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Stereochemistry and the Nature of Life

Mechanist, Vitalist, and Evolutionary Perspectives

By Paolo Palladino*

QUESTIONS about the stereochemistry of life processes provided the grounds for a fascinating and protracted debate over mechanist and vitalist explanations of organic phenomena during the second half of the nineteenth century. Chemists discovered that many molecules come in alternative structural arrangements that are not superposable on their mirror images; the relationship is identical to that between a right and left hand. The physical and chemical properties of the alternative forms, the *enantiomers*, were believed to be identical in all respects except the three-dimensional arrangement of their component atoms.¹ At the same time, microbiologists and biochemists discovered a peculiar feature of the chemistry of life. They knew that when the above-mentioned molecular types were produced abiotically, the outcome was always a mixture of the two enantiomers, that is, a *racemic* product was formed. But when these processes were mediated by living organisms or by substances of biological origin, the outcome was radically different. Biochemical transformations would start with racemic reactants and then yield only one of the alternative enantiomeric forms of the product, not both, as would be expected if the transformation were symmetric. This *stereochemical specificity*, the property of discriminating between the alternative enantiomers, was viewed by physicists, chemists, and biologists alike as one of the most striking features of biological chemistry.

Throughout the late nineteenth century, a number of influential, and not so influential, scientists attempted to explain this peculiar “handedness,” or chirality, of biological chemistry. They often did so independently of one another, and more often than not, this problem fell outside their respective areas of professional expertise. These facts attest to the perception of a generally unsettling problem. The issue was not merely a scientific one but one charged with metaphysical implications: Some scientists claimed that the laws of chemistry and physics were insufficient to account for the phenomenon, and they sought a

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I am grateful for the help I received from John Beatty, Erwin Hiebert, Sylvan Schweber, Lore Ruttan, and three anonymous reviewers.

¹ See W. A. Bonner, “Origins of Molecular Chirality,” in *Exobiology*, ed. C. Ponnampertuma et al. (London: North Holland, 1970), pp. 170–234. For a different interpretation see S. F. Mason, *Molecular Optical Activity and the Chiral Discriminations* (Cambridge: Cambridge Univ. Press, 1982).

solution by appealing to the intervention of an extraphysical agent, God. Others sought mechanistic explanations, presupposing the existence of yet undiscovered asymmetric physical agents that could induce an asymmetric reaction. A third option that found readier acceptance among scientists in the aftermath of the Darwinian revolution was to suggest that the evolution of biochemical stereoselection was in large part a matter of history. I will discuss these alternatives in detail, bringing into relief the philosophical assumptions that guided scientists' endeavors to understand the origin of this peculiarity of biological chemistry. It is my contention that this late nineteenth-century debate over vitalist, mechanist, and evolutionary accounts was, at bottom, a debate over the role of chance and contingency in shaping the world about us.

In the course of articulating this thesis, I will touch upon a wide range of issues. Any attempt to treat as separate the various philosophical concerns that underlay this debate would result in an unintelligible compilation of disjointed statements about the origin of biochemical stereoselection. Indeed, I suggest that the beauty of this episode lies in the very range and complexity of the issues raised by the participants in the debate.

I. PASTEUR: VITALIST, MECHANIST, OR NEITHER?

The episode begins with Louis Pasteur's investigations of the connections between organic chemistry and optical activity.² It was Pasteur who first realized that only living organisms could differentiate one optically active compound from its mirror image, and in so doing, he set out the crucial issues with which this essay is concerned.³

In the late 1840s Pasteur conducted a series of investigations of chemical isomerism, focusing his attention on the peculiarities of tartaric acid. With some difficulty, the crystals of this acid could be separated by sight into two distinct types, which were mirror images of one another. When the separated groups of crystals were redissolved, the resulting two solutions, which were absolutely identical from a chemical standpoint, deflected a beam of polarized light in opposite directions. Hence Pasteur argued that the deflection of polarized light had to be a property intrinsic to the molecular structure of the isomers.

Pasteur spent years trying to devise chemical methods for the separation of the

² The difference between the enantiomeric compounds is revealed only through their interaction with polarized light; when a polarized light beam is projected through a solution of one enantiomer it is deflected in the direction opposite to that imparted by the other enantiomer. In this essay, the terms *optical isomers* and *optical activity* will be used to refer to the objects of this interaction and the interaction itself. The term *organic* will be used loosely, equating organic products and those produced in biochemical processes.

³ There is an extensive secondary literature on much of Pasteur's work and on his philosophy of science. John Farley and Gerald Geison's joint article on Pasteur's work on spontaneous generation is now considered a classic study of the impact of social events on the articulation of scientific discourse: see Farley and Geison, "Science, Politics and Spontaneous Generation in Nineteenth Century France: The Pasteur-Pouchet Debate," *Bulletin of the History of Medicine*, 1974, 48:161-198; see also Françoise Dagognet, *Méthodes et doctrine dans l'oeuvre de Pasteur* (Paris: Presses Universitaires de France, 1967); and Nils Roll-Hansen, "Experimental Method and Spontaneous Generation: The Controversy between Pasteur and Pouchet," *Journal of the History of Medicine*, 1979, 34:273-292. For Pasteur's views on optical activity see Gerald Geison and James Secord, "Pasteur and the Process of Discovery: The Case of Optical Isomerism," *Isis*, 1988, 68:6-36; Dorian Kottler, "Louis Pasteur and Molecular Dissymmetry, 1884-1887," *Studies in the History of Biology*, 1974, 2:57-98; and Seymour Mauskopf, "Crystals and Compounds," *Transactions of the American Philosophical Society*, 1976, N.S. 66:1-82.

enantiomeric forms of tartaric acid, inspired by the ability of the microbe *Penicillium glaucum* to discriminate readily between the two forms and to metabolize only the right-handed form of the compound.⁴ Eventually he discovered that the only alternative to the manual separation of enantiomers effected by the experimenter was to crystallize the double salt of the desired chiral product; however, he also realized that this process still required the use of optically active acids of organic origin. This state of affairs led Pasteur to attribute great importance to this peculiarity of the chemistry of life. While speaking to the Société de Chimie in Paris in 1860, he argued that “all artificial products of the laboratory and all mineral species are superposable on their images. On the other hand most natural organic products . . . the essential products of life are asymmetric, and possess such asymmetry that they are not superposable on their images.” On the basis of this limitation of synthetic chemistry, Pasteur discriminated between the realms of organic and inorganic chemistry: “Thus we find introduced into physiological principles and investigations the idea of the influence of the molecular asymmetry of natural organic products, of this great character which establishes perhaps the only well-marked line of demarcation that can at present be drawn between the chemistry of dead matter and the chemistry of living matter.”⁵

To some, this demarcation appeared as yet another vitalist barrier to the integration of the organic and inorganic realms of nature. For instance, in 1904 Alfred Byk, a physicist at the University of Berlin whose perspective on the origins of optical activity is discussed in the next section, wrote that “because of his vitalist beliefs, Pasteur saw in the appearance of asymmetric substances a peculiarity of life, barring any connection with inorganic nature.” Thus Byk characterized the search for inorganic asymmetric synthesis as “like Wöhler’s artificial synthesis of urea . . . a stage along the road to achieving the unification of organic and inorganic nature.”⁶ We may question Byk’s appreciation of Friedrich Wöhler’s achievement, as the synthesis of urea certainly did not convert Wöhler to a program of uniting vital and inorganic chemistry. What is more important for our purposes, however, is Byk’s optimistic reductionist outlook, typical of an earlier generation of German scientists and of several of the actors in this story.⁷

Another problem with Byk’s assessment is that Pasteur’s demarcation between vital and inorganic chemistry was intended to be descriptive rather than prescriptive. This point was not lost on everyone. For instance, in 1882 Paul Schüt-

⁴ This peculiarity of microbial processes probably played an important role in the development of Pasteur’s later interest in the phenomena of fermentation. See Gerald Geison, “Pasteur on Vital versus Chemical Ferments: A Previously Unpublished Paper on Inversion of Sugar,” *Isis*, 1981, 72:425–445.

⁵ Louis Pasteur, *Researches on Molecular Asymmetry* (1860; Chicago: Univ. Chicago Press, 1914), pp. 29, 45.

⁶ Alfred Byk, “Zur Frage der Spaltbarkeit von Razemverbindung durch zirkular-polarisiertes Licht, ein Beitrag zur primären Entstehung optisch-aktiver Substanz,” *Zeitschrift für Physikalische Chemie*, 1904, 49:643. There is very little biographical information on Byk (1878–1938?). A very brief sketch can be found in *Who Was Who among English and European Authors, 1931–1949* (Detroit: Gale Research Co., 1978) and *Bibliographia Judaica: Verzeichnis jüdischer Autoren deutscher Sprache*, ed. R. Heuer (Munich: Kraus International, 1981). From the available information I surmise that he was a victim of the Holocaust.

