The Effects of Changes in Quantity, Combination, and Position of Genes

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THAT WE KNOW OF THE EXISTENCE OF GENES is intimately bound up with the fact that genic species occur in different varieties. If all mankind had identical eye color, no knowledge of eye-color genes would have been obtained. As it is, the differences between the eye colors of different individuals can be traced back to differences in causal agents, located at a specific region in a specific chromosome of these individuals. In one individual the specific region, or locus, controls, in collaboration with other agents, the developmental processes which lead to the appearance of one type of eye color; in another individual the same region exerts a control which leads to the development of another type of eye color. This region, or locus, we call the "gene," and its different varieties, as present in different homologous chromosomes, we call the "alleles" of the gene. What the gene consists of, or what distinguishes it from other genes at other loci, remains an unsolved problem. What the differences between alleles consist of remains likewise beyond the scope of the discovery that there *are* different alleles.

In its final form the problem of the nature of genes and their allelic varieties belongs in the sphere of the chemist. Someday, structural formulas will be available which describe the constitution of different genic species and their allelic varieties. At that time we will also understand in detail how the gene molecules, or molecular complexes, interact with their immediate cellular surroundings and initiate, or control, or enter into reactions which are part of the multidimensional network of processes which constitute cellular metabolism and development. The biochemical analysis of these processes themselves may lead us backward until primary genic action is reached. In particular, the biochemistry of metabolic differences caused by different alleles has led to most significant results and suggestive interpretations. Very likely certain initial reactions which the wild type strains of *Neurospora* can, and which strains with mutant alleles cannot, perform are very close to the gene end of reaction sequences. How close remains undecided, since it does not become obvious when the tracing backward of reactions has reached the unknown gene.

The geneticist can employ some methods of manipulating the conditions at the gene end. He can vary the quantities of given alleles present in the cells; he can assemble combinations of different alleles; and he can cause shifts in the position of genes within the chromosomal system. From determinations of the effects of such manipulations certain statements can be made about the reactions leading to the effects. Such analyses do not lead to specific recognition of the reactions but rather to knowledge of certain general characteristics. As in the discovery that there *are* genes and alleles, which falls short of showing *what* these entities are, the manipulation of gene quantities, combinations, and chromosomal positions will lead to recognition of some attributes of genic reactions but not to the reactions themselves. Undoubtedly, some day the biochemical and the genetic approaches will be combined in suitable material.

The following discussion will survey results of the genetic approach. Different workers, particularly R. Goldschmidt (*2*) and Sewall Wright (*11*), have contributed data and interpretations in this field. Instead of attempting a general summary, this paper will deal with one locus only, namely, the gene cubitus interruptus, ci, in *Drosophila melanogaster* (*3–10*). This gene is concerned with the formation of the fourth (cubital) vein on the wing of the fruit fly. The effect, under various genetic and environmental conditions, ranges from complete absence of the distal section of the vein, over the absence of only parts of this section, to its complete presence. By determining the length of the vein fraction present, one can read off the genic effect in a quantitative way—though it should not be supposed that primary gene effect and terminal vein effect are linearly related.

The ci locus is suitable for dosage studies since it is part of the small "fourth" dot chromosome which can be obtained in quantities from one to three in otherwise diploid flies. Furthermore, it is not necessary to study flies distinguished by the number of whole dot chromosomes. Dot chromosomes are available in which a short middle section, which includes the ci

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locus, is lacking. By the use of these deficient chromosomes a series of quantities of the ci locus can be built up, namely, one dose (one nondeficient chromosome, one or two deficient chromosomes), two doses (two nondeficient chromosomes, none or one deficient chromosome), and three doses (three nondeficient chromosomes). These dosage studies were carried out on different alleles of the ci gene. For the typical mutant allele ci, gene quantity and presence of venation are positively correlated: the more genes, the more vein is formed (Fig. 1, middle).

