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GENOME SEQUENCING

HUGE EFFORT ON CHROMOSOME

DALLAS, Tex.—It took \$3 million, 26 months, and three dozen laboratories to determine the complete sequence of the third chromosome of yeast, as well as three years to coax committees into starting the project. So reported Andre Goffeau of the Universite Catholique de Louvain (Louvain-la-Neuve, Belgium) at the May meeting of the American Society for Microbiology. The strategy, its breadth, and the preliminary scientific findings offer an hors d'oeuvre from the multi-genome banquet being planned in the U.S., Europe, and elsewhere for the years ahead.

The yeast genome contains some 15 million base pairs that are parcelled into several chromosomes. Chromosome three contains 300,000 of those bases, representing a relatively small but still-formidable fraction of the whole. When the paper describing the sequencing and analysis of this chromosome is submitted to *Nature*, says Goffeau, it will list more than 120 authors from all 12 member states of the European Community, the U.S., and Japan. The researchers composed a loose but remarkably coherent confederation in which friendly competition, cooperation, and pay-as-you-go inducements helped to propel the project to completion.

The data are "under frenetic analysis," Goffeau says. Already, inspections of DNA-sequence segments indicate more than 200 open-reading frames for putative proteins containing at least 80 amino acids each. Within this set, 10 percent correspond to previously sequenced genes. Another 15 percent represent apparent homologies to yeast or other known proteins. About 20 percent appear short or irregular and are likely not made into proteins. And another 55 percent seem to be new polypeptides but without homology to any proteins now catalogued in data bases. Most members of this latter group "are expressed as messenger RNA at least," says Goffeau. "But most of the genes have no obvious phenotype."

This comprehensive picture could only arise from "systematic sequencing rather than classical biochemistry and genetics," Goffeau continues. Extrapolations, which admittedly are risky, suggest that a full-genome analysis could at least double or triple the number of genes heretofore believed to be present in yeast. Based on a similar—and comparably risky—straight-line extrapolation, such an analysis is projected to cost about \$100 million and could last a century—the unit of time believed necessary for building a cathedral. In the face of such astronomic numbers, the yeast genome consortium has "agreed to increase its efficiency over the next few years, by aiming for fewer labs to bring the cost of sequencing down to \$2 (eurodollars) per base pair," says Goffeau.

Nonetheless, this initial effort has allowed Goffeau and his collaborators to rough out some management precepts for large-scale DNA sequencing projects: "We split the work into small parts and let the consumers of the data also be the producers. We paid for what we got in fixed eurodollar amounts. We used a first-come basis to get efficiency. And we controlled quality by peer pressure and some overlap in efforts," says Goffeau. He optimistically adds that the yeast cell will be "the first eukaryote to offer all its genome" for sequencing and analysis.

—Jeffrey L. Fox