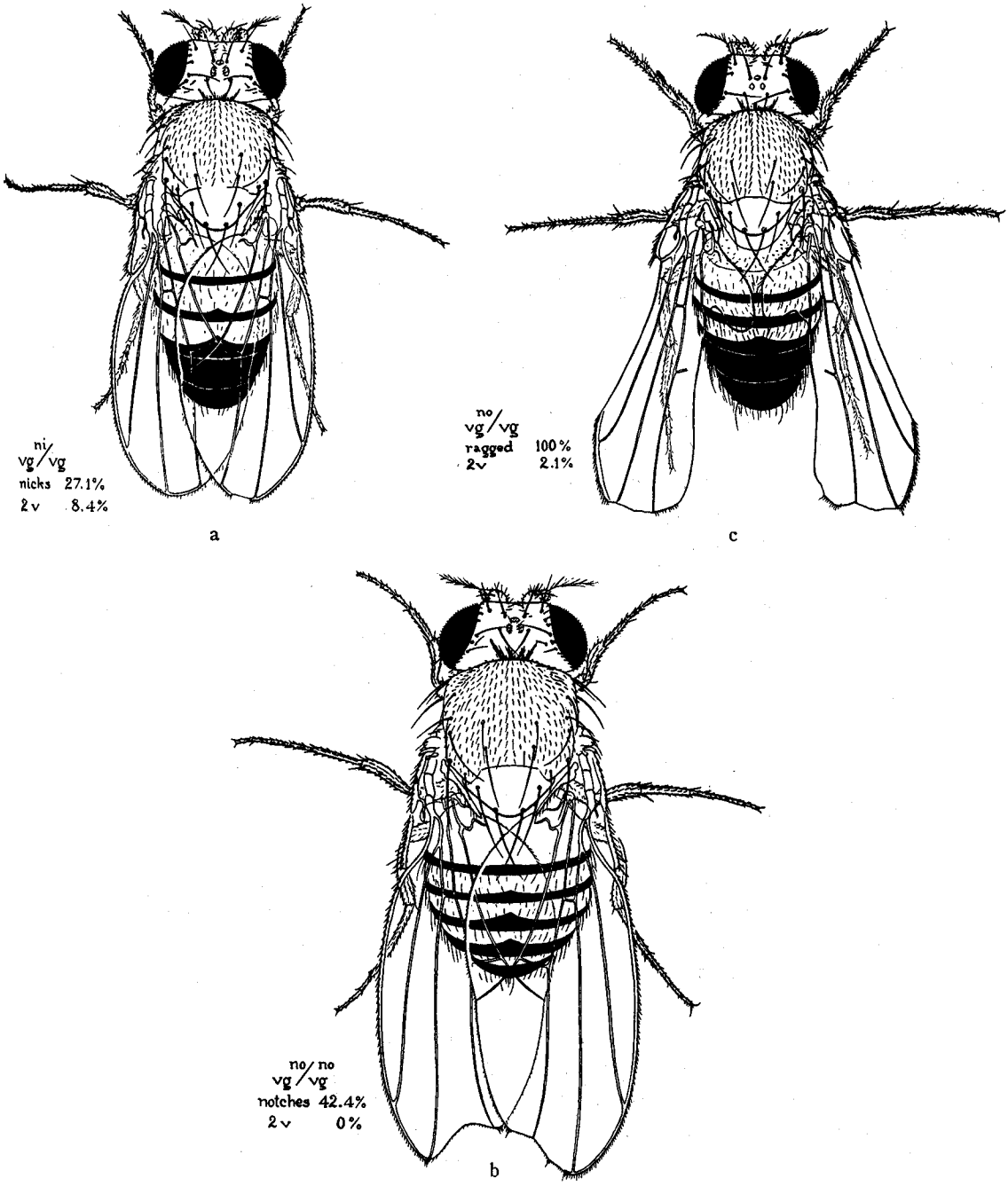

FIGURE 1.—a, Compound nicked/vestigial male. b, Homozygous notched female. c, Compound notched/vestigial ("ragged") male.

replaced the vestigial gene in the respective stocks, striking cases of "natural selection *in vitro*."

Three other supra-vestigial and infra-wild-type allelomorphs have earlier been described by BRIDGES and MORGAN (1919), namely, nick (v_g^n), antlered (v_g^a), and strap (v_g^s), the former found by BRIDGES, the two latter by MORGAN (see figure 2). Stocks of these are no longer in existence. Nick is very much like our nicked; homozygous nick flies are wild-type, while 65 percent of compound nick/vestigial flies have terminal nicks. Antlered produces large marginal incisions and the wings stand out at an angle of 30°. Strap, finally, causes still more pronounced alterations, the widely divergent, "leg-of-mutton"-shaped wings resembling those of the long-winged vestigial flies appearing under special temperature conditions (see below). The balancers are in strap somewhat reduced, and, judging from some illustrations, the posterior scutellars are slightly erect.

In addition to these allelomorphs there are about an equal number which produce changes that are farther removed from normal than those present in vestigial. (For stocks as well as for information dealt with below I am indebted to BRIDGES.) Nearest to vestigial comes No-wing, found and studied by MORGAN (1929). This gene which reduces both wings and balancers almost completely is treated by MORGAN as a recessive. But in our analysis of different vestigial allelomorphs (see below) it turned out that a terminal break in the second longitudinal vein belongs to the vestigial characteristics, and this alteration is present in 70 percent of heterozygous No-wing flies, which also have a terminal nick in the wing in rare cases. No-wing (v_g^{Nw}) is accordingly here considered as incompletely dominant. Homozygous No-wing flies have erect scutellars. The viability is extremely low.

No-wing connects vestigial with a series of incompletely dominant allelomorphs which are lethal in homozygous condition and which when heterozygous remove bites out of the wing margin (MORGAN, BRIDGES, SCHULTZ 1930). As representatives of these allelomorphs, which have not yet been analyzed in detail, may be mentioned vestigial-Beaded (v_g^{Bd}) found by BRIDGES, Carved (v_g^C) by DEMEREC, Snipped (v_g^{Sn}) by MULLER (1930) and Depilate (v_g^D) by BRIDGES.

