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Paramutation: Directed Genetic Change

Paramutation occurs in somatic cells and heritably alters the functional state of a locus.

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It was observed about 10 years ago that an R^r gene in maize, which conditions anthocyanin formation in seed and plant, invariably has lowered anthocyanin-forming potential following passage through a heterozygote with the stippled (R^{st}) allele. The changed form of R^r was gametically transmissible. It reverted toward the standard type when made homozygous, but only partially. This unusual kind of heritable change was termed paramutation. The R^r allele in question was said to be paramutable, and the stippled factor was described as paramutagenic (*1*).

The initial studies revealed that paramutation involved chromosome components that do not conform to the ordinary rules of gene stability and integrity in heterozygotes. Furthermore, the induced heritable changes were directed. *R* paramutation appeared to be comparable in these respects to certain phenomena reported much earlier in *Pisum* by Bateson and Pellew (*2*), in *Malva* by Lilienfeld (*3*), and in *Oenothera* by Renner (*4*) as anomalous exceptions to Mendelian inheritance. The *R* case in maize offered advantages for experimental analysis which these other systems lacked, and it has been intensively investigated. The present article is limited to discussion of the *R* studies, for the most part, but the results appear to be meaningful for paramutation in general.

The biological significance of paramutation rests on the fact that the phenomenon involves constraint on gene expression during development of the individual which is exerted by factors located within the chromosome itself. The illuminating advances made in recent decades in characterizing the genetic substance biochemically have disclosed genomic components in bacteria that function *in situ* to regulate the action of genes specifying protein structure (*5*). The chromosomes of higher organisms are vastly larger and more complex than their counterparts in bacteria, and one may expect to find that they too embody devices whereby gene action is regulated locally. Paramutation is of general interest for the clues it may give to the nature of gene-controlling mechanisms.

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Induction of Paramutation

The general problem which paramutation presents is illustrated by the results of a simple experiment. Pollen of three kinds of maize plants, with a common highly inbred background, is applied to the silks of $r^g\,r^g$ individuals as follows:

1) $r^g\,r^g\ ♀ \times R^r\,R^r\ ♂$
2) $r^g\,r^g\ ♀ \times R^{st}\,R^{st}\ ♂$
3) $r^g\,r^g\ ♀ \times F_1\,R^r\,R^{st}\ ♂$

R alleles condition anthocyanin formation in the plant and in the aleurone—the outer cell layer of the endosperm. The recessive r^g allele conditions development of colorless aleurone and colorless plant (lacking in anthocyanin). R^r, termed "standard R^r," represents a class of factors, of wide geographic distribution, that conditions pigment formation in both aleurone and plant. The endosperm is the product of a fertilization separate from that which gives rise to the accompanying embryo. It receives a double complement of genes from the female parent, and one set from the male parent, and so is a triploid structure. Standard R^r in single dose ($R^r\,r\,r$) gives darkly mottled aleurone, and in either two doses ($R^r\,R^r\,r$) or three doses ($R^r\,R^r\,R^r$), gives self-colored aleurone. R^{st} (stippled) gives a spotting pattern in the aleurone, directly proportional to dosage.

The endosperm genotypes which result from the above three testcrosses are

1) All $R^r\,r^g\,r^g$
2) All $R^{st}\,r^g\,r^g$
3) 50 percent $R^r\,r^g\,r^g$ plus
   50 percent $R^{st}\,r^g\,r^g$

Half of the seeds ($R^r\,r^g\,r^g$) resulting from mating 3 should conform genetically to those from mating 1, and the other half should conform to the seed resulting from mating 2. The latter

expectation is fulfilled: the stippled kernels resulting from testcrosses 2 and 3 are indistinguishable from each other. The correspondence, however, does not extend to the $R^r\ r^g\ r^g$ seeds from matings 1 and 3. All the $R^r\ r^g\ r^g$ kernels from testcross 3 are more weakly pigmented than those from testcross 1. The difference is illustrated in Fig. 1. The basis of the phenotypic difference is a heritable alteration in pigmenting potential of R^r by virtue of passage through the $R^r\ R^{st}$ heterozygote; R^r has been changed to a more weakly pigmenting form symbolized by $R^{r'}$. The change from R^r to $R^{r'}$ is attributed to paramutation.

The $R^r\ r^g\ r^g$ kernels from both mating 1 and mating 3 are mottled, and the degree of mottling varies somewhat within each group. A scoring procedure that has proved adequate to deal with the continuous variation in amount of anthocyanin pigmentation in kernels of these classes involves matching of each kernel in a 50-kernel random sample of the $R^r\ r^g\ r^g$ seed from a testcross ear against a set of six standard seeds ranging progressively from near-colorless to near-self-color, and defining seven classes. The mean aleurone-color score for the sample is then used as the measure of the pigment-producing potential of the R^r male gametes formed by the staminate plant under test.

The mean score for the $R^r\ r^g\ r^g$ kernels from a type 1 testcross in a representative experiment was 5.9. The value for the corresponding class of seeds ($R^{r'}\ r^g\ r^g$) from the type 3 mating was 2.4. Thus passage of R^r through the heterozygote with the stippled factor reduced pigment-producing potential of the allele by more than three units on the seven-grade aleurone color scale. The fall in pigmenting potential characterized all, or nearly all, the R^r gametes from the $R^r\ R^{st}$ parent. The change is thus unique in two respects: it is unidirectional and also invariable in occurrence.

As mentioned above, the stippled kernels resulting from matings 2 and 3 are alike in appearance. Supplementary tests prove that the R^{st} allele also is unaltered in strength of paramutagenic action by passage through an $R^r\ R^{st}$ heterozygote. Paramutation thus affects only the R^r factor in $R^r\ R^{st}$ plants.

A marked difference in pigment-producing action of R^r and $R^{r'}$ is again expressed if plants are grown from the $R^r\ r^g$ and $R^{r'}\ r^g$ seeds resulting from the matings referred to in the preceding section. The strength of action of $R^{r'}$, however, is found to have shifted partway back to that of R^r in standard form. The $R^{r'}$ genes from $R^{r'}\ R^{r'}$ homozygotes derived by self-pollination of $R^r\ R^{st}$ plants likewise have significantly weaker aleurone-pigmenting action than standard R^r genes from homozygous stock cultures. The difference is illustrated in Fig. 2. Thus $R^{r'}$ is gametically transmissible through the embryo, but not necessarily in the highly repressed form characteristic of $R^{r'}$ resulting directly from $R^r\ R^{st}$ heterozygotes.

Kermicle (*6*) observed that, in two $R^{r'}\ R^{r'}$ sublines derived by selfing an $R^r R^{st}$ plant, the partial reversion in strength of $R^{r'}$ action mainly occurred in the first $R^{r'}\ R^{r'}$ generation. Thereafter the $R^{r'}$ aleurone-pigmentation potential remained stable at a level about halfway between that of standard R^r and that of the primary $R^{r'}$ paramutant.

