SLAC-PUB-1359
December 1973

# ON THE ORIGIN OF MOLECULAR "HANDEDNESS" IN LIVING SYSTEMS*

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Submitted for Informal Discussion at the
International Symposium on
Generation and Amplification of Asymmetry in Chemical Systems
24-26 September 1973
Jülich, Federal Republic of Germany

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* Work supported in part by the U.S. Atomic Energy Commission.

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Any non-planar molecule containing four or more distinguishable atoms or groups separated by finite distances has a conceivable non-superposable mirror counterpart (cf. Fig. 1a); this mirror image would (granting parity conservation in the relevant interactions) have the same energy levels in any reflection-invariant environment. Yet terrestrial living systems organize a neutral environment to enhance the occurance of only one of the two alternative enatiomeric forms. This property has even been advanced as a defining characteristic of life. [1] Given a self-replicating molecule of one form, sufficiently stable to reproduce itself more than once (autocatalytic chain reaction) before degenerative processes reduce its molecular structure to an unbiased (racemic) mixture of both enatiomers, there is no mystery why subsequent evolution from an originally neutral (racemic) environment will steadily increase the handedness of biologically active compounds — natural selection guarantees this statistically in the long run. [2] But proposed mechanisms for the origin of life from non-living matter (biopoesis) yield self-replicating systems of either handedness with approximately equal probability. If it were easy to cross the threshold to self-replication these would result in two living ecosystems of opposite handedness competing for the same overall area but effectively isolated in terms of biologically active food supply. We know that interpenetrating ecosystems relying on different food chains are stable at higher levels of biological organization. [3] The general theory of autocatalytic molecular evolution developed by Eigen[4] makes it clear that within a single micro-environment only a single handedness can result from a single biopoetic event. Yet, this process could occur again at a geographically separated site, and if the time scale for diffusion from one biopoetic site to another is long

enough, systems of opposite handedness could obviously result. Once established, one or the other system could achieve dominance accompanied by the extermination of its enatiomeric competitor only by means of a selective advantage which depended on handedness. Mechanisms by which such a selective advantage could operate at a macroscopic level are even harder to conceive than mechanisms acting directly at the molecular level.

It is possible that life originated in both of its conceivable enatiomeric forms, but that a unique event at a later stage in evolution gave decisive selective advantage to one of them. Richard Noyes[5] suggests that the development of photosynthesis relying on chlorophyll, which is associated either causally or temporally with the transition from a reducing to an oxidizing atmosphere around $3.2 \times 10^9$ years ago, could be such an event. Photosynthetic forms have several times the biochemical efficiency of earlier life, and the evolutionary encorporation of chlorophyll into the planetray ecosystem is (perhaps) so unlikely that it could well have resulted from a unique event, which would necessarily imply a heritable handedness. The selective advantage would then lead to the conversion of biologically produced compounds to a single handedness. We are thus led to the conclusion that either terrestrial life originated from some unique event (i. e. unique to the surface of this planet, whether indigenous or as a consequence of extraterrestrial intervention), that there was some unique handed event conveying great selective advantage at a later stage of evolution, or that there is some bias in the non-living environment sufficiently potent to favor the growth of one handedness at the expense of the other during the overall biopoetic or evolutionary process.

We could leave the question there, since much of evolution is the probable consequence of events which, taken individually, are improbable. But this would give us no lead toward studying the question -- which soon, we hope[6], will become an experimental one -- of what handedness we might expect to find in living systems encountered beyond the surface of our own planet. We therefore continue with the question of what type of handed environmental bias could have affected the origin of life. The minimal requirements for producing handedness are (a) that the environment contain two vectors, one defined by a line through two points and the other by a rotation about some axis (since this suffices to distinguish left from right as is shown in Fig. 1b),[7] and (b) that there be some specific mechanism by which this handedness can dominate over the statistical racemizing events in the biopoetic or evolutionary process.

Prior to 1957, it was usually believed that the laws of nature are neither left nor right handed; hence early speculations about the origin of handedness in biological compounds had to be connected to some macroscopic handedness of the terrestrial environment, such as those illustrated in Fig. 1c, or relegated to the category of historical accident. But the discovery[8] that beta-decay of matter yields electrons of one dominant helicity, and consequently, via bremsstrahlung, photons with a dominant handedness of circular polarization[9], opened the possibility that this handedness of the environment could lead to handed biopoesis. At much higher intensity than any natural radioactivity can yield, circularly polarized photons have been demonstrated to bias chemical reaction rates so as to produce a preponderence of molecules with one handedness, and theoretically this effect should persist down to the smallest

intensities[10]: before a serious case for basing the origin of biological handedness on the non-conservation of parity in weak interactions can be made, however, it will have to be shown that (a) the handedness of the circularly polarized bremsstrahlung will bias actual or hypothetical biopoetic reactions in the unique sense that will yield the observed (levorotary) handedness of terrestrial biogenerated molecules, and that (b) the very weak beta-decay source provides a sufficient bias to override statistical racemizing effects.

