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EVOLUTION, RANDOMNESS, AND *HASHKAFA*

Randomness is an essential component of neo-Darwinian theory. It is also the main point of conflict between the neo-Darwinian *Weltanschauung* and Torah *hashkafa*. It turns out, however, that (1) the randomness of the variation called for in the theory is untenable theoretically, and (2) there is no evidence for it. There is, however, much evidence for *directed* variation, where the environment induces adaptive variations. A new theory is described that suggests that the capability of living organisms to adapt to a wide variety of environments is built into the genome, and there is good molecular evidence that such is the case. Moreover, the proposed theory can explain many phenomena that the neo-Darwinian theory cannot explain. It is pointed out that this approach was suggested almost two hundred years ago by Rav David Luria (רד"ל).

DARWINIAN EVOLUTION NEEDS RANDOMNESS

Charles Darwin suggested that life developed, and new forms of life arose, through what he called *descent* with *modification*. He led the way in offering a mechanistic explanation of descent as a natural phenomenon, a process that follows natural laws. His approach motivated later attempts to explain even the actual origin of life on a mechanistic basis.

To account for descent, Darwin strove to explain how the vast complexity of life could have arisen from some simple living form. If such an explanation could be achieved, there was hope that one could also discover how that simple living form could have arisen in a natural way from inert matter. The entire existence of life could then be accounted for as a purely natural phenomenon, not requiring supernatural intervention. Darwin's agenda, thus, called for him to find a natural process to account for descent.

Recognizing the need for a physical mechanism to account for descent, Darwin hit on the idea that many heritable variations normally exist in a population, and many new ones appear all the time. Some of these variations

can affect the fitness[1] of the organism in its environment. Organisms that are unfit will perish — only those that are fit will survive. His reading of Malthus[2] led him to conjecture that animal populations produce far more offspring than could possibly survive, and they hover constantly on the edge of misery and starvation. Under these circumstances, Darwin saw living organisms experiencing a fierce struggle for survival from which only the fittest would emerge.

He was mistaken in this conjecture, however, because plants and animals do not hug the brink of disaster. Population size is not controlled by starvation, disease, or predation. In most animal populations mass starvation and disease are rare; they occur only as the result of extraordinary catastrophes, such as droughts or epidemics. Moreover, predators do not overexploit prey populations. Many animal colonies are known to adjust their birth rates to match the available resources.[3] Plants also are known to adjust their seed production to the space and resources allotted to them.[4]

Darwin suggested that natural selection, acting over a long time on the variations in a population under conditions of a struggle for existence, could transform the population into a new species. He admittedly did not know the source of the variation, but he knew it was there. In the sixth edition of *The Origin*, Darwin was hesitant about labeling the variations as random, even though he had earlier referred to them as having occurred by "chance." He explained that he used the word "chance" only to indicate that their causes are unknown.[5]

He did not refrain from speculating on their causes, however. He felt there *were* definite causes for the variations. They could be caused by environmental conditions[6] or they could come from the use or disuse of organs.[7] But he did not want to call them random.

In the first third of the 20th century Darwin's theory was overtaken by new discoveries in biology. By the end of the 1930s the theory was in disarray. There were unanswered riddles and the theory was in serious need of repair and updating. In 1941, at a meeting of the Geological Society of America, a suggestion was made that geneticists join with morphologists, taxonomists, and paleontologists to try to synthesize, from the latest findings in these disciplines, a modernized and consistent version of Darwin's theory. Specialists in these fields responded to the call, and over the next few years, they developed a revised theory of evolution. They called it *the modern synthetic theory of evolution.* The theory gradually became known as the *neo-Darwinian theory of evolution,* and its framers and their followers became known as neo-Darwinians. Their agenda called for a theory that could explain the development of life in a natural way. If they could account for the development of all the present

complexity of life from some sufficiently simple first organism, the way would be prepared for a theory of a fully natural account of the actual origin of life.

Neo-Darwinian theory rejected Darwin's suggestion of the environmental induction of heritable variations, and even more emphatically rejected the inheritance of acquired characteristics. Hereditary elements, known as genes, had by now been discovered, and, although their molecular structure was still unknown, the neo-Darwinians had accepted the separation of the somatic and the germ cells as suggested half a century earlier by Weismann.[8] It seemed clear to them that neither environmental influences nor acquired characteristics could affect the germ cells, and that heritable variation could stem only from changes in the germ cells.

Unwilling to accept environmental influence as a cause of variation and unable to find a mechanism that could directly produce changes needed for descent, the neo-Darwinians rescued randomness from the rubbish heap to which Darwin had relegated it, and assigned it to function as the source of the variations. Some variations are detrimental to the organism, but others may be beneficial. The neo-Darwinians hold that a heritable variation of the latter kind, even if rare, will spread by natural selection, and will eventually take over the population.

The neo-Darwinians thus built their theory on random variation, culled and directed by natural selection. They identified the heritable variations required by the theory with the *mutations* discovered and named by De Vries in the early 20th century. A decade after the establishment of the neo-Darwinian theory, Watson and Crick identified the heritable variation of the theory with random errors in DNA replication.

If the neo-Darwinian agenda had worked out, there would be no place for a Creator in the origin of life except to establish the laws by which the evolution had taken place. Even that position would not be an honorable one if the appearance of man were not inevitable, as Gould believes it is not.[9]

THE MOTIF OF NEO-DARWINISM IS INCOMPATIBLE WITH RANDOMNESS

Random variation, however, turns out to be inadequate to account for evolution, and this inadequacy calls for a reexamination of neo-Darwinian theory. There is no evidence that *random* variation can play a role in major evolutionary advances as postulated by the theory. Indeed, there is evidence to the contrary — that randomness *does not*, and even *cannot*, play such a role.

The vast majority of random changes in the genome that have any effect on the phenotype are detrimental to the organism. The mammalian genome is a

sequence of about 4 billion nucleotides, and a single error in DNA replication could change one of these nucleotides into another. There are an enormous number of different sequences those nucleotides can assume, only a very small fraction of which can result in a viable phenotype, and only a smaller fraction still will have a positive selective value, yielding an improvement over an existing population.

Since DNA was discovered to hold the code of life,[10,11] conventional wisdom has held that errors in copying DNA are the source of the random variation called for by the neo-Darwinian theory. These errors occur in prokaryotes[12] with a probability of between 10^{-10} and 10^{-8} per nucleotide per replication.[13] In eukaryotes the rate is even lower. The error rate in eukaryotes is between 10^{-11} and 10^{-9} per nucleotide per replication.[14] These error rates are low because a special proofreading mechanism in each cell checks and corrects the replication. The rates are just below the level of intolerability to genetic damage.[15] Some think the system may even operate with the accuracy it does so as to maintain this level.[16] The error rates could not be much larger if a species is to survive.