Summing up, we are accordingly confronted with a very extensive spectrum of effects of uni-local genes. At one end subliminal, recessive members are found which closely approach the wild-type gene in potency, at the other dominant members which in homozygous condition cause such great changes that the zygote is non-viable. Between these extremes a graded series of intermediate steps occur. The series illustrates in a striking way that dominance and recessiveness are relative differences only.

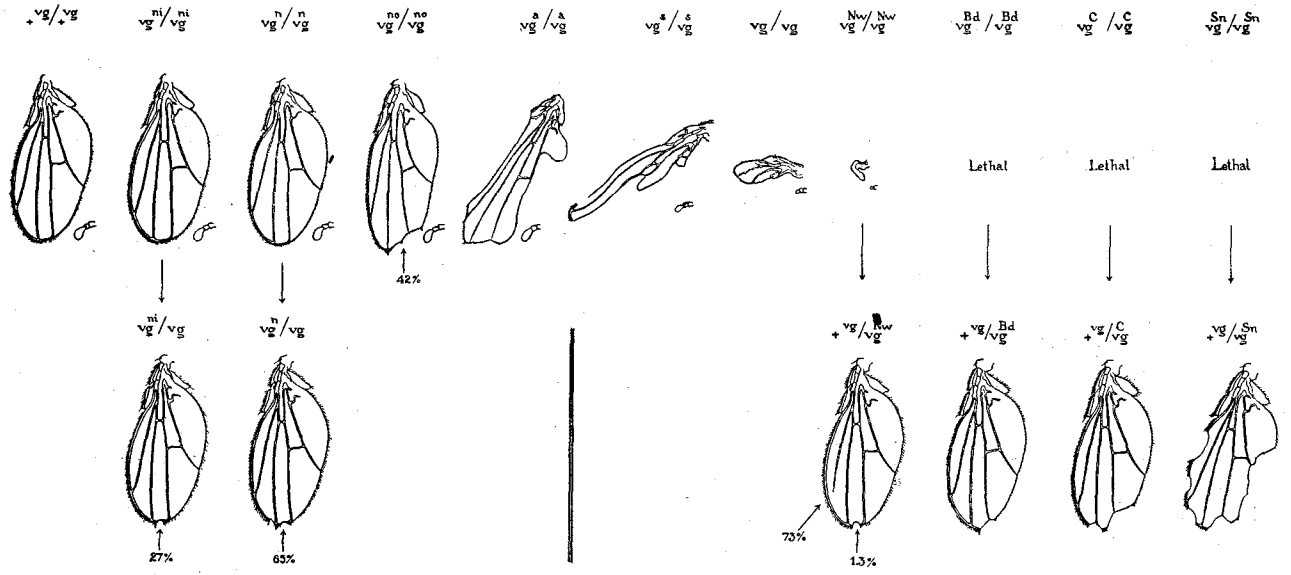

FIGURE 2.—Upper row: Modal wing-types and balancers of flies homozygous for the vestigial allelomorphs. From left to right: wild-type allelomorph, nicked, nick, notched, antlered, strap, vestigial, No-wing, (vestigial-Beaded, Carved, Snipped). Lower row to the left: wings from nicked/vestigial and notched/vestigial compound flies. Lower row to the right: wings from heterozygous No-wing, vestigial-Beaded, Carved and Snipped flies.

For a comparative study of the potency of the vestigial allelomorphs those members were used of which stocks were at hand, namely, No-wing, vestigial, notched, nicked and the wild-type allelomorph. Their relative effectiveness (at 25°; standard banana-agar culture medium) in producing marginal incisions, divergent wings, rudimentary balancers and erect scutellars was the object of this analysis. When it later turned out that a terminal

TABLE 1

Summary of quantitative evidence on the effect of the vestigial-allelomorphs No-wing (v_g^{Nw}), vestigial (v_g), notched (v_g^{no}), nicked (v_g^{ni}) and the normal allelomorph ($+^{vg}$). The numbers in parentheses represent totals on which the corresponding percentages are based.

GENOTYPE	INCISED WINGS Percent	DIVERGENT WINGS	ERECT SCUTELLARS	RUDIMENTARY BALANCERS	SHORTENED 2 VEINS Percent	VIABILITY IN RELATION TO v_g Percent
$+^{vg}/v_g^{ni}$	0	–	–	–	0	..
$+^{vg}/v_g^{no}$	0	–	–	–	0	..
v_g^{ni}/v_g^{ni}	0	–	–	–	2.6 (17:670)	..
$+^{vg}/v_g$	0	–	–	–	0	..
v_g^{ni}/v_g^{no}	nicks 0.2 (3:1206)	–	–	–	0 (0:765)	..
$+^{vg}/v_g^{Nw}$	nicks 1.3 (10:794)	–	–	–	73.3 (127:176)	..
v_g^{ni}/v_g	nicks 27.1 (288:1062)	–	–	–	8.4 (64:760)	111.8 (1062:950)
v_g^{no}/v_g^{no}	notches 42.4 (479:1162)	–	–	–	0 (0:757)	115.6 (267:231)
v_g^{ni}/v_g^{Nw}	scalloped 70.7 (606:857)	–	–	–	100 (138:138)	..
v_g^{no}/v_g	ragged 100 (2495:2495)	±	±	±	2.1 (10:468)	104.9 (450:429)
v_g^{no}/v_g^{Nw}	antler-like 100 (156:156)	+	+	+	100 (156:156)	..
v_g/v_g	stumps 100	++	++	++	uncontrollable	..
v_g/v_g^{Nw}	stumps 100	++	++	++	uncontrollable	..
v_g^{Nw}/v_g^{Nw}	absent 100	++	++	+++	uncontrollable	..

break in the second vein belonged to the vestigial characteristics, data were also secured on the frequency of this alteration in the different compounds. The results are summarized in table 1.

In combination with the wild-type gene, nicked, notched and vestigial have no detectable somatic influence. That the vestigial/wild-type ($v_g/+$) combination nevertheless has another potency than the homozygous wild genotype ($+/+$) is evidenced by DEXTER's (1914) finding that heterozygous vestigial enhances (as do also heterozygous antlered or strap) the effect of the incompletely dominant Beaded, which by itself produces mar-

ginal incisions in the wing blade. Homozygous nicked flies have wild-type wing margin, and so have also the nicked/notched compound flies. Only in very exceptional cases there occurred in the latter combination a slight and doubtful indication of nicks.

