WHAT IS A GENE?

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INTRODUCTION

In this paper, Demerec sums up what is known about the gene in the early 1930s. He begins by noting:

Our present information about genes is largely obtained by indirect, genetic methods. By studying the transmission of hereditary characteristics from one generation to another, genes were established as the mechanism instrumental in effecting this transmission; by following the inheritance of groups of characters, genes were placed in chromosomes and their location determined in respect to one another; by investigating different combinations of characters, evidence was obtained on the interaction of genes. The results of these indirect studies form the basis of our present gene concept. Studies of the effect of x-ray radiation and of unstable genes are the best means now available for broadening this concept.

Were we to attempt to define the term "gene," we could state that it is a minute organic particle, capable of reproduction, located in a chromosome and responsible for the transmission of a hereditary characteristic. This definition includes only statements of fact for which there is sufficient experimental evidence to prove them beyond reasonable doubt. In this presentation we shall endeavor to analyze the above definition, to discuss several directions in which this definition could be extended, and to present the concept of the gene which is used as our working hypothesis.

That genes control phenotypes and are carried on chromosomes are taken as given. To Demerec, the real question is, "what is the physical nature of the gene?" How big is it, what is it made of, is it a single molecule or a multi-molecular structure? Demerec believes that the available evidence suggests that genes are uni-molecular, and he notes:

If a gene is a complex organic molecule it would be expected to be similar in composition to other complex molecules, viz. molecular groups constituting this molecule (whatever these groups may be) would he arranged in chains and side chains. Figure 4 may serve as a crude diagrammatic example of what the structure of the gene molecule may look like.

Amazingly, Figure 4 offers the "tentative structure of thymus nucleic acid" – DNA! But Demerec is using this only as an example of a complex molecular structure, not as the actual chemical structure of a gene:

The diagram is not intended to give any implication as to the number, the type, or the arrangement of the molecules in a gene group. Its purpose is to illustrate the molecular structure of a complex organic molecule.

This drawing was produced twenty years before the correct Watson-Crick model of DNA structure had been developed and therefore Demerec's DNA is in a "tetranucleotide" form, which would not allow the encoding of genetic information. Still, in this early paper Demerec is tantalizingly close to the actual chemical nature of the gene.

He summarizes the present conception of the gene as:

We visualize genes as single organic molecules. The gene string, then, gives us an interesting picture of a group of molecules held together by some unknown force in a string, each molecule possessing a power of self propagation, and each one individually and all of them together having an almost magic power of governing life processes of cells in which they are located, and therefore of governing life processes of the organism of which these cells are an integral part.

With the publication of Thomas Morgan's book, *The Theory of the Gene*, the fundamental mechanisms for the transmission of hereditary information was well established. Attention then began to shift to the chemical nature of the gene itself – an investigation that could not really get underway until Watson and Crick worked out the structure of DNA.

Robert J. Robbins Seattle, Washington 2002 Frontispiece



A Chimeral Delphinium Due to Gene Instability

The gene which controls color-development in the lavender delphinium is unstable and occasionally mutates to purple. This is the explanation of the variegated flowers produced by certain strains of the delphinium. In the plant shown above a change in the lavender-gene at a very early stage in development has resulted in a flower-spike that is half purple and half lavender. We have learned what is known about the genes by studying their variations, and the ever-sporting genes of the delphinium are especially well adapted to certain phases of these studies.

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WHAT IS A GENE?*

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WTIL A FEW YEARS AGO when the effect of x-rays on genes was discovered by Muller¹⁶ the methods available to geneticists for direct studies of gene properties were highly unsatisfactory. High stability of the great majority of genes and inability to produce changes experimentally on any of the known genes made direct approach to the study of the gene a very difficult if not an impossible problem. A relatively small group of the so-called unstable genes was, before the x-ray discoveries, and probably still is, one of the best media for study of gene properties. However, a limitation is imposed on the usefulness of this material, by reason of the fact that even the frequent changes occurring naturally in these genes cannot be controlled experimentally. Muller's discovery that x-rays can induce changes in genes opened up a wide field of new possibilities. The work in this field, however, as far as gene properties are concerned, is in its infancy. The results are still small although the potentialities are great.