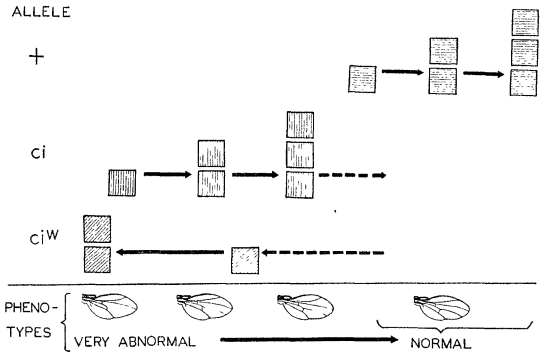

FIG. 1. The effect of different doses of the alleles +, ci, and ciW on venation in *Drosophila melanogaster*.

While the name cubitus interruptus might suggest that the allele ci is an active agent causing vein *interruption,* the dosage data show that the ci allele works toward the same effect of presence of venation as does the normal allele. However, even three ci alleles, while they approach it, are not yet sufficient to accomplish normality.

It fits in well with this result that a single quantity of a wild type normal allele of ci does not cause complete venation. Such normality requires two doses of a normal allele for its production. The effect on venation of three doses of a wild type allele does not go beyond that of two (Fig. 1, top).

The dosage studies of wild type alleles led to a further finding—that of different kinds of normal alleles. Each of them, in double dose, causes full venation, but by single doses different degrees of incompleteness of vein are produced.

A strikingly different dosage effect is observed with the mutant allele ciW. A single quantity of ciW results in a fairly high amount of vein material. Two ciW alleles, on the other hand, decrease this amount greatly (Fig. 1, bottom).

What may be deduced from these dosage data as to basic genic action? We visualize such action as taking place beween the chromosomal gene and a cellular—probably intranuclear—substrate S (Fig. 2). The fact that increased quantities of from one to three doses of the mutant ci allele result in increased venation means that S is present in excess

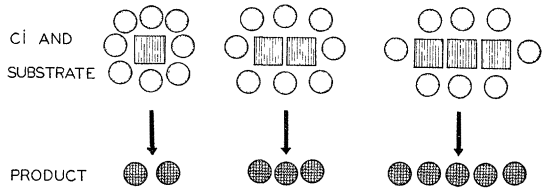

FIG. 2. An interpretation of the dosage effect of the ci allele in terms of substrate and different amounts of product.

of the amount turned over by one or two of these alleles. Furthermore, the simplest assumption regarding the product, P, of the interaction of ci and S is that P enters a chain of reactions which is positively correlated with the sequence of developmental processes leading to appearance of venation. It is also apparent that whatever the number of links in this chain of reactions is, no threshold effects occur which obliterate the result of the differences in amount of P which, in turn, are caused by the dosage differences of ci. These deductions are independent of specific hypotheses of gene action. If primary gene action should consist of production of total or partial replicas of genes which are sent into the cytoplasm and there enter metabolic and developmental processes, then P would represent these replicas.

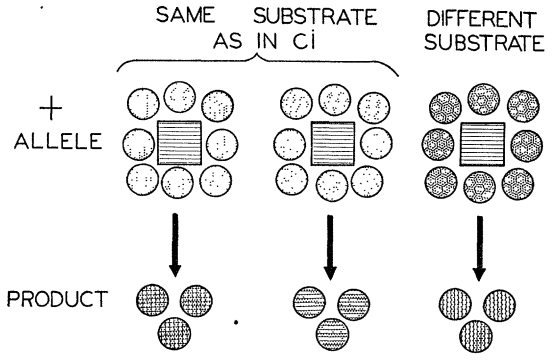

FIG. 3. Alternative interpretations of the difference in effect of the + and the ci allele: left, same substrate for + as in ci, and same product, in increased quantity as compared to ci; middle, same substrate for + as in ci, but different product; right, different substrate for + than in ci, and different product.

The dosage effect of normal alleles of the ci locus implies, again, excess of substrate present in the nucleus beyond the amount turned over by one dose. The absence of a phenotypic difference between organisms with two and three normal gene quantities shows that a limit is reached. Whether this limit is due to restriction of primary substrate or restrictions at later developmental stages remains unknown.

