THE ORIGIN AND AMPLIFICATION OF BIOMOLECULAR CHIRALITY

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Table of Contents

1. Chirality and Chiral Homogeneity in Nature 60
2. Biotic Theories 60
3. Abiotic Theories 62
   3.1. Chance Mechanisms 62
      3.1.1. Models for Spontaneous Symmetry Breaking 62
      3.1.2. Spontaneous Resolution on Crystallization 63
      3.1.3. Asymmetric Syntheses in Chiral Crystals 65
      3.1.4. Asymmetric Adsorption and Catalysis on Quartz 66
      3.1.5. Asymmetric Adsorption and Polymerization on Clays 67
      3.1.6. Conclusions 68
   3.2. Determinate Mechanisms 69
      3.2.1. Regional and/or Temporal Processes 69
         3.2.1.1. Electric, Magnetic and Gravitational Fields 69
         3.2.1.2. Circularly Polarized Light 72
            3.2.1.2.1. Asymmetric Photoequilibration 73
            3.2.1.2.2. Photochemical Asymmetric Synthesis 73
            3.2.1.2.3. Asymmetric Photolysis 74
            3.2.1.2.4. Sources of Circularly Polarized Light 75
      3.2.2. Universal Processes 76
         3.2.2.1. The Violation of Parity 77
         3.2.2.2. The Vester-Ulbricht (V-U) Hypothesis 77
         3.2.2.3. Radioracemization 80
         3.2.2.4. Direct Effects of Chiral Particles 81
            3.2.2.4.1. Electrons 81
            3.2.2.4.2. Protons 82
            3.2.2.4.3. Positrons and Muons 83
         3.2.2.5. Weak Interactions, Neutral Currents and Parity Violating Energy Differences 84
      3.2.3. Conclusions 89
4. The Amplification of Enantiomeric Excesses 90

Origins of Life and Evolution of the Biosphere **21**: 59–111, 1991.

4.1. Amplification during Incomplete Diastereomeric Reactions 90
4.2. Amplification during Evaporation and Crystallization 91
4.3. Amplification by Stereoselective Autocatalysis 92
4.4. Amplification during Polymerization 93
4.5. Conclusions 97
5. Racemization and Other Calamities 97
6. Summary and Speculations 99

1. Chirality and Chiral Homogeneity in Nature

The crucial organic molecules associated with life are *chiral* (i.e. they possess non-superposable 'right-' (D) or 'left-handed' (L) 3-dimensional mirror image structures) and are usually *optically active* (capable of rotating the plane of polarized light). Accordingly since the time of Pasteur chirality and optical activity have been considered a principal criterion for life, both on Earth (Gause, 1941) and elsewhere in the universe (Halpern *et al.*, 1966; Draffen *et al.*, 1969; Brack and Spach, 1987). It is also well known that the monomers associated with life's principal biopolymers have unique and characteristic chiralities associated with them, that is, they possess either all-D or all-L configurations. Thus with rare exceptions (Davies, 1977) the amino acid monomers occurring in proteins have only the L- (or (usually) S-) configuration, while the ribose and 2-deoxyribose monomers in RNA and DNA are exclusively of the D-configuration (related to D- (or R-)-glyceraldehyde), as are also the glucose monomers in glycogen, starch and cellulose. Additionally it is known that the monomers associated with these crucial biopolymers are characterized not only by their own unique chirality, but also by their complete chiral homogeneity. Thus such polymers are composed of monomer units which are 'chirally pure', and even small amounts of the enantiomeric monomers are not observed in them. Today the early assumption of Terent'ev and Klabunovskii (1957) that 'life cannot and never could exist without molecular dissymmetry' is generally accepted, with the further realization that absolute chiral homogeneity is both essential for the existence of life and that the self-replicating molecules essential for life would be impossible without it (Avetisov *et al.*, 1985, 1991; Keszthelyi, 1987: Gol'danskii, 1988). The fundamental questions of how molecules of a unique chirality arose in Nature and how they achieved their absolute stereoregularity have puzzled scientists since the time of Pasteur, and numerous theoretical and experimental studies addressing these questions have appeared since that time. (For recent reviews cf. Bonner, 1972a, 1988; Quack, 1988; Palladino, 1990). In this article we shall provide a brief but comprehensive overview of these studies, critically emphasizing the most recent literature and presenting conclusions at each stage of the review.

2. Biotic Theories

Historically, theories for the origin of chirality in nature can be classed as *biotic*

or *abiotic*. The former assumes that life originated on Earth through chemical evolution in a primordial racemic milieu, and that as life-essential molecules developed they came to utilize, for greater efficiency, the L-amino acids and D-sugars characteristic of the current biosphere. In short, chiral selection and chiral homogeneity were assumed to be the inevitable consequences of the evolution of living matter (Mills, 1932; Morozov, 1979). Thus Fox (1957) suggested that 'configurational one-sidedness may have originated during the biological era rather than before it', Rush (1957) maintained that 'a preponderance of right- or left-handed asymmetry before the advent of life seems unlikely', and Bada and Miller (1987) have recently argued that the origin of chiral molecules on Earth 'must have occurred at the time of the origin of life or shortly thereafter'. Other recent biotic theories have postulated that competing D- and L-organisms arose on the racemic primitive Earth, and that chance events eventually eliminated one of the species (Ageno, 1972; Harrison, 1973, 1974, 1977; Cairns-Smith, 1986; Gutman and Klemm, 1987), possibly through the fortuitous development of a 'killer enzyme' (e.g. a D-peptidase) by the surviving L-organisms (Balasubramanian, 1983, 1985).

Biotic theories might be stretched to include that of 'panspermia', in which living organisms (presumably containing chirally pure molecules) were transplanted to Earth from another solar system, thus 'infecting' the planet with life. Originally proposed by Arrhenius (1908), who invoked 'solar winds' as a transport mechanism, but later severely criticized by Sagan (1966), the concept was subsequently resurrected by Crick and Orgel (1973) who, basing their arguments on the alleged anomalous abundance of molybdenum in terrestrial organisms, proposed that 'directed panspermia' were deliberately transmitted to Earth by intelligent extraterrestrial beings. This suggestion inspired a series of papers relating to the panspermia hypothesis which were concerned with the abundances of trace elements in various environments on Earth as compared to that in biological samples (Chapell *et al.*, 1974; Orgel, 1974; Gaultieri, 1977; Hoyle and Wickramasinghe, 1981; Spaargaren, 1985), and induced Weber and Greenberg (1985; Greenberg and Weber, 1985) to initiate experiments designed to assess the potential damage to *Bacillus subtilis* spores in a simulated interstellar environment. They concluded that at very low interstellar temperatures (≤ 10 K) and pressures UV radiation would be lethal to the spores within a short time. Within dark interstellar clouds, however, where UV intensity would be vastly diminished and where spores might acrete protective mantels, survival times might be tens of millions of years, and interstellar clouds might transport spores from one solar system to another well within their survival times. While the panspermia hypothesis may diminish 'current difficulties with the establishment of life on the early Earth with an uncomfortably short time interval' – 400 million years or so (Schidlowski, 1989), it still suffers from the serious philosophical flaw that it does not solve the problem, but merely pushes the origin of chirality and life further back into time and space.

Amplifying Miller and Orgel's (1974) suggestion that replicating double stranded nucleic acids would not be possible with a mixture of D- and L-ribotides, Gol'danskii

and Kuz'min (1988) have recently concluded from molecular models that complete chiral purity of polynucleotides is a necessary condition for their complementarity in double-stranded helical structures, and that any 'unnatural' L-sugars in such structures would distort them in such a way that the H-bonding between their bases would be prevented and complementarity thus precluded. These conclusions rationalized the elegant observations of Joyce *et al.* (1984), which showed that in template-directed oligomerizations of nucleotides the assemblage of a complementary strand on a chirally pure matrix was strongly inhibited if the monomers incorporated were not chirally pure. These considerations led Gol'danskii and Kuz'min (1988) to conclude that a biogenic scenario for the origin of chiral purity was not viable even in principle, since without preexisting chiral purity the self-replication characteristic of living matter could not occur. They thus concluded that an abiotic and not a biotic mechanism was the only one possible for the primordial origin of chirality and chiral homogeneity – whether on Earth or elsewhere in the universe.

3. Abiotic Theories

Abiotic theories, postulating that the development of molecular chirality and chiral homogeneity preceded the origin of life on Earth, can be conveniently classified into three categories: chance mechanisms, determinate mechanisms and amplification mechanisms. The first two are concerned with the abiotic origins of small enantiomeric excesses (e.e.s.) on Earth (sometimes also specifying the chirality of the predominant enantiomer), while the third considers the subsequent development of such small e.e.s. into a final state of enantiomeric purity. These mechanisms have been the subject of such a plethora of theoretical and experimental investigations in recent decades that we can consider each investigation only briefly.

3.1. Chance mechanisms

Chance mechanisms presuppose symmetry-breaking processes at the molecular level which, analogous to the flip of a coin, have an equal probability of producing an excess of either the D- or L-enantiomer. Such mechanisms are summarized briefly in the five categories below.

3.1.1. *Models for Spontaneous Symmetry Breaking*

Anticipated by Strong (1898) fifty-five years earlier, Frank (1953) proposed a model for the spontaneous symmetry breaking of a racemic sytem by postulating an optical isomer which was both a catalyst for its own production and an anti-catalyst for the production of its enantiomer. He showed kinetically that such an autocatalytic system was unstable, and that any random fluctuation from the totally racemic state must result in the dominance of one enantiomer and the disappearance of the other. Similar models were independently proposed later by Calvin (1969a) and by Seelig (1971a, b, 1972), and these in turn gave rise to a host of more elaborate

subsequent variations (Decker, 1973a, b, 1974, 1975, 1977; Hochstim, 1975; Buvet, 1977; King, 1977, 1978; Iwamoto and Seno, 1979; Ferracin, 1982; Klemm, 1985; Szamosi, 1985; Babovic *et al.*, 1987; Gol'danskii *et al.*, 1987; Gutman and Klemm, 1987; Micheau *et al.*, 1987; Abbott, 1988; Gol'danskii and Kuz'min, 1988; Gutman *et al.*, 1988a, b; Anikin and Arinstein, 1989; Kondepudi, 1989). Calvin's (1969a) simple qualitative model of 'stereospecific autocatalysis' for spontaneous symmetry breaking is illustrated in Figure 1. In it we have two rapidly equilibrating enantiomeric reactants, each of which can undergo a slow reaction to yield a corresponding non-equilibrating enantiomeric product. When a statistical fluctuation favors the formation of a trace of one of the enantiomeric products, this product immediately catalyzes a rapid autocatalytic reproduction of itself from its own enantiomeric precursor. As the latter is removed by product formation the equilibrium rapidly shifts to replace it, resulting in the conversion of the entire mixture of racemic reactants into a product having a single chirality. Subsequent more elaborate mathematical models have been generally based on details of the kinetic behavior of hypothetical unstable, 'far from equilibrium' racemic systems which commence symmetry breaking randomly at some arbitrary 'bifurcation point', then plunge similarly into a state of enantiomeric homogeneity. The biotic theories discussed earlier might be considered as additional examples of random symmetry breaking, with the bifurcation point, however, occurring only after life began.

Not all authors subscribe to the above scenarios, however. Thus Czege and Fajszi (1977) and Fajszi and Czege (1981) have developed models in which small initial e.e.s. not only fail to develop into a state of enantiomeric purity, but actually vanish. That mathematical models based on slightly different assumptions should lead to absolutely contradictory conclusions may lead one to question the essential validity of any such models for explaining the origin of chiral homogeneity. In contrast, several *experimental* models for random symmetry breaking, discussed in the remainder of this section, do in fact afford enantiomerically enriched and sometimes chirally pure products.

3.1.2. *Spontaneous Resolution on Crystallization*

Racemic solids may crystallize from a supersaturated solution either as *racemic compounds* (equal numbers of molecules of each enantiomer in each crystal), or, less commonly, as *conglomerates* (mixtures with equal numbers of separate crystals of each enantiomer). In the crystallization of conglomerates sometimes one and sometimes the other enantiomer may crystallize preferentially, in which case a 'spontaneous resolution' is said to occur. This random process may be biased in favor of one enantiomer by consciously 'seeding' the solution with that enantiomer, a commercially important technique which has been reviewed extensively by Secor (1963), Collet *et al.* (1980) and Jacques *et al.* (1981). More recently additional examples of such spontaneous resolution have been reported (Edge *et al.*, 1981; Yamanari *et al.*, 1981; Blank *et al.*, 1982; Kaki *et al.*, 1982; Oberhansli, 1982; Dossena *et al.*, 1983; Okamoto *et al.*, 1984; Okazaki, *et al.*, 1985). The spontaneous resolution

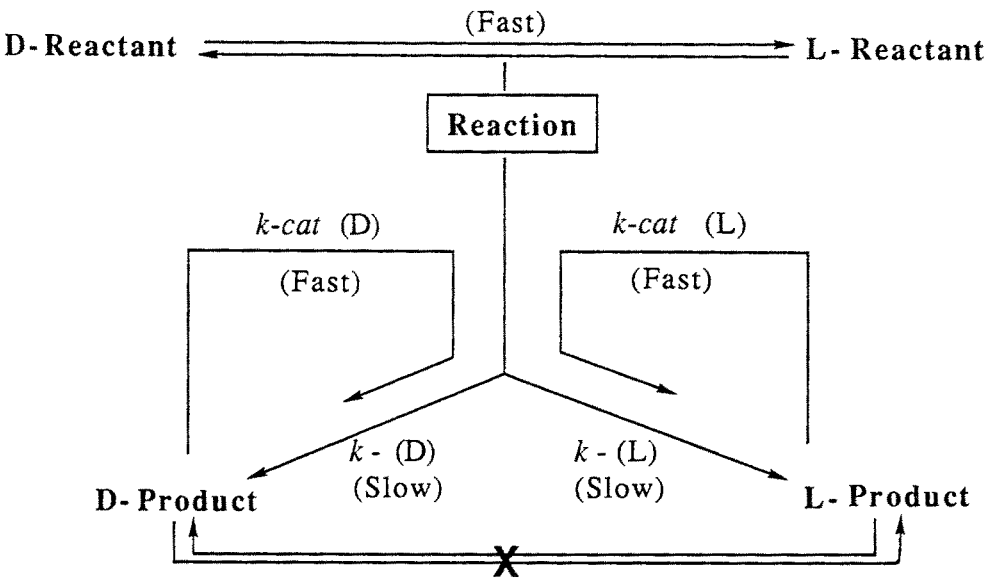

Fig. 1. Stereospecific Autocatalysis

of conglomerates was early and widely championed as the most plausible explanation for the origin of optical activity on Earth (cf. Bonner, 1972a), an idea which still is current today (Bernal, 1985). Resolution by crystallization is unquestionably the most effective means of chiral symmetry breaking presently known, permitting the isolation of optically pure enantiomers on scales ranging from grams to tons (Jacques, *et al.*, 1981). It would also appear to be the most likely terrestrial mechanism for producing the prebiotic enantiomeric homogeneity necessary for the emergence of life.

