# Diffusion Theory in Biology: A Relic of Mechanistic Materialism

PAUL S. AGUTTER
*Formerly of the Department of Biological Sciences*
*Napier University*
*Colinton Road*
*Edinburgh, EH10 5DT, U.K.*

P. COLM MALONE
*129 Viceroy Close*
*Birmingham B5 7UY, U.K.*

DENYS N. WHEATLEY*
*Cell Pathology*
*University of Aberdeen*
*MacRobert Building*
*581 King Street*
*Aberdeen AB24 5UA, U.K. (E-mail: wheatley@abdn.ac.uk)*

**Abstract.** Diffusion theory explains in physical terms how materials move through a medium, e.g. water or a biological fluid. There are strong and widely acknowledged grounds for doubting the applicability of this theory in biology, although it continues to be accepted almost uncritically and taught as a basis of both biology and medicine. Our principal aim is to explore how this situation arose and has been allowed to continue seemingly unchallenged for more than 150 years. The main shortcomings of diffusion theory will be briefly reviewed to show that the entrenchment of this theory in the corpus of biological knowledge needs to be explained, especially as there are equally valid historical grounds for presuming that bulk fluid movement powered by the energy of cell metabolism plays a prominent note in the transport of molecules in the living body. First, the theory's evolution, notably from its origins in connection with the mechanistic materialist philosophy of mid nineteenth century physiology, is discussed. Following this, the entrenchment of the theory in twentieth century biology is analyzed in relation to three situations: the mechanism of oxygen transport between air and mammalian tissues; the structure and function of cell membranes; and the nature of the intermediary metabolism, with its implicit presumptions about the intracellular organization and the movement of molecules within it. In our final section, we consider several historically based alternatives to diffusion theory, all of which have their precursors in nineteenth and twentieth century philosophy of science.

**Keywords:** diffusion theory, Fick, 19th century physiology, mechanistic materialism, oxygen secretion, metabolic organization

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* Author for all correspondence.

## Introduction

*Classical Diffusion Theory*

The phenomenon of diffusion is perceived in the scent of flowers permeating a room or a drop of colored ink spreading throughout a liquid. As a *descriptive* term for 'spreading in all directions from a source', diffusion is uncontentious. However, *diffusion* as a scientific term referring to the 'the net movement of matter, attributed to the random movements of molecules, taking place from a region of high concentration to one of lower concentration' requires greater delineation and precision. Like most scientific concepts, diffusion theory should not be construed as a fixed body of terms, laws and data, but rather as an evolving one. It has a 'classical' form (used, and sometimes abused, by biologists), and numerous variants of this classical form developed *ad hoc* for specific applications in different disciplines. The classical theory of diffusion has (a) a macroscopic, phenomenological aspect, and (b) a microscopic, mechanistic aspect, which we will briefly examine.

(a) It was proposed to Adolf Fick (by Carl Ludwig and others) that a mathematical relationship exists between the rate at which a substance travels through a medium (gas, liquid or solid) and the concentration gradient of that substance. Fick's work in the 1850s on this putative relationship seemed to add one more regular, seemingly predictable, pattern of nature to the knowledge base of classical physics. The relationship, known as Fick's *Law of Diffusion*,[1] states in its simplest form that the rate at which the concentration of a substance decreases at any point **x** in a system is proportional to the curvature of the concentration gradient at that point. The constant of proportional to the curvature of the concentration gradient at that point. The constant of proportionality, **D**, is the diffusion coefficient or diffusivity in the system.

(b) Early in the 20th century, Einstein and von Smoluchowski independently found an explanation for Fick's law in molecular terms.[2] Their need for a critical test of kinetic theory led them to an explanation for the then well-known, but poorly-understood, phenomenon of *Brownian motion*.[3] Part of the analysis also led, with the aid of a number of simplifying assumptions and approximations, to a derivation of Fick's law and to the general inference that the macroscopic diffusion process can be explained by the molecular-kinetic mechanism of Brownian motion in fluid systems where there are concentration gradients.

[1] Fick, 1855, pp. 59–86.
[2] Einstein, 1905, pp. 549–554; von Smoluchowski, 1906, pp. 756–780.
[3] von Smoluchowski, 1906, pp. 756–780.

