CURRENT PROBLEMS BEARING ON THE METABOLIC STABILITY OF DEOXYRIBONUCLEIC ACID (DNA)

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In considering the orderliness and precision involved in the development of an organism, such as in the structural and functional differentiation of cells and tissues in multicellular forms, it becomes immediately apparent that there must be some system on which final order and form are based.

Furthermore, when we consider the transmission of heritable characters from parent to offspring, it is still further apparent that such a system must be capable of retaining a storehouse of information or a memory of specificities from generation to generation. In this capacity, deoxyribonucleic acid (DNA) is generally regarded as being the principal encoding mechanism for genetic information (Beadle, 1957; Brachet, 1957; Hotchkiss, 1955). During recent years, with the advent of reliable information as to the structure of the genetic material (Watson and Crick, 1953), it has been possible to give much greater meaning to the term "genetic information." Such information is visualized as being represented in the specific molecular organization of DNA.

Also, in reference to the template hypothesis (Brachet, 1955; 1957), it is possible to visualize mechanisms which can facilitate the translation of the specific information stored in the genetic material into the equally specific structural identity of macromolecules such as those synthesized during periods of growth and differentiation. In this connection, an intermediate substance acting in the effective transfer of genetic information from the gene to the specific end products of genic action is usually acknowledged. At least for the most part, this intermediate substance would seem to be ribonucleic acid (Brachet, 1957; Spiegelman, 1957).

With specific reference to DNA, this material is generally regarded as being a very stable substance. Actually, many investigators regard the relative constancy of the deoxyribonucleic acid in the "resting" cell nucleus as constituting a generally accepted hypothesis in modern biology. This assumption of constancy arises from a number of observations. First, it is accorded support by the fact that, except for periods of duplication, the DNA content per chromosome set is supposedly constant for any one species. This was first suggested by Boivin, Vendrely and Vendrely (1948), Mirsky and Ris (1949) and was later supported by numerous other investigations (Alfert and Swift, 1953; Swift, 1950). A second supporting evidence for this hypothesis lies in the general acceptance that, except for periods of gene replication, the low rate of turnover exhibited by deoxyribonucleic acid is indicative of high metabolic stability (Kihara, *et al.*,

1956; Smellie, 1955; Swick, *et al.*, 1956). Finally, such data, of course, tend to fit in with the general belief that DNA, as the genetic encoding material, must be maintained at a constant level and carefully conserved in interest of the genetic integrity of living organisms.

Although much support has been amassed in favor of the constancy hypothesis, the question may still be raised as to the absolute universality of this concept for all biological systems and for all physiological circumstances. Indeed, a considerable amount of data has been accumulated over recent years which necessitates a re-examination of this concept, at least in certain instances. Inconstancy has been reported in various developing and secretory tissues (Finamore and Volkin, 1958; Leuchtenberger and Schrader, 1952; Moore, 1957; Pelc, 1959; Rudkin and Corlette, 1957; Stich and Naylor, 1958, and others) and has allegedly been induced by cold treatment (LaCour, *et al.*, 1956; Stich and Naylor, 1958), hormonal changes (Common, *et al.*, 1951; Lowe, 1955; McShan, *et al.*, 1950), etc. It is quite apparent that in many cases where instability in the metabolic activity of DNA has been reported, such behavior has been directly related to concomitant variations in cellular proliferation and, therefore, to DNA synthesis involved in chromosomal replication. Such data, of course, do not stand in refutation of the constancy concept. However, at least some of the studies referred to here (*e.g.*, Finamore and Volkin, 1958; Moore, 1957; Pelc, 1959; Stich and Naylor, 1958) apparently are not resolvable on this basis and, indeed, seemingly stand in contradiction to the original context of the constancy hypothesis.

It is not the principal intent in this study to present a comprehensive review of the literature which stands in contradiction to the constancy hypothesis, as this has been done by various other investigators (Brachet, 1957; Govaert, 1957; Moore, 1957). Instead, chief concern will rest with an approach to the causal analysis of factors which may possibly underlie *certain* cases of DNA instability and the possible functional significance of such reported phenomena in nucleic acid biology.

