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## ISOLATING MECHANISMS, EVOLUTION AND TEMPERATURE\*

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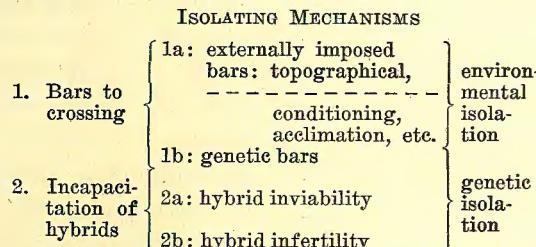
### INTRODUCTION

SEXUAL reproduction is not an unmixed blessing. Although by its genetic churning process it provides the fortunate combinations needed in evolution far sooner than they could occur otherwise, it would if carried on without any restraint continue to break down combinations that were useful only in certain places or in connection with certain ways of living, and so would completely prevent the diversification of organisms into different varieties, species, genera, orders, etc. To counter such excesses on the part of sexual reproduction, means are required for so hindering mixing between some of the genetically different, or potentially different, organisms as to allow the retention and continued accumulation, by different groups of them, of different sets of genes. To all such limitations on sexual reproduction Dobzhansky's apt term "isolating mechanisms" may conveniently be applied.

It is useful for our present purposes to divide isolating mechanisms into (1) bars to crossing, and (2) the incapacitation of hybrids. The former set of factors includes, among others, all those which tend to conserve reproductive energy by preventing its wastage in attempts at cross-breeding between the groups. This set of factors hinders the formation of hybrids in the first place, even of inviable ones. Under this category we may further distinguish two general sub-types, comprising

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(1a) influences like geographical barriers and conditioned behavior, which may in some sense be imposed on the organisms from without, preventing them from effective access to one another despite possible genetic similarity, and (1b) influences primarily dependent on genetic differences between the groups, that lead them to engage in intra- rather than inter-group matings, or fertilizations, although of course these two sub-types sometimes interlock and are not then entirely distinct. The second set of factors (2) include those which cause hybrid zygotes of the first or later generations to be ineffective, by being either (2a) more or less inviable, or (2b) more or less infertile, or both.



(All types of isolation below the broken line may be included under the term "physiological isolation.")

It is evident that full genetic isolation, comprising both (1b), genetic bars to crossing, and (2) the incapacitation of hybrid genotypes, always develops finally, when two groups of organisms have become very different from one another genetically. Moreover, they will become different enough if (1a) the external barriers continue to act for a long time, provided that one or both of the sequestered groups of organisms, not having reached a dead-end "optimum," are still subject to change by selection—even though selected in the very same phenotypic direction—or that they exist in populations of small enough numbers (continuously or intermittently) to be subject to change by drift. The study of life on islands and in similar isolated situations gives abundant evidence of this principle: that externally imposed non-mixing leads

to actual genetic immiscibility. This is not sufficient in itself, however, to justify the conclusion that the external isolating factors do necessarily precede the rest in all or even in most cases. Nor does it in itself answer the question as to how the genetic isolating mechanisms, those collectively included under (1b) and (2), come into existence. This question has often been regarded—rightly or wrongly—as a most puzzling mystery, lying at the crux of the problem of the origin of species, and Bateson and others since his time, in fact, some biologists very recently, have maintained, further, that genetics has as yet afforded little or no clue to its solution.

It was suggested by the organizers of the present Symposium that this problem of the manner of origination of isolating mechanisms might be the primary topic to engage our attention in the present paper, and that the possible relation of temperature to it be treated only secondarily, inasmuch as any conclusions regarding the former question, which is the more mooted one, would constitute a necessary basis for considerations of the latter. Naturally, too, it was expected that results derived from *Drosophila* would be stressed herein, both because of the present author's greater familiarity with that material and because this form has in fact provided an unusual abundance of genetically analyzed evidence on the subject. In preparing this paper, however, the author had no inkling, prior to the publication of the official programs, that there was to be a series of major papers on the same topic, presented almost simultaneously at other sessions of the A.A.A.S., otherwise he would have hesitated to accept the present invitation. Thus, if there proves to be overlapping of our remarks with those of these other authors, this will have been quite unintentional on our part. Since, however, the subject in its modern aspects is still so new and, as it were, amorphous, a discussion of it by various persons independently would not as yet seem supererogatory.

## BARS TO CROSSING

Considering now the nature of (1) the bars to crossing, it is to be noted first that the most conspicuous and probably the most important of the initial bars to crossing between two populations are those deriving from topographical factors. This of course includes "geographical isolation," *sensu strictu*, but the term "topographical" may be better for general application because it refers also to minor spatial limitations such as lines of woods bounding fields, which may be quite effective biologically yet are often on a scale too small to be in ordinary usage dignified by the term "geographical." The topographical divisions may at the same time be ecological ones if the conditions of existence are different in the separate regions. But if the ecologically different regions are really contiguous, so that the given populations are kept from mingling by differences in their own reactions or structures which either prevent their invading one another's territory, or which, though allowing that, prevent their mating with one another, then the bar to crossing is not essentially topographical but is in the same general class as the various so-called "physiological" bars to crossing existing between groups that habitually inhabit the same territory. The genesis of some of the latter may be illustrated by a consideration of cases involving differences in response to temperature, for these are among the best known examples of such physiological differentiations.

It is evident that where genetic differences in reaction to temperature exist, as for instance between two different species or sub-species of frogs, these may effectively separate the organisms into different breeding groups even where they are able to exist in the same locality, as by causing the groups to reproduce at different seasons of the year or times of day. In addition, this factor commonly allows one or both members of the two groups to extend into other localities, where the other group cannot

exist. In many cases of this sort it is not apparent whether topographical or physiological isolation has played the primary role, or whether the combination of the two was necessary.

In *Drosophila funebris*, however, the answer to this question seems fairly clear. As Timoféeff has shown, there are in this species genetically different, though morphologically indistinguishable geographical races, characterized by different temperature tolerances related to the temperature differences between the regions they inhabit. These races, being able to cross freely, would not remain isolated from one another if placed in the same region, since their respective temperature ranges for living and reproducing overlap so widely. Here then the geographical separation must serve to allow the development and retention of the physiological distinctions. And though the geographical separation is far from absolute here, there being no actual discontinuity of distribution, yet the distances involved are so wide that the very length of the connecting bridges serves to isolate the extremes of type in lieu of an abrupt wall—a result which, according to the calculations of Wright, must follow in such cases.

On genetic grounds, differences like the above are readily understandable, for many of the known mutants of *Drosophila* and other forms have a range of temperature tolerance different from that of the original type. For example, flies of "yellow white" stock in pre-imaginal stages withstand high temperature better than normals (H. Nilsson, 1932). The mutant "cloven thorax" becomes extreme at low temperatures and then acts as a lethal (D.I.S. 9). Again, I have observed that flies with the gene preventing crossing over, found by Gowen, become sterile following a rise in temperature that falls far short of sterilizing normal flies. In none of the cases thus far reported in *Drosophila*, however, has there been a single mutational step which by itself split the population into two distinct groups with non-

overlapping temperature ranges. These changes, then, did not by themselves suffice for isolation. In *Cladocera*, however, a mutation was found by Banta and Wood which at one jump raised the whole range of temperature tolerance, including both its upper and lower limits, by about 10° C. It would seem *a priori* that in organisms having a normal range of not more than 10° C. for reproduction such a major change as this would automatically bring about a split into two non-interbreeding groups (supposing that enough individuals of the mutant kind had arisen simultaneously to suffice for their reproduction). This would be true were it not for the fact that where such a major change is possible a still greater number of minor mutations of the same general type is also to be expected, and that these would tend to bring about an overlapping of types that prevented real isolation even here.

How then can an isolation of the sort in question arise? It might at first be supposed that the difference of insufficient distinctness, caused by the initial mutation, could gradually be widened by the accumulation of similar genes of lesser action—"multiple factors" in the ordinary sense of the term. However, it has just been pointed out that the presence of these very genes tends to have quite the opposite effect, obscuring the original difference, where there is no mechanism for keeping them from diffusing and recombining through the population. The relatively slight assortative mating existing in any such case would be insufficient to prevent such diffusion.

The origination of effective genetic discontinuity between two groups that remained in contact would usually require one or the other of two special genetic mechanisms. First, if "specific modifying genes" should arise and be selected that were of such a nature as to act differentially in the presence of the two alleles, they would tend to "buffer" (i.e. to better adapt—see Huxley, 1936) the aberrant type, also to exaggerate it through a specific intensifying action or by allowing selection of more

extreme alleles. Secondly, the same effect could be produced by the selective accumulation of ordinary "non-specific modifiers" provided these were completely linked with the original alleles; this could readily happen if one of these alleles was included in an inverted chromosome region. But selection would take either of these special forms, and be accompanied by the necessary elimination of ordinary modifying genes—those that resulted in intermediate phenotypes,—only if there were some advantage in such a discontinuous distribution of traits, occasioned by some discontinuous feature in the environment or in the mode of interaction of the physiological processes. As a putative example of such a special situation in the environment we might suppose for instance that there was a food supply especially favorable for reproduction at two rather different periods of the year, such as March and July, owing to the development at these respective periods of two different types of favorable flora, while the period between was an unfavorable one. In that case genes which in either of the two ways above mentioned tended to increase the spread between the types differing in the "chief" pair of alleles would, up to a certain point, tend to be selected, while those obscuring the difference would tend to become reduced in frequency, until at last two types that were actually isolated by their temperature reactions of reproduction would have become established in the same locality. Conceivably, similar differences might be established between nocturnal and diurnal forms, if for some reason the intermediate period of dusk was a more dangerous or otherwise unfavorable one for reproducing.

