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EDITED BY

G. H. BOURNE J. F. DANIELLI

ASSISTANT EDITOR

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The Evolutionary Role of Recombinational Repair and Sex

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I. Introduction: Molecular Replicators and Evolution

In this article we review a body of work relating to the hypothesis that sexual reproduction arose very early in evolution as a way of overcoming

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genome damage through recombinational repair. Dougherty (1955) was the first, to our knowledge, to argue that the origin of sex is based on overcoming DNA damage. This idea, however, lay dormant for over two decades until revived independently by H. Bernstein (1977), Martin (1977), and Maynard Smith (1978, p. 7). Since 1955, when the idea was first proposed, a much better appreciation of the importance of DNA damage and repair (see Sections II and III), and a firmer picture of early evolutionary events (see below) have been achieved. In order to be as general as possible in discussing these ideas, we first consider the properties of simple molecular replicators as they evolved in the earliest stages of life.

The most fundamental properties of life, we think, follow from the minimal requirements for natural selection to occur. The elemental condition necessary for natural selection to originate is probably the existence of a self-replicating informational molecule. In accord with the extensive work of Eigen and collaborators (Eigen, 1971; Eigen and Schuster, 1979; Eigen *et al.*, 1981), it is reasonable to hypothesize that life arose as a self-replicating heteropolymer similar to RNA. Self-replication and the capacity to encode information are thus the two most fundamental features of life. Variation, an additional basic property of life, arose simply as a result of errors of replication. Natural selection depends on competition between variants for limiting resources used in replication. Ribonucleotides, present in the early aqueous environment, were probably the first resources for self-replication. In this model for the origin of life natural selection results from competition among RNA replicators for nucleotides.

Bernstein *et al.* (1983) and Kuhn (1972) have argued that the most primitive adaptations were folded configurations of RNA molecules. Such conformations, representing the first phenotypes, were determined by specific base sequences of the RNA, the first genotypes (Michod, 1983). Three classes of phenotypic adaptation arising early in the evolution of replicators can be distinguished. These were configurations of RNA that promoted (1) increased rate and accuracy of replication; (2) protection of the replicator against physical damage; and (3) increased ability to incorporate nucleotides from the environmental resources. Fitness (per capita rate of increase) is determined, in the simplest cases, by these three adaptive capacities and the availability of resources in the environment (Bernstein *et al.*, 1983). The three adaptations are intrinsic to the organism in the sense that they are encoded in the organism's genome, in contrast to resources which are a property of the external environment.

As the capacity of RNA replicators to specify enzymes evolved, the three types of adaptation became associated with increasingly complex

structures. Replication, for example, in organisms where the process has been studied in any detail, depends on a polymerase. Such an enzyme catalyzes the elongation of a nucleotide chain, using a preexisting chain as a template. In organisms more complex than the simplest viruses, additional proteins are involved, which, in coordination with the polymerase, promote speed and accuracy of replication (the first type of adaptation).

In this article we will concentrate on the second type of adaptive function, protection against physical destruction, since this plays a fundamental role in the evolution of sex. We will not discuss further the third type, adaptations promoting resource utilization.

Genome damage refers to physical alterations of the RNA (or DNA). In Section II we discuss the nature of genome damage and how this provides the selective basis for the origin of recombinational repair and sexual reproduction. In Section III we discuss the further evolution of recombinational repair and sexual reproduction as it occurs in diploid multicellular organisms. Then in Section IV we consider briefly major alternative explanations for the origin and maintenance of sex, arguing that they cannot be generally adequate. Following this we explore some of the implications of sex. We argue in Section V that sexual reproduction acts as a constraint on the optimization of adaptation. Finally, in Section VI we propose that it is the dynamics of natural selection in sexually reproducing populations that provides the fundamental explanation for the existence of species as distinct entities.

II. The Origin of Sexual Reproduction

A. The Nature of Gene Damage

Our knowledge of damaging mechanisms in informational molecules is largely restricted to DNA, although the general problem of damage and recovery of lost information applies to any informational system (see Section II,B).

