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CHROMOSOME REARRANGEMENTS AND TRANSPOSABLE ELEMENTS

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■ **Abstract** There has been limited corroboration to date for McClintock's vision of gene regulation by transposable elements (TEs), although her proposition on the origin of species by TE-induced complex chromosome reorganizations in combination with gene mutations, i.e., the involvement of both factors in relatively sudden formations of species in many plant and animal genera, has been more promising. Moreover, resolution is in sight for several seemingly contradictory phenomena such as the endless reshuffling of chromosome structures and gene sequences versus synteny and the constancy of living fossils (or stasis in general). Recent wide-ranging investigations have confirmed and enlarged the number of earlier cases of TE target site selection (hot spots for TE integration), implying preestablished rather than accidental chromosome rearrangements for nonhomologous recombination of host DNA. The possibility of a partly predetermined generation of biodiversity and new species is discussed. The views of several leading transposon experts on the rather abrupt origin of new species have not been synthesized into the macroevolutionary theory of the punctuated equilibrium school of paleontology inferred from thoroughly consistent features of the fossil record.

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INTRODUCTION

The phenomenon of variegation among living organisms, namely, the mosaic appearance of some individuals, has long been a source of fascination. As early as 1588, Jacob Theodor von Bergzabern provided a lively description of the multicolored and variegated kernels of maize from the New World (101), and in 1623, Basilius Besler published an impressive figure of flower variation in *Mirabilis* in his *Hortus Eystettensis* (18). However, the concept of transposon activities for living organisms, first described by Barbara McClintock in 1944 and in the years following, was that of Ac/Ds (activator/dissociation) involved in the breakage-fusion-bridge cycle (23, 24, 62, 91). Her depiction of a phenomenon directly involved in gross chromosome rearrangements mediated by transposable elements (TEs) marked the onset of transposon research. However, since this general definition of chromosomal rearrangements as "rearrangements of the linear sequence of chromosomes including transposition, duplication, deletion, inversion or translocation of nucleic acid segments" (57), extensive molecular research has shown that large chromosome rearrangements are only the tip of the iceberg.

Throughout the existence of most plant and animal species, both gross and small quantitative chromosome reshufflings have often added up to enormous chromosomal changes—even only considering the overall mass of DNA—so that, for example, about 70% of the chromosomes of McClintock's model plant *Zea mays* is reported to consist of DNA-sequences due to TE-activities alone. The large majority of transposons of *Z. mays*, in addition to the examples described below, consists of class I element families, i.e., the retrotransposons. Similar conclusions have been reached for most other organisms studied to date, from *Arabidopsis thaliana* (14%) to *Vicia faba* (some 90%), *Drosophila melanogaster* (15%) to humans (45%).

As models of transposition and mechanisms of gross and small chromosome rearrangements mediated by TEs have already been extensively reviewed (3, 4, 11, 17, 27, 57, 67–70, 100, 101, 112, 127–129, 149), we refer to them only insofar as they relate to the problem of "what, if anything, the masses of TE-caused chromosome rearrangements biologically are good for in so many plant and animal species." Answering this question remains central to TE research; several hypothetical answers, often contradictory, have been advanced over the past 50 years (3, 4, 69, 84). We also focus on an interdisciplinary approach between TE-genetics (TE-induced gross and small genome reorganizations in time) and some particularly intriguing aspects of the fossil record (the abrupt appearance and stasis of most new life forms). We start the discussion with some of the main hypotheses advanced by the discoverer of TE-caused chromosome rearrangements, Barbara McClintock.

SOME NEW EVIDENCE FOR MCCLINTOCK'S VIEW ON THE FUNCTIONS OF TE-MEDIATED CHROMOSOME REARRANGEMENTS

Ontogeny

McClintock's hypotheses regarding a system of functions for TEs, both ontogenetically and evolutionarily, are still eminently thought-provoking and problematic (24, 69, 90, 91, 99, 101). She was struck by the gross chromosome rearrangements that are induced especially in connection with the "breakage-fusion-bridge-cycle," as well as a wide array of small to large effects of the *Ac/Ds*, *En/Spm* and *Dt* systems on gene expression, and the effects of transposons on the *R* and *B* loci and the stress activations of TEs, which were discovered later. Let us first briefly focus on her hypotheses on TEs and ontogeny. Arguing repeatedly that "the real point is control" for transposons, "she believed that precise transpositions of controlling elements successively inactivated suites of genes, thus executing the developmental program by which an embryo becomes a plant" (23, see also 24, 91, 124).