⁷ See John Theodore Merz, *A History of European Scientific Thought in the Nineteenth Century*, Vol. II (1904; Gloucester, Mass.: Peter Smith, 1976), p. 405; J. H. Brooke, “Wöhler’s Urea, and Its Vital Force?—a Verdict from the Chemists,” *Ambix*, 1968, 15:84–114; and C. A. Culotta, “German Biophysics, Objective Knowledge and Romanticism,” *Historical Studies in the Physical Sciences*, 1975, 4:3–38.

zenberger argued that Pasteur's proposed division between organic and inorganic nature was a well-supported but temporary assessment of the current state of knowledge. Schützenberger was certainly not a vitalist, and his comments on vital forces clearly reflect his materialist outlook. He firmly believed that "there is really no chemical vital force. If living cells produce reactions which seem peculiar to themselves, it is because they realize conditions of molecular mechanism which we have not hitherto succeeded in tracing, but which we shall, *without doubt* be able to discover at some future time."⁸ Although Pasteur was quite opposed to such intransigent materialism, his willingness to accept a demarcation between vital and inorganic chemistry should not be interpreted as motivated by vitalism. Rather, it was a reflection of his intransigent positivism.⁹ In 1875, he argued that the distinction he had drawn between vital and inorganic chemical processes was "based on fact and not on principle. . . . [N]ot only do I not believe that this barrier between the mineral and organic kingdoms is infrangible, but I have determined the experimental conditions proper, I think, to make this barrier disappear. Since these conditions have not been successfully realized, it is wise to believe the distinction we are dealing with, and take it as a guideline."¹⁰ In the next section I will consider the imaginative experiments Pasteur undertook to resolve this problem. These exemplify the approach pursued by physical scientists aiming to provide an answer to a most troubling question.

II. THE PHYSICISTS

To those scientists who rejected any prescriptive distinction between organic and inorganic nature, it seemed that the production of optically active substances in the laboratory would erase the demarcation perceived by Pasteur, and that it would bring them a step closer to the unification of these two realms of nature.

Pasteur himself was a pioneer in the pursuit of this goal. It was obvious to him that, if chemical syntheses were to yield asymmetric products, then asymmetric agents had to be brought into play. In the course of his 1860 lecture he asked: "Is it not necessary and sufficient to admit that at the moment of elaboration of the primary principles in the vegetable organism, an asymmetric force is present? . . . Do these asymmetric actions . . . reside in light, in electricity, in magnetism, or in heat? Can they be related to the motion of the earth, or to the electric currents by which physicists explain the terrestrial magnetic poles?"¹¹ At this time Pasteur did not reveal that he had already undertaken experiments aimed at bringing such asymmetric forces to bear on synthetic processes. Only in 1884 did he admit that "in Strasbourg I had already asked Ruhmkorff to build some powerful magnets; in Lille, I turned to rotating mechanisms, guided by clockworks: I attempted to have a plant live from germination, under the influence of inverted solar rays with the aid of a mirror connected to a heliostat."¹² This peculiar

⁸ Paul Schützenberger, *On Fermentation* (New York: Appleton, 1882), pp. 5–8, emphasis added. Biographical information in *Poggendorffs biographisch-literarisches Handwörterbuch der exakten Wissenschaften* (Berlin: Akademie Verlag, 1926–[1987]), Vol. IV.

⁹ Louis Pasteur, *Oeuvres de Pasteur*, ed. Pasteur Vallery-Radot, 7 vols. (Paris: Massou, 1922), Vol. VII, pp. 30–31.

¹⁰ *Ibid.*, Vol. I, p. 365.

¹¹ Pasteur, *Researches* (cit. n. 5), pp. 42–43.

¹² Pasteur, *Oeuvres*, Vol. I, p. 376. Pasteur held a professorship in Strasbourg during the period 1849–1854. He then took on a professorship in Lille, which he held until 1857.

scheme was designed to affect photosynthesis by altering the polarity of solar radiation. Even Pasteur felt that, besides being quite ineffective, these approaches to the resolution of the question were not very orthodox.¹³ His mentor, Jean-Baptiste Biot, attempted to discourage him from pursuing this line of work on the grounds that it was fraught with considerable technical and theoretical difficulties.¹⁴

Some years later Pierre Curie, a physicist whose disciplinary background, crystallography, was in the same field as Pasteur's, undertook an extensive mathematical analysis of symmetries. His views on symmetry included a priori beliefs as intuitively obvious to him as they had been to Pasteur and other crystallographers before him. Curie believed that "when certain causes produce certain effects, the elements of symmetry of the causes must be reflected in the effects produced. When certain effects reveal a certain dissymmetry, this dissymmetry must be found among the causes."¹⁵ For Curie, as for Pasteur, symmetric forces would yield only symmetric results, and thus asymmetric outcomes could not result from the action of symmetric forces. In 1894 Curie extended his analysis of symmetry to electric and magnetic fields, and in so doing he pointed out that some of the forces considered by Pasteur to be asymmetric were in fact symmetric. Based on theoretical considerations alone, Pasteur's work was therefore bound to be fruitless. However, Curie also demonstrated that there were a small number of physical interactions that possessed those characteristics required to affect the symmetric course of chemical reactions. According to him, the superposition of electric and magnetic fields, light rays propagated in parallel to a magnetic field, or circularly polarized electromagnetic radiation were all superpositions of symmetric physical agents that could be included in the group of potentially effective agents.¹⁶ Specifically, he cited the Wiedemann effect as an electromagnetic effect that could induce an asymmetric course of reaction, leading to optically active products without violating any conditions of symmetry.¹⁷

During the next few years, a few physical chemists attempted to elucidate Curie's notion of asymmetric photochemical action, bringing their more detailed arguments to bear on the origins of optical activity. In 1896 the French chemist Aimé Cotton observed that certain optically active substances showed abnormal optical dispersion when exposed to plane-polarized light whose wavelength corresponded to the absorption bands peculiar to the substances in question; this abnormality is now known as the Cotton effect. Cotton suggested that this effect could be linked to a hypothetical photodegradative process based on circularly polarized light, and possibly, given the right conditions, it could lead to a "stereoselective degradation," the preferential degradation of one of the two enantiomers. He proposed the following: "Suppose having a mixture formed of two

¹³ Louis Pasteur, *Correspondance de Pasteur, 1840–1895*, ed. Pasteur Vallery-Radot, Vol. I (Paris: Flammarion, 1940), p. 326.

¹⁴ Louis Pasteur, *Pages illustres de Pasteur*, ed. Pasteur Vallery-Radot (Paris: Librairie Hachette, 1968), p. 10.

¹⁵ Pierre Curie, *Oeuvres de Pierre Curie*, ed. Société Française de Physique (Paris: Gauthier-Villars, 1908), p. xii.

¹⁶ A. Amariglio et al., "La synthèse asymétrique," *Annales de Chimie*, 1968, 3:13.

¹⁷ Curie, *Oeuvres*, p. 136. The Wiedemann effect is the product of the superimposition of identically oriented electric and magnetic fields, which results in an asymmetric torsion along their axis of isotropy.

equal parts of two asymmetric compounds, one right, the other left, and degradable by the action of light. If the light beam is circularly polarized, it may be possible that two asymmetric compounds may be unequally destroyed and that the mixture may gain little by little a discernible rotatory effect on light."¹⁸

Following Cotton's line of thought, Byk then undertook an extensive theoretical analysis to show that the observed differential absorption of circularly polarized light by two enantiomers could be used to resolve the question about the origin of biochemical stereoselection. That is, he sought to establish that polarized light with the appropriate degradative properties existed on earth. Byk argued that some of the sunlight incident on earth would be reflected by the surface of water bodies, and a fraction of this reflected light would be plane polarized. The magnetic field of the planet would then cause a rotation of the plane of polarization such that over the entire surface of the planet there would be unequal amounts of the two forms of circularly polarized light.¹⁹ According to Byk, this asymmetry would account for the unequal abundance of optically active isomers, which was so evident in the living world about us.

In 1907 Paul Freundler performed a series of experiments following Byk's guidelines, since "Byk, guided by theoretical considerations, has assessed the question as having been resolved in a positive sense, and he has derived therefrom a theory on the natural genesis of natural, optically active compounds."²⁰ Freundler illuminated optically active metallic tartarates with polarized light of the appropriate wavelength for over four hundred hours with no visible effect. These experiments proved as fruitless as Pasteur's earlier experiments with magnets and sunlight.²¹ Although theoretical considerations suggested that a solution was at hand, there seemed to be no empirical evidence for the existence of such asymmetric agents that would explain the origin of biochemical stereoselection. The concepts and methods of the physicist appeared to be inadequate to resolve this problem, but as we shall see, this was not the only course available to those scientists who sought to bridge the gap between the organic and inorganic realms of nature.

III. THE CHEMISTS

No sooner had Pasteur set forth his ideas on the limits of synthetic chemistry than chemists of a materialist stamp sought to prove him wrong. In 1873 Emile Jungfleisch reported the results of his successful synthesis of a racemic salt of tartaric acid starting from inorganic reagents alone. Jungfleisch argued that

the progress in synthetic chemistry over the past twenty years has been so marvelous that the artificial production of the vital principles composing living organisms seems possible in the relatively near future. There is still a physical property, optical activity, which is common to a great number of natural compounds, that has not, so far,

¹⁸ Aimé Cotton, "Recherches sur l'absorption et la dispersion de la lumière par les milieux doués du pouvoir rotatoire," *Annales de Chimie et Physique*, 1896, 8:373.

¹⁹ Byk, "Zur Frage der Spaltbarkeit" (cit. n. 6), p. 686.

²⁰ P. T. Freundler, in *Bulletin de la Société de Chimie*, N.S., 1907, 1:658.