The most extreme allelomorph used, No-wing, gave in combination with the wild-type gene terminal nicks in 1.3 percent of the cases, and from here the frequency and degree of marginal incisions increase gradually in the nicked/vestigial, homozygous notched and nicked/No-wing ("scalloped") combinations (see table 1 and figure 3). When notched is combined with vestigial the threshold for constant production of large marginal incisions (ragged wings) is reached, and in this compound, especially in early-hatching females, we also encounter the first indication of divergent position of the wings, erect scutellars and reduced balancers. In the "antler-like" notched/No-wing compound all these characteristics are more pronounced and constant. In homozygous vestigial and in the vestigial/No-wing compound the wings are reduced to stumps, while finally in homozygous No-wing both wings and balancers are practically absent (see figure 3).

All this evidence may be accounted for if we assume that the allelomorphs studied form a quantitative series in the following order of potency: No-wing, vestigial, notched, nicked and the wild-type gene. But a glance at the summary (table 1, sixth column) makes it clear that, with respect to their influence on the fifth characteristic under control, the second vein, they behave quite otherwise. Here notched and nicked have changed places in the series, notched approaching more closely the wild-type allelomorph in effect. Vestigial and No-wing have retained their order, but their difference in potency is much more marked than was the corresponding difference in their influence on the other vestigial characteristics.

If we, in analogy with WRIGHT (1925) and with STERN (1929) in his analysis of the additive effect of the bobbed allelomorphs, give the different allelomorphs relative numerical values, which as well as can be approximated cover the experimental evidence, we arrive at the following relative values for the tendency to production of marginal incisions: v_g^{Nw}, 6; v_g, 10; v_g^{no}, 15; v_g^{ni}, 22; $+^{vg}$, 30. When these values are added in the respective diploid combinations the numerical series presented in table 2, third horizontal row, results. The threshold for the first and doubtful indication of nicks lies at 37. With decreasing values an increasing percentage of nicked, notched and scalloped wing types occur, until at 25 the threshold is reached for constant production of the ragged phenotype. At 20 the wings are reduced to stumps, at 12 practically absent. Modal wing-types and balancers from the different combinations are presented in figure 3.

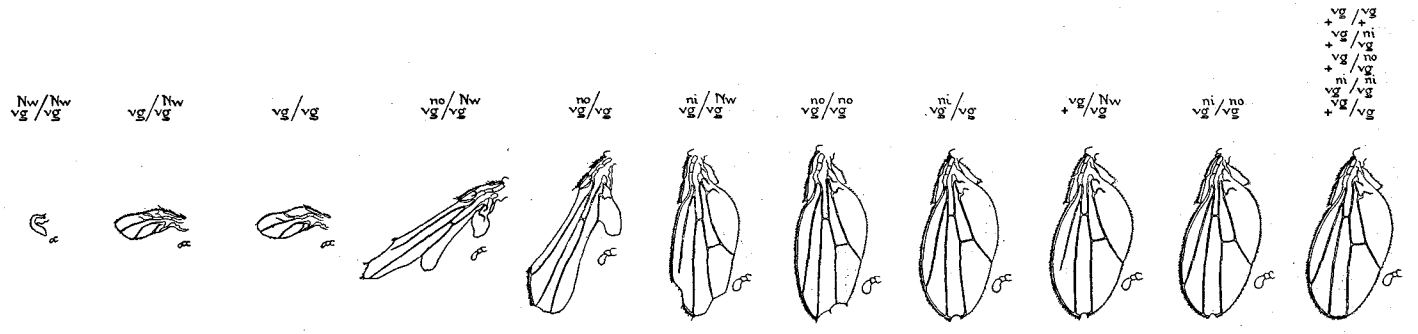

FIGURE 3.—Modal wing-types and balancers of flies representing all the possible diploid combinations of the vestigial allelomorphs No-wing, vestigial, notched, nicked and the wild-type allelomorph. Below: percentage of marginal incisions and relative numerical value for each combination.

TABLE 2

Numerical series illustrating the effect of the vestigial allelomorphs studied. For explanation see text.

GENOTYPE	vg^{N_w}/vg^{N_w}	vg/vg^{N_w}	vg/vg	vg^{no}/vg^{N_w}	vg^{no}/vg	vg^{ni}/vg^{N_w}	vg^{no}/vg^{no}	vg^{ni}/vg	$+^{vg}/vg^{N_w}$	vg^{ni}/vg^{no}	$+^{vg}/vg$	vg^{ni}/vg^{ni}	$+^{vg}/vg^{no}$	$+^{vg}/vg^{ni}$	$+^{vg}/+^{vg}$
Character of wing	absent	stumps		antler-like	ragged	scalloped	notches	nicks	nicks	nicks	wild-type	wild-type	wild-type	wild-type	wild-type
Percentage of incisions	100	100	100	100	100	70.7	42.4	27.1	1.3	0.2	0	0	0	0	0
Numerical value	12	16	20	21	25	28	30	32	36	37	40	44	45	52	60
Divergent wings	++	++	++	+	+−	−	−	−	−	−	−	−	−	−	−
Erect scutellars	++	++	++	+	+−	−	−	−	−	−	−	−	−	−	−
Rudimentary balancers	+++	++	++	+	+−	−	−	−	−	−	−	−	−	−	−

GENOTYPE	vg^{N_w}/vg^{N_w}	vg/vg^{N_w}	vg^{ni}/vg^{N_w}	vg/vg	vg^{no}/vg^{N_w}	$+^{vg}/vg^{N_w}$	vg^{ni}/vg	vg^{ni}/vg^{ni}	vg^{no}/vg	$+^{vg}/vg$	vg^{no}/vg^{ni}	$+^{vg}/vg^{ni}$	vg^{no}/vg^{no}	$+^{vg}/vg^{no}$	$+^{vg}/+^{vg}$
Percentage of shortened 2 vein	uncontrollable	uncontrollable	100	uncontrollable	100	73.3	8.4	2.6	2.1	0	0	0	0	0	0
Numerical value	6	13	17	20	22	23	24	28	29	30	33	34	38	39	40

For those characteristics which are correlated with the marginal incisions the threshold for the first deviation from wild-type lies considerably lower, namely, at 25 (table 2). From here the degree of these changes increases gradually with gradually decreasing values. But with respect to the remaining characteristic, the vein-shortening, the relative values which correspond to the experimental data are different, namely, v_g^{Nw}, 3; v_g, 10; v_g^{ni}, 14; v_g^{no}, 19; + ^{vg}, 20; and the resulting numerical series as in table 2, last row. The threshold for the first deviation from wild-type lies here at 29 and that for constant production of the vein-shortening at 22.