New evidence that may corroborate McClintock's views on the importance of TEs in ontogeny comes from two discoveries, albeit not in plants: TEs are involved in the unusual organization of telomeres in *Drosophila melanogaster* (43, 107) and in the parasitic protozoan *Giardia lamblia* (1, 108). In these organisms, TEs seem to contribute to chromosome stability by expanding the buffer between the ends of the chromosomes and the genes. Moreover, *Giardia* chromosomes display a developmentally impressive variation in length in reaction to environmental stress (TEs are also involved); for instance, chromosome 1 can vary between 1.1 and 1.9 Mb, i.e., an overall increase of about 73% (1.1 = 100%) or decrease to 58%, respectively (1, 108). Although chromosome stability is essential for development, it is still not clear whether these TEs have any function in normal development other than that of contributing to stability. Nevertheless, as the first results of regular TE functions in development, these discoveries may be viewed as a first step in the direction of the functional relevance that McClintock envisioned originally.

However, if we have learned anything over the past two decades about animal and plant development, it is that there are as yet no clearcut results to support the proposition that any of the major ontogenetic steps are caused and governed by any known transposable elements, i.e., by means of transposon movements accompanied by small TE-mediated chromosome rearrangements that successively inactivate or activate different suites of genes. To the contrary, this task has been largely assigned to gene classes such as the homeobox, MADS-box, and other regulatory gene families. Current data indicate that, during development, these classes of "controlling elements" do not normally move from one place to another within a given set of chromosomes.

Moreover, the telomeric functions referred to above are probably only substitutions of functional sequences that were originally equally useful but now differ from those found in the telomeres of most other known species (1). If, on the other

hand, a selective advantage is assumed, why did TEs not long ago overtake all of the telomeric sequences in the majority of life forms on Earth?

Due to insertional preferences to subtelomeric and telomeric regions, TEs have been detected in many species, although usually only as a minority of the overall sequences [reviewed in (1)]. It is assumed that they cannot do much damage in these regions and take on the buffer function referred to above. It is not known whether TEs are able to extend the buffer function during ontogeny, perhaps adapting chromosomal functions to stress in the species where they have been found.

However, active TEs can indeed modulate and modify plant and animal development, as demonstrated in many examples from the work of McClintock and more recent investigators. Yet, the ontogenetic modifications observed and identified to date are not the causes of normal ontogeny; rather they appear to constitute a set of factors that occur more or less concomitantly (and often even disruptive) and are tolerated during development as long as they do not become too heavy a burden for the affected organisms [for details, see (69, 84)]. Nevertheless, the outcome of TE activities may produce beautiful results, like the flower color variation shown in Figure 1, taken from Basilius Besler's *Herbarium*, published in 1613 (18). This is probably a depiction of some effects of TEs on normal pigment formation, whereby gene functions of the anthocyanine pathway are disrupted and released within certain developmental boundaries. Normal ontogenetic regulation and expression of the anthocyanine pathway, however, does not depend on the activities of transposable elements (ongoing rounds of excisions and insertions).

Origin of Species

In McClintock's view, phenotypic changes and the origin of new species by TE-induced macromutations, i.e., by abrupt and more or less simultanenous sequence changes in chromosomal organization and in a greater number of genes were the key to the problem of the origin of life in all its forms. Moreover, "late in life, she synthesized her life's work into a vision of the genome as a sensitive organ of the cell, capable of rearranging itself in response to environmental cues" (23), with TEs again playing the decisive role. New evidence appears to be somewhat stronger in support of this function generating variation for morphological species formation than for McClintock's views on TEs and ontogeny.

Among McClintock's favorite examples was the muntjac deer, one of the prime examples in this context. The diploid chromosome number of the Chinese *Muntiacus reevesi* is 46, but that of the closely related Indian dwarf *Muntiacus muntjak* is 6 in the female and 7 in the male deer, which is "the lowest chromosome number in any vertebrate" (64). As McClintock commented, "Observations of the chromosomes in the hybrid between these two species strongly supports chromosome fusion as the mechanism of origin of the reduced number and huge size of the Indian muntjac chromosomes" (90). However, the muntjac case may even be more significant and revealing than McClintock envisioned some 20 years ago. Recent investigations suggest that the Indian muntjac karyotype may be derived "directly

from 2n = 70 original karyotype rather than from an intermediate 2n = 46 Chinese muntjac-like karyotype" and that the 5 "old" as well as the several recently discovered muntjac chromosome races and species likely obtained their different chromosome numbers by parallel chromosomal fusions rather than by a simple line of descent (143, see also 73, 150).

M. muntjak displays a 20% difference in DNA content due to loss of middle repetitive sequences in comparison with *M. reevesi* (61). TEs are putatively ideal candidates to be involved in both the inferred chromosome rearrangements as well as in such gross differences in DNA content. Whether these DNA changes and the many other chromosome rearrangements that have been found are really causally related to TE activities in species formation in the genus *Muntiacus* (or in *Sorex*, *Mus*, *Rattus*, among others, and in plants; see below) has not been determined (69).