²¹ It was not until 1930 that the partial resolution of racemic mixtures was obtained with the aid of circularly polarized light; see W. Kuhn and E. Knopf, "Photochemische Erzeugung optisch aktiver Stoffe," *Naturwissenschaften*, 1930, 18:183. However, since the effectiveness of this photochemical process is minimal, and the presence of circularly polarized light in nature hardly significant, the value of this mechanism in affecting biological chirality has now been discounted.

been obtained through chemical synthesis of organic substances. Following certain ideas espoused by Biot and shared by many savants, it has been thought that optically active substances can only be produced by living organisms and through agents beyond the ken of science. I think I have resolved this problem[;] . . . optical activity can be created without the intervention of life.²²

Pasteur had originally claimed that the synthesis of a single optically active compound was beyond the ability of chemists. As we have seen, his argument had rested on considerations of symmetry; since the agents used by the chemist were all symmetric, they could not possibly engender asymmetry. However, Jungfleisch showed that an optically active compound could in fact be synthesized, albeit in combination with its enantiomer. In an interesting debate with Jungfleisch and Schützenberger, Pasteur argued that the former's accomplishment in no way affected his argument, as vital processes never yielded both enantiomers at once, but one alone. In fact, the intervention of the experimenter himself, or that of other living agents, such as microbial organisms, was still required to extract one enantiomer from the synthetic racemic mixture prepared by Jungfleisch. Pasteur criticized Jungfleisch's claim, writing that "to transform *one inactive compound into another inactive compound* which has the power of resolving itself simultaneously into a right-handed compound and its opposite, is in no way comparable with the possibility of transforming *an inactive compound into a single active compound*. This is what no one has ever done; it is, on the other hand, what living Nature is doing unceasingly before our eyes."²³

In 1884 Jungfleisch responded to Pasteur's challenge by publishing new experimental results showing that the crystallization of paratartaric acid was biased toward the right-handed, dextrorotatory form, from which he deduced that the two enantiomeric forms were differentially soluble. It thus seemed that the two enantiomers were endowed with unlike chemical properties, something that Pasteur and many others had consistently denied. Jungfleisch asserted, "I regard as established by my experiments that, without being inhibited by some sort of fatal restriction, chemists can strive to obtain, in the laboratory and without the intervention of any physiological phenomena, products like those optically active compounds furnished by living nature."²⁴ Had Jungfleisch finally managed to bridge the chasm that Pasteur had perceived as separating vital and inorganic chemistry? To answer this question we must turn to Joseph Le Bel's and Jacobus van't Hoff's work on molecular structure.

As soon as Pasteur formulated the notion of optical isomerism, questions about the spatial organization of the atomic components of molecules became unavoidable. In 1874 Le Bel and van't Hoff, independently of one another, presented explanations of optical isomerism in terms of the spatial arrangement of atoms, and these explanations also accounted for the racemic results of all artificial chemical reactions. There are significant differences between Le Bel's and van't Hoff's perspectives on the problems of stereochemistry, but they did agree on some fundamental principles. According to both, the four substituents linked to a tetravalent atom such as carbon could be imagined to occupy four fixed

²² Emile Jungfleisch, "Sur la synthèse des matières organiques doués du pouvoir rotatoire," *Comptes Rendus de l'Académie des Sciences*, 1873, 76:286–290.

²³ Pasteur, *Oeuvres* (cit. n. 9), Vol. I, pp. 360–363, 364–365; emphasis added.

²⁴ Emile Jungfleisch, "Sur le dedoublement des composés optiquement inactifs par compensation," *Bull. Soc. Chim.*, 1884, 41:232.

positions around the central atom. If two of the four substituents were identical, then the arrangement was bilaterally symmetric; if they were unlike one another, then there existed two arrangements that were identical and not superposable. The addition of the first three unlike substituents to the tetravalent central atom defined a geometric plane; the addition of the last substituent on either side of the plane defined two structures that were mirror images of one another. In an environment devoid of any physical asymmetry, the physical forces governing the addition of the last substituent would not favor the formation of either structure. Either form was equally probable, and as the number of molecules undergoing addition tended to infinity, the ratio between the two forms would approach unity. Thus, argued Le Bel and van't Hoff, all such substitution or addition reactions should yield racemic products.²⁵

There was obviously an incongruity between Le Bel's and van't Hoff's theoretical arguments and Jungfleisch's experimental accomplishment, but this tension failed to arouse anyone's interest until a "metaphysically" inclined chemist approached the subject of the asymmetric chemistry of life from a radically different perspective.

IV. THE VITALIST

An unabashedly vitalist position on the stereochemistry of life informed the presidential address to the chemistry section of the British Association for the Advancement of Science at its sixty-eighth meeting, held in Bristol in 1898. Delivered by the British chemist Francis Japp, the address was entitled "Stereochemistry and Vitalism." After having described the recent advances in stereochemistry, and the recent but still unsuccessful efforts to obtain absolute asymmetric syntheses, Japp asked "whether the phenomena of life are wholly explicable in terms of chemistry and physics." His own solution, he hoped, would contribute to the revival of the doctrine of vitalism that was then taking place among biologically oriented scientists. He presented his aims in the following terms:

Recent years have . . . witnessed a significant revival of the doctrine of vitalism among the physiologists of the younger generation.

It is not my intention to offer any opinion on the various arguments which physiologists of the neo-vitalistic school have put forward in support of their views; these arguments and the facts on which they are based lie outside my province. . . . I shall endeavour to show that living matter is constantly performing a certain geometrical feat which dead matter, unless indeed it happens to belong to a particular class of products of the living organism and to be ultimately referable to living matter, is incapable—not even conceivably capable—of performing. My argument, being based on geometrical and dynamical considerations, will have the advantage, over the physiological arguments, of immeasurably greater simplicity.²⁶

²⁵ J. H. van't Hoff, *The Arrangement of Atoms in Space*, trans. A. Eiloart (London: Longmans, 1898), pp. 1–4; and J. A. Le Bel, "Sur les relations qui existent entre les formules des corps organiques et le pouvoir rotatoire de leurs dissolutions," *Bull. Soc. Chim.*, 1874, 22:337–347.

²⁶ F. R. Japp, "Stereochemistry and Vitalism," *Report of the LXVII Meeting of the British Association for the Advancement of Science*, 1898, pp. 813–828; rpt. in *Nature*, 1898, 58:452–460, quotations on p. 453 (all citations here refer to the version in *Nature*). For biographical information see obituary of F. R. Japp (1848–1925) in the *Journal of the Chemical Society* (London), 1926, pp. 1008–1020. For a contemporary overview of the relations between biology and the physical sciences see R. Meldola, *The Chemical Synthesis of Vital Products* (London: Edward Arnold, 1904), pp. 1–19.

It may seem strange that a chemist whose claim to fame rested on his work on the stereochemistry of inorganic compounds should choose to defend a type of scientific explanation that was quite unfashionable among most chemists of the time. However, there were a few exceptions among the physiological chemists, and Japp's association with Alexander Crum Brown may explain his interest.²⁷ Crum Brown's reputation rested on his important contributions to both physiology and structural chemistry, and as is noted below, he had already expressed some interesting views on the issue at hand.²⁸

Japp's lecture continued with the following assessment of vital chemistry:

Non-living symmetrical matter—the matter of which the inorganic world is composed of—interacting under the influence of symmetric forces to form asymmetric compounds, always yields either pairs of enantiomorphous molecules (racemoid form), or pairs of enantiomorphous groups united within the molecule (meso-form), the result being, in either case, mutual compensation and consequent optical inactivity. The same will hold good of symmetric matter interacting under the influence of asymmetric forces (supposing that such forces exist) provided that the latter are left to produce their effect under conditions of pure chance.

If these conclusions are correct, as I believe they are, then the *absolute origin* of the compounds of one-sided asymmetry to be found in the living world is a mystery as profound as the absolute origin of life. The two phenomena are intimately connected for, as we have seen, these symmetric compounds make their appearance with life, and are inseparable from it.

How, for example, could laevo-rotatory protein (or whatever the first asymmetric compound may have been) be spontaneously generated in a world of symmetric matter and of forces which are either symmetric or, if asymmetric, are asymmetric in two opposite senses? What mechanism could account for such selective production? Or if, on the other hand, we suppose that dextro- and laevo-protein were simultaneously formed, what conditions of environment existing in such a world could account for the survival of the one form and the disappearance of the other? Natural selection leaves us in the lurch here; for selective consumption is, under these conditions, as inconceivable as selective production.

No fortuitous concurrence of atoms, even with all eternity for them to clash and combine in, could compass this feat of the formation of the first optically active organic compound. Coincidence is excluded, and every purely mechanical explanation of the phenomenon must necessarily fail.

I see no escape from the conclusion that, at the moment when life first arose, a directive force came into play—a force of precisely the same character as that which enables the intelligent operator, by the exercise of his Will, to select one crystallised enantiomorph and reject its asymmetric opposite.²⁹

A writer for the London *Times* dismissed Japp's argument, referring to "the national tendency of a Scot towards a metaphysical conception of Nature."³⁰ Japp's position could not so easily be discounted as merely "metaphysical," however.

The last passage from the above quotation expresses Japp's belief that, at the

²⁷ For Japp's interest see Japp, "Stereochemistry and Vitalism," p. 458. On current trends among physiological chemists see "The British Association for the Advancement of Science," *Science*, 1898, 8:436–439; Merz, *History of European Scientific Thought* (cit. n. 7), Vol. II, pp. 425–437; and W. D. Halliburton, "Physiological Chemistry," *Annual Reports on the Progress of Chemistry*, 1904, 1:169–191.