A comparison of the action of a normal, +, and the mutant, ci, allele involves assumptions regarding the substrate and the primary product (Fig. 3). Assuming that an allele utilizes a single substrate, it could either be that the two different alleles use the same substrate, S, or that they use different substrates, S_+ and S_{ci}. In the former case two possibilities exist in regard to the primary product. Both alleles may transform the same S into identical Ps, but in different amounts, or specifically different products, P^+ and P_{ci}, may be formed. The formation of qualitatively different products is also most likely, should the two alleles use different substrates, S_+ and S_{ci}. Whatever the situation, it is necessary to explain the similar, though quantitatively graded, action of the two alleles. With identical P, a lower rate of production under the influence of ci as compared to + is sufficient to account for the facts. With different P_+ and P_{ci}, the situation would be similar to that met in a great variety of physiological studies in which chemically related substances produce metabolic or developmental effects which can be arranged in a quantitative series.

The dosage effect of the ci^W allele, which leads to decrease instead of increase of venation with increasing gene quantity does not so readily fit into the schemes outlined. It is unlikely that ci^W produces the same kind of P as either one or both + and ci. This assumption could be made only if one is willing to postulate a relation between quantity of P and vein effect, such as to yield similar effects with large and small quantities but unlike effects with intermediate quantities. While such relations are not unknown in pharmacological studies, known variations of quantity in genic dosage studies have always shown simple relations between increase of gene quantity and increase of effect (often up to a maximum beyond which no further changes in effect take place). Admittedly such dosage studies are few in number, and the hypothesis of ci^W producing the same kind of P, but in a quantity outside of the range of those produced by the known doses of ci and +, cannot be disproven. However, in the light of further facts to be quoted below the hypothesis of identical primary products of various alleles would probably involve a whole series of maxima and minima of effects in relation to quantity of P and thus become increasingly improbable.

If ci^W results in a specific $P_{ci}{}^W$ unlike P_+ and P_{ci}, an explanation of why two $P_{ci}{}^W$s cause less venation than one $P_{ci}{}^W$ is still required. One might assume a destructive property of $P_{ci}{}^W$ in regard to the processes which lead to venation. This would mean that processes resulting in presence of the vein go on independently of the ci locus and that the alleles + and ci accelerate these processes while the alleles ci^W and ci^D (this latter will not be dealt with here) slow them down. One might either acquiesce with such a concept or try to fit it into a more unified picture. Considering the presumptive similarity of alleles of the same genic species, one might prefer a picture of basically similar, though quantitatively different, effects of different alleles. Such a picture would permit variations in effect from zero to some positive or negative value but not *both* positive and negative ones. As a specific illustration it might be assumed that the ci^W allele

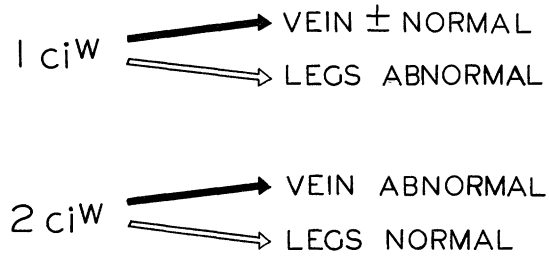

FIG. 4. Dosage effect of ciW on vein and legs.

controls two different processes, one leading toward (positive) production of venation and the other toward an unrelated phenotype. Assuming further that these two processes interfere with each other, a scheme could be developed according to which an increase in dose of ci^W strengthens the reaction to the unrelated phenotype at the cost of the vein reaction, resulting in a negative correlation between vein effect and gene quantity. Such a scheme is not completely without foundation, since the ci^W allele strikingly affects leg and bristle formation in contrast to the + and ci alleles, which, with every dose, lead to normal legs and bristles (Fig. 4). A single ci^W dose, while making for nearly normal venation, causes crippled legs and extra bristles; a double dose of ci^W reverses the situation, leaving a great gap in the vein but permitting nearly normal legs and bristles.

