Dr. Lederberg (Abstract of Remarks).

I. Bacterial Genetics. This does not seem the place to go into many technical details, The following chart will probably suffice to remind this audience of pertinent developments.

MECHANISMS OF BIOLOGICAL VARIATION
(With Special Reference to Bacteria).
(Cf. Braun, "Bacterial Genetics"; Luria, Bact. Rev. 1947;
(ORNL Symposium 1955: J.C.C.P. 45, Suppl.2)

1. Intraclonal Variation

"Mutation". Spontaneous. Induced (X-rays;ultra-violet;chemicals).

Segregation — from heterokaryons, heterozygotes, or cytoplasmic complexes (Completes cycles of interclonal variation).

Genetic Recombination.

2. Interclonal variation./ (Classified by dimensions of genetic unit exchanged).

Sex (Syngamy) — Fusion of whole nuclei. Examples: E. coli K-12 but collaboration of different nuclei.

Heterokaryosis — Fusion of cells without nuclear fusion/ Ex: Streptomyces griseus.

Cytoplasmic transfer ("endosymbiosis") — Ex. "kappa" in Paramecium; no certain examples in bacteria; (F+?). Glucosyl-nucleotides in phage?

Transduction — "transfer of a genetic fragment from a donor to a recipient cell".
A. Mediated by DNA: pneumococcus transformation
B. Mediated by phage: Salmonella; E. coli
B'.Phage itself as genetic fragment, lysogenic conversion

For present purposes it is perhaps sufficient to emphasize that genetic variation can be accomplished either by mutation or by recombination, and that efforts to find recombinational systems of one kind or another in various organisms have frequently been successful.

II. Some general remarks on genetic principles.

1. A given trait may be controlled by one or a few major genes (oligogenes) or by a great many, whose individual effect is much smaller (polygenes) or both. We have no a priori way of knowing which applied to paralytogenesis in polivirus. The former would be more encouraging for a mutational approach.

2. Because of the infrequency of mutation, the usual obstacle is the development of specific selective techniques for the desired mutant. For example, in E. coli it is easy to obtain a lactose-positive mutant (Lac+) from a Lac- stock, since one can select in a medium with lactose as sole carbon source. To obtain a Lac- from Lac+ is much more difficult, but can be done with the help of an efficient indicator medium by which individual Lac- colonies are easily recognized. In addition, E.M.Lederberg had found that Butyl Galactoside was a selective agent which favored Lac-, probably because Lac+ cells will intoxicate themselves with butyl alcohol when they split this substrate. Similarly, auxotrophic mutants can be selected from prototrophic populations by means of penicillin, under conditions where the auxotrophic cells are saved, and the prototrophs killed.

Every effort should be made to rationalize selective techniques for desired mutants. This is not always hopeless, if we know enough about the system/ to be able to define precisely what we are looking for. For example, it is just conceivable that nonparalytogenic mutants of polio occur that do not adsorb so readily on neurons, and these could be concentrated by differential adsorption.

Less important, but technically useful, is the augmentation of the incidence of mutants in general by various mutagenic agents. Unfortunately, the conditions of mutagenesis in viruses are still confused.

The same primary role of selective technique applies to recombination analysis.

3. When we don't know enough about the system, we may have to rely on irrational selection. Either we know (or hope for) a specific correlate that we can select with, or else we rely on the principle of "Imperfectibility", that evolutionary specialization can only be accomplished at a price in terms of general adaptation. This may be the explanation for the attenuation of viruses, e.g., of yellow fever. This has not been studied sufficiently that we are on sure theoretical footing. Since this type of selection alsp relies on sporadic mutations, and these may occur in different patterns, one should carry this kind of experiment in many-

fold replicate, in the hope that one of the mutational sequences leading to adaptation in a new environment involves a deadaptation to the old.
4. Recombinational analysis should be of primary importance in many ways. The first is the information it can give on the genetic basis of paralytogenic variation in existing material.

There are two ways in which it can be applied specifically. The first is a rather obvious extension of the oligogenic approach. There may be any number of X viruses in nature which are genetically related (enough to cross) with polioviruses, even though they cannot be recognized as relatives either from their pathogenetic or immunological characteristics. Where X viruses already has characteristic host adaptations, it should not be too difficult to screen for recombinants of X by polio which have the antigenic character of polio, and the other (in this case desirable) characteristics of X. This might be termed the recombinational introgression of poliovirus antigens into other strains. We know so little of the genetic relationships of viruses that there is no obvious criterion, before the trial itself, by which to recognize the relatives.

The second approach is based on the studies of "correlated variation" in the sense of Mather and Lerner (see the latter's book,"Genetic Homeostasis"for an excellent summary of examples from breeding experiments with fruitflies, chickens, and other higher organisms). When heterogeneous fruitflies are crossbred and subject to stringent selection for a single character,e.g., number of abdominal hairs, the trait increases steadily in successive generations, then reaches a steady peak when the stocks have become "fixed" or genetically homogeneous. But concurrently, there is a steady loss in the overall vitality, fertility, longevity, etc. of the flies, which is the correlated variation. This is understood by the selective effect of building up complex new combinations of various genes which have the maximum effect on the selected trait. This process is bound to break up similar

co-adaptive gene complexes which have previously been assembled under the impetus of natural selection/ for the viability traits. Concretely, this would suggest the/selection of repeated cross-progeny of two lines continued of poliovirus, or poliovirus + virus X, for any trait other than paralytogenesis, in the hope of breaking up previously evolved coadaptations for this trait. The advantage of this system over reliance on simple selection is the possibility utilization of inherent,"old" genetic variability between of lines.

If I had to choose an immediate program, my own predilection would be for antigenic introgression. I would also give continued thought to the rationalization of the selection program, realizing how much more fundamental knowledge is needed for it.

J.L.