Because of these low mutation rates, no more than one specific mutation of this sort can be expected in a population of 100,000 in 100,000 generations. Two specific mutations would require 10^{15} generations.[17] Since there is not enough time for 10^{15} generations,[18] a specific double mutation will almost never occur. The probability of a double mutation occurring, for example, in a population of 100,000 animals within 100,000 generations is only 10^{-10}. This is to be compared with the probability of a single specific mutation occurring in the same population within the same time, which is $1/e$, or about 0.37. Thus with higher organisms, such as mammals, evolution can make a specific change in the genome of no more than one nucleotide (or base pair) at a time. Moreover, even if such a mutation is beneficial, it is highly unlikely to be retained by natural selection to the point where it dominates the population.[19] To raise this probability to $1/e$ one would need about 1,000 times as many generations, or about 10^8 generations.

If evolution is to proceed through random nucleotide substitutions, then an adaptive improvement in the genome must be possible at any stage by a change of just one base pair. A long chain of such steps requires that there be long sequences of such changes, one after the other, each leading to an adaptive improvement of the organism. Moreover, because of the low probabilities involved, such evolution requires that there be not one, but many, long potential sequences of this kind. Indeed, the number is so large that many of these paths, or portions of them, would have been observed in the many genetic experiments performed since genetics became a science.

Whenever probability calculations have been made, they have shown that random point mutations cannot account for major evolutionary change.[20,21,22,23,24,25,26] Calculations on the evolution of the horse, as induced from the fossil record, bear this out. All calculations based on neo-Darwinian theory show that major evolutionary events are highly improbable. Events that a theory predicts to be very improbable cannot be said to be accounted for by that theory. If a theory can account for data only by declaring them highly improbable, then the theory must be rejected. This is a fundamental principle in the mathematics of hypothesis testing.

More than 30 years ago I predicted that contradictions to neo-Darwinian theory would emerge when probability calculations could be made of so-called convergences.[27] Such calculations can now be made. From the assumed convergence of the lysozyme enzymes common to ruminating cows and ruminating langur monkeys,[28] one can set an upper-limit probability of 10^{-54} to the probability that they evolved independently through random point mutations. It is less than the probability of your winning the New York State Lottery seven weeks in a row.[29] Most people would consider such an event impossible.

A striking identity has recently been found between a gene in *Drosophila* and a corresponding gene in many vertebrates that plays a role in the development of the eye.[30] The same gene has been found to control eye development in insects and in vertebrates, including humans. These genes are 94% identical between *Drosophila* and humans. The conventional wisdom until now has been that the eye is an extraordinary example of convergence in that it has developed independently as many as three or four dozen times.[31,32] This new finding makes convergence in eye evolution look so improbable that, even without making any probability calculations, one author suggests that: "the traditional view that the vertebrate eye and the compound eye of insects evolved independently has to be reconsidered."[33]

The neo-Darwinians claim they can account for the development of life from some very simple form. They must, therefore, account for the buildup of the information found today in the genomes of mammals and birds, fish and reptiles, all the invertebrates, and all the plants that inhabit the earth. This information is supposed to have been built up from such a simple organism as a single cell. If this information was built up, as the neo-Darwinians claim, by long series of small steps of random errors in DNA replication directed by natural selection, then each of these steps had to add, on average, a small amount of information. Information had to be generated little by little to accumulate to the large amount that resides in living organisms today.

It is easy to believe that single-nucleotide substitutions are random, but they

are not known to have *added* any information to the genome. They *are* known to have produced *minor* changes, even some with selective advantage in special cases. Geneticists have been studying mutations in the laboratory for nearly a century, and on the molecular level for a third of a century. But they have not found a single mutation that *adds* information to the genome! Yet these are the mutations the neo-Darwinian theory calls for to produce major evolutionary changes.

NO MUTATIONS ARE KNOWN THAT ADD INFORMATION

Random mutations do occur, but they do not add information to the genome. Some of these mutations may, under special circumstances, even have selective value and benefit the organism. But because they do not add information, they cannot represent the typical mutations required by neo-Darwinian theory. Most of the mutations in a chain of cumulative selection must be ones that *add* information. If evolutionary theory is to account for the increase of information in living things from a very simple primitive form of life to the complexity we find today, then each of its component steps must, on the average, add a little information.[34] If the theory is to account for the general buildup of information in life, then this information must be new — not just new to the genome of that organism alone, but new to the "global genome" of the entire biosphere.

I cannot prove there are no mutations that add information. I cannot even exhibit all *known* mutations to show that none of them adds information. Indeed, in principle, there *could* be such a mutation, but it would be improbable. The best I can do is to exhibit some well-known mutations that have been said to demonstrate neo-Darwinian evolution and show that they do not add information. I shall pick two examples of mutations. The first is perhaps the most well known among nonbiologists. The second, although not well known outside professional circles, is, I think, the most dramatic of the mutations that appear to lead to evolution.

My first example is a single nucleotide substitution in the DNA of a bacterium giving it immunity to streptomycin. Most cases of acquisition of drug resistance in bacteria involve the transfer of whole genes from other microorganisms that already have the resistance. Although the acquisition of a new gene does add information to the bacterial genome, the information is not new to the biosphere. It has already existed in other organisms. This is not the case, however, when a single copying error in the DNA leads to drug resistance. Let us take a look at how a random mutation leads to the evolution of streptomycin resistance.

Bacteria normally sensitive to streptomycin can undergo a random change of one nucleotide, granting them resistance to the drug. Is this an example of new information added to the genome? Can this mutation be a prototype of the mutations called for by the neo-Darwinian theory? Can it be of the kind that produce a long sequence of evolutionary steps that together add large amounts of information to the genome? Do we have here an example of neo-Darwinian evolution in action? Does this example contradict the theoretical consideration outlined above?

The mechanism of how streptomycin stops bacterial growth has been known for some time.[35,36] Mycin molecules attach to a matching site on the bacterial ribosome, preventing the correct assembly of amino acids into protein. The mycin molecule fits into the matching site on the ribosome like a key fitting into a lock, as shown schematically in Fig. 1. Because protein is incorrectly made, the cell cannot grow or replicate. Mammalian ribosomes do not have the matching site for the mycin molecule so, while the drug affects the bacterium, it does not affect its mammalian host. That is why mycin drugs are useful antibiotics.

A point mutation in the right place grants the bacterium resistance to streptomycin by *losing* information. Fig. 2 shows schematically how a change in the matching site on the ribosome can prevent the mycin molecule from fitting onto the ribosome and interfering with its operation. The change makes the bacterium resistant to the drug.