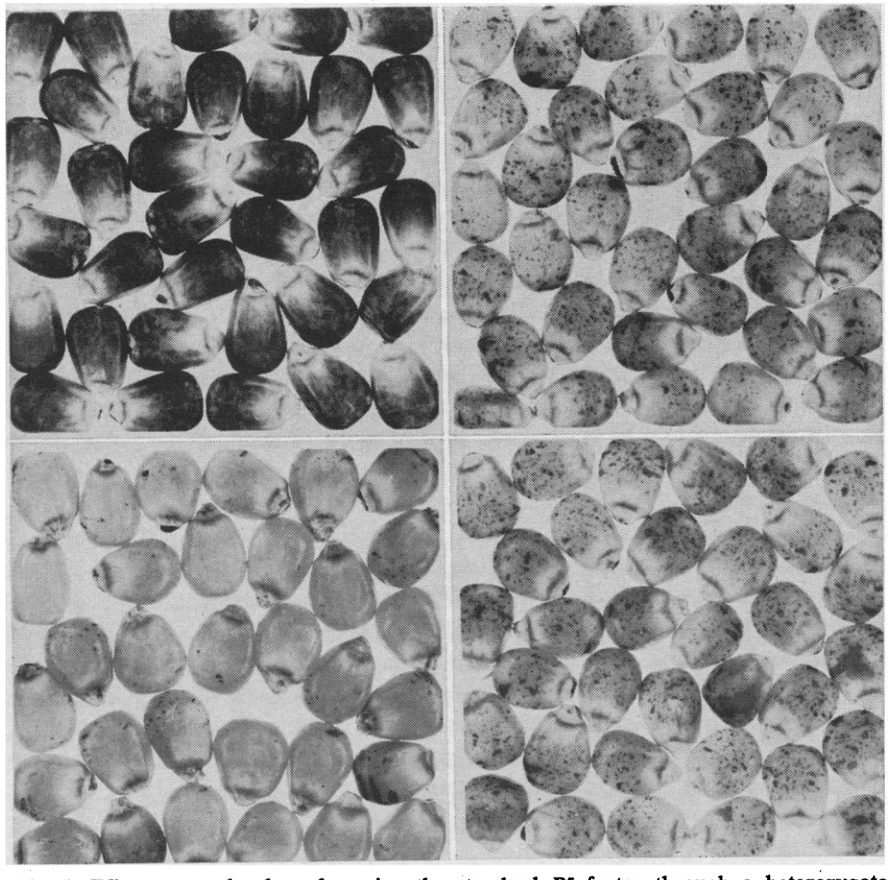

Fig. 1. Effect on seed color of passing the standard R^r factor through a heterozygote with the R^{st} allele. The two groups of kernels shown in the top row resulted from matings on a colorless $r^g\ r^g$ strain, with (top left) pollen from a standard $R^r\ R^r$ stock culture and (top right) pollen from an $R^{st}\ R^{st}$ stock culture. Note that the $R^r\ r^g\ r^g$ testcross kernels are darkly mottled. The two groups of kernels shown in the bottom row resulted from the application of $F_1\ R^r\ R^{st}$ pollen to the same colorless female strain. The seed phenotype associated with the R^{st} allele is unchanged, as is evident from a comparison of the spotting pattern of the $R^{st}\ r^g\ r^g$ testcross kernels (bottom right) with patterns of the $R^{st}\ r^g\ r^g$ controls (top right). The $R^{r'}\ r^g\ r^g$ testcross kernels (bottom left), on the other hand, are lightly mottled as compared with the standard $R^r\ r^g\ r^g$ testcross kernels (top left). The change in phenotype in this case reflects the markedly reduced aleurone-pigmenting potential of R^r that regularly follows passage of R^r through a stippled heterozygote.

Characteristics of the R Paramutation System

An analysis of the earlier work on paramutation at the *R* locus in maize was published in 1964 by Brink (*7*). Several of the questions discussed at that time are dealt with here only briefly, except as new evidence on them has been published. Many of the data on which the new conclusions in these cases rest may be found in the general review mentioned above (*7*) and in the primary articles cited therein. Particular attention in this article is accorded the results of recent studies of special significance for the interpretation of paramutation.

Association of the R Locus with Paramutation

The genetic elements involved in *R* paramutability are intimately connected with determinants situated at the *R* locus in the long arm of chromosome 10. The *R* locus is complex, and there is now extensive evidence supporting Stadler's (*8*) view that two, among several, components are (S) and (P), conditioning seed and plant color, respectively. Tests show that paramutability at the locus is closely associated, but probably not coincident, with (S). There is evidence also that paramutability is unaffected by loss from the locus of (P). These conclusions rest in part on the results of a comparative study of the response to R^{st} action of two types of mutants from standard $R^r : R^g$ (colored aleurone, green plant) and r^r (colorless aleurone, red plant). Stadler and Nuffer (*9*) postulated that one of the ways in which R^g and r^r mutants could arise is through crossing over, following oblique synapsis of (S) and (P) in $R^r R^r$ plants; such crossing over would result in chromosomes deficient in one or the other of these elements. Emmerling (*10*) showed that a high proportion of R^g mutants from R^r were, in fact, deficient in (P). Brown (*11*) found that nine R^g mutants from standard R^r were indistinguishable from each other and from the parent R^r allele in sensitivity to R^{st} action and in the ability to acquire "secondary paramutagenic potential" following passage through heterozygotes with the stippled factor. [Brown and Brink (*12*) observed that passage of standard R^r through an $R^r R^{st}$ heterozygote not only reduced the pigment-producing potential of R^r but also rendered the allele paramutagenic, although weakly so as compared with R^{st}. They termed this phenomenon secondary paramutation.] Application by Bray and Brink (*13*) of Emmerling's (*10*) test proved that some, but not all, of these R^g mutants were deficient in (P). It is apparent, therefore, that the potential for paramutation at the *R* locus is fully conserved in spite of changes in, and even loss of, the (P) component.

The response of the locus to action of the stippled factor, on the other hand, regularly is lost when R^r mutates to r^r (colorless seed, red plant). Brown (*11*) showed that all members of a random sample of 20 r^r mutants from standard R^r gave a negative result when tested for acquisition of secondary paramutagenic activity in $R^{st} r^r$ plants, whereas R^r and mutant R^g controls all gave positive results. Eleven of the r^r mutants were tested to determine whether, in any instance, the stippled factor reduced the plant-pigmenting potential of r^r as it does that of R^r. Again the results were negative throughout. Evidently loss of the (S) function, presumably either by mutation of (S) to (s) or by (S) deficiency, abolishes sensitivity of the locus to action of the stippled factor.