²⁸ D. C. Goodman, "Brown, Alexander Crum" (1838–1922) in *Dictionary of Scientific Biography*, ed. C. C. Gillispie, 16 vols. (New York: Scribners, 1970–1980).

²⁹ Japp, "Stereochemistry and Vitalism" (cit. n. 26), p. 459.

³⁰ *Times* (London), 19 Sept. 1898, p. 12.

moment of the origin of life, living matter was endowed with the property of discriminating between enantiomeric forms, in a manner comparable to the human "Will" which allowed an "intelligent operator" to discriminate between two enantiomeric forms. Japp found momentous implications in the fact that the crystallized enantiomers of a racemic mixture could only be separated manually, through conscious intervention of the operator. He referred approvingly to Crum Brown's lecture in defense of vitalism, delivered a year earlier, before the Académie Française d'Edimbourg. While discussing Pasteur's contributions to stereochemistry and musing on the stereospecific chemistry of living organisms, Crum Brown had asked whether it would ever be possible to "get rid of the action of a living organism? Is not the observation and deliberate choice by which a human being picks out the two kinds of crystals and places each in a vessel by itself the specific act of a living organism . . . ?"³¹ For Crum Brown, the deliberate separation of the enantiomers effected by the human operator was a manifestation of consciousness, and he speculated whether this also applied to microorganisms.

Although Japp would not go as far as Crum Brown in attributing consciousness to microorganisms, he unambiguously rejected Emil Fischer's materialist interpretation of the phenomena. Based on his pioneering work on enzymatic chemistry, Fischer had argued that the asymmetry of vegetable products was induced by the action of the chlorophyllic molecule. He viewed this molecule as a lock into which only one key could be fitted; the asymmetry of the chlorophyllic unit determined the asymmetry of the product of photosynthesis. Fischer asked, in conclusion: "Is the preparation of optically active substances a prerogative of the living organism; is a special cause, a kind of vital force, at work here? I do not think so, and incline rather to the view that it is only the imperfection of our knowledge which imports into this process the appearance of the miraculous."³² In his address, Japp quoted Fischer's conclusion and retorted that although the facts of microbial stereoselective consumption and enzymatic stereoselective chemistry

might be taken as evidence in favour of Fischer's view . . . [w]hat I wish to point out is that Fischer's statement that the *miraculous* character of the phenomenon is eliminated by his assumption appears open to question. It is just as much, or as little, miraculous after as before. The production of a single asymmetric form, and the destruction of one of the opposite forms, are problems of precisely the same order of difficulty, and there are only two ways in which either of them has ever been solved: firstly, by the direct action of living matter, and secondly, by the use of previously existing asymmetric non-racemoid compounds, which are in last resort, due to the action of life. Directly, or indirectly, then, life intervenes. . . . The contention . . . of E. Fischer, Buchner, and others, that the discovery of enzymes and zymases "has transferred the phenomena of fermentation from biological to purely chemical territory," is true only as regards the immediate process, and leaves intact the *vitalistic origin* of these phenomena. . . . Only the living organism with its asymmetric tissue, or the asymmetric products of the living organism, or the living intelligence with its

³¹ Alexander Crum Brown, "Pasteur as the Founder of Stereochemistry," *Revue Française d'Edimbourg*, 1897, 1:225.

³² Japp, "Stereochemistry and Vitalism" (cit. n. 26), p. 457, emphasis added. See Emil Fischer, "Synthesen in der Zuckergruppe, I," *Berichte der Deutschen Chemischen Gesellschaft*, 1890, 23: 2139; and Fischer, "Synthesen in der Zuckergruppe, II," *ibid.*, 1894, 27:3189–3232; for "lock and key" see p. 3229; for "chlorophyllic unit," p. 3231.

conception of asymmetry, can produce this result. Only asymmetry can beget asymmetry.³³

Fischer's hypothesis, informed by the most recent advances in biochemistry, undoubtedly forced Japp to circumscribe his thesis more carefully, but as Japp points out, it failed to address the central question he had raised, that of the *origins* of the peculiar synthetic capacities of living organisms.

V. JAPP AND THE MECHANICAL UNIVERSE

In this anachronistic defense of vitalism, Japp reveals a deep concern with the role of God in the origin and maintenance of the world, and I think we should view his argument not only as a contribution to the vitalist philosophy of his time but also as a response to the debates over the relationship between science and religion that had enflamed the Victorian scientific scene during the 1860s and 1870s.³⁴

Deists and vitalists alike questioned the notion that mechanical, materialist philosophy could account for everything, especially human free will. In the late 1840s this position was severely undermined by Hermann von Helmholtz, who argued that the irreducible forces often invoked by vitalists and deists were at odds with the principle of the conservation of energy. Japp was well aware of this fundamental criticism of deistic and vitalist theories, and in order to defend his own thesis he relied on the most sophisticated response to Helmholtz's intransigent materialism—Fleeming Jenkin's essay "Lucretius and the Atomic Theory."³⁵ Jenkin had argued that a force acting at right angles to the path of a material body performed no work, all the while continuously altering the direction in which the body moved. He then suggested that human free will should be understood as an agent analogous to such a perpendicular, directive force. The action of the will could then be classified among those active principles which could affect mechanical systems but could not themselves be determined by the laws of mechanics. Jenkin's argument left room for the action of the immaterial will in a completely deterministic world.

As was true for Jenkin's, Japp's deism and vitalism were in no way a repudiation of determinism. On the contrary, his universe was as deterministic as that of Helmholtz. Japp supposed, like most of his contemporaries, that like effects would proceed only from like causes in a completely symmetric and predictable fashion, and he, like the mechanists, had no choice but to recognize that "only

³³ Japp, "Stereochemistry and Vitalism," p. 458, Japp's emphasis.

³⁴ See Frank M. Turner, "The Victorian Conflict between Science and Religion: A Professional Dimension," *Isis*, 1978, 69:356–376; P. M. Heimann, "The Unseen Universe: Physics and the Philosophy of Nature in Victorian Britain," *British Journal of the History of Science*, 1972, 6:73–79; and also the debates in the pages of the *Monist* during the years 1893–1895. According to Turner, positivism was used as a weapon to preclude questions about the nature of *active principles* and to assert the independence of science with respect to deistic, natural theology. In the present debate, some of Japp's critics adopted this strategy to undercut his vitalist and deistic claims.

³⁵ Japp, "Stereochemistry and Vitalism" (cit. n. 26), p. 453; and Fleeming Jenkin, "Lucretius and the Atomic Theory" (1868), in *Papers Literary, Scientific etc. by the Late Fleeming Jenkin*, ed. S. Colvin and J. A. Ewing, Vol. I (London: Longmans, Green, 1887), pp. 177–214. James Clerk Maxwell and William Thomson (Lord Kelvin), both greatly concerned with the reconciliation of mechanical determinism and free will, found Jenkin's argument mechanistically sophisticated and very attractive: see Theodore M. Porter, "A Statistical Survey of Gases: Maxwell's Social Physics," *Hist. Stud. Phys. Sci.*, 1982, 12:110–111.

asymmetry can beget asymmetry.”³⁶ Hence it was obvious to him that the phenomenon central to the present debate could not be comprehended given the known, *symmetric* Newtonian laws of physics. Drawing inspiration from a classical source, Japp invoked the action of an immaterial will to account for this failure of the laws of physics. Whereas the mechanists invoked a yet unspecified asymmetric, deterministic physical force, Japp invoked the intervention of another equally deterministic agent, God. Astonishingly, Japp’s source of inspiration for this subtle argument was none other than Isaac Newton; he referred his audience to the General Scholium of the *Principia* in ultimately attributing the origin of biological stereoselection to the action of God. Japp concluded his address to the British Association with the following words:

Some of my hearers . . . may think that, instead of rendering the subject clearer, I have brought it perilously near to the obscure region of metaphysics; and certainly, if to argue the insufficiency of the mechanical explanation of a phenomenon is to be metaphysical, I must plead guilty to the charge. I will, therefore, appeal to a judgment—metaphysical, it is true, but to be found in a very exact treatise on physical science—namely Newton’s *Principia*. It has marked bearing on the subject in hand:

“A caeca necessitate metaphysica, quae utique eadem est semper et ubique, nulla oritur rerum variatio.” [Blind metaphysical necessity, which is certainly the same always and everywhere, could produce no variety of things.]

I will merely add this is certainly true of the particular *rerum variatio* in which optically active organic compounds originate.³⁷

Japp did not need to remind his well-versed audience of Newton’s claim that “all that diversity of natural things [the *rerum variatio*] which we find suited to different times and places could arise from nothing but the ideas and will of a Being necessarily existing.”³⁸ These excerpts from Newton’s *Principia* had been made famous by the 1717 debate between Gottfried Leibniz and Samuel Clarke, the latter acting as Newton’s spokesman. Leibniz had invoked the principle of sufficient reason to argue against Clarke’s and Newton’s appeal to divine intervention in order to explain the origin of active principles such as gravity. But Leibniz’s principle could hardly apply to Japp’s problem, for it could not be argued that the property of stereoselection should be “so and not otherwise,” quite the contrary.³⁹ Japp, like Clarke before him, invoked the action of God to replace accident with deterministic order.

VI. JAPP’S CRITICS

Japp’s address to the British Association was published in *Nature*, and soon thereafter a lively polemic over the origin of optical activity erupted in the pages of the magazine. As judged by the response, including that of some eminent personalities, Japp’s address touched upon a sensitive issue.