Some examples where TEs play a role in chromosome rearrangements in natural populations have been identified in *Drosophila*. In Hawaiian natural populations of *D. melanogaster*, for example, the transposable element *hobo* is associated with both cytological breakpoints of three endemic inversions, and a fourth such inversion has a solitary *hobo* insert at one breakpoint, all in clear contrast to cosmopolitan inversions in the same chromosome (86).

Another report has shown the involvement of TEs in chromosome rearrangements of the *virilis* group of *Drosophila*, in which species differ by multiple chromosome fusions and inversions, among other features (42). Although the causal relationship between these rearrangements and species formation has not been elucidated, the authors found that the *Penelope* and *Ulysses* transposons are "nonrandomly distributed in 12 strains of *D. virilis*" and that the insertion sites display a statistically relevant linkage with the breakpoints of several inversions detected in different species of the *virilis* aggregate (over half of 12 hybrid-dysgenesis-induced inversions, 2 translocations, and 2 deletions and others, totaling 16 rearrangements, have been reported as showing breakpoints in association with *Penelope* and *Ulysses* that are identical to those found in natural populations and species). An extrapolation to additional species of the group appears reasonable.

The most important problems still to be resolved on this topic have to do with causal relationships between chromosome rearrangements and species formations in the wild, selection, and the possibilities and limits of extrapolating from existing results.

1. What is the ratio between "normal" and TE-induced chromosome reshuffling in species in the wild?
2. To what extent is selection involved in the birth of chromosome races or are the majority of these phenomena simply the result of genetic drift (further points below)?
3. What are the exact possibilities and limits of the origin of species by TE-mediated gross and small chromosome rearrangements?

Before extending this topic at the end of our review, we first take a closer look at some seemingly contradictory phenomena whose unraveling appears to point to

certain constraints of transposon activities in the development and the origin of species.

"DYNAMIC CHROMOSOMES," SYNTENY, AND LIVING FOSSILS

Synteny

Molecular analyses have disclosed extensive syntenic regions not only in closely related species (often already considered to be millions of years apart from each other), but also in practically all the distinct genera within different plant and animal families thus far investigated, and even between higher systematic categories, to a certain extent. Hence, some strongly functional constraints have been postulated for chromosome rearrangements (75–79, 80, 109, 114, 115). Despite exceptions at the microlinearity level (often also TE caused) (10), the general phenomenon of synteny is so well established that reliable predictions can be made even for species and genera of a plant or animal family that have not yet been analyzed (34, 39, 47, 117). The chromosomes of man, cattle, and muntjac, even with the many chromosome reshufflings mentioned above, still display extensive homoeologies (46, 151). However, in plants as distinct as rice (monocot) and *Arabidopsis* (dicot), so far synteny appears to be hardly detectable (34, 35, 88, 117).

The significance of selection in the regular processes of chromosome rearrangements, with the "tendency for similar structural changes to establish themselves in one member of the karyotype after another" (146) in wild-type species, was the subject of lively debate in the 1970s and 1980s [reviewed in (80)]. Selection-directed (145, 146) versus autonomous chromosome rearrangements being selectively neutral (75–80, 109, 114, 115)—or perhaps even slightly disadvantageous—were the two most diametrically opposing views at that time, and the argument has still not been resolved. Despite some attractive examples that might be interpreted as being due to selection, no clearcut selective values for the chromosome rearrangements observed in the wild have ever been obtained, to the authors' knowledge. Since even such established textbook examples for natural selection as that of the peppered moth (26, 58a, 82) and the neck of the giraffe (53) have fallen into disrepute recently or at least have proved to be much more intricate than once was believed, Lima-de-Faria's words on chromosome reshuffling are particularly pertinent in the current debate (76): "What I am trying to convey is that due to the absence of knowledge of molecular mechanisms, selection has been employed like a kind of general remedy by the biologist. Every time a phenomenon appeared in biology, and one obviously ignored its mechanism, selection was invoked as an explanation and the matter was settled."

Whatever the preponderant causes prove to be, the commonality of chromosome rearrangements as well as synteny are equally true for both the animal and plant kingdoms. In general, the plant kingdom even appears to surpass the

animal kingdom in the frequencies and latitudes of chromosome rearrangements, especially in combination with different forms of polyploidy.