Our present information about genes is largely obtained by indirect, genetic methods. By studying the transmission of hereditary characteristics from one generation to another, genes were established as the mechanism instrumental in effecting this transmission; by following the inheritance of groups of characters, genes were placed in chromosomes and their location determined in respect to one another; by investigating different combinations of characters, evidence was

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obtained on the interaction of genes. The results of these indirect studies form the basis of our present gene concept. Studies of the effect of x-ray radiation and of unstable genes are the best means now available for broadening this concept.

Were we to attempt to define the term "gene," we could state that it is a minute organic particle, capable of reproduction, located in a chromosome and responsible for the transmission of a hereditary characteristic. This definition includes only statements of fact for which there is sufficient experimental evidence to prove them beyond reasonable doubt. In this presentation we shall endeavor to analyze the above definition, to discuss several directions in which this definition could be extended, and to present the concept of the gene which is used as our working hypothesis.

GENE DEFINITION ANALYZED

Size of the gene — Estimates of the size of the gene of *Drosophila melanogaster* were made by several investigators using two different methods. Morgan,¹⁴ Muller,¹⁷ and Gowen and Gay,¹² determined the volume of the chromosomes, estimated the number of genes present in the chromosomes, and, by dividing the volume by the number of genes, obtained an estimate of the average volume of a gene. Blackwood^{1,2} estimated the diameter of a gene from a comparison of the total number of gene changes with the number of ions produced by a given x-ray dosage.

The three estimates made by Morgan gave the gene diameter as 20, 60, and 70 millimicrons; Muller's estimate gave about 50 millimicrons; Blackwood's 20; and Gowen-Gay's, about 10 millimicrons. All these estimates give the upper limit for the size of a gene.

There is also a little direct evidence indicating that the gene is an ultramicroscopic particle. Professor A. F. Huettner^{*} (unpublished material) found the following condition in early cleavage divisions of *Drosophila melanogaster* eggs when these were stained with Fulgen stain, effective only on chromatin. The resting nucleus is entirely clear. When the nucleus prepares itself for division, minute chromatin granules appear which increase in size and number, soon making the thread-like structure of long chromosomes evident. It is of interest in this case that in a definite position in the central region of the nucleus two small chromatin dots invariably appear which later develop into

^{*} The author is greatly indebted to Professor A. F. Huettner for the permission to use this material.

two small chromosomes and that the other granules are grouped in three sectors where, later, three large pairs of chromosomes appear. This indicates that gene strings of chromosomes have a definite position inside of a nucleus but that they are visible only when enough of the chromatin matrix has been evolved by them to increase their size to the point of visibility. The unavoidable conclusion from this finding is that the individual genes constituting the gene strings are ultramicroscopic.

The results of the work with x-rays indicate that the action of x-rays is direct, viz. that the change in the gene is the result of a hit by a photoelectron. The estimates just discussed put the maximum size of the gene within the range of the size of several large organic molecules. The effects observed in the x-ray work are more easily explained if a gene is pictured as a single organic molecule rather than as a small group of molecules. There is no evidence against the single molecule gene assumption.

Capacity of reproduction — Since every cell of an organism contains a full complement of genes, each gene must divide at every cell division. This self-propagating property of the gene is one of its important characteristics.

Little is known about the nature of gene reproduction. The evidence adduced by the author⁹ from the study of unstable genes, however, indicates that the gene reproduces by formation of a new gene next to the old one rather than by the division of the old gene. This type of reproduction would favor the supposition that a gene is a single molecule.

Location of genes — A great mass of genetic and cytological evidence is now available to show that genes are located in chromosomes. The same evidence indicates that genes are arranged in a linear order. Since the individual genes behave as independent units a gene-string can readily be compared to a string of beads, each bead of which is ultramicroscopic in size.

The genetic and cytological evidence shows that genes are arranged in a definite order and that they retain this order with great regularity. Each gene has its permanent *locus* on a gene string. The order of genes may be changed by various influences but these changes are an abnormal rather than a regular occurrence.

Figure 1 shows the chromosome group of *Drosophila melanogaster* and Figure 2 the genetic map of the X-chromosome. Distances between the loci of this map were determined by genetic methods. Cytological studies of Dobzhansky¹⁰ and Muller and Painter¹⁸ indicate that genetical distances between loci do not always correspond with the actual distances as they exist in chromosomes.

