The discovery of a plausible precursor for RNA raises an issue that has been previously considered in the context of peptide nucleic acids (*6*, *7*). How is it possible to change genetic material in midstream? How could a primitive organism that, for example, used TNA as its genetic material switch to RNA? There are two extreme possibilities. In one version, the catastrophist scenario, a TNA-based primitive organism synthesized oligoribonucleotides for a purpose other than replication—perhaps to inhibit TNA synthesis in a competing organism. Then RNA replication evolved independently of TNA replication and ultimately took over as the means by which cells reproduce themselves. According to this scenario, there never were heteropolymers containing both TNA and RNA components, and no useful genetic information was ever transferred from TNA to RNA.

In the alternative gradualist scenario, ribonucleotides were at first substituted a few at a time and at random in TNA sequences. The proportion of RNA components increased over time from almost zero to 100%. The information present originally in the TNA sequence was, at least in part, preserved in the final RNA sequence. This attractive theory suffers from one major drawback. Introduction of a substantial number of ribonucleotides at random might not prevent replication of TNA, but it would almost certainly destroy the catalytic function of any particular TNA sequence and thus would render evolved TNA sequences useless when rewritten accurately as RNA. This flaw may not be fatal. The power of natural selection is easily underestimated, and it is possible that selection could find a "continuous" pathway from TNA to RNA in which the catalytic function of TNA was maintained.

It would be premature to conclude (and, indeed, Eschenmoser does not claim) that TNA was a precursor of RNA on the primitive Earth. Nevertheless, the existence of a polymer that is significantly "simpler" than RNA, that resembles RNA more closely than do peptide nucleic acids, and that forms stable heteroduplexes with RNA is encouraging to those who believe that RNA was preceded by one or more simpler genetic materials. It should also allow speculations of the type presented here to be subjected to the test of experiment.

References

1. K.-U. Schöning *et al.*, *Science* **290**, 1347 (2000).
2. P. E. Nielsen, *Acc. Chem. Res.* **32**, 624 (1999).
3. I. Kozlov, L. Orgel, P. Nielsen, *Angew. Chem. Int. Ed. Engl.* in press.
4. M. Beier *et al.*, *Science* **283**, 699 (1999).
5. F. Reck *et al.*, *Org. Lett.* **1**, 1531 (1999).
6. G. Joyce, L. E. Orgel, in *The RNA World*, R. Gesteland, T. Cech, J. Atkins, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, ed. 2, 1999), pp. 49–77.
7. M. Koppitz, P. E. Nielsen, L. E. Orgel, *J. Am. Chem. Soc.* **120**, 4563 (1998).

PERSPECTIVES: PHASE TRANSITIONS

Y's and Ends

Philip Pincus

Coexisting phases of matter are ubiquitous all around us. For example, we are all familiar with the simultaneous presence of water and steam in a tea kettle or of ice and water in the polar regions of Earth. Multiphase systems do not have to consist of a single molecular species; for example, oil and water coexist but do not mix. In all these cases, depending on external constraints such as temperature, pressure, or magnetic field, the two phases may be induced to undergo a phase transition to a single homogeneous phase. In a multicomponent system, this is a more or less intimate mixture of the components. One example for such a mixture is milk, which is a dispersion of small solid particles (milk solids) suspended in water.

The phase transition between the homogeneous phase and the two coexisting phases occurs at the thermodynamic "critical point." The transition is generally the result of a competition between entropy, which favors the homogeneous phase because of the strong disorder inherent in mixing, and short-range attractive forces ("like attracts like") between similar objects, which favor phase separation. Attractive dispersion forces between milk solids lead to phase separation (creaming) in precisely this manner.

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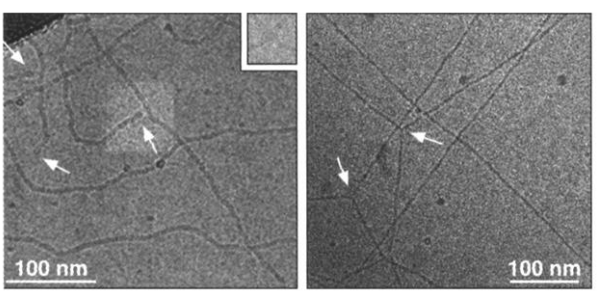

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Vital defects. (Left) Swollen end caps (arrows) of threadlike micelles imaged in a vitrified solution. **(Inset)** Four-micelle junction. **(Right)** Lower magnification image showing a sparse network of micelles. Arrows mark threefold (Y) junctions with 120° angles between micelles. Y junctions and ends play an important role in phase separations.

