Aging, Sex, and DNA Repair

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Preface

Both aging and sexual reproduction (sex) reflect a universal property of life, vulnerability of the genetic material to damage. This idea, and the evidence bearing on it, are the subject of this book. In the scientific literature, aging and sex are usually dealt with as separate subjects. However, because we hypothesize that both phenomena are related consequences of a single cause—genome damage—we consider it logical to treat them together. We begin with established properties of DNA and show, first, that aging is a direct consequence of DNA damage and, second, that sex is a consequence of the need to transmit damage-free genetic information to progeny. Organisms cope with DNA damage by special repair processes. Understanding these processes is crucial to understanding aging and sex. The scientific literature in each of the individual areas of aging, sex, and DNA repair is vast, and so we focus only on those studies which are relevant to our general thesis. Within this framework, however, we try to be complete in presenting evidence for and against our hypothesis.

Over the years we have worked collaboratively on the ideas presented here and discussed them with many individuals. We have enjoyed extensive fruitful collaborations with our colleagues Helen Gensler, Fred Hopf, and Rick Michod. We have also enjoyed collaborations with Henry Byerly, Greg Byers, and Jennifer Hall on specific aspects. In addition, we have benefited greatly from the intellectual stimulation of our current and past Ph.D. graduate students, Steve Abedon, Marian Baldy, Jim Cornett, Peh-yean Cheah, Davis Chen, John Delaney, Kathleen Fisher, Eric Floor, George Holmes,

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To Our Children, Beryl, Golda, and Benjamin
and
in Memory of Fred Hopf

Chapter One

Introduction: Major Ideas and Historical Perspectives

I. *Definitions of Aging and Sex*

Aging can be defined as inherent, progressive impairments of function (Sonneborn, 1978). It occurs in multicellular species as well as in many unicellular organisms.

Some meanings of sex, such as genital union and gender, refer to particular aspects of the sexual process in particular species. Such aspects are not universal. Sexual reproduction does, however, have two features that can be regarded as defining characteristics. The first is recombination, which is the exchange of genetic material between pairs of chromosomes. The second is outcrossing, which means that the two chromosomes exchanging information originate from two different parents. Other features of sex are present almost universally, so that for most organisms sex has the following four steps: (1) two haploid genomes, each from a separate parent, come together in a shared cytoplasm; (2) the chromosomes comprising the two haploid genomes pair so that homologous sequences are aligned; (3) exchange of genetic material occurs between the pairs; and (4) progeny containing the new recombinant chromosomes are formed.

In Section II below, we outline the subjects developed in each of the succeeding chapters. In Section III, we review the historical background of the key ideas on aging and sex that are the basis of this book. We also review the historical background of the major conflicting ideas.

II. *DNA Damage as the Basic Cause of Aging and Sex*

Genome damage is a universal problem for life. The genetic material, DNA (RNA in some viruses), is unstable under physiological conditions. DNA is further assaulted by reactive chemicals that are found in the intracellular environment. Both instability and assault by reactive chemicals cause DNA to become damaged. As noted by Haynes (1988), DNA is composed of rather ordinary molecular subunits, which are not endowed with any peculiar kind of quantum mechanical stability. He considered that its very "chemical vulgarity" makes DNA subject to all the "chemical horrors" that might befall any such molecule in a warm aqueous medium. Evidence that DNA damages are common in nature is reviewed in Chapter 2.

When DNA damages occur, they are either repaired or they remain in the genome of a cell. Unrepaired DNA damages can result in loss of genetic information and interference with transcription and replication (see Chapter 3). Thus, unrepaired DNA damages are deleterious and often lethal. Aging, we will argue, is mainly due to the accumulation of unrepaired DNA damages in somatic cells. On the other hand, we will argue that the primary function of sexual reproduction is to increase the repair of damages in germ cell DNA so that it can be passed on undamaged to progeny. Thus, we propose that aging and sexual reproduction are two sides of the same coin: Aging reflects the accumulation of DNA damage, and sex reflects the removal of DNA damage. These two ideas are referred to, respectively, as the DNA damage hypothesis of aging and the DNA repair hypothesis of sex.