Ashman (*14*) found that 13 colorless-aleurone, red-plant mutants isolated among the offspring of $R^r R^{st}$ plants, most of which were crossovers between markers bracketing the *R* locus, were nonparamutagenic throughout. All the evidence at present available, there-

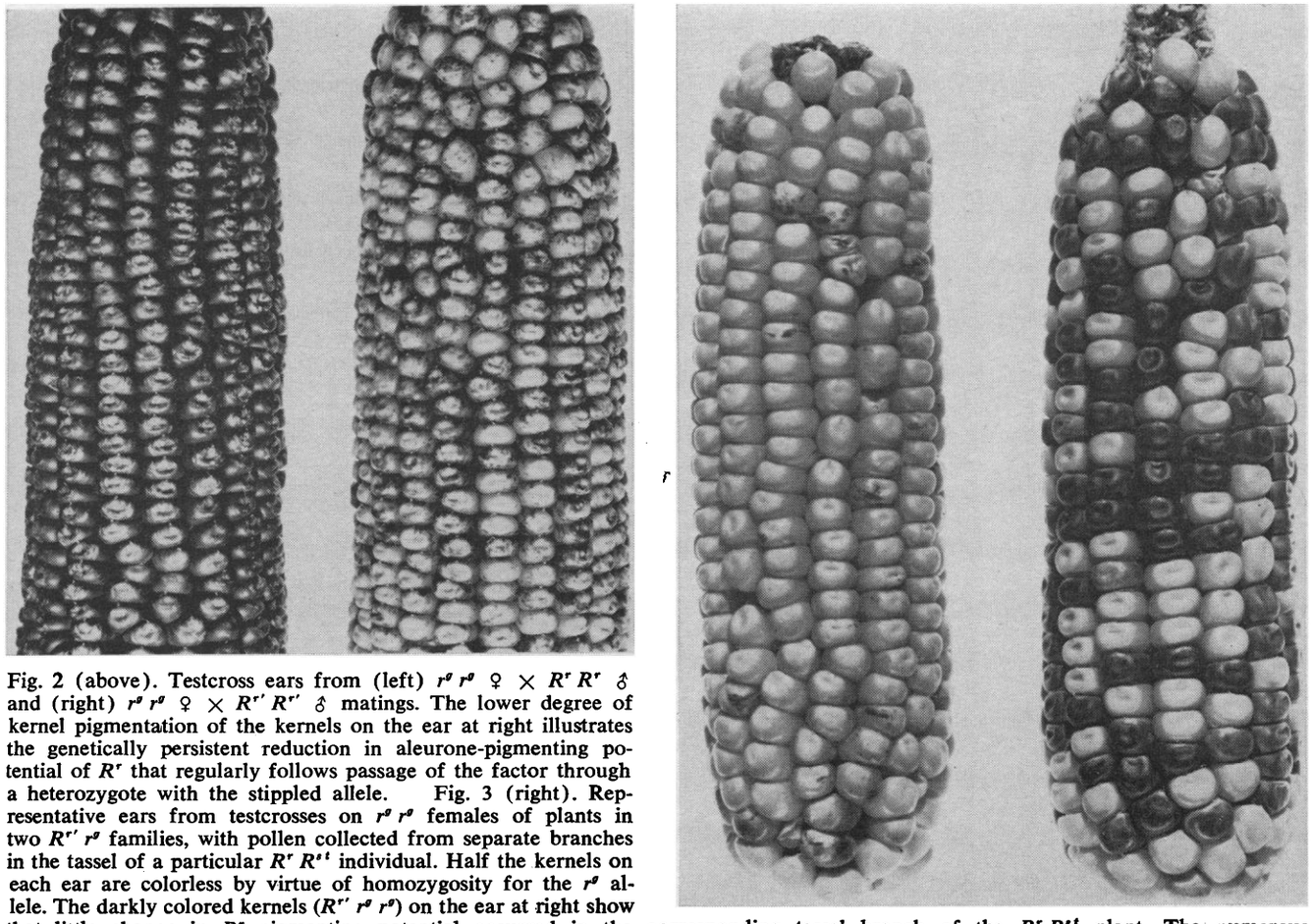

Fig. 2 (above). Testcross ears from (left) $r^g r^g$ ♀ × $R^r R^r$ ♂ and (right) $r^g r^g$ ♀ × $R^{r'} R^{r'}$ ♂ matings. The lower degree of kernel pigmentation of the kernels on the ear at right illustrates the genetically persistent reduction in aleurone-pigmenting potential of R^r that regularly follows passage of the factor through a heterozygote with the stippled allele. Fig. 3 (right). Representative ears from testcrosses on $r^g r^g$ females of plants in two $R^{r'} r^g$ families, with pollen collected from separate branches in the tassel of a particular $R^r R^{st}$ individual. Half the kernels on each ear are colorless by virtue of homozygosity for the r^g allele. The darkly colored kernels ($R^{r'} r^g r^g$) on the ear at right show that little change in R^r pigmenting potential occurred in the corresponding tassel branch of the $R^r R^{st}$ plant. The numerous colorless and near-colorless $R^{r'} r^g r^g$ kernels on the ear at left show that marked reduction in R^r aleurone-pigmenting potential occurred in another tassel branch on the same $R^r R^{st}$ plant. [From Sastry, Cooper, and Brink (*16*)]

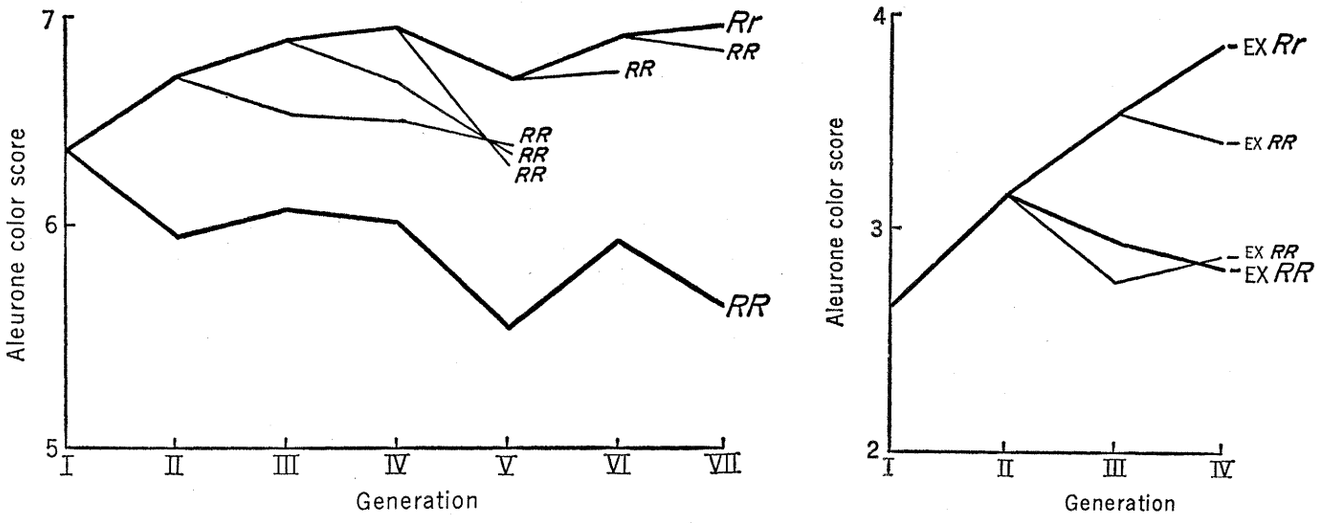

Fig. 4 (left). Progressive divergence in R^r aleurone color expression through six generations of matings, without selection, of $R^r\,r^g$ and $R^r\,R^r$ males with $r^g\,r^g$ females. The R^r allele in question was derived initially from a single source, and the background inheritance throughout was that of the W22 inbred strain. The $R^r\,r^g$ and R^rR^r lineages were separately propagated by self-pollination of the two kinds of plants within the respective $R^r\,r^g$ and $R^r\,R^r$ successions illustrated in the diagram. [From Styles and Brink (*21*)] Fig. 5 (right). Mean aleurone scores of $R^{r'}$ derivatives from standard R^r stocks maintained homozygous and heterozygous with r^g through four generations, showing changes in sensitivity of standard R^r to paramutation when subsequently tested in $R^r\,R^{st}$ heterozygotes. [From Styles and Brink (*21*)]

fore, supports the conclusion that the mutation of colored to colorless seed leads to a null condition at the locus for paramutation.