In this connection, reference should be made to the extra DNA known to occur in the cytoplasm of many yolk-laden animal eggs (Fraenkel-Conrat, *et al.*, 1952; Hoff-Jorgensen and Zeuthen, 1952; Solomon, 1957). It is thought that this material may represent a general storage reservoir which functions to support DNA synthesis during early embryonic development (Hotchkiss, 1955; Solomon, 1957). In reference to this "cytoplasmic DNA", Solomon (1957, p. 589) states, "The nucleic acids (or similar highly polymerized compounds) may be a convenient means of storing nucleic acid precursors, which could be obtained by degradation when required by the embryo." Commenting on the same point, Hotchkiss (1955) suggests that this substance may very likely exist as a genetically nonspecific precursory form of DNA.

Of interest here is the recent work of Foster and Stern (1958, 1959)

which indicates that extra sources of DNA are exploited to support DNA replication in developing pollen of lily anthers. They have shown that the breakdown products from DNA of certain neighboring tissues serve as a source of deoxynucleosides for DNA synthesis in the microsporocytes and microspores. These findings stress the possible worth of "extra sources" of DNA in providing prescursory substances for nucleic acid synthesis.

Attention should also be directed to studies on the "puffs" of the salivary gland chromosomes of certain species (Beermann, 1959; Rudkin and Corlette, 1957; Stich and Naylor, 1958, and others). Puff formation seems to be quite specific for particular chromosomal segments, varying characteristically with different cell types and developmental stages. As noted by Beermann (1959), such behavior perhaps reflects specific genic activity. Of special interest here is the localized build-up of DNA known to occur during puff formation in certain species. As shown by Stich and Naylor (1958), certain puffs in *Glyptotendipes* (Chironomidae) show as much as an 8-fold increase in DNA content at certain developmental periods. Also, it is apparent that the DNA content of a particular puff varies independently from other segments of the same chromosome. It seems possible that in some instances *specific fractions* of DNA (or high molecular weight polydeoxyribonucleotides) may form at certain chromosomal sites and, upon being released, perhaps serve in transmitting genetic information, similar to messenger RNA. As DNA does not commonly occur in cellular cytoplasm, such polydeoxyribonucleotides would perhaps function in the intranuclear synthesis of certain specific macromolecules, presumably by playing an intermediate role in information transfer from specific genic loci to specific end-products of genic action.

It is acknowledged that the suggestions noted above are largely tentative, and that the pertinence of such ideas to nucleic acid biology cannot be fully determined at present.

Reference

Alfert, M. and H. Swift. 1953. Nuclear DNA constancy: A critical evaluation of some exceptions reported by Lison and Pasteels. Exptl. Cell. Res., 5: 455-460.

Beadle, G. W. 1957. The role of the nucleus in heredity. *In* The Chemical Basis of Heredity, edited by W. D. McElroy and B. Glass. Johns Hopkins Press, Baltimore, pp. 3-22.

Beermann, W. 1959. Chromosomal differentiation in insects. *In* Developmental Cytology, edited by D. Rudnick. Ronald Press, New York, pp. 83-103.

Birge, W. J., G. W. Salisbury, L. de la Torre, and J. R. Lodge. 1960. Diminution of the deoxyribonucleic acid content of bovine spermatozoa during *in vitro* storage. Anat. Rec., 137: 340.

Birge, W. J., G. Anklesaria and F. D. Tibbitts. 1961. Differential response of DNA of fresh and stored bovine spermatozoa to Feulgen (HCl) hydrolysis. Trans. Ill. Acad. Sci., 54: 107-111.

Boivin, A., R. Vendrely, and C. Vendrely. 1948. L'acide desoxyribonucleique du noyau cellulaire, depositaire des characteres hereditaires; arguments d'ordre analytique. Compt. Rend. Acad. Sci., 226: 1061-1063.

Brachet, J. 1955. The biological role of the pentose nucleic acids. *In* The Nucleic Acids. Vol. II, edited by E. Chargaff and J. N. Davidson. Academic Press, New York, pp. 475-519.

BRACHET, J. 1957. Biochemical Cytology. Academic Press, Inc., New York, 1st Ed.

COMMON, R. H., D. G. CHAPMAN, and W. A. MAW. 1951. The effect of gonadal hormones on the nucleic acid content of liver and serum in the immature pullet and the difference between the nucleic acid content of livers of sexually mature pullets and cockerels. Can. J. Zool., 29: 265-275.

FINAMORE, F. J. and E. VOLKIN. 1958. Nucleotide and nucleic acid metabolism in developing amphibian embryos. II. Composition and metabolic activity of ovarian egg nucleic acids. Exptl. Cell. Res., 15: 405-411.

FOSTER, T. S. and H. STERN. 1958. Soluble deoxyribosidic compounds in relation to duplication of deoxyribonucleic acid. Science, 128: 653-654.