The data on effects of different doses of alleles take on a new aspect when combinations of different alleles are considered. In general, heterozygotes between two alleles either appear phenotypically similar to one of the homozygotes or show an intermediate phenotype. Conforming to these rules, the venation shown by ci/+ flies is intermediate between ci/ci and +/+, and ci^W/+ flies are intermediate between ci^W/ci^W and +/+. The heterozygotes ci/ci^W are close to ci^W/ci^W phenotypically. It thus appears as if the action of heterozygotes may be interpreted in terms of independent action of their constituent alleles, e.g. two doses of ci cause a certain small amount of

venation, two doses of + a large one, and the combiation of one dose of each results in an intermediate venation. This simple interpretation proves insufficient if a comparison is made not between heterozygotes and the homozygotes of their constituent alleles but rather with their constituent hemizygotes. It now turns out that heterozygotes ci/+ are less normal than the hemizygotes +/0. The most striking case of this nature is found if a certain normal allele, $+^3$, is employed. Homozygotes $+^3/+^3$ are normal, and nearly all $+^3$ hemizygotes are likewise so. More than 40% of the ci/$+^3$ flies, however, show incomplete venation. This constitutes an interference in the action of the alleles ci and $+^3$. The dosage studies had shown that ci acts in the same direction as + or $+^3$, namely, toward production of venation. Yet, when ci and one of the two + alleles are brought together in the same nuclei, their joint effect is smaller than that of the more effective allele alone. These facts might suggest some mechanism of competition. If + and ci make use of the same substrate present in a limited amount, a competition might result in which the ci allele deprives the + allele of its full share. If the ci allele turned the substrate over more slowly or less efficiently into the effective product P than the + allele, the joint action of the two alleles might be less than that of the "better" one alone. Should the two alleles lead to the production of different P_{ci} and P_+ substances, then the competition would not necessarily occur at the primary gene action-level but could also take place at a later stage of the genic reaction chain where P_{ci} and P_+, or their further derivatives, might compete for substrates. While the idea of competition at the gene level was earlier placed by the writer into the foreground, new data to be reviewed below suggest that a later stage is involved. In view of the unknown nature of the interaction between the different alleles, it now appears preferable to use the more descriptive, general term, interference. Competition may or may not constitute the mechanism of interference.

The type of effect of the ci/ci^W heterozygote is similar to, but much more extreme than, that of ci/+. The legs and bristles of ci/ci^W are normal, but the vein greatly deficient. In other words, the presence of the ci allele, instead of "adding" its share of vein production to that of the hemizygous ci^W allele, which in single dose causes a high degree of venation, results in an interference in gene action, leaving the vein nearly unformed. Most striking is the interference in the last combination to be discussed here, that of + and ci^W (Fig. 5). The hemizygotes of both these alleles appear normal in venation or close to it, whereas the heterozygotes $ci^W/+$ have greatly deficient veins. This case demonstrates not only that the interference phenomenon consists of an effect of one of the two alleles on the other but that it is a mutual interference of the two alleles since the heterozygote is less normal than either hemizygote.

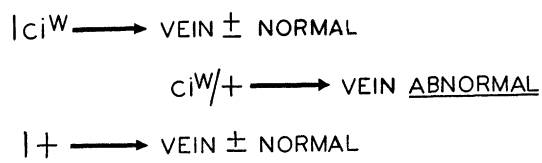

FIG. 5. Interference between + and ci^W.

The final manipulation of events at the gene end of the chain of genic action to be discussed consists of altering the chromosomal neighborhood of the ci locus. This can be done either by transferring a section of the dot chromosome which includes the ci locus to another chromosome or by removing part of the dot chromosome, exclusive of the ci locus, and replacing it by a section from another chromosome. Both methods of changing the position of the ci locus relative to neighboring chromosomal regions were used. Changing the position of a + allele gave rise to a number of rearrangements called R(+), with superscripts [$R^1(+)$, $R^2(+)$, etc.] denoting the different rearrangements as discovered one after the other in cultures derived from X-ray-treated flies. Changing the position of the ci allele similarly provided series of "position alleles R(ci)." R(+) alleles had first been studied by Dubinin and Sidorov, who discovered that homozygotes R(+)/R(+) and hemizygotes R(+) lead to normal venation just as the unchanged + allele, but that heterozygotes of many position alleles R(+) with the ci allele, R(+)/ci, show deficient venation. The observations seemed at first strange and peculiar to position alleles. It is now clear that these relations are quite similar to those characteristic for combinations of nonposition alleles as described above. They are an expression of interference phenomena which make combinations of alleles less effective in terms of venation than single doses of the alleles by themselves. The degree of interference varies with the kind of R(+) allele involved. Among 17 different R(+) alleles tested in our laboratory, interference was so strong in 4 cases that the heterozygotes R(+)/ci were more deficient in venation than either homozygote R(+)/R(+) or ci/ci. In the other 13 cases the degree of interference was less, making the heterozygote venation-deficient, though less or not more so than the homozygote with high vein deficiency, ci/ci. And to make the similarity with a nonposition allele, ci^W, still greater, one of the R(+) alleles, $R^2(+)$, turned out to cause