Most of the work on aging has been done with mammals; therefore, most of our discussion on aging will focus on that in mammals. In Chapter 4 we present evidence that, in some mammalian cell types, DNA damage accumulates with time. In Chapter 5 we present evidence that the accumulation of DNA damage is associated with a decline in gene expression as well as a decline in cellular, tissue, and organ function. This implies a cause and effect relationship between DNA damage and the functional declines that define aging. In Chapter 6 we present evidence that oxidative free radicals, produced as by-products of metabolism, are a general source of DNA damages, which are important in mammalian aging. In Chapter 7, we show that, among different mammalian species, life span correlates with

DNA repair capacity, suggesting that DNA repair is a determinant of longevity. Additionally, in Chapter 7 we present evidence that irradiation of mammals with X-rays or treatment with DNA-damaging chemicals shortens life span and causes some features of premature aging. Furthermore, we review evidence that genetic syndromes in humans with higher than normal levels of DNA damage have features of premature aging. The evidence from Chapter 7, taken together, implies that an increased rate of accumulation of DNA damage causes an increased rate of aging. In Chapter 8 we compare aging in mammals with aging in other species. We conclude that the strategy used by mammals to cope with DNA damage is but one of several options in nature. The range of DNA repair processes available to overcome DNA damages is reviewed in Chapter 9.

In multicellular organisms, DNA damage in germ cells causes the death of those cells and loss of potential progeny. Meiosis is a key stage of the sexual cycle. It is the process by which germ cells are produced. A distinctive feature of meiosis is an intimate pairing of homologous chromosomes, accompanied by the exchange of DNA between them. This exchange is called recombination. We argue that recombination reflects a particularly effective type of DNA repair process—recombinational repair. In Chapter 10 we review substantial evidence that recombinational repair is efficient at removing various types of DNA damage. Evidence is presented in Chapters 11 and 12 that meiosis is an adaptation that specifically promotes production of germ cells that have been freed of DNA damage through recombinational repair.

As noted in Section I above, sexual reproduction has a second basic characteristic in addition to recombination—outcrossing. We argue in Chapter 13 that outcrossing in diploid organisms is selected because it promotes masking, or complementation, of deleterious mutations. Thus, a full explanation of sex must take into account the influence of both DNA damage and mutation; therefore, from now on we will refer to the DNA repair hypothesis of sex as the DNA repair (and complementation) hypothesis of sex. From the evidence discussed in Chapters 10 and 13, plus evidence on the molecular basis of sex in simple organisms, we propose in Chapter 14 an explanation for the origin and early evolution of sex.

Most earlier theories of aging are consistent with the DNA damage hypothesis of aging, with some small changes in emphasis or

content. We review these basically consistent theories in Chapter 15 as well as some hypotheses on aging that are not consistent with the DNA damage hypothesis of aging. Furthermore, we review three general theories on sex. One of these is consistent with the DNA repair (and complementation) hypothesis of sex whereas two are not. In Chapter 16 we present an overview of the major ideas in the first 15 chapters. We discuss the implications of these ideas for future efforts to forestall aging and also describe the future research directions suggested by these ideas. In Section III, below, we discuss the historical background of the DNA damage hypothesis of aging, the DNA repair (and complementation) hypothesis of sex, and some of the prominent competing ideas.

III. *Historical Background*

Historical perspectives on aging, sex, and DNA repair have been presented previously. In particular, reviews were presented by Comfort (1979) on aging, Ghiselin (1988) on sex, and Bernstein (1981) on DNA repair. Here, however, we will briefly outline the historical background of the specific concepts that figure prominently in this book. In Section A, below, we describe the historical background of the idea that DNA damage is the basis of aging. We also review the history of the major conflicting idea that aging is a genetically programmed adaptation, selected for the benefit of the species. In Section B, we review the historical background of the two hypotheses that form the basis of our explanation for sex. These are the hypotheses that recombination is an adaptation for repairing DNA damage and that outcrossing in multicellular organisms is maintained by the benefit of masking deleterious mutations. In addition, we explain the main idea that is in conflict with these hypotheses. This is the idea that sex is an adaptation for promoting genetic variation. We also review the historical background of this conflict.

A. The DNA Damage Hypothesis of Aging

The hypothesis that DNA damage directly causes aging was preceded by the concept that somatic mutation is the basis of aging and that DNA damage is only indirectly involved because it can cause mutations. The somatic mutation hypothesis was first pro-

posed by Failla (1958); other early proponents of the idea were Szilard (1959) and Harmon (1962). As we discuss in Chapter 2, Section I, DNA damage and mutation have fundamentally different properties and consequences. In Chapter 15, Section I.H, we review evidence showing that somatic mutation probably is not the primary cause of aging, although it may account for specific kinds of aging problems, as discussed in Chapter 8, Section III.C.