As you can see from Fig. 2, the change could be in any one of several places on the matching site to make the bacterium resistant. Any one of

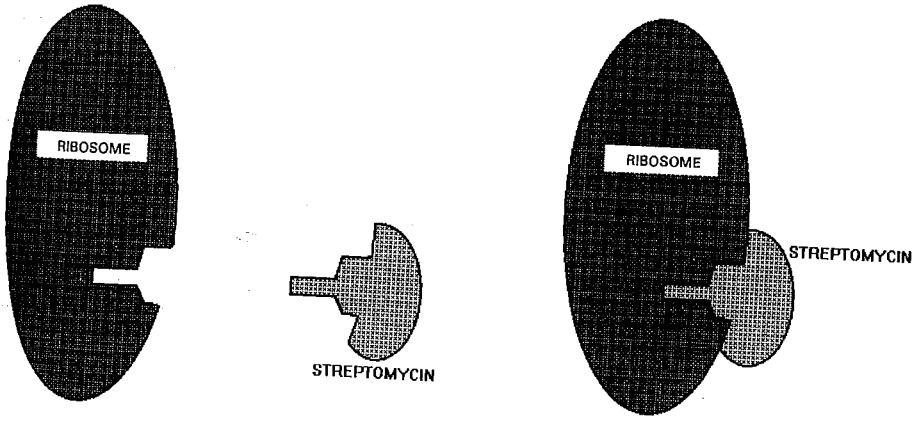

Fig. 1. Schematic sketch of how the streptomycin molecule attaches to a matching site on the ribosome to interfere with protein synthesis

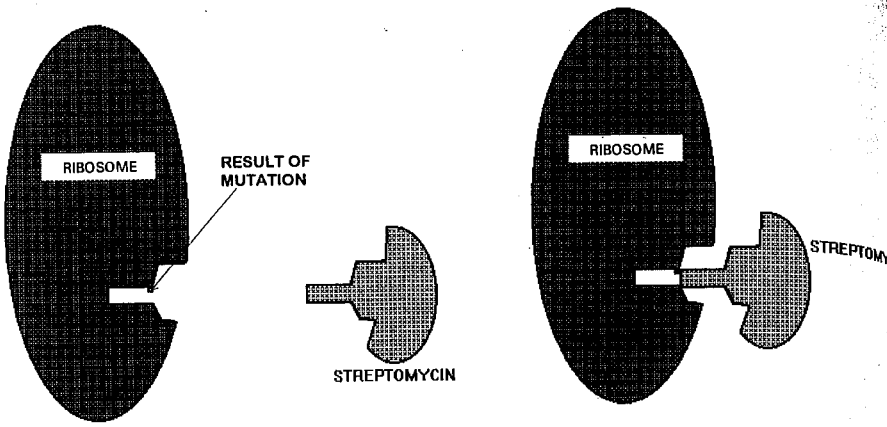

Fig. 2. Schematic sketch of how a mutation in the matching site on the ritosome can prevent the streptomycin molecule from attaching, granting the cell resistance to the streptomycin

several changes in the attachment site on the ribosomal protein is enough to spoil its match with the mycin. That means that a change in any one of several DNA nucleotides in the corresponding gene can grant resistance. Indeed, several different mutations in bacteria have been found to result in streptomycin resistance.[37] We see then that the mutation reduces the specificity of the ribosome protein, and that is a *loss* of genetic information. This loss of information leads to a *loss of sensitivity* to the drug, resulting in resistance. Since the information loss is in the gene, the effect is heritable, and a whole strain of resistant bacteria can arise from the mutant bacterium.

Although such a mutation has high selective value in the presence of streptomycin, the mutation *decreases* rather than *increases* the genetic information. It therefore cannot be typical of mutations that neo-Darwinian theory requires for macroevolution. The steps required by the neo-Darwinian theory must, on average, add information. Even though the bacterium acquires resistance to the drug, it acquires the resistance not by *gaining* information, but by *losing* it. Rather than say that the bacterium *gained resistance*, we would more correctly say that it *lost sensitivity*. In genetic-information content, the mutation is a *loss* rather than a *gain*. The loss of information is, moreover, manifest in the mutant's loss of viability.[38] In the absence of streptomycin the mutants are less viable than the wild type.

My second example is the most striking illustration I know of random mutations granting selective value to an organism. It is actually a series of three mutations in the soil bacterium *Aerobacter aerogenes*. Experiments with

these bacteria have shown what seemed to some investigators to be an example of the basic processes of evolution — namely, the evolution of new enzymes. Bacteria grown in culture have shown they can learn to live and grow on new substances that they originally could not use.[39] Several experiments of this kind have been reported.[40,41,42,43,44,45]

The experimenters tried to see if the bacteria could evolve an enzyme that would metabolize a nonnatural sugar, similar to their natural nutrients, but on which their repertoire of enzymes would not work. They put the bacteria under strong selection pressure. They denied them their normal pentose-sugar nutrients, ribitol or D-arabitol, and tried them instead on several artificial pentoses. When they gave them xilitol, they found that, although the wild-type bacteria could not grow, mutants appeared that could. The experimenters extracted these mutants, denoted them as X1, and grew cultures from them. They found that the X1 strain grew on xylitol, but its rate of growth was only one ninth that of the wild type on ribitol.

They isolated the X1 strain and continued it on xylitol. A new mutant appeared within the culture that could grow even faster on xylitol. The experimenters extracted the second mutant, cultured it, and named the resulting strain X2. The growth rate of X2 on xylitol was nearly 2.5 times that of X1, but still less than the rate of the wild type on ribitol.

They isolated the X2 strain from the X1 and continued it on xylitol. A third mutant appeared that grew still faster on xylitol than did the X2. They extracted the new mutant, cultured it, and called the resulting strain X3. They found that the X3 grew on xylitol about twice as fast as did X2; but its rate of growth on xylitol was still not much more than half that of the wild type on ribitol. The three mutations were all found to be single-nucleotide substitutions, and there is every indication that they were random.

These experiments show that bacteria can sometimes find other ways of getting what they need when their normal nutrients are denied them. Moreover, they did it through random single-nucleotide changes. These experiments surely looked like neo-Darwinian evolution in action. The experiments appeared to show bacteria evolving through a series of three small steps. Can this short series of steps be part of a potentially long chain of steps leading to cumulative selection? Can these three steps, performed in a few months under artificial selection, serve as a model for long series of millions of steps over geological times under natural selection that might lead to macroevolution? Could these steps show the sort of evolution that primitive bacteria might have undergone? Could this be how bacteria developed their enzymes for the first time?

If we examine these experiments in detail, we see *no new information entering the genome.* Each of the three mutations made a gene less specific and lost

information. Therefore, none of them can serve as a prototype for the small steps that neo-Darwinian theory says lead to macroevolution. None of the above experiments show the evolution of enzymes — enzymes cannot be built by mutations such as these.

The wild type of *Aerobacter aerogenes* normally feeds on ribitol. The cell takes in ribitol from the outside and breaks it down in a series of steps, using a special enzyme for each step. The first of these enzymes is ribitol dehydrogenase (RDH).