normal phenotype in hemozygous but deficient ci/ci-like venation in the homozygous state.

When position alleles of the mutant ci allele were produced, new facts came to light. No comprehensive survey can be given at present which covers the more than 40 different R(ci) alleles which have been tested. Dosage studies were made with a few of those that proved to be viable in homo- and hemizygous doses. (Rearrangements frequently are associated with recessive lethals.) With only one exception the R(ci)/R(ci) homozygotes studied did not cause the appearance of less veins than the ci/ci constitution, while several proved to be more effective in vein formation than ci/ci. Some of these R(ci) alleles—for instance, R^{29}(ci)—while leading to less than normal venation in double dose, lead to fuller venation, in some cases nearly normal, in single dose.

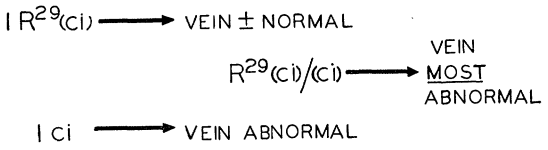

FIG. 6. Interference between R^{29}(ci) and ci.

Yet, in combination with both ci or a + allele—that is, as R(ci)/ci and R(ci)/+ heterozygotes, these same as well as nearly all other R(ci) alleles lead to more deficient venation than ci/ci and ci/+, respectively. In some case, as in R^{29}(ci)/(ci), the amount of vein present was less than in either of the two constituent hemizygotes R^{29}(ci) or ci (Fig. 6). Thus, again we meet the interference phenomenon in its extreme, clearly mutual expression.

One further fact appeared in studies of recombinations involving position alleles. When the R(ci) alleles were arranged in order of increasing effectiveness in vein production, if combined in heterozygotes with a + allele, and this arrangement was compared with one based on increasing effectiveness in vein production, if the R(ci) alleles were combined with the ci allele, it was found that the two arrangements did not follow the same order. For example, R^{52}(ci)/+ leads to more venation than R^{18}(ci)/+, but R^{52}(ci)/ci to less venation than R^{18}(ci)/ci.

What distinguishes the position alleles from the nonposition alleles which gave rise to them, and what differentiates the different R(+) and the different R(ci) position alleles from each other? No final answer to these questions seems to be available, but it is at least possible to suggest which apparent answers fail to solve these problems. The change which transforms a normally located allele into a position allele is of a different nature from mutant changes which transform alleles. The latter are caused by changes directly at the locus in question, and they are essentially irreversible. The former may be caused by breakage at considerable distance from the locus and replacement of the normally neighboring chromosomal material by different chromosomal material, and the change in the action of the gene reverts immediately when its normal position is restored. It appears, thus, that position alleles owe their properties not to intrinsic alterations of the original alleles but to changes in their chromosomal environment.

