of the final protein, Gilbert says.

Another example is the globin protein that combines with heme to become hemoglobin, which carries oxygen in animal blood. Gilbert says that the protein has three structural segments — the central piece that contacts the heme and two wing portions. He suggests that the central piece represents a primitive "miniglobin." The wings may have been added for greater efficiency during later evolution.

The association of functional and structural areas of a protein with separated segments of its gene excites molecular biologists. It makes the DNA sequence appear to be more than a linear sequence of arbitrary code. "It's a delightful outcome. At the DNA level, structural and functional aspects are written out," Gilbert says. He anticipates that biologists in the future will be able to infer the underlying functional units of proteins from the structure of their genes.

Restacking the deck

A different mechanism often considered in gene "shuffling" is more like cutting a deck of cards. When the chromosomes of a cell pair up before cell division, homologous DNA strands frequently break and the strands from the two chromosomes join. This phenomenon, called "crossover" (SN: 7/8/78, p. 27), is analogous to two identically arranged decks of cards being cut in the same spot and the top portions exchanged. The result is that the genes at one end of the chromosome are linked to new associates at the other end. Generally, the more distance there is between points on the chromosome, the more likely it is that a crossover event will recombine them. By analogy, if the queen of hearts and the ten of diamonds have 42 cards between them in the pack, it is far more likely that a cut of the deck will separate them than if one was on top of the other.

To extend the analogy even further, if a fistful of jokers were inserted in each deck between the cards of interest, the probability of cutting the cards so as to separate the cards of interest would again increase. Thus Gilbert says that inserting unrelated DNA sequences between parts of the gene coding for different portions of a protein increases the ability of crossover to recombine those pieces of DNA. If, for instance, two individuals had beneficial mutations in different portions of the gene for one protein, in the offspring those mutations are most likely to recombine into one chromosome if they are spaced far apart on the DNA.

Crossover does not always involve breakage at exactly the same point on two chromosomes. Sometimes the DNA molecules pair out of alignment, especially when regions of the DNA that are not completely homologous have similar sequences. In those cases crossover creates one molecule with extra DNA and another missing a stretch. In the card analogy, cutting two decks at different places and exchanging the top stacks results in one pile of cards being thicker than the original decks and the other being thinner.

That sort of unequal crossover could bring together domains of separate proteins to make a new composite product. Work by Leder, Jonathan G. Seidman and colleagues supports the idea that such crossover could also increase or decrease the number of copies of a gene. The increase could be another way of generating diverse genes during evolution.

Leder and Seidman were interested in knowing how the large number of DNA regions coding for one protein segment (kappa variable region) of the antibody molecule might have arisen and how they are maintained. The investigators found that the hundreds of kappa variable region genes consist of subgroups, each with about 10 members that have similar DNA sequences.

In other cases, the researchers had found little similarity in the sequences of DNA that flank closely related genes. The genes within each kappa subgroup, however, are flanked with similar intervening sequences. These flanking regions with their similarity should be inviting sites for unequal crossover, Leder says. Because the unequal crossover can dramatically vary the number of genes, limiting recombination to single subgroups would protect against catastrophic loss of all the kappa coding regions. The most that would be lost in a "mini-catastrophe" would be a single subgroup.

This evolutionary model can be tested, Leder reasons. He predicts that closely related species of animals would differ occasionally in the number of genes within one of the subgroups. To test this hypothesis, Leder looked at eight species of Asian wild mice collected by Robert Callahan. All the mice have similar numbers of genes in one subgroup, but one species almost totally lacks another subgroup. This result, Leder says, supports the possibility that coding DNA can be lost or gained during evolution through unequal crossover.

It is difficult to argue about the evolution that has already occurred, because scientists can never know all the past pressures that shaped natural selection, Leder says. The investigators need instead to make models that generate testable predictions. For instance, the evolutionary origins of antibodies, which are found even in simplest vertebrates but not in lower animals, may be unraveled by looking for functionally different proteins that contain similar DNA sequences.

Using the details of the contemporary DNA to answer questions about the evolutionary past is the most satisfactory procedure now available. "We can't think of an experiment that will allow us to evolve the immune system again," Leder says, adding jokingly, "with the time and money available." □

BOOKS

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COPING WITH CANCER — Avery D. Weisman — McGraw, 1979, 138 p., paper, $6.95. This book is a result of a systematic inquiry by a leading psychiatrist into how cancer patients cope or fail to cope with issues related to their illnesses.

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