FRAENKEL-CONRAT, H., N. S. SNELL and E. D. DUCAY. 1952. Avidin I. Isolation and characterization of the protein and nucleic acid. Arch. Biochem. Biophys., 39: 80-96.

GOVAERT, J. 1957. Etude quantitative de la teneur en acide desoxyribonucleique des noyaux des cellules somatiques et germinatives chez *Fasciola hepatica*. Arch. Biol. (Liege), 68: 165-200.

HOFF-JORGENSEN, E. and E. ZEUTHEN. 1952. Evidence of cytoplasmic deoxyribosides in the frog's egg. Nature, 169: 245-246.

HOTCHKISS, R. D. 1955. The biological role of the deoxypentose nucleic acids. *In* The Nucleic Acids, Vol. II, edited by E. Chargaff and J. N. Davidson. Academic Press, New York, pp. 435-473.

KIHARA, H. K., N. AMANO, and A. SIBATANI. 1956. Stability of deoxypentose acid in growing and non-growing livers of young rats. Biochem. et Biophys. Acta, 21: 489-499.

LACOUR, L. F., E. M. DEELY, and J. CHEYEN. 1956. Variations in the amount of Feulgen stain in nuclei of plants grown at different temperatures. Nature, 177: 272.

LEUCHTENBERGER, C., and F. SCHRADER. 1952. Variation in the amounts of desoxyribose nucleic acid (DNA) in cells of the same tissue and its correlation with secretory function. Proc. Natl. Acad. Sci., 38: 99-105.

LOWE, C. V. 1955. Effects of cortisone on nucleic acid composition of rat liver. J. Natl. Cancer Inst., 15: 1619-1622.

MCSHAN, W. H., J. S. DAVIS, S. W. SOUKUP, and R. K. MEYER. 1950. The nucleic acid content and succinic dehydrogenase activity of stimulated pigeon crop gland tissue. Endocrinology, 47: 274-280.

MIRSKY, A. W. and V. ALLFREY. 1957. The role of the cell nucleus in development. *In* The Chemical Basis of Development, edited by W. D. McElroy and B. Glass. Johns Hopkins Press, Baltimore, pp. 94-102.

MIRSKY, A. and H. RIS. 1949. Variable and constant components of chromosomes. Nature, 163: 666-667.

MOORE, B. C. 1957. DNA in diploid and androgenetic amphibian hybrids. J. Morph., 101: 227-274.

PELC, S. R. 1959. Metabolic activity of DNA as shown by autoradiographs. Lab. Invest., 8: 225-236.

RUDKINS, G. T. and S. L. CORLETTE. 1957. Disproportionate synthesis of DNA in a polytene chromosome region. Proc. Natl. Acad. Sci., 43: 964-968.

SALISBURY, G. W., W. J. BIRGE, L. DE LA TORRE, and J. R. LODGE. 1960. Decrease in nuclear Feulgen-positive material (DNA) upon aging in *in vitro* storage of bovine spermatozoa. J. Biophysical and Biochemical Cytology, 10: 353-359.

SMELLIE, R. M. S. 1955. The metabolism of the nucleic acids. *In* The Nucleic Acids, Vol. II, edited by E. Chargaff and J. N. Davidson. Academic Press, New York, pp. 393-434.

SOLOMON, J. B. 1957. Nucleic acid content of early chick embryos and the hen's egg. Biochimica et Biophysica Acta, 24: 584-591.

SPIEGELMAN, S. 1957. Nucleic acids and the synthesis of proteins. *In* The Chemical Basis of Heredity, edited by W. D. McElroy and B. Glass. Johns Hopkins Press, Baltimore, pp. 232-267.

STERN, H. 1959. Mitosis and metabolic organization. The Botanical Review, 25: 351-384.

STICH, H. F. and J. M. NAYLOR. 1958. Variation of desoxyribonucleic acid content of specific chromosome regions. Exptl. Cell. Res., 14: 442-445.

SWICK, R. W., A. L. KOCH, and D. R. HANDA. 1956. The measurement of nucleic acid turnover in rat liver. Arch. Biochem. and Biophys., 63: 226-242.

SWIFT, H. 1950. The desoxyribose nucleic acid content of animal nuclei. Physiol. Zool., 23: 169-198.

WATSON, J. D. and F. H. C. CRICK. 1953. Molecular structure of nucleic acids. Nature, 171: 737-738.