This classical theory, comprising Fick's law, the Brownian motion concept and the Einstein-von Smoluchowski model, developed from a number of salient advances in nineteenth and early twentieth century physics and physiology, e.g. the study of Brownian motion, osmotic theory, the theory of heat conduction, kinetic theory, and the study of "diffusion" *per se*. In turn, it provided a basis for the general acceptance of atomic theory.[4] From the chemical viewpoint, Ostwald had written, "I am convinced that we have recently come into possession of experimental evidence of the discrete or grained nature of matter ... the agreement between Brownian movement and the predictions of the kinetic theory (has been) established by many investigators, and most conclusively by J. Perrin."[5] And it aided the computation of Avogadro's number,[6] and in this regard Perrin's long article summarizes the work that he and others published between 1907 and 1909. Most physicists of the time used the term "Loschmidt's number" to denote what is now called Avogadro's number (the number of molecules in one gram molecular mass of a substance).

The work of Einstein and Smoluchowski further assisted in the development of the theory of stochastic processes, Wiener using the Einstein-Smoluchowski equation for the probability distribution of diffusing particles to derive the probability that an individual particle would pass during a stated interval of time between any two points in a defined space.[7] In 1921, he demonstrated that almost all the possible paths of such a particle were non-differentiable; any path is continuous but is nowhere smooth. This work solved relatively simply the major mathematical problem of how one motion could be chosen at random from an infinite set of possible motions. Stochastic theory has been influential in quantum mechanics (e.g. Feynman's path integral method), in mathematics (leading to the discovery of profound connections between functional analysis, differential equations and probability theory), and in several other fields.[8] And hence, it is fair to say that diffusion theory has played a widely significant role in the emergence of modern scientific thought. However, the Einstein-von Smoluchowski model is (approximately) valid only under a very limited range of conditions, and Fick's law follows only approximately from this model. Conditions in biology deviate markedly from those in which the Einstein-von Smoluchowski model can, apply, so the theory cannot legitimately be applied to organisms.

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[4] Einstein, 1908, pp. 235–239.
[5] Ostwald, 1909; translated 1912.
[6] Perrin, 1909, pp. 1–114.
[7] Wiener, 1964.
[8] Wax, ed., 1954.

*The Nature of the Problem*

Organisms die unless water, oxygen, nutrients, waste products and other substances enter and leave their cells with sufficient facility for their needs. Some of these material movements involve *active transport* (i.e. transport depends on specific biological machinery and the expenditure of cellular energy), whereas others are perceived as having no need for such, being attributed to "*diffusion* alone". (It should be noted that while active transport can be an assisted form of diffusion, much of it occurs *against* existing gradients, and therefore is resisting rather than aiding an underlying diffusion process.) There is abundant evidence, old and new, that diffusion theory is an inadequate basis for explaining much of the movements of substances in organisms, yet a less than critical application of diffusion theory persists as a cornerstone of biology and medicine. It is frequently a tacit assumption in many scientific explanations, with authors often oblivious of this fact. The problems then are: how did this come about in the first place, and why has it survived in twentieth century biology? A better understanding of the *origins* of the theory should certainly help. Our thesis is principally, but by no means entirely, that the roots of the theory lie in the mechanistic materialist philosophy of the mid-nineteenth century, with its attempt to analyze physiology in purely physicochemical terms. This period coincided with the acceleration of the modern experimental tradition in biology. While the origin of diffusion theory itself may not be surprising, its survival with so much impact on biological thinking should be, and we need to know how and why this came about. But we also wish to assert that the issue raised is indeed a significant problem; diffusion theory's proven inadequacy in accounting for much of biological transport processes is not one we should continue to brush aside. While diffusion continues as the "default option" for transport of biological molecules, conveniently "explaining" the mechanism of solute movement and while a "biologically interesting" process, such as active transport, falls to be identified, we need more definite evidence of what exactly is going on under these circumstances. The default position continues to be asserted in encyclopedia[9] entries, textbooks,[10] papers and review articles;[11] its prominence demonstrates that diffusion theory continues to be an integral part of the paradigm of modern biology.[12] Its pedagogical influence has already provoked us into educational counterinitiatives.[13]

[9]  Encyclopedia Britannica 15th edition. Volume 2, 1973–1974, p. 1130.

[10]  Alberts et al., 1998, pp. 508–509; Lodish et al., 1995, pp. 619–640 (*cf.* similar entries in 1986 and 1990 editions): Vogel, 1988, Chapter 8; Berg, 1993, especially Chapters 1 and 2.

[11]  Paine, 1984, pp. 188s–195s.

[12]  Kuhn, 1962.

[13]  Wheatley, 1993, pp. 181–188; Agutter, 1994, pp. 32–35.