Damage should not be confused with mutation, although they both involve changes in the molecule encoding the information. Damages to DNA include a variety of chemical alterations in the polynucleotide structure of the double helix, such as pyrimidine dimers, apurinic sites, single strand or double strand breaks, interstrand crosslinks, and both large and small chemical additions, referred to as adducts. By contrast, mutations are changes in the sequence of the genome's nucleotides in which the standard AT or GC base pairs are substituted, added, deleted, or rearranged. Even when mutations result from large changes, such as extended

deletions, the DNA retains its characteristic physical regularity. Unlike damaged DNA, mutated DNA consists of an uninterrupted sequence of standard nucleotide pairs. Mutations can be copied indefinitely, affecting successive generations. DNA damages, by contrast, are not duplicated by replication. DNA damages, unlike mutations, can be recognized and removed directly by repair enzymes, since they are irregularities of the double helix. Evidence indicates that when they are not removed they interfere with DNA replication (Cleaver, 1969) or transcription (Hackett and Sauerbier, 1975; Nocentini, 1976; Leffler *et al.*, 1977; Zieve, 1973). In bacteria it has been shown for X-ray induced double strand breaks (Krasin and Hutchinson, 1977) and psoralen crosslinks (Cole, 1971) that even a single unrepaired lesion can kill the cell. DNA damage can also be eliminated from a population of cells by death of the individual cells containing them. There is a direct connection between DNA damage and mutation, since during the processing of damages by repair enzymes, mutations occasionally arise (Witkin, 1976). However, when damages are repaired accurately, their potential lethal or mutagenic effect is avoided.

DNA damage appears to be a problem for all life. This conclusion is based on experimental evidence for the existence of DNA repair in a wide range of organisms, including viruses (Harm, 1980; Bernstein, 1981), bacteria (Hanawalt *et al.*, 1979), protozoa (Smith-Sonneborn, 1979), fungi (Prakash and Prakash, 1978; Cox, 1978), slime molds (Welker and Deering, 1978), algae (Davies, 1967), insects (Boyd, 1978), higher plants (e.g., Trosko and Monsour, 1969; Howland, 1975; Jackson and Linskens, 1978), and mammals (Hanawalt *et al.*, 1979). H. Bernstein (1983) has also recently summarized studies of one type of repair, recombinational repair, in viruses, bacteria, fungi, and mammals. An important general cause of DNA damage is UV irradiation from the sun. Intrinsic processes, such as spontaneous hydrolysis of purines and pyrimidine bases from the deoxyribose phosphate backbone of DNA, may also be important natural sources of damage (Lindahl, 1977). For humans and members of the animal kingdom generally, food may be an unavoidable source of chemicals which damage DNA (Ames, 1983).

Gensler and Bernstein (1981) have proposed that somatic cells of multicellular organisms, in contrast to germ line cells, are vulnerable to the accumulation of DNA damages because of the lack of efficient repair. This, they suggested, is the primary cause of aging. Medvedev (1981), after reviewing the evidence bearing on the immortality of the germ line, concluded that the most important process in rejuvenating germ cells are meiotic recombination and repair—"unique processes which are capable of restoring the integrity of DNA and chromosomes from lesions and alterations which are irreversible in somatic cells."

B. Information, Mutation, and Damage

In order to understand the evolutionary role of basic mechanisms operating at the molecular level it is useful to view the genome as a means of transmitting information. The transmission of information from parent to offspring via replication is basic to life. Information encoded in the genome is transmitted both in replication and in transcription.

The information capacity of a string of symbols—in the genome the sequence of nucleotides—depends on an absence of an intrinsic bias to the order of the sequence. The less bias, the more information the sequence can carry.

The fundamental principles of transmitting accurate information from a source to a destination are independent of the kind of information and the mechanisms involved. One can draw precise parallels between communication from ground to satellite and transmitting a working genome from parent to offspring. In either case the critical difficulty is the possibility of disruptions due to noise, i.e., random influences which change the sequence in unpredictable ways. These disruptions can have one of two possible results; change of one allowed symbol to another (which corresponds to a mutation) or change of an allowed symbol to a disallowed symbol (i.e., one which cannot be replicated). The latter corresponds to genetic damage.