A simple hypothesis which might be invoked is the assumption that the specific substrate for each gene is present in a specific concentration in the neighborhood of a normally located gene but in a different concentration in those other regions to which the gene had been shifted. Such a hypothesis would account for the whole range of effects of different position alleles according to range of concentrations of the substrate. This idea has met with great difficulties as more data have become available. Since nearly all R(ci)/+ heterozygotes cause less venation than ci/+, one would assume that in general the concentration of the substrate is less at the R(ci) loci than at the ci locus. Why, then, do some of these R(ci) homo- and hemizygotes cause more venation than ci/ci and ci? If the lesser amount of venation in R^{18}(ci)/+ as compared with R^{52}(ci)/+ were due to greater limitation of substrate at the R^{18}(ci) than at the R^{52}(ci) locus, why does R^{18}(ci)/ci make for more vein than R^{52}(ci)/ci? Furthermore, the observed interference from position allele to normally located allele in terms of the hypothesis of changed quantity of substrate would reasonably imply a sharing of the localized substrate by the two alleles, interference being the result of increased competition for a more limited quantity of the substrate. But if the R(ci) alleles had retained their original ci-like attributes, they should behave in R(ci)/ci heterozygotes toward ci as typical ci alleles in an additive, but not an interfering way. Finally, there is evidence against the concept of direct sharing of a localized substrate. Such sharing would involve very close spatial approximation of the two alleles within the nuclei of heterozygotes. In *Drosophila,* approximation of homologous chromosome regions is indeed normally present due to somatic pairing. There are, however, exceptions to this rule. In our collection of position alleles there occur two in which the chromosomal rearrangement consists of the removal of a short middle section from the dot chromosome, including the ci locus, and the insertion of this section

into another chromosome (Fig. 7). In heterozygotes in which one dot chromosome is typically whole while the other is "divided up" into the deficient dot chromosome and the insertion within another chromosome, no pairing takes place between the insertion and its homologous region in the complete dot chromosome. Yet, interference between position allele and

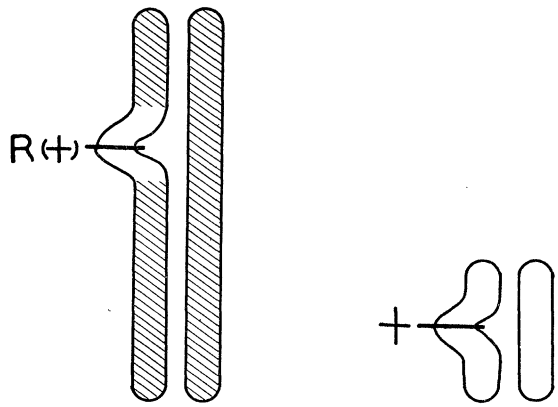

FIG. 7. Interference in absence of pairing between R(+) and +: left, chromosome pair with an insertion R(+) into one homologue from chromosome 4; right, chromosome pair 4, with one homologue deficient for the translocated R(+) section.

normally located allele occurs in typical fashion. This shows that close proximity is not necessary for the interference of position alleles with the action of normally located alleles.

The significance of these and other cases of position alleles in which no immediate proximity exists between the interfering alleles goes beyond its bearing on the hypothesis of substrate limitation. It shows that whatever the nature of interference is, it acts over distances which exclude a direct inhibition from gene to gene. Interference, if its site is the chromosomal locus, either must be mediated by the primary or derived gene products or takes place at a later stage in the reaction sequence or outside the nucleus between gene-dependent products.

Some years ago Ephrussi and Sutton (*1*) proposed an ingenious, different scheme to account for the properties of position alleles. They pictured genes as chain-like molecules which, under the influence of forces in their environment, could assume folded and unfolded configurations. These different configurations would endow the genes with different activities. Position alleles, particularly in heterozygous combinations with normally located alleles, were regarded as less extended and therefore less reactive chains than nonposition alleles. In order to account not only for the decreased activity of position alleles but also for their interference with the activity of the normally located alleles, a specification of the molecular folding theory was made. It was assumed that the pairing forces between homologous chromosomal regions in *Drosophila* are responsible for the degree of molecular folding, normal pairing resulting in normal extension of the two alleles, and pairing stresses, due to structural heterozygosity in case of position allele heterozygotes, resulting in reduced extension. One of the merits of this hypothesis is that it can account for reduced activity of the normally located allele under the influence of the abnormal pairing forces exerted by a position allele and its chromosomal neighborhood. There are, however, various facts which do not fit the scheme. Here we shall refer only to the same observations which also were in conflict with expectation derived from the hypothesis of variable amounts of substrate. As in that hypothesis, the idea of abnormal pairing forces as a basis for interference in heterozygotes between a position allele and a normally located allele demands a close approximation of the two. The absence of such approximation is not compatible with that idea.

What, then, is the basis of the changed activity of position alleles? One might speculate to the effect that different positions provide an allele with qualitatively different substrates with which it can interact. In this fashion the problem of not simply quantitatively related differences of genic action, in dosage, in combination, and in position experiments, is passed on to the hypothetical level of not simply quantitatively different gene-substrate relations.