The property of overt paramutagenicity likewise resides at the *R* locus. McWhirter and Brink (*15*) found that when the stippled factor (R^{st}) mutates to self-colored aleurone (R^{sc})—an event that occurs with a frequency of about two occurrences per 1000 gametes—paramutagenicity may be unaltered, lost entirely, or changed in varying degrees. The mutation of R^{st} to R^{sc} in some instances without alteration in paramutagenicity demonstrates that the genetic bases of the stippled phenotype and paramutagenicity are distinct from each other. The fact that, in other cases, both functions change together suggests that the two kinds of elements in question are close enough to each other in the chromosome to be involved frequently in a single mutation.

Additional evidence for the compound nature and divisibility of the genetic material involved in *R* paramutagenicity has been adduced by Ashman (*14*) from a study of intralocus recombination at meiosis. He characterized three classes of seed-color mutants among the offspring of

$$+\,R^r\,+\,/\,g\,R^{st}\,M^{st} \times g\,r^g\,+$$

crosses, one of which, comprising 12 near-colorless-aleurone, red-plant individuals, is of particular interest in this context. (M^{st} is a modifier of R^{st} aleurone spotting, about six units distal to the *R* locus.) All 12 mutants were recombinants between the outside markers. It may be inferred from the phenotype that they carried the basic aleurone-color component of R^{st} and also the red-plant-color element of R^r. If these inferences are valid, then we may conclude that the mutants were products of recombination within the *R* locus itself. Ashman showed that all 12 members of the group were paramutagenic, but less so than R^{st}, and, furthermore, that they differed significantly from each other in degree of paramutagenicity. Ashman interpreted this evidence as indicating that the physical basis of paramutagenicity was a chromosomal region that was partitionable by crossing over.

Bray and Brink (*13*) explored the relation between mutation and paramutation at the *R* locus and found it to be complex. Certain regularities, however, were brought to light. The normal form of the standard R^r allele, for example, was observed to mutate to r^r (colorless aleurone) at the rate of 12.7×10^{-4}, whereas the rate for paramutant $R^{r'}$ was much lower—namely, 7.4×10^{-4}. Similarly, the paramutant forms of four out of five R^g mutants from standard R^r had lower mutation rates than their normal counterparts. For the fifth, the mutation rates for R^g and $R^{g'}$ were equal. Paramutant $R^{r'}$ tends to revert toward the pigmenting potential characteristic of standard R^r following extraction from $R^r\,R^{st}$ heterozygotes, as Kermicle (*6*) reported. Bray and Brink observed that, as the pigmenting ability of $R^{r'}$ rises in such cases, the mutability to r^r also increases.

Paramutation as a Somatic Phenomenon

Sastry, Cooper, and Brink (*16*) found, on sampling separately the pollen in different tassel branches, that many individuals heterozygous for a paramutable and a paramutagenic *R* allele were clearly mosaic with respect to aleurone-pigmenting potential of the paramutable member of the pair (Fig. 3). The occurrence of somatic mosaicism also was established in $R^{r'}\,r^g$ plants resulting from $r^g\,r^g$ ♀ × $R^r\,R^{st}$ ♂ matings, in which partial reversion of the $R^{r'}$ factor toward the pigmenting potential of standard R^r is known to occur. Sectoring for paramutation in the tassel would be expected if paramutation occurs during vegetative growth of the plant and also takes place independently in different cell lineages. The results obtained by Sastry, Cooper, and Brink show that easily recognizable differences in strength of *R* pigmenting potential between tassel sectors within a plant in which paramutation is occurring are sufficiently frequent to give credence to the conclusion that all such plants are paragenetically mosaic in one degree or another.

McWhirter and Brink (*15*) found that a given paramutable *R* allele may

be brought to different average levels of aleurone-pigmenting potential by being passed through a series of heterozygotes carrying R^{sc} alleles of varying paramutagenicities. They observed also that paramutation was progressive through successive plant generations. Since the only somatic structures that may be sampled directly in maize are terminal products of growth—namely, tassel and ear shoot—the course of paramutation as plant development proceeds cannot be ascertained directly in this species. The indirect evidence strongly suggests, however, that paramutation is progressive during ontogeny. The occurrence of mosaicism shows that the amount of change varies in different cell lineages, and it may be supposed that the progression is irregular.

Paramutation-like phenomena that were described long before the term *paramutation* was used afford the most direct evidence for the occurrence of paramutation during development of the plant. Hybrids that were morphologically inconstant were found in *Pisum* by Bateson and Pellew (*2*), in *Malva* by Lilienfeld (*3*), and in *Oenothera* by Renner (*4*). Progeny tests, in which seed from phenotypically different branches within a single mosaic plant were used, showed, in each of these cases, that the distribution of offspring varied in accordance with the phenotype of the parent somatic tissue. More recently Hagemann (*17*) has found that in *Lycopersicon* also the heritable changes induced by paramutagenic alleles may appear initially as sectors during vegetative growth.

If paramutation at the *R* locus in maize is comparable to the phenomena described in *Pisum, Malva, Oenothera,* and *Lycopersicon,* pollen collected from an entire $R^r\,R^{st}$ tassel will embody an array of paramutant $R^{r'}$ alleles representing the terminal states in all the cell lineages that extend into the sporogenous tissue, and in which successive changes in R^r potential during plant development have been accumulated. If the reduction in R^r potential is far advanced in all cell lineages within a plant, all the resulting $R^{r'}$ testcross kernels will have low aleurone-pigmentation scores. Testcrosses involving heterozygotes between standard R^r (an allele highly sensitive to paramutation) and R^{st} (a strongly paramutagenic factor) often yield $R^{r'}$ kernel populations which appear to have uniformly low aleurone-color scores. By means of progeny tests, Kermicle (*6*) has shown, however, that even such seemingly uniform kernel samples may be heterogeneous for level of *R* pigmenting potential. Evidence of this sort suggests that somatic mosaicism for *R* paramutation is the rule. Much variability of *R* pigmenting potential between different cell lineages that arises early in plant development may be extinguished at later stages. The tests of pollen from different tassel branches within the plant made by Sastry, Cooper, and Brink demonstrate, however, a large residuum of mosaicism at the flowering stage.

Recently Coe (*18*) has postulated that paramutation at the *B* locus on chromosome 2 in maize does not occur during vegetative growth of the plant but occurs late in ontogeny, probably at meiosis. Coe reports that $F_1\ B\,B'$ hybrids between normal $B\,B$ and homozygous paramutant $B'\,B'$ plants are paramutant in phenotype, and produce only B' gametes. He suggests, however, that the basis of the paramutant phenotype, in this instance, is not change of the $B\,B'$ to the $B'\,B'$ genotype during plant growth but dominance of B' over *B*. Experiments designed to test this suggestion did not provide clear evidence on the question. Coe (*18*) reports, however, that the comparatively infrequent primary mutation of normal *B* to the paramutagenic form, B', has a somatic basis. He found that such mutants appear as visible sectors during plant development. It may be concluded, therefore, that there is no established exception to the general rule exemplified in *Pisum, Malva, Oenothera,* and *Lycopersicon,* and also at the *R* locus on chromosome 10 in maize, that paramutation takes place in vegetative cells during plant growth.