Carriers of the Genes

Figure 1. The four pairs of chromosomes of the fruit-fly have been more intensively studied than those of any other species. The genes are arranged in a definite order in the chromosomes, and by genetic analysis the relative positions of over two hundred genes have been determined in Drosophila. The "map" of one of these chromosomes, the X or sex-chromosome, is shown in Figure 2.

By changing its constitution a gene may attain several forms. Different forms of the same gene are called *allelomorphs*. Certain genes have a larger known number of different distinguishable gene forms than certain other genes. For example, for the gene located in the white locus of *Drosophila melanogaster*, at least eleven different allelomorphs are known, all of which affect the color of the eyes.

Transmission of hereditary characteristics — This property of the genes is the one through which the existence of genes was discovered. The study of the mode of transmission of hereditary characteristics gave the basis for the postulate that there exist mechanical particles responsible for this transmission. These particles were named genes.

We know today, however, that no single gene has the sole responsibility for the appearance of any one character. The final effect is produced through the interaction of the whole complement of genes, although certain genes may have a greater influence on the expression of certain characteristics than some other genes have.



A "Chromosome-Map"

Figure 2. This map shows the genes of Drosophila located in the X-chromosome, and arranged in the order in which genetic "charting" places them. The "yard stick" used in making these measurements is the relative frequency of crossing-over of the various genes.

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STABILITY OF THE GENE

What produces natural changes in genes is not known, but we know that these changes, called mutations, occur in nature continuously at a very low rate. X-rays and radium radiation increase the rate of mutations.

The experimental evidence shows that mutations occur with different frequency in different genes. The data of Stadler²³ on the frequency of mutations in seven genes of maize are a good illustration of this fact. (Table I). While gene *R* changed with frequencies of 492 times per million gametes, gene *Sh* changed with a frequency of 1.2, and, in the case of the gene *Wx*, no change was observed among more than one and one half million gametes. From the data of Morgan, Bridges, and Sturtevant¹⁵ on recurrent mutations found in *Drosophila melanogaster* it may be inferred that a condition similar to that observed in maize exists also in *Drosophila*.

Gene	Gametes tested	Number of mutations	Average per one million gametes
R	554,786	273	492
Ι	265,391	28	106
Pr	647,102	7	11
Su	1,678,736	4	2.4
Y	1,745,280	4	2.2
Sh	2,469,285	3	1.2
Wx	1,503,744	0	0

Table I. Stadler's data on the frequency of changes in seven genes of maize

In the group of so-called "unstable genes" changes occur with a rather high frequency. There is, however, no sharp division between the stable and unstable genes. Using the rate of change as a criterion, genes can be arranged in a continuous series in which the highly stable forms constitute one extreme and the highly unstable forms the other extreme. It is known, furthermore, that the rate of change in various genes may differ in different tissues or at different stages of the development of the organism. In case of *Delphinium ajacis*, for example, two unstable genes affecting the color of the flowers are known, viz. the unstable rose and the unstable lavender (Fig. 3 and Frontispiece). Both of these genes change to purple.

Purple spots on flowers, therefore, mark the cells which originated from the cell in which the change in the gene had occurred. The number of spots indicates the number of changes, and the size of the spots indicates the stage of the ontogeny when the change occurred. It was evident from Figure 3 that lavender flowers have small spots only, while rose flowers have spots varying in size from small up to large ones.



Two Types of Gene-Changes

Figure 3. Above are shown two flowers of the lavender strain. Each spot is formed by the mutation from lavender to purple of a single cell. The spots are all approximately the same size, showing that the change in the color-gene occurs only at a definite stage in development. Below are shown two flowers of the rose strain. Here the spots vary from tiny dots to half a petal in extent. It is evident that in this strain the change from rose to purple occurs at any time during the development of the flower. The chimeral (half-and-half) petals represent a mutation that occurred when the petal was in a very early stage of development and each tiny dot a mutation which occurred when the development of the flower was nearly completed.

Since small spots represent late changes and large spots early changes, the size of the spots indicates that the lavender gene is unstable only late in the development of the flower and that the rose gene is unstable during all the developmental stages of the flower. Moreover, plants with large purple sectors (Frontispiece), representing early embryonic changes, are frequent in the lavender line but they are rare in the rose line. The lavender gene, therefore, changes with a high frequency early and late in the ontogeny and is constant or changes with a low frequency at other stages. The observations indicate that the rose gene changes at a uniform rate throughout the whole life cycle.

