Robert H. Haynes

Genetic Stability and Change

Geboren 1931 in London, Canada. Studium an der University of Western Ontario (B. Sc., physics, 1953; Ph. D., biophysics, 1957). Forschungsstipendiat, St. Bartholomew's Hospital Medical College, London, U. K. (1957-58); Assistenz-Professor für Biophysik, Universität Chicago (1958-64); außerordentlicher Professor für Biophysik; University of California, Berkeley (1964-68); zur Zeit Forschungsprofessor für Biophysik, York University, Toronto. Präsident des XVI. International Congress of Genetics. Forschung über die Rheologie des Blutes, Strahlenphysik und -biologie; DNA repair and mutagenesis in microorganisms; genetic consequences of deoxyribonucleotide pool imbalance in yeast. Adresse: Department of Biology, York University, 4700 Keele St., North York, Ontario, M3J 1P3, Canada.

During the nine month period (January — September, 1989) that I was in residence at the Wissenschaftskolleg my primary task was to begin work on an advanced monograph on the molecular basis of genetic stability and change in cells. I also wrote two papers[1,2] and completed work on another[3] each of which will, in expanded form, become a chapter in my book. In addition, I was invited to give several lectures at various institutions in Germany (West and East) and in Moscow. Some of these lectures concerned another, very `far-out', topic which is my current intellectual folly: the exploration and assessment of the technical, philosophical and public policy aspects of recent informal proposals to undertake a feasibility study of prospects for establishing an indigenous microbial ecosystem, or biosphere, on Mars. At present so little is known about environmental conditions on the Red Planet that current discussions of this exotic enterprise tend to be more `philosophical', or `political', than scientific. Thus, I benefitted greatly from many lively conversations with other Fellows of the Kolleg on some of the novel questions that arise when considering any such project even as a *'Gedankenexperiment'*.

Genetic stability and change: Heredity, the fact that `like begets like', is a manifestation of the *stability* of genes and chromosomes from one generation to the next. Heritable variation is a manifestation of their *instabil-*

ity, or mutation, recombination, rearrangement and reduplication within cells and chromosomes. Over the past 25 years research in many laboratories has revealed that there exists at the *molecular* level an intimate relation between these countervailing processes of genetic stability and change. It is rooted in the macromolecular structure of the genetic material (DNA) and the biochemical mechanisms for its replication, recombination and repair. Indeed, it has become clear that one must first elucidate the molecular basis of genetic stability in order to understand the processes of genetic change. It is important to elucidate the mechanisms of genetic change and variation, not only on account of their basic physiological and evolutionary significance, but also for another, very practical reason: mutations, and heritable defects in DNA repair, are critical etiological factors in genetic disease and cancer. There exist many potential sources of DNA alteration or damage. If these had free rein, the mutation rate in cells would be so high that their genetic integrity, and even their viability, could not be maintained: most would die of lethal mutations, blockage of DNA replication, or physiochemical erosion of the genome. DNA structural alterations also can be produced by agents which do not attack DNA directly. For example, cells treated with drugs which inhibit enzymes involved in the biosynthesis of deoxyribonucleotides exhibit elevated levels of genetic change. Arrayed against these destabilizing influences is an amazing battery of diverse biochemical processes that promote genetic stability and cell viability. It would appear that natural selection has moulded all major aspects of DNA metabolism to minimize mortality and mutability, but with cellular viability taking precedence over genetic fidelity. Since mutation rates are so extremely low, it is clear that the genetic machinery of cells constitutes a remarkable example of a highly reliable, dynamic system built from vulnerable and unreliable parts. The book on which I began work at the Wissenschaftskolleg will trace the historical development of ideas in this field, beginning with the first, purely physical, theory of genetic stability put forward by Max Delbrück in 1935. The main body of the text will summarize the essential features of our current understanding of the biochemical mechanisms of DNA replicational fidelity and repair, with special emphasis on the significance of these processes for the origin and evolution of cells.