The above numerical values are used for the sake of illustration in order to bring out more clearly the relative difference in potency among the genes studied, and the series have clearly the character of a rough approximation. But their general trend corresponds well with the experimental evidence. Not until the collected data were analyzed was it realized that the material lent itself to such a treatment as that above. (The data on the vein-shortening in the No-wing compounds have later been increased. These additional data are in line with those presented.) It then turned out that the vein character of one particular compound, the nicked/vestigial, had not yet been investigated. By aid of the numerical value of this compound it was then predicted that it was to be expected that this would have the vein-shortening in a percentage of cases lying between 73 percent and 3 percent. The low percentage actually found, 8.4 percent, is in accordance with STERN's results (1929) which indicate that the potency curve rises very smoothly when it approaches the threshold for the production of the wild phenotype. This is also the case with respect to the marginal incisions (see table 2).

In connection with the above evidence the results of ROBERTS (1918), HERSH and WARD (1932) and especially of HARNLY (1930) on the influence of temperature on the development of the wings of vestigial flies should be recalled. HARNLY found that a rise in temperature from 29° to 31° had a striking effect on the wing length of vestigial males, while a rise from 30° to 31° had an analogous effect in the female. At the critical temperature flies occur with wings resembling strap, antlered, cut or even Beaded. Correspondingly, the divergent position of the wings and the erect position of the scutellars were in the males changed toward the wild-type. The latter point is interesting since in the different genotypical combinations the correlated vestigial characteristics are generally more pronounced in the females.

Thus, a critical rise in temperature modifies vestigial into phenotypes which approach the normal and which parallel those which we, within the

refractory temperature limits, are able to produce by combination of different vestigial allelomorphs. When we remember the slow development of ordinary vestigial flies, analyzed by HARNLY (1929) and by ALPATOV (1930) this situation falls well into line with GOLDSCHMIDT's conception of *Abgestimmte Reaktionsgeschwindigkeiten,* and the effect of the vestigial allelomorphs on the correlated characteristics may also be accounted for by the aid of GOLDSCHMIDT's quantitative interpretation. But when we also consider their influence on the vein-shortening, we are up against the same difficulties as DOBZHANSKY (1930) in his analysis of the three Stubble allelomorphs, which, according to potency, range in one order with respect to influence on bristle length, and in another as regards their effect on size of wings and length of legs. As emphasized by DOBZHANSKY, this disproportionateness of the effect on different characteristics seems very hard to bring in accordance with GOLDSCHMIDT's theory in its simple form, even though we are aware that between the primary reaction and the end result there lies a long chain of intermediate reactions.

In the above the normal allelomorph was given the highest potency value. Correspondingly among the mutant genes those which produce the slightest deviation from standard, that is, which in their effect most closely approach the wild-type gene, have been considered most potent, and *vice versa.* In order to obtain further light on this point we are going to consider another line of evidence, namely, the behavior of mutant and normal genes in deficiency where we are able to study their effect in single quantity, that is, without any normal or mutant partner gene being present at the same time. That a deficiency represents an actual loss of a chromosome section may be regarded as established in view of the combined genetical and cytological evidence of BRIDGES (1921) from the haplo-IV case and of PATTERSON and PAINTER (1931) from the mottled notched X-IV translocation.

In his above-mentioned analysis STERN (1929) bases the evaluation of the normal allelomorph on the "soweit bekannt, allgemein gültigen Tatsache, dass ein Faktorenausfall (that is, deficiency) auf die Ausprägung eines *normalen* Allels keinen Einfluss hat, dass also die Wirkung eines einzigen normalen Allels noch zur Erzeugung des Normaltypus ausreicht."

While this may be true in the bobbed case, it cannot, as we shall see, be the general rule. In table 3 is collected evidence from deficiency cases in *Drosophila melanogaster* studied by different investigators. For quite a few only preliminary accounts are as yet available so the data may be subject to later completion. Still, a comparison of the cases brings out some outstanding facts.

Firstly: Most deficiencies are accompanied by dominant character changes.

This may simply be due to the fact that deficiencies with dominant changes are most easily detected, and BRIDGES' (1917) forked-Bar deficiency forms a clear exception to the rule. STURTEVANT's reverted Bar, which represents a short deficiency at the Bar locus, comes in a special category since STURTEVANT (1925, 1928) has demonstrated that there exists no normal allelomorph at the Bar locus. The dominant changes are either as in Notch, Gull, in BRIDGES' Plexate (MORGAN, STURTEVANT, BRIDGES 1927) or in a new

TABLE 3

Comparison of deficiency cases in Drosophila melanogaster.

CHROMOSOME	INCLUDED MUTANT LOCI	DOMINANT CHANGES	EXTENT±
I	f, B	—	0.7
	s_{pb}, f_a, A_x,	Notch	0.5
	w, s_{pb}, f_a, A_x, A	Notch	3.8
	$p_m, w, s_{pb}, f_a, A_x, A\ e_c$	Notch	>4.0
	Left end to e_c (14 loci)	Lethal (Notch)	>5.5
	c_v	Minute (M-30)	?
	y, s_c, a_c	Bristle character	0.1
II	ft	Gull	1.1
	s_p, b_s, b_a, l_{IIax}	Plexate	0.5
	a, p_x	Minute (M_1)	1–1.5
	—	Minute (M_{1_a})	0.5
	h_k, p_r	Minute (Def. "H")	0.4
	$h_k, p_r, (B_l), l_t$	Lethal (Def. "G")	1.1
	p_x to right end (12 loci)	Lethal (Pale-Def.)	7.0
III	j_v, d_v, M_o	Vein	11.—
IV	all IV (7 loci)	Minute (Haplo IV)	?
	r_t, c_i	Minute (M IV)	?

III-chromosome deficiency Vein quite like those typical of any ordinary dominant gene, or they belong to the well-known dominant Minutes.