Herbert Spencer was one of the more famous, if ineffective, critics of Japp’s thesis. He argued that there was a very simple solution to the problem:

³⁶ Japp, “Stereochemistry and Vitalism,” p. 458.

³⁷ *Ibid.*, p. 460.

³⁸ Isaac Newton, *Principia*, trans. A. Motte (1687; Berkeley: Univ. California Press, 1934), p. 546.

³⁹ H. G. Alexander, ed., *The Leibniz-Clarke Correspondence* (Manchester: Manchester Univ. Press, 1956), p. 16.

Prof. Japp appears to have taken no account of a universal law displayed throughout that continuous redistribution of matter and motion which constitutes Evolution. In the second part of *First Principles* will be found a chapter entitled "Segregation" in which this law and its results are set forth. . . . The abstract propositions involved are these: —First, that like units, subject to a uniform force capable of producing motion in them, will be moved to like degrees in the same direction. Second, that like units if exposed to unlike forces capable of producing motion in them, will be differently moved—moved either in different directions or to different degrees in the same direction. Third, that unlike units if acted on by a uniform force capable of producing motion in them will be differently moved—moved either in different directions or to different degrees in the same direction.⁴⁰

As Japp pointed out, Spencer failed to understand that, except for circularly polarized light, all physical forces interact indifferently with respect to the enantiomers; furthermore, Spencer was unable to specify how his "Law of Segregation" explained the observed peculiarity of living organisms. But Spencer had other grounds for criticizing Japp's approach. According to Spencer, discussions of the origin of life were merely metaphysical, since questions about origins were outside the realm of positive science.⁴¹ Spencer's opposition to discussions of origins may seem strange in view of his evolutionism; keep in mind, however, that his conception of "Evolution" was very mechanistic and deterministic. The initial germ of life was taken as a given; it was an active principle whose nature could not be investigated, and thereafter the "Law of Segregation" determined the progressive unfolding of its potentialities.

Some other critics sought an explanation in terms of what they supposed were asymmetric physical agents. The famous mathematical physicist George Fitzgerald, together with the biochemist Percy Frankland, sought an explanation in terms of the very kinds of forces that had been discounted by Curie just a few years earlier. Japp responded to these suggestions by showing a keen awareness of contemporary developments in physics. He dismissed all these allegedly asymmetric forces, although he would not commit himself on the possibly asymmetric effects of circularly polarized light. He did remark, however, "that all attempts to form optically active compounds under the influence of . . . circularly polarised light have hitherto signally failed."⁴²

Most of Japp's other critics attempted to provide an alternative explanation based on statistical fluctuation phenomena. The British chemists Frederick Stanley Kipping and William Pope extended Jungfleisch's earlier study of the crystallization of racemic compounds and confirmed that it was indeed possible to obtain the spontaneous resolution of such substances. However, they also argued that the experimental results upon which they based their assertion did not contradict Le Bel's and van't Hoff's theses. Kipping and Pope performed forty-six separate crystallizations of aqueous sodium chlorate, and in only two cases were both enantiomeric crystals formed in equal numbers. The other forty-four cases yielded between 24 and 77 percent right-handed crystals, an apparent contradiction of the stereochemical theory. But the overall mean yield for all forty-six cases was 50 percent, a striking confirmation of Le Bel's and van't Hoff's theories, and a reconciliation of the theories and Jungfleisch's experimental findings.⁴³

⁴⁰ Herbert Spencer, in *Nature*, 1898, 58:592.

⁴¹ See n. 34.

⁴² Japp, "Stereochemistry and Vitalism," p. 459.

⁴³ Frederick S. Kipping and William J. Pope, in *Nature*, 1898, 59:53.

Clement Bartrum and the Italian astronomer Giorgio Errera proposed models that would explain the accidental precipitation and formation of local abundances of some optically active molecules; these models would supposedly explain the origin of biochemical asymmetry.⁴⁴ FitzGerald also considered the possibility that statistical fluctuations could account for this vexing problem, but he much preferred an explanation in terms of what he supposed were effective asymmetric forces.

The famous biometrician Karl Pearson was the most persistent and thoughtful of Japp's critics. As noted earlier, Japp had adopted Jenkin's argument in defense of the independence of the will to fend off the type of criticism raised by Helmholtz against an earlier generation of vitalists and deists. Pearson dismantled this defense, arguing that the directive force advocated by Jenkin violated the principle of conservation of linear and angular momentum.⁴⁵ He then argued in support of an account based on statistical fluctuations, suggesting that Le Bel and van't Hoff's stereochemical theory entailed the improbability, but not impossibility, of spontaneous resolutions. Both Japp and Pearson agreed on the statistical nature of Le Bel and van't Hoff's argument; they agreed that a single molecule in a racemic mixture could only be either left- or right-handed, but, like a tossed coin, an initially optically inactive molecule stood an even chance of being transformed into a dextro- or laevorotatory molecular type. Therefore, as large numbers of molecules were involved in any single transformation reaction, the outcome would of course be a racemic product. However, in the first of his three letters to *Nature* Pearson also argued that, given a large number of such transformations, it was possible that some of them would yield optically active products. This is exactly what had been observed by Kipping and Pope. According to Pearson these chance deviations could account for the origin of the peculiarly biased chemistry of life.

Japp, however, was not prepared to accept such an account. Recall that in his address to the British Association, he had linked the origin of optical activity to the origin of life; and none of the participants in the *Nature* debate, except Errera, thought of separating the two problems. Thus from Japp's perspective, any appeal to a "play of chance" was tantamount to suggesting that life itself originated accidentally. Furthermore, picking up on FitzGerald's suggestion that life probably started from a single molecule, which could have been either dextro- or laevorotatory, Japp cleverly noted that if an accident of such momentous importance never repeated itself, how certain could one be that it was only an accident? What better evidence was there for arguing special origins?

⁴⁴ C. O. Bartrum, in *Nature*, 1898, 58:545; and Giorgio Errera, *ibid.*, p. 616. For biographical information on Errera (1860–1933) see *Poggendorffs* (cit. n. 8), Vol. VIIb(2). It is interesting that Errera thought that the original asymmetric molecule that seeded the racemic solution and caused the biased crystallization was of extraterrestrial origin. This recourse to cosmic origins was characteristic of those nineteenth-century mechanists who were confronted with problems that defied mechanical explanation. Hermann von Helmholtz and Svante Arrhenius approached the problem of the origin of life in just such a manner, and Errera seems to have this in mind when he says: "Supposing molecular asymmetry to have come on to our planet from outward space (an origin ascribed by some to life) . . ." See J. Farley, "The Spontaneous Generation Controversy (1859–1880): British and German Reactions to the Problem of Abiogenesis," *Journal of the History of Biology*, 1972, 5:285–319.

⁴⁵ Karl Pearson, in *Nature*, 1898, 58:496, 59:30. Pearson's "statistical fluctuation" argument is very similar to Ludwig Boltzmann's reconciliation of the apocalyptic vision implicit in the second law of thermodynamics with the striking order and lawfulness found in the natural world. See Ludwig Boltzmann, in *Nature*, 1895, 51:413–415.

VII. THE PLAY OF CHANCE

It is clear thus far that the mechanistic approach failed to resolve the problem, other than in a speculative sense. The number of unsuccessful experimental attempts at isolating effective asymmetric physical agents, and Curie's theoretical explanation of the difficulties inherent in such efforts, attested to the fruitlessness of this approach. The only effective biasing agents still appeared to be peculiar to biological systems, and the problem did not seem immediately reducible to physicochemical order. In last analysis, the more intransigent materialists could only provide promissory notes; Schützenberger and Fischer asserted that the problem would ultimately be resolved in physicochemical terms.

Insofar as the vitalist thesis is concerned, Japp's explanation should be considered as reasonable as the mechanistic alternative, for the biasing agent he called upon to resolve the problem was not dissimilar from that invoked by the mechanists; it was equally deterministic and equally unknown. Yet, as the American chemist William McPherson pointed out in later years, Japp's appeal to an inscrutable divine agency compelled one to deny the possibility of future advancement, and thus this vitalist and deist thesis was unacceptable to anyone endowed with the scientific curiosity to dig further for answers.⁴⁶

An entirely new conceptual schema was required to break out of the impasse. The tentative accounts in terms of statistical deviations from the symmetric course of chemical reactions offered by Pearson and others suggested such an alternative. However, this new schema seemed to require the abandonment of a fundamental creed of nineteenth-century science, the one fundamental point of agreement between vitalists and mechanists, namely, intransigent determinism.⁴⁷ Until this time, probabilistic arguments had been viewed as explicit admissions of ignorance or limited knowledge, attributable to human shortcomings. In 1873 Stanley Jevons epitomized this creed in his assertion that "there is really no such thing as chance, regarded as producing and governing events."⁴⁸ Against this philosophical background, the appeal by Japp's critics to chance events to explain the observed peculiarity of vital processes could be viewed in one of two ways: either as a profession of ignorance about the ultimate cause of the phenomenon and hence as a refusal to meet Japp's challenge, or as an assertion that the present form of the world was not predictable from its initial conditions, that is, as an explicit acceptance of the notion that the world need not be just "so, and not otherwise." Given the constraints imposed by this philosophical framework, Japp could be only skeptical of any account in terms of statistical fluctuations; and in his longest and most detailed reply to his critics, he wrote: "All my critics

⁴⁶ William McPherson, "Asymmetric Syntheses and Their Bearing upon the Doctrine of Vitalism," *Science*, 1917, 45:80. McPherson's skepticism about the explanatory power of traditional chemical concepts may reflect contemporary changes that were dramatically altering the field of physical chemistry. See Halliburton, "Physiological Chemistry" (cit. n. 27).

