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Sparing Genes for Further Evolution

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The first step in biological evolution, according to the classical concept, was the ability of an organic entity, the gene, to duplicate itself by utilizing available inorganic molecules which themselves were incapable of reproduction. The next step was the acquisition by the gene of the property of catalyzing the production of a substance other than itself to be utilized as its host. In this way an aggregate of genes, each responsible for a specific reaction, could give rise to more complex structures. The manner of development of a simple organism would then depend upon the actions of the genes which it possessed. In this sense a gene which catalyzes a reaction which is necessary for an organism may be defined as an essential gene. It is this type, the essential gene, which has been considered to be of major significance in progressive evolution. In contrast to this widely accepted viewpoint, it is the intention of the present paper to show how the real materials for further evolution may be genes of another type, those which have lost their primary catalytic function while retaining their primary reproductive function and become neutral genes. These neutral genes have been spared from their essential roles by the taking over of their previous primary functions by the genes of other species. A neutral gene will be defined as a gene which may participate in the production of a substance, but the substance in turn is not essential to the organism. Such a gene is not necessarily inactive.

According to the classical concept, the evolution of complex forms must have involved an increase in gene number. This is undoubtedly true up to a point, yet an extension of this hypothesis must eventually lead to an impasse. The physical size of the nucleus, if nothing else, must impose definite limitations to the accumulation of genes. The problem is, in fact, not unlike that of maintenance of the chromosome number within a species, a problem which necessitated the adoption of the mechanisms of mitosis and meiosis. Similarly a mechanism for holding the number of loci within the limits of cell size is seemingly necessary.

It is not an easy matter to evaluate the significance of the increase in gene number which has occurred during the evolution of a species. It is sufficient here to say that ways in which such an increase may have come about are known. Yet amphidiploidy, for example, which has undoubtedly been a potent force in the evolution of certain plant species, is by no means universal.

The existence of a large number of gene loci in the individuals of a particular species may be taken for granted. But the problem which confronts us is not so much the absolute number of genes within a

species, as a comparison between different species. Here, on the basis of an hypothesis that a correspondence exists between gene number and the complexity of an organism, we might expect that a complex species such as man would be very close to the limit with respect to gene number, whereas simple organisms would have considerable leeway. Between the two extremes all gradations should exist.

Although the above hypothesis is formally logical, there is no evidence to indicate that such a state of affairs is the rule in nature. There is, on the contrary, a lack of high correlation between chromatin content of the nucleus and complexity of species. Evolutionary progress apparently does not depend on an increase in gene number.

The question then arises, how can an organism acquire new functions without an increase in gene number? Several possibilities present themselves. First of all, by crossing, different alleles are brought together so that every possible combination may be tried out. In this manner hybridization, involving groups which differ in a number of genes, followed by isolation, has undoubtedly been important in building up groups which we classify as species. But Mendelism creates no new variations. Nearly all of the observed differences between related individuals are due to genetic segregation of variations which occurred long ago. The low mutation rate necessary to maintain variability under Mendelism allows heredity to be an essentially conservative agent, but new variations must in the last analysis come from mutation.

Secondly, in terms of gene action, the acquisition of new functions could be of two sorts. Either essential genes might mutate to new forms in such a manner as to acquire new functions in addition to the old, or neutral genes mutate to acquire new essential functions. The former would require of the essential gene a type of change for which experimental evidence is lacking; the latter requires an accounting for the origin of neutral genes. First, however, the modern view concerning the nature of gene action will be briefly reviewed in so far as it impinges upon the matter of sparing genes.

THE SPECIFICITY OF THE GENE

Consideration of examples such as tyrosine-phenylalanine metabolism in man, pigmentation in animals, eye pigments in insects, flower colors, and a number of others has led to the idea that there exists for most genes a one-to-one relation between gene and specific reaction (Beadle, 1945a). Beadle and Tatum (1941) were able to establish in *Neurospora* the existence of a number of gene-controlled steps in specific biochemical syntheses which further substantiates this hypothesis.

The findings have been extended by various members of the Stanford group until a number of cases are quite well understood. In arginine synthesis, for example, they found that the inactivation of any one of seven non-allelic genes prevented the synthesis from taking place. On the one-to-one reaction hypothesis, at least seven differ-

ent catalyzed steps are involved in the synthesis. Of the steps identi-
fied chemically each has proven to be controlled by a single gene
A mutated gene, which blocks the synthesis of a compound of known
nutritional significance, as found in *Neurospora,* is a defective gene
in terms of biochemical synthesis. On a complete medium, in which
the substances is always provided, this gene, as well as others in
the chain, would be neutral and available for further evolution.