A much less accessible way to make the beta-decay hypothesis plausible would be the experimental demonstration that all living systems on planets which (like the earth) are composed of matter are levorotary, but that all living systems on planets composed of anti-matter are dextrorotary. This would be pretty convincing since the helicity of electrons from the decay of anti-matter is the opposite to that of matter. Yet even were we to discover a biologically active planet composed of antimatter, it would be a difficult object to study; any material probe would annihilate on contact. Hence any direct experimental proof for this origin of handedness in biopoesis will be hard to come by. In the remainder of this paper we will therefore confine ourselves to considering only macroscopic handed effects, but should keep in mind that the bias produced by beta-decay could be important, and that in the long run it could either enhance or mitigate against other biases in a unique direction.

The possibility of an environmental bias for the earth is easily established since the direction from the illuminated side of the earth to the sun provides a line while the earth's rotation provides an axis (Fig. 1c). During the course of a year, the earth's axis changes by $\pm$ 23.5$^{o}$ relative to this direction, but the

average handed bias persists[11]. The sense of the revolution of the earth about the sun could not have changed since the solar system assumed approximately its present configuration without disrupting the orbits of the other planets, and the sense of the earth's rotation about its own axis could not be significantly changed without releasing enough energy to destroy the surface of our planet[12]; we therefore assume that both have persisted for $4.5 \times 10^9$ years.[13]

The existence of a macroscopic geometrical bias does not in itself guarantee a means for influencing the rates of chemical reactions. Thus most mechanisms which one can invoke do not rely on the rotation of the earth but on the fact that the magnetic field of the earth is correlated in direction with the mechanical axis of rotation. For example, sunlight scattered by fluctuations in the atmospheric density acquires a linear polarization. This in itself does not help, since linear polarization is not handed. But an electron accelerated in a magnetic field radiates light which is partially circularly polarized, and consequently the handedness of the circular polarization for scattered sunlight arriving at the surface of the earth persists throughout the period of illumination.[14] Furthermore, chemical reactions taking place at the surface of the earth are influenced both by the local magnetic field and by the gravitational gradient, which again define a line and an axis. Reaction rates depend on concentration, which couples the effects of the gravitational gradient to the handedness of the magnetic field, and therefore could conceivably provide a source of bias in the reaction products. Both effects retain their sense throughout the day, but are influenced differently by temperature and latitude variations, so can also couple to macroscopic parameters

such as land-mass distribution and other geographical features defined relative to the earth's axis of rotation. Thus to the extent that the earth's magnetic field is correlated with the direction of the earth's axis there will be a secular accumulation of reaction products of a particular handedness.

Unfortunately there is a difficulty connected with invoking any mechanism which depends on the direction of the earth's magnetic field[15]. It is now well established that the earth's magnetic field reverses polarity in a semi-random fashion.[16,17] Consequently, on the average, the handedness of the environment still cancels out, except for macroscopic effects due to land-mass (and correlated geological) distribution. While geographical features shift over times of the order of hundreds of millions of years due to continental formation and drift, they provide an environmental bias for periods of time much longer than the interval between magnetic reversals. Thus, if we are looking for a very small but persistent handed bias, it appears that we should try to tie it to the geographical handedness of the planet. The main difficulty lies in imagining a mechanism by means of which these macroscopic features could couple in a handed way to a biopoetic or selective mechanism. Conceivably this could come about through tidal flow patterns differing on the east and west borders of land masses, but this does not look promising.

Although the magnetic effect (ignoring geographical bias) cancels in the mean, Halpern[18] has pointed out that the magnetic effects already referred to could still produce significant accumulations of handedness. The magnetic reversals are not periodic, but semi-random, so that effects which depend on fluctuations away from the mean period (mean-square effects) will <u>not</u> vanish. Indeed, if the magnetic field of the earth is due to the liquid metal core of

the earth acting as a unipolar generator, large deviations from the mean period of reversal are to be expected, although specific predictions for the frequency distribution of these fluctuations are not in precise agreement with the paleomagnetic data.[19] In order to show that these statistical fluctuations could give rise to molecular handedness, it would be necessary to prove that the atmospheric scattering and local magnetic phenomena, whose chemical effects are in principle calculable, could give rise to a sufficient accumulation of handedness to persist in the mean over subsequent racemizing influences. Whether there is a biopoetic mechanism which could achieve this bias on a short enough time scale is not yet clear.