Mutations tending to result in assortative mating or selective fertilization by means of other effects than those concerned with temperature adaptation would be subject to the same limitations as the latter, in serving as foci for the genesis of effective genetic isolation. Evidence has been adduced in several cases in *Drosophila*—especially by Diederich—that in mixtures of normal flies and

given mutants, distinguished by only one or two "visible genes," there are more matings between likes (especially between normal and normal but also, in some cases, between mutant and mutant) than would occur in the course of purely random breeding. Such partial assortative mating could grow into real isolation, between groups that continued to inhabit the same territory, only by a mechanism like that depicted above, in which the spread between those characteristics that lay at the basis of the assortative mating was increased by the selection of "specific" or completely linked modifiers, accompanied by elimination of ordinary cumulatively acting gene differences. And that could happen only where there was some peculiar discontinuity in the environment, or in the conditions of physiological interaction, which favored this sharp dimorphism.

That such situations must sometimes exist is illustrated by the existence of cases of elaborate, discontinuous di- and polymorphism in which the given set of character differences do not in fact serve as a basis for assortative mating and thus continue to appear side by side in the same interbreeding population. As Fisher and Ford have pointed out, the evolution of these required selection of modifiers, and the discontinuity (involving mimicry in some of the cases) was in itself advantageous, by reason of the ecological set-up. If the characters in these cases had been such as to result in assortative mating, the species could have been split into two or more parts by this process, despite the lack of topographical separation. It is quite evident, however, that only a minority of character differences have, *per se*, a strong tendency to assortative mating, especially to two-way assortative mating, the only type effective for splitting. Some even show the opposite tendency, to negative assortative mating, and if this tendency is strong enough, the development of di- or polymorphism in such cases, by the mechanisms above pointed out, must lead to the formation of exogamous groups, *e.g.*, short and long-styled

flowers that only pollinate the opposite kind. The most noteworthy case of the latter type is of course sexual dimorphism: the differentiation of male from female. In this differentiation both complete linkage (resulting in the X-Y and W-Z chromosome divergences) and "specific modifiers" have been found to have played important parts. In a sense, then, the existence of these cases serves as evidence that splitting into actually distinct species can come about by a related process, in which, however, positive assortative mating is substituted for that of negative or indifferent sign.

Situations like those just depicted would seem to be rather special ones, for a population occupying one given region. On the other hand, the difficulties in the way of species splitting tend to disappear when along with the genetic differences there are also topographical ones. If for example the high-temperature *Cladoceran* mutant had escaped to a pool on the south side of a range of hills, where the original type could live with difficulty (or not at all), it would tend to supplant the latter in this locality and its descendants could freely retain all minor mutations that tended beneficially in the same direction, even if they were not of the "specific modifier" type or completely linked with the original gene. In this more or less separated locality, then, a race could evolve without hindrance which at last contained few or no individuals able to breed at the same temperature as the original one; it would then be effectively isolated both genetically and topographically. The same would happen if the organisms lived over a vast but continuous range of territory from North to South, for the genes giving higher temperature tolerance would accumulate differentially in the southern portion of the range, and in fact would tend to push the range farther south still; at the same time the distance would so limit the migration of genes between the northern and southern extremes that this interchange fell below the rate of differentiation occasioned by selection and/or drift. Thus types would evolve which, though

both breeding with intermediates, would not be likely to breed with one another if somehow brought together. In these ways genetic changes making for a physiological bar to crossing which are individually insufficient actually to achieve isolation may readily be accumulated by the aid of topographical factors until, together, they attain the necessary level of differential effect.

A rather exact adaptation of organisms to temperature is often required, when they live in a given environment. Hence in our illustrations involving temperature it was assumed that the mutations differentiating populations in this respect became established largely through the operation of some sort of natural selection. For traits in which considerable leeway in the form of adjustment exists, however, populations that are already prevented from interbreeding by external or internal barriers will also tend to become differentiated through drift, that is, through the accidental multiplication of different mutant genes, and even temperature adaptation would be subject to some changes of this kind. This cause of divergence operates most effectively in small populations, differentiating them in diverse ways which are, initially, of a non-adaptive (though not, ordinarily, anti-adaptive) character. The non-adaptiveness would not prevent some of the differences thus established from acting, secondarily, as genetic bars to crossing. It is also to be observed that, as Wright has shown, where there is a combination of considerable drift within small groups, on the one hand, and active inter-group selection, operating amongst numerous such small groups, on the other hand, the speed of evolutionary divergence tends, other things being equal, to be maximal. This would also lead to a maximally rapid accumulation of those genetic differences that serve as bars to crossing, in cases where the larger groups were kept effectively isolated by topographical or other primary barriers.

In all the types of cases above considered, including those in which topographical isolation was primary, the

initial stages of the actual "physiological isolation" were brought about by genetic changes. This need not always be the case, however. For groups can also become differentiated in their proclivities, tolerances, habits, and even to some extent in details of their physical structure that may affect their mating, through non-genetic acquired characteristics. In these cases the offspring resemble the parents not by reason of heredity but by force of the similar circumstances in which they grow up. In the case of temperature, for example, it is well known that organisms undergo acclimation. Thus, in some of my experiments, normal *Drosophila* when placed immediately at 4° C. were irreparably injured in their nervous systems, acquiring a "shaker" reaction and becoming sterile, whereas flies of the same genetic type brought very gradually to this temperature survived it without apparent damage and were later able to breed. In work just reported by Fry, Brett and Clawson, it was found possible gradually to acclimate goldfish, over a period of weeks, to high and low temperatures, respectively, but when for example those acclimated to 10° C. were placed at 32° they all died within a day or so, while those acclimated to 32° C. died at 10° C. Thus under conditions where only the two temperatures were open to them they would, though genetically alike, form two groups quite isolated from one another physiologically and hence unable to interbreed. It will be seen, however, that in such a case, just as in those previously considered, more or less discontinuity in the extra-genetic circumstances is required for effective isolation—or, what amounts to the same thing, a connecting bridge that is, in effect, very thin or very long. And where the two or more populations in question lived in the same region, without the aid of topographical isolation, such a discontinuity of temperature adaptation would usually require a rather special set of circumstances.

It might be maintained that, in the case of non-genetic adaptation to some conditions other than temperature,

the occurrence of this discontinuity may not always be so unusual. Among such conditions might be counted, for instance, different degrees or qualities of light, types of food and odoriferous substances in general, immunization to the different types of disease germs present under divergent conditions, and differences in responses of the nervous system dependent on conditionings of varied kinds. Thus, Thorpe (1939) has shown that the aversion of *Drosophila* to the odors of peppermint may be overcome in the larva—whether by conditioning or other acclimation is not clear—and that this acquirement is probably retained after hatching of the imago (and Cushing, 1941, reports a similar effect with fungus food, although his data do not yet appear statistically convincing).

The conservatism of birds and mammals in their choice of mates, based upon their conditioning, is often very marked, as Hogben has noted (witness for instance the ostracism, by other members of the flock, of penguins born without their black-tie markings, observed by Kerton), and that this discrimination may itself extend to non-genetic traits in forms below man is shown by the traditional character of some of the elements of song and courtship in certain bird species. But it is only where the fixation of the acquired trait from generation to generation is exceedingly strong, and where it shows marked discontinuity between the groups concerned, that this sort of thing could result in effective physiological isolation between populations inhabiting the same or contiguous regions. Otherwise, topographical isolation must help, and it is difficult to believe that the latter is not usually involved to some extent in effective splitting of populations into divergently evolving groups. The topographical separation need not, however, be as absolute, where combined with either "acquired" or genetic adaptation to different ecological conditions, as where it constitutes the only isolating factor. It is moreover to be expected that if the "acquired" physiological isolation is enabled—by the aid of topography or otherwise—to con-

tinue over a long period, it will be followed up by the selection of genetic changes similar in expression, of a supporting nature.

But even at best, in species subject to eventual changes in topographical or ecological conditions, many of the isolating mechanisms listed under 1a and 1b, the external and the ecologically adapted bars to crossing, are by themselves alone, from a longer point of view, temporary. Remove the outer source of discontinuity—bring together again the forms that have been separated by physical barriers, or provide ecological bridges for those kept apart only by their mode of life—and a reversal can often set in if the isolation has not proceeded so far as to include more deepseated bars to crossing (such as incompatibilities of genital organs and/or gametes) or to include (2) the factors making for hybrid incapacitation. Certainly, so far as the acquired adaptations are concerned, these are completely reversible. As for the genetic ones, if there has not been a differentiation in too many genes, the results of contrary selection as well as of the gradual infiltration of genes from the other group must usually bring about a phaenotypic reversal which, although not actually restituting the original genotype, will undo the bars to crossing in so far as these merely involve differences of adjustment to ecological circumstances. The above mechanism, or set of mechanisms, will therefore often be insufficient, in itself, to give rise to separated species capable of permanently inhabiting the same area without fusing. In other words, there is no use in being an isolationist unless one's defenses are very strong! We may at this point turn to a consideration of (2), the incapacitation of hybrids, for among the principles there involved are to be found those which operate to effect permanent genetic isolation in general.

#### THE ORIGINATION OF HYBRID INCAPACITATION

There is good reason to conclude that the development of such incapacitation is very seldom a primary step in

isolation, i.e., that it hardly ever occurs except after bars to crossing have become fairly well established. For we may note, in the first place, that that effective isolating mechanisms of type (2), resulting in inviable or sterile heterozygotes, cannot become established as a result of a single mutational step. Where a mutation in but one locus is concerned, the heterozygous form in the vast majority of cases is intermediate between or not more extreme than either of the homozygotes in respect to any given phenotypic character, including viability and fertility. It is true that a special type of allelic interaction does sometimes occur where the combined action of two different alleles is enabled to transcend these limits of effect, as in the production of the "femaleness" reaction by heterozygous sex alleles in *Habrobracon* (Whiting) and of the pollen-tube growth reaction by the co-working of different alleles in style and pollen in *Nicotiana* (East and Mangelsdorf). Thus it is conceivable that lethality and sterility also may on rare occasions result from heterozygosis in respect to alleles that by themselves would have no such influence. But since practically all mutant genes must exist in heterozygous condition in the first individuals which inherit them, it is evident that any such lethal or sterilizing effect on the heterozygote would *ipso facto* incapacitate the very individuals necessary for the perpetuation of these genes. For this reason individual mutations causing complete hybrid incapacitation at one bound cannot become established.