Let us assume that any string (linear sequence) of Latin letters is allowable in the sense of being a proper set of characters for transmitting the English language. In Fig. 1a it is not possible to determine at the point of reception that the received string is incorrect. This is the essence of mutation. In Fig. 1b, however, the error can be recognized since the Greek letter α is not part of the allowed set of characters. However, there is no way to recover the lost information unless a redundant copy of the string is also transmitted. This is illustrated in Fig. 2. In Fig. 2a one sees that upon reception of information containing a mutation, redundancy can be used to determine that there is an error. There is, however, no way of determining at the point of reception which received string is correct. In contrast, with damage the error can be recognized as such and so it can be

a Mutation
Source string: message
Received string: massage
b Damage
Source string: message
Received string: mαssage

FIG. 1. Recognition of error.

a Mutation
Source string: message
Received string 1: message
Received string 2: massage
b Damage
Source string: message
Received string 1: message
Received string 2: massage

FIG. 2. Role of redundancy.

corrected by utilizing information in the undamage redundant string (Fig. 2b). This of course assumes that the likelihood of two disruptions occurring at precisely the same point in the string is small.

There are limits to the level of redundancy in any informational system. Redundancy is costly and so in the satellite analogy, one can either build in two separate channels to carry the redundant information, or one can use a single channel with half the efficiency. The key issue in engineering design is the importance of the information. For example, if the information is essential for the proper functioning of the satellite, then clearly the cost of redundancy is a minor consideration compared to the benefits of not losing the satellite. In such cases, substantial redundancy is built into the device in spite of the added weight etc. If the information is a phone call for which the satellite is just a relay, then the loss of information is not disastrous, and it does not pay to have redundancy. In living systems, much of the encoded information is critical, and so we can expect evolution to have produced mechanisms which recover lost information in a way which keeps the costs of redundancy to a minimum.

C. Recombinational Repair and the Advantages of Sex

The cost-benefit analysis of redundancy is, in our view, the key to understanding the origin of sex. The critical problem in correcting errors by redundancy is the cost. In Fig. 3 we contrast a recovery strategy, i.e., one in which redundancy is used to repair disfunctional genomes, with a replicative strategy in which no recovery takes place. What we call a recovery strategy here is, in most contexts, referred to as recombinational repair. Recombination refers to the fact that the recovered genome is composed of information derived from both parents. Repair refers to the overcoming of genome damage. The basic idea in the recovery strategy is that it generates a new functional genome from damaged ones, as illustrated in Fig. 3a. In so doing it pays a cost which might be a slower replication rate in the absence of damaged genomes. A purely replicative strategy ignores damaged genomes, but may allow faster replication in the

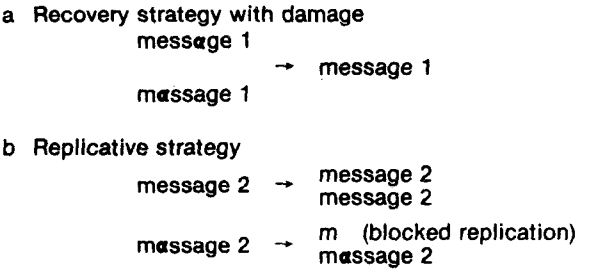

FIG. 3. Recovery and replicative strategies.

presence of unlimited resources. If there are many damaged genomes around, then the recovery strategy pays off in a higher per capita rate of increase especially if resources are limiting; if not then the replicative strategy is superior. As organic evolution proceeded to make the information more complex and hence the message more lengthy, damage became an increasingly important factor. The advantages of recovery eventually predominated over the advantages of pure replication, in achieving transmission of viable genomes to offspring.

While recovery is clearly advantageous, it is less clear why sex is favored over diploidy or some degree of polyploidy. The critical issue is the cost of redundancy in cells, as illustrated in Fig. 4. Let us assume for simplicity that each cell can accrete resources at the same rate as any other. In Fig. 4, each arrow represents the time interval needed for one cell to accrete enough resources to make one copy of the genome. One can see that without damage, a haploid cell (Fig. 4b) makes new copies of the genome at twice the rate as the diploid. However as illustrated in Fig. 4c, a purely replicative strategy is not competitively superior in the presence of damage; in this case the haploid can barely hold its own and is eliminated in competition with the diploid.