⁴⁷ J. S. Haldane, "Vitalism," *Nineteenth Century*, 1898, 44:400–413. For an overview of late nineteenth-century views on statistical thinking see J. Jauch, "Determinism in Classical and Quantal Physics," *Dialectica*, 1973, 27:13–24; Porter, "Statistical Survey of Gases" (cit. n. 35); and Sylvan S. Schweber, "Demons, Angels, and Probability: Some Aspects of British Science in the Nineteenth Century," in *Physics as Natural Philosophy*, ed. A. Shimony and H. Feshbach (Cambridge, Mass.: MIT Press, 1982), pp. 319–363.

⁴⁸ Stanley Jevons, *The Principles of Science* (1873; New York: Dover, 1958), p. 198; see also J. S. Mill, *Philosophy of the Scientific Method*, ed. E. Nagel (New York: Hafner Press, 1974), pp. 259–286.

seem to be moving in that unreal world where a fount of type, if jumbled together sufficiently often, ends by setting up the text of *Hamlet*.”⁴⁹ Not uncoincidentally, this complaint echoed John Herschel’s earlier description of evolutionary theory as the “law of higgeldy piggeldy.”⁵⁰

VIII. DARWINIAN ACCOUNTS

Yet at the turn of the century there appeared deep cracks in the consensus about determinism, and as we have seen in the discussions of Le Bel and van’t Hoff’s rule, all the scientists involved in the *Nature* controversy accepted statistical arguments, albeit to varying degrees. Twenty years after Jevons, the views of the philosopher Paul Carus on the role of “chance” in the universe reflected the evolution of a less dogmatic commitment to determinism. He wrote:

While absolute chance cannot be admitted, partly because we are not in need of it, since the irregularities of nature can be sufficiently explained otherwise, and partly because the idea of absolute chance if it were needed, is incompatible with our world conception, we shall, nevertheless, have to concede to chance, as we understand the term, a very important role in the evolution of life. The formation of worlds and the history of mankind depend to a great extent upon chances similar to the throws of dice. There are many possibilities, and now this, now that, will, according to the circumstances, be realized—of course in each case with strict necessity. . . . The conditions may vary, nay, so far as we can judge they actually do vary; and any apparently slight variation of them, or even one of them, will result in different effects of great consequence. Without a detailed knowledge of all these special conditions, simply from a supposed *a priori* knowledge of the world substance, the idiosyncrasy of this or that particular solar system could not be *a priori* determined. Here it will be such, and there, under perhaps slightly different circumstances, it will be entirely other.

From this point of view we call these results product of chance.⁵¹

Carus was presenting a rather counterintuitive argument; he acknowledged that contingency, the determinant of “idiosyncrasy,” played a great role in the formation of the universe known to us, but he found no conflict between this view and a belief in determinism. This was the result of a subtle argument, in which he allowed room for explanations appealing to chance but not for complete descriptions of the world also appealing to chance. Probabilistic arguments continued to be viewed as admissions of limited knowledge, but the prevailing attitude toward such accounts was now far more ambiguous than at the time of Jevons’s pronouncement.

Charles Darwin’s theory of evolution was perhaps the most striking example of the ambiguous relation between chance and determinism in late nineteenth-century scientific discourse. This theory suggested that the organic forms currently found in nature were accidental outcomes of the evolutionary process. For

⁴⁹ F. R. Japp, in *Nature*, 1898, 58:618.

⁵⁰ See David L. Hull, *Darwin and His Critics* (Chicago: Univ. Chicago Press, 1973), p. 61; and John Beatty, “Chance and Natural Selection,” *Philosophy of Science*, 1984, 51:183–211. Japp relied on Jenkin’s mechanical argument in defense of vitalism, as espoused in “Lucretius and Atomic Theory” (cit. n. 35). Yet in that very essay, Jenkin went on to criticize those who would oppose the molecular philosophy using “Hamlet”-type arguments. For further information on the status of Darwin’s theory at the turn of the century see Peter J. Bowler, *The Eclipse of Darwinism: Anti-Darwinian Evolution Theories in the Decades around 1900* (Baltimore: Johns Hopkins Univ. Press, 1983).

⁵¹ Paul Carus, “The Idea of Necessity, Its Basis and Its Scope,” *Monist*, 1893, 3:84–85.

example, Darwin argued that the innumerable species of orchids then found in Britain exemplified innumerable different solutions to the same problem, cross-fertilization; he was astounded by the incredible variety of solutions to the same problem, all based on a common ancestral plan and using the same materials. According to Darwin, the process of adaptation “carried on during many thousand generations in various ways, with the several parts of the flower, would create an endless diversity of coadapted structures for the same general purpose.”⁵² Since Darwin suggested that these variations could not be understood as adaptive responses to different environmental circumstances, it seemed to many contemporaries that he was arguing that evolutionary histories, all beginning from exactly the same initial conditions, if replayed, would lead to very different outcomes. It is this apparently outrageous argument that motivated Herschel’s sarcastic description of Darwin’s theory. Yet Darwin’s appeal to unknown causes to explain the origin, if not the perpetuation by natural selection, of these differences was not a denial of the mechanical causes underlying the differences in forms; he simply did not consider a discussion of these unknown causes of the origin of variation, which we would now call mutation, particularly relevant to understanding the evolution of a particular morph, and in this sense the differences were a matter of “chance.”⁵³

Ludwig Boltzmann’s later appraisal of the Darwinian theory brings into relief the uneasy compromise between mechanism and chance sought by some late nineteenth-century scientists. Boltzmann, the scientist most responsible for the introduction of probabilistic arguments into physics, and at the same time the most adamant defender of mechanism, often praised Darwin’s theory, the appeal to chance notwithstanding. He once remarked:

“We . . . have to remember that most wonderful mechanical theory in the field of the biological sciences, namely, the theory of Darwin. It undertakes to explain the whole diversity of the world of plants and animals through the purely mechanical principle of heredity—which admittedly in itself is dark like all the fundamental principles of mechanics.”⁵⁴

Boltzmann recognized that the mechanisms underlying the mutations upon which Darwin’s theory was constructed were at the time obscure, yet not unknowable. The phenomena of mutation and heredity could not be investigated directly, but taken as givens they could be marshaled into a coherent account of the evolution of species. In this sense, an arbitrary given permitted the construction of a fruitful theory. Yet, according to Boltzmann, as long as the probabilistic analysis of the second law of thermodynamics could not be reduced to the “fundamental principles of mechanics,” it remained an incomplete account of thermodynamic phenomena. Analogously, as long as the “principles of heredity”

⁵² Charles Darwin, *On the Various Contrivances by which British and Foreign Orchids are Fertilized by Insects, and on the Good Effect of Intercrossing* (London: John Murray, 1862), p. 351.

⁵³ John Beatty, essay in Gerd Gigerenzer et al., *The Empire of Chance: How Probability Changed Science and Everyday Life*, (Cambridge/New York: Cambridge Univ. Press, 1989), pp. 175–187.

⁵⁴ Quoted in E. Broda, “Philosophical Biography of L. Boltzmann,” *Acta Physica Austriaca*, Suppl., 1973, 10:44. See Erwin Hiebert, “Boltzmann’s Conception of Theory Construction: The Promotion of Pluralism, Provisionalism, and Pragmatic Realism,” in *Proceedings of the Pisa Conference on the History and Philosophy of Science, 1978*, Vol. II: *Probabilistic Thinking, Thermodynamics . . .*, ed. J. Hintikka, D. Gruender, and E. Agazzi (Dordrecht/Boston: D. Reidel, 1981), pp. 175–198; and Schweber, “Demons, Angels, and Probability” (cit. n. 47).

remained unexplained, the Darwinian theory remained a very fruitful, if incomplete, analysis of the evolution of species. And in this sense Darwin's theory, the appeal to chance notwithstanding, was fully compatible with the predominant determinist philosophy.

This conceptual framework was very influential in the development of an alternative argument to account for the evolution of the asymmetric chemistry of life. To some of the scientists involved in the *Nature* debate it seemed that a Darwinian account could provide a framework that would succeed where the mechanistic and vitalist accounts had seemed to fail. Scientists like FitzGerald proposed that the agency of "section" (selection) would somehow explain the evolution of this asymmetric chemistry from "accidental" beginnings. However, Japp questioned the meaning of such an appeal, pointing out that "several of my critics seem to think that a mere sensible preponderance of one enantiomorph is sufficient [to account for the phenomenon]. This is not the case unless the minority can be *bred* out of existence; and I do not think that under symmetrical conditions this is possible."⁵⁵ He realized that the appeal to statistical fluctuations alone was rather ad hoc, and that it failed to explain how the occasional, accidental resolution of some primeval chemical solution could have resulted in the predominance of absolute stereoselection throughout the living world. Essentially, Japp presented his critics with a serious challenge: to provide the mechanistic component of the tentative Darwinian account of the origin of the asymmetric chemistry of life.