Life on Mars: `Ecopoiesis' is the word now used to describe the fabrication of a sustainable microbial ecosystem on an initially lifeless planet, thereby establishing a new arena in which biological evolution might proceed independently of further human husbandry. Mars is the only possible target for ecopoiesis available to us as it is, apart from Earth, the only other biocompatible planet in the solar system. In January 1988, a small group of scientists met at the NASA Ames Research Centre to dis-

cuss whether or not it is reasonable to initiate a feasibility study of ecopoiesis within the next few years. Present environmental conditions on Mars are extremely hostile, indeed destructive, to any known form of carbon-based life. However, the surface of the planet possesses substantial quantities of the basic materials needed to support life, in particular, water and carbon dioxide. The general scenario for ecopoiesis would include two main phases: first planetary engineering designed to warm the planet, release liquid water, and produce a thick carbon dioxide atmosphere. Second, biological engineering to design, construct and implant a community of symbiotic microorganisms capable of proliferation as a primitive ecosystem in the newly `salubious' Martian environment. Obviously, a number of ethical and political concerns are raised by this proposition which merit the attention of everyone, scientists and non-scientists alike. I have emphasized these philosophical issues in my recent papers and lectures on this subject.

It is interesting to note that the idea of bringing life to Mars has attracted the attention not only of scientists, but also of humanists. For example, the American poet, Frederick Turner, has just published a 10,000 line epic entitled *Genesis.'* In this poem he lays out in mythic form the many technological, political, ethical, theological, esthetic and psychological problems which would be associated with ecopoiesis, as well as the spiritual resources necessary for such a task. He believes that the cultivation of Mars is the most exciting challenge for mankind to-day — one that, if taken up, might well give lie to Francis Fukuyama's[5] naive prophecy that the apparent collapse of communism in the face of liberal democracy dooms our descendants to a tedious, uninspiring `post-historical' world!

References

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2 Haynes, R. H., Evolutionary significance of genetic stability and change. *Proceedings of the 6th International Conference on Environmental Mutagens,* Plenum Press, New York, in press, 1989.

3 Groot de Restrepo, H. and R. H. Haynes, The human mutagen burden and other problematic aspects of genetic toxicology. *Rev. Latinoamericano de Genetica,* in press, 1989.

4 Haynes, R. H., Ecce ecopoiesis: playing God an Mars. In „Moral Expertise: Studies in Practical and Professional Ethics" (C. D. MacNiven, ed.), Routledge, London, in press, 1989.

5 Turner, F. , "Genesis", Saybrook Publishing Company, Dallas and New York, 1988.
6 Fukuyama, F., The end of history? *National Interest,* No. 16, pp. 3-18, 1989.

Lectures

1 "Empirical equations and mechanistic models for the interpretation of doseresponse relations in mutation research", Deutsches Krebsforschungszentrum, Heidelberg (Jan. 30/89).
2 "Molecular mechanisms in genetic stability and change", Justus-Liebig-Universität, Institut für Biophysik, Giessen (May 9/89); Zentralinstitut für Genetik, Akademie der Wissenschaften der DDR, Gatersleben (Aug. 29/89); Deutsche Forschungs- und Versuchsanstalt für Luft- und Raumfahrt, Institut für Flugmedizin, Köln (Sept. 4/89).
3 "Prospects for establishing a microbial ecosystem on Mars", Freie Universität Berlin, Fachbereich Biologie (April 28/89); J. W. Goethe Universität Frankfurt/Main (May 2/89); Humboldt Universität Berlin, Ges. für physikalische und mathematische Biologie der DDR (May 25/89); Urania, Berlin (Ost), Sektion Biologie (July 4/89); Deutsche Forschungs- und Versuchsanstalt für Luft- und Raumfahrt, Köln (Sept 4/89); UNESCO-USSR Academy of Sciences Symposium on Biotechnology in the 21st Century, Moscow (Sept 13/89).