That the genetic set-up for causing hybrid incapacitation can arise by two or more steps, each individually harmless (or, more rarely, only partially incapacitating) to its heterozygous carrier at the time of its origination, will be shown later. But for a group of individuals to become genetically isolated from another group by two (or more) such steps requires that either external isolation, or genetic isolation of another kind, that is, brought about by some other means than these steps themselves, exist beforehand between the two groups in question. For

otherwise there will be a class of intermediate genotypes, separated from either extreme by only one step (or by less than the full complement of steps necessary for incapacitation), and thus crossable with both and serving as a genetic bridge between them. Moreover, in the absence of the other source of isolation, the occurrence of free crossing between the extreme classes, that give the incapacitated hybrids, would subject the mutant genes responsible for these effects to a disastrously adverse selection preventing their establishment.

It would not help, in such a case, to have the co-acting genes completely linked, as by an inversion, for the incapacitating effect of the combination upon the heterozygous form would still lead to the selective elimination of such a combination. Neither would it help if we invoked, in place of ordinary gene mutations, structural changes in chromosomes as the prime cause of the hybrid infertility. Individual structural changes that can survive at all in nature are capable of causing only partial incapacity or incapacity of only a fraction of the hybrids. These changes then are subject to the double difficulty of establishment in the face of this hybrid elimination (only overcome by the isolation, through other means, of groups so small at the time of the mutation as to consist of but a very few individuals), and of failure, by themselves, to maintain effective genetic isolation. While, as Sturtevant has pointed out, a succession of inversions can lead, by individually innocuous mutations, to a type giving partial hybrid sterility with the original, and while, as we shall see, there are other sequences involving structural changes that have a similar effect, nevertheless in these cases too (if the degree of the infertility is noteworthy) some other source of isolation is necessary for the original accumulation of these changes, in order to avoid the elimination of the double or multiple type, through its heterozygous infertility, before it can become sufficiently established for permanent survival. Moreover, in such a case also the genetic isolation af-

fended by the hybrid infertility itself is very far from complete.

We may then turn to consider the way in which effective hybrid incapacity can come into existence, when some other means of isolation does exist beforehand. This involves us first in a consideration of what the genetic basis of such incapacity consists in. In the simplest practicable genetic situation giving subnormal or incapacitated first-generation hybrids, each of the two groups has a different dominant gene, which we may call *A* and *B*, respectively, giving them capital letters to show their dominance and italicizing them to emphasize their potentially harmful character. The genes are necessarily dominant in regard to their harmful effects, inasmuch as they exert these effects upon the heterozygotes (except in the case of sex-linked genes affecting only the heterozygous sex, and of such genes as act only "maternally," through the extra-genic egg protoplasm). As for the harmfulness of these dominant genes, it is evident that each of them "by itself," that is, in combination with the recessive allele of the other (giving the formula  $\frac{Ab}{Ab}$  or  $\frac{aB}{aB}$  of the unmixed groups), is innocuous, and that only the two different ones acting together (as the phenotype "*AB*," found in the hybrid  $\frac{Ab}{aB}$ ) produce a harmful effect. This is a sort of result well known in genetics, where it is designated by the purely descriptive term "complementary genes." That the effect produced by this complementary action is lethality or sterility of some degree is not at all strange, for these are also the effects oftenest produced by individual mutations. The individual mutations having detrimental effects are *ipso facto* eliminated, however, while cases of the complementary kind would not tend to be eliminated so long as the complementary genes were kept isolated from one another.

In less simple situations than that above pictured,

more than two genes interact to produce the harmful result, but it is essentially the same story. For the genes must, ordinarily, be dominant to produce their effect on the heterozygote (at least, on that of homozygous sex), and the set of these genes contributed by one parent, corresponding to the single gene *A* above, must interact with the set from the other parent, corresponding to *B*, to bring about the hybrid incapacity.

What now is the mode of origin of such cases? Considering only the simplest type, which sufficiently illustrates the main principles, it is evident that, since the two mutations originated in separate steps, there must once have been an intermediate type, *ab*, through which the now existing types *Ab* and *aB* were phylogenetically connected. This *ab* may have been the original type, in

$\begin{matrix} & ab \\ & \swarrow \searrow \\ Ab & aB \end{matrix}$

which case the phylogeny was

present types having arisen from the original by a separate dominant (or, better to say, potentially dominant) mutation, which could not as yet produce its harmful expression because of its isolation from the other and which was accordingly able to become established in its own population. Alternatively, one of the present types, say *Ab*, may have been the original, the sequence then being  $Ab \rightarrow ab \rightarrow aB$ . Here the first mutation, that from *A* to *a*, was a recessive one, which may be described as having introduced in place of *A* a gene *a*, that later served as an "inhibitor" of the lethal action of *B*. When, by the second step, there was a dominant mutation of *b* to *B*, the latter gene was able to become established in its group because of the presence of this "inhibitor."

In a sense, these events may be considered as involving a transfer of function. Thus, in the second phylogenetic sequence just discussed there is to begin with a gene *A* which, though probably useful in its own way, does not originally help in fulfilling some given function that is necessary for life, or for reproduction. *A*, however, be-

comes changed to the form "a" which, after the complementary mutation of b to *B*, is now necessary for bringing about the result originally effected (though often in a different way) by b. That is, after the mutation of b to *B*, the so-called inhibitor "a" has become vitally necessary for a function for which, originally, it was not necessary, but for which b (as contrasted with *B*) had been necessary.<sup>1</sup> And even in the case of the first phylogenetic sequence above dealt with, the functions in question have become differently distributed among the genes in the two contrasted groups in the course of evolution from their common ancestor, so that, in one group as compared with the other as they now exist, the functions have been transferred.

By some types of transfers in the position of genes, effects similar to those of complementary genes can be produced in hybrid recombinants that come to contain the given gene in neither position. Ordinarily the affected individuals are only second and later generation recombinants, except in the important special case of X-Y exchange, discovered by Stern. In the ordinary cases of positional change the original and the transferred loci (or rather, their "absences") operate as complementary factors much like the *A*'s and *B*'s in our former type of illustration, except that in these cases of positional change both the harmful factors act as recessives. Thus the transfer of locus is in effect like the

<sup>1</sup> Whether this is a purely formal description or represents the actual situation in a less symbolical sense depends upon the types of mutant genes that arose. If *B*, despite its dominance, is hypomorphic or amorphous with respect to b, as is often true of dominants in *Drosophila* (e.g., Notch wing and many Minute bristles), then it is evident that b had fulfilled a positive function, and that its place in doing so has been taken over by a; a in turn may be fulfilling this role either in a positive way, in case it is a hyper- or neomorph or, in case it is a hypo- or a-morph, by allowing some other genes to play the real part. If, on the other hand, *B* is a hyper- or neo-morph, it does not exert its harmful effect by having lost a function, but by having acquired a positively harmful action of a new kind, which "a" directly or indirectly counteracts, and in this case the transfer of function concept is applicable only in a formalistic way.

transfer of function between loci above referred to. And here too it is probable that the establishment of the new type occurs in two steps, each individually innocuous or nearly so: first, the addition of the gene or block of genes in the new position (by a small insertion, or by recombination between similar but non-identical rearrangements), and second, the loss of one or more of the genes in the old position (by gene mutation or deficiency). Isolation is obviously a prerequisite for the establishment of the latter step.

The sex chromosomes introduce a complication into the above story. For if one of the complementary genes, or (complete) sets of genes, were located in the X chromosome, then it need not be dominant in order to find expression in hybrid offspring receiving a single X of this kind and one Y that is in this respect inert. Thus, in cases where the male is heterozygous for sex, a female of the group having the potentially harmful sex-linked recessive gene *a* and the innocuous autosomal gene *b*, when crossed to a male of a group that had *A* and *B*, must produce sons of type  $\frac{ab}{YB}$ , in which both *a* and *B* can express themselves and inviability or sterility must result. In the daughters, however, of composition  $\frac{ab}{AB}$ , the presence of the innocuous dominant *A* prevents *a* from exerting its harmful combination-effect with *B*.

The high frequency of this type of situation is attested to by the widespread applicability of Haldane's rule, according to which the hybrid of heterozygous sex is so much oftener incapacitated than that of homozygous sex. This is not primarily because the harmful genes in question are so much more apt to be in the X chromosome (though that is true to some extent of sterility genes), but because they are so apt to be recessive, and, being recessive, would produce detectable results in the first generation only when they did happen to lie in the X chromosome.

In accordance with the same principle, there should

also be many—even more—cases of recessive “conditional lethals” and steriles in autosomes than in the X, but as these could not produce their harmful effects in  $F_1$ , but only in a fraction of the later-generation segregates, it is not surprising that they have not been recorded hitherto, except in the very recent cases mentioned in the next section. The difficulty of finding these cases is greatly increased by the sterility or infertility so often encountered in the  $F_1$ , which prevents or hinders the obtaining of the recessive segregates of later generations. Necessarily included among these cases are most of those due to actual transfer of locus.