Secondly: The dominant changes are as a rule different from those produced by the included mutant genes. This relation is so striking that it may help in deciding between the alternatives lethal allelomorph or deficiency in cases where only one mutant gene is included (see MOHR 1928). For this reason Minute-30 of SCHULTZ (1929), Minute-IV of BRIDGES (MORGAN, STURTEVANT, BRIDGES 1926, 1928) and Vein have long been regarded as deficiencies in spite of only one gene being included, BELIAJEFF's (1931) rotated abdomen in Minute-IV (MORGAN, STURTEVANT, BRIDGES 1926, 1928) and BRIDGES' divergent in deficiency Vein. The legitimacy of this

view was proved when recently both a new recessive, javelin (j_v), located half a unit to the left of divergent, and MULLER's moiré (M_o) were found to be included in Vein, and correspondingly cubitus interruptus in Minute-IV. The latter observation was independently made by STURTEVANT. Without the above criterion the deficiency interpretation remains doubtful in the so-called vermilion-deficiency case (BRIDGES 1919) and also in the case of the dominant Truncate which, as shown by MULLER, acts as a lethal member of the Truncate allelomorph series (see MOHR 1928).

Thirdly: All known deficiencies are lethal when homozygous, and from cases of translocations we know that several are lethal also in heterozygous condition. It is not justified, as has frequently been done, to correlate this heterozygous lethal action with the extent of the deficient section. DOBZHANSKY's (1930b) short deficiency *"G"* (see RHOADES 1931) is lethal when heterozygous, while much longer Notch deficiencies and deficiency Vein are not (see below). PATTERSON (1932b) has demonstrated that a very limited deficiency to the left of prune in the X chromosome is lethal when heterozygous. Clearly, the heterozygous lethal effect is not due to the number, but to the special quality of the genes involved.

Fourthly: In combination with the deficiency the included mutant genes are exaggerated in their effect (MOHR 1919, 1923). With increasing evidence, it has been all the more firmly established that the character is in the compound shifted away from, not toward, the wild-type. Occasionally an included mutant gene fails to exhibit exaggeration effects. This applies to yellow in L. V. MORGAN's yellow-scute-achaete deficiency (MORGAN, STURTEVANT, BRIDGES 1927), to prune in PATTERSON's Notch 172b and to purple in DOBZHANSKY's deficiencies *"G"* and *"H"* (DOBZHANSKY 1930b, MORGAN, BRIDGES, SCHULTZ 1930). This relation is readily explained as due to the homozygous effect of the gene in question representing by itself the bottom of the differentiable mutant changes possible at this locus (see MOHR 1928). This conception is supported by the fact that in none of these cases have more extreme mutations at the same locus been encountered. To my knowledge only a single case forms here an apparent exception. But since the stock in question had been lost before the exaggeration phenomenon had been detected, it is not now possible to decide what importance should be attributed to this case.

After the establishment of the above rules we may now turn to the question of their explanation.

The best known and frequently recurring deficiency is the sex-linked Notch, which has been encountered more than 30 times in untreated ma-

terial and apparently still more frequently in PATTERSON's (1932c) X-ray experiments. The majority involve short sections including the facet locus (at 3.0±), but some, such as Notch 8 (MOHR 1919, 1923) or Notch 18 found by BRIDGES (see LI 1927, LI and BRIDGES 1929), extend far enough to the left to include white, while in still others involved in PATTERSON's chromosomal aberrations (see PATTERSON 1932a, 1932b, 1932c), the entire left end of the X chromosome to and including echinus (at 5.5) has been removed. Such a deficiency involved in the mottled notched translocation (PATTERSON 1932a) is lethal for the zygote, but somatic mosaic tissue resulting from elimination of the translocated fragment later in development is viable and Notch.

Now PATTERSON (1932b) was able to demonstrate that this zygotic lethal effect is due to the very limited section between scute and prune not being present in duplicate. If the deficiency is combined with a fragment containing the loci for yellow and scute, the zygote is non-viable. But if it, as in Notch 172b, is combined with a *Theta* fragment which in addition contains the normal allelomorph of broad (*b^+*), then the zygote is viable and Notch (see diagram, figure 4). From various tests of this type PATTERSON concludes that the small section between scute and prune contains a "gene for viability" which must be present in duplicate if the zygote is to survive.

A comparison of these Notch deficiencies of very different length (figure 4) leads to the following conclusion: Genetically, the only thing which they have in common is that a short section around facet is not present in duplicate. Still, disregarding the total extent of the haploid section, the phenotypical result is essentially the same in all, namely, the Notch complex: the thickened veins with Δ-like insertions, the notches, the supernumerary, irregularly arranged acrostical hairs and the bristle irregularities (figure 5). This was confirmed by special experiments with four short (N26 to 29) and two long (N8 and N172b) Notch deficiencies. This can only mean one thing: In the short section mentioned there must be present one or more normal allelomorphs which when present in single quantity in the female are not potent enough to produce the wild phenotype. They are haplo-insufficient. Accordingly the dominant character complex results.

It is not justified to identify as has repeatedly been done the locus responsible for the Notch character with the facet locus proper. I have recently tested the mutant split bristles (*s_p*) of DUBININ (ROKIZKY 1930) with the above-mentioned four short and two long Notch deficiencies, and split, located at 2.7±, proved to be included in all of them. The same was also found to be true of NASARENKO's (1930) incompletely dominant Ab-

rupt-X (A), located very close to split (no crossing over in more than 2000 flies). Neither split nor Abrupt-X is allelomorphic to facet. Hence, what we know is that when the very short s_{pb}-f_a-A_x region with its contents of normal allelomorphs is not present in duplicate, then the Notch character results.