Ribitol is a pentose sugar normally found in the soil. Xylitol, on the other hand, is a pentose sugar not found in nature, but its structure is similar to ribitol. Xylitol and ribitol are made up of the same atoms in almost the same arrangement. The difference between them is slight, yet the cell's RDH enzyme is specific to ribitol and discriminates against xylitol as well as other substrates. Fig. 3 shows the structures of ribitol, xylitol, and another nonnatural sugar residue, L-arabitol (which I shall get to shortly). The figure does not show the three-dimensional arrangement of the atoms, but it does give an idea of how small the differences are between these sugars. Because the two sugars are so much alike, the same RDH enzyme that works on ribitol works also on xylitol, but with less activity. RDH hydrolyzes xylitol to make the same product it makes from ribitol. After this one step, all other steps in the metabolism of ribitol and xylitol are identical and are effected by the same enzymes. But, because the RDH is highly specific to ribitol, it works but poorly on xylitol.

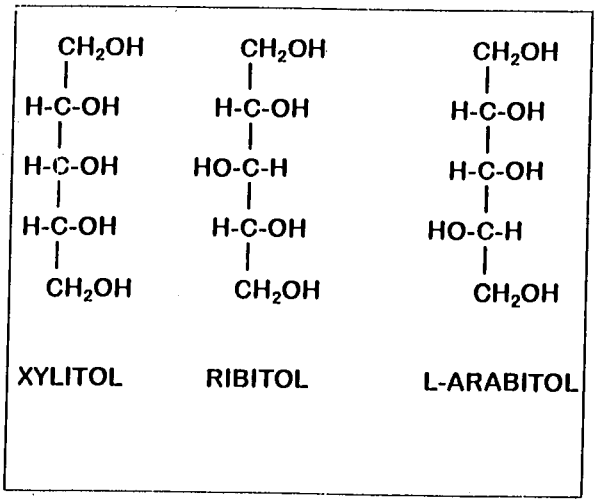

Fig. 3. Comparison of the structures of ribitol, xylitol, and L-arabitol

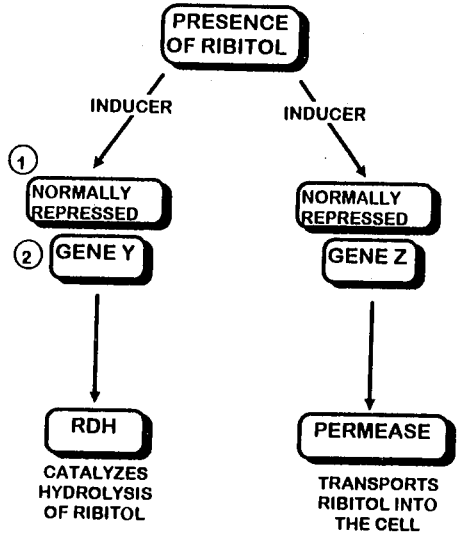

Fig. 4. Diagram of some of the control for the gene that encodes the RDH enzyme and for the gene that encodes the permease that transports the ribitol into the cell. The diagram shows the points where the first two mutations act.

The genes responsible for the metabolism of ribitol are turned ON only when ribitol is present. The parts of this control system relevant to our present discussion are shown in Fig. 4. The gene, denoted in the figure by Y and which encodes RDH, is normally repressed, and therefore the RDH enzyme is not normally made in the cell. The presence of ribitol will induce gene Y to turn ON, leading to the synthesis of RDH. Moreover, molecules cannot easily enter a cell unless they are brought in by a special permease enzyme in the cell wall. The cell is selective about what it brings in from the outside. The permease enzyme is also not normally found in the cell until it is synthesized by the gene denoted by Z in the figure. Gene Z is normally repressed, and therefore the permease is not present. The presence of ribitol will induce gene Z to turn ON to transcribe the permease.

In summary, there are three problems that prevent the wild-type cell from using xylitol. They are:

1. Although RDH has a small activity on xylitol, that activity is much lower than it is on ribitol.
2. Since ribitol is absent, gene Y will not turn ON and RDH will not be synthesized.
3. There is no permease enzyme to bring xylitol into the cell.

The X1 mutant partially overcame the above problems through a point

mutation in the gene that regulates the synthesis of RDH. This regulatory gene encodes the protein that represses RDH transcription. The mutation, whose point of effect is shown labeled (1) in Fig. 4, did not change the RDH molecule itself. What it did was to disable the repressor protein. As a result, there was no repressive control and RDH was synthesized constitutively. The gene transcribed RNA without having to be induced, and it did so at its maximum rate. RDH was made in such abundance that, in spite of its low activity on xylitol, it converted enough xylitol to allow the cell to function. The cell could function because:

1. Since the mutation disabled the repression of the gene transcription, the cell synthesized the RDH constitutively.
2. Unrepressed, the gene synthesized the RDH enzyme at its maximum rate. The large amount of RDH that was made helped compensate for its low activity on xylitol.
3. Although the cell has no transport system to admit xylitol, a small amount does enter by diffusion.

The X1 strain did not have a perfect solution to the three problems. It therefore grew much more slowly on xylitol than does the wild type on ribitol. Nevertheless, X1 can grow on xylitol alone, and the wild type cannot. But the benefit of the mutation came through a *loss of information.* Note that the mutation that destroyed the activity of the repressor could have been one of several mutations. It did not have to be a particular one: it was not specific.

The second step in the chain of three single-nucleotide substitutions converted the X1 strain into X2. This mutation changed the enzyme itself and raised its activity on xylitol. The point of effect of this mutation is shown as (2) in Fig. 4. Because of the higher activity of the enzyme, the growth rate of X2 on xylitol was about 2.5 times that of X1. Because the mutation made the enzyme more active on xylitol, one might think the enzyme became more specific, and that genetic information increased. But it turns out that the mutation leading to the X2 strain is just another example of a mutation making the enzyme *less* specific. Brian Hartley and his group at Imperial College in London studied this enzyme.[46] They compared its activity in the X2 mutant with that of the wild-type enzyme, and they measured the activity of the two enzymes on ribitol, xylitol, and L-arabitol, another unnatural substrate. They found that, compared to the wild type, the mutant enzyme was less active on ribitol, more active on xylitol, and more active on L-arabitol.

