



## Interpreting the code of life

By ROBERT POLLACK

IT SEEMS ONLY yesterday, but it was more than 20 years ago, that summer at Cold Spring Harbor in the early 1970s, when [David Baltimore](#) showed up in great agitation and gave a last-minute, unscheduled little talk at a meeting, explaining that both his lab and [Howard Temin](#)'s had found unmistakable evidence for an enzyme that converted RNA to DNA. In textbooks this moment usually is described as the breaking of a dogma- that DNA makes RNA and RNA makes protein-but to those of us lucky enough to be there, the sound was not the lugubrious thud of a fallen idol but the shivery squeak of an unexpected door, slowly but inexorably opening before us.



Once we had the way to make DNA from RNA, the technology for manipulating DNA was complete. We could now decode and edit not only genes, but the messengers made from them; this gave us the power to understand-in principle-not only the archival files of genes in our chromosomes, but also their actual meanings in our cells. The closing quarter-century of this millennium has only begun to unravel the stories that discovery made possible, and few Nobel Prizes have been more richly deserved or more rapidly conferred than the ones Temin and Baltimore soon got. They came more quickly, in fact, than the Nobels given for the earlier, even more astounding revelation of [James Watson](#) and [Francis Crick](#), that DNA's double helix of phosphate-sugars and its perfectly free choice of base pairs inside made it the perfect exemplar of Schrödinger's model for the gene, an "aperiodic crystal" come to life.

With DNA as the self-copying storehouse of life's information, and with the tools for capturing the cell's processing of that information in the form of complementary DNAs made from cellular messages, we are embarked on the greatest adventure of science today: to understand ourselves, from the DNA out. The articles that follow are brief reports from the frontiers of this enterprise, by and about Columbia-based scientists.

Newman describes Columbia's contribution of vast numbers of sequences of human genetic messages to a national public library of DNA sequences, an altruistic decision that has placed Columbia squarely between two very large millstones, the [Merck](#) and SmithKlineBeecham pharmaceutical companies. This gift has already sped the isolation of at least one gene associated with [Alzheimer's](#) disease; it will be interesting to see how-or whether-the discovery can eventually ameliorate the course of this incurable disease, but no one can doubt the utility of getting the job done faster.

Stern's article shows how the common ancestry of all living things enables the students of fruit flies to be the intimate and mutually illuminating colleagues of the students of human inherited disorders and makes the case that the Human Genome Initiative will be only the first of many microbe, plant, and animal genome initiatives. The full DNA sequence of one simple microbe is already available on the Web and as a paper in *Science*; one can imagine the day when the Chimpanzee Genome Initiative shows us precisely which regulatory regions of which genes active in early development give us and not chimps the capacity for language.

Fischetti's essay on DNA forensics and Benowitz's on the uses of genetic information in diagnosis of future medical conditions are variations on a common theme: that each person's DNA is a unique sequence and that the information in that DNA includes the genetic component of that person's fate. The courts struggle with the technical minutiae of DNA identification when a felon is on trial, as they should when a person's life is in their hands. But neither legislatures nor courts have yet come to terms with an equally serious issue (albeit one for the civil, not criminal jurisdictions): How can society preserve each person's right to his or her own DNA, each person's privilege to not know-or not to have anyone else know-what is in it?



Schon and DiMauro look past the massive edifice of the Human Genome Initiative's 3 billion base pairs to the few tens of thousands of base pairs that make up the genome of a mitochondrion. Our mitochondria are ancient guests, now in an embrace of total interdependence with each of our cells but still carrying their primeval prokaryotic genomes. Mutations in these genomes-especially

deletions-occur slowly, cryptically, and universally over time; they may be the key to understanding the aging process. They are certainly the source of many conditions and syndromes whose patterns of inheritance would have stumped Mendel.

Fischetti takes a look at a new and clever use of DNA's capacity to carry vast amounts of information in a small volume: the construction of DNA-based computing schemes. I suspect that DNA is an imperfect molecule for this use and that if this technology ever matures, it will be through the merging of DNA-based sequence-annealing with the solid-state structures of silicon-based computation. But whether we ever see the day when [CompUSA](#) sells computers by the milliliter, DNA scientists and computer scientists are unlikely to disentangle themselves now that they have met once in a productive way. Down the line we may see a merger of ideas that generates, at last, an understanding of the mind.

I hope that, taken all together, this special section of 21stC has been able to show you something of the excitement and the shocking newness of human molecular genetics, and of the remarkable place Columbia continues to have in its ongoing evolution. The last article, my own, is an attempt to look inward, at the obligations this science places on those who practice it.

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