Alexander (1967) was the first to suggest that DNA damage per se, apart from its role in inducing mutation, may be the primary cause of aging. Alexander noted that the term somatic mutation has a very definite meaning and must not be used to refer to every change involving the cell's DNA. He indicated that a number of experiments independently suggest that the accumulation of somatic mutations throughout life does not play a major role in initiating aging in mammals. However, he proposed that damage to DNA does play a part in the death of postmitotic cells. Alexander postulated that DNA damages accumulate during life in postmitotic cells. These interfere with RNA synthesis and, therefore, protein synthesis until they are lethal to the cell. He also emphasized that at the time (1967) no experimental evidence existed to support such a hypothesis.

Since Alexander's original proposal, the evidence bearing on the DNA damage hypothesis of aging was reviewed by several workers. Gensler and Bernstein (1981) evaluated and unified the numerous diverse lines of argument that support this hypothesis. Tice and Setlow (1985) presented an examination of evidence on DNA damage and repair in aging organisms and cells. Evidence bearing on the DNA damage hypothesis of aging has also been reviewed by Hart *et al.* (1979), Rothstein (1982: pp. 132–173), Eichhorn (1983), Ames *et al.* (1985), Hanawalt (1987), Gensler *et al.* (1987), and Rattan (1989).

The DNA damage hypothesis of aging assumes that aging is a nonadaptive consequence of DNA damage. Therefore, this hypothesis is incompatible with all theories that assume that aging exists because it is beneficial. The idea that aging evolved as a beneficial adaptation for the species traces back to Weismann (1889: p. 24). His argument was based on the supposition that even if individuals were somehow able to maintain immortality they would be progressively worn out by injuries from external factors. From this he argued that worn out individuals are not only valueless to the species but are

even harmful, because they take the place of those that are sound. He considered that by the operation of natural selection the life of the hypothetically immortal individual would be shortened by the amount that was useless to the species. Weismann further considered that death is not a primary necessity but that it has been secondarily acquired as an adaptation. He believed that life is endowed with a fixed duration, not because it is contrary to its nature to be unlimited but because unlimited life span would be a "luxury without corresponding advantage."

Kirkwood (1984) has pointed out that the view that aging is adaptive is still widely held and is implicit in the popular idea that aging is a programmed process under its own strict genetic control. He noted that if this idea is to withstand close scrutiny it must explain why, other things being equal, an organism that ages is fitter in a neo-Darwinian sense than one that does not. He then argued that on this crucial test adaptive theories have failed. One part of Kirkwood's argument is that for aging to have arisen adaptively the benefit to the *species* must be more effective in selection than the benefit to *individuals* that results from the reproductive advantages of a longer life. Chronologically older individuals who did not age should have more progeny and, therefore, greater fitness. Superiority of selection based on a species advantage rather than on an advantage to individuals occurs only under special circumstances. Therefore, aging as an adaptive mechanism cannot normally be stably maintained. The issue of programmed aging is discussed further in Chapter 15, Section I.J.

Even if aging is not a programmed adaptation, the rate of aging may still be under genetic control. For instance, by the DNA damage hypothesis, genes that encode enzymes that inactivate DNA-damaging agents or repair damage are adaptive and should be selected for. These genes should reduce the rate of aging. In this limited sense, aging may be regarded as genetically programmed. This, however, does not imply that aging itself is a beneficial adaptation.

B. The DNA Repair (and Complementation) Hypothesis of Sex

The hypothesis that the function of sex is to repair damages in germ line DNA was first proposed by Dougherty (1955). He postulated that the evolution of sex was the result of a single phy-

logenetic sequence. He thought that sex is advantageous because it allows two damaged DNA molecules to "pool their undamaged parts" and reconstitute an intact unit. Dougherty's idea, however, lay dormant for two decades until it was revived independently by Maynard Smith (1975), Bernstein (1977), Martin (1977), and Walker (1978).