Pearson attempted to address this challenge, suggesting that accidental resolutions in the primeval environment could be of historical import because the accidentally generated molecules could act as breeders, "endowed with a power of selecting their own kind of asymmetry from other racemoid substances."⁵⁶ However, Japp quickly pointed out that this hypothetical breeder concept could not be justified in terms of current chemical knowledge. Pearson replied to this criticism, claiming that

Japp speaks of the "vague and elastic" way in which I speak of the "breeding" process—I notice that Prof. Errera also uses the phrase "asymmetry begets asymmetry as life begets life." Let us confine the term then, for the present, simply to the process (of which so far the mechanism is unintelligible) by which chance having given a slight preponderance of one type of enantiomorph, a group of the same type, visible and touchable is formed there. It is perfectly conceivable that this is only a visible representation of the process by which living asymmetry selects like, even in a non-crystalline compound. It is only the mechanism which is vague, not the fact.⁵⁷

Just as it was used earlier in the century to ban deism from scientific discourse, here again intransigent positivism served to sweep aside another vexing problem confronting nineteenth-century scientists. However, it seems that even Pearson realized that his account was inadequate, because in his third and last contribu-

⁵⁵ George FitzGerald, in *Nature*, 1898, 59:76; and F. R. Japp, *ibid.*, 58:617 (emphasis in original).

⁵⁶ Karl Pearson, *ibid.*, 59:30. The "breeder" type of mechanism suggested by Pearson is very similar to that offered in 1940 by another physicist interested in the present question, Pascual Jordan. His proposal, based on quantum mechanical arguments, was subjected to devastating criticism by Linus Pauling and Max Delbrück. See Hermann Weyl, *Symmetry* (Princeton, N.J.: Princeton Univ. Press, 1952), p. 32; and Horace F. Judson, *The Eighth Day of Creation* (New York: Simon & Schuster, 1979), p. 140.

⁵⁷ Pearson, in *Nature*, 1898, 59:30.

tion to the *Nature* controversy he appealed to hypothetical asymmetric forces.⁵⁸

The author of Japp's obituary was quite right, then, to claim that Japp had answered all his critics. As John Theodore Merz pointed out, the origin of the asymmetric chemistry of life was a difficult problem. Here "no mechanical physico-chemical explanation . . . is imaginable, and the word *selection*, with which Darwin charmed away so many mysteries, has revealed new ones in their place."⁵⁹

IX. DARWINIAN ACCOUNTS: A REPRISE

Soon after the *Nature* controversy had run its course, the Italian microbiologists C. Ulpiani and S. Condelli presented a report on the British controversy in the *Gazzetta Chimica Italiana*. They then discussed how their own work could contribute to resolving the contentious issue. On the basis of observations of a number of microbial species, they came to the conclusion that "as one descends the organismic hierarchical ladder, stereospecificity becomes progressively less typical and precise, to the point that in certain cases one observes an abnormal specificity, including reversals. And when one thinks that as one descends the hierarchical ladder, one comes closer to the absolute origins of life, then the possibility of demonstrating that life originally arose and developed in both asymmetric directions becomes more plausible."⁶⁰ It seemed to them that the origin of stereoselection was connected to the process of complexification of organic activities; only as evolutionary forms became more complex did they come to rely on stereoselective chemistry. Ulpiani and Condelli thus strengthened Errera's case for separating the question about the origin of life from that about the origin of optical activity. It is interesting that no one ever noted that Errera's phylogenetic study effectively undercut all accounts based on an unequal abundance of optical isomers in the primordial environment. If such inequality had prevailed, then even in primeval times all organisms should have exhibited the same specificity. In concluding their detailed report, Ulpiani and Condelli suggested that there existed two competing approaches to explain the evolution of the stereoselective chemistry of life:

When and how the chlorophyllic function [a reference to Fischer's hypothesis] happened to develop in only one of these directions, so that the surface of the earth came to be covered almost exclusively by a series of enantiomorphs, can be explained either admitting the influence of the earth's enantiomorphism [i.e., the direction of diurnal rotation], or including the phenomenon among that order of historical contingencies, which do not belong to the domain of Physics and Chemistry.⁶¹

Ulpiani and Condelli admitted that historical explanation was an argument *sui generis*, not comparable to physicochemical explanation. These two types of account addressed two different questions: the physicochemical approach could explain the mechanisms whereby the asymmetry of one molecule could affect the

⁵⁸ *Ibid.*, p. 125.

⁵⁹ Merz, *History of European Scientific Thought* (cit. n. 7), Vol. II, p. 437.

⁶⁰ C. Ulpiani and S. Condelli, "Asimmetria e vitalismo," *Gazzetta Chimica Italiana*, 1900, 30:370 (emphasis added). I have been unable to locate any biographical information on Condelli; the only information I have found on Celso Ulpiani is an obituary in *Giornale di Chimica Industriale*, 1919, 1:249.

⁶¹ Ulpiani and Condelli: "Asimmetria e vitalismo," p. 382.

symmetry of all the molecules with which it interacted, but the question about the origin of the asymmetric chemistry of life was a purely historical question. But what did this history look like? This had been the crucial challenge launched by Japp, the challenge that Pearson had been unable to meet.

It was another of Japp's earlier critics who took up the problem where Pearson had left it, formulating a detailed historical account that incorporated chemistry, chance, and natural selection. In 1903, in a review of recent advances in stereochemistry, Pope argued that the problem at hand had been cloaked in mystery by the fact that the evolution of organisms constituted of optically active substances had resulted in an accentuated enantiomorphism "to such an extent that physiological chemistry is now almost entirely the chemistry of enantiomorphous substances."⁶² To account for this evolution, he argued that when life originated on earth, the primitive organic systems at first consumed both forms of some enantiomorphous nutritive substance. However, as the competition for the nutritive substrate intensified, these primitive organisms, in order to increase the efficiency of resource utilization, evolved highly tuned digestive apparatus. This hypothesis was in agreement with the observations of Ulpiani and Condelli, who had specifically studied the correlation between phylogenetic relatedness and accuracy of stereoselection. Ultimately, some of the organisms developed such a high degree of stereospecificity that they could consume only the dextro- or the laevorotatory form of some optically active chemical nutrients. These types of organisms outcompeted the more flexible but less efficient consumers of both enantiomers. A subsequent fortuitous event, such as one of the many hypothesized by the participants in the *Nature* debate, could then cause one of the enantiomeric forms of the optically active nutrients to crystallize out of solution. Only one of the stereospecific organisms would then survive (it seems that Pope assumed that the organisms consumed only the dissolved form of the substrate). Stereospecificity of a particular sort proved advantageous under the accidentally changed environmental circumstances and insured the survival of one variant form. Pope then went on to draw an analogy to explain why the primitive, more flexible consumers could not possibly coexist with the more specialized ones:

The kind of difficulties involved in the existence, side by side, of dextro- and laevo-individuals such as these may be shown by a simple illustration. There is no reason connected with human enantiomorphism why vehicular traffic should be forced to keep to one side of the road rather than the other; as, however, the conditions of civilized life have gradually become more complex, economic reasons have arisen causing us to make an enantiomorphous selection, and in this country we arbitrarily force the traffic to keep to the left; other countries also make an arbitrary and sometimes different selection. Even if, when legislation on this matter first became necessary, the population had been equally and obstinately divided upon the question of the rule of the road, we cannot doubt that by this time the question would have been satisfactorily and finally settled by the extermination of one or the other of the enantiomorphously inclined parties without the cooperation of any intelligent enantiomorphous agency.⁶³

Admittedly, Pope's explanation was incomplete, and it was difficult to envision the biological correlates of the vehicles and the road; nonetheless, the model

⁶² W. J. Pope, "Recent Advances in Stereochemistry," *Nature*, 1903, 68:283.

⁶³ *Ibid.*

and the analogy would have been supported by available phylogenetic data, such as that collected by Ulpiani and Condelli.⁶⁴ Furthermore, the explanation relied on empirically verified mechanisms, not on asymmetric physical agents whose effectiveness could not be demonstrated. One might then suppose that it would be cited as an important alternative to Japp's theory, but it was not. Why not?

It seems that even the author of this Darwinian account was not entirely satisfied with his explanation. A year later, in 1904, Pope cited Byk's work on photochemical degradation in another review article, suggesting that this work changed the contours of the problem and that this physical approach could serve as a basis for resolving the question of the origin of optically active substances:

The question of the primeval origin of optically active substances has been reopened in a new way by A. Byk who recalls an old experiment of Jamin's, which indicates that terrestrial magnetism uses the partially plane polarized light reflected from such surfaces as that of the ocean to become partially circularly polarized. In the circularly polarized light thus produced, one component—say d-light—predominates on the earth's surface. Byk then confirms the observation of Cotton that d-circularly polarized light is differently absorbed by copper ammonium d- and l-tartrates. The preponderance of d-light on the earth's surface must therefore be more favorable to the persistence of one optically active component of racemic acid than the other.⁶⁵

Pope does not specify how Byk's work would resolve the problem, and thus this appeal to a hypothetical photochemical mechanism providing a relative abundance of one molecular form rather than the other is not significantly different from the earlier appeals to chance fluctuations alone. Both approaches left unanswered the question about the development of the exclusive stereoselectivity of vital chemistry, which Pope himself acknowledged to be the most intriguing issue. Why then did Pope suggest that this obviously incomplete account reopened the issue in a new way? The views of another chemist may shed some light on this problem.