INACTIVATION OF GENES

There is considerable evidence to suggest that observed gene mu-
tations are in the nature of inactivations. For example, Stern (1943)
reported on dosage effects in *Drosophila* in which an increase from
one to two and from two to three doses of a mutant recessive allele
produces a phenotype more nearly approaching the normal. Also,
it has been found that agents which are effective in producing muta-
tions are harmful and produce their greatest effect just short of kill-
ing the individual. Dominant mutations are rare and many of them,
upon close study have been shown to involve chromosomal changes.
In *Drosophila,* Bar and Star are duplications, Notopleural and a
number of Minutes are deficiencies, and Curley and Plum are associ-
ated with inversions. Moreover each of these is detrimental to the
organism.

In the light of this evidence, the chance of the occurrence of a
mutation which will benefit an organism must be extremely slight
so long as that particular gene is responsible for a reaction which
is essential to the organism. A species is faced with the problem of
either acquiring extra gene loci which are not restricted from a
standpoint of their immediate usefulness or in sparing existent genes
from their essential roles. Neutral genes bridge this gap.

THE SIGNIFICANCE OF NEUTRAL GENES

The following is offered as a theoretical explanation to account
for the origin and significance of neutral genes. A chain of chemical
reactions, each step governed by one gene, results in the production
of a substance which we may designate as S and which is essential
for growth. An organism possessing the ability to synthesize S will
grow in an environment deficient in S so long as each gene in the
chain-retains its heterocatalytic property. Under such conditions a
mutation in any one of the genes concerned would be harmful or
lethal, depending on the importance of S to the life of the individual.
The probability of a beneficial mutation occurring in any of these
essential genes would be virtually zero. If S, now, were to be provided,
as the product of gene action of another species, the genes respon-
sible for S would immediately lose their essential nature and become
neutral genes. So long as the organism finds itself in an environ-
ment abundant in S, there would be no selection for or against neu-

tral genes, which, by subsequent mutation, could acquire new functions. The task of synthesizing S would thus be relegated to the genes of species upon which the organism feeds.

Clearly the difference between an essential gene and a neutral gene does not hinge upon any specific attribute of the gene per ce. It is entirely a matter of whether the product of gene action is or is not required by its host. The neutral gene is therefore a spare gene and is available as potential material for further evolution.

Differences in the nutritional requirements of different individuals within a species are known. For example, Gowen (1936) fed rats on a low vitamin D, high calcium diet and found that between the separate inbred lines on the deficient diet there were distinct differences in length of life. The genetic differences between strains is ascribable to the action of essential genes as shown by the fact that heredity accounted for over half of the residual variation. Yet in the control group on a normal diet, these genes were not essential.

Hormones differ from vitamins in that they are normally synthesized by the organism. The deficiency of anterior pituitary hormones in the dwarf mouse may be compensated for by implanting the glands of normal mice (Smith and Macdowell, 1936). Mice so treated grow to the same size as normal individuals of the same strain, and the males may become fertile. In this way the provision of a specific hormone has compensated for the loss of a specific gene product.

In *Neurospora* there are a number of examples in which an intraspecific symbiosis exists between different strains. For example, Horowitz et al (1945) found that in two strains, each requiring choline, in the presence of a small amount of choline, one excreted a substance into the medium which was not choline, but which replaced choline in promoting growth of the second mutant.

The nutritional requirements of a number of higher animals have been determined in a general way by studying the effects of deficiencies in specific dietary components or by analyses of feeding stuffs which produce normal growth and development. For example, if a particular amino acid is withheld from the diet, and protein synthesis is inhibited, then that amino acid is considered as essential. Rose (1938) has shown that in the rat there are ten such amino acids, which are either not synthesized rapidly enough for the animal's needs, or not at all. Nine of these are normally synthesized by *Neurospora* (Horowitz et al, 1945). If we make the assumption that the usual diet of an organism in its natural habitat contains at least its minimal requirements, we may define a complex organism as one having complex nutritional requirements.

Not only do individuals differ in their nutritional requirements, but species also differ. For example, primates and guinea pigs require vitamin C in their diet whereas other animals studied do not. Man's vitamin C is synthesized for him by plants and animals, and

so long as the diet is complete he suffers no ill effects. But loss during the course of evolution of the ability to synthesize ascorbic acid need not have been a disadvantage. Indeed, the process responsible for such a loss would confer a distinct advantage to the species. For what then was to prevent the spared genes from mutating and initiating new characters for further evolutionary progress of the species or toward a new species?