If the enantiomer remaining in solution during the slow crystallization of a racemic conglomerate can rapidly convert into the other enantiomer before crystallization is complete, a 'second order asymmetric transformation' (Harris, 1958) may occur, with the entire racemate then crystallizing as a single enantiomer. Such 'total spontaneous resolutions' (Collet *et al.*, 1980), which provide examples of Calvin's (1969a) 'stereospecific autocatalysis' scheme for total symmetry breaking (Fig. 1), were first observed by Newman and Powell (1952) (Cf. also Arad-Yellin *et al.*, 1980, 1981) and by Havinga (1954) during crystallizations of tri-*o*-thymotide and of methylethylallylanilinium iodide, respectively. More recent examples are provided in the total spontaneous resolutions of tri-*o*-thymotide analogs (Edge *et al.*, 1981), of the nickel chloride complexes of α-aminocaprolactam (Sifniades *et al.*, 1976; Boyle *et al.*, 1979; van Mil *et al.*, 1987), of an oxazobenzodiazepinone derivative (Okada *et al.*, 1983) and of 1,1′-binaphthyl and some of its derivatives (Pincock and Wilson, 1971, 1975; Pincock *et al.*, 1971, 1974, 1981; Wilson and Pincock, 1977; Lu and Pincock, 1978). An interesting inorganic example of a total spontaneous resolution was provided recently by Kondepudi *et al.* (1990). Extending studies

originally undertaken by Kipping and Pope (1898a) and Soret (1900), Kondepudi *et al.* found that sodium chlorate, crystallized from unstirred solutions, gave equal numbers of dextro- and levorotatory crystals. When the solutions were stirred during crystallization, however, almost all (99.7%) of the sodium chlorate crystals in particular samples had the same chirality, either dextro or levo. Curiously, the authors attributed their results to 'autocatalysis and competition between L- and D-crystals', although almost 100 years earlier Kipping and Pope (1898b) had shown that crystals of sodium chlorate having only one handedness could be produced simply by appropriate seeding of saturated solutions.

3.1.3. *Asymmetric Syntheses in Chiral Crystals*

4,4'-Dimethylchalcone, Me-C_6H_4-CO-CH=CH-C_6H_4-Me, (**1**), crystallizes as separable enantiomeric crystals. Exposure of individual enantiomeric **1** crystals to bromine vapor led to an optically active dibromo product, Me-C_6H_4-CO-C*HBr-C*HBr-C_6H_4-Me, (**2**), having either sign of optical rotation and in optical yields as high as 6% (Penzien and Schmidt, 1969). Green and Heller (1974) later found that if **1** was crystallized along with 3.97 mol % of (-)-**2**, crystals were obtained whose bromination now yielded (+)-**2** exclusively. In short, the chirality of the crystal lattice of **1** was determining the molecular chirality of **2** during the bromination. The authors thereupon proposed the following autocatalytic scenario for the origin of molecular chirality. A racemic reactant having enantiomers interconvertible in the liquid state crystallizes as crystals of a single chirality, which then undergo a solid state reaction to form a chiral product. The nonracemizable product then induces further crystallization of the chiral crystal form of the reactant which leads to additional product of the same chirality.

Other instances of chiral crystal lattices directing asymmetric syntheses to yield optically active products are found in the γ-ray induced isotactic polymerization of *trans*-1, 3-pentadiene in an all-*trans* perhydrotriphenylene crystal lattice (Farina *et al.*, 1967; Audisio and Silvani, 1976), in the assymmetric photocycloaddition of 1,4-diarylbutadienes to form optically active cyclobutane products (Elgavi *et al.*, 1973), in the formation of optically active polymers by the photopolymerization of enantiomeric monomer crystals of various *p*-divinylbenzene derivatives (Addadi *et al.*, 1975, 1976; Addadi and Lahav, 1978, 1979a, b, c, 1982; Lahav *et al.*, 1976), in the unimolecular di-π-methane type and Norrish Type II photorearrangements of a maleic diester and of α-(3-methyladamantyl)-*p*-chloroacetophenone, respectively (Evans *et al.*, 1986) and in the Norrish Type II solid-state photocyclization of the achiral oxo amide, N,N-diisopropylphenylglyoxylamide, into an optically active ß-lactam (Toda *et al.*, 1987; Toda, 1988, 1989; Sekine *et al.*, 1989). The pertinence of such solid state photoreactions to the origin of chirality on Earth is stressed by several of these authors, and the principles behind such asymmetric syntheses in the crystalline state have been extensively reviewed (Addadi and Lahav, 1979a, b, c; Addadi *et al.*, 1979; Green *et al.*, 1975, 1979).

3.1.4. *Asymmetric Adsorption and Catalysis on Quartz*

A number of inorganic substances are optically active in the crystalline state due to the morphological chirality of their crystal structures. One enantiomer of any of these might in principle act as a chiral adsorbent, permitting the resolution of a racemate by stereoselective adsorption of one of the enantiomers. Quartz, often found in nature as well defined enantiomorphic crystals, has been extensively investigated as a possible chiral adsorbent since the resolution of racemic cobalt salts by quartz was first alleged by Tsuchida *et al.* (1935). Karagounis and Coumoulos (1938) first suggested that asymmetric adsorption by quartz might be responsible for the origin of molecular chirality, a view subsequently popularized by Bernal (1949, 1951), and several subsequent confirmatory reports of the partial resolution of racemates on quartz crystals seemed to support the hypothesis (cf. Bonner, 1972a). In a carefully conducted later study, however, Amariglio *et al.* (1968a, b) were unable to duplicate these earlier observations, and concluded that the positive findings claimed were due to experimental artifacts. With the question of the validity of the phenomenon thus thrown open, Bonner *et al.* (1974a, 1975; Bonner and Kavasmaneck, 1976) undertook a reinvestigation of the problem using amino acids as 'prebiotically realistic substrates' and employing analytical techniques not dependent upon small and possibly spurious optical rotations. The radioactivities of dilute solutions of ^{14}C- and ^{3}H-labelled D- and L-alanine hydrochlorides in dimethylformamide were measured under anhydrous conditions before and after exposure to finely powdered d- and l-quartz. It was found that the 'differential adsorption' of alanine hydrochloride (% adsorbed on d-quartz – % adsorbed on l-quartz) was as high as 20%, and that d-quartz preferentially adsorbed D-alanine while l-quartz preferentially adsorbed L-alanine. Kavasmaneck and Bonner (1977) later investigated the asymmetric adsorption of amino acid derivatives on quartz mechanistically and found that D-alanine isopropyl ester was preferentially adsorbed from chloroform solution by l-quartz and L-alanine ester by d-quartz, with differential adsorptions as high as 12%. The preferential adsorption of D-alanine hydrochloride by d-quartz and the L-enantiomer by l-quartz was later confirmed by Furuyama *et al.* (1978, 1982), and racemic α-aminopropionitrile, another subtstrate of prebiotic relevance, has also been reported as resolvable by adsorption on quartz (Morimoto *et al.*, 1978). Attempts to resolve several organic and inorganic racemates on chiral inorganic crystals other than quartz (e.g. $NaClO_3$, $NaBrO_3$, $NaIO_4.3H_2O$, $Ni_2SO_4.6H_2O$) have proved unsuccessful (Gillard and da Luz de Jesus, 1979).

While asymmetric adsorption on quartz is thus presently a well authenticated phenomenon, that of asymmetric catalysis by quartz surfaces is still unsubstantiated and debatable. Schwab *et al.* (1934) first suggested that the 'origin of the first asymmetry in living nature' might be found in catalytic processes occurring in asymmetric crystal lattices, and a large number of reports appearing between 1932 and the early 1950s claimed that d- and l-quartz, either alone or surface-coated with thin layers of Cu, Ni or Pt, were capable of inducing a variety of catalytic

conversions of racemic or achiral reactants into optically active products (cf. Bonner, 1972a). However, subsequent meticulous attempts by Amariglio *et al.* (1968a, b) to duplicate a number of these experiments consistently resulted in failure, again prompting the suggestion that the previous positive results were attributable to artifactual errors.

Whatever merits may reside in earlier (cf. Bonner, 1972a) or more recent suggestions (Klabunovski, 1982) that quartz, either as an asymmetric adsorbent or asymmetric catalyst, might be implicated in the origin of chirality, the fact remains that any chirality so produced would not be unique, but instead would be randomly D- or L-over the surface of the Earth. This follows from examination of over 27 000 natural quartz crystals by a variety of techniques, which revealed that the chirality of the samples was essentially random, 49.83% l- and 50.17% d-quartz (Frondel, 1978).

3.1.5. *Asymmetric Adsorption and Polymerization on Clays*

While common clays such as kaolinite and montmorillonite have no known chirality associated with their crystal structures (Brindley, 1961; Grim, 1968; Wellner, 1979) and thus should foster no stereoselective interactions with chiral molecules, nevertheless asymmetric effects involving both clays have been claimed by several authors. Degens *et al.* (1970) first reported that kaolinite catalyzed the stereoselective polymerization of aspartic acid, with L-aspartic acid polymerizing over eight times as fast as the D-enantiomer. Jackson (1971a, b) subsequently repeated these claims and reported further that kaolinite preferentially adsorbed L- rather than D-phenylalanine at pH 5.8, while the effect was reversed at pH 2.0. He suggested that the 'edge faces' of the kaolinite crystals were responsible for these stereoselective effects and that there might be a preponderance of such 'L-fixing' minerals in nature. Using a variety of alternative analytical techniques, however, Bonner and Flores (1973) found no differences whatsoever in the adsorption of D- *versus* L-phenylalanine on kaolinite, and furthermore that kaolinite failed to promote the asymmetric polymerization or even significant gross polymerization of aspartic acid as well (Flores and Bonner, 1974; Bonner and Flores, 1975). These findings were later confirmed by McCullough and Lemmon (1974) using still other analytical techniques. Citing an additional claim of asymmetric effects of clays on amino acids by Thompson and Tsunashina (1973) as supporting his earlier observations, Jackson (1975) subsequently argued that the failures of Bonner, Flores, Lemmon and McCullough to duplicate his observations were caused by possible differences in experimental conditions such as the presence or absence of traces of 'promoters' or 'poisons', despite an additional rebuttal by McCullough (1975).

Bondy and Harrington (1979a, b) later attempted to assess the relative binding of 'natural' *versus* 'unnatural' enantiomers on clays. They incubated very dilute ($\sim 10^{-8}$ M) solutions of the D- and L-enantiomers of ^{3}H-labelled leucine, aspartic acid and glucose with small quantities of montmorillonite, then assayed the clay samples for bound radioactivity. Their claim that the natural enantiomers were

bound from 6.5 to 11.3 times more effectively than the unnatural enantiomers and their suggestion that primordial clays with some unspecified asymmetric structure might have been responsible for the prebiotic selection of L-amino acids and D-sugars led to immediate controversies both as to the chirality of clays (Jackson, Wellner and Bondy, 1979) and the validity of their experimental protocol. Youatt and Brown (1981) subsequently showed in experiments carefully designed to preclude artifacts that there was no stereoselective binding whatsoever of L-amino acids by the clay, and that Bondy and Harrington's results could be largely attributed to the adsorption of the radiochemical decomposition products of the substrates. Friebele *et al.* (1981), using analytical gas chromatography to monitor the adsorption of several racemic amino acids in solutions of pH 3, 7 and 10 which had been exposed to sodium montmorillonite, similarly failed to observe any unambiguous stereoselectivity in the adsorptions.

Ignoring or unaware of all previous experiments disproving the asymmetric interaction of clays with amino acids, Julg (1986) has recently calculated by a 'self-consistent molecular field method' that the adsorption energy of L-amino acids on one enantiomeric form of allegedly chiral kaolinite is greater than that for D-amino acids by 0.03 to 0.19 kcal/mol. He then argued that the resulting differential adsorption would explain the L-chirality of amino acids in nature, providing that the preferred chirality he assumed for kaolinite was more abundant. He later (Julg, 1987) postulated that the addition of cyanide ion to an ethyliminium cation adsorbed on one allegedly enantiomeric form of a kaolinite crystal could lead to a chiral α-aminopropionitrile product, the precursor of chiral alanine. Similar calculations of the adsorption energy of the iminium cation on the allegedly more abundant kaolinite enantiomer purported to show that the formation of the L-alanine precursor was favored over that of the D-precursor by 0.36 kcal/mol, again explaining the L-chirality of amino acids. Finally, after elaborate calculations, Julg (1988) concluded that, due to the weak interactions (see Section 3.2.2.5 below), the enantiomeric form of kaolinite which he had previously postulated to lead to L-amino acids was in fact the more abundant, thus substantiating his earlier arguments 'for the role played by kaolinite in the appearance of the first proteins and their L-homochirality'. It should be emphasized that none of Julg's speculations and conjectures is supported by a single shred of experimental evidence and that, on the contrary, they are totally untenable in the light of the earlier conclusions and experiments cited above.

The stimulating and controversial hypotheses of Cairns-Smith (1982, 1985) regarding the role of clays in the origin of life unfortunately fail to account for the crucial role that the chiral homogeneity of biopolymers plays in the development of self-replicating organic systems (Avetisov *et al.*, 1985; Gol'danskii and Kuz'min, 1988; Gol'danskii, 1988), and are likewise without relevant experimental foundation.

3.1.6. *Conclusions*

The above random chance mechanisms, even when demonstrably efficient (Section

3.1.2), require that if an L-enantiomer is produced at one location on Earth there is an equal probability for the D-enantiomer to prevail at another site. Mann and Primikoff (1983) have argued that 'succesful protein formation' at only 20 sites would reduce the probable dominance of a single chirality by $(1/2)^{20}$, or 10^{-6}, and Shapiro (1986) has more recently emphasized the utter improbability of producing replicating molecules by repetitive chance events, even assuming that eons were available for their occurence. To be effective, random mechanisms must thus involve a very small number of sites for symmetry breaking, perhaps just one, which would clearly and logically make the process a non-random one. On the other hand, the probability that symmetry breaking was produced by a specific mechanism 'would increase linearly with the number of terrestrial sites'. Thus on the greater likelihood of a large number of symmetry breaking sites on Earth, Mann and Primikoff (1983) have concluded that random fluctuations are arguably less probable as a source of asymmetry than are determinate mechanisms. We now turn to the variety of determinate mechanisms which have been proposed and investigated in recent years.

3.2. Determinate mechanisms

Determinate mechanisms presuppose that some non-random external physical force, itself chiral by nature, may interact with racemic or prochiral organic substrates in such a manner as to produce 'absolute' asymmetric syntheses or degradations which lead to chiral products. Such determinate mechanisms may involve either a) regional and/or temporal processes, or b) universal processes, and we shall review them in these categories.

3.2.1. *Regional and/or Temporal Processes*

These processes involve external forces whose intrinsic asymmetry may alter in direction or magnitude at different locations on Earth or in different epochs. Thus the chirality of the products resulting from the effects of these forces may, in principle, vary with location and time throughout the history of the Earth. The external forces in this category which have been studied for their capability of producing chiral products include electric, magnetic and gravitational fields and circularly polarized light.