Alfred Stewart's assessment of the *Nature* controversy suggests that in some way the photochemical mechanism filled an apparent lacuna in the historical account. In a review in 1908 of recent developments in stereochemistry, Stewart, a physiological chemist by training, dismissed all the arguments espoused in the controversy as merely theoretical and based on no empirical evidence. Even so, he suggested that the equally unsupported photochemical mechanism proposed by Byk settled the question. It is hard to understand why Byk's account was any better than explanations offered by the participants in the controversy, since they were all equally "theoretical arguments based on no experimental evidence."⁶⁶ But the replacement of the appeal to statistical fluctuations with this "new" mechanism changed Pope's original Darwinian account in a fundamental manner: it removed accident from the explanation and resulted in the predetermination of the outcome of the historical process; thus this historical account effectively ceased to be a Darwinian one. On the basis of these considerations, I

⁶⁴ Although the work of Ulpiani and Condelli figures prominently in Byk's discussion, I have no reason to believe that Pope was familiar with it. However, similar information would have been readily available to any chemist interested in the problems of biosynthesis.

⁶⁵ W. J. Pope, "Stereochemistry," *Ann. Rep. Prog. Chem.*, 1904, 1:133.

⁶⁶ A. W. Stewart, "Stereochemistry and Its Application to Physiology," *Science Progress*, 1908, 2:449–481. For biographical information see obituary of A. W. Stewart (1880–1947) in the *J. Chem. Soc.* (London), 1948, pp. 396–398.

suggest that Pope perceived in Byk's proposition the possibility of explaining the intriguing development of the asymmetric chemistry of life without recourse to contingency. Viewed from this perspective, Pope's interest in the photochemical hypothesis was tantamount to a rejection of the claim made by Ulpiani and Con-delli that historical and mechanical accounts were incommensurable. In the last analysis, Pope's position seems closer to that articulated by Boltzmann: at times historical accounts can be very useful, but at bottom they are incomplete and fail to predetermine natural phenomena.

X. SCIENTIFIC EXPLANATION OR THEOLOGY?

Pope's ambivalent attitude toward the historical account of the origin of the asymmetric chemistry of life exemplifies the uneasiness that late nineteenth-century scientists exhibited toward the role of chance and contingency in shaping the universe. The full extent of this unease is even clearer in Ulpiani's retraction of his earlier thesis on the relation of mechanical accounts to historical ones. This reversal was prompted by the claims of another scientist who, like Japp, questioned the competency of physics and chemistry to account for the phenomena of the organic world.

In 1911, some years after the *Nature* controversy had subsided, the British morphologist Edward S. Russell argued that although physical concepts could be used to analyze the generalities of nature, they could not be used to analyze its individuality, what Carus had called its "idiosyncrasy." Russell introduced his argument by admitting the relevance of physics and chemistry to the study of the organic world, but he challenged "the utility of their application."⁶⁷ He argued that the peculiarities of biological organisms could only be understood in terms of their particular histories, and that such accounts were fundamentally different from those of physics and chemistry. Such had been Ulpiani's original thesis.

The history of the eel's migration to its ancestral spawning grounds was Russell's favorite case for the separation of what Ernst Mayr would later call "proximate" and "ultimate" explanations of biological phenomena.⁶⁸ Russell admitted that eels may be guided in their migration by temperature gradients, and that the mechanics underlying their sense of direction could be reduced to physicochemical interactions; moreover, he even admitted that it would be possible to give a complete physicochemical description of an eel's swimming movements in some unspecified body of water. However, this mechanistic description would not differ in any way from a complete physicochemical description of an eel's movements while swimming toward its spawning grounds. The phenomena to be explained, motion in any body of water, and motion toward a specific destination, were distinct; yet the mechanistic analyses of the two phenomena were indifferent to this distinction. It was therefore obvious to Russell that the mechanistic approach could not answer the question, Why does the eel migrate to the ancestral spawning grounds? The physical and chemical approaches could potentially account for the *how* of the eel's migration, but not the *why*; the latter question called for an explanation in terms of the history of the species.

Of course, an intransigent determinist could reject this categorical distinction

⁶⁷ E. S. Russell, "Vitalism," *Scientia*, 1911, 9:330.

⁶⁸ Ernst Mayr, "Cause and Effect in Biology," *Science*, 1961, 134:1501-1506.

between historical and mechanistic accounts by describing the evolutionary process that led to the neural imprinting of the migratory behavior of eels in molecular terms. Yet such an account would require a complete molecular redescription of a long historical process and, to say the least, would quickly prove unmanageable. Nonetheless, this approach did not lack for advocates; it was no straw man. In 1913, in an essay critical of Russell's categorical distinction, Ulpiani advocated just such an extremist position.⁶⁹ In a complete reversal of his earlier distinction between historical and physicochemical accounts, he argued that if the individual features of an organism could be analyzed in physicochemical terms, something not denied by Russell, then the entire problem had to be equally amenable to such an analysis. Inspired by Vito Volterra's mathematical analyses of hereditary phenomena, Ulpiani imagined a very complex equation wherein the initial positions of all the molecules affecting the migration of the first eel were specified; the interactions between the molecules were determined by the laws of physics. In order to explain why modern eels migrated to ancestral spawning grounds, it would be necessary merely to observe the changes in the values of the parameters as the time index of this imaginary equation advanced. Yet it is not clear how this act of observing the evolution of this perfectly accurate mathematical model differed from a complete redescription of the history of the eel.

The inescapable similarities between Ulpiani's and Pierre Simon Laplace's views are quite apparent. It should be noticed that, to draw a distinction between God and Laplace's intelligent observer, who could predict the course of history given the laws of physics and the initial state of all the particles composing the universe, would be most difficult. Was there a real difference between vitalists like Japp and mechanists such as Ulpiani? The former invoked the action of God to answer an apparently intractable problem. The latter argued that, had he been as omniscient as God, he could have provided a true answer to the question of the origin of biochemical stereoselection. At this point it is worth recalling that McPherson had criticized Japp's vitalist thesis because in his view it signaled the end of science; now the same could have been said of Ulpiani's approach, for scientific investigations are conducted by humans, not God.

XI. CONCLUSION

To return to the question about the origin of optical activity, the historical, evolutionary hypothesis did not defy symmetry restrictions or physical law and went some way toward an explanation of the origin of biological stereoselective chemistry. Furthermore, unlike the mechanist and vitalist alternatives, it could be substantiated by a fair amount of corroborating empirical evidence. Yet the hypothesis was viewed ambivalently. This situation cannot be attributed to the uncertain status of the Darwinian theory during the late nineteenth century alone. Since the mid-nineteenth century, no consensus on the origins of the asymmetric chemistry of life has been achieved, and contemporary chemists continue to argue that "the origin of optical activity presents problems to the hypothesis of chemical evolution that are at present insoluble."⁷⁰ This may in

⁶⁹ C. Ulpiani, "Applicazioni della termodinamica alla biologia," *Atti della Società Italiana per il Progresso delle Scienze*, 1913, 7:509–543.

⁷⁰ Bonner, "Origins of Molecular Chirality" (cit. n. 1), p. 223.

fact be a valid assertion; yet to the present day there have been only two studies that have taken evolutionary explanations into serious consideration, and these studies have received little attention in the most detailed surveys of the literature bearing on this question.⁷¹ Pope's thesis is not even cited in these surveys. Why?

During the nineteenth century, the commitment to finding a formula that would completely predetermine the unfolding of all events constituting our realm of experience may account for both the vitalists' and the mechanists' ambiguous attitude toward historical explanations of the origin of this asymmetry. This view may also account for current attitudes toward the evolutionary explanation. Yet I wonder what kind of explanation would appease the dissatisfaction of those scientists interested in chemical evolution. In an ironic twist of fate, J. B. S. Haldane, one of the founders of the synthetic theory of evolution, may have provided the answer to this question. In his brief essay on the origin of life, he argued that all theories on the origin of optical activity were no more than speculations, and that the question would be resolved only when "living creatures have been synthesized in the biochemical laboratory."⁷² But at this point, what is the difference between science and science fiction? Maybe Ijon Tychy got it right when he asked in his dream:

Is it not true that, bereft of all sense of decency and ethical restraints, both these miscreants then emptied on the rocks of lifeless Earth six barrels of gelatinous glue, rancid, plus two cans of albuminous paste, spoiled, and that to this ooze they added some curdled ribose, pentose, and levulose, and—as though that filth were not enough—they poured upon it three large jugs of a mildewed solution of amino acids, then stirred the seething swill with a coal shovel twisted to the left, and also used a poker, likewise bent in the same direction, as a consequence of which the proteins of all future organisms on Earth were LEFT-handed?!⁷³

⁷¹ W. A. Mills, "Some Aspects of Stereochemistry," *Journal of the Society of Chemistry and Industry*, 1932, 51:750–759; and George Wald, "The Origin of Optical Activity," *Annals of the New York Academy of Science*, 1957, 69:352–368; for reviews of the literature see Georgii F. Gauze, *Optical Activity and Living Matter* (Normandy, Mo.: Biodynamica, 1941); Amariglio et al., "La synthèse asymétrique" (cit. n. 16); Bonner, "Origins of Molecular Chirality"; and Mason, *Molecular Optical Activity* (both cit. n. 1).

⁷² J. B. S. Haldane, "The Origin of Life" (1929), in J. D. Bernal, *The Origin of Life* (London: Weidenfeld & Nicholson, 1967), p. 248.

⁷³ Stanislaus Lem, *The Star Diaries* (San Diego: Harcourt, Brace, Jovanovich, 1985), pp. 35–36.