Where Haldane's rule applies—if we neglect the special cases involving XY exchanges, which in *Drosophila* cause only sperm immobility—one of the loci, A–a, is in the X and the other or others, B–b, in the autosomes. Here the extreme groups, with the connecting form between them, are ab, Ab, AB, and the phylogenetic sequence may be either (1) ab → Ab → AB or (2) the exact reverse or  
 $\begin{array}{c} \text{Ab} \\ (3) \swarrow \searrow \\ \text{ab} \quad \text{AB} \end{array}$ . By a process of calculation the details of

which, although individually simple, would take us too far afield for presentation here, it is possible to estimate the approximate likelihood of finding cases to which Haldane's rule applies, in comparison with those in which both sexes are similarly affected, on different assumptions regarding the frequency of establishment of dominant versus recessive mutations, and of potentially harmful versus potentially favorable mutations.<sup>2</sup> If we make the reasonable *appearing* assumption that potentially harmful mutations (*i.e.*, those that are harmful when in combination with some complementary mutant) occur and are established oftener than mutations of like dominance which are potentially advantageous (when in com-

<sup>2</sup> Sex limited lethals and steriles would tend to obscure this picture, especially where more likely to occur in one sex, but that such obscurement is not usually serious is shown by the dearth of cases in which the homozygous sex is the more affected one.

bination with another mutant gene that would otherwise be harmful)—basing this assumption on the very great preponderance of origination of harmful over helpful mutations in general—then our calculation shows that, to get such a high proportion of cases conforming to Haldane's rule as is actually found to occur, recessive mutations must become established oftener than dominant ones. This result would appear to be of a broad evolutionary interest, if generally applicable, but it should not be forgotten that in this case the dominance or recessiveness concerns itself with “potential” characters, that are not, themselves, being subjected to selection at the time of their establishment. Moreover, the bases of the above premise require further examination, since we are there making a comparison, not of any ordinary mutants, but of mutants which become established, with their predecessors that had been established before them. Hence although this line of inquiry merits further prosecution, present conclusions appearing to arise from it should be taken with reserve. This in no way renders less secure, however, our inference regarding the prevalence of already established recessive genes that act as complementary lethals, steriles or abnormalities, provided we do not specify by which of the possible phylogenetic routes the situation arose.

#### EXPERIMENTAL ANALYSES OF HYBRID INCAPACITATION

Although the above discussion may have the appearance of being purely theoretical, it follows closely the experimentally observed facts. The ascertainment of the actual genes involved in species incompatibilities is usually subject to considerable technical difficulties, chiefly because of the complicated multiple heterozygosity and the very infertility or inviability of so many species hybrids. Analysis is easier where a gene in question is not yet completely established in the “pure” species and so may be identified primarily by means of intra-specific crosses involving it and its allele. The most widely known

instance of such a gene, having a complementary harmful action in the hybrid, was that worked out long ago by Bellamy, by Gordon and by Kosswig in their crosses of killifishes, where a gene present in some individuals or varieties of the pure species and merely causing melanism in them was found to cause melanotic tumors of malignant type in the species hybrids. Similarly, in Hollingshead's work on *Crepis* a quite innocuous gene present in some individuals of one pure species proved lethal in hybrids between it and another species. Instances of the same kind have since been reported in other plants.

Complementary genes for hybrid infertility that were already established in the subgroup of organisms in which they occurred were proved by Dobzhansky to distinguish the so-called "races" A and B of *Drosophila pseudo-obscura*. His genetic analysis, by means of back-crosses involving identifying genes or "markers" for the different chromosomes, utilizing the type of crossings employed in *Drosophila* work for the analysis of multiple factors in general, showed that the sterility of the F<sub>1</sub> males was due to the cumulative effect of different sets of complementary genes, each set individually having but a slight effect on hybrid fertility. These genes proved to be located in all the chromosomes except the Y; in fact it was shown that there was usually more than one such gene per chromosome. In certain cases there was a delayed or "maternal" sterilizing effect, acting through the cytoplasm of the egg produced by an individual having a given genotype, to sterilize the zygote of the next generation provided it had a complementary gene in its own X, and there were also maternally exerted lethal effects. The mode of transmission of all of the genes concerned nevertheless proved to be chromosomal. For recombinants of later generations, irrespective of their formal ancestry, were found to be quite fertile provided all of their and of their mother's chromosomes happened to have been descended from the same race.

A still more detailed analysis of a part of the comple-

mentary lethal effects in these crosses has recently been made by Gottschewski. He has found that in some individuals of race A there is an X chromosome containing not merely one gene but two, both of which have to be present together to cause the production of a dominant lethal or semi-lethal effect upon certain hybrids containing them. A further condition for the production of the lethal effect is that the zygote in question shall have come from an egg whose cytoplasm was formed by a hybrid female, and Mampell adds the finding that this female must have been hybrid in respect to its X's. This indicates the interaction of at least four pairs of genes in this complementary system, before the lethal effect in question can be produced. But, besides this, there is, according to Gottschewski, a similar combination of two other lethals in the X of some of the individuals of race B, which when together also cause the death of zygotes starting with hybrid cytoplasm, although in this case Mampell reports that the cytoplasm, to have the co-acting lethal effect, must have been formed by a mother that was hybrid in respect to her fourth chromosomes. Here then is another complementary system which likewise probably involves at least four pairs of genes.

Both the work just cited, and, more especially, the earlier work of Dobzhansky's, have shown that, within each of the major races A and B, local varieties differ from one another in regard to the number of cross-incompatible sterilizing and lethal genes that they contain. Thus the differentiation between *pseudo-obscura* populations, in regard to such genes, is not wholly confined to the major divisions ("A" and "B"), but to a lesser extent distinguishes even the lesser subdivisions, although not in most cases sufficiently to cause noticeable sterility in crosses between them.

The above work on *pseudo-obscura* illustrates, among other things, the fact that a very considerable degree of hybrid incapacitation may develop, having its basis in numerous and widely scattered genes, without the in-

vement of the Y chromosome in any of these effects (even though the Y is known to vary greatly in its morphology in different individuals and local races of this very species), and also without the direct involvement of translocations or other rearrangements in the production of the major effects. Some evidence regarding the genetic basis of three other cases of hybrid incompatibility between "races" or "sub-species" of *Drosophila* has recently been reported, however, and it happens that in all these cases the sterility studied has proved to be of one or both of the kinds absent in *pseudo-obscura*. Thus, in *macrospina* Mainland, and in *micromelanica* Sturtevant and Novitski, have each found a case of X-Y incompatibility between geographically separated groups, resulting in sterility of the heterozygous sex in one of the two reciprocal crosses. It would seem probable that these cases originated by the transfer of incompletely homologous or non-homologous material between the X and Y, essentially according to the scheme devised in 1929 by Stern, in laboratory races of *melanogaster*. In the slower natural evolution, however, which tends to avoid the establishment of types that are at a disadvantage, it is probable that the addition to one of the chromosomes became established as a first step, and the loss from the other chromosome as a later step. A possible complication, in the *micromelanica* case, is that the gene concerned in the X was found to lie between certain other genes, both of which are probably in "active" regions of the X; thus the transfer was evidently interstitial, or was followed by a later rearrangement, within the X. A mechanism alternative to transfer of non-homologous material, by which the same effect would have been produced, is the recessive mutation or loss of a given gene, necessary for fertility of the male, occurring in the X of one group, and in the Y of the other. On this scheme the parent population must have contained the same gene in homologous or semi-homologous regions of both X and Y, presumably keeping them alike through occasional

X-Y crossing over, while in the descendant populations some differentiation in the gene arrangement or composition of these regions of the X and Y presumably occurred, or a reduction in crossing over between them due to some other cause, which rendered them virtually autonomous in respect to the non-allelic mutations they accumulated.

Another kind of involvement of the Y has been found in the *Drosophila virilis* complex, by Patterson, Stone and Griffen. In crosses between the "grey" and the "red" groups, sterility of the males occurs if they inherit their Y from the red group but no second and/or no fifth chromosome from this group. Owing to the restricted number and nature of the genes in the Y it is likely that this result is due to translocations that occurred between the Y and these autosomes in the previous evolutionary history. These are the kind of translocations that were postulated by the author and Painter (1932), in suggesting that the Y, by virtue of its possession of a centromere but of very few genes having important dosage effects, had furnished an "anchorage" for the attachment of chromosome arms. More recent evidence for the semi-homologous nature of the proximal regions of different chromosomes, and for the more frequent establishment of whole-arm than of part-arm translocations in evolution, have given added reasons for adhering to this conclusion, and so far regarding the Y and the chromocentral (heterochromatic) regions of the other chromosomes as much more closely related to one another, phylogenetically, than the "active" regions are, owing to the comparatively frequent interchange of material by translocation between the former (see Muller, 1940; Sturtevant, 1941). As previously pointed out, however, the fertility genes of the Y are of very limited action, affecting only sperm mobility. Hence we are not justified in looking to translocations of the Y or its derivatives for explanations either of the more deep-seated male sterility usually found in species crosses, or of female sterility, or of any but very limited inviability phenomena, confined to the

male sex. For all these other effects we must look, in the main, to differences caused by complementary gene mutations, such as those so abundantly differentiating the chromosomes of races A and B of *pseudo-obscura*.