Although the line of argument followed above does not lead to any very compelling model for the development of handedness, we present it both as a review of some earlier speculations, and because it led us to a much more specific model for the origin of molecular handedness which will be the main focus of the remainder of the paper. Granick[20] has proposed that the supply of chemical free energy, which any[4] biopetic process must rely on, could be supplied steadily (if in small amounts) over long periods of time by a particular inorganic system which substitutes for photosynthesis. This consists of magnetite crystals contaminated with sulfur which, when exposed to sunlight in an aqueous environment, concentrate electrons on one of the surfaces. Thus one surface of the crystal supplies energy for reducing reactions and the other for oxidizing reactions. Prebiotic protein or nucleic acid chains attached to such surfaces could therefore become active catalytic sites for endothermic polymerizing reactions, and hence ultimately for statistically self-replicating processes. Dramatic support for his conjecture was subsequently provided

by the discovery that all photosyntheic organisms retain to this day a molecule (ferridoxin) which functions as an electron carrier and consists of a single strand of protein wrapped around an Fe-S backbone. [21] The primitive nature of this molecular fossil is clear from the fact that the amino acids in the chain contain only those 14 amino acids which are coded for by the first two letters of the three-letter DNA codon, and not the remaining six which require all three letters. These 14 amino acids are arrived at by simple metabolic pathways in the cell, while the remaining six require much more complicated metabolic chains. Eigen[4] makes it clear, both on grounds of chemical stability, and because of an evolutionary argument due to Crick, that the codon probably always consisted of three letters. But the metabolic fact mentioned above suggests that only the first two letters were used in the early stages of evolution. The fact that ferridoxin contains only the 14 amino acids of this early stage, an Fe-S chain, and is universal in phosynthetic organisms thus provides indirect but powerful evidence that it is a molecular fossil left over from Granick's mechanism for biopoesis.

This focuses our attention on magnetite as a possible biopoetic site for entirely different reasons than the origin of handedness. But magnetite crystals preserve, on the average, a magnetic axis aligned in the direction of the earth's magnetic field to which they were subjected at the time they were formed. Being ferromagnetic, this local field at the surface of the crystals reinforces (in fact is much stronger than) the earth's magnetic field at precisely the spots where, if Granick's mechanism is right, active biopoesis should take place. This could have a much stronger effect on the handedness of polymeric chains than any of the mechanisms considered above. In order to preserve a long-term handed bias, it is necessary that this local field not reverse when the

polarity of the earth's field reverses. In ore bodies the polarity of magnetite reverses with the changes of the polarity of the earth's field, but a percent or so bias persists. In lava flows the magnetization is frozen in and cannot be reversed by subsequent changes of the geomagnetic polarity.[23] This fact is particularly interesting because for still different reasons Fox[24] has already proposed lava flows as the site of the origin of many pre-biotic molecules. The polymerizing processes which he has demonstrated experimentally produce both amino acid and nucleic acid chains at the temperatures encountered in lava flows, and require only half an hour. Since these occur within a particular magnetic polarity, there will be a handed bias in these products. It is therefore obvious that the bias of the initial mix will be reinforced in subsequent autocatalytic reactions, particularly if Granick's mechanism for feeding chemical free energy into the system is in operation. Thus particular geographic sites, active in biopoesis, would acquire a handedness which would persist through many reversals of the polarity of the earth's magnetic field. This long scale persistence is important, since the aqueous environment within which the biopoetic processes occur could dry up and be reestablished many times before the threshold to self-replication was crossed, but always with a secular increase in the handedness with which each new episode started. Further, dried material blown from one site to the next during dry periods would reinforce the handed bias in all such biopoetic regions within a non-equatorial continent. We therefore suggest on three separate lines of evidence (Granick, Fox, and handedness) that the primordial biopoetic sites were water pools containing magnetite crystals produced by lava flows.