Since 1955, when the idea was first proposed, a much better appreciation of the importance of damage and repair (see Chapters 2 and 9) and a firmer picture of early evolutionary events (Chapter 14) have been achieved. Maynard Smith (1975: p. 190) suggested that the enzymes required for genetic recombination between chromosomes may have evolved originally to repair damaged DNA, and that genetic exchange may have arisen very early in the history of life. Bernstein (1977) presented evidence that germ line recombination may be a manifestation of DNA repair processes. Martin (1977) reviewed observations that related aging with DNA damage, meiosis with DNA repair, and rejuvenation with meiosis. C. Bernstein (1979, 1981) and H. Bernstein (1983) presented evidence that the ability of recombinational repair to efficiently overcome different kinds of damage in various organisms supports the DNA repair hypothesis of sex. In addition, proposals for the evolution of sex (Bernstein *et al.*, 1981) and the origin of sex (Bernstein *et al.*, 1984) based on the DNA repair (and complementation) hypothesis were presented. This hypothesis was also developed by Bernstein *et al.* (1985a) from the perspective of the general problem of random noise in transmitting information. The various lines of evidence bearing on the hypothesis were reviewed by Bernstein *et al.* (1987).

More than 60 years before Dougherty's 1955 proposal that the function of sex is the repair germ line DNA, other workers had proposed the similar idea that the function of sex is rejuvenation. In 1892, Weismann commented that a widely held view among his contemporaries was that the advantage of sex is rejuvenation. Weismann himself did not agree with this view. A major observation supporting the rejuvenation concept was that in some protozoans vitality declines during the course of successive asexual divisions by binary fission, but that after sexual reproduction (conjugation) vitality is restored. Maupas, a principal advocate of the rejuvenation idea, contended that conjugation is needed to ensure the continuation of the species, because it imparts to the animal the power "de renoveler

et rejeunir les sources de la vie" (Maupas, 1889 [quoted by Weismann, 1892]). Weismann (1892: p. 197) found it difficult to understand how an "almost exhausted vital force" could be raised again to its original state of activity as the result of a union with another equally exhausted force.

Work during the last 40 years on DNA damage and repair has provided a rational basis for explaining the rejuvenation that occurs during sexual reproduction. We present evidence in Chapter 8, Section I.B, that restoration of vitality in paramecia is likely to be based on the repair of DNA damage during conjugation. Medvedev (1981) reviewed the genetic and biochemical mechanisms bearing on the immortality of the germ line. He concluded that rejuvenation of germ cells occurs, in part, by meiotic recombination and repair—unique processes capable of restoring the integrity of DNA and chromosomes that have damages which are irreversible when they occur in somatic cells.

One way in which DNA damage is repaired involves replacement of damaged information in one DNA molecule by undamaged information from another homologous molecule. The two homologous DNA molecules need not be identical in sequence to exchange information but may contain mutational or allelic variations. The process of physical exchange of parts between two homologous DNA molecules is recombination. Recombination generates genetic change because it breaks up associations of linked alleles and randomly generates new allelic associations. As pointed out by Shields (1982: p. 67), the majority of new associations are likely to be either selectively neutral or disadvantageous, because they were generated by random changes in parental DNAs that had survived previous natural selection. Recombination is one source of the inheritable variation upon which natural selection operates, the other is mutation.

There are two contrasting views on the adaptive advantage of recombination. One view argues that recombinational variation is the primary selective force maintaining sex (for recent examinations of this idea, see Bell, 1988; Bernstein *et al.*, 1988; Crow, 1988; Felsenstein, 1988; Maynard Smith, 1988; Shields, 1988; and Williams, 1988). The alternative view is that, because new allelic associations are more often disadvantageous than advantageous to the individual, the process of recombination would be selected against if

not for the benefit of recombinational repair. We think that recombination persists as the central feature of sex because of a trade-off between the benefit to the individual of efficiently repairing germ cell DNA damages (which if unrepaired are deleterious and often lethal) and the disadvantage of generating, as a by-product, recombinational variations (which are most often neutral or mildly deleterious to the individual, but rarely lethal).

The difference in the two points of view about the adaptive advantage of recombination ultimately comes down to whether or not one considers DNA damage in germ cells to be a serious problem that needs to be handled by recombinational repair. If it is not serious, one could suppose that the process of recombination is selected for independently of its repair function, perhaps for the benefit of recombinational variation. On the other hand, if DNA damage is a serious problem leading to the death of gametes, then recombination could be selected solely for its role in repair. In Chapters 2 and 3 we review evidence showing that DNA damage is prevalent and is a likely cause of functional decline. In Chapters 11 and 12 we discuss the importance of DNA damage in relation to germ cell formation.