Effect of Abnormal Chromosome Structure on R Paramutation

The *R* locus lies in the distal half of the long arm of chromosome 10 (10L). Reciprocal translocations involving a break in 10L, and a chromosome carrying a large, distinctive, terminal knob, known as K10, both influence the function and paramutability of *R*.

Insertion of standard R^r into a translocated chromosome (*T*) involving a break in 10L either proximal or distal to the *R* locus, and not necessarily close to the latter, leads to two changes in *R* action: (i) R^r aleurone-pigment-producing potential is enhanced and (ii) the allele is rendered relatively insensitive to paramutation in TR^r/R^{st} heterozygotes. These changes are irregularly expressed, and they persist for at least one generation following return of R^r to a structurally normal chromosome by crossing over. The latter fact proves that the changes in sensitivity are not position effects in the conventional sense of the term (*19*).

Brink and Weyers (*20*) tested a single crossover of standard R^r into a K10 chromosome and observed that sensitivity of the allele to paramutation was significantly reduced as compared with sensitivity of the same factor in a structurally normal chromosome 10. The possibility that the observed change in R^r sensitivity was due, not to the knob, but to some linked factor incidentally present in this particular K10 chromosome has since been explored by testing 12 additional crossovers of paramutable *R* alleles into K10 chromosomes. Three mutant R^g alleles from standard R^r, termed $R^g{}_1$, $R^g{}_2$, and $R^g{}_3$, which coincided with standard R^r in aleurone-pigmenting action and in sensitivity to R^{st} action, were used. The outcome of the experiment was decisive; the R^g alleles that had been incorporated in the knob-carrying chromosome were significantly less sensitive to paramutation in R^{st} heterozygotes than their R^g controls in structurally normal chromosomes in all 12 of the cases tested.

Additional tests have shown that R^r is not made relatively insensitive to paramutation by passage through a plant in which R^r and K10 are present in repulsion—that is, are borne by homologous chromosomes. A number of $R^r\ R^r$ and $r^r\text{K10}/r^r$ plants were mated with each other, and the two resulting classes of offspring, $R^r/r^r\text{K10}$ and R^r/r^r, were then crossed with $R^{st}\ R^{st}$. Testcrosses showed that $R^{r'}$ alleles derived from the two groups of R^r/R^{st} plants were indistinguishable from each other in aleurone-pigmenting potential.

The experimental results for chromosome K10 suggest, but do not prove, that the terminal knob exerts an indirect effect on sensitivity of R^r to action of the stippled factor by genetically altering the component of the *R* locus immediately involved in paramutation. Since the *R* locus and K10 are widely separated from each other in 10L, and a condition of the change in question is that the two factors be present in the nucleus in coupling, it

is inferred that the stimulus exerted by the K10 knob is propagated along the chromosome to the *R* locus, where the paramutable component then responds by changing quantitatively.

Inherent Metastability of Paramutable R Alleles

Recent investigations have revealed that the functional state of a paramutable *R* allele can change heritably without association of the allele in a heterozygote with a paramutagenic factor such as R^{st}. The capacity for heritable change in action is a built-in characteristic. The R^{st} allele in a standard $R^r\,R^{st}$ heterozygote does not "contaminate," or confer any new property on, standard R^r; rather it directs and amplifies a kind of genetic change that standard R^r is capable of undergoing quite independently of R^{st}, or any other partner.

The chain of evidence which leads to this conclusion began with the confirmation by Styles and Brink (*21*) of an earlier observation by Brink and Blackwood (*22*) that R^r genes derived from otherwise comparable $R\,r$ and $R\,R$ plants differed regularly, and the demonstration that the difference resulted from an inherited change in *R* action. Standard R^r, initially derived from stock $R^r\,R^r$ cultures, becomes progressively enhanced in aleurone-pigmenting potential when the allele is maintained through successive generations in $R^r\,r^g$ heterozygotes (Fig. 4). The further fact was established that the sensitivity of standard-R^r action to repression in $R^r\,R^{st}$ heterozygotes becomes progressively reduced as the aleurone-pigmenting potential of the allele becomes progressively enhanced (Fig. 5). The evidence suggests, therefore, that both phenomena reflect a single kind of change in standard R^r.

Styles and Brink (*21*) noted that the heritable enhancement in pigmenting potential of standard R^r in $R^r\,r^g$ plants is a paramutational process in that it is a regular and directed change. Standard R^r is thus subject to heritable alterations in both directions in terms of aleurone-pigmenting potential, and the direction of change is controllable. The possibility exists that *r* is influential in directing the enhancement of standard R^r action, just as R^{st} is influential in directing its repression. Proof that *r* is paragenetically amorphic in $R\,r$ plants, however, has now been obtained by Styles and Brink (*23*) in a comparative study of the aleurone-pigmenting potentials of $R^g\,r^r$ heterozygotes and $R^g/\,r{-}x_1$ hemizygotes. (The symbol $r{-}x_1$ represents a small deficiency spanning the *R* locus; the deficiency is female-, but not male-transmissible.)

In that study, $R^g{}_2$, a mutant from standard R^r which conditions the development of colored aleurone and green plant and is indistinguishable from R^r in sensitivity to paramutation, was maintained for three successive generations in a lineage of $R^g{}_2\,r^r$ heterozygotes and also in an otherwise closely comparable lineage of plants hemizygous for the *R* locus. The two lineages were maintained by recurrent pollinations of $r^r/r{-}x_1$ individuals by $R^g{}_2\,r^r$ and $R^g{}_2/r-x_1$ plants. The effects on $R^g{}_2$ aleurone-pigmenting potential were determined in matings on $r^g\,r^g$ females. Mean testcross scores for control $R^g{}_2\,R^g{}_2$ plants, of stock-culture origin, ranged between 5.63 and 5.85. Mean testcross scores from $R^g{}_2\,r^r$ lineages in generations 1, 2, and 3 were 5.72, 6.07, and 6.48, respectively. The corresponding mean values from the parallel $R^g{}_2/r{-}x_1$ testcrosses were 5.80, 6.03, and 6.42. Thus the aleurone-pigmenting action of $R^g{}_2$ was progressively enhanced in both experimental lineages and, on the average, by almost identical amounts (Fig. 6). It is evident, therefore, that enhancement in the pigmenting potential of a paramutable *R* allele can occur autonomously, and that paramutational change in the upward direction is not necessarily directed by a partner allele.

Tests with *R* alleles in paramutant (partially repressed), rather than normal, form provide further evidence of the capacity of paramutable *R* factors to undergo heritable changes spontaneously. Kermicle (*6*) showed that paramutant *R'* alleles represented by first-generation progeny of $R\,R^{st}$ plants undergo partial reversion in an *R'* hemizygote. The amount of reversion is equivalent to that occurring in $R'\,r$ individuals. This conclusion has been amply confirmed by Styles and Brink (*23*) in tests extended over three generations.

