

## Mechanisms of drug resistance (Dr. E.M. Lederberg)

The importance of the development of drug resistant strains of bacteria in the long-term success of chemotherapy is now well recognized but the biological basis of the development of drug-resistant strains has been the subject of bitter controversy for several years. One of the reasons that this question has been mooted for so long has been that, ordinarily, the only means by which a drug-resistant mutant strain of a bacterium could be produced in the laboratory was by exposing a culture of the bacteria to the drug. This left open the question as to whether a very small number of spontaneously occurring resistant mutants had been already present in the treated bacterial populations prior to exposure to the drug, or whether the drug itself played some specific role in inducing the adaptation. Many indirect lines of evidence had already pointed to the validity of the former mechanism but many workers continue to insist on the latter, pointing to the absence of any direct proof of the spontaneous occurrence of drug-resistant mutants. This difficulty has been circumvented by the development of the new method, "indirect selection", which is based on the technique of "replica plating" for faithfully transferring a whole pattern of bacterial growth from one Petri dish to another by means of a sheet of velvet. This has now allowed an indirect method of selection of resistant mutants based on going back to the sites on a plain agar plate where resistant mutants are indicated to be by tests on replicas and ultimately, thus, to isolate drug resistant mutants from bacteria that have never been directly exposed to the drug. These experiments which were initially done in our laboratory with streptomycin and *Escherichia coli* have since been confirmed and extended by several other workers.