In *Drosophila virilis*, also, unstable genes are known which change at a different rate at different stages of ontogeny. Reddish-I-alpha, for example, is unstable at the maturation division of heterozygous females only; miniature-3-alpha is unstable in somatic cells and in germinal tissues and miniature-3-gamma is unstable in somatic cells only. All these genes possess a high degree of stability at all other stages of ontogeny.

Changes occurring in the somatic cells are much easier to detect than changes occurring in the germ cells, since it is much simpler to observe a large number of somatic cells than to observe a large number of germ cells. Of the two genes, therefore, both changing at the same rate, one which changes in somatic cells might be considered unstable while the other one, changing in germ cells only, might be considered stable. A double flower of Delphinium, for example, has about two million epidermal cells on which color changes can be detected. A medium sized plant bears about one hundred flowers. Changes occurring in the epidermal cells of flowers at a rate as low as one in ten millions could readily be detected and a gene changing at such a rate would be considered unstable. A gene, however, changing with that rate in germ cells only, would be considered to be highly stable. Insuch a case, therefore, not the rate of change but the tissues in which this change occurs would be used as a criterion of stability. The R, I, Pr, Sn, Y, and Sh genes of maize, investigated by Stadler, would be considered unstable if they changed in somatic cells at the rate they change in germ cells, according to data of Table I.

It appears, therefore, that unstable genes differ from the stable ones only in the fact that they change with a relatively higher frequency and that, in the majority of cases, the change occurs in tissues where this change can be readily detected.

NATURE OF GENE CHANGES

The changes in genes cannot be observed directly. The only possible way of studying them is by studying the effect which the changed gene produces in a character. It has been found that a change in a gene at a certain locus produces a certain effect. Change in the wild type gene of yellow locus of *Drosophila* produces a gene which makes the body color yellow, change in the wild type gene of the miniature locus produces a gene which makes wings miniature, in the forked locus a gene which makes bristles forked.

In a few loci, however, through different changes in the same gene several different genes may result, each producing a different though similar effect. As it has been mentioned before, eleven gene forms (allelomorphs) are known in the white locus, each form being responsible for a different eye color. These can be arranged in a series as follows: red, coral, blood, cherry, apricot, eosin, ivory, tinged, buff, ecru, and white.

Changes in genes occur in both directions, from the wild-type to the mutant type and in the reverse direction from the mutant-type to the wildtype. Changes from the wild-type to the mutant-type appear to be more frequent. The evidence is ample that under the influence of x-ray radiation these changes are much more frequent than the changes in the opposite direction.

In the case of unstable genes the mutant gene is the one which is usually unstable and in the majority of the known cases the change occurs from the mutant to the wild-type with a higher frequency than the reverse change.

The rate of change in unstable genes is sufficiently high to be measured and therefore evidence is being accumulated from that source which can be used to make an inference as to the nature of the gene changes. This evidence suggests that changes in genes are chemical processes. It may be summarized as follows:

(1) The end product of the change is always the same. There are no intermediate forms. The unstable rose gene of *Delphinium* changes always into its wild type allelomorph, which is purple, and unstable lavender changes into its wild-type allelomorph which is also purple. The same condition exists in unstable genes of *Drosophila virilis* (Demerec)^{4,5,6} maize (Emerson),¹¹ Portulaca (Blakeslee),^{3a} Pharbitis (Imai),¹³ and of other plants.

(2) The change is not always a random process; it may be favored by certain tissues or even it may be limited to certain tissues, as shown in the previous discussion. In order that the change may take place a certain environment is apparently required and this requirement is fulfilled in certain tissues.

(3) Several genetic factors are known to stimulate the rate of change in certain unstable genes. This situation is best analyzed in case of the unstable miniature-3 gene of *Drosophila virilis* (Demerec)^{7,8} and is partially summarized in Table II. From this table it can be seen that factors *S*-1, *s*-2, *S*-3, and *S*-4 increase the rate of change in somatic cells and that factor *M* increases that rate in the germinal tissues. These factors, apparently, produce environmental conditions which favor the occurrence of the change.