There is one suggestion of a particular chromosome neighborhood being different from all others. It was stated above that most R(ci) alleles in heterozygotes with ci result in less vein production than in the case of ci/ci. There are 6 R(ci) alleles which fall out of line, since they have consistently shown a greater vein amount in R(ci)/ci heterozygotes than ci/ci. These are the only cases in which the ci locus had been left in the dot chromosome but the tip of the chromosome had been replaced by a section of the right arm of chromosome 2. In 5 rearrangements the break in chromosome 2 was located (strangely enough!) within the limited region 45–48 as defined in Bridges' salivary chromosome map. In the sixth the break in chromosome 2 was in region 58. It appears from these data that the right arm of chromosome 2 is peculiarly different from other chromosomes. The nature of this difference is not apparent, but it is not of the same type as that between eu- and heterochromatin. The latter two kinds of chromosomal materials act differently from each other if brought into changed relation with a position allele. Strongly altered gene effects of the ci locus are produced only by transfer-

ring it into euchromatic regions, while heterochromatic regions alter the effects of position alleles either little or not at all.

We may summarize the main points briefly:

(1) One, two, or three doses of an allele may produce different effects. This means excess of substrate beyond that used in normal diploid cells. Some alleles act, with different degrees of success, toward normal venation; others, toward abnormal venation. In the latter case different competing reactions controlled by the same allele may be involved.

(2) Combinations of two alleles may be less effective than the "better" of the two or than either alone. There is, thus, not additive action of two alleles but interference, in some cases clearly of mutual nature.

(3) Position alleles also show interference with normally located alleles of their own kind. If different position alleles are arranged in two series according to grade of effect when they are heterozygous for a normal or a mutant allele, it is found that the two seriations do not agree with each other. It seems that qualitatively different phenomena are involved in the shifting of an allele to different positions.

(4) Certain chromosome regions have specific properties causing a specific type of position effect.

If we look back at the material presented, it appears that much can be learned still by genetic methods about the action and interaction of alleles. The genetic analysis, in spite of its lack of biochemical precision, remains at present a more delicate tool for the probing of immediate genic action than even the most advanced methods of the microanalyst. But the vagueness of the geneticist's results lets us look forward eagerly to the time when the biochemist has caught up with him.

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Foreword From *Vernalization and Photoperiodism*

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IT IS AN HONOR TO BE ASKED TO CONTRIBUTE a foreword to this stimulating publication. The book, of course, owes its inception to Dr. Verdoorn's enthusiastic interest in the documentation of plant science. As a matter of history, it is the last of a series of titles which were originally announced by him before the war and have one by one been published during the last seven years. The authors of these chapters have cooperated generously and have produced conscientious and thorough reviews of their several fields. They are authoritative and familiar with the ramifications of the work they discuss. One of them is himself the author of a book in the same general field (*8*). At the moment, therefore, these comprise almost the last word.

Nevertheless, although the present seems a particularly opportune moment for the appearance of this book, there can be no doubt that in this field, which is developing so rapidly, fundamental changes in outlook might well come at any moment. Such a highly flexible situation is of course typical of experimental plant science, which in many respects is still somewhat embryonic, but it is perhaps particularly so of the branches of plant physiology and agronomy which are discussed here.

The reasons for this are basically simple. The physiology of flowering, with which this book deals, has as yet no basis in the general physiology and biochemistry of the plant. The fundamental discoveries on which it rests are the effects of the chilling of germinating seeds and of the varying of the length of day in mature plants approaching the stage of "readiness to flower (Blühreife)." Both of these are essentially *ad hoc* discoveries which did not arise directly from a continuing chain of closely-knit research and deduction, such as, for instance, that on which genetics rests today, or even that which led

This foreword from *Vernalization and photoperiodism: a symposium*, by A. E. Murneek, R. O. Whyte, *et al.* (Waltham, Mass.: Chronica Botanica; New York: Stechert Hafner, 1948. Pp. xiv + 196. $4.50), is reprinted in *Science* by permission of the author and the Chronica Botanica Company.