What more direct evidence have we for regarding such changes as forming the basis of the hybrid incapacitation obtaining in crosses between actual "species"? We have seen that the genetic differences that cause the cross-sterility and inviability between the major "races" A and B have been found by Dobzhansky and others to differentiate, though to a lesser degree, even local varieties and individuals of this species. It is apparent, on the other hand, that the A-B divergence represents an incipient species differentiation. The *pseudo-obscura-miranda* differences seem merely to be greater in degree than this. Very recently there has been a flood of new work on the taxonomy, geographical distribution, chromosome morphology, and crossability of a number of super- and intra-specific groups of *Drosophila*, by Spencer, Patterson, Sturtevant and their co-workers. If all this work has proved anything at all—and students of the subject will agree that it has proved a great deal—it has fully confirmed the conclusion here at issue. That is, it has demonstrated that in this genus at least no sharp line can be drawn between sub-divisions of one rank, such as races or sub-species, and of another rank, such as species. For although published analyses of the actual genetic bases of the phenomena here concerned have necessarily been very limited as yet (we have already cited most of those so far reported in *Drosophila*), it is clear that the same kinds of taxonomic, physiological, and cytological differences, and the same general characteristics of crossability, which differentiate so-called species, also differentiate the lesser sub-divisions, although of course to a lesser degree. Hence it seems legitimate to extend the wealth of results of the genetic analyses that have been carried through on the "races" of *pseudo-obscura*, by Dobzhansky and others, together with the supplementary observa-

tions on the other forms, to the differences between acknowledged species as well.

We are, however, no longer limited to reasoning entirely by extrapolation, in deciding on the nature of full-fledged "species" differences in *Drosophila*. In some recent work by Pontecorvo and the writer (1939-41) it has proved possible to analyze directly the genetic basis of the interspecific sterility and inviability of the two "good" (albeit very similar) species *Drosophila melanogaster* and *simulans*, despite the impossibility of breeding the ordinary  $F_1$  hybrids of either sex. This  $F_1$  hybrid sterility was, as it were, circumvented, by means of a special genetic technique, involving the use of X-rays to remove one or another *simulans* chromosome present in the spermatozoa of that species and the use of triploid *melanogaster* females, to provide extra chromosomes of the latter species in the eggs, in compensation for the induced losses of chromosomes from the sperm. By this means there were obtained, among the immediate offspring of this species cross, the various whole-chromosome recombination types which were to have been expected if the  $F_1$  hybrids had been fertile and had been backcrossed to *melanogaster*. Moreover, it was possible to distinguish these different types from one another by means of "markers" which had been provided.

By the use of these methods it was shown that in this "species" cross, as in the *pseudo-obscura* "race" cross, all the hybrid sterility is caused by the deleterious complementary action of chromosomal factors. The one individual which happened to have all its major chromosomes derived from one species was at the same time the one individual, among some 450 hybrids, that was fertile. Each of the major chromosomes of *simulans* was found to differ from its homologue in *melanogaster* in regard to a factor or factors making for some sort of incapacitation of the hybrid. Thus, either of the large autosomes of *simulans*, present heterozygously in a female having all its other major chromosomes from *melanogaster*, is

completely sterilizing in its effect, *i.e.*, it contains a dominant complementary sterility gene or genes acting upon the female. The same may be said of the effect of chromosome II of *simulans* upon the male, while the effect of III was too lethal for its sterilizing action on a male of otherwise *melanogaster* genotype to be studied, although, when in company with a *simulans* X, it too was found to be associated with deep-seated sterility in a male of otherwise *melanogaster* composition. The sterility genes, or groups of genes, of the different chromosomes, were different from one another in their effects, as histological studies made by Koller showed. Thus the presence of one *simulans* II in an otherwise *melanogaster* male allows the development of nearly normal testes, in which the germ cells show abnormalities only in the spermatid stage, whereas a *simulans* X and III result in very reduced testes. Again, in the female, one *simulans* II results in a more rudimentary ovary than does one *simulans* III.

In regard to inviability, it was found, among other things, that a recessive factor or set of factors in the *melanogaster* X produces a partially lethal effect when in combination with a complementary dominant in the *simulans* III, and a fully lethal effect when it is present along with complementary dominants of both the II and III of *simulans*. And a dominant in the *simulans* X, combined with a complementary dominant in the *melanogaster* II, was found to be responsible for the abnormal lack of bristles of the  $F_1$  hybrids that had long ago been noted by Sturtevant. This characteristic undoubtedly lowers the viability of the imaginal stage, since a normal complement of bristles is necessary to protect the flies against adhesion of wet materials to their integument. In this connection the similar finding recently reported by Crow should be noted that, in crosses of *Drosophila aldrichi* with *mulleri*, and *aldrichi* X chromosome has a dominant lethal effect on these hybrids.

That there is probably not one, but many cross-incom-

patible loci in the major chromosomes of the *melanogaster-simulans* species cross is indicated by the fact that even the minor chromosomes were found to have such genes. A study of the action of these minor chromosomes was made possible by breeding the one  $F_1$  individual which, having all its major chromosomes from *melanogaster*, escaped the action of the genes that caused the sterility of the other  $F_1$  females. Tests conducted on its descendants showed that both the Y and the tiny fourth chromosome of *simulans* contain genes (or else "gene-absences") making for sterility and other abnormalities in individuals having their other chromosomes from *melanogaster*. The sterilizing effect which the *simulans* Y was found to exert in males of otherwise *melanogaster* genotype is like that occurring in males that lack a Y. It almost certainly owes its origin to translocations of material, or at least to transfers of function, that occurred between the Y and another chromosome—most probably the X—in the past evolution of these species from their common ancestor. This constitutes only a minor part of the hybrid sterility found in the present case, however. As for the sterility gene found in the fourth chromosome, it proved possible to determine its locus rather precisely, despite the inapplicability of crossing over tests, by virtue of its happening to lie within the region of a small known deficiency ("Minute IV"), which acts to "uncover" it. The *simulans* gene in question sterilizes males only, and it acts as a recessive, so that only certain recombinants occurring in the back-cross, the  $F_2$  and still later generations would ordinarily be affected by it. There is every reason to infer that this gene stands as the representative of a large class of recessive complementary incapacitating genes, a class much larger than the dominants, which usually escapes observation, however, except where the gene is in a sex chromosome, because of the indetectability of its effects in the  $F_1$  generation.

It is noteworthy that various of the other loci in the

small fourth chromosome, including loci of previously known visible mutations, were also found to be somewhat different, at least in their "potency," in *simulans* and *melanogaster*, as judged by certain of their morphological effects. This situation must have been the result of numerous minor mutations, occurring in the evolutionary divergence of the two species, that altered the manner in which the necessary "balance" of developmental processes was attained (and thus involved some "transfer of function") even in the case of characters that retained an outward identity. Genically, then, their differences may sometimes be as multiple as those between characteristics showing an obvious phenotypic divergence—in the case of which work of Spencer and others, especially on the *virilis* group, has shown multiple gene differences to be the rule. Abundant evidence for the existence of similar cryptic species differences in cotton has been presented by Harland. And Lamy (*ex lit.*), attacking the *pseudoobscura* A-B cross by special methods, finds cases of the kind even here. There is no reason to suppose that most of the major effects observed for interspecific sterility and inviability belong in a fundamentally different category from most of the changes in other characters which show little or no outward alteration when the two "pure" groups are compared. The effects in question, detectable only on crossing, may legitimately be regarded as automatic by-products of the general differentiation, produced by a combination of drift, and of selection for other characters than those here observed, utilizing gene mutations and, to a much lesser extent, positional changes.

Despite the above conclusions and despite all the evidence that has been given of the existence of multiple sets of complementary incapacitating genes, and of multiple genes in many of these sets, even in crosses between related species and between sub-species of *Drosophila*, the sterility and inviability effects in most of the hybrids studied must be due, in large measure, to only a small proportion of the very great body of gene differences dis-

tinguishing the species and even the sub-species from one another. This fact is proved by the finding that the fertility, as well as the viability, of males derived from reciprocal crosses are so often very different, even though the pressures of selection and of drift making for the types of divergence that resulted in the respective effects in the two crosses must have been nearly equal. The difference in results of reciprocal crosses must therefore be an expression of the high statistical error to which the sampling of small numbers is subject. That is, the effects in question were in the main dependent on only a very few loci each of which had a considerable influence on viability or fertility, while the great majority of the gene differences between the species or sub-species had very little effect of this kind. Thus the curve relating the number of gene differences (ordinate) to the amount of their complementary incapacitating action (abscissa) is of the one-sided, initially steep but later tapering, mountain-slope type so commonly found in the case of things whose mode is at (or sensibly at) one of the extremes of their range of possible values.

#### HYBRID INCAPACITATION AND BARS TO CROSSING IN RELATION TO SELECTION

It has sometimes been postulated that the establishment of the two or more steps involved in the incapacitation of hybrids has come about by selection, owing to the advantage derived from non-mixing of the groups. While, as we shall see, this must sometimes be true in an ulterior sense, and serves to explain in part why a given sub-species or species, as a whole, contains such genes, it can hardly be the explanation of how the mutations became established in the first group containing them, since the genes themselves suffer from a disadvantage to their perpetuation and multiplication (as compared with that of their original alleles) wherever the mixing occurs, despite the advantage they give their group. Moreover, it will be noted that in certain of the sequences, e.g.

$Ab \rightarrow ab \rightarrow aB$ , previously discussed, "a" must become established before "B," although without "B" it is unable to confer any isolationist advantage upon the group containing it, when the latter is in contact with the related group. Thus a must have become established, within its immediate group at least, without having been selected for its as yet purely potential property of aiding in isolation. It should further be recalled that this "*AB*" situation is the simplest one. In the more complex genetic set-ups, that is, in the cases where there is a greater number of genes the complementary action of all of which together is required for the incapacitation of the hybrid (as in the inviability effects in *pseudo-obscura* studied by Gottschewski and Mampell), the present objection applies more strongly, for here a larger number of genes have to become established in the group, before the isolating effect of any of them can be exerted.