3.2.1.1. Electric, Magnetic and Gravitational Fields

In the mid-1800s Pasteur investigated the possibility that magnetic or gravitational forces might induce asymmetric syntheses. His experiments uniformly failed to produce optically active products, and Curie later pointed out that such phenomena as magnetic fields, mechanical motions, etc. were in fact not asymmetric forces (cf. Mason, 1982). Despite this, a number of later investigators conducted related experiments with allegedly positive results. Radulescu and Moga (1939) claimed to produce optically active spirane type products by the addition of HBr and Br_2 to 2-allyl-2-carbethoxy-1, 3-indanedione under illumination with linearly polarized light in a magnetic field, but Pracejus (1967) was later unable to corroborate these

results. Gerike (1975) subsequently conducted six reactions leading to potentially optically active products under the influence of combined electric and magnetic fields in various configurations. His polarimetrically examined products proved to have random rotations of magnitudes ± (0.001–0.032 °). Soon thereafter Meade *et al.* (1977) disputed the claims of Gerike on theoretical grounds, suggesting that the results were artifacts. This in turn elicited a theoretically grounded rebuttal by Rhodes and Dougherty (1978), who calculated that a small e.e. of ~ 0.3 ppm might result with fields of $E = 10^3$ V cm^{-1} and $H = 1$ T.

Shortly thereafter Dougherty and his collaborators (Dougherty, 1980; Edwards *et al.*, 1980) made additional claims for absolute asymmetric syntheses, mediated this time by gravitational fields. Gerike's epoxidation of isophorone was repeated in a rapidly spinning (6000–14 000 rpm) turbine juxtaposed in several configurations to the Earth's gravitational field. The epoxide products were found, depending on the juxtaposition, to have optical rotations varying from –0.0031 to +0.0172 °, which were claimed to be 'well beyond experimental error'. These allegedly positive results, interpreted as due to combinations of gravitational and coriolis forces, were said to demonstrate that asymmetric syntheses were possible 'with chiral gravitational fields alone', and that 'prebiotic organic syntheses could have been partially asymmetric' due to these gravitational effects. These claims were immediately criticized on theoretical grounds by Mead and Moscowitz (1980) and by Peres (1980), who concluded that the results were artifacts and not possible to be taken seriously. Related experiments to test chiral effects of gravitational and centrifugal forces were later conducted by Kovacs *et al.* (1981), who polymerized γ-benzyl DL-glutamate N-carboxyanhydride to poly-(γ-benzyl glutamate) in rapidly stirred solutions, and who crystallyzed sodium ammonium DL-tartrate from similarly stirred solutions. No unequivocal asymmetric effects were observed. Likewise, the reported (Honda and Hada, 1976) optical activity of 1,1′-diethyl-2, 2′-cyanine chloride induced by conical swirling was later shown due to artifacts (Norden, 1978).

Dougherty's controversial studies were subsequently extended (Piotrowski *et al.*, 1980) to other reactions, conducted now under the influence of a 1.1 T magnetic field whose orientation could be varied with respect to Earth's geometrical axis. Again optically active products were reported, whose rotations now varied capriciously from –0.0074 to +0.0109 ° depending on the calendar and the time of day. More recently Dougherty (1981) has reiterated and summarized his uncorroborated experiments and conclusions, making no rebuttal, moreover, to the serious criticisms of Meade, Moscowitz and Peres.

Gilat (1985; Gilat and Schulman, 1985) has recently proposed a possible symmetry breaking interaction between a chiral solute (e.g. an amino acid zwitterion) and a solvent (*e.g.* water) which, in Earth's magnetic field, allegedly results in the selection of a preferred solute chirality. A chirality dependant clock- or counterclockwise 'intramolecular electrical current' (and magnetic moment) is postulated, which results in a preferred mechanical rotation (molecular angular momentum) for the amino acid. The magnetic moment, coupling with Earth's magnetic field while constrained

to a specific orientation at the surface of the water, is presumed to lead to the 'natural selection of one chirality for certain amino acids'. Energy differences between enantiomers of $\sim \pm 10^{-9}$ kT, the sign of which depends on the hemisphere, are estimated for locations a few degrees above or below the magnetic equator, so that 'prebiotic selection occurred on a limited area'. Needless to say, this hypothesis is unsupported by any experimental evidence whatsoever, although an experiment is suggested to test for the chiral solute / solvent interactions allegedly involved.

Additional experiments regarding the production of chiral molecules under the influence of magnetic fields have been described. Thiemann and Jarzac (1981), reporting that the magnetic circular dichroism (MCD) of benzene did not reverse symmetrically with magnetic field reversal, suggested that magnetic fields might render prebiotic solvents optically active with MCD, and that these might then react asymmetrically with prochiral substrates. However, the anomalous MCD effect was later shown (Haberditzl *et al.*, 1983) to be an artifact. Extrapolating calculations of Wagniere and Meier (1983) concerning photochemically mediated reactions in magnetic fields, Thiemann (1984) later proposed an experiment, not yet performed, where one might 'freeze' the allegedly chiral effects of crossed electric and magnetic fields parallel to a light beam on a photochemical reaction, by interrupting the reaction prior to equilibrium and examining a small fraction of the product for optical activity. Teutsch and Thiemann (1986; Teutsch, 1988) attempted to verify the predictions of Wagniere and Meier by conducting a photochemical synthesis of hexahelicene using unpolarized ultraviolet light travelling parallel or antiparallel to a 1.1 T magnetic field. No optical activity was noted in the product, however, confirming earlier results of Bernstein (1972) who also found no optical activity in hexahelicene produced photochemically in the 6.5 T field of a superconducting magnet.

Barron (1986a, b, c; 1987) has recently examined the above conflicting reports on the enantioselective effects of electric, magnetic and gravitational fields in terms of his concepts of 'true chirality' (time invariant enantiomorphic systems) and 'false chirality' (time non-invariant enantiomorphic systems). He concluded that only true chirality systems can induce absolute asymmetric synthesis in a reaction which is isotropic in the absence of the influence and is allowed to reach thermodynamic equilibrium, but that false chirality might suffice for reactions under kinetic control.

The most recent positive report of asymmetric syntheses mediated by a magnetic field is that of Takahashi *et al.* (1986), who conducted electrolytic reductions of phenylglyoxylic acid (PhCOCOOH) and pyruvic acid ($CH_3COCOOH$) to mandelic acid (PhC*H(OH)COOH) and lactic acid ($CH_3C^*H(OH)COOH$), respectively, at a mercury cathode whose surface was perpendicular to magnetic fields of 0.098–0.168 T. The reduction products were reported to be uniformly dextrorotatory regardless of the direction of the perpendicular field, and optical yields were claimed to increase proportionately with increasing magnetic field strength. In contrast to the trivial optical yields reported earlier for asymmetric syntheses in magnetic fields, Takahashi *et al.* claimed optical yields as high as 25% for the mandelic acid produced

in a field of 0.168 T, and then extrapolated their data to predict that optically pure (+)-mandelic acid should result with fields of 0.6–0.7 T. These amazing claims were later reinvestigated by Bonner (1990a, b), who performed electrolytic reductions of phenylglyoxylic acid under a variety of conditions in magnetic fields of 0.14 T and, using a superconducting selenoid, of 7.05 T. The crystalline mandelic acid reduction products were examined polarimetrically and found to be totally racemic in every case. It was concluded that the observations of Takahashi *et al.* were due to artifacts and that, based on an earlier caveat by Jaeger (1930), who pointed out that the external chiral agent must actually *cause* the reaction to occur, there was no reason to expect any asymmetric syntheses whatsoever to result from electric, magnetic or gravitational field effects.

3.2.1.2. Circularly Polarized Light

Circularly polarized light (CPL) may be considered either as an electromagnetic wave whose electric vector spirals clockwise or counterclockwise along its direction of travel, or as a photon having a forward (right) or reverse (left) spin along this direction. Right- or left-CPL (RCPL or LCPL) thus constitute physical forces having 'true chirality' (Barron, 1986a, b, c, 1987), and as such would be capable of stereoselective interactions with chiral or prochiral molecules. In the last century LeBel (1874) and Van't Hoff (1894) appreciated this and suggested that CPL might be responsible for the origin of optically active molecules in nature, but early attempts to verify these suggestions failed. Jaeger (1930) later pointed out that, to be succesful, reactions conducted in the presence of CPL must actually be photo-initiated, and Kuhn and Brown (1929) and Kuhn and Knopf (1930a, b) first described succesful asymmetric photolyses of racemic ethyl α-bromopropionate and racemic N,N-dimethyl-α-azidopropionamide using ultraviolet CPL. Soon thereafter other successful experiments were reported, and a growing number of scientists championed CPL as the agent responsible for the natural origin of optical activity (cf. Bonner, 1972a).

CPL-mediated reactions depend on the circular dichroism ($\Delta\epsilon = \epsilon_R - \epsilon_L$) of the substrate, that is, on the difference in its molar absorption coefficients for RCPL and LCPL (Buchardt, 1974; Rau, 1983). Since the rate of a photochemical reaction depends upon the amount the light absorbed by the reactant, circular dichroism, where $\epsilon_R \neq \epsilon_L$, thus leads to different reaction rates for enantiomeric or prochiral reactants, inducing a reaction with a positive asymmetric bias for one enantiomer and an equal negative bias for the other. An important quantity related to $\Delta\epsilon$ is the 'anisotropy factor', g defined by Kuhn (1930) as $g = \Delta\epsilon/\epsilon$ where $\epsilon = 0.5$ $(\epsilon_R + \epsilon_L)$. Its importance lies in the fact that g determines the enantiomeric purity (optical yield) of the chiral product generated by the CPL. $\Delta\epsilon$ and g, are at a maximum at a wavelength close to the absorption maximum of the pertinent chromophore in the substrate, and CPL experiments are ordinarily conducted using wavelengths close to this maximum. It should be emphasized, however, that since there are discreet energy thresholds for photochemical effects, the photochemical

action spectrum of an enantiomer will in general differ from its absorption or circular dichroism spectrum, so that broad-band CPL can also suffice. That is, as long as $\epsilon_R \neq \epsilon_L$ in the wavelength region pertinent for the photochemistry, an asymmetric effect may ensue independent of the circular dichroism in other spectral regions, despite a recent mistaken claim to the contrary (Mason, 1988b). This is important, since natural CPL sources (Section 3.2.1.2.4) are spectrally broad-banded. CPL-mediated asymmetric reactions fall into three categories: a) asymmetric phtoequilibration, b) photochemical asymmetric synthesis and c) asymmetric photolysis (Buchardt, 1974; Rau, 1983), and we shall review each category briefly.

3.2.1.2.1. Asymmetric Photoequilibration

If D and L enantiomers are interconvertible photochemically, the equilibrium constant after complete equilibration will be $[D]/[L] = 1$ if ordinary light is used. With CPL, however, the circular dichroism of the substrate causes the rates of the forward and reverse reactions to be unequal and, since the rates are proportional to ϵ, the final equilibrium constant will be determined by the extinction coefficients of the two enantiomers, $[D]/[L] = \epsilon_L/\epsilon_D$. The optical yield in such processes, defined as $([D]-[L])/([D]+[L])$, increases with time until equilibrium is reached, whereupon it is limited to the value $g/2$. Since the g values for optically active compounds are rather small ($g \approx 0.01$ (Buchardt, 1974)), however, the maximum optical yields obtainable on completion of an asymmetric photoequilibration reaction is limited to $< 1\%$ or so.

Asymmetric photoequilibration (also called partial photoresolution and photoenantiomerization) was first described experimentally and theoretically by Stevenson and Verdieck (1968, 1969), who irradiated solutions of racemic Cr^{+3} complexes with CPL. The optical rotations of the solutions increased with time, positively with RCPL and negatively with LCPL, until final equal and opposite steady-state values were attained. Stevenson (1972), Stevenson and Vanden Driesche (1974), Stevenson and Baker (1976) and others (Norden, 1970, 1977a; Kane-Maguire and Langford, 1972; Yoneda *et al.*, 1973) subsequently extended such asymmetric photoequilibration studies to a number of other systems.

3.2.1.2.2. Photochemical Asymmetric Synthesis

Photochemical asymmetric syntheses constitute CPL-induced reactions in which an optically active product is formed from an optically inactive precursor. Mechanistically, such reactions involve the photoexcitation of rapidly equilibrating pro-D or pro-S substrates, whose enantiomeric intermediate excited states than rapidly transform into non-equilibrating enantiomeric products (Buchardt, 1974). Due to the circular dichroism of the prochiral substrates, the enantiomeric excited intermediates are produced at different rates and in unequal concentrations, thus affording unequal amounts of the enantiomeric products. The optical yields in such processes are independent of the extent of reaction, but again are limited to $g/2$, or $< \sim 1\%$.

The first unequivocal photochemical asymmetric syntheses involved CPL-induced

ring closures of several 1,2-diarylethylenes which, after subsequent aromatization, afforded hexahelicenes, octahelicenes and nonahelicenes which had optical rotations as high as $\sim \pm 30$ ° and optical yields of $\sim 0.2\%$ (Moradpur *et al.*, 1971, 1975; Tsoucaris *et al.*, 1971; Kagan *et al.*, 1971; Kagan and Fiaud, 1978). Calvin and coworkers (Bernstein *et al.*, 1972a, b, 1973) independently conducted a variety of similar photochemical asymmetric syntheses of hexa-, hepta-, octa- and nonahelicenes, finding that RCPL gave levorotatory and LCPL dextrorotatory products. On the basis of the varying optical yields obtained they proposed the mechanism summarized in simplified terms above (Bernstein *et al.*, 1972a), conclusions which were confirmed and refined by subsequent studies involving ring-substituted diarylethylene precursors (Bernstein *et al.*, 1972b, 1973; Buchardt, 1974). More recent CPL-mediated ring closures producing optically active products have included as precursors bis(arylvinyl)arenes (Moradpur *et al.*, 1975), N-alkyl- N-aryleneamines (Nicoud and Kagan, 1976/1977) and 2-methoxytropone (Zandomeneghi *et al.*, 1981). Attempts to perform asymmetric syntheses involving carbene additions and photodimerizations using CPL, however, proved unsuccessful (Boldt *et al.*, 1971).

3.2.1.2.3. Asymmetric Photolysis

Asymmetric photolysis, first demonstrated successfully by Kuhn and coworkers (1929, 1930a, b), involves the preferential destruction of one enantiomer during the photodegradation of a racemic mixture by CPL. Because of their circular dichroism, CPL of a given handedness will be absorbed unequally by the two enantiomers, resulting in the preferential destruction of the one having the higher extinction coefficient. Thus if the photolysis is interrupted before completion, the unphotolyzed residue will be enriched in the enantiomer having the lower ϵ. In 1974 Kagan and coworkers (Balavoine *et al.*, 1974; Kagan *et al.*, 1974a, b) analyzed asymmetric photolyses in detail both theoretically and experimentally and showed that the optical yields were not limited to the mere $g/2 \approx 1\%$ characteristic of the other CPL-mediated processes, but could actually approach 100% if the g value of the substrate is large enough and if the extent of photolysis is sufficient. Substantiating their conclusions experimentally, they found that when racemic camphor was photolyzed to the extent of 99% with CPL, the undecomposed camphor residue had an enantiomeric purity of $\sim 20\%$, by far the highest ever recorded for an asymmetric photolysis. Shortly thereafter Bonner and coworkers (Flores *et al.*, 1977a) studied the asymmetric photolysis of DL-leucine as a 'prebiotically important substrate'. With RCPL the residual leucine after 59% photolysis had an $L > D$ excess of 1.98%, while 75% photolysis with LCPL produced a $D > L$ excess of 2.50%. In the same year Norden (1977b) reported the asymmetric photolyses of tartaric acid, glutamic acid and alanine, and other successful asymmetric photolyses were subsequently reported (Schneider *et al.*, 1977; Litman *et al.*, 1978; cf. also Nelander and Norden, 1974; Norden, 1975; Tran and Fendler, 1979; Hormann *et al.*, 1981; Mason, 1982).