The left-hand adjacent section, to and including prune, and the right-hand section, to and including echinus, can not contain analogous haplo-

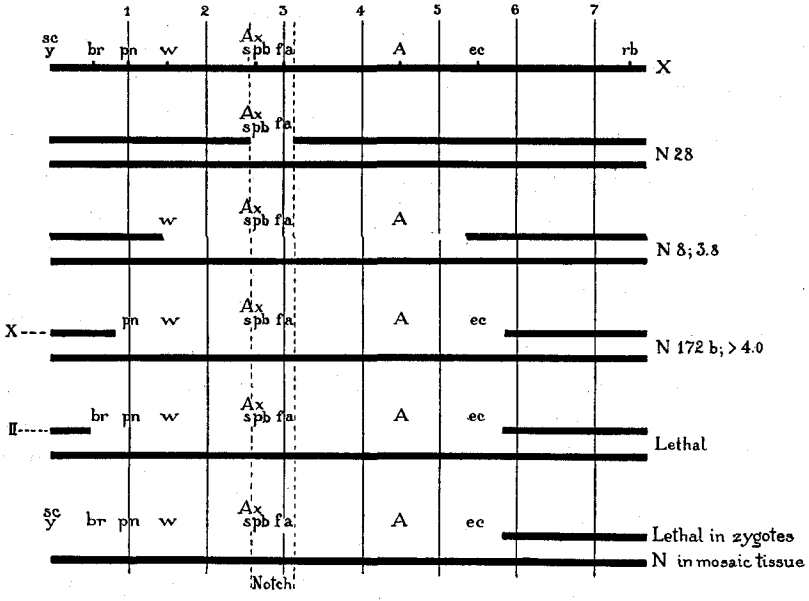

FIGURE 4.—Diagram of the X chromosomes in five different Notch deficiencies. In the three most extensive a loss of the left end of the X, to and including echinus (e_c), is combined with attached fragments of different length, as indicated to the left in the diagram. Above: Map of the left part of the X chromosome. The relative location of the closely linked genes s_{pb}, f_a and A_x is provisional. According to later information from NASARENKO A_x is located close to the right of f_a (1 crossover in about 5,000 flies).

insufficient normal genes since the absence of one representative of these additional sections does not alter the Notch phenotype. Deficiencies in these sections are accordingly not expected to produce dominant somatic character changes. But between scute and prune we encounter another haploinsufficient normal allelomorph, which, if left alone, induces such great changes that the zygote is as a rule non-viable. This is in our opinion the nature of PATTERSON's gene for viability.

An analysis of the exaggeration of the commonly included mutant genes in the same six Notch deficiencies of very different length proved that the

exaggeration is also of the same type and degree in all, entirely disregarding the extent of the section involved. This indicates that the exaggeration can not be due to the difference in ratio of plus to minus modifiers within the lost section as compared with that of the normal X chromosome (BRIDGES 1921, 1922, 1923) and gives support to GOLDSCHMIDT'S (1927, 1928) view that the exaggeration is due to the mutant gene being present in single quantity only, with a corresponding shifting of the character further away from the wild-type. This relation which also holds in cases of autosomal deficiency demonstrates that the exaggerated mutant genes in question are more potent in duplicate than singly.

It may of course happen that neighboring included haplo-insufficient normal genes may produce character changes which modify the effect of a particular included mutant gene. An illustration of this relation forms in my opinion the Notch/Abrupt-X compound studied by NASARENKO (1930) where Notch and Abrupt, which separately produce opposite character changes, neutralize the effect of each other so that Notch is suppressed and the exaggerated Abrupt character somewhat less pronounced than in homozygous Abrupt (figure 5). (In NASARENKO'S (1930) linkage tests with A_x there was a reduction in crossing over around the A_x locus. This in combination with the exceptional character of the N8/A_x compound led NASARENKO to the hypothesis that the A_x mutant is possibly due to a duplication. In our linkage tests $\frac{A_x}{w^a\ s_{pb}\ e_c\ r_b}$ the linkage values were normal.) An analogous situation is found in the haplo-IV eyeless flies in which the exaggeration of the eye character is almost negligible due to the opposite tendency of the haplo-insufficient normal allelomorphs which cause the enlarged eye of ordinary haplo-IV flies (see MOHR 1932). In this special sense the change in balance may modify the end result, but it can not be the cause of the exaggeration proper.

Already in the first account of the exaggeration of the included mutant genes the question was raised whether normal genes opposite to the deficient section were not influenced in a similar way, and it was stated (MOHR 1919): "To some extent this seems to be the case. . . . It is natural to suppose that these somatic peculiarities (that is, the dominant Notch character complex) are a result of the modification of one or more of the normal genes in the region opposite to the deficient piece, similar to that which has been demonstrated in the case of the mutant genes. It is superfluous to regard the character Notch as due to an independent specific mutant gene contained in or linked to the deficient region.