Fig. 5 presents the Hartley group's results in graphic form, showing a comparison of the reaction rates of the two forms of the enzyme for the three substrates. The enzyme in the wild type and the X1 strain is denoted in the figure by A; the enzyme in the X2 strain is denoted by B. The vertical scale

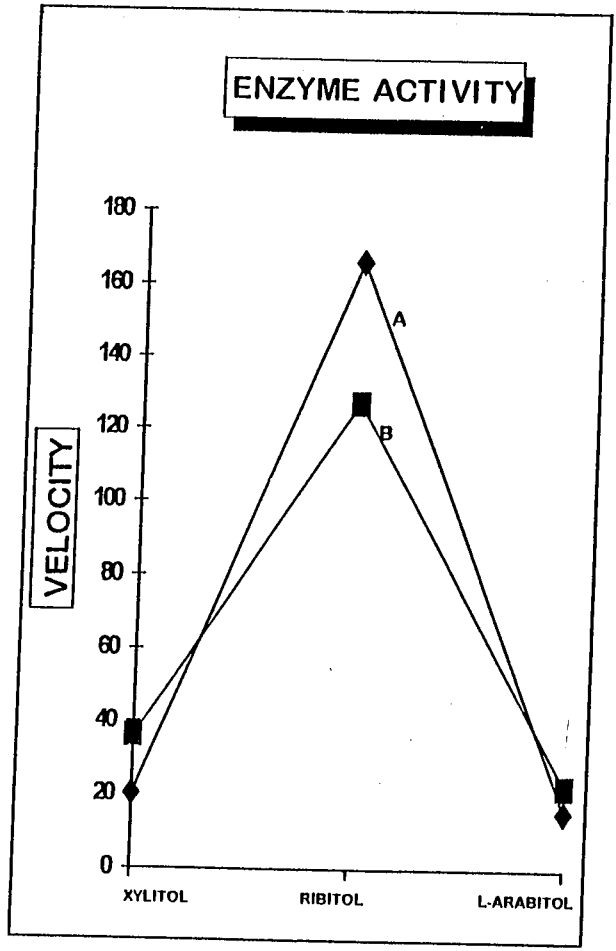

Fig. 5. Comparison of the activity to wild-type ribitol dehydrogenase with the mutant form on three different substrates. The velocity scale is in units / mg.

shows the relative rate of catalysis. Note that the mutation transforming the Xl strain into X2 broadened the range of substrates that the enzyme could catalyze. The enzyme of the wild type (A) has a reaction-rate curve higher and narrower than that of the mutated type (B). An enzyme that is very specific would show a high and sharp plot of reaction rate. One that is less specific would be lower and broader. Fig. 5 shows that the reaction rate of B is less specific than that of A. The new enzyme could accept a wider range of molecules as substrates than the old one; thus the mutation made the enzyme less specific, not more, and *reduced* the information in the genome.

One might have thought that if a mutation causes an enzyme's activity to increase on a particular substrate, it must be because the enzyme has become more specific to that substrate; but we see that this is not necessarily true. If an enzyme were really to become more specific to one particular substrate, it should become not only more active on that substrate, but it should become less active on all other substrates. Fig. 5 shows the wild-type enzyme's activity (A) with a high sharp plot, indicating high specificity, and the mutant enzyme's activity (B) with a lower and broader plot, indicating a lower specificity.

The specificity of an enzyme to its substrate is no less important to the cell than its level of activity. An enzyme that accepts any molecule as its substrate can be harmful. For an enzyme to be useful to the cell, it must limit its activity to its proper substrate.

The mutated enzyme of X2 also turns out to be less stable than that of the wild type.[47] Typically, when an enzyme loses information, its function is degraded. The mutation leading to the X2 strain is a point mutation and is indeed an example of a small random change; it is an example of *microevolution*, but it cannot be typical of a step in *macroevolution*. The typical step must gain some information. The steps of macroevolution must, on average, add information to the genome.

The third mutation, which converted strain X2 into X3, improved the cell's ability to metabolize xylitol. This mutation was a single-nucleotide substitution in a regulatory gene controlling the synthesis of a permease enzyme for D-arabitol. The point of effect of this mutation is shown as (3) in Fig. 6. Although the permease normally functions to transport D-arabitol into the cell, it turns out also to be able to transport xylitol. Normally the transport enzyme is not synthesized unless its gene is induced by the presence of D-arabitol. In the absence of D-arabitol a repressor protein keeps the gene OFF. So, even though the D-arabitol transport enzyme can work on xylitol, it is not normally present in the cell in the absence of D-arabitol. The mutation leading to strain X3 disabled the gene encoding a repressor protein that normally represses the gene encoding the permease. As a result the permease was synthesized constitutively. It was synthesized at the maximum rate and in large amounts without regulation. There was no need for its induction by D-arabitol.

Xylitol then gets a free ride into the cell on the transport enzyme intended for D-arabitol. Much more xylitol could then enter the X3 cell than could enter the X1 or X2 cell. Therefore, X3 could grow on xylitol better than X2 could. As with the X1 and X2 mutations before it, the mutation leading to X3 also reduced the specificity of an enzyme and therefore caused a *loss* of information.

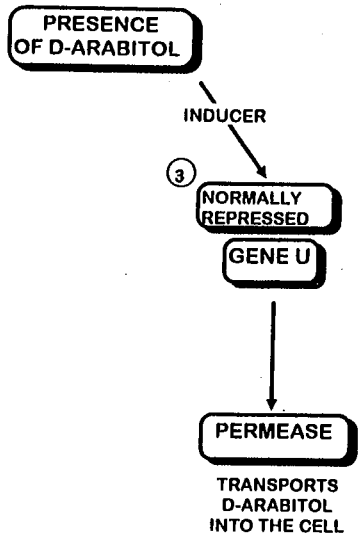

Fig. 6. Diagram of some of the control for the gene that encodes the permease enzyme for D-arabitol. The diagram shows the point where the third mutation acts.

THERE ARE NONRANDOM MUTATIONS THAT CAN LEAD TO EVOLUTION

I have indicated that it is highly improbable for random variation in the form of DNA replication errors to lead to any sizable amount of information getting into the global genome of life. I have also declared that I know of no example of a mutation that has added information to the genome. I have given examples of mutations that have been alleged to add such information. In each case, even though the mutation is beneficial to the organism under special circumstances, I have shown that it actually leads to a *loss* of information from the genome. The important feature of these examples is that even though they can offer the organism a selective advantage, they cannot serve as prototypes of the mutations called for by the neo-Darwinian theory.

But there is a large and ever-growing body of evidence that heritable changes *do* occur in living organisms that adapt them to their environments, and that these changes do not stem from simple errors in DNA replication. In the last decade and a half, we have seen mounting evidence on the molecular level of large genomic changes that confer selective advantage and occur just when they are needed. These observations have so far been made only on bacteria. Directed mutations are also known to occur in plants, and there is

evidence that they occur in animals as well. These mutations are not random, but are apparently induced by the environment. They are not merely errors in DNA replication, but seem to be mutations of a totally different kind.

In 1982 Barry Hall reported on an experiment in which he prepared a strain of *E. coli* bacteria lacking the β-galactosidase gene lacZ, which normally hydrolyzes lactose. When these bacteria grew and multiplied on another nutrient, but in the presence of lactose, they gained the ability to metabolize lactose, an ability that proved to be heritable. The gained ability was found to be due to the presence of a *new gene*. The new gene encodes a new enzyme that can perform the function of the β-galactosidase, enabling the mutant bacteria to metabolize lactose. The gene was present all the time, but in a dormant state. It was turned ON by two mutations that occur *in the presence of lactose and do not appear in its absence*. Hall declared that the "normal function" of this gene is unknown, and he called it a "cryptic" gene.[48]

Neither of these two mutations alone gives the bacterium any advantage, so there could not have been any selection for them separately. For the cryptic gene to become active, *both* mutations have to occur. In the absence of lactose, these two mutations are independent. They can occur together only by chance, and will do so with a probability of only about 10^{-18} per replication. If they occur at random and independently, the expected waiting time for one of these double mutations to occur in Hall's population would be about 100,000 years. But, in the presence of lactose, he detected about 40 of them *in just a few days*! One can conclude that the lactose in the environment was *inducing* these mutations.