Because of the high optical yields obtainable by asymmetric photolysis and because

of its potential applicability to any racemic substrate having absorption bands at photochemically pertinent visible or ultraviolet wavelengths, there can be little doubt that asymmetric photolysis constitutes the most plausible of the CPL-processes from the viewpoint of the primordial origin of molecular chirality.

3.2.1.2.4. Sources of Circularly Polarized Light

Sunlight, rich in the ultraviolet and visible wavelengths which promote electronic excitations leading to photochemical reactions, may become linearly polarized by reflection or by Rayleigh and/or Mie scattering from atmospheric molecules and/or aerosols. Additional reflections or multiple scatterings may then produce elliptically or circularly polarized light (Hecht and Zajac, 1974). Such processes are presumably responsible for the small CPL component in the reflected sunlight from Jupiter, Venus and Mercury (Angel *et al.*, 1972; Kemp *et al.*, 1971a, b; Kemp and Wolstencroft, 1971), and Hokkyo (1984) has suggested that radio-frequency CPL solar bursts associated with sunspots might be implicated in the origin of optical activity. While earlier workers assumed that RCPL predominated at Earth's surface (Ritchie, 1933), it has recently been found that LCPL predominates in the early morning hours, while an equal and cancelling excess of RCPL prevails in the late afternoon (Angel *et al.*, 1972; Wolstencroft, 1985), thus making the net diurnal handedness of terrestrial CPL zero for a smooth 'billiard ball' Earth. Wolstencroft (1985) has pointed out, however, that the irregular terrain on Earth might permit regional excesses of a particular CPL handedness by partially obscuring portions of the sky, while Bonner and Rubenstein (1987, 1990) have noted that subsequent temperature- dependent non-photochemical reactions resulting from 'late afternoon' RCPL-induced products would be favored by the warmer terrestrial postmeridian temperatures, thus giving them a 'chemical evolutionary" advantage.

Mörtberg (1971, 1974) has suggested an alternate source of terrestrial CPL. Due to the Faraday effect and the presence of Earth's magnetic field, the RCPL and LCPL components of linearly polarized sunlight are refracted differently as they traverse the increasingly dense atmosphere toward Earth, with one component preferentially refracted towards Earth and thus slightly predominating there. Mörtberg showed that with Earth's tilted axis and its elliptical orbit about the sun there would be a persistent excess of CPL of one chirality reaching the surface, and that this would not be cancelled at any geographical location on Earth during its yearly orbit. While cognizant of several factors diminishing the efficacy of his mechanism, Mörtberg neglected other potentially invalidating factors such as the periodic reversals of Earth's magnetic field (McElhinny, 1971) and the precession of the equinoxes, which reverses the tilt of Earth's axis every 13000 years. While these factors would be capable of reversing any unique chiral consequences of Mörtberg's mechanism over extended periods, it was noted that the global asymmetry of Earth's land mass might nevertheless insure that there be no overall cancellation of the effects of the mechanism (Bonner and Rubenstein, 1987).

Sunlight itself provides an extraterrestrial source of CPL. Kemp *et al.* (1987a;

Kemp, 1988) have recently measured the circular polarization of sunlight at a sensitivity of a few parts in 10^7, and found that light from the Sun's whole disk had a net LCPL excess of 0.1- 1.0 $\times$ 10^{-6} (from red to blue). While admitting that such excesses would average to zero over long time periods, the authors suggested that 'if biogenesis began not slowly but in a burst of photochemistry' over short periods, then the net circular polarization of sunlight 'might have promoted chirality'. Broad band optical circular polarization has also been observed in the starlight from Lambda Andromedae (Kemp *et al.*, 1987b). Finally, an additional extraterrestrial source of CPL leading to terrestrial enantiometic inequalities has recently been proposed (Rubenstein *et al.*, 1983; Bonner and Rubenstein, 1987, 1990; Roberts, 1984). In this scenario ultraviolet synchrotron CPL, produced off-angle to the orbit of electrons accelerated around the rotating neutron star remnants of supernova explosions, interacts with the organic mantles of inorganic grains in intergalactic dust clouds (Greenberg, 1983a, b, 1984a, b), producing chiral organic molecules in the mantles by customary CPL processes. As the solar system periodically traverses these clouds while revolving about the center of the galaxy, Earth accretes vast quantities of organic matter with these grains (Greenberg, 1983a, 1984a, b), including the optically active mantle constituents which have remained unracemized due to the cold interstellar temperatures. Recent laboratory simulation experiments of the formation of organic mantles on interstellar grains have shown that the simulated mantle material does in fact contain such potentially optically active molecules as glyceric acid and glyceramide (Agarwal *et al.*, 1986). The above neutron-star/synchrotron-CPL/interstellar grain scenario suggests that the chirality of the biomolecules generally associated with extraterrestrial life need not be similar to that on Earth, but should vary randomly throughout the galaxy (Bonner and Rubenstein, 1987, 1990).

While several other authors have suggested the formation and presence of stable organic polymers on or in interstellar grains (Sagan, 1972; Hoyle and Wickramasinghe, 1977; Wickramasinghe *et al.*, 1977; Goldanskii, 1977a, b; Sagan and Khare, 1979; Greenberg, 1983a, b, 1984a, b) only Khasanov and Gladyshev (1980; Gladyshev and Khasanov, 1981) have previously suggested that *chiral* molecules, formed by unspecified interstellar force fields, might exist in interstellar grains and persist because of low interstellar temperatures and infrequent grain collisions. In contrast to the panspermia hypothesis (Section 2), which offers no explanation for the extraterrestrial origin of life, the extraterrestrial origin of molecular chirality is at least understandable in terms of known CPL mechanisms which have been demonstrated experimentally.

3.2.2. *Universal Processes*

While the above Regional and/or Temporal processes may have varied at different locations or in different epochs on Earth, another class of Universal Processes for the abiotic production of chiral molecules has persisted on Earth in an invariant manner during its entire history. These processes, which are the result of the violation

of the principle of parity in certain interactions within the nucleus of the atom, are considered below.

3.2.2.1. The Violation of Parity

The principle of parity states that natural laws are invariant under spatial reflection, i.e., any natural process can also occur as seen reflected in a mirror. Because of certain anomalies in the decay patterns of θ and τ mesons, Lee and Yang (1956) suggested that the parity principle might be violated for certain 'weak interactions' such as those involved in the ß-decay of radioactive nuclei. This Nobel prize-winning prediction was verified by Wu *et al.* (1957), who showed that the electrons emitted during the ß-decay of ^{60}Co nuclei were longitudinally polarized with a 'left-handed' bias, with their spins predominately antiparallel to their propagation direction. The parity principle, which predicted equal numbers of electrons having both parallel and antiparallel spins, was clearly violated (Ulbricht, 1959; cf. Bonner, 1972a). It is now thought that parity is conserved in strong (hadronic) and in electromagnetic interactions, but that it is violated in all of the weak interactions mediated by charged or neutral bosons (cf. Bonner, 1988). Shortly after the verification of Lee and Yang's prediction, potential biological implications of parity violation became apparent, and a number of theoretical and experimental investigations followed.

3.2.2.2. The Vester-Ulbricht (V-U) Hypothesis

The homochirality of contemporary biomolecules itself has the characteristic of a parity violation, that is, the mirror images of these molecules are absent in our biosphere. The first attempt to link the demonstrated violation of parity at the subatomic level with that observed at the biomolecular level was made by Vester (1957; Vester *et al.*, 1959) and Ulbricht (1959, 1962), who suggested that the longitudinally polarized electrons emitted during ß-decay might impinge on matter to form, as also predicted by Lee and Yang (1957), circularly polarized 'Bremsstrahlen' photons, which in turn could induce stereoselective photochemical syntheses or degradations with organic substrates to yield chiral products. This ingenious Vester-Ulbricht (V-U) hypothesis was then tested experimentally by Vester *et al.* (1959; Ulbricht and Vester, 1962), who conducted various synthetic and degradative reactions capable of yielding chiral products in the presence of a number of ß-emitting radionuclides (^{32}P, ^{90}Sr, ^{90}Y, ^{152}Eu, ^{108}Ag) under a variety of conditions. The irradiated products were then examined polarimetrically, and found all to be optically inactive within experimental error. Gol'danskii and Kharpov (1963) also conducted ß-irradiations (using ^{104}Rh) of a number of racemic organic compounds, and likewise found that no optical activity was induced in any of the substrates.

Five years later Garay (1968) reported the first positive observation regarding the V-U hypothesis. Alkaline solutions of D- and L-tyrosine were irradiated using ~0.36 mCi of dissolved $^{90}SrCl_2$ as the ß-ray/Bremsstrahlen source, and after 18 months the 242 nm absorption band observed for the D-tyrosine solution was found to be eradicated to a greater extent than that for the L-tyrosine solution. Garay

suggested that the apparent asymmetric decomposition of the tyrosine was caused by an oxidative degradation biased in favor of the D-enantiomer by the ^{90}Sr chiral ß-particles and/or their Bremsstrahlen. His observations, while never duplicated precisely by himself or by others, quickly encouraged a number of related investigations into the potential validity of the V-U mechanism.

One of the first of these was that of Bonner (1974), who employed a ß-ray/Bremsstrahlen source consisting of 61.7 kCi of ^{90}Sr-^{90}Y oxides to irradiate a number of amino acids for increasing time intervals. Analytical gas chromatographic (GC) techniques, which had been developed for the evaluation of both the enantiomeric compositions (Bonner, 1972b; Bonner *et al.*, 1974b; Flores *et al.*, 1977b; Van Dort and Bonner, 1977; Blair and Bonner, 1980a) and the extents of degradation of amino acids (Bonner, 1973; Bonner and Blair, 1979), were employed to examine the irradiated samples, which were retrieved after 0.3, 1.3 and 10.9 years. While the samples had undergone increasing radiolysis with increasing radiation dosage, none of them showed any evidence whatsoever for asymmetric degradation, even after a total exposure dose of $\sim 2.5 \times 10^9$ rads. It was suggested (Bonner and Liang, 1984) that the lack of asymmetric degradation might be due to the insufficient circular polarization of the predominantly low energy Bremsstrahlen employed.

Testing the V-U hypothesis with another natural ß-emitting radionuclide, Darge *et al.* (1976) conducted the asymmetric radiolysis of D,L-tryptophan in frozen aqueous solution containing ^{32}P-phosphate. After 12 weeks the substrate appeared 33% radiolyzed and was claimed (based on an optical rotation of $0.0007 \pm 0.0004°$) to have a 19% enrichment of D-tryptophan in the undegraded residue. In careful duplications of Darge's experiment but using analytical GC to estimate both the extents of radiolysis and the enantiomeric compositions, however, Bonner *et al.* (1979a) were unable to detect any stereoselective radiolysis whatsoever of either D,L-tryptophan or, in later ^{32}P experiments, of D,L-leucine (Blair and Bonner, 1980b). Another stereoselective interaction of ^{32}P ß-rays with enantiomers has recently been reported by Garay (1987b; Garay and Ahlgren-Beckendorf, 1990) who found that the stopping power for ^{32}P ß-rays was 8–10% greater for R-2-phenylbutyric acid than for the S-enantiomer, while that of the racemate fell in between. The results were interpreted (Garay, 1987b) as due to a 'difference of internal timing of the two enantiomers', though contamination could not be totally excluded. Another unconfirmed positive report of a novel stereoselective reaction involving ^{32}P is that of Akaboshi *et al.* (1978), who observed that when 'hot' recoiled ^{32}S atoms from ^{32}P-phosphate impinged on alanine or serine to produce cysteine, the D-enantiomers were converted to cysteine considerably more rapidly than the L-enantiomers.

A third natural ß-emitting radionuclide which has been considered as a test for the V-U hypothesis is ^{14}C. Bernstein *et al.* (1972c) examined five crystalline ^{14}C-labeled D,L-amino acids, synthesized 12–24 years earlier, for optical activity using a spectropolarimeter, but found no optical rotation within the sensitivity (0.002°) of the instrument. The examination of additional racemic ^{14}C-labeled amino acids, 17–25 years old and subjected to ~ 5.4–11.4×10^7 rads of self-ß-irradiation, was

subsequently undertaken by Bonner *et al.* (1978) using analytical GC techniques. Again, despite gross radiolysis ranging from 17 to 68%, no stereoselective degradation whatsoever was evident. Possible reasons for these negative ^{14}C-radiolyses have been discussed (Noyes *et al.*, 1977), and a number of weaknesses of the V-U mechanisms in terms of its Bremsstrahlen step have been emphasized by Keszthelyi and Vincze (1975), Walker (1976) and Bonner and Liang (1984). On the other hand Tokay *et al.* (1986) have reported stereoselectivity in the ß-ray-induced autoradiolysis of ^{14}C-labeled leucines. Thus the decarboxylation of ^{14}C-D-Leu was found to be 1.9 times that of ^{14}C-L-Leu for a 2.24×10^4 rad dose during one year of autoradiolysis, and the EPR spectra showed a 10% higher radical concentration in the ^{14}C-D-Leu than in the L-enantiomer. The authors suggested that ^{14}C-labeled amino acids, produced by cosmic rays on the primitive Earth, might have undergone similar stereoselective autoradiolysis, giving a prebiotic excess of amino acids of one chirality.

In other experiments not directly related to the V-U hypothesis, positive stereoselective interactions between enantiomers and the radiation from ß-emitting radionuclides have also been reported. Kovacs and Garay (1975) examined the possibility that the ß-particles and/or Bremsstrahlen from ^{32}P might bias the otherwise random spontaneous resolution of conglomerates (cf. Section 3.1.2) towards the selective crystallization of one enantiomer. When sodium ammonium DL-tartrate was crystallized 63 times from solutions containing 0.16 mCi of codissolved $K_3{}^{32}PO_4$ per sample, a slight preference for crystallization of L(+)-tartrate was noted. Kovacs (1978, 1979a, b, 1981) subsequently extended these experiments to over 1000 additional crystallizations and found that the stereoselective bias increased with higher radioactivity levels. He then concluded (1979a) that the selective bias in crystal seed nucleation was due to the ^{32}P ß-particles, and suggested (1979b) that similar stereoselectively biased crystallizations induced by ß-emitting radionuclides might have caused a preferential chirality on the primitive Earth.