As mentioned in Section II, above, we assume that outcrossing in diploid organisms is selected because it promotes masking, or complementation, of deleterious mutations. This view has a long history. Charles Darwin, in his book "The Effects of Cross and Self Fertilization in the Vegetable Kingdom" (1889), came to clear and definite conclusions about the adaptive advantage of sex. For instance, on page 462 he concluded that the offspring from the union of two distinct individuals, especially if their progenitors have been subjected to very different conditions, have a great advantage in height, weight, constitutional vigor, and fertility over the self-fertilized offspring from either one of the same parents. He considered that this fact was amply sufficient to account for the development of sexual reproduction. The reduced vigor associated with inbreeding is now recognized as being due largely to the expression of deleterious recessive alleles. The progeny of outcrosses are more vigorous because such deleterious recessive alleles are usually masked. Masking occurs because distantly related parents are unlikely to carry the same deleterious recessive alleles.

Weismann proposed another explanation for outcrossing based on the advantage of inheritable variation. Weismann (1892) was moti-

vated by a need to explain the source of inheritable variation on which natural selection must operate. In the absence of knowledge about mutation (a concept that had not yet emerged), he adopted the reasonable view that outcrossing was the source of inheritable variation. He further contended that production of inheritable variation was *the* adaptive function of sex. Thus, although he was otherwise a staunch Darwinian, Weismann advocated a different view on the adaptive advantage of sex than Darwin himself. Weismann (1892: p. 195) held that the deeper significance of every form of amphimixis—whether occurring in conjugation, fertilization, or in any other way—is the "creation of the hereditary individual variability," which is requisite for the operation of the process of selection and arises from the periodic mingling of two different hereditary substances. This explanation assumes that the advantage of sex is at the level of the evolution of the species rather than at the level of the individual organism's ability to produce viable progeny.

Interestingly, Weismann was aware of the problem that variation did not appear to be advantageous to the individual organism. He noted (Weismann, 1892: p. 213) that conjugation must have had some beginning, and although he believed that in its present form it signifies a source of variability, he considered that it originally must have had some other meaning, because two Monera would scarcely coalesce to ensure variability in their descendants.

Weismann's general explanation for the advantage of sex, rather than Darwin's, has prevailed during most of the past century. Recently, Michod (1986) pointed out the fallacy of reasoning that because variation is essential for evolution selection will tend to produce phenotypes that produce variation. Michod further commented that although most modern evolutionists would agree that this logic is faulty it is precisely what many evolutionary biologists, over the past century, have had in the back of their minds, and to this day it is what motivates biologists to accept the variation hypothesis even though there is little evidence for it.

In recent years, much effort has gone into trying to show an advantage of recombinational variation at the level of competing individual organisms rather than competing groups of organisms. There is, however, widespread skepticism that any particular variation model can provide a general explanation for the adaptive benefit of sex (Maynard Smith, 1978; Williams, 1975). Maynard Smith (1978:

p. 10) commented in his authoritative book "The Evolution of Sex" that he feared the reader may find these models "unsubstantial and unsatisfactory"; however, he noted that they are the best we have.

The alternative view (Darwin's), that the advantage of outcrossing is the greater vigor of the progeny of outcrosses, has been presented in a modern genetic interpretation by Bernstein *et al.* (1985b) as part of the repair (and complementation) hypothesis of sex (see Chapter 13, Section III.B). Supporters of this view do not deny the necessity of genetic variation for evolution; however, they consider that the variation produced by sex arises as a natural by-product of the DNA exchanges employed in the repair of DNA damage.

References

Alexander, P. (1967). The role of DNA lesions in processes leading to aging in mice. *Symp. Soc. Exp. Biol.* **21,** 29–50.

Ames, B. N., Saul, R. L., Schwiers, E., Adelman, R., and Cathcart, R. (1985). Oxidative DNA damage as related to cancer and aging: Assay of thymine glycol and hydroxymethyluracil in human and rat urine. *In* "Molecular Biology of Aging: Gene Stability and Expression" (R. S. Sohal, L. S. Birnbaum, and R. G. Cutler, eds.), pp. 137–144. Raven Press, New York.

Bell, G. (1988). Uniformity and diversity in the evolution of sex. *In* "The Evolution of Sex: An Examination of Current Ideas" (B. Levin and R. Michod, eds.), pp. 127–138. Sinauer, New York.

Bernstein, C. (1979). Why are babies young? Meioses may prevent aging of the germ line. *Perspect. Biol. Med.* **22,** 539–544.