In the plant kingdom, chromosome rearrangements that often accompany chromosome and genome duplications are so common that fixed chromosome numbers and strict gene sequences alone have long been considered insufficient to identify and define a plant species (50). Literally thousands of species and genera display extensive gross chromosome rearrangements (in part, probably TE-induced), and widely different chromosome numbers have been detected all within a species and/or genus (for examples displaying both phenomena, see Table 1). Because synteny is equally well established among plant species and genera as well as some

TABLE 1 Selected examples of different chromosome numbers often accompanied by chromosome rearrangements within plant species and genera[a]

Family	Species	Chromosome numbers *within* the species
Nymphaeaceae	*Nymphaea alba*	2n = 48, 64, 84, 105, 112
Ranunculaceae	*Caltha palustris*	2n = 16, 32, 56, 64, 80
	Anemone nemorosa	2n = 16, 24, 30, 45
Moraceae	*Morus nigra*	2n = 26, 28, 30–308
Caryophyllaceae	*Arenaria multicaulis*	2n = 80, 120, 160, 200
	Arenaria biflora	2n = 20, 22
	Stellaria media	2n = 40, 42, 44
	Cerastium pumilum	2n = 72, 90, 94, 96,100
	Cerastium cerastoides	2n = 36, 38, 40
Polygonaceae	*Polygonum bistorta*	2n = 24, 44, 46, 48, 120
	Polygonum viviparum	2n = 88, 100, 110, 132
Salicaceae	*Salix helvetica*	2n = 36, 38, 39
Brassicaceae	*Cardamine pratensis*	2n = 16, 28, 30, 40, 48
	Cardamine palustris	2n = 56–96
	Cardaminopsis arenosa	2n = 16, 20, 24, 32, 39, 40
	Erophila verna	2n = 14–64
	Diplotaxis muralis	2n = 20, 22, 42, 44
Resedaceae	*Reseda luteola*	2n = 24, 26, 28
Primulaceae	*Primula auricula*	2n = 62, 63, 64, 66
	Primula integrifolia	2n = 62, 66, 68, 70
	Lysimachia nummularia	2n = 32, 36, 43, 45
Crassulaceae	*Sedum montanum*	2n = 34–136
	Sedum acre	2n = 16, 24, 48, 60, 80
Saxifragaceae	*Saxifraga bulbifera*	2n = 26, 28
Rosaceae	*Fragaria moschata*	2n = 28, 35, 42, 56

[a]See References (20, 48, 72).

higher systematic categories, both these phenomena, albeit seemingly contradictory, are almost all-pervading for most life forms on Earth.

To put this problem in the context of this nearly paradigmatic table: It will not be easy to establish selective advantages for all the chromosome rearrangements seen within the many plant species. How then is synteny to be explained in the face of the apparently endless chromosome reshufflings found in the history of nearly all forms of life on Earth?

According to Lima de Faria, there are a range of essentially nonfunctional and thus "forbidden" chromosome rearrangements (disruptive and destructive translocations). Thus the chromosome mutations are potentially channeled in certain directions, and the conservative reshufflings [reciprocal symmetrical, centric fusion (Robertsonian), and dissociation] are found most frequently in natural populations (76, 80, 114, 115).

As mentioned above, extensive new investigations have corroborated the fact that there are hot spots of TE integrations (1–4, 11, 19, 22, 36, 42, 74, 86, 106, 112, 125, 149), so that TE-mediated gross chromosome rearrangements participate in forming a predestined path of possible breakage and fusions, although the extent is still to be determined. Combining the chromosome field theory with TE-predestined nonhomologous or illegitimate recombination of host DNA segments could provide another explanation for synteny in the face of the seemingly endless chromosome reshufflings that are widely found in plants and animals alike (for further discussion of site-specific transposon integration, see below).

Extending the discussion of phenomena that at first sight appear to be mutually exclusive, yet on closer inspection display some promise of a solution, let us turn to the topic of TE-mediated chromosome rearrangements and the numerous occurrences of living fossils, or the phenomenon of paleontological stasis in general.

TE-Mediated Chromosome Rearrangements and Living Fossils

Longstanding differences between molecular biology and paleontology as to the phylogenetic relationships and times of origin of many different plant and animal groups (14) underlie the reluctance among molecular biologists for interdisciplinary discussion. However, avoidance does not solve the problem. We should differentiate between rather tentative hypotheses and clearcut results that have been independently corroborated and consolidated by diverse research groups over the years—in the following case even over some 200 years.

The paleontological point in focus here is the abrupt appearance and stasis (morphological constancy) for the overwhelming majority of life forms in Earth's history (13, 31, 40, 41, 51, 55, 56, 65, 66, 80, 81, 85, 89, 97, 111, 113, 116, 132, 133, 139). Originally proposed by Cuvier in the 1790s (31, 113, 131) and subsequently reworked and reelaborated (40, 41, 55, 56, 96, 116, 133), the phenomenon led in the 1970s to the theory of punctuated equilibrium and in the 1990s, to its consolidation

as a widely acknowledged paleontological view of life in the western world (40, 55, 56). This view, which is based on some 200 million catalogued fossils in museums worldwide but is not consistent with the strict neo-Darwinian theory of essentially continuous evolution, seems to be in agreement, at least phenotypically, with the McClintock hypothesis of saltational generation of new species.