In other experiments Akaboshi *et al.* (1979) irradiated crystalline D-, L- and D,L-alanine at 77° with the ß-rays and Bremsstrahlen from ^{90}Y, then measured the extents of free radical formation in each sample using ESR techniques. Radicals were produced in D-alanine 14–21% more plentifully than in L-alanine, but not at higher temperatures (Akaboshi *et al.*, 1981a) or using unpolarized electrons (Akaboshi *et al.*, 1981b). Such stereoselective radical formation in alanines irradiated with ^{90}Sr- ^{90}Y ß-rays has since been confirmed by Conte (1985; Conte *et al.*, 1986). Akaboshi *et al.* (1982, 1983, 1984) subsequently extended their experiments to include the 'internal' ß-radiation from ^{3}H-labeled alanine, finding again that radical formation was greatest in the D-enantiomer and concluding that polarized ß-rays rather than their Bremsstrahlen were responsible for the stereoselective interactions. More recently Akaboshi *et al.* (1989, 1990) have reported that in ^{60}Co- γ-radiolyses of DL-aspartic acid, the presence of L-alanine suppresses the radiolysis of L-Asp as compared to D-Asp, whereas D-alanine produces the reverse effect. The authors, as later does Tennakone (1991), postulated that such a phenomenon might have played a role in the prebiotic selection of molecular chirality, though neither suggests

where or how the all-important optically active alanines originated.

Making extrapolations and arbitrary assumptions about ß-emitting nuclides on Earth 4 Gyr ago, Keszthelyi (1976a) calculated that asymmetries as low as 10^{-5} percent caused by ß-radiolysis could have survived susbsequent racemization. Hegstrom *et al.* (1985) later made additional calculations that the VU-mechanism might be a viable one, a conclusion also reached earlier by Mann and Primakoff (1981), but questioned by Fajszi and Szege (1977). More recently Conte (1987) has fearlessly calculated that, with an appropriately sensitive amplification mechanism and the proper assumptions of arbitrary parameters, ß-radiolysis could have determined the domination of L-amino acids in the biosphere with a 98% chance over a mere 1500 year time span. Zel'dovich and Saakyan (1980), on the other hand, have estimated that the asymmetry of reactions caused by longitudinally polarized electrons would be less than that caused by circularly polarized photons by a factor of $\sim 10^6$. Finally, Pacheco (1987) and Membrano *et al.* (1988) have suggested yet another mechanism for the transfer of the asymmetry of a nuclear event to a molecule. This consists of a two-step ß–γ cascade disintegration process involving internal electron capture (EC) and the formation of a continuous spectrum of circularly polarized internal Bremsstrahlen (IB). Such two-step IBEC decays were argued to be potentially more effective for inducing asymmetric effects than the external Bremsstrahlen of the V-U mechanism.

3.2.2.3. Radioracemization

While examining their aged samples of ^{14}C-labeled amino acids, Bonner *et al.* (1978) noticed that several of the optically active samples had undergone small amounts of racemization along with their ß-radiolysis. Since such *radioracemization*, i.e. racemization induced by ionizing radiation, had been reported only twice previously (Feng and Tobery, 1959; Evans, 1966), and since the phenomenon might be important as regards the V-U mechanism, a systematic investigation of it was undertaken. Several amino acids were irradiated in a ^{60}Co γ-ray source under a variety of conditions, with the finding that significant radioracemization of the samples occurred in both the solid state and in solution (Bonner and Lemmon, 1978a, b). Even the non-racemizable non-protein amino acid isovaline was found susceptible to radioracemization (Bonner *et al.*, 1979b; Lemmon and Bonner, 1979), and the cosmochemical, geochemical and paleontological implications of these observations were subsequently discussed (Bonner *et al.*, 1979c, d; 1980). Radioracemization studies were later extended to include the presence of silica as well as clay mineral surfaces, with the general finding that such mineral surfaces rendered amino acids even more susceptible to radioracemization (Bonner and Lemmon, 1981; Bonner *et al.*, 1985).

Early in the above studies it was emphasized (Bonner and Lemmon, 1978b) that radioracemization could have a deleterious effect on the overall efficacy of the V-U mechanism since, depending on the relative rates of formation of an excess of one enantiomer by stereoselective ß-radiolysis and its radioracemization, the

latter effect could in principle negate the former. Since it has been estimated that ~20% of the total energy over Earth's surface some 2.6 Gyr ago resulted from the ß-decay of ^{40}K (Calvin, 1969b) and since several more powerful sources of ionizing radiation during that era have been postulated more recently (Hegstrom *et al.*, 1985), it seems evident that radioracemization might have been an important factor on the primitive Earth. The phenomenon of radioracemization thus renders questionable the earlier conclusions of Keszthleyi (1976a; Keszthelyi *et al.*, 1979) that chiral molecules formed by ß-radiolysis could survive racemization, and augments the recent conclusions of Bada and Miller (1987) that optically active amino acids would be unlikely to survive racemization during long geological periods.

3.2.2.4. Direct Effects of Chiral Particles

The use of artifically produced chiral particles offers a number of advantages over the ß-radiation from natural radionuclides for investigating possible stereoselective interactions between chiral particles and matter. First, particle energies can often be varied and selected for specific values. Second, the longitudinal polarization of the particles may usually be accurately known, and is generally much greater than that characteristic of 'natural' ß-particles. Third, interactions can be studied directly on crystalline target substrates, thus minimizing the production and effects of any accompanying Bremsstrahlen. Finally, the polarization of artifically produced particles can usually be reversed, thus providing a crucial 'symmetry check' for any stereoselective effect observed. Accordingly, many studies have been undertaken in recent years to investigate possible stereoselective interactions between a number of different 'man-made' chiral particles and organic molecules, with the hope of gaining insight into possible universal mechanisms for the origin of molecular chirality.

3.2.2.4.1. Electrons

The first attempts to bypass the Bremsstrahlen step of the V-U mechanism and to study the direct interactions of artificially produced longitudinally polarized electrons with racemic amino acids were those of Bonner *et al.* (1975b, 1976/1977), who allowed parallel (P) and antiparallel (AP) spin 120 keV electrons of 13–23% net polarization, produced in a linear accelerator, to impinge on crystalline DL-leucine. After 53–75% radiolysis of the target samples the enantiomeric composition of the residual leucine in each was determined by analytical GC. Three 'natural' AP-spin irradiations appeared to favor selective decomposition of the D-leucine in the racemic target, with e.e.s (%D–%L) of –1.42, –0.86 and –0.60% for ~53% gross degradation, while three P-spin irradiations preferentially decomposed the L-leucine, producing e.e.s of +0.8, +0.74 and +1.4% for ~75% gross degradation. Six other irradiations with 120 keV P- or AP-spin electrons, however, showed no stereoselectivity, nor did two irradiations with 60 keV AP-spin electrons. Shortly thereafter Keszthelyi (1976b) and Walker (1976) independently concluded that Bremsstrahlen could not have produced either the gross or the stereoselective

degradations observed, leaving the mechanism of the apparent effect an open question (Bonner *et al.*, 1976).

The potential importance of the above observations prompted Hodge *et al.* (1979) to attempt their duplication using 120 keV P- and AP-spin electrons of 36–47% net polarization produced using an alternative source. Twenty-seven separate irradiations were conducted, the last five after consultation with Bonner and coworkers in order to duplicate their experimental parameters and analyses as closely as possible. With 14 P-spin and 13 AP-spin irradiations, however, the undecomposed leucine residues proved to be totally racemic, having average compositions of D = 50.06, L = 49.94 ± 0.03%. While the reasons for the divergent results were not immediately apparent, Bonner *et al.* (1979e) suggested the possibility that concomitant radioracemization might have been responsible for the null effects observed both in some of their own experiments and those of Hodge *et al.*

Walker (1985) subsequently pointed out that the possible chiral effects of polarized ß-particles in the above electron beam experiments would be seriously 'diluted' by non-stereoselective effects of the predominant non-chiral secondary electrons (δ-rays) simultaneously produced in the target samples. He attempted to circumvent this drawback by irradiating a 50:50 mixture of crystals of pure D- and L-2-hydroxytetrahydropyran in which each enantiomeric crystal was of a size that would exceed the ranges of the secondary δ-rays, so that the entire effect of irradiation with the primary polarized ß-particle would be experienced separately in each crystal. Within the experimental accuracy of CD measurements on the irradiated samples, however, no stereoselective radiolysis was observed after 7–8% gross degradation.

In somewhat related experiments involving electrons, Ulrich and Walker (1975) studied possible stereoselective interactions between 'inherently chiral' solvated electrons trapped in chiral molecule solvent cages and added chiral substrates, but again no selective effects were observed. Close (1978) reported that 'natural' AP-spin electrons had a 10^{-5} greater tendency to interact with unpolarized protons than did P-spin electrons, and Campbell and Farago (1985) found a spin dependence on the scattering of 5 eV polarized electrons by the enantiomers of vaporized camphor, the beam being attenuated with a (+)-asymmetry by L- and with a (–)-asymmetry by D-camphor. Previous theoretical calculations (Rich *et al.*, 1982; Hyashi, 1985) had predicted asymmetries on the order of 10^{-5}–10^{-6} for the scattering of unpolarized electrons by molecules of an optically active medium.

3.2.2.4.2. Protons

Anticipating that polarized protons, due to their larger mass and slower velocity (for the same kinetic energy), might have an advantage over electrons in V-U type experiments, Lemmon *et al.* (1981) undertook irradiations of D,L-leucine samples with 10–14 nA beams of cyclotron-produced P- and AP-spin protons of 0–10 MeV energies and ~80% net longitudinal polarization. Irradiations were conducted on pairs of samples in tandem, such that the proton beam passed completely through the first sample but was stopped by the second. Three irradiations each using P-

and AP-spin protons with radiation doses up to 9×10^8 rads resulted in 7–50% gross degradation, but GC analyses revealed in every case that the residual leucine was still racemic. It was suggested (Lemmon *et al.*, 1981) that the lack of stereoselective radiolysis might have been due to the magnetic moment of the proton being only $\sim 1.5 \times 10^{-3}$ that of the electron, such that the spin-spin interactions between the polarized protons and the electrons of the chiral target substrate might have been too small to be effective. In a later study designed to see if radioracemization might have been implicated in the above negative results, Bonner *et al.* (1982) irradiated D- and L-leucine targets with 0–11 MeV polarized protons as above, causing 39–55% gross radiolysis of the samples. In all of the experiments the extent of radioracemization proved negligible (1.1–1.7%), suggesting that radioracemization or secondary degradative effects were not important factors in the above negative results.

3.2.2.4.3. Positrons and Muons

Positrons (e^+), emitted with parity violation during the decay of neutron-deficient radionuclides such as ^{22}Na, have a predominant 'right-handed' (spin forward) longitudinal polarization. Their initial high ($\sim 10^3$ keV) energy is rapidly degraded to near thermal energy (~ 10 eV) by collisions with matter, whereupon a fraction of them is annihilated by electrons into γ-ray photons and a smaller fraction combines with electrons to enter the transient ground states of positronium (Ps; $e^+ e^-$), either in the parallel-spin 'ortho' state (o-Ps; mean lifetime $\sim 1.4 \times 10^{-7}$ sec) or the antiparallel-spin 'para' state (p-Ps; lifetime $\sim 1.25 \times 10^{-10}$ sec) (Jean and Ache (1979)). Assuming that positrons retain their longitudinal polarization while slowing down to form Ps and looking for possible stereoselective effects, Garay *et al.* (1973; 1974a, b) studied the annihilation of positrons by the D- and L-isomers of tryptophan, phenylalanine, tyrosine and dihydroxyphenylalanine. They reported that the intensity of long-lived o-Ps was higher in D-amino acids than in the L-enantiomers, concluded that D-isomers of amino acids favor the ortho states in the case of positrons, and interpreted their observations in terms of a 'helical electron gas' model. Garay's results were immediately questioned by Rich (1976), who argued that the chirality of the positron would be lost during deceleration before Ps formation could occur, and that the reported results, if valid, must have another explanation. These arguments were bolstered by the inability of several other investigators (Dezsi *et al.*, 1974; Brandt and Chiba, 1976; Jean and Ache, 1977, 1979) who, again using ^{22}Na positron sources, were unable to find any significant differences whatsoever in the lifetimes or intensities of short- or long-lived components of the positron lifetime spectra observed between D- and L-enantiomers of a variety of organic compounds.

To circumvent difficulties perceived in the above annihilation experiments, Gidley and coworkers (Zitzewitz *et al.*, 1979; Gidley *et al.*, 1981a, b) constructed equipment for the 'artificial' production of low energy polarized positrons of reversible longitudinal polarization. This equipment and a subsequent improved version were

then employed to measure the asymmetry of triplet o-Ps formation, A_{Ps}, with D- and L-enantiomers as targets (Gidley *et al.*, 1982; Van House *et al.*, 1984). They found that A_{Ps} was not significantly different for the enantiomers of several amino acids at the $\sim 10^{-4}$ level. However, since A_{Ps} is proportional to Z^2 (Z = the atomic number of the dominant heavy atom in the chiral environment of the substrate), subsequent measurements were made of A_{Ps} using substrates containing atoms of higher atomic number, such as selenium (Z = 34) and iodine (Z = 53) (Van House *et al.*, 1985). Again, however, A_{Ps} values were consistent with a null result. In contrast to the above negative results, Conte and Pieralice (1987) have concluded on the basis of their own more recent ^{22}Na positron experiments using D-, L- and DL-alanine that 'more triplet state (o-Ps) was formed in the scattering of positrons from D-alanine respect to DL-alanine and L-alanine'. Reasons for the discrepancies of this with the earlier reports were not suggested.

Muons (μ^+), which may be produced in the laboratory by the decay of a positive pion (π^+), are $\sim 100\%$ longitudinally polarized, have a 2.2×10^{-6} sec lifetime before decaying to a positron and two neutrinos, and retain their polarization on deceleration (Spencer *et al.*, 1979; Walker, 1985). When a muon is slowed or stopped by matter it may capture an electron forming neutral 'muonium' (Mu; μ^+e^-). Mu may exist in either the triplet state, with the spins of μ^+ and e^- parallel, or in the singlet state having antiparallel spins. Because of the persistent polarization of μ^+, the formation and/or subsequent chemical reactions of Mu might be different for two enantiomers and, since μ^+ is a component of cosmic rays, such stereoselective interactions might provide yet another universal mechanism for the origin of chirality. Lemmon *et al.* (1974) investigated this possibility experimentally by irradiating crystalline D- and L-alanine and liquid D- and L-2-octanol enantiomers with cyclotron-generated μ^+ beams, then measuring the residual polarization and asymmetry of the μ^+ after being stopped in the targets. No differences beyond experimental error were found with either pair of enantiomers. A subsequent study by Spencer *et al.* (1979) of the amount of triplet Mu formed by irradiating d- and l-quartz crystals with μ^+ beams in a transverse magnetic field again revealed that the amount of Mu formed was independent of the chirality of the quartz target to within 1%. Thus there is no corroborated experimental evidence at the present time for any stereoselective interactions between either longitudinally polarized positrons or muons with enantiomeric molecules.