Modifying	Rate of change of miniature-3 alpha in			
factor	Soma	Germinal tissues		
none	low	low		
S-1, s-2 S-3, S-4	high	low		
М	low	high		
M and S-1, s-2, S-3, S-4	high	high		

 TABLE II.
 Influence of Modifying Factors on the Rate of Change of the Unstable Miniature-3 Alpha Gene of Drosophila virilis.

The results of x-ray experiments, especially the discovery that changes produced in genes are reversible and that the x-rays produce the changes directly, favor the conception that changes in genes are chemical changes.

A WORKING HYPOTHESIS

It should be made clear that the present knowledge of the gene is inadequate for the formulation of a definite hypothesis about the nature of the gene. Any concept of the gene has to be temporary, and designed primarily not for the purpose of explaining the data now available but for use in planning experiments to test the validity of various assumptions. Assumptions which cannot be tested, or which are not being tested, have the tendency to hinder rather than to facilitate progress. The gene concept as presented here is the working hypothesis we are using in our investigations. The essential points of this hypothesis are either being tested by experiments now in progress or will be tested as soon as the physical facilities of our laboratory will permit.

PHYSICAL PICTURE OF A GENE

The experimental evidence indicates that genes are not larger than a particle containing a few complex organic molecules. This same evidence suggests that genes are probably uni-molecular structures.

In developing our working hypothesis, we shall assume, therefore, that genes are single, complex organic molecules. This assumption appears to be the more probable of the two and it is also the simpler of the two to use.

The assumption of the uni-molecular structure of the gene, however, is not the essential part of our hypothesis. Only a few insignificant changes would he required in the hypothesis to adapt it to the multi-molecular gene concept.

If a gene is a complex organic molecule it would be expected to be similar in composition to other complex molecules, viz. molecular groups constituting this molecule (whatever these groups may be) would he arranged in chains and side chains. Figure 4 may serve as a crude diagrammatic example of what the structure of the gene molecule may look like.

The diagram is not intended to give any implication as to the number, the type, or the arrangement of the molecules in a gene group. Its purpose is to illustrate the molecular structure of a complex organic molecule.

ALLELOMORPHS

It has been mentioned before that through different changes in the same gene several different genes (allelomorphs) may be formed.

The allelomorphs of the miniature locus of *Drosophila virilis* may he arranged into a two-dimensional series as follows:

mt-1
$$\bullet$$
 mt-3
mt-3
mt-3 alpha beta \bullet mt-2 \bullet mt-5 beta \bullet mt-4
alpha alpha

In the horizontal line, allelomorphs are arranged according to the size of the wings and in the vertical line according to the degree of stability (mt-3 and mt-5 allelomorphs being unstable). There is a much

closer connection between the allelomorphs of the two vertical groups than between the allelomorphs of the horizontal group, since a transformation of one allelomorph into another in the vertical groups occurs rather frequently and this transformation has never been observed for the allelomorphs of the horizontal group. This evidence suggests that changes producing different allelomorphs are independent of each other and indicates that they might arise by changes in different groups of a gene molecule.



Map of an Organic Molecule

Figure 4. Above is shown the tentative structure of thymus nucleic acid. The generalized formula is given in the center and simply shows the chemical constitution of the various groups. These each have a definite and complicated structure, as is shown in the detailed "maps" of four of the groups, adenine, guanine, cytosine and thymine. These groups also occur as separate molecules. The detailed map of the entire molecule would be an extremely complicated affair. This sketch is a sample of an extremely complex organic molecule which may serve as a crude diagrammatic picture of what the structure of the gene molecule may look like. Any variation in the constitution of any of the properties of the entire complex. Changes in one or more of the atoms making up gene molecules can be pictured as the basis of the mutations which, at varying rates, take place in many of the genes that have been studied in the laboratory.