The more recent experiment was made in triplicate; the respective $R^{g'}\,r^r$ and $R^{g'}/r{-}x_1$ offspring from three $r^r/r{-}x_1$ ♀ × $R^g\,R^{st}$ ♂ matings were used. The mean $R^{g'}$ testcross score for the three initial testcrosses was 2.29 on the commonly used seven-grade aleurone color scale. Matings were made in series, and $r^r/r{-}x_1$ plants were used recurrently as the female parents throughout, continuous $R^{g'}\,r^r$ and $R^{g'}/r{-}x_1$ lineages being thereby produced in each of the three replicates. The mean testcross scores in generation 3 for the corresponding $R^{g'}\,r^r$ and $R^{g'}/r{-}x_1$ lineages were 5.04 and 4.62. Thus, pronounced reversion in level of $R^{g'}$ action occurred in both lineages. The difference between the two values was no greater than that between values from several parallel mixed lineages, a fact which suggests that the disparity was not meaningful for the comparison in question.

The important deduction from the experimental evidence summarized in this section is that a paramutable *R* allele, in standard as well as paramutant form, may change spontaneously in directed fashion. The basic condition underlying paramutation is the metastability inherent in sensitive alleles.

Interactions between Paramutable R Alleles

Recent studies by Styles (*24*) have shown that paramutable *R* alleles of unlike geographic origin and initially unlike in strength of aleurone-pigmenting action are not necessarily permanently unlike. Furthermore, such *R* alleles were found to interact with each other in heterozygotes in a characteristic way.

Styles chose for detailed study four *R* alleles from different geographic sources that, in single dose, give complete, or nearly complete, self-color and four that give distinctly mottled aleurone, in plants of the W22 inbred strain. Some of the alleles carried the red-seedling marker; the others gave green seedlings. All eight alleles were shown to be inherently metastable, like standard R^r. The significant fact newly established was that the initial differences between the eight factors were impermanent. Each allele could be altered, by simple mating procedures, until it was essentially indistinguishable from any other. Furthermore, heritable, but not necessarily stable, differences in aleurone-color expression could be produced in different sublines carrying the same allele. The R^r or R^g factors that initially, in single dose, conditioned development of very dark,

or self-colored, aleurone gave progressively more mottling when bred as homozygotes, but retained their potential for conditioning self-color when kept heterozygous for *r*. Alleles that initially conditioned aleurone mottling, in single dose gave progressively divergent degrees of mottling when propagated as homozygotes or heterozygotes. The stocks bred as *R r* heterozygotes usually became more darkly mottled, whereas corresponding stocks bred as homozygotes either became more lightly mottled or did not change in *R* expression.

Styles (*25*) also observed that paramutable *R* alleles which differed significantly from each other in aleurone-pigmenting potential when propagated routinely in stock cultures of the W22 inbred strain changed genetically in a characteristic way when maintained as heterozygotes with each other. If R_1 represents a paramutable *R* allele of relatively high aleurone-pigmenting potential in stock culture and R_2 represents one of lower potential, then, in successive generations of self-fertilized $R_1 R_2$ plants, the level of pigmenting potential of R_1 tends to fall to that of R_2. Eventually expression of the two alleles becomes indistinguishable.

The parallel between the effect of R_2 on R_1 in $R_1 R_2$ heterozygotes and the phenomenon which Brown and Brink (*12*) called secondary paramutation is apparent.

It thus becomes clear that the metastability inherent in paramutable *R* alleles may be manifested in a variety of ways. Apparently uniformity of *R* expression in these cases, if achieved, is a contingent condition, and does not reflect permanent stabilization of the factor.

Model of a Paramutable R Factor

Brink (*7*) and Sastry, Cooper, and Brink (*16*) have attempted to account for the experimental evidence on *R* paramutation in terms of the following model. The *R* locus is assumed to comprise two main components: (i) a structural gene (more probably a gene complex) specifying a particular enzyme involved in anthocyanin formation, and (ii) a heterochromatic segment closely associated with the structural gene, which affects expression of the latter during seed and plant development. The heterochromatic segment, termed the repressor segment, is assumed to consist of varying numbers of a common repeating unit, called a metamere, the effect of which is to repress *R* action. The degree of repression is assumed to be proportional to the number of metameres making up the repressor segment. An *R* gene accompanied by a large number of metameres is only weakly expressed, whereas *R* action is strong if only a few metameres are present. All paramutable *R* alleles are assumed to possess at least one metamere.

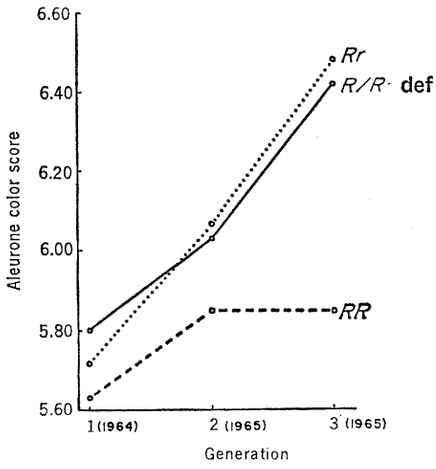

Fig. 6. Aleurone testcross scores following pollination of $r^g r^g$ plants with generations 1, 2, and 3 of *Rr* and *R*/*R*-deficient individuals, and scores for *R R* controls. It is apparent that the *R*-pigmenting potential rises, as the generations advance, at the same rate in *R*/*R*-deficient hemizygotes and *Rr* heterozygotes.

Paramutation is assumed to be a change in the number of metameres making up the repressor segment. It is postulated that such change results from misreplication within the segment during somatic mitosis. The copying of a given repressor segment more than once in a mitotic cycle would lead to an increase, and failure to copy some part of the segment would result in a decrease, in the total number of metameres. The potential strength of *R* expression would be altered accordingly.

The directed nature of paramutation is assumed to reflect sensitivity of the metamere replication process to regulation in definite ways. It may be supposed, for example, that the stippled allele in an $R^r R^{st}$ plant establishes a metabolic condition in the nucleus that favors overcopying of metameres at the *R* locus in the homologous chromosome. The immediate effect of R^{st} might be to prolong the period in mitosis during which the metameres in the repressor segment serve as templates for the formation of daughter metameres; or first copies of the parent metameres might not be sequestered at once from the replication process but might serve in turn as templates for second copies within the same mitotic cycle. Hemizygosity for R^r, or heterozygosity of R^r for the paragenetically amorphic allele r^r, on the other hand, is assumed to shift the balance of conditions affecting replication in a direction that favors undercopying of metameres.

The postulated effects on metamere replication, however, must be assumed to be permissive rather than determinative. The presence of R^{st} in the nucleus of an $R^r R^{st}$ plant, for example, merely increases the probability that, at a given mitosis, the number of metameres associated with R^r will be increased. It does not ensure that such change will always occur, nor does it regulate the amount of change at each mitosis. The mosaicism, in $R^r R^{st}$ plants, for level of R^r pigmenting potential is explainable on the assumption that changes in metamere number occur at varying rates in different cell lineages within the individual.