3.2.2.5. Weak Interactions, Neutral Currents and Parity Violating Energy Differences

In the above sections we reviewed experiments designed to determine whether the chirality of several elementary particles resulting from parity violation during the decay of certain radionuclides might interact 'externally' with molecules in a stereoselective manner. More fundamentally, parity violation is also believed to influence the intrinsic properties of enantiomers themselves, resulting 'internally' in stereoselective differences in their reactions with themselves or other molecules. The parity-violating weak interactions (WI) involved in ß-decay are 'mediated' by

the exchange of charged ($W^{\pm}$) or neutral (Z^0) bosons between the interacting particles, giving rise to 'charged currents' and 'neutral currents', respectively (Keszthelyi, 1977a, 1978; Hegstrom *et al.*, 1980). Neutral current WIs are predicted to result in a small energy difference, $\pm E_{pv}$, equal in magnitude but opposite in sign between enantiomers (Yamagata, 1966; Rein, 1974, Ulbricht, 1975; Rein *et al.*, 1979a, b; Hegstrom *et al.*, 1980). This 'parity-violating energy difference' (PVED = $+E_{pv} - (-E_{pv}) = 2\ E_{pv}$) between two enantiomers, which varies in magnitude depending on the enantiomers as well as their conformations (Mason and Tranter, 1983, 1984, 1985), is further thought responsible for minuscule differences in physical properties, equilibria and reaction rates for enantiomers, which in turn have potential implications regarding the origin of our current biomolecular homochirality (Yamagata, 1966; Tranter, 1985a).

The connection between PVEDs and biomolecular chirality was first suggested by Yamagata (1966), who postulated that small reaction rate differences between enantiomers caused by PVEDs might ultimately be amplified by an 'accumulation principle' into terrestrial homochirality (Cf. Section 4.4). Garay and Hrasko (1974) subsequently suggested that small differences in binding energies and reaction rates between enantiomers, caused by PVEDs of unspecified magnitude, could lead to almost complete selection of one enantiomer during millions of years of evolution, and Garay (1979, 1987a) later extended such speculations to higher biological phenomena. The magnitude of PVEDs has been of considerable interest, and the first suggestion for their magnitude was that of Thiemann and Wagener (1970) who, on the basis of crystallization experiments with sodium ammonium DL-tartrate, suggested that crystal lattice energies might differ by 10^{-5}. Rein (1974) later calculated the energy difference between enantiomers as $< 10^{-10}$, and 'possibly smaller by orders of magnitude', and hence probably experimentally unobservable. Letokhov (1975) has dogmatically argued that reaction rate differences as small as 10^{-16} due to PVEDs would be 'quite sufficient for full selection of either of two stereoisomeric forms of all the amino acids' over 10^8–10^9 years. Keszthelyi's (1977b) later estimate of 10^{-10} as the relative energy difference between enantiomers, based on crystallization experiments with sodium ammonium D,L-tartrate, cannot be considered valid since the asymmetric bias in the crystallizations was ascribed (Kovacs and Garay, 1975) to the presence of the ^{32}P ß-particles present, not to PVEDs. Mason and Tranter (1983; Tranter, 1985b) subsequently made *ab initio* calculations that the PVEDs for various amino acids in their 'preferred conformations in aqueous solution' favored the natural L-enantiomers over the D-enantiomers by approximately 10^{-14} J/mol, and that natural L-polypeptides in either α-helix or ß-sheet conformations have lower energies than D-polypeptides by *ca.* 0.6×10^{-14} J/mol for each peptide unit (Mason and Tranter, 1984, 1985, 1987; Tranter, 1985a, b, 1986a). Taken as a free energy difference, 10^{-14} J/mol corresponds to an excess of some 10^6 L-molecules per mol in the corresponding racemic mixture at thermodynamic equilibrium at ambient temperature, or 1 part in 10^{17} (Tranter, 1985b). Such calculations were subsequently extended (Tranter, 1985c, 1986a) to the hypothetical reaction pathway

leading to the formation of enantiomeric α-aminopropionitriles, precursors of D- and L-alanine. Again, the natural L-isomer was naturally preferred. Similar calculations (Tranter, 1986b) quite naturally concluded that D-glyceraldehyde is slightly favored over the L-enantiomer in aqueous solution, and that therefore the 'natural' D-sugars were similarly favored by their PVEDs because they were formally related stereochemically to D-glyceraldehyde! Similar implausible *ab initio* calculations were later extended to tetrahydrofuran derivatives by Tranter and MacDermott (1986; MacDermott *et al.*, 1987), with inferences drawn for the PVED preference for D- over L-pentofuranoses in DNA. Not only are 'natural' L-amino acids, their corresponding α-helix or ß-sheet polypeptides and D-sugars calculated to be slightly favored by PVEDs, but chiral inorganic crystals, e.g. quartz, have been alleged to adopt a PVED-preferred handedness as well (Mason, 1984). Tranter (1985d, 1987) accordingly postulated that allegedly non-racemic inorganic minerals such as quartz or possibly clays might, in conjunction with their stereoselective catalytic action, engender e.e.s in chiral substrates greater than those induced by the PVEDs themselves, thus enhancing the overall PVED effect. Tranter (1985e) has also calculated that PVEDs produce slight *structural* differences in enantiomers which, however, he considers to be inconsequential as regards the origin of chirality. In a series of interesting reviews which unfortunately persist in ignoring both the essentially random terrestrial distribution of d- and l-quartz (Frondel, 1978) and the fact that no stereoselective interactions whatsoever have been observed involving clay minerals (Cf. Section 3.1.5), Mason (1985a, b, 1986a, b, 1987, 1988a, b, 1989; cf. also MacDermott and Tranter, 1989) has recently reiterated on an annual basis all of the above experimentally unsupported calculations and speculations.

How do the minute PVEDs alleged in the above reports subsequently induce a state of enantiomeric homogeneity? We recall (Section 3.1.1) that spontaneous symmetry breaking in far from equilibrium racemic systems which pass through a 'bifurcation point' may randomly divaricate (in mathemathical models) into a condition of enantiomeric purity. Nicolis and Prigogine (1981) showed theoretically that such bifurcations far from equilibrium endow the system with a pronounced sensitivity to external factors, such that the slightest environmental asymmetry might induce the non-random selection of a preferred molecular chirality. Related analyses and models were later proposed by Wei-min (1982a, b), Nicolis (1984), Nelson (1984), Tennakone (1984), Shimizu (1984) and Ding and Xu (1985). Extending earlier ideas of Yamagata (1966), Garay and Hrasko (1973) and Letokhov (1975), Kondepudi and Nelson (1983) later suggested that the requisite environmental asymmetry might be provided by the PVEDs. Then, adapting earlier ideas of Frank (1953), the authors (Kondepudi and Nelson, 1984a, b, 1985, Kondepudi, 1987) postulated an autocatalytic amplification scheme acting on minute PVED-produced e.e.s, and estimated that energy differences as small as $\Delta E/kT \approx 10^{-17}$ to 10^{-15} would be sufficient for the complete chiral selection of preferred enantiomers of amino acids within relatively short time spans.

Not all experts in the field, however, subscribe wholeheartedly to the calculations

and conclusions cited above. As early as 1979 Rein *et al.* (1979a, b; Hegstrom *et al.*, 1980) recalculated the PVEDs between several molecules previously studied, alkyl sulfide and 'twisted' ethylene, and concluded that the energy differences, 10^{-21} and 10^{-18} eV, respectively, were appreciably smaller than previously estimated, and that PVEDs of these magnitudes 'might hardly be taken to be responsible for the ultimate optical asymmetry through which life is thought to have evolved'. After critically reviewing the previous literature Keszthelyi (1981, 1984) likewise concluded that 'it seems very improbable that the weak interaction played any role in establishing the nearly complete asymmetry of biomolecules'. Hegstrom (1982) has estimated the cross-section asymmetry for the ß-radiolysis of amino acids to be 10^{-11} to 10^{-10} for 100 keV electrons, while the asymmetry for PVED effects is $\sim 10^{-17}$ (Tranter, 1985a, b, 1986a, b; Hegstrom *et al.*, 1985). He then concludes that the chiral selection parameter for ß-radiolysis can be 10^6 larger than that for neutral current effects, that 'ß-radiolysis can produce a much larger systematic chiral perturbation than produced by weak neutral currents', and that 'the Vester-Ulbricht hypothesis is viable notwithstanding the small magnitude of chiral polarization produced by asymmetric radiolysis' (Hegstrom, 1984, 1985). These contentions have been more recently questioned, however, by Meiring (1987). In further disputing earlier claims of Mason and Tranter (1985) that weak photoabsorption asymmetries produced by PVEDs might be implicated in a photochemical discrimination between enantiomers by unpolarized light, Hegstrom's (1987) more recent calculations again lead him to conclude that 'differential radiolysis by beta electrons is likely to produce the largest symmetry breaking effect by the weak interaction'. Meanwhile Keszthelyi (1987) has refuted on theoretical grounds the earlier calculations of Tranter (1985d, 1987) alleging a PVED-induced excess of l-quartz crystals on the surface of Earth, while Morozov *et al.* (1983, 1984a, b), after analyzing the 'advantage factor' due to neutral current effects as compared to statistical fluctuations, have concluded that the former 'is incapable to play any role in dissymmetry forming on Earth' and that, as regards the PVED hypotheses, 'much stronger arguments are needed to substantiate this hypothesis than suppositions about mere multiplication of possible slight energy differences of two mirror isomers'. Dunne (1985) has maintained that in systems where PVED effects might lead to a crystal symmetry breaking of enantiomers, strongly attractive L-L or D-D interactions and repulsive L-D interactions would favor an inequality in the numbers of right- and left-handed crystal forms, but that this imbalance does not require the total exlusion of one of the forms, as in the Kondepudi and Nelson model (1983, 1984a, b, 1985; Kondepudi *et al.*, 1985). Later Avetisov *et al.* (1987) and Gol'danskii and Kuz'min (1988), pointing out theoretical difficulties in assumptions made by Kondepudi and Nelson regarding the sensitivity of vanishingly small advantage factors to 'a slow passage of the critical point', have concluded that since 'the grounds for such assumptions are lacking, the role of (weak neutral current effects) in the origination of the biomolecular chirality should be regarded as inessential'. Kondepudi's (1989) most recent rebuttal to these arguments emphasizes the tenuity of the above theoretical

conclusions regarding the efficacy of PVED effects in generating molecular chirality.

On the experimental side, only a few investigators have attempted to observe the macroscopic consequences of PVEDs. Because of the trivial magnitude of PVEDs, such experiments as have been undertaken (or proposed) have involved processes in which subsequent replicating or cascading steps might amplify the original minute enantioselective PVED phenomenon into an experimentally observable effect. Thiemann and Wagener (1970) performed carefully controlled fractional precipitation experiments with sodium ammonium D,L-tartrate and consistently obtained products having spectropolarimetrically observed rotations of ~ -0.001 °. After eliminating potential sources of error, they interpreted their findings as due to differences of $\sim 10^{-5}$ in the lattice energies of the enantiomeric crystals. Yamagata (1974) subsequently proposed but failed to investigate a technique for concentrating the minuscule PVED-induced e.e.s thought to prevail in a racemate. This involved repeated fractional crystallization of the racemate followed by concentration of the mother liquors, and final examination of the small volume of residual mother liquors for optical activity. Wagener (1974) later analyzed various physical processes such as chromatography, ion exchange, electrophoresis, polymerization and precipitation from the viewpoint of potential efficacy in amplifying the effects of small PVED-induced lattice energy inequalities, and concluded that fractional crystallizations and precipitations offered the best possibility. Thiemann (1974) thereupon attempted to observe an 'asymmetry effect' on repeated recrystallizations of D,L-asparagine samples, reporting very slight polarimetrically measured e.e.s in the precipitates, with D > L for precipitations conducted at <7.5 °C and L > D for those conducted at >8 °C.

A different sort of PVED manifestation was later alleged by Merwitz (1976), who reported that the rate of the γ-ray induced solid-state decarboxylation of ^{14}C-labeled D-phenylalanine was 2.7 times greater than that of L-phenylalanine, with that of the racemate lying in between. Such observations were subsequently extended by Norden *et al.* (1985) to labeled leucine enantiomers, with similar results. These enantiomeric rate differences were ascribed to PVED effects which were then amplified by cascade processes in a radiation-induced solid state chain reaction. Garay (1978) has interpreted Merwitz' results as due to differences in the 'helicities' of the electron systems of the enantiomers, resulting in differences in their 'internal timing'.

Polymerization has also been considered as an experimental tool for amplifying PVED effects (See Section 4.4). Thiemann and Darge (1974) conducted polymerizations using the N-carboxyanhydrides (NCAs) of carefully racemized samples of several amino acids, then measured the optical rotations of the polymers. They reported minute negative rotations varying between -0.00025 ° and -0.00084 ° ($\pm$ 0.00025 °) for six polymers isolated, and boldly concluded that there was an intrinsic polymerization rate difference favoring L- over D-amino acid NCAs of the order of 8×10^{-6}. Yamagata *et al.* (1980) later made a number of computer model experiments simulating prebiotic polymerizations of racemic monomers

having slight enantiomeric inequalities. They found that asymmetry developed much more slowly than polymer growth, and that the degree of asymmetry increased with the extent of polymerization.

Finally, in another area where PVED effects would definitely be expected to be amplified (cf. Morozov *et al.*, 1984a), namely, during crystallizations allegedly subject to 'autocatalysis', the few results available appear ambiguous. In their statistical studies on the spontaneous resolution of 1,1′-binaphthyl, for example, Pincock *et al.* (1971) found that 'nucleation occurs in a random manner' giving crystals having 'a symmetrical distribution of both (+) and (-) optical activities, with a mean close to $[\alpha] = 0.0$'. On the other hand, in recent crystallization experiments with sodium perchlorate, the formation of dextrorotatory crystals seemed to be favored when the solutions were stirred, but levorotatory crystals if unstirred (Kondepudi *et al.*, 1990).

3.2.3. *Conclusions*

In summarizing and briefly evaluating the numerous experiments performed during investigations of determinate mechanisms proposed for the origin of molecular chirality, we find first that all 'Regional or Temporal' mechanisms based on electric, magnetic or gravitational field effects have been theoretically unsubstantiated and experimentally unconvincing or refuted. Mechanisms involving circularly polarized light are well understood theoretically and lead to large (particularly in the case of asymmetric photolysis) and readily verifable experimental effects. Their terrestrial applicability is jeopardized, however, by the questionable availability of sufficiently intense circularly polarized sunlight on the surface of Earth, while the intervention of extraterrestrial CPL sources remains only speculative.