The complementary genes for hybrid incapacitation, as well as any chromosome structural changes having such an effect, must therefore have become established in their given groups either through selection for other advantages than that of the isolation associated with them, by virtue of their "pleiotropy," or through mere accidental multiplication (drift). The local group containing them may, to be sure, have multiplied later, in inter-group competition with the remainder of the species or sub-species, because of the advantage which the isolating action of these mutations, when already established within this local group, conferred upon the latter, in comparison with the other local groups. But that even such inter-group selection for isolation is by no means a necessary condition for the establishment of such mutations throughout a considerable geographical region is proved by the various well established cases (*e.g.*, in birds, in *Lymantria*, etc.<sup>3</sup>) where, in a series of geographical races, the mem-

<sup>3</sup> Since the above was written, it was reported by Patterson, in the symposium on isolation held at the same meeting of the A.A.S., that this situation was found by him and his co-workers to hold in certain species or sub-species complexes of *Drosophila*.

bers furthest apart and therefore least subject to selection for mutually isolating factors are found to have the strongest tendency to hybrid incapacitation.

Further evidence for the latter conclusion is to be found in the incapacitation of later-generation products of crossing, by means of complementary genes or structural changes that act in a recessive way, for these cause incapacitation of only a fraction of the descendants, after most of the damage due to the crossing has already been done. And besides these cases of too low effectiveness, there are those of too high effectiveness to be readily explained by any selection for their isolating effect. That is, where one group of complementary mutations already exists which is adequate to cause sterility or inviability in the hybrid, there is no advantage in accumulating further groups of mutations which themselves accomplish the same thing. This happened, for instance, in the *melanogaster-simulans* and, insofar as the male hybrids alone are concerned, also in the *pseudo-obscura* race A-B divergences. A series of successive splittings might be postulated in order to explain by selection such apparently superfluous differentiation. But where, as in the *pseudo-obscura* case, only one sex is concerned, so that the superfluous isolation thus brought about is ineffective after all, the argument for even an inter-group selective effect here becomes stretched to the breaking point.

It may then be concluded that the establishment of the genes that result in the incapacitation of hybrids comes about in large measure as an automatic consequence of evolution in general. Much of the change in question may be described as consisting in "transfers of function" from one gene to another (although often no doubt introducing new biochemical processes), whereby some of the innocuous or adaptive mutant genes that become incorporated into one kind of genotype happen to act detrimentally when combined with another genotype or with a part thereof. And the further the genotypes diverge, the more pronounced this result inevitably becomes.

By analogy, we may reason that many of the genetically conditioned bars to crossing come about in the same way. Some of these bars to crossing, somewhat like the mechanisms for hybrid incapacitation, obviously require for their effective working the complementary action of two or more different genes, as for example where the females of two groups have different odors and the males have corresponding genetic preferences for just these respective odors, or where male and female genitalia fit only intra-specifically, or where sperm do not function adequately in the genital tracts of females of the other species. For two groups to have accumulated a divergence in regard to such a system of genes required the prior existence of fairly effective isolation between them, due to some other cause, except in the rare cases where the different co-acting genes in question were connected by complete linkage or by a "specific modifier" type of interaction. Bars to crossing of this complicated kind would therefore seldom have constituted the initial isolating factor, but they could have arisen, like hybrid incapacitation, as a casual by-product of evolution, once isolation had become established by means of topographical or other external barriers, or by means of genetic barriers which (like genetic differences in temperature adaptation?) required a less complicated mechanism.

On the other hand, the genes for even complicated bars to crossing seldom suffer from the same selectional limitations as do the genes making for hybrid incapacitation, for most of the former cause isolation in such a way as to conserve themselves and so to further, rather than to hinder, their own perpetuation and multiplication. Hence, in addition to arising as automatic consequences of evolution, there will also be the tendency for bars to crossing to become established as a result of selection for the isolationist advantage they confer. This can occur in the case of populations which are already fairly but not completely isolated, or which are completely isolated but by wasteful means. A case in point is that of groups

formerly topographically isolated which had acquired genes causing complete hybrid incapacitation but not effective bars to crossing, and which are now again in contact. Thus selection as well as "automatic" processes will continue to act in such cases, until the least wasteful (among other things, usually the earliest-acting) method, or combination of methods, of preventing crossing, have been evolved to separate them (see, for instance, Fisher, 1930). Even after that, additional isolating mechanisms, quite superfluous as such, will necessarily accumulate as long as evolution goes on, but their acquisition will now be completely "automatic," that is, entirely independent of any selection for an isolating effect between the two groups in question.

#### ISOLABILITY OPTIMA

Whether or not isolation develops as a direct result of selection for the effect itself, it is evident that, where it has developed between related forms differently adapted (or having differently working systems) and likely to come into contact, they will possess the advantage of being able to conserve their sets of distinctive features while those which undergo a mixing too extensive to be so well controlled by selection will be at a relative disadvantage, in comparison with the former. Thus a long-term inter-group natural selection will tend to preserve and increase the former as against the latter. But a very long-term selection will go even further. For it will tend to preserve, in general, those kinds of organisms in which, owing to the general nature of their reproductive and life processes, isolation comes about readily enough. It must not come about too readily, as happens for instance to an extreme degree when sexual reproduction is given up entirely or when the organisms take to selfing, for as we have seen a certain amount of crossing is invaluable in the long run, but neither must isolation come about with too great difficulty. Hence we may expect given great groups of organisms that achieve a long-term success to

have various generalized mechanisms of isolability, lying behind their specific mechanisms of isolation, and balanced against the mechanism of sexual reproduction, so as to give an approach to an optimal amount of mixing in the course of evolution.

These mechanisms of isolability may often be very different in different major groups. In some kinds of organisms, easily isolated topographically, like the snails in Tahiti, the environment itself may be virtually sufficient for purposes of isolation, so that the major internal feature of the isolability mechanism is that which limits the migration rate of the organisms. In many higher plants inviability of recombinational gametophytes derived from species crossing tends to occur long before the level of divergence is attained that prevents the  $F_1$  zygote from developing and going through its meiotic processes; for this reason the allotetraploids are fertile. Brink and Cooper have recently shown that in some higher plants the readiness with which inadequacy of the hybrid endosperm (in competition with the maternal nucellar tissue) is brought about provides the most labile mechanism of isolability. In many higher animals, on the other hand, the growth period of the spermatocytes and oocytes is an especially sensitive stage, showing deleterious effects from crossing long before other structures or processes are disturbed. In some insects, it has been claimed that the male and female genitalia constitute lock and key mechanisms, for which the males fail to possess master keys. In the *Drosophila* genus, one especially sensitive and unstable set of structures is the distribution of genes between the X and Y chromosomes, so that species probably do not diverge very far before an incompatibility of that sort arises; however, since it affects only the hybrid males, this feature by itself is insufficient for effective isolation. Odors, courtship behavior, and other features of the psychology of mating present the most ready means of isolation in some animals. It is probable that the readiness with which these mechanisms

are affected by divergence is not entirely accidental: that is, that they were preserved in an unstable condition partly because it was in the long run useful to have them so. For by this means the evolving organisms of these great groups were enabled to undergo a beneficial amount of divergence, whereby such a great range of species was presented for inter-specific selection as to allow a much more effective series of advances in the long run. This is a process which, for selection between species, must play a somewhat parallel role to that process of intra-specific selection between small semi-isolated local groups within a species, the importance of which for evolution has been so justly emphasized by Wright.

In the case of the partial isolation of local groups, dealt with by Wright, certain advantages accrue from the fact of the isolation's not being complete, for this eventually makes possible new trials, by later local groups, of synthetic combinations of genes derived from different local sources. So too it is probable that we must qualify our remarks about the benefits of isolation on the grander scale constituted by species and sub-species, by adding that, as Patterson, Stone and Griffen have suggested, a certain small leak in the isolating mechanism, even for actual species, may be beneficial, if (as we must add) the leak is small enough for its effects to be readily controlled by selection. For this kind of migration of genes would, like mutation with drift, provide material for further evolutionary testing within the species, but the genes and gene systems here in question would on the average be much better than the crude material provided by ordinary mutation and drift, since they would already have passed through a more thorough selective sifting. Some would of course be misfits in their new gene surroundings, and it is because of the action of these in causing hybrid inviability, infertility and disharmonies in general, that the isolation is necessary at all, but it would seem worth suffering the infiltration and elimination of a few of these to gain the advantage of having a better chance than

intra-specific mutation and drift alone would provide, of testing out the potentialities of the remainder. Naturally, the wider apart the groups are, the smaller the optimal amount of such leakage must be, because of the greater proportion of disharmonious gene combinations thereby formed and the very rapidly mounting difficulty of disentangling the useful gene systems from the harmful ones. Yet, just because of the greater divergence involved, a distant cross might provide a greater absolute number of potentially useful genes than a near cross, if only they could be thus disentangled, so that a small amount of leakage might be beneficial even at considerable degrees of divergence.

Some evidence that crossing between different groups has in fact occurred in the establishment of *Drosophila* sub-divisions has recently been given in demonstrations by Patterson, Stone *et al.* (A.A.A.S. meeting, 1940; see also Patterson, 1941), dealing with the salivary chromosomes of the *virilis* complex. Here it was shown that the differences in conformation (involving inversions) between a given chromosome in four different sub-species or species (as we choose to call them) were such as to have required one of the observed conformations to have originated by crossing, followed by crossing over, between two of the others. Which the recombination type was cannot be specified in such a case, without evidence from some other source to indicate which the original type was, but this does not affect the validity of the conclusion that, whichever the original type was, the one furthest from it must have arisen by crossing between two different, independently derived, connecting types. At the same time, however, it should be understood that these facts by themselves provide no way of knowing to what extent the two groups that engaged in the crossing were, at the time of this crossing, already differentiated from one another, beyond their differentiation in respect to the two inversions noted in the given chromosome, nor can it even be assumed with confidence that the differ-

ently inverted chromosomes were at that time segregated into different populational groups at all. However, this would seem likely, in view of the present tendency to topographical separation of the types. It is, moreover, a question permitting of further investigation by other means, as for example through a study of associated gene differences.