Experimental Tests of the Model

An early observation by Stadler (*26*), since verified by others, suggested a method of testing this model of a paramutable *R* allele. Stadler found that in maize, contrary to the results with various other plants and animals, high-energy radiations do not ordinarily induce point mutations that give viable homozygotes. Such induced mutations appear to be small deficiencies that behave like recessive lethal genes. If the level of pigmenting potential of a paramutable *R* factor is a function of the number of metameres in a repressor segment adjacent to *R*, and if ionizing radiations always cause deficiencies, then effective treatment with x-rays of individuals carrying a partially repressed *R* allele should always shift the *R* phenotype in the plus direction. That is, such an *R* allele, if altered at all, should tend to be derepressed by virtue of the loss of some metameres. It is assumed that such loss of metameres would be only partial in most instances, hence not lethal to the plant.

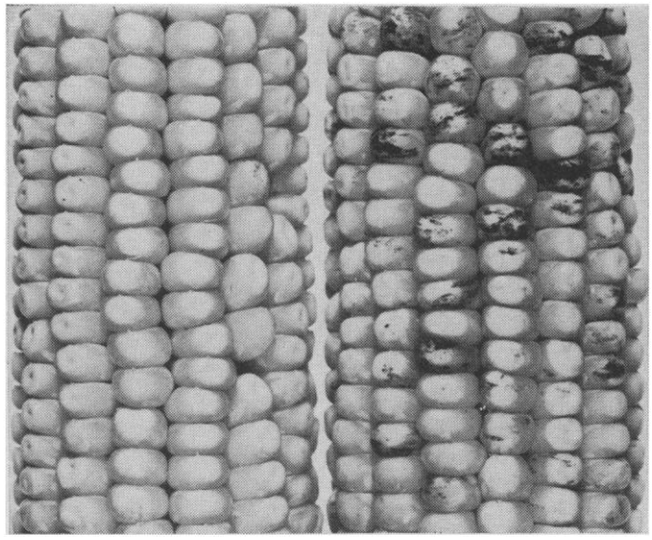

Fig. 7 (left). Testcross ears from matings on strain-W22 $r^r\ r^r$ females with (left) pollen from a plant grown from untreated strain-W22 $R_c'\ R_c'$ seed and (right) pollen from a plant reared from $R_c'\ R_c'$ sib seed treated with diethyl sulfate. [From Axtell and Brink (*27*)] Fig. 8 (right). Testcross ears from matings on strain-W22 $r^g\ r^g$ females with (left) pollen from a plant grown from untreated $R^r\ R^{st}$ seed and (right) pollen from a plant grown from $R^r\ R^{st}$ sib seed treated with diethyl sulfate. The very lightly spotted kernels, on both ears, are the stippled segregates. It is evident that only the $R^{r'}\ r^g\ r^g$ class of testcross kernels has been affected by the diethyl sulfate treatment. [From Axtell and Brink (*27*)]

Experiments were initiated in our laboratory to determine whether in fact high-energy radiations cause unidirectional change in the strength of the action of paramutated *R* genes. Parallel tests were undertaken with chemical mutagens. The two series of investigations are currently in progress.

Chemical Paramutagenesis

Experiments with two chemical mutagens, diethyl sulfate and ethyl methanesulfonate, have advanced to a stage at which a meaningful assessment of the results can be made. The following summary account is based upon recent tests by Axtell and Brink (*27*).

1) The strength of the pigmenting action of paramutated *R* alleles is altered markedly and with high frequency by treatment of seed with either of these chemicals in fresh aqueous solution. The treatment of pollen with saturated diethyl sulfate vapor for periods such that subsequent seed set is reduced even to about 20 percent of normal does not affect the strength of paramutant *R* action.

2) More than 90 percent of the M1 plants reared from diethyl-sulfate-treated seed homozygous for a particular highly repressed paramutant *R* allele, designated R_c', yielded kernels with higher levels of aleurone pigmentation (Fig. 7). Anderson *et al.* (*28*) observed that the average size of tassel sector showing partial fertility following exposure of maize seed to high-energy radiation was approximately two tassel branches. If this observation is generally valid, then pollen collected from a single tassel branch usually would represent a cell lineage in the mature plant based upon a single cell in the embryo of the treated seed. Pollen from individual lateral branches of three $R_c'\ R_c'$ plants reared from diethyl-sulfate-treated seed was used in testcrosses on colorless individuals. Nine of the ten branches yielded kernels more heavily pigmented than the control seeds. Thus, considered on a cellular basis, the incidence of change in response to the chemical treatment is very high. Obviously the frequency of change is far higher than that characteristic of ordinary mutation, which diethyl sulfate is known to promote also.

3) The altered forms of the R_c' allele recovered from plants reared from seeds treated with diethyl sulfate were heritable, and the deviant phenotypes were found to be dependent on the *R* locus in each example tested.

4) Repressed *R* alleles whose aleurone-pigmenting potential had been raised by treatment with diethyl sulfate were again repressed by passage through R^{st} heterozygotes. This result shows that the effect of the alkylating agent is on the *R*-locus component concerned with paramutation.

5) Paramutation of R^r to $R^{r'}$ in $R^r\ R^{st}$ plants grown from seed treated with diethyl sulfate is regularly and markedly reduced (see Table 1 and Fig. 8). Significant amounts of change in the strength of *R* action were observed following testcrosses involving all the treated M1 plants. Present data do not serve to distinguish between three possible interpretations of this result: (i) the sensitivity of the R^r allele to R^{st} action may have been reduced; (ii) paramutation of R^r to $R^{r'}$ may have occurred in response to R^{st} action in the heterozygote and then have been reversed by the treatment with diethyl sulfate; or (iii) the paramutagenic action of R^{st} may have been impaired by the chemical.

6) Two lines of evidence suggest that the changes induced in R' action by an alkylating agent, such as diethyl sulfate, are directed. First, the mean pigment-producing potential of R' alleles of initially intermediate potential is regularly raised by treatment of the seed, but not to the original standard-*R* value. Although the average change in phenotype is upward on the pigmenting scale, the possibility that R' may sometimes be changed by the treatment to a more weakly pigmenting form is not excluded. The second body of data supporting the conclusion that the changes are directed is derived from the experiment in which $R^r\ R^{st}$ seed were treated with diethyl sulfate (Table 1). Scores for the entire population of $R^{r'}\ r^g\ r^g$ testcross kernels

derived from each of the ten treated individuals were shifted upward by nearly two grades on the seven-grade aleurone-pigmentation scale. There was no indication in any instances of a reduction in level of $R^{r'}$ pigmenting potential in the progeny of the treated $R^r R^{st}$ plants below that of the untreated $R^r R^{st}$ controls.

It is significant, of course, that the effect of diethyl-sulfate treatment of seed on the pigmenting potential of the R^r allele in $R^r R^{st}$ heterozygotes is opposite to the effect on the potential by the R^{st} allele. The R^{st} allele invariably causes repression of R^r action, whereas the alkylating agent gives a response in the other direction relative to the average $R^{r'}$, or paramutant, value. The changes are directed in both instances, upward on the aleurone-pigment scale in one case, downward in the other.