On page 1328 of this issue, Tlusty and Safran (*1*) bring the understanding of a particularly complex type of phase separation to a new level. They consider colloidal particles suspended in a solvent. This is similar to milk, but the matter is complicated by the fact that the particles have either magnetic or electric dipole moments. Such suspensions are called ferrofluids or electrorheological fluids, respectively. They respond strongly to externally applied fields (*2*), and this is the basis for their diverse technological applications as clutches, in ink-jet printing, as seals, and so forth. However, the mechanism by which phase separation occurs in these systems has remained obscure both theoretically and experimentally (*3*, *4*). Recent simulations (*5*) suggest an unusual critical point for the phase transition. The dependence of the position of the critical point on the concentration of particles is especially low, and the simulations suggest that the connectivity in the two phases is quite distinct. One phase resembles a dense network of polymerlike strands that span the sample, whereas the less concentrated phase looks like a dilute polydisperse polymer solution. In contrast, the traditional "liquid-gas" transition is characterized by two phases that only differ in concentration, not topologies. Experimental observation of the unusual behavior is problematic because of the long relaxation times associated with extended objects.

The reason for the unusual behavior of these systems is the strong anisotropy associated with dipolar forces. We know from experience with compass needles that dipoles have a strong preference for lining up head to tail. In colloidal suspensions, this property leads to the formation of long polymerlike self-assembled chains of particles (*6*), which interfere with the normal liquid-gas transition. This occurs because the chain formation tends to saturate the dipolar attractions, leading to a crude type of screening.

Tlusty and Safran demonstrate, theoretically, that a transition is restored when the "dipolar polymers" are considered as the fundamental units. Much like real polymers (*7*), the dipolar chains have "defects," that is, free ends and Y-shaped branching points (see the figure). All defects are favorable from

the entropic point of view, but the Y's are energetically more favorable than the ends. The Y's and ends may thus phase separate as the temperature is lowered, resulting in a dense connected network (the Y's) in equilibrium with a dilute gas of polymers (the ends). This scenario is not unique: Identical symmetry and global topological arguments describe a very different system, namely microemulsions, which are (at least) ternary systems of oil, water, and surfactant (*8*).

The Tlusty-Safran transition may be viewed as a specific example of a phase transition in a hierarchical system, in which the basic elements involved in the phase transition are composite objects. Such hierarchical assemblies are characteristic of biological structures (*9*), and it is likely that analogous transitions will be observed in biogels. The Tlusty-Safran transition can also be viewed as a topological transition, similar to the Blue liquid crystalline phases (*10*), which are ordered arrays of disclinations (the typical defects of orientationally aligned liquid crystals). As the soft condensed matter community becomes familiar with topological transitions, the development of general models providing a unified description of these diverse and seemingly distinct phenomena may be expected.

References

1. T. Tlusty, S. A. Safran, *Science* **290**, 1328 (2000).
2. R. E. Rosensweig, *Science* **271**, 614 (1996); T. C. Halsey, *Science* **258**, 761 (1992).
3. Y. Levin, *Phys. Rev. Lett.* **83**, 1159 (1999).
4. E. Dubois, V. Cabuil, F. Boué, R. Perzynski, *J. Chem. Phys.* **111**, 7147 (1999).
5. P. J. Camp, J. C. Shelley, G. N. Patey, *Phys. Rev. Lett.* **84**, 115 (2000).
6. P. G. de Gennes, P. A. Pincus, *Phys. Kondens. Mater.* **11**, 189 (1970).
7. P. J. Flory, *Principles of Polymer Chemistry* (Cornell Univ. Press, Ithaca, NY, 1953).
8. T. Tlusty, R. Menes, S. A. Safran, R. Strey, *Phys. Rev. Lett.* **78**, 2616 (1997); A. Bernheim-Grosswasser, T. Tlusty, S. A. Safran, Y. Talmon, *Langmuir* **15**, 5448 (1999); T. Tlusty, S. A. Safran, R. Strey, *Phys. Rev. Lett.* **84**, 1244 (2000).
9. D. Tirrell, *Hierarchical Structures in Biology as a Guide for New Materials Technology*, Committee on Synthetic Hierarchical Structures, National Materials Advisory Board, Commission on Engineering and Technical Systems, National Research Council (National Academy Press, Washington, DC, 1994).
10. P. G. de Gennes, J. Prost, *The Physics of Liquid Crystals* (Clarendon Press, Oxford, Oxford Univ. Press, New York, ed. 2, 1993).
11. D. Danino, A. Bernheim-Groswasser, Y. Talmon, *Colloids Surf.*, in press.

