PHAGES

Evolving Sequences

from a Correspondent

COLIPHAGES T7 and T3 show considerable base sequence homology, so much so that it seems probable they must have had a common ancestor. Unlike the lambdoid phages they exclude each other, do not recombine, and they destroy their host DNA. As a result they are genetically isolated from each other and from the host. This, then, is an ideal model system for studying evolutionary divergence and to that end, and with great elegance, Davis and Hyman (*J. Mol. Biol.*, **62**, 287; 1971) have examined the DNA base sequences of the two phages. Their approach is disarmingly simple. They separated the strands of T3 and T7 in CsCl by using poly r(U,G). Heteroduplexes containing the T7 *l*-strand and the T3 *r*-strand were constructed and these were examined by electron microscopy at various stages of denaturation. The resolution was such that distances of 100 base-pairs in length could be seen. This allowed them to measure the percentage homology as a function of distance along the heteroduplex, and they were able to compare this with the genetic map of T7.

A whole series of fascinating observations followed because several of the regions of the homology map can be assigned to specific genes or functions. The initiation site for T7 early mRNA synthesis maps in a position where there is a "spike" on the homology map of 400 base pairs showing 80 per cent homology. This region is bounded on both sides by regions of very little homology. The termination site for early T7 mRNA synthesis is also at a position corresponding to an 80 per cent homology spike. Because these two sites are both necessarily involved in a recognition interaction with *Escherichia coli* RNA polymerase, presumably there must have been strong pressures for the base sequences to be conserved.

A large region (about 25 per cent of the genome) towards the right hand end of the heteroduplex is more than 90 per cent homologous and covers the genes coding for minor structural components of the mature phage. Presumably changes here, too, must be particularly disadvantageous.

By contrast, two protein products, lysozyme and ligase, both of which are dispensable for successful infections of T3 and T7, have genes which show low homology by this technique. In short, the homology map may be seen as a map showing how essential are the various functions carried out or coded by the base sequences concerned.

The picture of evolution which emerges is perhaps not surprising. Mutations occur at random in the DNA. If the gene has an essential function much less variation can be tolerated than otherwise so that divergence occurs principally in the inessential regions. This is probably no more than we have learnt from the analysis of haemoglobin, but it is useful to see such experiments carried out on DNA base sequences and with the broad range of genes that these phages afford.

HEPATITIS

Introducing the Icron

from our Medical Virology Correspondent

THE precise biological nature of Australia antigen remains obscure in spite of intensive studies in many laboratories. This antigen was discovered in 1963 during the search for new serum protein polymorphisms and considerable data have since been accumulated to support the concept that Australia antigen is indeed a polymorphism. And when the antigen is disrupted with 'Tween 80' the released soluble products are serum proteins, including IgG, β-lipoprotein, transferrin, albumin, complement and traces of ribonucleic acid. It seems likely, therefore, that the Australia antigen particle itself is made up of human serum proteins, although not necessarily proteins from the host from which the antigen was isolated.

On the other hand, Australia antigen is closely associated with serum hepatitis and with infectivity, and it has a number of properties in common with known viruses. The antigen is made up of particles with organized morphology, a small amount of RNA has been identified in antigen purified from serum (Józwiak *et al.*, *Nature New Biology*, **229**, 92; 1971), a reverse transcriptase has been detected by Hirschman and his colleagues (*Lancet*, i, 1099; 1971), and apparent replication of Australia antigen in tissue culture of human liver cells has been demonstrated by Brighton and his colleagues (*Nature New Biology*, **232**, 57; 1971) and by Coyne and her colleagues (*Bact. Proc.*, 175; 1971).

Almeida and her associates (*Microbios*, **2**, 117; 1969) suggested that there were many similarities between serum hepatitis, scrapie in sheep and kuru in man, three conditions where there would seem to be both a genetic and an infectious element. Blumberg and his colleagues (*J. Exp. Med.*, **134**, 320s; 1971) now suggest that Australia antigen is an infectious agent which causes hepatitis in some people infected with it, and that it has the characteristics of an inherited serum protein polymorphism. They propose the term "icrons" for the postulated new class of infectious agents and this provocative concept should stimulate further work in different directions.

SOMATIC CELL GENETICS

Ploidy Mutants

from a Correspondent

IT has become commonplace to attempt to induce mutations in animal somatic cells *in vitro*. A wide range of mutagens increases the spontaneous frequency of variants and it has been assumed that many such apparent mutations are in structural rather than control genes. To be sure, such mutations are abundant in nature, but the successful isolation of an altered gene product from a mutant induced *in vitro* has not been reported. Many of the variants isolated can be induced with surprisingly high frequencies, and also revert easily. Indeed, in some quarters it has become customary to avoid altogether using the term "mutants" for these "phenotypic shifts".

The issue is clearly of great importance, not only for the proper conduct of somatic cell genetics but also because of recent reports of the introduction of a structural gene from one cell into another (Schwartz *et al.*, *Nature New Biology*, **230**, 5; 1971) where the recipient used was a variant induced *in vitro*.

The recent report of Morgan Harris (*J. Cell. Physiol.*, **78**, 177; 1971) is therefore of great interest. He has examined the mutation rates in cells at different ploidy levels. Whether structural gene mutations are dominant or co-dominant, the mutation rate should rise with the level of ploidy. If the mutations are recessive, the rate should fall very rapidly as the number of copies of the gene per cell increased. Harris has studied the acquisition of resistance to 8-azaguanine and to heat in a diploid, tetraploid and octaploid series of Chinese hamster cells. He finds that the rates of mutation for these markers remain constant or decline slightly with increasing numbers of chromosome sets. Clearly, these results are not consistent with either of the simple explanations and Harris suggests that at least some variations may arise in somatic cells by stable shifts in phenotypic expression rather than by structural gene mutations. Such shifts are commonplace in differentiating cells, but we must wait for evidence that structural gene mutations ever occur *in vitro*; that will only be convincing when someone manages to identify an altered gene product.