Hence, the following discussion on TEs, "dynamic chromosomes," and living fossils [i.e., any life forms existing essentially unchanged over geologic times up to the present] with a brief consideration of stasis in general, [for further discussion, see (80)] consists of two phenomena, stasis and genetic flux. Each is equally well established in its respective discipline, yet is seemingly irreconcilably at odds with the other: How is it possible that the genomes have always been in a permanent state of flux possibly by TE-mediated and other small- to gross-chromosome rearrangements (11, 12, 44, 45, 58, 59, 60, 91, 95, 99, 101, 123, 126–130, 137) or other "normal" mutations as well as molecular drive (38), yet produce life forms that are so regularly morphologically and anatomically constant for enormous periods of geological time?

This conflict between an all-pervasive genetic flux and overwhelming evidence of morphological constancy and stasis in the fossil record has led to questioning of the quality of the fossil evidence. However, the richness and often extraordinary quality of the fossil record (15, 37, 63, 80, 116, 139), e.g., the rich fossil amber floras and faunas of the world (66, 111, 144) show all relevant morphological and anatomical features of the entrapped organisms in microscopic detail, or the silica-embedded flora of the Rhynie cherts to the fossilized fauna of Grube Messel, near Darmstadt, Germany, leave no reasonable doubt in the minds of most qualified observers as to the existence of stasis. This conclusion has found increasing acceptance even among staunch neo-Darwinians: "Stasis is a real perspective and a fascinating one" (89).

The following points may help solve this dilemma.

1. TE-induced and other gross chromosome rearrangements can lead to postzygotic isolating mechanisms that result in almost total cross-fertilization barriers between different lines of the same species in experimental organisms in a relatively short time period, as, for instance, in *Pisum sativum* (71). So-called twin species, i.e., "species" with no corresponding morphologic differences to distinguish one systematic species from another (80), have regularly been generated experimentally. This lack of phenotypic differences prevents twin species from being discriminated in the fossil record.
2. Due to TE-induced changes in DNA mass (see Introduction), the amounts of DNA in the haploid genomes of closely related species that are hardly distinguishable from each other morphologically can differ enormously (the C-value paradox). Species of the genus *Vicia*, for example, vary between 1.8 and 13.3 pg (95, 103, 104) of DNA per haploid genome. Even within the same nonpolyploid plant species, the C-value can vary significantly, even though some original examples for this phenomenon were attributable to technical

problems (7, 8). For such "selfish" TE-proliferations (3, 4, 7–9, 59, 69, 87, 98) in combination with chromosome reshuffling, both gross chromosome rearrangements and strong differences in haploid DNA mass (pg) need not be correlated to morphological disparities. The same conclusion likely holds for many reshufflings in microcolinearity. Assuming that the more or less erratic molecular clocks (80, 81) will run on and that molecular drive will continue, larger changes can also be expected to accumulate on the level of the functional nucleotide sequences. For a living fossil or some of the many fossil genera that existed essentially unchanged anatomically throughout millions of years, from their abrupt appearance in the paleobiological record until their usually equally abrupt extinctions, this could mean enormous changes on the levels of chromosome rearrangements, gene sequences, and DNA mass despite eons of morphological stasis. In short, this could perhaps be referred to as the constancy of the vessel (morphology), versus changes in contents (genetics). Of the many possibly neutral sequence rearrangements accumulating over geologic time, none would be detectable by an anatomical comparison between a living organism and its morphologically corresponding "ancestor" species in the fossil record.

3. However, McClintock and other TE geneticists discussed the phenomenon of TE activation in the wake of stress, all the way from radiation-caused induction in the vicinity of nuclear testing in the 1950s to recent tissue culture experiments (69, 90, 91, 101, 110). These observations led to the hypothesis that TE activities can remain dormant over eons of time, usually in a methylated state of inactivity, and be "awakened" in new stressful environmental situations to produce the genetic flexibility necessary for further adaptations (90, 91, 131). This hypothesis brings us back to some of the basic ideas on periodic induction of mutations formulated by Hugo de Vries in the early twentieth century (24, 140, 141). Relatively short intervals of genetic instabilities in restricted areas of the distribution of a species generating new forms alternate with longer periods of low or no changes in the constitution of the species. If true, to what magnitude could the rise of such new species be predetermined by constraints of TE activities and the genetic potential of their host?