The above appears to be the first case yet reported, for animals other than domestic animals and man, of the probable origination of one established local group by crossing between two others. It is likely, however, that this paucity of data is not due to a paucity of cases, and in plants in which ploidy, translocations and other features of chromosome morphology furnish data on the subject with comparative readiness, numerous instances are already known. This should serve to emphasize our thesis that isolation has its two sides, and that in its most advantageous form it will present a curve only gradually approaching the level of completeness, as the degree of divergence becomes greater and greater. The point where isolation finally attains this level, as well as the point where it is most advantageous for this level to be attained,—whether at the distance represented by "species," "genus," "family," or still wider divergence—will vary according to the type of organism in question, according to its whole system of living and breeding, and—not least—according to the language habits of the systematist who sits in judgment.

#### THE INFLUENCE OF TEMPERATURE ON ISOLATION AND EVOLUTION

In view of the nature of the mechanisms of isolation above discussed, what part may we expect temperature, or differences of temperature, to play in the isolation process? We have seen that temperature differences themselves may be an aid in isolation, by leading to the differentiation of groups adapted to breed, or to live and breed, at these different temperatures, and that, in the

end at least, some of these different groups may even inhabit the same locality, preferentially reproducing, as well as feeding and growing differentially, at their respective optimal temperatures as these occur. Here then these genetic differences in temperature adjustment do act as bars to crossing. It is also to be observed that the mating between genetically warm and cold adapted forms may sometimes be expected to give, not intermediate types, but inviable hybrids, if we may reason from the experiments of Porter (1941), in which merogonic frog hybrids, produced by fertilization of enucleated eggs, showed systematic abnormalities when the eggs of northern groups were fertilized by sperm of southern groups or *vice versa*, the amount and direction of the abnormality being correlated with the amount and direction of the difference in climate to which the respective parental groups were adapted. These results appear to have been caused by the improperly interadjusted rates of different biochemical processes of development in the hybrid. Such effects furnish an illustration of the mode of working out of what in genetic parlance is, without thought commonly being given to the developmental mechanism concerned, referred to as "complementary lethal genes." Moreover, it is evident in such a case that the genotypic difference responsible for the hybrid incapacitation did not arise as a consequence of selection for that effect itself, but for something quite different, namely, in the given case, adaptation to development at higher or lower temperatures, respectively.

Important as the above types of effect may be, the influence of temperature on the process of isolation, that is, of evolutionary divergence, goes much further. For temperature—both warm versus cold, and also inconstant versus constant—has important direct effects on the fundamental processes of mutation, selection and drift which furnish the motive power of all divergence. These effects may now be reviewed briefly.

In the first place, a higher temperature, within the

range normal to the organism, is found, in *Drosophila* at least, to multiply the frequency of mutation per generation some two to three times, for each rise of 10° C., as has been brought out in the paper of Plough in this Symposium. Temperature shocks, as he showed, have a similar effect. Where mutation rate constitutes the limiting factor—a point on which we have little real information as yet—such a raising of the rate by high or varying temperature, in organisms not having temperature control, would make for faster evolution of them, including more rapid genetic isolation and divergence in general. It is to be strongly suspected, however, that the rate of mutation tends continually to be kept within a certain range, by means of natural selection. This must act, on the one hand, against individuals having genes that result in an especially high rate, inasmuch as such individuals produce too many degenerate forms, and it must act, on the other hand, against small local groups which, having genes for an especially low rate, are not plastic enough in undergoing genetic changes that would allow them to meet changes in their conditions of life. Thus the mutation rate, pressed in both directions towards a middle value, would tend towards an equilibrium, though not necessarily either a very stable one or one that represents the real optimum so far as the group is concerned. It is probably somewhat below the real optimum since, as Sturtevant has pointed out, the pressure of selection towards lower values seems to be of a more effective type than that towards higher values.\* In any case, however, it is evident that the selection pressure towards a lower rate will, other things being equal, be stronger in organisms which themselves have a higher rate. Hence, after organisms have lived for many generations at a high or very variable temperature, selection would have tended to counteract this environmental raising of the mutation rate by selecting genotypes which had an inherently lower

\* It is, however, difficult to accept the thesis that the entire force of selection will be in the direction of lower rates.

rate than that which would otherwise be established. If this inference should prove justified—and it is entirely open to experimental testing if the means of carrying out the necessary laborious experiments on the spontaneous mutation rates of different natural populations can be found—then the differential influence of their natural temperatures on the mutation rates of two comparable species or geographical races living in different climates would not be nearly as great as the influence found on one and the same stock, when artificially separated into two groups and tested under these respective temperature conditions.

Whatever the answer to the above question may turn out to be, however, there can be no doubt of the profound influence of temperature on the other phases of the process of speciation. Even assuming the same mutation rate per generation, and equality of other factors, the rapidity of the process of selection, and also that of accidental differential multiplication of genes (drift) is necessarily proportional to the number of generations per year, and this, at least in most small animals lacking temperature control, and in saprophytic plants, is much greater in warmer climates.

Added to this is the factor of total population of reproducing individuals present at any given time. For individuals of a given size and length of generation this is proportional to the total amount of growth occurring. In the case of green plants *in general*, when other conditions—especially the supplies of water, CO<sub>2</sub> and other inorganic materials—are favorable, the amount of growth depends closely upon the amount of radiation received which is of the wave lengths absorbed by chlorophyll, and, aside from such radiation, it is largely independent of temperature in the range from freezing to the protein coagulation level (except that any given species is by selection and acclimation adapted to grow best at a given temperature). But as both the temperature and the amount of light available for photosynthesis depend,

among other things, upon the amount of incident solar radiation (though modified by the screening and trapping effects of humidity and cloud blankets, air density, wind, etc.) a considerable correlation indirectly results between available light and temperature, from one great geographical region to another. Thus, in general, the warmer regions can support far more land plants than the cooler regions (although it must be observed that the humidity tends to be further below the optimal in the warmer regions). In the sea, however, these conditions often fail to obtain, partly owing to the lesser abundance of certain dissolved materials at higher temperatures. Now since the plants must ultimately furnish the food for the animals there will in consequence tend to be more food available for animals in the warmer than in the cooler land areas, and at the same time they will be able to utilize the food more rapidly and probably more efficiently.

The much larger total population of plants and of animals in warmer terrestrial zones gives a correspondingly greater opportunity for the occurrence of the accidental processes that form the primary basis of evolution. At least, if the populations of warmer regions are naturally subdivided into local groups of average size not too much greater than elsewhere—a condition which it is reasonable to infer would usually obtain—there would on account of the greater number of these groups be correspondingly more chance for divergence and so, in the end, for evolution in general. The shorter life cycle, previously noted, works powerfully in the same direction. But the very fact of more different kinds of organisms having thus come into existence in these regions would in turn react to increase the diversity of the ecological conditions presented to the organisms there, and so would tend to increase both the splitting of populations into local and ecological groups, and also the occurrence of divergent and more rapidly changing *selection* within these groups. That is, the splitting reacts in a sense auto-catalytically, back upon itself, to encourage still more

splitting. In addition, the more complicated habitat tends to induce a more complicated type of selection within any given group. And it is probable that not only the biological but even the physical environment *per se* tends to be more diverse in hot than in cold regions.

Inconstancy in temperature also must tend, other things being equal, to accelerate evolution, by putting a greater premium on devices which help the organism to meet its climatically more complex conditions of existence, encouraging greater specializations in some respects, and in some organisms, and more generalized adaptability in others. Such inconstancy, moreover, by bringing about periodic reduction in numbers must increase the amount of drift, that is, the number of trial and error evolutionary processes on the part of local groups. And here too the increased divergence would tend to react, ecologically, to induce still more divergence.

Taking all of the above factors together, it is evident that, for land animals at any rate, and especially for those lacking temperature control, there should in a given length of time be much more divergence and, associated with this, much more evolutionary advance, in warm than in cool regions, and, for regions of similar average temperature, in those of at least moderately inconstant than in those of constant temperature, although we must except here regions with such extremes of temperature as are too deleterious to be effectively overcome by the organisms. It is no doubt for these reasons that the tropics have such a large number of species, as well as of individuals, and that in the main the cooler regions have been more or less dependent on the warmer ones in evolution, periodically drawing from them a part of the more advanced forms as these are produced there, and readapting them to the cool conditions. For these reasons too it would seem safe to predict that, even if other conditions were roughly as favorable for life, a planet receiving as little radiation and having a temperature as low as that of Mars would in the same length of time have

evolved a flora and fauna far less advanced than those evolved on the earth.

In qualification of the above conclusions it should, however, be noted that the very fact that cold climates present conditions in various respects more difficult for the success of living things tends to create conditions of selection under which various innovations become of adaptive value that would not be able to play an effective role—at least, not in their early stages of development—under climatically easier conditions. This factor acquires more importance after a more advanced stage in evolution has already been reached, where there is a better basis for the development of features really useful in this connection. So, for example, it was not until evolution had made possible the attainment of a certain size, combined with mobility, that the development of means of keeping the body temperature high became practicable, since a small animal has too big a surface, relatively to its volume, to be able to maintain a high temperature in cold surroundings. Meeting cold conditions in this way, the birds and mammals were able to obtain a great advantage over their nearest competitors, the reptiles, in cold and temperate regions especially, and even to overcome, in part, those very features of the cold environment which act as a brake on the evolutionary process. Moreover, the coat of feathers or hair which adapted them to a lower outside temperature later formed important parts of the bases of their advances in other respects. Thus it is probable that in birds feathers gave the possibility of wings (*not vice versa*), and so opened the way for all the advances that wings in turn made possible. In mammals, as in birds, the maintenance of the warmth of the embryos, and later of the young as well, was associated with the development of other forms of assistance and care for them. And probably through a transfer of function of some of the sebaceous glands, evolved originally as accessories to the hair, the mammary glands and a great system of characters centering about these distinctive organs

of the mammals came into being. These "secondary" advances, then, would probably have occurred much more slowly, if at all, if these animals had been confined to conditions of constantly high temperature.