There is a possibility to test this concept and experiments planned for this purpose are now under way. The procedure is as follows: white locus of *Drosophila melanogaster* has about eleven allelomorphs, four of which are red, eosin, apricot, and white. White can be obtained by a change from red as well as from eosin and apricot. Now, if it is true that by a change in a certain molecular group an eosin gene is produced, by an independent change in another group apricot is produced and that a change in still another group gives white, then whites obtained from red, eosin, and apricot should be different from each other in that a reversion from white obtained from red should give red, a reversion from white procured from eosin should give eosin, and that coming from apricot should give apricot as indicated below:

red	+	white	+	red
eosin	+	white	+	eosin
apricot	+	white	+	apricot

One fact in support of this contention is available in the results obtained by Timofeeff-Ressovsky.²⁴ By use of x-rays he produced several reversions in the white gene. In the only case in which the origin of the treated white was mentioned the white originated from eosin and reverted back into eosin. This process may be outlined as follows:

 $eosin \rightarrow white \rightarrow eosin$

THE NATURE OF GENE CHANGES

Where there are several allelomorphs known in the same locus they usually affect the same character, differing only slightly in the degree of their effect. This suggests that slight changes in the gene molecule are responsible for the occurrence of different allelomorphs.

If we examine changes produced by x-rays in different loci of *Drosophila melanogaster* (Patterson²⁰) it will be noted that out of 24 tested changes in the white locus, 20 were lethal and 4 were visible; out of 18 changes in the yellow locus, 16 were lethal and 2 visible; and out of 17 changes in the miniature locus, 15 were lethal and 2 were visible. It is evident from these data that only 14 per cent of changes observed in these loci gave allelomorphs which produced a visible effect and 86 per cent of changes acted as lethals, viz. eliminated all homozygous flies.

The question now arises: what are these lethals? The answer to that question is suggested in the results of work on deficiencies by Bridges. ³ It has been found that the absence or inactivation of a small region of a chromosome acts as a lethal similar to lethals observed in the loci mentioned above. This would indicate that either the observed lethals are due to deficiencies of a region of the chromosome or that they are eliminations (deficiencies) of a single gene. The second assumption seems more probable.

How a gene can be eliminated? The process of elimination could be conceived either as a direct destruction of the gene or as a loss of power of reproduction by the gene. The second process would be the simpler of the two and it may be expected to occur with a higher frequency.

According to this concept a gene molecule can stand but a very slight change. Any radical change eliminates the gene from the gene complex and the elimination of a single gene (with certain exceptions) has a lethal effect on the organism. This leads us to an important conclusion that a full complement of genes is required for the organism in order to live. The evidence is even available¹⁹ which indicates that a cell without a full complement of genes cannot function properly. Experiments are now under way to obtain more data on this point.

If a whole complement of genes is necessary for an organism to live or even for a cell to function properly, the primary function of a gene is not the one by which we recognize it, viz. the determination of a visible characteristic, but it is the regulation of the life processes of the cell. The effects which different genes exert on different visible characteristics of an organism are only incidental to their primary function. Furthermore, if one line possesses only a few loci not present in another line that fact would cause a high degree of sterility among the offspring produced by crossing these two lines. Even a difference in one locus of the type described by Patterson²¹ as a "viability gene" would be sufficient to produce an almost complete incompatibility between two lines, one possessing the gene and the other not possessing it. Such a difference would be sufficient for the formation of a new species.

EVOLUTIONARY PROGRESS THROUGH GENE CHANGES

Since the change in any of the established loci is limited because any radical change in the gene is either lethal to the gene or lethal to the cell not adjusted to such a change, no great evolutionary progress could be expected through changes in genes which we now call mutations. Such progress could be expected through gene changes only if an extensive change occurs in the environment in which the species lives. In that case the change in the environment would require a new adjustment in the gene complex which may bring out as a most suitable form (wild type) a form different from the one which was most suitable in the original environment.

Evolutionary progress may take place through additions of new loci to a gene complex. It would require time, however, for a new locus

to become established as an integral part of the gene complex, but once that is accomplished such a change would go a long way toward formation of a new species. It seems possible that the bar locus of *Drosophila* may be such a new locus which has not yet become established in the gene complex of that species. Experiments are now under way which may give an answer to this question.

CONCLUSION

This presentation may be concluded by summarizing briefly our present conception of the gene. We visualize genes as single organic molecules. The gene string, then, gives us an interesting picture of a group of molecules held together by some unknown force in a string, each molecule possessing a power of self propagation, and each one individually and all of them together having an almost magic power of governing life processes of cells in which they are located, and therefore of governing life processes of the organism of which these cells are an integral part.

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