HOT SPOTS OF TE INSERTION AND THE PREDETERMINED ORIGIN OF SPECIES

Sequence-specific target site selection can be due to the sequence specificity of the integrase, which is an intrinsic feature of the endonuclease cutting the acceptor locus for class I elements such as LINEs and SINEs, both of which are non-LTR retrotransposons. Further elements prefer certain types of genes: *Ty1*, an LTR retrotransposon, preferentially integrates near tRNA or other genes transcribed by RNA pol III. Most likely, this is caused by the interactions necessary to transcribe these

genes. Sequence preference can also be observed for *Ty1* that displays nonrandom integration in N A/T A/T A/T N sites. Insertion site preference has also been reported for the *P* elements in *Drosophila* (class II, i.e., DNA transposon). A 14-bp palindrome containing the sequence of the 8-bp target duplication can be identified for this element (74). Furthermore, the state of the chromosomal DNA can apparently limit the access for a transposon to a locus. The maize *Ac* transposon, for example, preferentially transposes into transcribed regions, perhaps because of loose packaging (strongly acetylated and less tightly bound histones) of the chromosomal DNA at these positions (3, 4).

New results on transposon target site selection, i.e., hot spots for TE integration (1, 2, 11, 19, 22, 36, 42, 74, 86, 106, 112, 125, 149), combined with the theory of chromosome field (see above), suggest that there is an appropriate degree of channeling of the future course of chromosome diversification, corresponding to something like a constraint and predestination concerning biodiversity. Hence, a largely TE- (and otherwise) preestablished chromosome rearrangement potential might eventually replace the idea of an infinite array of purely random shufflings of chromosomal nucleotide sequences following TE host nonhomologous recombinations. Moreover, retrotransposons inserting in members of the same class and the same or even different family (19) could increase the possibilty of illegitimate recombination of host DNA sequences due to longer stretches of TE sequence similarities in different parts of the genome. However, the exact extent of the constraints and the ratio of random to nonrandom chromosome shuffling have not yet been determined.

The synthesis of a partially predetermined generation of biodiversity seems to be reinforced by some observations on the level of small nucleic acid segment rearrangements, i.e., on the gene level. Our current understanding is that multiple, independently arisen TE footprints (123, 124) result in differently altered host sequences that do not usually restore the wild types, in agreement with most observations. A mechanism for TE-generated footprints has been suggested by Nevers & Saedler (100). Indeed, Scott et al., in their extensive investigations of transposon footprints in one locus (125), found that over 90% of >800 analyzed *Ds* excision products of maize *Waxy*-alleles showed mutant sequences that did not restore the wild type. The sequence deviations proved, however, to be "surprisingly nonrandom." Depending on the allele and the insertion site, between 37% and 88% carry a predominant footprint, and even the less prevalent footprints are often similar to the prevalent ones. Moreover, in 1% to 6% of the excisions, no footprint at all was formed. This implies that only the rest appears to consist of random sequences.

Since the vast majority of TE insertions into gene sequences can be classified as loss-of-function mutations, the first step of such TE activities constitutes a partially predestined method for essentially one aim: to switch off the function of a specific gene more or less permanently. The second step, excision with footprint formation in Class II elements, leads either to reversion to approximately wild-type gene functions or to a certain amount of foreordained variation of promoter and/or

gene functions. Both phenomena could be significant in the context of morphological species formation, especially regressive evolution including resistances and the origin of ecotypes (see below).

As discussed elsewhere (69, 80, 84), the mechanisms in TE gene inactivation could be relevant to the origin of cultivated plants and domestic animals, as well as to regressive evolution in general. Indeed, a few cases have already been definitely established in plants (69). Moreover, ectopic gene expression and thus the generation of dominant traits have been reported in one case of domestication: *Zea mays* (142, 147), although it is still unclear whether TEs were involved. Nonetheless, genetic redundancy in combination with nonrandom gene inactivation and release mechanisms could also be pertinent for explosive species radiations such as those found in the cichlids in East African lakes. Here, in time lapses of merely a few hundred to several thousand years, there occurred a huge amount of regular morphological and ethological convergences in four independent radiations (93). Certain gene sets of the redundant potential may be switched off and others switched on. It is conceivable that there are still other mechanisms such as gene methylation (28), differential splicing (118), alternative promoters (83), or accelerated formation of alleles of regulatory and other genes, perhaps even caused by TEs (102, 148). As in regular chromosome rearrangements in the wild (see above), selection versus autonomous species formation and combinations of both have been widely postulated in the cichlid example, termed "one of the most spectacular examples of convergence in all evolutionary biology" (94). On one decisive point, however, there is widespread agreement: The time spans for conventional point mutations in combination with gene duplications are too short to give rise to novel genes and gene reaction chains to explain the phenomena (93). An inclusive genetic potential appears to be a more realistic approach to the problem. But this could open up another question, the origin of the genetic redundancy itself (83).