The inapplicability of diffusion theory to transport processes within the living cell is well established, because of the difficulties in applying physico-chemical principles in general to the crowded, heterogeneous and highly organized interior of the cell.[14] Diffusion theory itself is fraught with experimental and theoretical difficulties,[15] and despite considerable elaboration of the mathematics beyond its classical beginnings,[16] no variant easily transforms it into a manageable equation applicable to the conditions within the cell internum. Einstein himself was fully aware of the difficulties in principle in applying his model to such complicated systems: "if the molecular model were extrapolated to include every individual particle, calculation of the integral ... would be so difficult that exact calculation (of the free energy of the system) could scarcely be attempted".[17] Elsewhere we have shown that none of the assumptions of the Einstein-Smoluchowski model are even approximately met *in vivo*.[18] The cell contains a highly concentrated and heterogeneous assembly of deformable, interacting and inelastically colliding particles; much of the solvent (water) is bound to solid structures which, although not necessarily long-lived, have huge surface areas; and in any case the conditions only tend to thermodynamic equilibrium after death. The model representing the "microscopic" aspect of diffusion theory assumes a dilute, homogeneous suspension of rigid, non-interacting and elastically colliding particles, a monophasic system with the solvent (largely) unbound, and a tendency towards equilibrium. Also, the model assumes that there are no net solvent movements,[19] and this is undoubtedly relevant in intracellular transport.[20] The fact that biologists *acknowledge* all these arguments but still use the term "diffusion" to account for transport phenomena – at least when they teach students and write textbooks – indicates that the problem we are exploring here persists and remains indeed significant. If the theory of diffusion does not apply, and diffusion is not adhered to as a specific, defined scientific term, its use in the vernacular sense can be misleading.

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[14] Donnan, 1927, pp. 685–688; Halling, 1989, pp. 317–318; Polyani, 1968, pp. 1308–1312.

[15] Robinson and Stokes, 1956; Tyrrell, 1961.

[16] Crank, 1975.

[17] Einstein, 1905, p. 532, n. 2.

[18] Agutter et al., 1995, pp. 251–272; Wheatley and Malone, 1987, pp. 171–173; Agutter and Taylor, 1995, pp. 21–52.

[19] Chambers, 1940, pp. 49–67.

[20] Wheatley and Malone, 1993, pp. 1–5; Wheatley, 1999, pp. 275–284.

## Development of Classical Diffusion Theory

*Mechanistic Materialism: Its Origins and Influence*

How, then, did diffusion theory ever come to be a part of biological thought? Our contention is that Fick's Law was an outcome of its author's commitment to explaining all living phenomena of the principles of physics and chemistry that apply to non-living matter and, equally, to isolated parts of an organism. Implicitly and explicitly, it was anti-vitalist in regard to both theory and experiment.

A binary opposition between mechanistic materialism and vitalism is commonplace but clearly an oversimplification, since neither category was homogeneous or fixed in character.[21] For almost all biologists in the first half of the nineteenth century, the presumption of vital functions or vitalism was the basis of scientific biology. It was a radical, revolutionary position, welcomed by dissenters and other opponents of Church and State throughout Western Europe because in its time it provided a means of explaining biological phenomena without invoking divine intervention.[22] Its attractiveness to those who sought a genuine science of biology, ideally on a par with what was contemporaneously the one great explanatory system of physics (Newtonian mechanics), can be appreciated. The phenomena of growth, reproduction, embryo development, movement, responses to environmental stimuli, and thought – and the diversity of species itself – all seemed so far removed from classical mechanics that biologists had largely confined themselves to classification and description. The idea that organisms and their parts would "obey" the same chemical and physical laws as inanimate matter, yet be distinguished from it by virtue of endowment with a vital property, opened wide many doorways of inquiry.

By the 1840s, however, there was an explicit tendency amongst some biologists to repudiate the notion of "vital property" and particularly the notion of "vital force." Mechanistic materialism was articulated in Germany at the time that Prussia and other states were becoming industrialized. Broadly, the mechanistic materialists held that all phenomena of animal and plant physiology could be explained wholly in terms of physics. At that time, "physics" comprised mechanics, optics, thermodynamics, and the studies of electricity and magnetism. Moreover, it was held that the properties of a biological entity, however complicated the entity, could be deduced entirely from the properties of its components; the whole was the sum of its parts. A full

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[21] Ruse, 1989; Mandelbaum, 1971; Merz, 1964; Hall, 1969, vol. II., pp. 245–251.
[22] LeFanu, 1946; Desmond, 1987, pp. 77–110; Desmond, 1989; Jacyna, 1983, pp. 311–329.

exposition of this belief can be found in Durbin's book,[23] which characterizes the main features of the mechanistic materialist ideology.