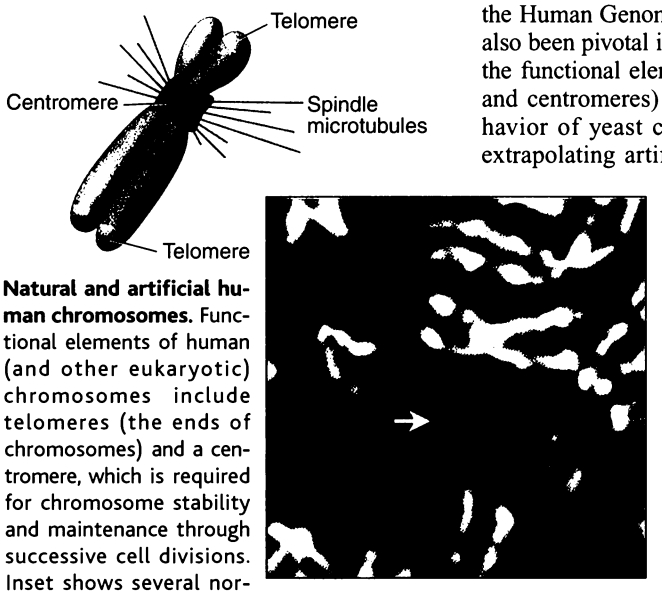
PERSPECTIVES: GENOMICS AND GENE THERAPY

Artificial Chromosomes Coming to Life

Huntington F. Willard

Most advertisements that arrive on my desk rapidly find their way into the trash with barely a glance; however, occasionally a piece will catch my eye. "Make Biology Come Alive," cried the headline of an advertisement for educational software that promised to teach the reader about Genetic Engineering, including Gene Therapy. Following on the footsteps of the first reported death of a gene therapy patient, Jesse Gelsinger, at a time when nearly everyone is urging caution and calling for more balanced reporting of results of gene therapy research (*1*), I was curious to see how "Gene Therapy" would be portrayed.

"Gene therapy is the use of genes for correcting genetic disorders." So far, so good, although the lead statement ignores the fact that, with two exceptions, no such correction (at least not to the point of proven clinical benefit) has been convincingly demonstrated by any of the hundreds of gene therapy protocols currently being pursued. Indeed, the first two clinical gene therapy successes were reported only earlier this year (*2*). The software then invites the reader/viewer to click on different "techniques for transferring DNA to humans," including "DNA coated in lipids," "viruses," and "artificial human chromosomes." What? Artificial human chromosomes being transferred to human beings?



Natural and artificial human chromosomes. Functional elements of human (and other eukaryotic) chromosomes include telomeres (the ends of chromosomes) and a centromere, which is required for chromosome stability and maintenance through successive cell divisions. Inset shows several normal human chromosomes and a single artificial human chromosome (arrow). Natural human chromosomes range in size from ~50 to ~250 megabases. The artificial human chromosomes constructed so far range from 2 to 6 megabases in size.

Have I been missing something?

In the early 1980s, artificial chromosomes came to life with the construction of a fully functional yeast chromosome from its component parts (*3*). Yeast artificial chromosomes (YACs) can be assembled from cloned telomeres (the specialized DNA sequences found at the ends of chromosomes), a centromere (to ensure proper segregation through each cell division), and genomic fragments carrying origins of DNA replication (so that DNA synthesis is correctly initiated at sites along the chromosomal DNA). YACs are fully stable in both types of cell division (mitosis and meiosis) and have proven to be of inestimable value as a workhorse for assembling overlapping clones of DNA as part of the Human Genome Project (*4*). They have also been pivotal in defining and dissecting the functional elements (such as telomeres and centromeres) required for normal behavior of yeast chromosomes. However, extrapolating artificial chromosome technology to mammalian cells and chromosomes has proven to be a difficult task.

Mammalian chromosomes are two to three orders of magnitude larger than yeast chromosomes. The molecular components of their telomeres—well conserved among a wide range of eukaryotic organisms (*5*)—have been identified and are increasingly well understood. In contrast, the composition of mammalian and other non-yeast centromeres has been much more difficult to determine. Mammalian centromeres are likely to be structurally complex because they have to attach large and complex chromosomes to the spindle apparatus during cell division.

Without a functional centromere, artificial chromosomes are unstable, fail to attach to the spindle, and are quickly lost. Thus, many researchers are seeking to identify the sequence elements in centromeres that enable them to work properly during cell division. Attempts to define the mammalian centromere have taken one of two

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