In 1981 Ann Reynolds and her coworkers reported experimenting with *E. coli*, which cannot normally metabolize salicin because they lack an enzyme to catalyze the first step.[49] They found that a mutation involving a DNA rearrangement occurs in the presence of salicin and turns ON what they called a "cryptic" gene, permitting the bacterium to metabolize salicin.

Hall later also grew bacteria in the presence of salicin.[50] He found that Reynolds's cryptic gene encodes an enzyme that can catalyze the first step in the metabolic pathway of salicin. The cryptic gene is normally repressed by a regulatory gene, and it will become active if one of a few mutations occurs in the regulatory gene.

He used a strain of bacteria whose cryptic gene did not work. The cryptic gene did not work because there was an insertion sequence (IS), known as IS103, sitting upstream of the cryptic gene. The IS keeps the gene OFF because it shifts the coding frame and garbles transcription to *mRNA*.

For a bacterium of Hall's strain to metabolize salicin, two mutations had to occur. First, the sequence IS103 had to be precisely deleted. Then, a base substitution had to occur that would make the regulatory gene stop repressing

the cryptic gene. Hall tried to measure the spontaneous rate of the precise deletion of IS103, and found it too low to measure. He could do no more than assign an upper limit of 2×10^{-12} to its probability. In the absence of salicin, the probability that the necessary two mutations would occur in a particular cell in a single replication is less than 10^{-19}. That they occurred many orders of magnitude more frequently in the presence of salicin indicates that salicin may be inducing the mutations.

Cairns and his coworkers described another experiment with bacteria.[51] They used a Lac- strain of bacteria, so called because the bacteria had a defective *lacZ* gene. The strain could not synthesize β-galactosidase, and therefore could not metabolize lactose. Cairns's team fed lactose to these bacteria and looked for the appearance of mutants that could metabolize it. They found such mutants, and from the statistics of their appearance they concluded that the mutations appeared only in the presence of the lactose. They wrote:

> The cells may have mechanisms for choosing which mutations will occur.... Bacteria apparently have an extensive armory of such 'cryptic' genes that can be called upon for the metabolism of unusual substrates. The mechanism of activation varies.... *E. coli* turns out to have a cryptic gene that it can call upon to hydrolyze lactose if the usual gene for this purpose has been deleted. The activation of (this cryptic gene) requires at least two mutations.... That such events ever occur seems almost unbelievable.[52]

When these experiments were first reported, they were met with skepticism. Their results brought into question the status of the principle of the independence of mutations from the environment.[53,54] There were many attempts to explain the phenomena as resulting from the same kind of random mutations called for by the NDT. Although some have suggested that Cairns's results indicate the failure of the principle, others have offered explanations that leave the principle intact.[55] Further experiments, however, have dispelled these notions. Recent studies have shown that, in the presence of lactose, adaptive mutations activating a dormant gene encoding an enzyme that will hydrolyze lactose in *E. coli* are different from mutations that occur in the absence of lactose.[56,57,58,59]

In addition to these recent observations of nonrandom mutations in prokaryotes, there has long been evidence of nonrandom variation in eukaryotes, including plants and animals. Seventy-five years ago Victor Jollos experimented with *Paramecium aurelia*, and found an environmentally-induced variation that was heritable.[60] When the environmental stimulus was removed, the variation persisted in subsequent generations. An interesting feature of this work is that

the original state of the organism returned after 40 generations without the environmental stimulus.

Many other examples can be given of environmentally-induced variations in plants and animals observed over the past hundred years. Taken together, the evidence indicates that nonrandom variation, induced by the environment, may play an important role in evolution. These varied examples share a common feature: namely, that an adaptive variation can appear in large numbers in a population when it is needed. When adaptive nonrandom variation does occur, it is far more frequent than chance, and it appears in a large fraction of the population.

PROPOSED MECHANISMS

On the one hand, the kind of evolution envisioned by Darwin and the neo-Darwinians cannot occur. Genetic information cannot be built up by random variation even with the directive force of natural selection. Yet we see that plants and animals can change when stimulated by environmental changes. We have even seen molecular details of such changes occurring in bacteria in response to environmental stimuli. Permit me now to speculate on how the phenomena of environmentally-directed mutations observed in bacteria might be generalized and extended to multicelled organisms.

Living organisms respond to their environment on several levels. As Jacob and Monod have shown, the genetic control system senses the presence of an enzyme's substrate and turns ON the gene that encodes the enzyme.[61] The cell's control system turns genes ON or OFF as they are needed, but makes no heritable change in the genome. This kind of control permits the organism to operate efficiently through specific *short-term* changes in the environment.

I have suggested[62] that a straightforward extension of such controls, making their results heritable, can lead to changes in the *long term* — on an evolutionary time scale. Moreover, if the control is in the development process, even a small change of the "right" kind can lead to a large adaptive change in the phenotype. The "right" kind of change is unlikely to occur by chance. If the changes are random, the probability of a "right" change occurring is a function of the fraction of "right" changes among all possible ones. The number of "wrong" changes is so much greater than the number of "right" ones, that a "right" change is unlikely to occur by chance even in large populations and over immense periods of times. But, if the genome had the built-in ability for an adaptive change to be triggered by an environmental cue, then chance would not be a factor — the right adaptive change would be elicited when it is needed.

What physical mechanism can produce environmentally-induced heritable variations? How could large amounts of genetic information be generated quickly? Environmental influence on the variation does not have to imply that it generate a substantial amount of information in the DNA. Indeed, if the environment merely triggers the genome to switch between n potential states, it generates no more than $\log 2n$ bits of information. I suggest that most of the information necessary for organisms to adapt to their environment is already present in the organism, and no mysterious or ill-defined mechanism need be invoked to account for the generation of the few bits of information needed to switch.

As has been shown with the bacteria, the environmental trigger induces a change to an adaptive phenotype with no apparent role left to chance. There may, however, be some role here for chance. The environment may trigger not one, but a set, of genetic switches leading to a set of potential phenotypic outcomes. The trigger may be to one switch in some individuals, and to different switches in others. The resulting phenotype would then vary from one individual to another. Natural selection may then favor one of these types. The switch, triggered by the environment, may be seen as a coarse adjustment to adaptivity, and natural selection among the outcomes as a subsequent fine adjustment.