Once these more complicated and, shall we say, "less probable," innovations have come into existence, the animals possessing them often find themselves at an advantage over other types under high temperature conditions as well. In an analogous way, the more difficult conditions of land animals finally resulted in their making advances which enabled them to re-enter the water possessed of advantages, even for such life, over the types which never left it. Thus, among higher forms, there should be more tendency than among lower ones for interchange of types in both climatic directions, rather than so preponderantly from warm to cool.

And though the primate stock is one which since early times has been so largely tropical, yet what we consider its highest member, man, owes so much at even a very remote period of his social evolution to the influence of cold, and to the fight against it in glacial and other times, that it is probable that his biological evolution also has been considerably affected thereby. It is known that his use of fire dates back some hundreds of thousands of years at least. Both through its primary help against the cold, and through the other important uses of which it was found capable, it and other devices (clothing and shelter) for combatting a lowering of temperature opened up new environments and ways of living for man, and allowed him to be brought into contact with diverse conditions that stimulated still further changes. There can be little doubt that biological (genetic) changes were included among these: for instance, the disappearance of the hair which was originally so important for mammals, as a result of the development of superior artificial substitutes that took over its function. Here again, then, we see the role of temperature to some extent reversed, in that moderate cold in some ways favors divergence and

evolution, when once that stage has been reached where its paralyzing influence can be effectively met.

In the past, however, such advance, on the biological plane (at least), has only been accomplished with the collaboration of a great deal of trial and error, on the part of numerous diverging groups that became fairly effectively isolated from each other, and of which only the more successful remained, to branch again. For the genus *Homo*, it seems clear, the days of isolation, whether on the petty or on the grand scale, are done—even though lack of sufficient temperature adjustment and other comparative inadequacies of adaptation on the part of one of the large groups are helping to put a useful brake on the process of merger, that will probably allow it to take a less disastrous form. We do not imply here that the aggregation of groups stands opposed, *per se*, to social evolution. On the contrary, when carried out with a view to the good of the whole, it constitutes one of the most essential features of such progress. But the great question then arises, will artificial means eventually be developed for overcoming the genetic disadvantages entailed by this drastic change of evolutionary procedure, or will mankind remain content simply to take the natural biological consequences?

#### RESUMÉ

An indispensable factor in animal speciation, that must precede the establishment of mutations giving sterile or inviable heterozygotes, is the prolonged prevention of interbreeding between the given populations. In the case of populations inhabiting the same or contiguous areas, such non-interbreeding may conceivably be brought about through gene mutations (*e.g.*, those changing the temperature tolerance) that result in assortative mating, or through acquired responses (*e.g.*, conditioning, acclimation) to differing environmental circumstances, but such isolation would be adequate only where a marked, protracted discontinuity of the effects was

achieved. Sufficient discontinuity, of genetic origin, would in the absence of topographical separation usually involve the accumulation, by selection, of a series of co-acting genes, either completely linked or having the nature of "specific modifiers" that acted differentially in the presence of two major alleles (as in some known cases of dimorphism), together with a tendency to elimination of the ordinary modifying genes that give rise preponderantly to intermediate types. Such selective effects, as well as directly acquired discontinuous "modifications," would depend upon a preexisting discontinuity either in the ecological conditions or in the inner physiological reactions of the organisms. The necessary isolation in breeding could, ordinarily, be attained more readily in cases where the mutational or acquired differences predisposed the individuals to living in topographically different situations. But adequate topographical isolation can of course occur readily, in most cases, even in the absence of any such primary mutations or of any priorly acquired physiological differences.

Granted effective isolation of one of the above kinds, mutations will accumulate differentially either if selection occurs (even where this tends in the same phaenotypic direction in the different isolated groups) or if there is opportunity for drift. Among these mutations must eventually be included those giving rise to complementary potentially harmful genes that render the products of crossing sterile or inviable. Such genetic differentiation may in many cases be described as involving a kind of transfer of function, or at least a different distribution of function, among the loci in the contrasted groups of organisms. Actual change of position of loci (translocation, etc.) may give the same kind of effect but, except in certain special cases, this effect would be recessive, and not exerted in  $F_1$ . When both complementary harmful genes, or sets of genes, are dominant, the  $F_1$  hybrids are rendered infertile or inviable, regardless of sex;<sup>5</sup> but, in

addition, infertile or inviable hybrids, of the heterozygous sex alone, result from the action of complementary harmful genes that are recessive, provided they are sex-linked. The high frequency of incapacitation of hybrids of heterozygous sex as compared with those of homozygous sex shows that the complementary harmful genes of recessive type are present oftener than the dominants. It appears probable, further, that recessive mutants become established oftener than dominants. Autosomal recessive genes of harmful complementary action should occur even oftener than sex-linked ones, but their effects are not commonly observed since they would be manifested only in generations later than the  $F_1$ .

There is evidence that all these "incapacitating genes" constitute only the few extreme examples, in the direction of harmful complementary effect, of the multitude of genes which ordinarily differentiate any two species that can be crossed, and which attain largely the same phenotype in the two species but by a somewhat different system of "balancing" of the developmental and physiological interactions concerned. That only a few of the genes play a considerable role in the marked effects observable in  $F_1$  is proved by the differences commonly found between the amount of incapacitation of the individuals of heterozygous sex derived from reciprocal crosses.

The results of the genetic analyses of the basis of hybrid incapacitation in crosses between "species," "sub-species" and "races" of *Drosophila* are summarized, and it is shown that they provide evidence for the application of the above principles at all levels in speciation, there being no sharp line between the different ranks.

It is shown that, in the evolution of the genetic basis of hybrid incapacitation, selection based on the advantage accruing from the resulting genetic isolation cannot have played an important role in the original establishment of the given genes within their first local group, and was not usually essential even in their establishment in the larger group throughout which they later spread.

<sup>5</sup> Except for genes of sex-limited action; see footnote 2.

Many genetically conditioned bars to crossing must have spread in the same way, as mere by-products of the general evolution, but some of them were probably helped considerably in their establishment by selection based upon their isolating influence, since such selection would be much more effective in some of these cases than in the case of genes for hybrid incapacitation.

Types of organisms in which either primary isolation or the secondary acquisition of genetic immiscibility cannot occur readily enough will tend to be at an evolutionary disadvantage. Thus those great groups of organisms will tend to remain which possess as fundamental features of their make-up an advantageously delicate balance—easily upset genetically—in one or more of their reproductive or somatic processes. These systems, which differ in the different groups, constitute, in effect, generalized mechanisms for *isolability*, which set limits to the operations of sexual reproduction, the generalized mechanism for miscibility. On the whole, the most favorable results for evolution would ensue when the isolability mechanisms were of such a nature as to lead groups of organisms to become progressively more isolated from one another as their genetic differences increased, without the isolation becoming absolute even when the differentiation was considerable. For a certain amount of gene infiltration from group to group tends to furnish valuable material for evolutionary advance, as well as immediately deleterious material, but the greater the degree of divergence the less is the amount of gene exchange which is advantageous.

There are several ways in which temperature affects the speed of the processes of divergence. (a) Temperature differences may give the ecological setting for the establishment of bars to crossing, both genetic and acquired. (b) Genetic differences in adaptation to temperature may also provide complementary genes that directly result in the death or abnormality of hybrids. (c) High temperature, as well as inconstant temperature, causes a

high mutation rate, although it is probable that such an influence would eventually be counteracted by increased selection in the direction of a lower mutation rate.

(d) The increased number of generations in a given time caused by higher temperature must, other things being equal, be reflected in a directly proportionate increase in the speed of divergence and of evolution in general.

(e) On the whole, in areas of land where there is enough humidity, higher temperature is correlated (through the common cause, greater amount of incident solar radiation) with a greater abundance of vegetation produced, and so with a greater total animal population. In so far as this allows an increase in the number of small local groups of animals it makes for more effective, faster intra-specific selection between the local groups on the basis of differences that arose by drift and by intra-group selection, and so hastens intra- and inter-specific divergence and evolution in general. (f) The greater amount of diversification and the greater complexity of the ecological conditions brought about in warmer regions as a result of the co-action of the above factors reacts back upon the organisms inhabiting these regions to increase their diversification and their general evolutionary change still more, in response to these conditions. For the last three reasons (d-f), at least, the warmer regions have been the chief centers within which new types have arisen and from which they have spread elsewhere.

There are, however, certain evolutionary advantages possessed by regions of inconstant or of cooler temperature, especially where these are not so extreme as to be paralyzing or incapable of being effectively adapted to. For the very difficulties of living thereby created constitute, for certain highly advanced animals especially, potent and peculiar selective factors that make possible important advances, as well as diversifications, which could otherwise have become established only at a much slower, more uncertain pace or not at all. Nevertheless, in their more elaborated later forms, these changes can

prove to be of great value even in the warmer regions. Some of these advances, moreover, serve as foundations for the establishment of still other progressive innovations, of use in warm as well as in inconstant or cool regions.

In the past, inter- and intra-specific isolation, of varying degrees, has been one of the most essential features in evolutionary divergence and, through this, in evolutionary advance. Since the possibility of any further natural isolation of these sorts in our own species is now being removed, the problem arises of what means can be found of avoiding the biological consequences which this situation would naturally entail.

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