# REVIEW

# GENETIC CONSTITUTION AND THE CAUSATION OF DISEASE

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One of the greatest mysteries of biological science has been the self governed ability of an organism to grow, differentiate and reproduce-an ability which above everything distinguishes all living beings, from the non-living matter. This differentiating characteristic is now being ascribed to the content of Desoxyribosenucleic acid (DNA) in the nucleus of the fertilized egg which is inherited from its parents. Watson and Crick in 1953[8] first formulated the chemical structure of DNA, the correctness of which has subsequently been proved.[9]

According to the present day knowledge, DNA molecule is composed of two long parallel chains composed of alternating phosphate and sugar groups. The sugar in the DNA molecule is desoxyribose and this is united with a molecule of a nitrogenous base. The corresponding nitrogenous bases on the two parallel chains are linked together by a hydrogen bond and constitute cross linkages between the two chains as shown in Fig. I. There are only four nitrogenous bases (Adenine, Guanine, Thymine and Cytosine) in the DNA molecule and their chemical configuration is such that adenine always pairs with thymine and guanine always pairs with cytosine to constitute the cross linkages referred to above. If the nitrogenous bases are depicted only by their initials (A, G., T and C respectively), the possible types of pairs can be only four viz AT, TA, GC and CG. These four pairs occur in a definite sequence on the long chain of DNA molecule and each unit of this sequence constitutes a gene. Since innumerable patterns of sequence can be had from these four pairs, therefore a corresponding number of genes can also be had on the DNA molecule, each gene representing a single function. All this genetic pattern is contained in the chromosomes of the nucleus.

DNA molecule has got a unique property that the hydrogen bond (indicated by dotted line, Fig. I) between the two nitrogenous bases can disappear resulting in longitudinal splitting of the DNA molecule[3] and thus two halves of the DNA molecule each having a single chain constituted by phosphate and sugar radicles and the nitrogenous bases attached to sugar in the same sequence as in the original DNA molecule. Since each nitrogenous base can combine with only one of the other three nitrogenous bases, each half of the split DNA molecule reconstitutes the other half from the common pool of phosphate, desoxyribose and nitrogenous base radicals resulting in two new

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Received for publication on 5-5-1965.

molecules of DNA resembling the original molecule in every respect. This process precedes every mitotic division of the cell and is responsible for growth of the organism.

In almost the same way as the DNA molecule duplicates itself, it also gives rise to RNA molecule. RNA[7] is a single chain molecule having alternate phosphate and sugar radicals. The sugar in RNA is ribose and out of the nitrogenous bases, it contains uracil in place of thymine. RNA molecule is produced inside the nucleus. Since the chemical configuration of DNA and RNA molecules is very much similar, except for the differences enumerated above, RNA molecule is assigned the role of a messanger which forms on the DNA molecule and carries the information from inside the nucleus out into the cytoplasm. In the cytoplasm RNA molecule acts as a model on which amino acids arrange themselves in a sequence determined by the RNA code, and lead to the

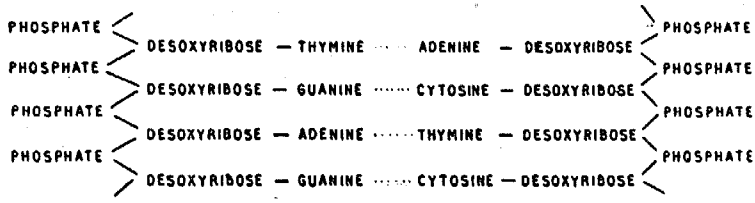


FIG. 1. A SEGMENT OF DNA MOLECULE

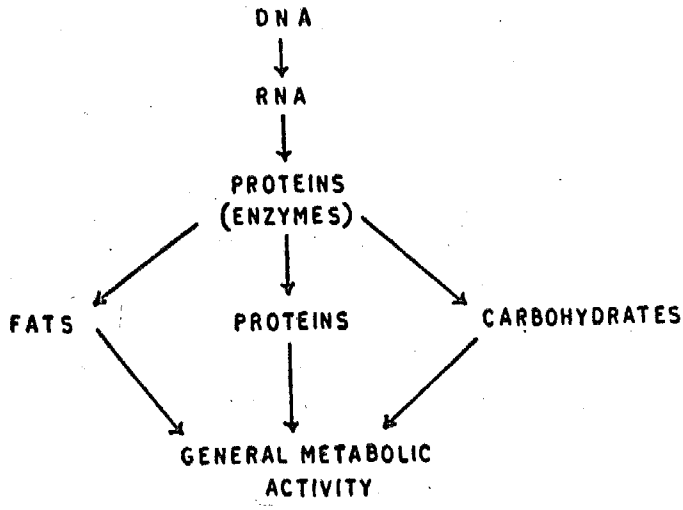


FIG. 2

formation of proteins[7]. These proteins are believed to be enzymic in nature and thus each gene gives rise to one enzyme[7] with its specific functions. The other genes also give rise to their respective enzymes with their own specific functions. These enzymes act on the substrates derived from the metabolic pool of the organism and several of these enzymes act at different stage of metabolic processes leading to chain reactions which result in the formation or breakdown of complex compounds. At each stage of metabolic processes there are activator enzymes as well as inhibitors which control the speed of the reaction. These processes are further controlled by the presence of certain co-enzymes as well as metallic ions. Although the actual mechanisms are far complex and intricate than the concept outlined above and there are many other subsidiary processes, yet this is in general, the main line of activity (Fig. 2) several aspects of which have already been proved.