Table 1. Frequency distributions and mean aleurone color scores for the $R^r r^g r^g$ kernels from testcrosses on $r^g r^g$ females of $R^r R^r$ (untreated), $R^r R^{st}$ (untreated), and $R^r R^{st}$ (diethyl-sulfate-treated) plants. The amount of reduction in level of R^r action ordinarily associated with passage of the allele through a stippled heterozygote is greatly reduced if the F_1 $R^r R^{st}$ seed from which the test plants are grown is treated with diethyl sulfate. [From Axtell and Brink (*27*)]

Staminate plant No.	Aleurone color class							Mean score*
	1	2	3	4	5	6	7	
				R^r R^r, *untreated*				
38-3						6	34	6.85
38-4						8	32	6.80
38-6						20	20	6.50
38-8						14	26	6.65
39-1						12	28	6.70
39-3						17	23	6.58
39-7						10	30	6.75
39-10						16	24	6.60
				R^r R^{st}, *untreated*				
103-1		7	15	11	7			3.45
103-2		3	11	14	12			3.88
103-3		3	6	11	19	1		4.23
103-4	2	2	12	16	8			3.65
103-5	1	2	3	10	17	7		4.53
103-6		1	9	10	20			4.23
103-7	1	4	20	10	5			3.35
				R^r R^{st}, *treated*†				
98-1				2	17	9	12	5.78
98-2				2	5	14	19	6.25
98-3		1	5	8	15	8	3	4.83
98-4						13	27	6.68
98-5			1	6	8	17	8	5.63
98-6			1	7	21	7	4	5.15
98-7			1		11	16	12	5.95
98-8				1	9	16	14	6.08
98-9					9	19	12	6.08
98-10				1	13	18	8	5.83

* Overall mean scores: families 38 and 39, 6.55; family 103, 3.90; family 98, 5.83. † Treatment: 2 ml of diethyl sulfate per 1000 ml of H_2O per 400 minutes ($1.5 \times 10^{-2}M$).

Discussion and Conclusions

A conclusion of major interest to which the recent studies on the *R* locus in maize leads is that paramutability is an intrinsic property of certain alleles. Paramutagenic factors do not confer the means for this kind of genetic change on their partners in heterozygotes; they alter the expression of the paramutability the basis for which the partner already embodies. A paramutagenic factor may exert an influence which leads to a major change in level of pigmenting potential of its partner in a heterozygote, but it is not self-sufficient in this respect. The paramutagenic factor does not instigate paramutation; it acts as an adjuvant to the process, which can occur independently of it. The primary consideration in paramutation is thus the metastability inherent in sensitive alleles.

This point of view has been implicit in earlier reports from our laboratory (*7*). It is now supported by critical evidence. The aleurone-pigmenting potential of a paramutable *R* allele from an *R R* stock-culture origin rises significantly, and at the same rate, in successive generations of otherwise identical *R r* heterozygotes and *R*/*R*-deficient hemizygotes. The capacity for paramutation, as a directed form of heritable change, is inherent in the paramutable allele itself. Paramutation is not dependent, in heterozygotes, on paramutagenic factors. The latter modify the process, and the modifications result in changes in level of pigmenting potential—changes which vary over a wide range.

The evidence for change in the functional state of *R* in plants hemizygous for the locus rules out, of course, any form of interallelic particle transfer as the basis of paramutation. Conversion, as visualized in 1930 by Winkler (*29*) or as shown by Mitchell (*30*) to result from intragenic recombination, does not apply to *R* paramutation. Excluded also is the hypothetical form of conversion recently suggested by Coe (*18*) in seeking an interpretation of paramutation at the *B* locus in maize.

Obviously conversion has no relevance for a hemizygous locus, and if paramutation can occur at such a locus, as has now been proved in the *R* case in maize, the essential basis of the phenomenon cannot be any form of copying from a model in a homologous chromosome or particle transfer between alleles. The term *conversion* as applied by some other investigators to paramutation is misleading in its basic implication, and its use in this context should be abandoned.

It is not yet possible to formulate a general rule applicable to the spectrum of interallelic relations exhibited by the *R* paramutation system. Variation in level of pigmenting potential of paramutable *R* alleles appears to become minimal in lineages of *R R* plants maintained as homozygotes by continued self-fertilization. The two representatives of a given *R* allele in diploid individuals seem to attain a condition of metastable equilibrium in relation to each other under this mating system. The observed relative uniformity of *R* expression in such cases, however, clearly is contingent, and does not reflect permanent stabilization of the allele. The metastability inherent in all such factors regularly comes to expression in the descendants, following intercrosses between different paramutable *R R* stocks and after outcrosses, for example, to $R^{st} R^{st}$, $r^r r^r$, or $r^r/r{-}x_1$ plants.

The general significance of the extraordinary sensitivity of the *R* paramutation system to alkylating agents remains to be determined. The available data do not provide a decisive test of the validity of the model de-

scribed above, wherein level of pigmenting potential of a paramutable *R* factor is assumed to be a function of the number of metameres making up a repressor segment associated with the *R* gene. The seemingly regular increases in pigmenting potential of paramutable *R'* alleles resulting from treatment of seeds with diethyl sulfate could be due to loss of metameres either by direct deletion or though an effect on the chromosome replication process that leads indirectly to metamere losses. The direct deletion of metameres is considered unlikely because of the high frequency of induced changes appearing in the offspring following treatment of the seed from which the parent plant was reared, and because of the insensitivity of *R'* alleles in the sperm present in pollen grains to the action of alkylating agents. Perhaps the striking effects of alkylation result from impairment of the repressor segment as a template in somatic cells—impairment such that undercopying of metameres, and hence partial derepression of *R'*, during chromosome replication results.

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How May Congress Learn?

Amitai Etzioni

An important question arose recently during a congressional hearing about "The Full Opportunity and Social Accounting Act" (S. 843), an act in which the United States is to review annually the "health" of American society. The question is: Who will be in charge of providing the data about the changing state of the society and how will it be made available to Congress? Stated more broadly, the issue concerns the mechanisms available to the national legislature to update its knowledge. In seeking an answer to this question, one must take into account: (i) the inevitability that knowledge about society will be politically "colored"; and (ii) that the slant of and the access to knowledge is affected by the distribution of resources used in its production and processing.

Political Elements of Knowledge

The current debate among social scientists concerning the "objectivity" of social scientific knowledge is not central to our discussion. Even if it were shown that the social sciences could be completely free of value judgments, this would not mean that they are so at the present time. More importantly, the question of how a society (or its decision-making bodies) "learns" does not concern a "pure" scientific exploration but, rather, knowledge as it is applied to actual social situations. Here pragmatic considerations take priority, and these include political considerations.

Since the writings of Immanuel Kant, it has been clearly established that scientific knowledge is always incomplete and tentative. The gap that exists between what we are capable of learning and what we in fact know is unbreachable. And the knowledge we do have must be continually revised. Hence, one can never rely on the information one receives as such, even when it is the best available; one must always add interpretations to attempt to close the gap between the knowledge available and that which a rational decision would require. Also, scientific knowledge tends to be contained within comparatively abstract and specialized disciplines; it thus provides a highly fragmented picture of reality. Decision-making, however, requires synthesized knowledge and an inter-disciplinary perspective. Thus, science per se provides only limited help for the decision-maker who must find connections among the facts of numerous disciplines, each incomplete in itself.

In short, the relationship between the social sciences and a societal decision-maker is not very different from that between the natural sciences and a medical practitioner: Even if either practitioner had mastered all knowledge which the scientific discipline contains,

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