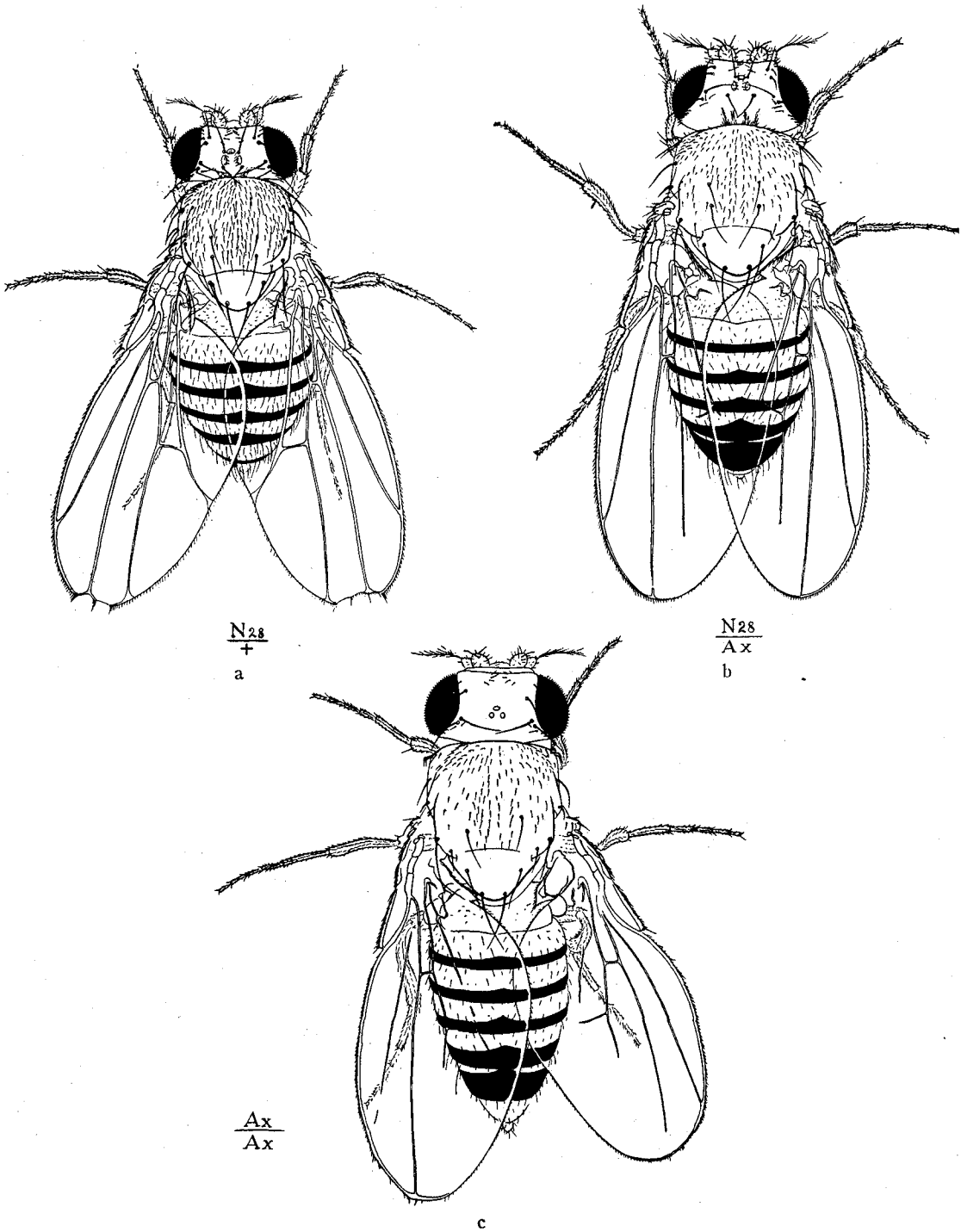

FIGURE 5.—a, Notch-28 female. b, Notch-28/Abrupt-X female. c, Homozygous Abrupt-X female.

"It would seem probable that many normal genes are contained in such a piece of the X chromosome as that opposite to the deficient region. *The fact that more extensive alterations are not caused when the deficient chromosome is present could perhaps be said to point in the direction that the normal genes must have different potencies. The mentioned mutant genes and some of the normal ones in the region opposite are affected, while other normal genes, supposedly present in the same region, are not visibly influenced.*"

The correctness of this at the time necessarily more tentative opinion has been confirmed by the now available additional evidence discussed above.

We may now try the application of this view to some additional cases:

BRIDGES' Minute-1 deficiency (MORGAN, STURTEVANT, BRIDGES 1924, BRIDGES 1930) covering the arc-plexus section of the second chromosome produces Minute bristles and female sterility. SCHULTZ's shorter allelomorphic Minute-l_2 deficiency closely to the right of plexus (MORGAN, BRIDGES, SCHULTZ 1930) and overlapping the right-hand end of Minute-1 produces Minute bristles, but no female sterility. BRIDGES (1930) accordingly concludes that the latter characteristic is due to the loss of genes located in the left part of the Minute-1 region. Conversely, when BRIDGES combined Minute-1 with the Pale-III duplication, a translocated section extending from (and including) plexus to the right-hand end, the resulting $M_1/ + P_{III}$ flies were deficient for the arc locus, female sterile and non-Minute (see diagram, figure 6). Obviously, in the left part of the Minute-1 section there are haplo-insufficient normal allelomorphs which, when left alone, cause the female sterility and correspondingly in the right part analogous haplo-insufficient normal genes which are responsible for the Minute reaction.

Further: The hook-purple deficiency in DOBZHANSKY's II-Y translocation *"H"* (see SCHULTZ and BRIDGES 1932) produces a dominant Minute, while his longer allelomorphic hook-purple-light deficiency involved in his analogous *"G"* translocation studied by RHOADES (1931) is lethal when heterozygous. When SCHULTZ combined deficiency *"G"* with the shorter duplication *"H,"* the net result was a short deficiency which produces an extreme Minute and acts as a deficiency for light (MORGAN, BRIDGES, SCHULTZ 1931) (see diagram, figure 7). Hence both inside and outside the section which the two deficiencies have in common there must be haplo-insufficient normal allelomorphs which, when left alone, induce Minute reactions. And if the entire hook-light region is represented in single quantity only, the sum of the action of all the haplo-insufficient normal genes present in this section leads to deleterious character changes.

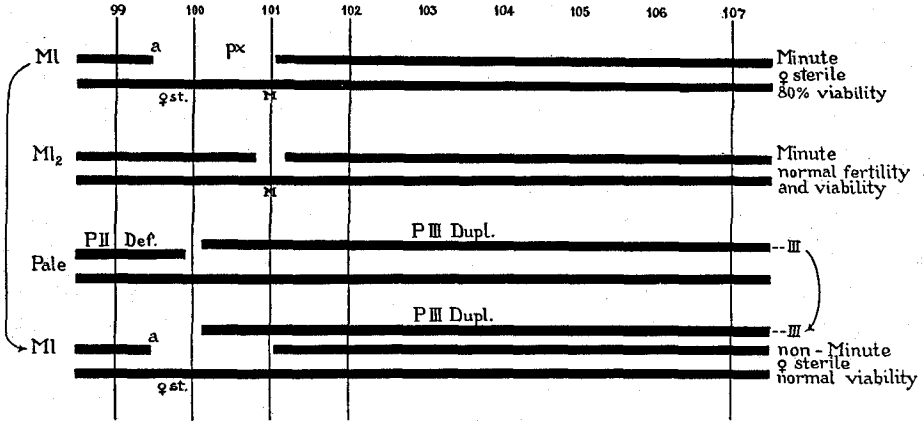

FIGURE 6.—Diagram for comparison of the allelomorphic II chromosome deficiencies Minute-1 and Minute-l_2. Below: the combination of deficiency Minute-1 with the Pale III duplication.

