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EDITORIALS

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BACTERIAL GENETICS

One of the most actively cultivated fields of investigation in microbiology at the present time is that of bacterial and viral genetics. Its possible importance for leprosy investigators has been high-lighted in a review article in this number of THE JOURNAL by Jacinto Convit, which is partly speculative in character, setting forth the concept of mutation of *Mycobacterium leprae*, as it exists in the human body, into mycobacterial variants capable of multiplying in hamster skin tissue and in some cases in artificially prepared nutrient laboratory media.

Without attempting to pass on the validity of the concept, the Editor would like to review briefly a few of the major contributions of recent years that have encouraged the development of such a theory. The analysis will have to be elementary, first because of spacial restrictions in this issue, and second because of the Editor's incompetence to attempt anything more detailed. A good take-off point for such a review has been found in a semipopular discussion of the subject by the geneticist and recently honored Nobel laureate George W. Beadle, who has recounted new knowledge of genetics under the attractive subtitle "Threads of Life."[1]

Pointing out that the last decade has seen some of the most remarkable and significant advances in biology in the present century, Beadle noted that an astonishing series of Nobel prizes in physiology and medicine had been awarded to participants in this "veritable revolution in biology," 13 of them within the last 5 years alone. He made it clear that recent discoveries have gone far to explain some of the mysteries of life itself. Remarkably, a large proportion of the basic discoveries in the field were made, not in mammalian or other large cell genetics, but in the field of bacterial mutation.

The earliest significant experiments were made with pneumococci. These involved transformations among rough and smooth and virulent

[1]BEADLE, G. W. The New Genetics: The Threads of Life. Britannica Book of the Year. Chicago, Ill., Encyclopaedia Britannica, Inc., 1964, Pp. 44-72.

and avirulent forms. F. Griffith, in 1928, working with pneumococci in mice, found that when he inoculated (1) susceptible mice with rough mutant, avirulent pneumococcus cells derived from a type II smooth strain, and (2), simultaneously, heat-killed smooth strain cells from an avirulent type III mutant, the inoculated mice occasionally developed typical pneumococcus disease, in spite of the fact that they were inoculated only with nonvirulent or dead material. Controls injected with either one alone of the pair of inoculated materials, developed no disease. It was evident that something from the dead type III pneumococcus cells had caused the live cells of the inoculated avirulent rough mutant from type II cells to mutate to the pathogenicity characteristic of virulent type III cocci.

In succeeding years much clarifying work was carried on. It is an oversimplification to pick out just the high points, but special credit is always given to the epochal investigation of Avery, MacLeod and McCarty in 1944, who isolated a transforming principle in type III pneumococci, consisting of a polymerized form of deoxyribonucleic acid, acting in high dilution, causing R cells derived from one pneumococcal type to form the capsule of the type supplying the transforming principle. The converted cells subsequently formed more of the deoxyribonucleic acid as well as the new capsules. The results suggested that the transferred nucleic acid replaced nuclear material (genes) of homologous kind in the recipient cells.[2] This finding, that pure deoxyribonucleic acid extracted from one genetic type of pneumococcus, apparently could replace a defective gene of a related type, dispelled the old belief that genes were proteins.

Another old belief removed about the same time was that bacteria reproduced only by asexual processes. Beginning in 1947, J. Lederberg and E. L. Tatum showed that in *E. coli*, the current prototype, as Convit has indicated, for such studies, a process analogous to sexual union does occur. Whether that process is truly sexual or not is apparently a matter of terminology and semantics. At any rate the passage of material from one cell to another (recombination) does occur and the passage can be observed through appropriate optical means. Cells may be seen adhering side by side, and the operation of a microscopic conjugation tube can be observed. Nuclear material passes through this tube from one cell to the other. The transfer is said to take about an hour, and can be interrupted at will at any stage.

Other bacterial species have since been subjected to careful genetic study, and the process of reproduction is now far better understood than was the case a short time ago. The role played by deoxyribonucleic acid (DNA) is everywhere recognized. As will be indicated later, the syntheses involved in growth are brought about through the action

[2]RAFFEL, S. Immunity. 2nd ed. New York, N. Y., Appleton-Century-Crofts, Inc., 1961. 513 pp. See this work for a more extended analysis.

of remarkable threads consisting of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein, which, through a process of "coding," determine the sequence in which protein building blocks are put together. It is a remarkable mechanism. But, as Beadle says, despite the amazing precision with which DNA molecules replicate the essential structure, the process is fallible. Mistakes occur, rarely perhaps, but in such a way as to induce mutational change.

Mutational change can come about in a number of ways. For example, when mutants of *E. coli* requiring biotin but not requiring threonine, are grown in association with mutants requiring threonine but not biotin, new cells requiring neither may be produced (Lederberg and Tatum). To explain the formation of the cells with the new properties the crossing over (transduction) of genetic material from one cell to another must be postulated.[3]

The role of bacterial viruses or bacteriophages is important. Nuclear material of heterologous type may be introduced in one bacterial cell through the medium of a bacteriophage in such a way as to become a permanent constituent of the recipient cell. Bacteriophages may add nuclear material of their own. Such "transduction" may occur in nature yielding a multiplicity of antigenically related types in some genera of bacteria (see Raffel [2]).

Some work, limited thus far, but promising, has been carried out with mycobacteria in this respect. The latest of which the Editor is aware has to do with the addition of DNA, chemically extracted from a bacteriophage, to the body of *Mycobacterium smegmatis*.[4]

It is to be hoped that much more work will be done in the mycobacterial field, perhaps clearing up some puzzles in the growth characteristics of the many pathogenic and nonpathogenic forms, which are marked, as is well known, by noteworthy antigenic relationships. After all, few bacterial groups have been investigated more intensively with respect to their chemistry and metabolism than the mycobacteria. Some of that knowledge can now be put to new use.

The nature of the master substance in all these complicated processes was recently made clear, with remarkable fidelity in the light of later studies, by J. D. Watson of Harvard University and F. C. H. Crick, who carried out much of their work together in the latter's laboratory at Cambridge University in England, and who were awarded a Nobel prize for their success. For a concise, if by no means simple, summarization of the complex matters involved, the reader is referred to the article by Beadle cited above. It deals with the manner in which the DNA-RNA-protein threads are produced, and their indispensable

[3]From DARZINS, E. The Bacteriology of Tuberculosis. Minneapolis, Minn. University of Minnesota Press, 1958, Chap. 5. The Editor has found this book highly useful for the analyses here given and for an exhaustive discussion of nuclear material, its morphology and staining reactions in bacterial cells.

[4]TOKUNAGA, T. and SELLERS, M. I. Infection of *Mycobacterium smegmatis* with D29 phage DNA. J. Exper. Med. **119** (1964) 139-149. Related literature is cited.

role, through a complex biologic messenger service, in replication of this vital material, and the proteins specific for the products formed.

There is every reason to believe that the future will reveal information making present understanding seem fragmentary and superficial. But paths have been thrown open by the recent discoveries that will make a better understanding possible.

There is good reason, too, to believe that leprosy investigation will profit through the opening of these paths. In the light of past failures, and in spite of the new knowledge, it is unlikely that the solution of the problem of growth and reproduction of *M. leprae* will come easily. But new means, fresh ideas, and new leads, are at hand now, which should overcome many of the handicaps to which the older investigators were subject.

—Esmond R. Long