If the phenomenon of regressive evolution is applied to the structures and functions of TEs themselves, it is plausible that mechanisms for stress activation, target site selection, as well as gene inactivation and release originally were more effective in several transposon lines and organisms. Conversely, target site selection has also been found for heterochromatic and other regions with low or no gene content (1, 11, 103, 147), and this kind of selectivity may be part of the survival strategy of selfish TEs. They can proliferate there with minimal harm to their hosts and thus to themselves.

A phenomenon that may also be relevant in the context of possible transposon functions is that of the flax genotrophs (29, 30, 105, 119). The process of environmentally induced changes in the flax genomes "does not appear to be the generation of random variation" (30). Cullis et al. postulate that the heritable changes in flax are due to specific rearrangements at distinct positions of the genome. Low-copy-number, middle-repetitive, and highly repetitive sequences have been shown to be involved in the polymorphisms detected, and sequence alterations of specific subsets of 5SrDNA have been identified (119). TEs may also be involved in these rearrangements. If so, this evidence could be added validation for McClintock's

view on the functions of TE-mediated chromosome rearrangements in ontogeny. In this case, transposon-mediated nonrandom genomic reshuffling would have some direct effects on gene regulation in ontogeny and, due to its heritability, on biodiversity also.

However, a discriminating, in-depth discussion and final evaluation of these topics call for much more evidence. Future investigations will require precise determination of (*a*) the overall ratio of nonrandom TE-induced sequence changes of relatively small nucleotide segments to the rest, which can only be obtained by concentrating on statistically relevant numbers of independent TE visits and their footprints in individual loci; (*b*) the causes and percentages of TE target site selections in relation to accidental insertions, especially for larger chromosome rearrangements; (*c*) the amount of genetic redundancy and its potential for generating morphological and other differences; and (*d*) the magnitude, if any, of TE involvement in the heritable genomic changes of the flax genotrophs mentioned above.

At present, the limited evidence for constraints caused by chromosome rearrangements consisting of TE target site selection (largely predetermining gross chromosome rearrangements), TE-induced nonrandom sequence deviations on the gene level, and the theory of the chromosome field are in agreement with the suggestion of a nonselection-driven, autonomous origin of a part of biodiversity and chromosomal species (29, 49, 75–79, 80–84, 90, 91, 93, 97, 109, 114–116, 119, 121, 122, 135, 140, 141).

TE-MEDIATED CHROMOSOME REARRANGEMENTS AND THE POSSIBILITY OF ABRUPT BOOSTING OF BIODIVERSITY AND SPECIES FORMATION

The following section focuses on possible TE-mediated chromosome rearrangements and the likelihood of an abrupt appearance of biodiversity and new life forms.

In agreement with McClintock, Syvanen (137) remarked, "I believe that transposons have the potential to induce highly complex changes in a single event." Shapiro (128) agreed that "there must exist mechanisms for large-scale, rapid reorganisations of diverse sequence elements into new configurations" for the integrated mosaic genome to make evolutionary sense [for further discussion, see (69)]. As noted above, this view seems to accord, at least phenotypically, with the findings of paleontology over the past 200 years. The question then centers on the extent to which TE-mediated chromosomal rearrangments can really explain the abrupt appearance not only of species but also of higher systematic categories in the face of the typical stasis of new life forms that so consistently characterizes the fossil record, i.e., the theory of punctuated equilibrium. Particularly apposite here are the following words of "so tough and influential a man" (52) as the German paleontologist Otto H. Schindewolf (116):

"According to Darwin's theory, evolution takes place exclusively by way of slow, continuous formation and modification of species: the progressive addition of ever newer differences at the species level results in increasing divergence and leads to the formation of genera, families, and higher taxonomic and phylogenetic units. Our experience, gained from the observation of fossil material, directly contradicts this interpretation. We found that the organizing structure of a family or an order did not arise as the result of continuous modification in a long chain of species, but rather by means of *a sudden, discontinuous direct refashioning of the type complex from family to family, from order to order, from class to class*. The characters that account for the distinctions among species are completely different from those that distinguish one type from another." (Italics by Schindewolf).

The existence in many animal groups such as foraminifers, brachiopods, corals, and others of an overwhelmingly rich fossil material consisting of literally millions (and generally in micropaleontology, billions) of individual exemplars led many paleontologists to emphasize that the objection most often raised against this view, i.e., the imperfection of the fossil record, is no longer valid [(15, 16, 37, 63, 116, 133, 139); see also discussion in (80, 85)]. Although Schindewolf's causal explanations of evolution from inner compulsion are not accepted by most contemporary paleontologists, there is general agreement on his factual representation of the punctuated mode of appearance of new organisms in the fossil record. Given that Schindewolf's description is phenotypically essentially correct, albeit with some exceptions (15, 56, 133), to what extent could TE-mediated small and gross chromosome rearrangements cope with the problem raised by the origin of families, orders, and classes?

