Experiments aimed at verifying many of these calculations are now under way. A. Hubler (University of Illinois) noted that some recent theoretical results suggest that much more complex systems (perhaps even as complex as enzymes) might be amenable to quantum control, particularly in the strong response limit; relaxation mechanisms actually serve to stabilize specific excitations, or intense fields may dramatically simplify the internal dynamics. The role of theory is likely to be quite different in complex systems than it is in diatomics; Rabitz noted that it is unlikely that calculations alone will be able to produce useful waveforms, and feedback between experiment and calculation (perhaps through computer programs that use molecular response to a waveform to determine optimal corrections) will be important. J. Schiano (University of Illinois) has experimentally demonstrated such feedback in the simpler case of control in nuclear magnetic resonance.

Participants of the workshop also identified a number of important directions for future work. One of the most important goals of theory is to help develop intuition as to what is possible; much work remains to be done here, and in many cases it is presently very difficult to rationalize the waveforms predicted by computerized optimization, or even to understand which features are crucial and which might be secondary. Detection of quantum control is also an important and developing field; it is central to all of the proposed schemes for the use of feedback between theory and experiment to improve waveforms. Promising methods for taking "snapshots" of molecules with ultrafast electron or x-ray diffraction (*7*) are being explored by a variety of groups as noted by Wilson.

Although the participants felt it was important to avoid perceptions of "oversell" to the broader scientific community, the consensus was that both the short-term and long-term prospects for important experiments in quantum control were excellent. The near term applications will be limited to simple systems (photons remain expensive reagents), but they will lead to a better understanding of molecules and devices and may ultimately change the way chemists approach molecular design.

References and Notes

1. The Telluride workshop (9 to 23 August 1993) was chaired by W. S. Warren with H. Rabitz, S. Rice, and D. Tannor as co-organizers. The participants agreed to meet again at Telluride in 2 years. More information can be obtained from the Telluride Academy, P.O Box 2255, Telluride, CO 81435.
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An Expanding Universe of Introns

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Eleven years after bursting onto the scene, autocatalytic introns (*1*) continue to amaze. Although representing two structurally distinct groups (I and II) that splice by different pathways, these introns share two remarkable features. Not only do they have the potential to self-splice, but they may also act as mobile genetic elements [reviewed in (*2*)]. The dynamic properties of the group I and group II introns may reflect their parallel evolution, yet their biological niches overlap only partially. Whereas both intron families cohabit fungal and plant mitochondria and plant chloroplasts, the group II introns seemed conspicuously absent from prokaryotes, which host their group I counterparts. Absent, that is, until the recent report of group II introns in both proteobacteria and cyanobacteria, the putative progenitors of mitochondria and chloroplasts, respectively (*3*). These introns reside in unidentified reading frames, one in the γ-purple proteobacterium *Azotobacter vinelandii* and two others in the cyanobacterium *Calothrix*. Not only do these findings extend the taxonomic range of group II introns, but they also raise provocative questions about intron ancestry and more recent dispersal.

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To address these questions, one must consider the potential invasiveness of these genetic elements. The mobility of both group I and group II introns appears to be imparted by the products of open reading frames (ORFs) contained within them. However, different proteins drive distinct mobility pathways in the two intron families. The mobile group I introns encode endonucleases that promote their movement within niches as diverse as bacteriophage and slime mold genomes (*2*). The well-defined group I mobility pathway is DNA based and is initiated by endonuclease cleavage in an intronless allele. Ensuing repair of the double-stranded DNA breaks results in a homing event in which the intron is duplicated between homologous exons of the recipient (Fig. 1A). This event is accompanied by coconversion of flanking exon sequences.

In contrast, mobile group II introns encode reverse transcriptase (RT)–like proteins, some of which have recently been shown to be active intron-specific enzymes (*4*). Interestingly, the presence of RT in the bacterial group II introns was used as the basis of their detection, with polymerase chain reaction (PCR) primers directed at conserved RT and splicing domains (*3*). The group II RTs have striking similarity to RTs of LINE-1 retroelements, consistent with the emerging concept of the group II introns as site-specific retroelements (*4*, *5*). Although the mobility mechanism is presently unresolved, some insights are being gained from work with two group II introns, aI1 and aI2, next-door neighbors in the *cox1* gene of *Saccharomyces cerevisiae* mitochondria (*4*, *5*). Like that of group I introns, aI1 and aI2 mobility is a highly efficient homing process in which the introns, accompanied by flanking exon sequences, move to cognate intronless alleles at efficiencies approaching 100%. However, unlike group I mobility, which is strictly DNA-based, group II homing appears to depend on the splicing proficiency of the intron (*5*).

Any plausible scenario for group II intron mobility should accommodate the coinheritance of flanking exons, the nature of the RT complementary DNA products, and the apparent requirement for splicing (Fig. 1B). Given exon coconversion (*5*) and the observation that a significant fraction of complete intron cDNA contains flanking sequences (*4*), the cDNA for integration is likely to be derived from the pre-mRNA. Splicing might then generate a mediator of, rather than a template for, mobility: A primer for cDNA synthesis? A template for RT synthesis? An RNA endonuclease to promote site-specific integration of the cDNA into the intronless allele? The last possibility is most exciting, given that endonuclease activity, which is predicted on the basis of the efficiency of homing, is well