'Universal' mechanisms based on various consequences of parity violation do not fare much better. The V-U hypothesis has been both controversial in theoretical details and quite unamenable to experimental validation, while experiments concerned with the direct effects of chiral pareticles, be they natural ß-rays (and/or their Bremsstrahlen) or artificially produced polarized electrons, protons, positrons or muons, have generally been negative or inconclusive (Bonner, 1984, 1988). Exceptions are the stereoselective radical formation experiments of Akaboshi *et al.* (1979, 1981a, b, 1982, 1983, 1984) and Conte (1985, Conte *et al.*, 1986), the stereoselective ß-autoradiolysis experiments of Tokay (1986), the stereoselective crystallizations of tartrates in the presence of a ^{32}P ß-emitter (Kovacs and Garay, 1975; Kovacs, 1978, 1979a, b, 1981) , the stereoselective recoil ^{32}S experiments of Akaboshi (1978), and the triplet positronium formation experiments of Conte and Pieralice (1987). Many of these positive reports of alleged stereoselectivity remain currently uncorroborated, however, nor is the pertinence of most of them to the origin of biomolecular chirality immediately apparent. As for 'universal' mechanisms based on PVEDs, their trivial 10^{-17} magnitude (equivalent to one star out of the total in a million of our galaxies) seriously compromises any credibility for their alleged consequences, and the efficacy of subsequent amplifications following such

minuscule effects remains controversial. Thus the experiments of Merwitz (1976) and Norden *et al.* (1985) allegedly confirming PVEDs are subject to possibly more mundane interpretations (Norden *et al.*, 1985), while those of Thiemann and Wagener (1970; Thiemann and Darge, 1974) have involved optical rotations ambiguous because of their minuteness. In few of the above studies have the potentially deleterious effects of radioracemization been considered even qualitatively. Meanwhile, Walker (1985) has stressed that while there are no theoretical arguments against selectivity differences between chiral particles and enantiomers or against PVED effects, 'the only question is whether these differences are large enough to cause observable chemical or biological effects'. To date the answer appears generally negative.

Recent 'Creationist' criticisms by Gonzalez (1985) regarding the general efficacy of all physical mechanisms for the origin of optical activity have been effectively refuted by Brewster (1986). Nevertheless, considering the heroic efforts expended to demonstrate the validity of deterministic mechanisms for the origin of chirality, it is perhaps discouraging that so little by way of definitive positive results has been forthcoming. Thus, from the viewpoints of either chance or determinate mechanisms, the basis for the origin of biomolecular chirality still remains obscure.

4. The Amplification of Enantiomeric Excesses

With few exceptions the e.e.s produced by the mechanisms proposed above for the origin of molecular chirality have proved small, ranging from the $\sim 20\%$ found experimentally for asymmetric photolysis with CPL to the $\sim 10^{-17}$ alleged theoretically for PVED effects. It has accordingly been generally recognized that an effective mechanism for the subsequent amplification of these small e.e.s is absolutely essential to ensure development of the state of terrestrial homochirality requisite for the emergence of life. Physical processes capable of enhancing optical purity have been summarized by Wagener (1974) and by DeMin *et al.* (1988), and in the following section we examine briefly those mechanisms which have been considered experimentally and/or theoretically as a means of accomplishing e.e. amplification in the prebiotic era.

4.1. Amplification during incomplete diastereomeric reactions

Since the reaction of one enantiomer with another to form two diastereomeric products occurs with different rates for each diastereomer, it follows that when an optically impure substance reacts to an incomplete extent with itself or with another optically active substance, the enantiomeric purities of both the product and the unreacted starting material will in general be different than those characteristic of the original reactants. These consequences of the more general phenomenon of 'kinetic resolution' have been utilized as a means of achieving the amplification of the e.e. of one enantiomer in optically impure samples. Langenbeck and Triem (1936), after a mathematical analysis, showed experimentally that the

thermal dimerization of L-tyrosine methyl ester having an e.e. of 27.4% yielded a dimer whose tyrosine residues had a 30.8% e.e. when the reaction was interrupted at 40% completion. Hayakawa *et al.* (1972) studied the reactivities of a number of DL-amino acids N-carboxyanhydrides with a 50% deficiency of (–)-menthol. The esterification rates for the D-acids proved greater in all cases, leaving the unreacted amino acid derivative always enriched in the L-enantiomer. Horeau (1974) found that when 10 equivalents of an optically active alcohol having a 20% e.e. was acylated with 9 equivalents of a racemic acyl chloride, the one equivalent of unreacted alcohol now had a 50% e.e. He later showed (Horeau, 1975) that when racemic α-phenylbutyric anhydride reacted with a molar deficiency of (+)-α-phenylethanol the (–)-enantiomer of the anhydride reacted faster, resulting in unreacted anhydride enriched in the (+)-enantiomer. He finally reported (Briaucourt and Horeau, 1979) that if optically impure (+)-α-phenylbutyryl chloride reacts incompletely with an optically impure (–)-alcohol, the e.e.s of both unconsumed reactants were higher than those prevailing at the outset. He also demonstrated that, starting with very low e.e.s for the precursors, such a series of incomplete esterification steps could lead to e.e. amplifications approaching 100% for the residual reactants. Jacques *et al.* (1981) and more recently Kagan and Fiaud (1988) have reviewed the topic of kinetic resolution and emphasized its applicability to the problem of enantiomeric enrichment.

4.2. Amplification during evaporation and crystallization

If a solubility difference exists between a racemate and its individual enantiomeric components, e.e. amplification can occur during the processes of partial evaporation of a solution or partial dissolving of a solid in which the original enantiomeric compositions are unequal. Morowitz (1969) developed a mathematical model showing that partial evaporations and precipitations in such a solution where the racemate was less soluble results in the concentration of the predominant enantiomer in the supernatant. He then demonstrated the validity of his model by conducting several evaporation/crystallization experiments involving solutions of L>D mixtures of phenylalanine and isoleucine. Thiemann (1974) later pointed out that if the racemate is more soluble in such a situation, there will be an e.e. enhancement of the predominant enantiomer in the initial precipitate from a saturated solution or in the residual solid remaining after partial dissolving.

Addadi and coworkers (Weissbuch *et al.*, 1984; Addadi *et al.*, 1985) have recently proposed a novel scheme for the spontaneous resolution of amino acids which involves the enantioselective occlusion of enantiomers on the opposite faces of growing centrosymmetric crystals such as glycine. Glycine crystals were found to selectively occlude one amino acid enantiomer on one of their faces and the other enantiomer on their opposite face. If one face of such a crystal is blocked during growth (by exposure to an air interface, for example), the floating crystal will then selectively occlude that enantiomer of a racemic amino acid which is preferred by its opposite face, thus removing that enantiomer preferentially and leaving the

solution enriched in the other enantiomer. The latter (hydrophobic) enantiomer would then preferentially direct new floating crystals of glycine to the same orientation, and these again would occlude only the opposite enantiomer. Thus a statistical fluctuation in the orientation of prebiotic glycine crystals floating on the surface of an initially racemic amino acid solution 'could lead to the generation and amplification of optical activity'.

Finally Teutsch and Thiemann (1989; Thiemann and Teutsch, 1990) have invoked liquid crystals as a potential means for generating and amplifying optical activity prebiotically. They reported that the commercially available detergent 'Tween 80' forms lyotropic liquid crystals with water, providing a mesophase which, due to the chirality of the detergent, adopts a helical macrostructure. When potassium trioxalato chromate was 'dissolved' as a guest molecule in such a mesophase and then irradiated with ordinary light, a stereoselective photoequilibration occurred producing an excess of the levorotatory S-enantiomer. The authors then postulated such liquid crystals may have been implicated in the origin and amplification of chirality on the primitive Earth, if the helical macrostructures and their ability to engender optically active molecules included within them could be attributed to some combination of the Earth's magnetic field and circularly polarized light, and if the small e.e.s allegedly produced were subsequently capable of amplification by repetitive collapsing and rebuilding of the liquid crystals during intertidal wet and dry cycles.

4.3. Amplification by stereoselective autocatalysis

Mathematical or pictorial models for spontaneous symmetry breaking (Section 3.1.1) (Fig. 1), first proposed to amplify the small e.e.s resulting randomly from 'statistical fluctuations', are of course equally applicable to e.e.s generated by determinate mechanisms, and indeed such schemes have been considered crucial for amplifying the minuscule e.e.s allegedly resulting from PVED effects (Section 3.2.2.5). In view of their potential importance, it is thus somewhat surprising that so little experimental effort has been expended to develop demonstrable autocatalytic amplification schemes. Kondepudi and Nelson (1984b) have proposed a system in which a rhodium hydrogenation catalyst having self-reproducing chiral ligands might not only induce stereoselective hydrogenation but also breed its own chirality. The experimental realization of such a system was never attempted, however, nor was the relevance of catalytic hydrogenation to the prebiotic environment clarified. van Boeckel *et al.* (1987) have suggested yet another embodiment of Frank's (1953) amplification scheme, a rather complicated sequence of reactions involving the autocatalytic formation of single homochiral strands of D- and L-RNA, reversible combinations of such strands to form duplexes, and irreversible removal of some of these duplexes from the system. They then reported that preliminary NMR spectra of mixtures of 'natural' D- and 'unnatural' L-ribonucleotides showed evidence for strong attraction between pentanucleotide RNA strands whose monomers had opposite chirality. This ingenious scheme, as well as others involving homochiral prebiotic

ribonucleotides (Nelsestuen, 1978; Cedergren and Grosjean, 1987) is rendered highly unlikely, however, by the exceedingly limited availability, if any, of ribose on the primitive Earth (Shapiro, 1988).

Addadi and coworkers (Addadi *et al.*, 1981a, b, c, d; van Mil *et al.*, 1981, 1982) have made a number of attempts to develop their solid-state photodimerization and photopolymerization reactions of crystalline divinylbenzene monomers (Section 3.1.3) into autocatalytic systems capable of generating and amplifying chirality. They designed experiments to test whether the chiral polymeric products from such reactions might subsequently participate in a 'feedback' step which would induce a preferred crystallization of the parent monomer, which in turn would polymerize into additional polymer of the same chirality. Their experiments uncovered a general 'inversion effect' in crystal growth, however, in which the selective incorporation of trace impurities on a specific growing face of a crystal inhibits the growth of this face with respect to the growth of the other faces of the same crystal. This effect unfortunately introduced a fatal 'negative feedback' step precluding amplification in their autocatalysis scheme, and led them to conclude that the amplification problem will 'require very specially designed experiments'.

Wynberg (1989) has recently postulated that the enantiomeric forms of the chiral autocatalytic products formed in Frank's (1953) spontaneous symmetry breaking scheme (Section 3.1.1) might be able to form semi-stable dimer complexes, thus resulting in an enrichment of the e.e. of the uncomplexed catalytic product. He then tested the scheme experimentally using several reactions which lead to chiral products of possible catalytic activity, but the initial results were unsuccessful. Alberts and Wynberg (1989) later showed, however, that enantiomerically enriched alkali metal alkoxides, which can give aggregates in solution with both products and reactants, can act as chiral catalysts for their own formation from achiral reactants, yielding products with enhanced e.e.s of the same chirality. They defined this effect as 'enantioselective autoinduction'.

The previously discussed (Section 3.1.2) second order asymmetric transformation during crystallization leading to the 'total spontaneous resolution' of a racemate, of course, constitutes an additional stereoselective autocatalysis mechanism for e.e. amplification. Indeed, of all such mechanisms so far examined experimentally it is unquestionably the simplest and most efficient, and would appear also to be the most probable prebiotically.

4.4. Amplification during polymerization

Anticipating by nearly a decade Yamagata's (1966) oft-cited 'accumulation principle' for e.e. amplification during polymerization, Wald (1957) first suggested that the α-helical secondary structure of a homochiral polypeptide chain might dictate the selection of amino acids of the same chirality as those already present during subsequent growth, thus preserving and augmenting the homochirality in the larger polypeptide. Evidence supporting Wald's hypothesis was soon forthcoming in a number of experiments involving the base-initiated polymerization of γ-benzyl

glutamate N-carboxy anhydride (NCA) into poly (γ-benzyl glutamate). Such studies showed, for example, that configurational randomness introduced by incorporating D-glutamate units into the chain of the L-polymer progressively weakened its α-helix structure, that the polymerization rate of the DL-NCA was only 5% that of the L-NCA, and that the rate of polymerization of the L-NCA was slow up to the octapeptide stage, at which the α-helix secondary structure first became viable, whereupon a dramatic 5- to 6-fold increase in the polymerization rate occurred. (For a summary of these and related studies, cf. Bonner, 1972a, pp. 217–221). Matsuura *et al.* (1965) first demonstrated that e.e. amplification did in fact accompany such stereoselective polymerizations by polymerizing alanine NCA mixtures having the L-enantiomer in excess. Isolating the polymeric products at various stages of the polymerization, they showed polarimetrically that the predominant L-alanine was being selectively incorporated into the polymer during the early stages of polymerization, and the D-alanine only in the later stages. Such observations were later confirmed and extended by Tsuruta *et al.* (1967) and Inoue *et al.* (1968), while Spach (1974a, b, c) later demonstrated that the helical conformation of the peptide was more important than the configuration of the N-terminal propagating group during polymerizations of γ-benzylglutamate NCA. Akaike *et al.* (1975), on the other hand, found no stereoselection in similar polymerizations using L>D mixtures of valine NCA monomers, results which were ascribed to the inability of polyvaline to form an α-helix and its adoption of a ß-sheet secondary structure instead. Other stereochemical and mechanistic details of amino acid NCA polymerizations have been described more recently by a number of other Japanese investigators (Imanishi *et al.*, 1977; Cf. Bonner, 1988; ref. 253). Blair and Bonner (1980c) subsequently undertook a quantitative study of e.e. amplification during the polymerization of enantiomerically unequal mixtures of the NCAs of leucine and valine. Monomer NCAs having known e.e.s were polymerized to the extent of $\sim$50%, whereupon the e.e.s of both the amino acids in the polymers and in the unreacted monomer NCAs were established (after hydrolysis) by GC. For leucine the e.e. of the predominant monomer was enhanced in the polymer and correspondingly depleted in the unreacted monomer, with the polymer e.e. enhancement being greater as the e.e. of the monomer was increased, until a plateau was reached. The reverse was observed for valine NCAs, where the predominant e.e. of the monomer proved lower in the polymer and higher in the unreacted monomer, suggesting that here the racemate was being preferentially incorporated into the polymer. It thus appeared that Wald's (1957) selection mechanism was applicable only to those amino acids whose polymers formed α-helix secondary structures and not to those which, as suggested by Akaike *et al.* (1975), adopted non-helical ß-sheets structures.

Brack and Spach (1979; Spach and Brack, 1979), however, have argued that ß-sheet structures are also chiral entities capable of amplifying amino acid e.e.s during polymerization, and have tried to compare α-helices and ß-sheets from this viewpoint. Studying ß-sheets produced from synthetic poly(leucyl-lysyl) peptides

having alternating hydrophobic (leucyl) and hydrophilic (lysyl) residues whose configurations were randomly distributed, they found that if monomer residues of opposite configurations were progressively introduced into the polymer chains the formation of ß-structures was progressively diminished. They concluded that, depending on the ratio of L- and D-residues in the polymer, one could achieve essentially homochiral ß-sheet cores attached to random-coil portions of the polymer containing both D- and L-residues. On partial hydrolysis of such polymers it was found that their random coil portions hydrolized more readily, allowing the isolation of unhydrolyzed ß-sheet fractions enriched in one enantiomer (Brack and Spach, 1980). This provided yet another mechanism for e.e. amplification during amino acid polymerization and led them, with no actual supporting evidence, arbitrarily to conclude that, while e.e. enhancement can occur *via* either α-helix of ß-sheet secondary structures, the latter should be more probable on the prebiotic Earth (Brack and Spach, 1981).