Finally, as BRIDGES (1921) has shown, diploid haplo-IV flies are Minute. As pointed out by SCHULTZ (1929) there is reason to assume that the Minute-IV section, a deficiency for rotated abdomen and cubitus interruptus, represents the section responsible for the Minute bristle change. BRIDGES has found that whereas diplo-IV triploids are viable and fertile, haplo-IV triploids die. And the responsibility for this lethal action has been definitely placed by SCHULTZ with the Minute-IV section, since he found that triploids with two fourth-chromosomes of which one carries the Minute-

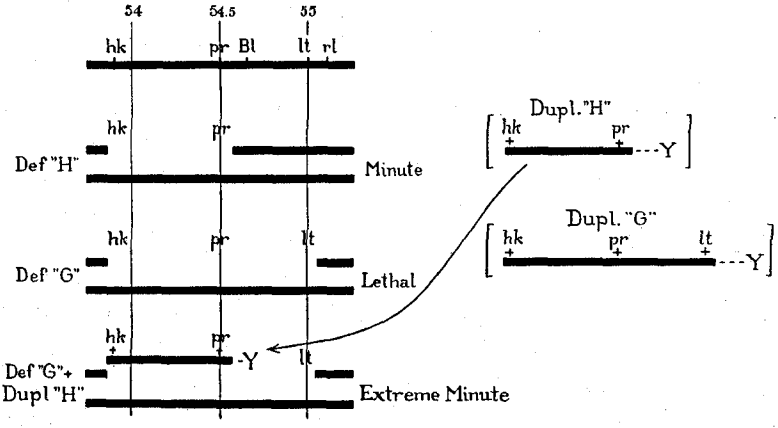

FIGURE 7.—Diagram for comparison of the allelomorphic II chromosome deficiencies *"H"* and *"G."* Above: Map of the corresponding region of the second chromosome. Below: The combination of deficiency *"G"* with duplication *"H."*

IV deficiency are also non-viable (see diagram, figure 8). Indirect evidence supporting the same view is presented by SCHULTZ and may also be derived from BOLEN'S (1931) analysis of a reciprocal X-IV translocation. Hence, the Minute-IV region contains haplo-insufficient normal genes which, when left alone, in the diploid system cause the Minute bristles and correspondingly in the triploid have a lethal effect.

The striking phenomenon that so many deficiencies produce Minute character changes seems in view of SCHULTZ's evidence to indicate that many of the haplo-insufficient normal genes are concerned with early growth processes. In this connection it is also of interest to recall that the haplo-insufficient gene between scute and prune in the X chromosome produces lethal changes if present in single quantity during the early

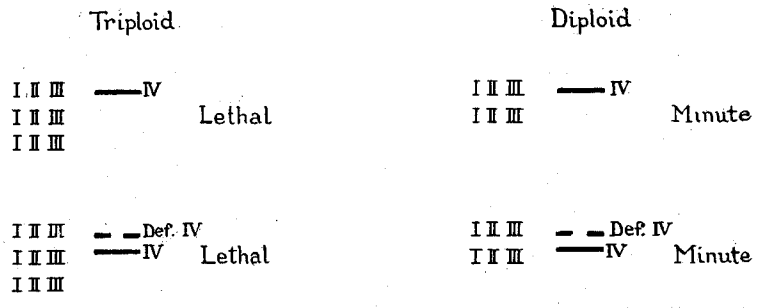

FIGURE 8.—Diagram for comparison of the effect of haploidy for the entire fourth chromosome and for the Minute-IV section in diploid and triploid individuals.

growth stages, but not so if the loss of the section takes place during the later somatogenesis. Correspondingly, as shown by STERN (1927), deficiencies involving large sections of an autosome have no lethal effect in somatic mosaic cells, which we know from translocations that they have during the early development of the zygote. For a series of Minutes, including clear cases of deficiency, BRIDGES, REDFIELD and especially SCHULTZ (1929) have found that two doses of a Minute in the triploid have a lethal effect while one dose is completely recessive. In the latter respect the Minutes differ from other dominants such as Curly, Dichaete or Stubble (SCHULTZ 1929, REDFIELD 1930). All these dominants are lethal when homozygous, but in spite of this SCHULTZ found in the case of Stubble that triploid flies with two doses of Stubble are of good viability, and they have very pronounced Stubble characteristics (DOBZHANSKY 1930a).

This special behavior of many Minutes seems very natural. If we consider a particular Minute character in the diploid as due to the action of the haplo-insufficient normal allelomorph *a*, then in the triploid with one dose of the

deficiency *a* is represented twice, equalling 2*a*, while in triploids with two doses of the deficiency only one *a* is present (see diagram, figure 9). In order to make the potency values for the triploid system comparable to those of the diploid, we have to reduce the former by multiplication with 2/3. This gives for the triploid combinations mentioned the values 4/3 *a* and 2/3 *a* respectively. While the potency value 2/3 *a* is generally so low that the lethal threshold is passed, the value 4/3 *a* is, conversely, in most cases sufficient to reach the threshold for the production of the non-Minute, wild phenotype.

That two doses of an ordinary recessive gene have as a general rule no somatic effect in the triploid (MORGAN, BRIDGES, STURTEVANT 1925, SCHULTZ and BRIDGES 1932) seems also natural since to the effect of the two mutant genes is here added that of the normal allelomorph simultaneously present so that the sum of these combined effects passes the wild-

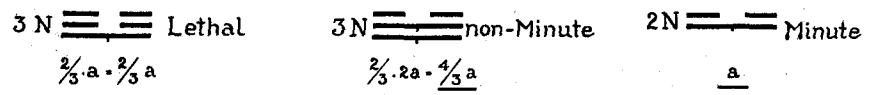

FIGURE 9.—Diagram for comparison of the effect of Minute deficiencies in diploid and triploid individuals.

type threshold. Conversely, triploids carrying a deficiency plus two doses of an included recessive gene show the corresponding recessive character, but not the dominant character of the deficiency (MORGAN, BRIDGES, SCHULTZ 1930).

We have in the above concentrated our attention on certain evidence from multiple allelomorphism and from the action of genes in single quantity, two of the indirect ways accessible for inferences respecting the potency of mutant and wild-type genes. Both these lines converge in supporting the conception that mutant and normal genes are essentially similar and additive in their effect, a result which is in accordance with that arrived at by STERN (1929) and, for certain classes of genes, by MULLER, LEAGUE and OFFERMANN (1932) in the studies of changes in gene dosage. The mutant genes dealt with are less potent than the corresponding wild-type genes, and they are more potent in duplicate than singly. Of the normal allelomorphs some are so potent that the wild-type threshold is reached even when they are present in single quantity only. They are haplo-sufficient. Others, the haplo-insufficient normal genes, are less potent, and the latter are responsible for the dominant changes encountered in deficiency.

A reasonable corollary from this view would be that there is also an upper potency threshold for the wild phenotype. If this threshold is passed by

provision of additional gene doses (possibly also by gene mutation to allelomorphs which are more potent than the corresponding wild-type gene) then again dominant changes will result. Evidence supporting this conception may be derived from cases of duplication.

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