Sometimes during the process of duplication of DNA molceule, there occurs a mistake i. e. one of the nitrogenous bases gets attached at the wrong place or the nitrogenous base does not belong to one of the four bases normally present, but it is some analogue. This results in an altered segment of the new DNA molecule and thus an abnormal gene which gives rise to its own pattern of metabolic activity. This process, commonly known as mutation[7] is occuring at random during the normal course, but sometimes under the influence of external agents (like radiations) mutations are produced much more in frequency.

Some of the mutations alter the metabolism of the organism in a favourable way making it more suited to the environment (basis for evolution) but others are definitely harmful and responsible for the production of disease.

A fully developed organism has to perform two main functions. Firstly, it has to undertake the routine metabolic activity to maintain itself and replenish older molecules with newer ones in order to keep up the optimum functional efficiency of the units they constitute. A defect in one of the genes which gives rise to deficiency of a particular enzyme will produce a block in the metabolic pathway. This results in the absence of the end product of that particular metabolic pathway and in addition it gives rise to the presence of unusual chemical substances resulting from the metabolic block and by alternative metabolic pathways. These abnormal metabolites may thereby become responsible for producing pathological changes in tissues and the clinical signs and symptoms characteristic of well recognised disease entities. For example diseases like Alkaptonuria[4] and Phenylketonuria[5] have already been accepted based on such mechanisms, while others, like xeroderma pigmentosum[1] are being worked out on these lines. The second main function of the organism is to protect itself from or adapt itself to the environmental conditions like physico-chemical changes, infections and allergenic substances. These environmental conditions keep on changing and posing new hazards for the organism which normally has the potentiality to protect itself in various ways e. g. by formation of antibodies against infections, by changes in peripheral circulation to the varying environmental temperature and by stimulation of adrenal cortex in allergy. Protection from the damaging effects of sunlight is affor-

ded by the production of melanin and hyperkeratinization, though the degree to which an individual can protect himself from these environmental agents is always limited. The genetic pattern of every individual being different from all other individuals (except in the case of identical twins) the capacity of every individual to protect himself from environmental agents also varies. Some individuals who completely fail to produce antibodies (congenital agammaglobulinaemia) succumb easily and repeatedly to infections Similarly individuals who have got defective vascular pattern show the manifestations like chillblains and Raynaud's phenomenon. Evidence of individual variations in protective capacity is further noticed in epidemics during which most of the individuals succumb to the infection, but there are always a few who possibly have got a better resistance (or greater capacity to produce protective antibodies) and thus escape. Even in the case of allergic sensitization, the essential pre-requisite is that the individual must have the potentiality to get sensitized, since all persons exposed to the same allergen need not get sensitized. Thus even in diseases where an external agent seems to play a dominant role, the factor of individual susceptibility also plays an important part.

The same could apply to diseases of obscure aetiology. In some of them like the collagen disorders, there is evidence of a metabolic block in the phenylalanine and Tyrosine metabolism (Nishimura et. al. 1958[6] and Grupper et. al.1962[2]) based on an enzymic deficiency. In others like malignant tumours too there is speculation of mutations in certain groups of cells which start uncontrolled cell proliferation. Even in the rest of the diseases, the factors of individual susceptibility and familial transmission are too evident to ignore.

As explained earlier, the factor of 'Individual susceptibility' depends upon genetic constitution of an individual and is determined by the potentialities as well as limitations of the organism to perform certain functions in order to maintain itself, grow and reproduce its kind and to protect or adapt itself to the ever changing environmental conditions. It has however to be realised that an organism may harbour a defect in its constitution, but it manifests only when a demand is made on that particular function. It thus follows that if the defect involves a routine metabolic function, it will be manifest early as in alkaptonuria but on the other hand if the defect involves one of the protective mechanisms, such as formation of protective antibodies, it will consequently manifest only when there is a demand on the individual e. g. on exposure to infection. Similarly, the individual may have a susceptibility to light eruptions, but it will not be manifest unless the individual is exposed to light. Further still, the defect may only be partial in as much as the individual may not be able to cope up with increased demands. This hypothesis is used to explain the special localisation of psoriasis lesions on the extensor aspect of joints, because these are the sites which are subjected to greater friction and hence greater demand for keratinization. The same factor may be responsible for Koebner's phenomenon seen in psoriasis.

Such examples can therefore be multiplied, though the crux of discussion remains that the basis of every disease lies within the organism (the factor of individual suscep-

tibility) which consequently is based on the genetic constitution of the individual as inherited or acquired later on by mutations. The role of the environment is only to make it evident sooner or later in the life of the individual (Fig. 3).

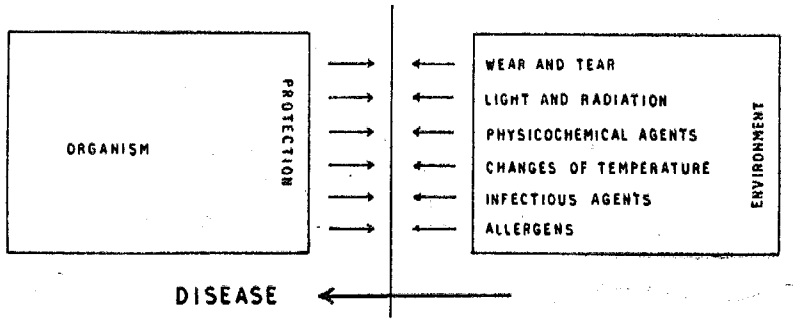


FIG. 3

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