Mechanistic materialism was the philosophy integral to the rise in Germany of experimental physiology during the third quarter of the nineteenth century.[24] The advances in physiology at this time fostered the belief that a successful experimental biology depended on the acceptance of this doctrine and the concomitant exorcising from all biological discourse of anything implying immaterial "vital forces". Although the project of a complete "physics of biology" failed before 1900 and the reductionist enterprise in twentieth century biology came to depend instead on chemistry,[25] the suspicion of any argument redolent of vitalism survived. Because many areas of biological research did not seem amenable to reductionist accounts during the late 1800s and early 1900s, some workers in these areas came to defend the vitalist position (the pioneering experimental embryologist Hans Driesch is one of the most outstanding examples).[26] The effect was a polarization of the mechanist and vitalist viewpoints, a dichotomy we hope to resolve in Part II. Classical diffusion theory, however, was a product of the early and optimistic days of mechanistic materialism and biological physics, which we shall now explore in more detail.

*Ideas on Diffusion Before Fick's 1855 Paper*

The notion that diffusion is a physical process obeying quantitative laws and explicable in terms of the behaviour of individual molecules can be traced back to the work of Dalton at the beginning of the nineteenth century.[27] In the period before the mechanistic materialist philosophy was fully articulated, there had been two salient contributions to its study, neither of which had revealed the hoped-for quantitative relationship. One was the work of Dutrochet which related diffusion in liquid systems to its dynamic counterpart, osmosis.[28] The other was produced by Thomas Graham in England. Graham had found that gas diffusion depended in a simple way on the relative molecular mass of the gas molecules, and he went on from there to the study of liquids. Unfortunately, this proved to be a much less tractable problem and his ramblings on the subject are barely comprehensible.[29] Ludwig and Brücke recognized the importance of the question for their scientific concerns and,

[23] Durbin, 1988.
[24] Mendelsohn, 1965, pp. 201–209; Temkin, 1946, pp. 322–327; Gasking, 1970.
[25] Cranefield, 1957, pp. 407–423.
[26] Driesch, 1914.
[27] Dalton, 1808; Cardwell (ed.), 1968.
[28] Dutrochet, 1827, pp. 411–437; Dutrochet, 1827, pp. 393–400.
[29] Graham, 1833, pp. 175–204; Graham, 1850, pp. 1–46.

paying due tribute to the efforts of Dutrochet and Graham, attempted – with limited success – to address it.[30]

On presumption of their model was that diffusion was a process occurring across a passive physical barrier. It was a natural presumption. Graham's successful quantitative law related gas molecular masses to diffusion rates across porous membranes.[31] Dutrochet had observed water movement ("osmosis") between the outsides and insides of cells. Brücke had constructed a theory of water diffusion through pores in thin physical barriers, a theory adopted by Ludwig and applied to his studies on urine formation.[32] This presumption is remarkably persistent. Pfeffer's experimental measurement of osmosis in 1877 involved a semi-permeable membrane (i.e. one that admits the passage of solvent but not solute) and osmosis is taught, even to today's students, *as though a semi-permeable membrane was a prerequisite for the process.* This is not the case; all that is required for osmosis, i.e. for following *solvent* rather than solute diffusion, is a concentration gradient. But this assertion is just so much *post hoc* wisdom. When Fick confronted the problem, he inherited a tradition in which diffusion (and osmosis) had invariably been conceived in terms of passage through some sort of physical barrier, a porous membrane.

Ludwig's especial interest in fluid movement and kidney filtration, and in the question of how respiratory gases are exchanged between lungs and tissues (which was to be a recurrent obsession throughout his career),[33] inevitably affected the direction of inquiry followed by his disciple, Fick. Fick's talent and commitment needed a serious challenge, one that was relevant to the emergence of a true physics of biology, and Ludwig's particular interests seem to have been enough to decide what that challenge was to be.

Perhaps it is a tribute to Fick's achievement that, notwithstanding the persistence of the above-mentioned misunderstanding of osmosis, few nowadays conceive of diffusion in terms of physical barriers. It is considered a process that occurs in *continuous* liquid media. In this respect the model assumed by Fick when he addressed the problem was revolutionary,[34] and his abandonment of the barrier assumption was responsible for his success in obtaining the long-sought quantitative law. It simplified the mathematical model. However, the numerical relationship that Fick determined between net rate of solute movement and local curvature of concentration gradient was (impli-

[30]  Ludwig, 2 volumes, 1852 and 1856.

[31]  Graham, 1833, pp. 175–204.

[32]  Ludwig, 2 volumes, 1856; du Bois-Reymond, 1848. The Preface to this latter work contains a clear statement of the underlying philosophy of the new experimental physiology, which seems to have made a particularly profound impression on Fick.