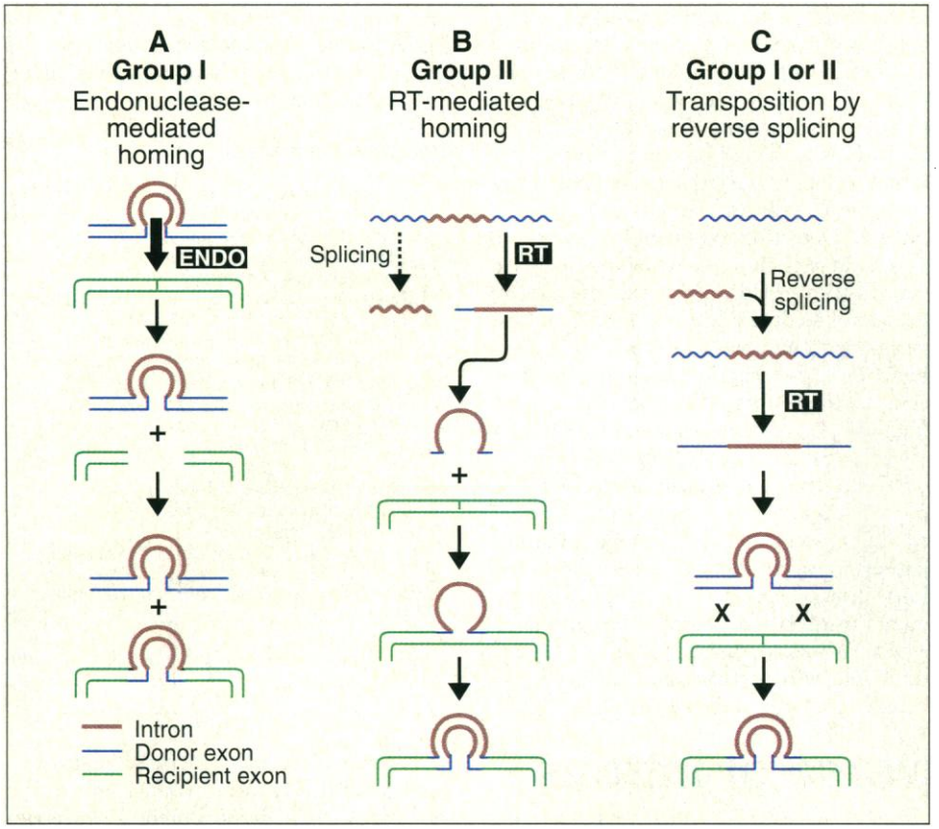

Fig. 1. Intron mobility pathways. RNA is depicted as wavy lines, DNA as straight lines, introns as thick lines, and exons as thin lines.(**A**) Group I intron homing through repair of double-stranded DNA breaks. Endonuclease-mediated cleavage of the recipient allele stimulates a gene conversion event that results in intron inheritance in a DNA-based pathway. (**B**) Group II intron homing through an RT-mediated pathway. Here, pre-mRNA is postulated to act as a template for cDNA synthesis by RT. The role of splicing (dashed arrow) and the mechanism of site-specific integration of the cDNA remain conjectural (see text). (**C**) Intron transposition by reverse splicing. Although reverse splicing is depicted here with RNA as the recipient, it is also mechanistically possible for DNA to be the recipient. The cDNA is then proposed to act as a recombination substrate with genomic DNA in double-stranded (as shown) or single-stranded form.

within the ribozyme repertoire. Group II introns are not only capable of cleaving DNA, but of doing so specifically at the exon-exon junction (*6*). Alternatively, integration might be promoted by site-specific endonuclease activity contained within the RT itself, or by non–intron-encoded endonucleases (*2*).

Resolution of the group II homing mechanism is unlikely to provide the final word on mobility pathways. The haphazard distribution of these highly conserved families of introns suggests that group I and group II introns each arose from a single common ancestor and spread by transposition to heterologous sites within genomes. Whether the homing pathways described for either group I or group II mobility could result in low-frequency illegitimate events that move introns to new sites is uncertain. A third pathway that relies on reverse splicing requires RT, but need not be limited to any intron type (Fig. 1C). This model posits reverse transcription of a reverse-spliced RNA and recombination of the cDNA with genomic DNA. This process could result in transposition if the intron reverse splices into nonallelic RNA or single-stranded DNA, as is mechanistically feasible for both group I and group II introns (*6*, *7*). Gratifyingly, there is recent evidence consistent with transposition of the aI1 intron in vivo to nonallelic sites through an RNA intermediate (*8*). Additionally, twintrons, composite group II introns, are likely to have originated by transposition of one intron into another by this pathway (*9*).

Although the propensity of the self-splicing introns for mobility confounds arguments as to their origins, a phylogenetically coherent picture was painted by the discovery of the cyanobacterial group I introns. These introns are devoid of ORFs and therefore are unlikely to be mobile (*10*). Furthermore, they occur in the same genetic context (namely, the $tRNA^{LEU}$ gene) as similar introns in plant chloroplasts. Because the cyanobacteria are progenitors of chloroplasts, these "fixed" group I introns probably entered the eukaryotic lineage with the endosymbiont from which chloroplasts originated, more than a billion years ago. Their conservation in diverse cyanobacteria dates these introns back 3 billion years to the beginning of the phylum—indeed, close to the origin of the first living cell.

The evolutionary history of RT-encoding group II introns in bacteria is much less clear-cut. Not only do the introns possess a mobility apparatus, but they occur in different genes than their organellar counterparts, which suggests that they are horizontally transmitted. This situation is vexing, given the high degree of interest in the origins of the group II introns, which are likely ancestors of the spliceosome-dependent nuclear introns in modern metazoans (*11*). Firm conclusions about the evolutionary span of group II introns await identification of ORF-less members of this family within prokaryotes, at sites similar to those in eukaryotic genomes. In addition, the congruence of phylogenetic intron trees with those of their host genomes must be established. Nevertheless, the conjecture that the group II introns are widespread in prokaryotes (*3*) offers the eventual prospect of tracing their origins.

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