The point of a sexual strategy, which is a compromise between diploidy and haploidy is that the cost of redundancy in diploidy is quite high, while, at the same time, a lack of recovery in the haploid is disasterous. Hence there is a competitive advantage to a strategy in which the fusion of cells into a diploid state is transient, thus reaping the rewards of redundancy and recovery, while minimizing the costs. The result is illustrated schematically in Fig. 5. One can see that, over an interval of three time units, the number of genomes in the diploid strategy has increased by a factor of three, while in the sexual strategy the number of genomes has increased by a factor of four. This assumes that there are no costs associated with fusion itself, that cells with genome damage can still fuse, and that damages which arise in the diploid strategy are immediately repaired

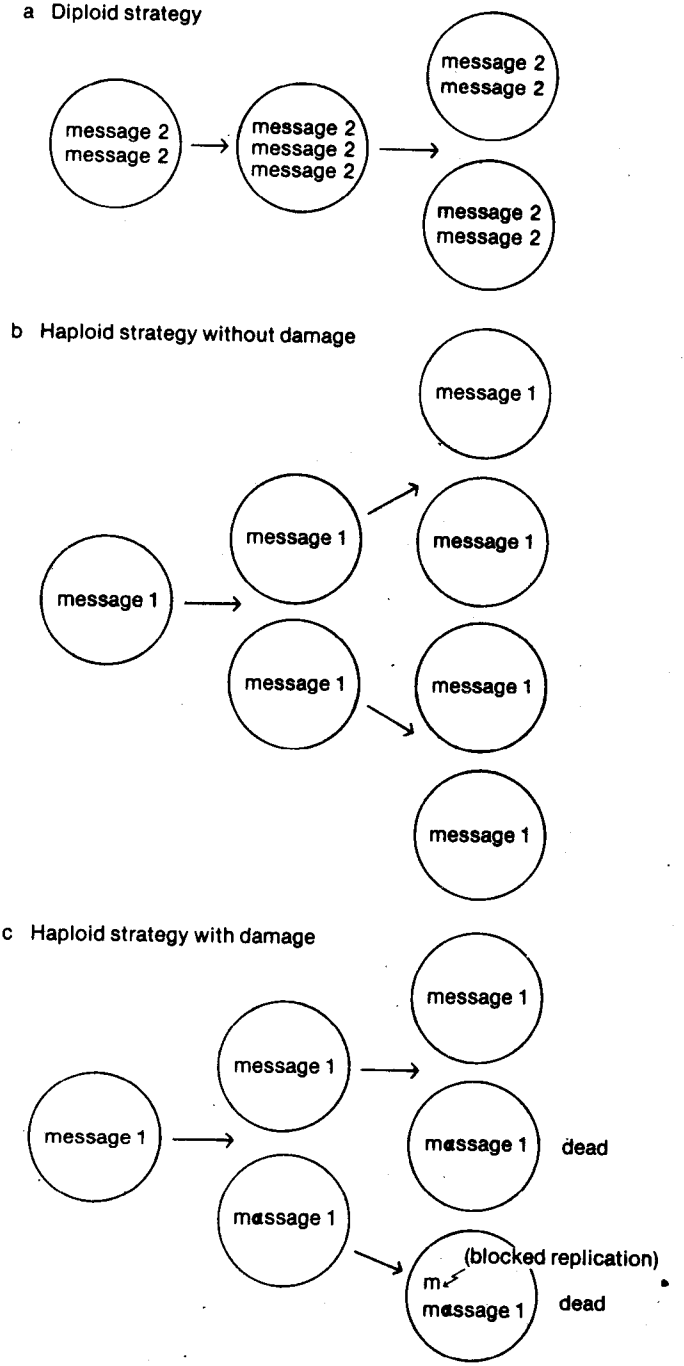

FIG. 4. Cost and benefit of redundancy in diploidy.