Bernstein, C. (1981). Deoxyribonucleic acid repair in bacteriophage. *Microbiol. Rev.* **45,** 72–98.

Bernstein, H. (1977). Germ line recombination may be primarily a manifestation of DNA repair processes. *J. Theor. Biol.* **69,** 371–380.

Bernstein, H. (1983). Recombinational repair may be an important function of sexual reproduction. *BioScience* **33,** 326–331.

Bernstein, H. , Byers, G. S., and Michod, R. E. (1981). Evolution of sexual reproduction: Importance of DNA repair, complementation and variation. *Am. Nat.* **117,** 537–549.

Bernstein, H., Byerly, H. C., Hopf, F. A., and Michod, R. E. (1984). Origin of sex. *J. Theor. Biol.* **110,** 323–351.

Bernstein, H., Byerly, H. C., Hopf, F. A., and Michod, R. E. (1985a). The evolutionary role of recombinational repair and sex. *Int. Rev. Cytol.* **96,** 1–28.

Bernstein, H., Byerly, H. C., Hopf, F. A., and Michod, R. E. (1985b). Genetic damage, mutation and the evolution of sex. *Science* **229,** 1277–1281.

Bernstein, H., Hopf, R. A., and Michod, R. E. (1987). The molecular basis of the evolution of sex. *Adv. Genet.* **24,** 323–370.

Bernstein, H., Hopf, F. A., and Michod, R. E. (1988). Is meiotic recombination an adaptation for repairing DNA, producing genetic variation, or both? *In* "The Evolution of Sex: An Examination of Current Ideas" (B. Levin and R. Michod, eds.), pp. 139–160. Sinauer, New York.

Comfort, A. (1979). "The Biology of Senescence." Elsevier, New York.

Crow, J. F. (1988). The importance of recombination. *In* "The Evolution of Sex: An Examination of Current Ideas" (B. Levin and R. Michod, eds.), pp. 56–73. Sinauer, New York.

Darwin, C. (1889). "The Effects of Cross and Self Fertilization in the Vegetable Kingdom." D. Appleton and Co., New York.

Dougherty, E. C. (1955). Comparative evolution and the origin of sexuality. *Syst. Zool.* **4,** 145–190.

Eichhorn, G. L. (1983). Nucleic acid biochemistry and aging. *In* "Review of Biological Research in Aging," Vol. 1 (M. Rothstein, ed.), pp. 295–303. Alan R. Liss, New York.

Failla, G. (1958). The aging process and carcinogenesis. *Ann. N.Y. Acad. Sci.* **71,** 1124–1135.

Felsenstein, J. (1988). Sex and the evolution of recombination. *In* "The Evolution of Sex: An Examination of Current Ideas" (B. Levin and R. Michod, eds.), pp. 74–86. Sinauer, New York.

Gensler, H. L., and Bernstein, H. (1981). DNA damage as the primary cause of aging. *Q. Rev. Biol.* **56,** 279–303.

Gensler, H. L., Hall, J. D., and Bernstein, H. (1987). The DNA damage hypothesis of aging: Importance of oxidative damage. *In* "Review of Biological Research in Aging," Vol. 3 (M. Rothstein, ed.), pp. 451–465. Alan R. Liss, New York.

Ghiselin, M. T. (1988). The evolution of sex: A history of competing points of view. *In* "The Evolution of Sex: An Examination of Current Ideas" (B. Levin and R. Michod, eds.), pp. 7–23. Sinauer, New York.

Hanawalt, P. C. (1987). On the role of DNA damage and repair processes in aging: Evidence for and against. *In* "Modern Biological Theories of Aging" (M. R. Warner, R. N. Butler, R. L. Sprott, and E. L. Schneider, eds.), pp. 183–198. Raven Press, New York.

Harmon, D. (1962). Role of free radicals in mutation, cancer, aging and the maintenance of life. *Radiat. Res.* **16,** 753–763.

Hart, R. W., D'Ambrosio, S. M., Ng, K. J., and Modak, S. P. (1979). Longevity, stability and DNA repair. *Mech. Ageing Dev.* **9,** 203–223.

Haynes, R. H. (1988). Biological context of DNA repair. *In* "Mechanisms and Consequences of DNA Damage Processing" (E. C. Friedberg and P. C. Hanawalt, eds.), pp. 577–584. Alan R. Liss, New York.

Kirkwood, R. B. L. (1984). Towards a unified theory of cellular aging. *Monogr. Dev. Biol.* **17,** 9–20.