This proposal opens a number of avenues for experimental and theoretical investigation. For example, biopoetic experiments could well start from the mix which would produce magnetite in lava flows and whose end products would be governed by the reducing atmosphere of the primitive earth. Polymerizing reactions could be studied with respect to whether the local magnetic field of the magnetite crystals could give a sufficiently large handed bias to persist against racemizing influences prior to the initial autocatalytic biopoetic process in single micro-environments which passes the self-replicative threshold. Quantitative studies of the handed bias as a function of magnetic field strength at the catalytic surfaces are possible. The time history of the growth of the liquid core, continents, and the early history of the earth's magnetic field is crucial to establish whether the earth's magnetic field could have had any influence on the early stages of biopoesis. It is also important to see whether photochemical reactions induced either by circularly polarized sunlight or by bremsstrahlung from beta-decay are quantitatively more or less important than the mechanism for the production of handedness we propose here. We offer the hypothesis to our colleagues at this stage because it crosses so many disciplinary boundaries, and possible flaws or strengthening new insights could be easy to see from other points of view than our own; the proposal might also suggest new lines of research in many fields. We eagerly solicit both negative and positive comment.

FOOTNOTES

1. Dorothy L. Sayers, The Documents in the Case, uses this characteristic of terrestrial living systems as the point of resolution in a murder mystery, and produces a detailed and lucid description of biologically generated optical activity at the phenomenological level. Pasteur discovered the unique handedness of some biologically generated compounds over a century ago. Currently this definition has reached the hardware stage in the sense that it is being built into life detection systems to be soft landed on Mars.
2. The term "natural selection" is used here at the molecular level in the same sense that it is employed to explain the secular increase of any particular aspect of biological organization at any level: those heritable aspects of any self-replicating system which, compared to available alternatives, will — statistically — increase the probability of occurrence of those aspects in the progeny of the system, increase the likelihood of the preservation or recurrence of those aspects (necessarily including heritability) in later systems, relative to the alternatives. For a precise mathematical statement of the necessary conditions that a system of molecules must meet before it can evolve by selection, see Ref. 4.
3. This point has been made with specific reference to handedness by G. Wald, Annals of the New York Academy of Sciences 69, 352-68 (1957).
4. M. Eigen, Die Naturwissenschaften 58, 465 (1971); we are indebted to W. Ebenhöh for bringing this basic reference to our attention and for constructive criticism of some of the ideas contained in this paper.
5. Richard M. Noyes, private communication to HPN, 17 August 1972.
6. We put the matter this way because only information from off planet would give us clues as to the essential conditions for meeting the current unique world crisis (cf. H. Pierre Noyes, Bull. Amer. Phys. Soc. 18, 24 (1973)). Such clues might come, for example, from garbage left behind by an interstellar expedition which it is conceivable is still preserved under the lunar dust. As discussed by I. S. Shklovsky and C. Sagan in Intelligent Life in the Universe, Holden-Day, San Francisco, 1965, the drag coefficients of the satellites of Mars once suggested that they were hollow, and hence could be space stations or orbiting interstellar ships; recent photographs

of their surfaces make this unlikely, unless they have been carefully camouflaged. Elusive UFO's might profitably be studied from the point of view of the hypothesis that they are probes sent to determine the questionable proposition that there is intelligent life on earth (P. Sturrock, private communication). But we will probably have to find ways to make the transition from societies based on photosynthesis to one world relying on nuclear energy without such information.

7. A line (polar vector) reverses direction when all three coordinate axes are replaced by their negatives, while the direction of an axis of rotation (axial vector) does not; hence, if both are present it is possible to distinguish left from right. This definition is more general than the mirroring in one coordinate illustrated in Fig. 1b.

8. C. S. Wu, E. Ampler, R. W. Hayward, D. D. Hoppes, and R. P. Hudson, Phys. Rev. 105, 1413L (1957).

9. M. Goldhaber, L. Grodzins, and A. W. Sunyar, Phys. Rev. 106, 826L (1957).

10. The first-order Zeeman effect which gives a handedness to atomic and molecular energy levels in a magnetic field is linear in the field strength, while the quadratic Zeeman effect is reflection invariant. Thus if the handed bias is due to this splitting affecting the reaction rate directly, it will extrapolate down to the lowest magnetic field intensities at whatever power the (linear) effect enters the reaction rates; the only exception would be a case in which the first order effect vanishes due to some symmetry, but this will not happen for the complicated molecules under consideration. However, if the handedness of the products results from some collective mechanism in the solvent rather than directly from the participating molecules, the extrapolation to low intensity could prove to be less reliable. Handedness of the reactions products has been demonstrated to result from circularly polarized light (W. Kuhn, Naturewissenschaten 18, 183 (1930); H, Kagen et al., Jour. Amer. Chem. Soc. 93:9, 5 May 1971), but further study would be needed to make an accurate extrapolation to low intensity, and in particular to show whether the effect is direct or comes from the solvent. The difficulty about the extrapolation due to solvent behavior was pointed out to us privately by D. Mason.

