ture of the arrangement of bacterial DNA is not entirely clear, nor is it certain that it is actually linked to mesosome or to linear arrangements of ribonucleoprotein within the cytoplasm. Finally, further information is needed on correlation of anatomic and enzymatic data in cell wall replication, with particular emphasis on "normal" growth in balanced situations as compared with the mechanisms in unbalanced and "abnormal" states.

The participation of our European colleagues was generously supported by the National Science Foundation. Most of the presentations and pertinent discussion will be published in a forthcoming issue of *Bacteriological Reviews*.

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Subunit Structure of Proteins

Biochemical and genetic aspects of the subunit structure of proteins was the topic of the annual symposium in biology held at Brookhaven National Laboratory, Upton, New York, 1–3 June 1964. Investigators from the fields of genetics and biochemistry convened to review progress in their particular areas and to integrate their findings into an understanding of proteins composed of two or more polypeptide chains and of the genes which govern such structures.

Of great importance, genetically, is the phenomenon of allelic complementation. Two differently mutated forms of a gene governing a single polypeptide chain cooperate to restore a function which is absent in cells containing only one of the defective genes. The biochemical explanation of such findings is that the function involved depends on an enzyme composed of identical polypeptides. A protein composed of two such polypeptides, altered in different places, may exhibit activity absent in a dimer composed only of identically altered chains. D. G. Catcheside's presentation of this phenomenon also pointed to the prevalence of proteins composed of identical subunits; he found that among 30 carefully analyzed genes in *Neurospora* more than one-half showed allelic complementation. It may well be that, aside from secretory proteins, the majority of proteins produced by the cell are composed of identical subunits.

One of the most intensively studied gene systems has been the histidine biosynthetic region of *Salmonella*. J. Loper, in discussing this system, pointed out that of eight enzymes governed by the region, four appear to be composed of subunits. Only two of the corresponding loci, however, exhibit allelic complementation. This indicates that dimeric composition, although essential for such complementation, does not by itself assure that the appropriate interactions will occur.

An interesting comparison of the histidine loci of *Neurospora* with those of *Salmonella* was made by Catcheside. Two corresponding loci in *Neurospora* and in *Salmonella* showed complementation in both cases. In addition, the loci corresponding to the two other *Salmonella* loci, which produce oligomeric products, did, in *Neurospora*, show the phenomenon. The other four histidine loci failed to show allelic complementation in either organism. However, in an analysis of a histidine locus in *Neurospora*, A. Ahmed pointed out possible pitfalls in this area; "polarity" mutants, which interfere with the for-

mation of products from several adjacent cistrons, might be erroneously used as evidence for a single cistron exhibiting allelic complementation.

Complementation between differently defective polypeptide subunits has been demonstrated in vitro. In a further analysis of the mechanism involved in the case of *E. coli* alkaline phosphatase, M. Schlesinger elaborated the conditions necessary for dimerization of which the most striking is a requirement for zinc ion. The conditions for dissociation and reassociation of another enzyme, pig heart fumarase, were reported by R. L. Hill and L. Kanarek. They presented strong evidence for the existence of four identical subunits in the enzyme molecule.

H. A. Itano reviewed his work on the genetics and biochemistry of hemoglobin, a protein which contains two pairs of identical chains and can be symbolized as $\alpha\beta\beta\alpha$. One mystery with regard to hemoglobin appears to have been resolved at the conference. Although in most cases nearly identical polypeptide subunits appear to associate randomly in the cytoplasm, it has not been possible to isolate molecules with mixed β-chains in hemoglobin. This failure has now been attributed to the rapid equilibria which exist between associated and dissociated forms, and lead to the disappearance by continual separation of any mixed β-structures in the course of separative procedures such as electrophoresis.

An interesting approach to the identification of the bonds holding subunits together was discussed by C. Tanford. Such identification involves comparison of free energy differences between associated and dissociated protein subunits in various solvents. The free energy of solution of protein side chains is in the same solvents in order to identify the side chains newly released on dissociation and hence presumably bound together in the associated form.

With regard to the kinetics of association, K. E. Van Holde presented an intriguing picture of the situation in squid hemocyanin, which, in the electron microscope, appears as a radially symmetrical disk composed of five dimeric components. Together with L. B. Cohen he was able to demonstrate, in the ultracentrifuge, breakdown of the decamer to dimers and monomers in response to changes in the *p*H. Analysis of the rate of reformation of the complete protein indicated that intermediate linear poly-

mers of dimers were unstable until insertion of the fifth member which effectively locked the structure in the stable cyclic decamer form.

Subunit structure is the basis of one class of isozymes (enzymes of similar function but different composition). C. R. Shaw demonstrated how genetic analysis could be used to predict and verify the subunit composition of isozymes. A single mutation, for example, increases the number of isozymes of lactic dehydrogenase to 15. Lactic dehydrogenase normally exists in five forms composed of all possible tetrameric combinations of two different subunits. N. O. Kaplan proposed that the subunit composition of lactic dehydrogenase was related to cellular requirements for aerobic or anerobic metabolism. He has found that the forms of the isozymes composed of identical chains are differently adapted to these two functions.

From the reports of C. Frieden, J. C. Gerhart, and J.-P. Changeux, the subunit structure of enzymes appears to be intimately related to the control of their activity in cellular metabolism. Gerhart has succeeded in dissociating into subunits an enzyme, aspartate transcarbamylase, which is subject to feed-back inhibition. He is now analyzing the properties of the subunits with regard to binding of substrate and inhibitor. Such allosteric effects in general, in which a metabolite is specifically bound and enhances or impedes the activity of an enzyme, appear to involve, in all cases, a protein composed of subunits. Changeux put forward a theory for this phenomenon based on a shifting of the equilibrium between loose and compact states of the protein by the metabolite exerting the allosteric effect. One of the states could bind substrate less readily so that, depending on the shift in equilibrium, activation or inhibition would result.

One class of proteins of which the function of their subunit structure is readily apparent is antibodies. A dimeric structure composed of identical subunits would provide the specific bivalency needed for precipitate formation. In a review of antibody structure, A. Nisonoff presented evidence for an ABBA configuration reminiscent of that found for hemoglobin. From his own work it is clear that a single binding site is present on each AB subunit of a specific antibody. He was able to form only univalent antibody by reassociating such fragments with AB fragments of normal gamma globulin.

A panel discussion, chaired by R. D. Hotchkiss, provided an opportunity for speculation about the significance of subunit structure. Clearly, the occurrence of allelic complementation in diploid organisms would allow an increased variability and plasticity of the genetic makeup. Similarly, the quaternary structure of proteins offers a new dimension for the control of cellular processes.

The proceedings of the conference will be published as volume 17 of the *Brookhaven Symposia in Biology*.

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Forthcoming Events

October

29–31. Society for the **Scientific Study of Religion**, Washington, D.C. (S. Z. Klausner, SSSR, 1424 16th St., NW, Washington, D.C.)

30–31. **Nuclear Medicine** Clinical Applications, symp., Shaker Heights, Ohio. (Cleveland Nuclear Medicine Symp., P.O. Box 7084, Cleveland, Ohio 44128)

30–1. **Meteoritical Soc.**, 27th meeting,