The potential importance of partial hydrolysis in the overall amplification of amino acid e.e.s by polymerization mechanisms, previously suggested in the computer simulations of Yamagata *et al.* (1980) and the studies of Brack and Spach (1980), have more recently been demonstrated for α-helix mediated polymerizations by Bonner and coworkers. When D-, L- and D,L-leucine polymers of comparable chain lengths were subjected to partial hydrolysis, Blair *et al.* (1981) found that the poly-DL-leucine was more readily hydrolyzed than the homochiral polymers, and that when polyleucine entiomerically enriched to a known degree was partially hydrolyzed, the unhydrolyzed polymer proved to be enriched in that enantiomer originally present in excess, with a corresponding decrease in the e.e. for the monomer recovered from the hydrolysate. Extending these observations, Bonner *et al.* (1981; Blair and Bonner, 1981) proposed a detailed e.e. amplification model involving the partial polymerization of a slightly enriched amino acid mixture, followed by an autocatalytic sequence of additional partial hydrolysis and polymerization steps. They further suggested that such a cyclic sequence might be driven by environmental wet-dry cycles on the primitive Earth, similar to those postulated for prebiotic thermal polymerizations of amino acids in 'fluctuating clay environments' (Lahav *et al.*, 1978) and for the preferential prebiotic formation of 3',5'-linked oligonucleotides (Usher, 1977; Usher *et al.*, 1984).

Since early NCA polymerization experiments suggested that the α-helix essential for further homochiral peptide growth first became viable at the octamer stage, one might ask how the original requisite homochiral octapeptide became available. While Cloud (1982) has assumed that the 1 in 256 (i.e. 2^8) chance of building a homochiral octapeptide by a stepwise oligomerization sequence does not constitute insurmountable odds, later experiments have painted a considerably more optimistic picture. Kricheldorf and Mang (1983; Kricheldorf *et al.*, 1985) prepared di- and tripeptides from a number of N-protected DL-amino acids or esters by condensing them with other DL-amino acids or esters in the presence of a variety of condensing agents. The stereochemical sequences formed in the condensations were then

elucidated using ^{13}C NMR spectroscopy, with the finding that the preferential formation of enantiosymmetric ('isotactic') L-L or D-D sequences (as opposed to L-D or D-L) occurred in ~80% of all condensations, with a preference ratio of $\leq$6:1. In a series of elegant experiments spanning a decade Goldberg and coworkers (Goldberg and Younes, 1977; Goldberg *et al.*, 1987) have recently studied the stereoselectivities of peptide bond formation in a series of competitive condensation reactions with which they converted amino acids sequentially into small oligopeptides. Two equivalents of a DL-amino acid N-carboxyanhydride were allowed to react with one equivalent of an optically pure L'-amino acid derivative to form DL' and L-L' dipeptides. The latter, optically pure, were similarly reacted to form tripeptides, and these in turn were converted into tetrapeptides, with the percentage of major and minor peptide diastereomers being determined after each step. All of such competitive reaction forming a total of 34 di-, tri- and tetrapeptides from glycine, alanine and aspartic acid proved to be stereoselective, the majority (70%) displaying biases in favor of enantiosymmetric growth with diastereomeric enrichments between 4.2 and 56.6%. These results supported the notion that the stepwise assembly of chiral monomers into even small peptides can occur with significant stereoselectivity and provided a non-random process for achieving the smaller enantiosymmetric peptides leading to homochiral α-helices. Goldberg *et al.* (1990) later speculated on the mechanism of such stereoselective condensations, and emphasized some of the experimental parameters to which such stereoselectivity is sensitive.

While the above experiments showing e.e. enrichment during polymerizations were conducted using amino acid or peptide derivatives and condensing agents which were scarcely prebiotically realistic, the conclusions and principles established are presumably applicable to analogous but more probable prebiotic systems. Thus Rohling and Fouche (1972) have reported that, in contrast to earlier assumptions, several amino acids were not extensively racemized during their thermal copolymerization (170–195 °) with L-lysine and L-glutamic acid to form 'proteinoid' polymers, and have suggested that stereo-enriched primitive protenoids might catalytically select between D- and L-substrates and preferentially form L-products, thus providing a self-propagating e.e. enrichment of the prebiotic amino acid environment. In experiments designed to test a hypothesis (Weber, 1987) that glyceraldehyde might act as a source of energy and of monomers on the primitive Earth, Weber (1989) has recently reported that L-glyceric acid polymerizes much more rapidly then does DL-glyceric acid, that the DL-polymer is considerably more soluble than the homochrial L-polymer, and that a marked decrease in the yield of L-polymer occurred when a small amount of D-monomer was present during polymerization of L-glyceric acid, observations quite parallel to those involving amino acids and peptides. He then suggested that regions of homochirality in random polymers of this type might aggregate into homochiral domains which, due to their greater insolubility, could result in the preferential separation of polymer strands having a greater abundance of homochiral regions. The intriguing possibilities

(Weber, 1987; Orgel, 1986) of autocatalytic and rudimentary replicating capabilities of such glyceraldehyde based systems remain to be demonstrated.

4.5. Conclusions

Examining the above mechanisms suggested for the amplification of e.e.s, one is struck by the limited generality of most of them. Even when they are unambiguously demonstrable on a laboratory scale, most of these experiments have no apparent relevance whatsoever to any conceivable prebiotic scenario. Although the potentially more efficient polymerization mechanisms involving e.e. enrichments *via* α-helix and ß-sheet secondary structures during polypeptide growth have to date been demonstrated only in model experiments, nevertheless their principles at least appear conceptually applicable to plausible prebiotic environments. A similar conceptual prebiotic validity also attaches to the 100% stereoefficient 'total spontaneous resolution' of racemates during crystallizations involving second order asymmetric transformations. Either of these mechanisms would thus apprear potentially viable on the prebiotic Earth.

5. Racemization and Other Calamities

While all mechanisms for the origin and amplification of molecular chirality have racemization as their ultimate nemesis, relatively few authors have considered the implications of this phenomenon even qualitatively. Fajszi and Czege (1977) have attempted to include racemization as a factor in their model for the appearance of enantiomeric excesses due to ß-radiolysis, and Hegstrom (1984; Hegstrom *et al.*, 1985), in evaluating the relative importance of VU and PVED mechanisms, has attempted to take concomitant racemization into account. Other authors have been even less optimistic. Stryer (1966) argued early on that 'optical purity is bound to deteriorate since the free energy of racemization is negative', Miller and Orgel (1974) have maintained that because of the relative ease of racemization of amino acids and of degradation of sugars 'the optical rotation on the primitive ocean must have been zero', and Keszthelyi *et al.* (1979) have emphasized that 'processes leading to "perfect" optical purity and maintaining it have to be faster than racemization' and must occur 'within a much shorter time interval than the racemization time'. Since the half-life for the racemization of amino acids is typically $\sim 10^5$–10^6 years at ambient temperatures, and since metal ions may enhance these racemization rates (Bada and Miller, 1987), it is clear that the origin, amplification and protection of the chirality of amino acids must have been a rapid and efficient prebiotic process indeed. The contention of Dose (1981) that incorporation of amino acids into water-insoluble polymers serves to protect them from racemization, however, is a view not shared by others who have documented the enhanced susceptibility of protein-bound amino acids to racemization (Williams and Smith, 1977; Bada and Miller, 1987). Nor does the absorption of amino acids on clays appear to protect them from racemization (Bada and Miller, 1987; Bonner *et al.*,

1985). The phenomenon of radioracemization induced by ionizing radiation (Section 3.2.2.3) only exacerbates the racemization of prebiotic molecules by more conventional means. The potentially catastrophic impact of racemization has compelled Bada and Miller (1987) to revive the earlier notion that life on Earth must have preceded optical activity, a presumption quite contrary to that currently accepted (Section 1).

Nor was racemization the only obstacle on the prebiotic Earth which required surmounting before chiral polymers could achieve the homochirality now thought essential for life. Additional and perhaps more devastating hazards were inherent in the harsh and chaotic prebiotic environment itself. In contrast to Darwin's 'warm little pond' scenario for the origin of life, the first billion or so years of Earth's history, which saw the emergence of microorganisms apparent from their microfossil records, were characterized by 'rampant volcanism, scorching heat, and a murderous bombardment from comets and asteriods' (Waldrop, 1990; cf. also Bailey *et al.*, 1990). Recent authors have argued that such catastrophic collisions effectively frustrated the origin of life during this period by the sterilization of Earth's surface and the evaporation (or partial evaporation) of its primitive oceans, and that only after the frequencies of such devastating impacts diminished sufficiently was there a possibility for the viable emergence and continuity of life. These authors (Maher and Stevenson, 1988; Sleep *et al.*, 1989; Oberbeck and Fogleman, 1989a, b, 1990) have provided estimates based on lunar and terrestrial impact records of the frequencies, sizes and impact energies of various extraterrestrial impactors during this period, as well as speculations of the effects of such impacts at various sites of potential biogenesis. With minor differences in the quantitative calculations for their models, they generally conclude that at around 3.8 Gyr ago the intervals between life-annihilating impacts became great enough to permit the continuity of life on Earth, particularly in the deep ocean environment. Thus the interval between sterilizing impacts just before the evolution of a stable ecosystem can be taken as the maximum time needed for the origin of life. Oberbeck and Fogleman (1989b) have estimated this maximum time to be only 6 million years if life originated 3.8 Gyr ago as suggested by $^{12}C/^{13}C$ isotope ratios in sedimentary rock (Schidlowski, 1988), and only 165 million years if life originated 3.5 Gyr ago as indicated by the oldest microfossils (Schopf and Walter, 1983). Such considerations clearly render untenable the earlier paradigm involving the slow accumulation of prebiotic reactants in a primordial soup and their gradual evolution into self-replicating biomolecules (Oberbeck and Fogleman, 1990). If we grant that the homochirality of prebiotic biomolecules is a prerequisite for the origin of life (Section 1), and if the above time constraints on the emergence of life are valid, how much more stringent must be the time restraints on the origin and amplification of molecular chirality into the condition of homochirality which preceded the beginning of life?

6. Summary and Speculations

The harsh environmental conditions and limited time span suggested above as available for the origin of chirality, the requirement for terrestrial homochirality preceding the origin of life (Avetisov *et al.*, 1985), and the necessary occurrence of a 'global symmetry breaking' of the terrestrial racemic organic medium as a prerequisite for achieving homochirality (Keszthleyi, 1987; Gol'danskii, 1988) give us demarcations within which to evaluate the numerous mechanisms reviewed above for the origin and proliferation of prebiotic chirality.

The random Chance Mechanisms discussed in Section 3.1 vary in their efficiency from nil or marginal to potentially 100%. It would seem unlikely, however, that such logically questionable (Section 3.1.6) mechanisms could ever be effective in a uniquely one-handed sense over the entire surface of the chaotic primitive Earth, or that equally probable enantiomeric systems of 'competing' handedness arising at different locales could resolve their competition within the time span available. Such mechanisms thus appear quite improbable as candidates for global symmetry breaking.

As to Determinate Mechanisms (Section 3.2), the only Regional or Temporal processes having any experimental substantiation are those involving circularly polarized light (Section 3.2.1.2), and of these only asymmetric photolysis has been shown experimentally to have reasonable capability. The theoretical efficacy of the process, however, has never been demonstrated to be more than minuscule even on the present Earth, and the periodic restriction of sunlight due to climatic events resulting from impacts (Maher and Stevenson, 1988) would clearly diminish the importance of CPL as a factor at the surface of the prebiotic Earth. Extraterrestrial CPL involvement (Section 3.2.1.2.4), of course, would be independent of the above considerations.

Universal determinate mechanisms based on the consequences of parity violation (Section 3.2.2) present an equally desolate picture. The effects of chiral elementary particles even in the most favorable experimental environments have led either to null results or to small and mainly unconfirmed results having no obvious prebiotic relevance, and the consequences of PVEDs have never been shown unambiguously to exist at all. Even the remote possibility for the efficacy of such mechanisms in the harsh prebiotic environment is inconceivable.

If the chance and determinate mechanisms previously proposed for the origin of terrestrial molecular chirality are recognized as patently ineffectual *per se* and/or as inapplicable within the time constraints imposed by the frequencies of extraterrestrial impacts on the prebiotic Earth, what alternative remains? The logical conclusion is that the source of terrestrial chirality must then have been extraterrestrial, and furthermore that it must have been capable of providing an ongoing influx of chiral molecules having uniform chirality. Only in this way, and not through the gradual accumulation of chiral molecules after statistical fluctuations in the prebiotic soup, could the 'chiral catastrophe' of global symmetry breaking occur

during Earth's turbulent prebiotic era. How might such an influx of uniformly chiral molecules occur?

Khasanov and Gladyshev (1980; Gladyshev and Khansanov, 1981) were the first to suggest that optically active molecules might form in outer space and persist on interstellar grains, and we have proposed that optically active molecules produced in the mantels of interstellar grains by extraterrestrial CPL might be transported to Earth as the Solar System passes through interstellar clouds (Section 3.2.1.2.4). An equally plausible mode of delivery might be cometary and asteroidal impacts during Earth's turbulent period preceding the emergence of life. Oró (1961) and Delsemme (1984) have previously suggested that amino acids and other prebiotic molecules formed in outer space might be transported to Earth by comets arising during the final state of Earth's cold accretion from dust, suggestions more recently extended by Chyba *et al.* (1990, and references therein). Zahnle and Grinspoon (1990) have proposed that the extraterrestrial amino acids detected in rocks at the Cretaceous/Tertiary boundary were deposited with the dust from a giant comet trapped in the inner Solar System, a fragment of which constituted the impactor, and Chyba (1990a, b) has maintained that planets could have acquired their oceans as late-accreting veneers from the impacts of comets and carbonaceous asteroids during the heavy bombardment period 4.5 to 3.5 Gyr ago. That such extraterrestrial impacts could well have been a source for terrestrial chiral molecules is suggested by recent studies of amino acids isolated from the Murchison meteorite, where it was found that L-alanine exceeded D-alanine by $\sim 18\%$, and where the ^{13}C content of each enantiomer indicated an extraterrestrial origin (Engel *et al.*, 1990). This excess of the L-alanine, and presumably that of other L-amino acids in the Murchison meteorite (Engel and Nagy, 1982), was therefore concluded to be indigenous and not due to terrestrial contamination, suggesting the presence of optically active materials in the early Solar System before terrestrial life began. Bloch and Wirth (1980) suggested earlier that the thermal decomposition of metal carbonyls in the presence of ammonia and other hydrides in comets might yield amino acids and other organic compounds which, if formed in magnetic fields, might lead to optically active molecules in the comets. These novel ideas have yet to be substantiated experimentally, and the intriguing observations of Engel *et al.* (1990) have yet to receive crucial independent corroboration. In any case, if the plethora of comets and asteroids which struck Earth during its first billion years transported $L > D$ excesses of amino acids while forming its hydrosphere and parts of its lithosphere, and if these e.e.s were amplified by such known mechanisms as polymerization or 2nd order asymmetric transformations, then a rational basis would exist for the global symmetry breaking required for the subsequent rapid emergence of life on Earth.

The above conclusions and speculations, perhaps unfortunately, transfer the problem of the origin of chirality out of the realm of terrestrial science and into that of astrophysics. In doing so, however, they serve to emphasize again the summation of Gol'danskii and Kuz'min (1988) that 'in this problem formulated

by L. Pasteur ... the number of questions still remaining to be solved exceeds the number solved in spite of one hundred years of investigations'.

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