11. Since the change in direction of the earth's axis relative to sunlight ($\pm 23.5^{o}$) averages out over a year leaving only the component perpendicular to the orbital plane, we need not concern outselves in first approximation with the longer period (25,000 years currently) averaging due to the precession of the equinoxes. Precise calculations of solar intensity show fluctuations due to this effect and also minor changes due to changes in excentricity of the orbit and the line of nodes, but these fluctuations would have to be invoked only if we had to rely on a mean square deviation from handedness and not on a first order effect. We discuss why we wish to avoid having to consider higher than linear effects, if possible, in the text in connection with reversals of the polarity of the earth's magnetic field.
12. Minor changes in the orbits of the planets have occured, as evidenced by the retrograde moons of the outer planets which were presumably lost by one and recaptured by another, and the possibility that Pluto is an escaped moon of Neptune. But Laplace showed long ago that although the present configuration is basically stable, major deviations from a system in which all the orbits lie close to the same plane and have the same sense of revolution would disrupt the whole system. With regard to the rotation of the earth, it is easy to calculate the energy which would be released if its rotation were suddenly stopped; it is enough to raise the temperature of the whole planet by several hundred degrees!
13. For a general review of the lines of evidence which establish the age of the solar system and our own planet as $4.55 \pm 0.05 \times 10^{9}$ years, see, for example, Frank D. Stacey, Physics of the Earth, Wiley, New York, 1969.
14. Scattered skylight arises from the acceleration of electrons in atmospheric molecules by the electric vector of incident sunlight. Since the acceleration starts in this direction, geometrical averaging gives a net linear polarization to the scattered light arriving at the surface of the earth, but since the acceleration takes place in a magnetic field, the motion of the electron is deflected from the initial line in a counter-clockwise sense about the magnetic field direction giving a left circular polarization to the scattered light measured relative to that direction. Viewed at the surface

of the earth, the sense of the polarization persists, in the mean, over a given day and also over the course of a year. Averaging this effect over latitude washes out the component perpendicular to the (magnetic) axis, but the component parallel to that axis retains its sense throughout the year. Thus the calculation of the net circular polarization at the surface of the earth is complicated in detail, but we know that a net mean effect will persist so long as the direction of the magnetic field roughly follows the direction of the earth's axis of rotation. The same analysis also applies to a small component of circularly polarization produced by Brewster scattering at a liquid interface, or rescattering from a smooth surface at the bottom of a pool.

15. This objection to the magnetic hypothesis was made by a student in a seminar given by WAB; so far as we know, it has not been mentioned in any publication on the origin of handedness in biological systems.

16. A. Cox, Science 163, 237 (1969) reviews the data for the last 4.5 million years.

17. M. W. McElhinny, Science 172, 157 (1971) reviews the data for the last 550 million years; this data seems to indicate a much longer period between reversals than appears on the shorter time scale covered in Ref. 16. There also might be a long term period of 350 million years.

18. We are indebted to H. Halpern for pointing out the importance of mean square fluctuations and for discussion of our paper in the preparatory stages.

19. I. K. Crain and P. L. Crain have attempted to create a stochastic model for the reversals, but McElhinny does not find good agreement between their model and the data (cf. Ref. 17). That some stochastic model is to be expected from a monopolar generator has been demonstrated by Cox.

20. S. Granick, Ann. N. Y. Acad. Sci. 69, 292-308 (1957). One of us (HPN) is deeply indebted to Ledyard Stebbins for pointing out this very important speculation to him, and for many discussions of the relationship between molecular biology and evolutionary theory.

21. Taneka, in Non-Heme Iron Proteins, A. San Pietro Ed., 1965.

22. T. H. Jukes, Molecules and Evolution, Columbia University Press, New York, 1966.

23. We are indebted to A. Cox for a discussion of the magnetic structure and permanence of magnetic field in magnetite crystals, and particularly pointing out the difference between lava flows and ore bodies.

24. S. W. Fox, The Origins of Prebiological Systems, Academic Press, New York, 1965.

## FIGURE CAPTION

Figure 1

(a) Minimal three-dimensional configuration for non-superimposability: four distinguishable points not in a plane.

(b) Minimal vectors required to distinguish left from right: a direction and an axis of rotation.

(c) Illustration that our earth is handed both due to the relation between its axis of rotation and the direction of sunlight and due to the configuration of the continents with respect to the axis of rotation; the view in the mirror is not the world we live on in either respect.