As with many biological phenomena, there is, I suggest, more than one mechanism that can lead to nonrandom adaptive variation. Nonrandom variations in the genome induced by the environment can be divided into two types, which I shall call *Type I* and *Type II.* Type I produces a change in the DNA base-pair sequence, and Type II produces only a change of state of the genome, but leaves its nucleotide sequence unchanged.

An environmental trigger that could produce a change in the genome was suggested about a decade ago by Wanner.[63] Any change in the genome can be called a mutation, and all mutations have been conventionally assumed to be random and unrelated to the environment. Although many mutations apparently are random in the sense used here, there are many that are not. Single-base substitutions resulting from uncorrected random errors in DNA replication are indeed random. Their effects on the phenotype are independent of environmental influences, and they occur without regard for the organism's needs. They are simply errors.

As opposed to errors in the working of the complex cellular mechanism, there are mutations that are not errors, but that are *directed* by that cellular mechanism. They are called up when they are needed, and they are executed under tight cellular control. Genetic rearrangements, including insertions, deletions, amplifications, and inversions, have been observed to be under strict

cellular control. An insertion sequence sometimes enters a gene and prevents it from transcribing its protein. The cell can also remove the sequence with perfect precision, allowing the gene to return to working order. Until recently, genetic rearrangements were thought to have no known function and, therefore, were considered to be random.[64] The experiments of Hall, Cairns, and others, however, have shown that through insertions, deletions, and point mutations, a bacterium can turn ON a cryptic gene, permitting the cell to metabolize a carbon source that was otherwise denied it.

A transposon is a large mobile genetic element that can transpose itself from one place to another in the genome. It carries within itself genes encoding some of the enzymes needed for its transposition, and the cell provides several others. Some transposons serve their host bacterium by carrying genes granting resistance to antibiotics. The jumping of a transposon is one of several kinds of genetic rearrangements. Deletion, amplification, and inversion are others.

Three adaptive deletions have been found in prokaryotes that are triggered by environmental cues. Two of them are found in the cyanobacterium *Anabaena*. If these cells are deprived of a nitrogen source, a DNA sequence is deleted from the genome. Deletions of sections 11 kilobases (kb) long[65] and 55 kb long[66] have been found. These deletions lead to the cell becoming dormant, presumably in an effort to conserve nitrogen. An adaptive deletion of 42 kb has also been found to occur in the bacterium *Bacillus subtilis*.[67] Environmentally-induced DNA changes have also been reported in plants.[68,69,70,71,72,73,74,75,76,77,78] The mechanisms of these inductions, however, are as yet unknown.

Many important genetic rearrangements are known to be nonrandom. Some are nonrandom in time, and all are nonrandom in their position on the genome. Some occur when they are needed, and seem to be environmentally induced (as in the bacteria in Cairns's and in Hall's experiments). And some, which are always needed and therefore do not require environmental induction, occur at random times in just the right place on the genome where they can be effective (as in *Salmonella*[79,80,81] and in *Trypanosoma*[82]). These nonrandom mutations are executed with precision and are under elaborate cellular control. Although genetic rearrangements have until now been thought of as random, to dismiss them as nothing more than chance events in an attempt to preserve the neo-Darwinian theory would be to ignore what nature is telling us. Various forms of genetic rearrangement help make up the set of Type I environmentally-induced adaptive variations.

Type II variations are different. They are environmentally-induced changes in only the *state* of the genome and they do not change the DNA sequence. Genetic states that dictate the current metabolic activity of the cell through enzyme synthesis are usually not heritable. A gene that is normally OFF needs

a signal to turn it ON. It will be ON only as long as the turn-ON signal is present. Take that signal away, and the gene turns OFF. Similarly with a gene that is normally ON. The state of a gene or an operon[83] depends on the presence of inducing or repressing signals, and is usually not heritable.

But some altered genetic states are known to be heritable. The most outstanding examples of heritable genetic states are the programmed changes that occur in embryonic development. As cells differentiate, genes are selectively turned ON and OFF, and their ON/OFF states are passed from mother to daughter cell: the state is heritable. Not every method of turning genes ON and OFF lends itself to being heritable. How cells during development pass on their genetic state to daughter cells is not yet well understood.

One way the cell has of establishing a genetic state and making it heritable is to attach a methyl group to one of the carbon atoms of the cytosine bases in the DNA. Methylation serves to keep the gene OFF by preventing regulatory proteins from attaching. When the cell wants to turn ON selected genes, it first has to remove the methyl groups, and then apply the regulatory protein. Methylation has been suggested as one of the ways in which the organism might control gene activity during development.[84,85,86] The pattern of methylation is made heritable through an enzyme that acts during DNA replication. The enzyme copies the methylation pattern from the template strand of DNA onto the daughter strand as it is being constructed.

Another way of making a genetic state heritable is to have the gene (or operon) turn ON and OFF with a locking trigger. A trigger that turns ON an operon will lock it ON, if the operon's activity itself leads to the synthesis of a control protein that keeps it ON. Once such an operon is turned ON, it will remain ON even after the trigger is removed. Such a state can be heritable.[87]

So far I have indicated only how an environmental cue can enter an exposed cell and cause a heritable effect on its genome. How could an environmental cue produce a heritable change in a plant or animal? Having the environment cause a heritable effect on an exposed cell is one thing. But creating a heritable effect on a multicelled organism, where the reproductive cells are isolated from the somatic cells, seems to be something entirely different.

Environmentally-induced heritable changes seem more difficult to achieve in plants or animals than in single cells. For one thing, in multicelled organisms the environmental cue has to penetrate to the protected reproductive cells, or gametes. Second, the environmental stimuli that have been seen to trigger bacteria are relatively simple, while those that would trigger plants or animals would have to be complex. Can complex environmental cues get into the organism? We know they can because animals, for example, adjust their birth rate to match available resources.[88] Plants are known to adjust their seed

production to the available space.[89] We know that complex stimuli can enter through the sense organs and be processed by the brain to produce appropriate physiological or psychological states such as stress. These states stimulate the production of hormones, which travel throughout the bloodstream to reach their targets in any part of the body. The target sites of some of these hormones could well be the reproductive cells, and there they could make a heritable change. These suggestions must remain speculative for the present until more is known of how environmental cues act. But herein lies a possible mechanism for observed evolution.

NONRANDOM EVOLUTION AND TORAH *HASHKAFA*

I have here described the important role neo-Darwinian theory assigns to random variation. I have also noted that random mutations are unable to play that role, and that all the evidence points to the absence of a major role for randomness in evolution. I have suggested, instead, that any significant evolutionary change that occurs does so principally through nonrandom variations induced by environmental cues. A role has been left open for randomness and for natural selection, but this role is much attenuated from that assigned to randomness by neo-Darwinian theory. I suggest that changes in the environment drive the evolution of living organisms by triggering a switch to alternative genetic programs. The organisms have the built-in capability to adapt to a wide variety of environments.

