while Mr E. F. Harding (Statistical Laboratory, Cambridge) expounded and criticized Dr Hacking's principle of irrelevance, both in its original form and in a form proposed by Dr Edwards. He then found himself still unable to decide whether one could validly leap the fiducial chasm, to which Professor D. R. Cox (Imperial College, London) answered that he thought one could, but only at the risk of falling flat on one's face on the far side. With added support from Professor G. A. Barnard (University of Essex) and Professor D. A. Sprott (University of Waterloo), it become clear that the fiducial argument is by no means dead.

Technical problems arising in interpreting multiparameter models in the likelihood theory were considered by Professor Sprott and Dr O. Barndorff-Nielsen (University of Aarhus), while Professor Cox and Dr J. A. Nelder (Rothamsted) presented papers on randomization, and statistical inference in practice. On the Tuesday afternoon Dr F. Yates took the chair in an historical session addressed by Sir Harold Jeffreys and Professor E. S. Pearson. Dr O. Irwin added some personal reminiscences which prompted a number of amusing anecdotes from the others. The session was followed by the fifth Fisher Memorial Lecture entitled "Statistical Inference in its Historical Development" by Professor Barnard.

MOLECULAR BIOLOGY

Starting DNA Synthesis

from our Molecular Genetics Correspondent

ONE of the puzzles about the control of DNA replication in bacteria is that many cells must have more than one control system. As well as the system which acts on the bacterial chromosome, to ensure that there is one replication for every cell division, some other mechanism exists to control the replication of episomes in those cells that carry these extra circles of DNA in addition to their chromosomes. Episomes and chromosomes each constitute a replicon, in other words.

Although the general operation of the chromosomal control system is well characterized, little is known about the control of episome replication. Each bacterial cell may carry several copies of the F factor, and since this number remains constant in a stable population, they must double during every cell division cycle. In the September issue of the *Proceedings of the National Academy of Sciences* (**69**, 2706; 1972), Cooper now presents evidence that the manner of this control has a form analogous to that of the bacterial chromosome.

Replication of the bacterial chromosome takes about 40 min at 37° C; a cell division always follows completion of a round of replication in about 20 min. Because these two times are constant, a round of replication must therefore be initiated 60 min before a division. This means that when bacteria grow rapidly, one round of replication may be initiated before the last has been completed and before the consequent cell division. In other words, the round of replication corresponding to one division cycle may in fact be initiated in the preceding cycle, or even earlier.

Replication of the F factor takes place in a similar manner. The activity of β-galactosidase in cells which have their copies of the lactose operon carried upon an F′ factor is proportional to the number of copies of the gene; a doubling in enzyme activity therefore shows that the factor has replicated. By following the activity of β-galactosidase when cells are "shifted up" by changing their growth conditions so that they grow more rapidly, Cooper has found that successive doublings in enzyme activity in induced cultures seem to be related to the divisional cycle in the same manner as chromosome replication—and can therefore be explained by the same idea, that rounds of replication of DNA are initiated when the cell reaches a critical size.

These results conflict with the previous conclusion of Zeuthen and Pato (*Molecular and General Genetics*, **111**, 242; 1971) that replication of episomes takes place by a different mechanism. They are therefore comforting, for they restore the idea that—in teleological terms—a successful mechanism is likely to be used by cells whenever possible in similar circumstances. Titration of cell mass is, accordingly, used to determine initiation of both chromosomal and episomal replication.

An interesting sidelight of these results is that they go some way towards explaining the viability of cells in which the normal replication control has been lost so that bacterial replication comes under control of the F factor. Cells which contain an episome fall into two classes. In one the episome is free in the cell and replicates under independent control from the bacterial chromosome. In the other, the episome is integrated into the bacterial chromosome and is no longer replicated independently—it is repressed and is replicated only as part of the bacterial chromosome itself.

But in a third instance, discovered by Nishimura, Caro, Berg and Hirota (*J. Mol. Biol.*, **55**, 441 ; 1971), the bacterial control system may be inactivated and the cells may survive by placing the bacterial genome under the control of an integrated episome. It is now easy to wonder in retrospect, given Cooper's results, how such cells would achieve coordination of chromosome replication and cell division if the F factor control system were quite different in form from that of the chromosome itself. The general relationship between the control of episomal and chromosomal replication—molecular details of the interaction of regulator proteins with DNA control sites remain to be discovered, of course—now answers this question.

Left-handed Nucleic Acids

ONE promising way of approaching the problem of helix sense in polynucleotides is by spectroscopic studies of dinucleotides and oligonucleotides. Such oligonucleotides can be called left or right-handed according to the helix sense of the structure which would be generated if the folding in the oligomer were repeated throughout a polymer. The change in optical properties with chain length can be followed, and this allows the spectra of polynucleotide polymers to be catalogued with more certainty.

In next Wednesday's *Nature New Biology* (November 1) Ikehara, Uesugi and Yano report ultraviolet absorption and circular dichroism observations on a dinucleoside phosphate and oligonucleotides in which each nucleoside residue has, in addition to the normal glycosidic linkage, a second covalent bond between the sugar and base. In every nucleoside the base is adenine and the sugar is arabinose, that is the 2′ OH is on the opposite side of the sugar ring from its position in the normal ribose sugar. The additional covalent bond is between C8 of adenine and the oxygen of the ribose 2′ OH, and constrains the nucleoside to a particular conformation about the sugar-base link. The analogous compounds in which the 2′ O is replaced by a sulphur atom were also studied. From their spectroscopic studies Ikehara *et al.* conclude that the dinucleoside phosphates and oligonucleotides containing these nucleosides have a left-handed helical conformation.

The interest in the work of Ikehara *et al.* goes beyond the handedness of the structure itself. For example they report that the oligomer does not form complexes with poly (U). The development of such studies will be extremely important in investigations of the stereochemical restrictions on double helix formation. The fact that the nucleoside in the polymers studied by Ikehara *et al.*, with its two covalent bonds between sugar and base, is more rigid than a normal nucleotide is also relevant to the mechanism of melting out of nucleic acid secondary structure; some work on this is also reported.