Estimates vary for the total number of variable region genes for κ chains. One of the higher estimates is that of Weigert and his colleagues. Based on a statistical analysis of the known amino acid sequences of κ chains, they concluded that the proteins could be subdivided into about 50 groups. If six or seven genes are needed to code for the members of each group, there should be about 350 variable region genes for the κ chains. This is more than previously thought but still far short of 1000. Weigert says he now thinks that the number of germ-line genes is sufficient to account for only about 10 percent of antibody diversity, with other mechanisms providing for the rest. These other mechanisms would include somatic mutation and combination between a number of J and variable region genes.

Some investigators, including Potter, do not think that all the κ chain groups have been identified, however. He has identified a number of new lines of antibody-producing cells from an inbred strain of mice and says that it is easy to find new light chains. If the number of groups continues to grow, then the magic number of 1000 may yet be reached. Potter agrees that somatic mutation generates some antibody diversity but relegates it to a secondary role compared to that of germ-line gene number.

Although Leder has come to a similar conclusion, he has recently suggested a novel mechanism for generating additional diversity. He bases the hypothesis on the results of the gene-sequence studies being carried out in his laboratory. In addition to finding a high degree of similarity in the nucleotide sequences of the two variable genes they have analyzed, the NICHD group has determined that the similarities extend well beyond the genes themselves into the nucleotides on either side of the genes.

This close structural resemblance over a long stretch of nucleotides would facilitate association between related genes carried on the two members of a pair of chromosomes. These associations may occur during cell division and when they do, the two genes may recombine, that is, exchange nucleotides with one another. Such exchanges by themselves can generate alterations in gene structure and thus increase diversity. Moreover, during the exchange, mistakes may happen with the potential for producing still more variability.

Leder points out that the situation regarding the antibody genes presents a striking contrast to that observed with the two genes coding for one of the proteins that make up hemoglobin. Mutations in the genes for this protein, which may alter or even destroy its function, are poorly tolerated. According to Leder and his colleagues, the nucleotide sequences flanking these structural genes are very dissimilar, a situation that would tend to minimize recombination between them and consequently reduce the likelihood of the genes being altered.

If recombination is one of the mechanisms for generating antibody diversity, then a way to prevent catastrophic gene loss, which might result from extensive recombination between dissimilar groups of genes, would be needed. Loss of variable genes could deprive the animal of needed antibodies. Leder suggests that such losses could be prevented if the ability to recombine were restricted to the few variable region genes within a single group. And this may be the case. Experiments in his laboratory indicate that similarities in the flanking sequences are restricted to members of the same group. This would mean that recombination would occur primarily among the six or so genes belonging to one group and not between genes of different groups. Such an arrangement would make catastrophic loss of many variable region genes unlikely.

Although Tonegawa has also observed extensive similarities in the nucleotide segments flanking variable genes of κ chains, he is still cautious about the significance of the findings. In this context, he thinks a mechanism like that proposed by Leder is possible but as yet unproved.

Although all the issues concerning antibody diversity have not yet been resolved, current research is illuminating the mechanisms by which the immune system can generate the multitude of antibodies it needs to deal with the essentially unlimited number of antigens it encounters. It now appears that multiple germ-line genes, somatic mutations, and gene rearrangements are all involved to some degree. No one expected that a system this complicated would be easy to unravel. And it has not been. But at last the antibody diversity problem is yielding to techniques that are becoming increasingly capable of tackling a question of this magnitude.—JEAN L. MARX

UPDATE

Grapes Inactivate Viruses, but Not in Body

Wine lovers rejoiced last year when Jack Konowalchuk and Joan I. Speirs of Health and Welfare Canada demonstrated that grape juice and wine can inactivate viruses in test tubes (*Science*, 3 June 1977, p. 1074). New results from Dean O. Cliver and Kenneth D. Kostenbader, Jr., of the Food Research Institute at the University of Wisconsin at Madison, however, suggest that the antiviral effects of grape products may be healthful only if used to bathe wounds to prevent infections.

In studies supported by the Concord Grape Association and Welch Foods, Cliver and Kostenbader replicated the experiments of the Canadian investigators and found that grape juice does, indeed, inactivate several types of viruses in the test tube. But they also found that the inactivated viruses were reactivated when exposed to biological systems.

The Wisconsin investigators have been studying viral infections of the gastrointestinal tract in baby pigs maintained on food normally given to human beings; this system closely mimics the human gastrointestinal system. After killing a small number of the piglets, the investigators mixed the contents from six different sections of the digestive tracts with viruses that had been inactivated by grape juice. After 30 to 60 minutes of exposure, they found that 50 to 75 percent of the virus particles had been reactivated. They also mixed inactivated viruses with human blood serum and observed that 94 percent of the virus particles were reactivated. They thus conclude that ingested grape juice probably provides no protection against viruses.

The studies have not been a total loss, however. It is clear, Cliver says, that some relatively small molecule from grapes—Konowalchuk thinks it is phenol or its derivatives—is binding to the surface of the virus. This chemical prevents as many as 80 percent of the virus particles from binding to normal cells, and renders them almost completely noninfective. It could thus be a valuable tool, Cliver says, for investigating the mechanism by which viruses infect human cells, and may provide a lead to other agents that could produce irreversible inactivation. In the meantime, though, neither the Concord Grape Association nor Cliver recommends bathing wounds in grape juice or wine. Other topical disinfectants are more effective and have the added advantage of not staining the user purple.—T.H.M.

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