How does this suggestion fit with Torah *hashkafa*? Is there room for such evolution, or for any evolution at all, within Torah? It turns out that the suggestion made here is derivable from Talmudic sources. Rabbi David Luria (רד"ל) indeed made such a derivation in his commentary to the Midrash פרקי דרבי אליעזר. From Talmudic and Midrashic sources he derived the necessity of animals to evolve.[90] As Rabbi Luria interpreted the Midrash, there were 365 basic species (מינים) of beasts created, and the same number of birds. All the others were derived from these. As each basic species moved into a different environment and found itself a new niche, it changed. The changes were dictated by the conditions under which it lived, including the food it ate. Rabbi Luria's conclusion is very much like the suggestion presented here.

The basic species, according to Rabbi Luria, can transform into new species as they are influenced by the conditions under which they live.[91] The Sages of the Talmud (תנאים, אמוראים) as well as the medieval commentaries (ראשונים) were aware of the phenomenon of domestic animals changing their characteristics in a heritable way when they become feral and vice versa. There is discussion in the Talmud, and in subsequent rabbinical literature, on whether the domestic

ox (שור) and the wild ox (שור הבר) are of the same or different species.[92] One opinion is that the wild ox was originally a domestic ox that became feral, and therefore they are the same species (מין). Another opinion is that the two animals belong to two entirely different species (מינים).

It is well known that feral animals change on domestication. Darwin noted that domestic cattle undergo changes when they become feral.[93] Some of the pigs given to the Maoris by DeSurville in 1769 and by Captain Cook in 1773 became feral. They were observed to have become very wild, cunning, and speedy.[94] The boars had large tusks, were covered with bristles, and the young were striped. They were very different from the domestic pigs from which they descended. These wild pigs were indistinguishable from wild pigs elsewhere.[95] It has also been observed that whenever wild pigs become domesticated the tusks of the boars become very much reduced, they loose their bristles, and the young are no longer striped. These changes are hereditary but the animals gradually revert back if they again become feral. Moreover, the changes from domestic to feral are always the same. They are not random.

Lurian evolution is the change of an organism under environmental influence. It is not the neo-Darwinian kind, but rather the kind I have just described. Conventional wisdom in biology states that characteristics acquired by an organism cannot be inherited. The environment may change an animal, but these changes have conventionally been held not to be heritable.

According to the central dogma of molecular genetics, the environment cannot cause an organized change in the genome. There is no way an outside influence can alter the genetic program in such a way as to make the organism adapt to that influence. There would have to be some way of reversing the genetic coding, and that seems difficult to do. One biologist has recently speculated how such an influence might be possible,[96] but no one else seems to accept his speculation. The heritable variations appearing in living creatures are conventionally thought to be random in the sense that their effects on the phenotype are independent of the environment.

If living organisms had within their genes not just one development program, but several alternative programs that could be called up by a cue from the environment, then we could see how the environment can influence the genes. The environment can change the structure of the genes, or it can change their state. It can turn some genes ON and others OFF in such a way that the new state is heritable.

The randomness of the variations claimed by neo-Darwinian theory, and which is essential to it, stands in major contradiction to Torah *hashkafa*. The neo-Darwinians need the randomness to arrive at a "natural" explanation for the development of life from a simple beginning. Had it worked, they would

have reduced the development of life to a simple natural law. Much like the way the law of gravity accounts for a falling rock, so neo-Darwinian theory would have accounted for the development of life, from a simple unicellular organism to the great complexity of life we see today. Had they done that, they would have made the appearance of man a mere chance event.[97]

Had the neo-Darwinians succeeded in establishing their case, the Torah believer would have had two choices: (1) he could simply reject the theory, believing that no matter how good the logic seems to be, there must be something wrong with it; or (2) he could engage in apologetics to show how the Creator and creation could be accommodated by smuggling Divine control into the randomness.

The first of these choices has been the one favored over the centuries. It is a robust choice, and has proved its merit as one scientific theory after another has fallen by the wayside. The second choice would be unsatisfying to any but the most committed accommodationist. If the theory works well, then a creationist explanation is superfluous. But the Torah believer is not faced with this dilemma. I have shown that the neo-Darwinians have not successfully established their case, and randomness therefore cannot play the important role which they have assigned it.

Evolutionists will not easily accept my solution. The suggestion that living organisms have within themselves the ability to be switched ON or OFF by a cue from the environment may be satisfactory as an explanation of special cases of evolution, but evolutionists will not accept it as the explanation of evolution in general. They will ask for my explanation (on scientific, not on supernatural, grounds) how such a built-in capability arose. How could such a general capability have arisen in the development of life from a simple beginning? How could my suggestion fit the neo-Darwinian agenda?

I reject the neo-Darwinian agenda. I do not attempt to explain on a scientific basis how the built-in capabilities arose. I do not attempt to explain the development of life from a simple beginning; nor do I attempt to explain the buildup of complexity from a simple beginning to the forms of life we find today. Such development and buildup have never been observed, and there is thus no imperative for a theory to account for them. The inability of my hypothesis to account for the spontaneous origin and development of life, events that have never been observed, is not a valid criticism of it. If the hypothesis can account for observed adaptations, it will be doing all that should be aksed of it.[98]

NOTES

1 Words such as "fitness" are not really scientific when used to characterize variation. Such attributes are only evident *a posteriori* and one has no way of knowing beforehand what a given change will produce. These terms are nevertheless used by evolutionists, and I use them here with the expectation that their meanings will be obvious to the reader even if they are not precise.

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90 כתבי הגאון ר' דוד לוריא זצ"ל, הפירוש הגדול על פרקי דרבי אליעזר (Jerusalem, 5750), pp. 52a-b. Rabbi Luria died in 1855, just four years before the publication of Darwin's *The Origin*.

91 Rabbi Luria does not of course use the English word *species*, because he writes in Hebrew. I am translating his word מין as *species*. Therefore my use of the word *species* is not necessarily to be taken as identical with present-day taxonomic use of the word *species*. I do think, however, it is close.

92 תלמוד ירושלמי כלאים פ' ח, הל' ו ובפני משה שם, משניות כלאים, פ' ח, משנה ו, ברטנורה ומשנה ראשונה שם, רדב"ז על הרמב"ם הלכות כלאים פ' ט, הל' ה, ש"ך על יו"ד רצ"ז הלכות כלאי בהמה, ס"ק ו.

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97 Gould (Note 9), on the assumption that the variations are random, concludes from the pre-Cambrian and early Cambrian fossils and the many near extinctions of life that have happened since, that there were so many possible paths for evolution to follow that the one it in fact took is the result of chance. Gould's thesis is that the appearance of man was not inevitable. There was not even any inevitability of intelligence.

98 An elaboration of the points made in this paper, as well as related points, can be found in my recent book *Not by Chance* published by the Kest-Lebovits Foundation, P.O.B. 16068, Bayit Vegan Station, Jerusalem 91160, Israel.

* Lecture to the Third Torah and Science Conference, March 1996.