The selection of a balanced diet is by no means a prerogative of man, although it must be conceded he may often have an advantage in this regard. Many animals have an uncanny ability to seek out the nutrients which they lack. It is a common observation that anemia in young pigs does not occur so long as the young animal is not prevented from eating soil and thus obtaining its iron. Cattle which lack calcium and phosphorus will chew bones. Richter, by extirpation of various endorcrine glands, found that rats could counteract the results of such severe interference by selecting for themselves the necessary dietary components (Richter, 1945). When the adrenals were removed, the rats maintained their sodium level by taking salt; when the parathyroid glands were removed, they took more calcium. Similarly, if thiamin was withheld from the diet of normal rats, proteins were chosen in preference to carbohydrates. When thiamin was added, the rats' preference shifted accordingly. Richter was able to demonstrate also that cutting of the taste nerves resulted in the loss of ability to make beneficial choices. On the basis of this evidence, it is apparent that an animal possessing the ability to seek its requirements may survive under adverse circumstances even after it lacks certain synthetic abilities. Conceivably, the adptation of taste choice could have accelerated the process of evolution in certain forms by protecting individuals with neutral genes, the materials for further evolution, during periods of nutritional scarcities.

The lack of correspondence between complexity of organisms and their respective chromosome numbers presents no difficulty when this viewpoint is adopted. An end product does not necessitate possession by the organism of all the genes involved in the total synthesis, and loci are spared for further evolution. Since *Drosophila* supplements the activity of its own genes with the activity of yeast genes, the existence of apparently frivolous genes, such as those which place bristles here and there, need not be surprising. If, as under the classical concept, a gene were necessary for each vital process, the relationship between gene activity and vital phenomena would impose severe limitations to such energy wastage.

It has been argued that genes which are of no use to the organism will be lost eventually. This is improbable since the reproductive capacity of the gene must be of very special organization requiring high fixed energy and as such could not be easily lost. Genetically inert portions of the chromosome, the heterochromatic regions, therefore may contain neutral genes. The rate at which such genes will be lost, if indeed they are eliminated at all, would not be expected

to exceed the rate at which they could acquire new micro-evolution-ary significance. On the macro-evolutionary level many non-adaptive characters are known which have not been eliminated in spite of natural selection.

FAILURE OF CHROMOSOMES TO PAIR

Failure of chromosomes to pair in crosses of *Sciara* species, despite the absence of major inversions or translocations has been reported by Metz and Lawrence (1928). A possible interpretation of such results is offered. In one isolated population genes may be spared in the manner which has been described. These neutral genes, in turn, acquired new essential functions. In another group, not exposed to the same nutritional advantages, the same genes remain essential and are thus barred from mutation to new essential functions. The accumulation of such genetic diversities will eventually lead to failure of chromosome pairing in the hybrid due to lack of homology of the genes. Development of incompatabilities between strains, and finally species isolation through sterility, could arise in this manner without the necessity for mass inversions of a chromosome.

THE ORIGIN OF DOMINANCE

A gene which performs a function which is essential to the individual may be dominant, and a mutation to a less active form would give rise to a recessive gene. If the gene locus is spared from its immediate purpose, a neutral gene would result. If, now, the neutral gene should acquire a new essential function, which might be in a totally different reaction chain, its former dominance relationship would have no bearing. In terms of gene action, it becomes a new dominant gene even though it may have been recessive in its former reaction chain. Any additional mutations in this new organization would again be likely to be deleterious and recessive.

THE INTEREPENDENCE OF SPECIES

An interdependence between species on an ascending scale is the rule among living things. Thus alfalfa, by means of its gene complex, can utilize the nitrogen provided as a result of gene action in nitrifying bacteria; ruminants, aided by the organisms in the paunch, synthesize proteins from alfalfa; carnivora carry the process one step further. Return to the soil of animal proteins and their decomposition by micro-organisms completes the cycle. Plant genes catalyze anew the inorganic compounds into organic materials.

In the course of evolution, according to this theory, an increase in complexity of plants as a result of mutations of spare genes, followed the advent of soil by breakdown of rock and addition of organic materials. This in turn altered the nutritional environment

of herbivora and finally carnivora. By such a process, genes which were once essential would continually be spared as potential materials for further evolution.

If new synthetic processes were merely added to existent ones, no such preying of one species upon another should exist. There would be merely a competition for existing substances. Environment, in addition to determining which genotypes will survive, must be thought of as itself being influenced by genes. An historic change in the nutritional environment of an animal, for example, is the result of genotypic changes in the species of plants or animals upon which it depends.

Man living on a highly complex and varied diet and clothing himself with products of animal and plant life is probably the most parasitic of all animals. Yet during the process he may have been spared the genes which formed the raw materials for his advancement in the evolutionary scale.

ACKNOWLEDGMENT

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