Martin, R. (1977). A possible genetic mechanism of aging, rejuvenation, and recombination in germinal cells. *ICN-UCLA Symp. Mol. Cell. Biol.* **7,** 355–373.

Maupas, E. (1889). La rejeunissement chez les cilies. *Arch. Zool. Exp. Gen.* **7(2),** 149–517.

Maynard Smith, J. (1975). "The Theory of Evolution," 3rd ed. Penguin Books Ltd., Harmondsworth, England.

Maynard Smith, J. (1978). "The Evolution of Sex." Cambridge University Press, London.

Maynard Smith, J. (1988). The evolution of recombination. *In* "The Evolution of Sex: An Examination of Current Ideas." (B. Levin and R. Michod, eds.), pp. 106–125. Sinauer, New York.

Medvedev, Z. A. (1981). On the immortality of the germ line: Genetic and biochemical mechanisms. A review. *Mech. Ageing Dev.* **17,** 331–359.

Michod, R. E. (1986). On fitness and adaptedness and their role in evolutionary explanation. *J. Hist. Biol.* **19,** 289–302.

Rattan, S. I. S. (1989). DNA damage and repair during cellular aging. *Int. Rev. Cytol.* **116,** 47–88.

Rothstein, M. R. (1982). "Biochemical Approaches to Aging." Academic Press, New York.

Shields, W. M. (1982). "Philopatry, Inbreeding and the Evolution of Sex." State University of New York Press, Albany.

Shields, W. M. (1988). Sex and adaptation. *In* "The Evolution of Sex: An Examination of Current Ideas." (B. Levin and R. Michod, eds.), pp. 253–269. Sinauer, New York.

Sonneborn, T. M. (1978). The origin, evolution, nature and causes of aging. *In* "The Biology of Aging." (J. A. Behnke, C. E. Finch, and G. B. Moment, eds.), Chapter 21, pp. 361–374. Plenum Press, New York.

Szilard, L. (1959). On the nature of the aging process. *Proc. Natl. Acad. Sci. U.S.A.* **45,** 30–45.

Tice, R. R., and Setlow, R. B. (1985). DNA repair and replication in aging organisms and cells. *In* "Handbook of the Biology of Aging." (C. E. Finch and E. L. Schneider, eds.), pp. 173–224. Van Nostrand Reinhold, New York.

Walker, I. (1978). The evolution of sexual reproduction as a repair mechanism. Part I. A model for self-repair and its biological implications. *Acta Biotheor.* **27,** 133–158.

Weismann, A. (1889). "Essays upon Heredity and Kindred Biological Problems," Vol. I. Clarendon Press, Oxford.

Weismann, A. (1892). "Essays upon Heredity and Kindred Biological Problems," Vol. II. Clarendon, Oxford.

Williams, G. C. (1975). "Sex and Evolution." Princeton University Press, Princeton, New Jersey.

Williams, G. C. (1988). Retrospect on sex and kindred topics. *In* "The Evolution of Sex: An Examination of Current Ideas." (B. Levin and R. Michod, eds.), pp. 287–298. Sinauer, New York.

Chapter Two

DNA Damage

In this chapter, we review the nature of DNA damage and, especially, emphasize the distinction between DNA damage and mutation. We then discuss each of the various kinds of DNA damage that appear to be common in nature.

I. *DNA Damages as Physically Distinct Alterations in Polynucleotide Chains*

DNA damage is very different from mutation. A DNA damage is a DNA alteration that has an abnormal structure. A mutation, on the other hand, is a change in the DNA sequence rather than a change in DNA structure. Biologically, DNA damages and mutations have different consequences. A damage cannot be replicated; therefore, it cannot be inherited. A mutation is a change in the polynucleotide sequence in which standard base pairs are substituted, added, deleted, or rearranged. Even when mutations are large changes, such as extended deletions, the DNA is still an uninterrupted sequence of standard nucleotide pairs. Because of this, mutations can be replicated; thus mutations, unlike damages, can be inherited.

Another way in which DNA damages and mutations differ is with respect to repair. Because a DNA damage is an abnormal alteration in DNA structure, it can be recognized by enzymes. The altered structure can be removed and replaced; thus, DNA damage can be repaired (discussed further in Chapter 9). On the other hand, a mutation has a regular DNA structure. There is no correction mechanism for converting a new base pair, or an added or deleted sequence, back