GENETICS

Structural Mutations

The premise that linear and continuous sequences of nucleotides in the genetic material (deoxyribonucleic acid (DNA) in most organisms, ribonucleic acid (RNA) in some viruses) specify corresponding linear and continuous sequences of amino-acids in the proteins, that is, the gene products of these organisms, is so fundamental to present-day thinking in the field of molecular biology that it has rightfully been referred to as the 'central dogma'[1,2]. Another premise, inherent in this dogma, is the principle of colinearity of the genetic map with the nucleotide sequence and the definition of a mutation as an alteration in this sequence giving rise in turn to an altered structure in the product proteins. The conclusion has therefore been implicit that every mutation must necessarily result in some alteration in a gene product.

It is the purpose of this communication to point out that this syllogism is neither logically sound nor necessarily reflective of the situation existing in Nature even on the basis of the fragmentary evidence at present available. It is conceivable that there exist regions in the genetic nucleic acid primarily concerned in the specification not of gene products but with nucleic acid structure itself. The structure here referred to is a 'tertiary' folding or other configurational alteration superimposed on the 'secondary' structure (the hydrogen-bonded helix). That such folding must exist in native genetic material is self-evident from a consideration of the dimensions of the heads of bacteriophages *T2* or *T4* (95×65 mμ)[3], as contrasted with those of the DNA contained therein were it to assume the fully extended, rigid, configuration demanded by the Watson–Crick hypothesis ($6{\cdot}3 \times 10^4$ m$\mu \times 2$ mμ). We[4,5] and others[6,7] have speculated that the secondary constituents associated with the DNA of these phages (internal protein(s)[7,8], polyamines[8,9]) may be concerned with the attainment and/or maintenance of this tertiary structure. The hypothesis of scattered regions concerned with tertiary structure has, however, other important consequences which can be tested.

It may be fruitful, for example, to institute a search for phage mutants, which possess *solely* an altered DNA, as a consequence of which they differ in their tertiary structure and in their DNA-protein interaction without, however, any significant alteration in the primary structure of any of the individual proteins specified by this DNA. It is possible that in *T2* and/or *T4* at least such mutations may already have been reported. One such might be the well-known class of acridine-resistant mutants[10,11]. On the basis of work by others[6,12–15] and investigations now in progress in our laboratories, it is likely that, in the dark under carefully controlled conditions, acridines in general and proflavine in particular exert a very specific inhibitory action on phage reproduction. This action occurs during that stage of maturation which is concerned with the integration of previously synthesized, structurally intact, and fully functional DNA with the structural phage proteins, mainly those of the head. The dye has no effect on the elaboration of either DNA (refs. 6, 15) or proteins[14,15] separately. The inhibitory effect may find its cause in the formation of a relatively strong and specific complex between the dye and phage DNA which is, however, rapidly and reversibly dissociated by dilution in the presence of normal phage constituents. Four predictions can then be made: (1) that a one-step proflavine-resistant mutant should be one possessing an altered DNA but normal proteins which allows maturation to proceed at concentrations of dye completely inhibitory to the wild type; (2) that it should be possible to detect this alteration in the DNA by comparing interactions of dye and DNA's from wild-type and mutant respectively by appropriate physical and chemical techniques, while phage proteins isolated from mutant and wild type should be identical in structure and indistinguishable by all criteria; (3) that a relatively large number of different mutants of this type should be isolatable and that these markers should be distributed more or less at random along the full length of the phage genome; (4) that multi-step mutants, which are resistant to higher levels of dyes, should manifest enhanced resistance by the criteria enumerated under (1) and (2).

Prediction (3) brings to mind another class of mutants. The *ht* (extended host range, turbid) markers studied and mapped very carefully by Baylor and her collaborators[16] appear to possess just such a distribution. Yet recent genetic and immunochemical work by Streisinger[17] and structural investigations by Williams and Fraser[18] make it apparent that, phenotypically, host-range and attachment to cells are manifested through just one species of protein, that of the tail fibres[19]. Once again those mutations may control not the structure of a protein *per se* but only that of the nucleic acid itself: in turn this structural alteration controls the interaction of the DNA with some protein(s), itself specified by quite a different section of the genome. Indications of this may be provided by Baylor's recent work on the stepwise and additive nature of these *ht* mutations with respect to their stability to incubation in buffer (Baylor, M. B., private communication).

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[19] See Discussion by Brenner, S., in *Adv. Virus Res.*, **6**, 137 (1959).