In regard to the question of species formation in muntjac deer and cyclops, McClintock (90) suggested, "it is difficult to resist concluding that some specific "genomic shock" was responsible for origins of new species" in these genera. Despite the reservations and open questions noted above, her hypothesis is intrinsically attractive and a promising possibilty that warrants further investigation. However, if all the proof that is still lacking to substantiate her view on the origin of species were available, would that also give us the mode of origin of the higher systematic categories and types of life referred to by Schindewolf? To be more specific: If so, to what extent can any of the TE-incited rearrangements contribute to the origin of novel genes and new gene reaction chains as well as the genesis of irreducibly complex structures? All three of these may be especially relevant for the origin of higher systematic categories (3–5, 33, 69, 80–85, 121, 122, 130).

We could apply these same questions to a well-known problem of the fossil record: To what extent could small and gross chromosome rearrangements mediated by TEs and other factors solve the Cambrian explosion (6, 13, 14, 25, 51, 80, 92, 120, 132, 133)? (*a*) Even if one does not accept the assumption of the rather abrupt appearance of approximately 100 new animal Baupläne (51, 92), suggesting instead that lower systematic categories make their debut there, at least in part; (*b*) assuming further that some limited links to the Ediacara Fauna are probably established (25); and (*c*) accepting the hypothetical relevance of some fossilized Precambrian embryos (21, 54, 120, 152) as a tiny step in the origin of at least some

450 unexpected animal families, including many novel phyla, Darwin's 1859 verdict (32) still seems to have some force for the uncommitted observer: "The case at present must remain inexplicable; and may be truly urged as a valid argument against the views here entertained."

If we reject Darwin's idea of a strictly gradual evolution of most life forms, to what extent could TEs contribute to a resolution of such problems as the Cambrian explosion and the origin of higher systematic categories in general?

An exact evaluation of the possibilities and limits of TE-mediated contributions to the origin of species and especially higher systematic categories is only in its early stages. Extensive research on these and related questions is still needed.

Still pertinent to the state of experimentally induced species formation at the beginning of the twenty-first century is the view of McClintock's personal friend and intellectual soulmate, Richard Goldschmidt (49), on the abrupt origin of species by sudden genome reorganizations: "Needless to say, I did not succeed in producing a higher category in a single step; but it must be kept in mind that neither have the Neo-Darwinians ever built up as much as the semblance of a new species by recombination of micromutations. In such well-studied organisms as *Drosophila*, in which numerous visible and, incidentally, small invisible mutations have been recombined, never has even the first step in the direction of a new species been accomplished, not to mention higher categories."

CONCLUSIONS AND PERSPECTIVE

The Darwinian centennial in 1959 (138) provided the occasion for many voices to declare that all the basic problems of the origin of species and higher systematic categories had fully been solved by the modern synthesis. The speakers and authors of the centennial were, of course, aware of some outstanding problems, but it would be only a matter of time and effort before these were also resolved within the frame of the synthetic theory. In any case, there was nothing of substance to be really worried about. This was in stark contrast to the many opposing views advanced in 1909 at the 50th anniversary celebration of the publication of Darwin's *Origin of Species*. TEs had no part in these discussions.

Extrapolating from the wide range of current opinions (3–5, 14, 29, 30, 33, 38, 40, 55, 56, 64, 69, 71, 75–85, 89–93, 101, 109, 121, 122, 126–130, 132–138), we might safely predict that if similar meetings are held in 2009, the climate of opinion will be much closer to that of the 1909 semicentennial than to that of the 1959 centennial, and transposable elements will have played a special part in discussions on the origin of systematic species, from small to large chromosome rearrangements in muntjac deer to many different plant chromosome lines.

However, in the face of the numerous scientific problems still unresolved in the context of the origin of species and higher systematic categories, we would probably be well advised to continue to welcome the plethora of different and diverging ideas and hypotheses on the origin of life in all its forms as well as to remain open-minded on real results of investigations, wherever they may lead.

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Figure 1 *Mirabilis jalapa* L. published by Basilius Besler in 1613 in his *Hortus Eystettensis*. In plants, transposable elements (TEs) reveal their presence by generating variegation patterns as in the candidate depicted here. In these cases, each patch of variegation means that a TE has left the locus so that the wild-type function of a respective gene involved in flower color synthesis is restored. The earlier the event, the more widespread the resulting cell line and the larger the restored color dot or sector.