[33]  Lombard, 1916, pp. 363–375.

[34]  Fick, 1855, pp. 59–64.

citly) assumed to be valid both for free solution and a solution containing a passive porous membrane. It is not that diffusion was modelled exclusively for free solution, but rather that the presence of a passive porous barrier was shown to be irrelevant.

*Adolph Fick (1829–1901)*

Adolph Eugen Fick was born in Kassel, Hessen, in 1829, the youngest of the nine children of the city's municipal architect. During his childhood he watched the transformation of Kassel (in which his father played an instrumental part) from a tangle of mediaeval streets, haphazard and insanitary, to a new planned community of broad thoroughfares and modern houses. This substitution of the modern and rational for the traditional and unstructured serves at least as a metaphor for the contributions he was later to make to medicine and physiology.

In 1848, Adolf Fick went to study physics and mathematics in Marburg, but on his elder brother's advice he turned to medicine; and so he met Carl Ludwig, newly returned from Berlin, inspired by his discussions with du Bois-Reymond, Brücke and Helmholtz, and doubtless excited by the pervading atmosphere of revolutionary change throughout Europe, not least in Prussia. While Ludwig had been in Berlin, Bismark had been locked in argument with the King about the financing of the East Prussian railway, crucial for industrialization; throughout Europe, governments trembled and in some cases fell before political insurgence; for Ludwig the radical, these were stimulating times. Finding in the younger Fick a physico-mathematical talent equal to his own and a willingness to accept modern thought, he became the youth's mentor, thus repaying has debt for the elder brother's earlier kindness to him. Throughout his life, Ludwig remained a great teacher, the list of whose students contains numerous physiology professors in many lands.[35] The effect of his no doubt fervent exposition of mechanistic materialism and the virtues of a physico-experimental approach to physiology on a talented twenty-year-old can readily be imagined.

Indeed, Fick was to become one of the most consistently committed of all mechanistic materialists, a fine teacher in his own right, and an exponent of the faith that a rational (and therefore improved) medicine would emerge only when each pathological process was attributed to a specific physiological cause, itself understood in the language of physics, on the basis of experimental evidence.[36] His first paper dates from 1849,[37] and analyzes the

[35] Burdon-Sanderson, 1895–1896, pp. 1–8.
[36] Burdon-Sanderson, 1895–1896, pp. 1–8.
[37] See Fick, writings collected posthumously, 1904, Vol. 1.

musculoskeletal system of the pelvis in terms of mechanics, relating experimentally measured torques to the forces generated by the muscles and the geometry of the system.[38] Ludwig's influence is immediately apparent. Fick's commitment to the cause was clear in his *Medizinische Physik* of 1856, whose content was true to its title: the mechanics of limbs and other structures, the optics of ophthalmology, bioelectricity, sound and its production, heat and its generation in organisms, the hydrodynamics of circulation, and diffusion.[39] In many of these areas he made lasting contributions, and some now traditional instruments of medical physiology, the ophthalmotonometer and the plethysmograph, were his inventions.

Fick followed his mentor Ludwig to Zürich in 1852 and remained at the university there for sixteen years before becoming professor of physiology in Würzburg. He retired from Würzburg when he was 70 and died at Blankenberge, Belgium two years later. Amongst the students who were influenced as much by his blend of materialism and neo-Kantianism as by his precise and definite views about scientific data and their handling, two who stand out were his biographer, Franz Schenck,[40] and the author of *The Mechanistic Conception of Life*, Jacques Loeb.[41] Significantly, this highly influential book retains the insistence on experimentalism and anti-vitalism of the pioneering mechanistic materialists, but places more emphasis on specifically biological cause-effect relationships, such as plant tropisms, than on the usually vain quest for direct interpretations of them in the language of physics. What Loeb had learned from Fick had been a rigorous approach to *physiological* experimentation; by the 1870s, Fick had recognized that he – and others – had been forced to play down if not abandon their quest for a pure physics of physiology.[42] The quest had by and large proved impossible. In any case, by the time Loeb's book was published (1912), the torch that du Bois-Reymond, Ludwig and the others had thrust into the incapable hand of physical theory had been picked up, still burning, by organic chemists, and they were running with it.

*Evaluation of Fick's Paper*

Like many classics of science, Fick's 1855 paper is far more widely acknowledged than read. It is reputed to have established the law of diffusion inductively from experimental data, but this imaginative reconstruction – inspired by old-fashioned empiricist beliefs about science – is far from reality.

[38]  Cranefield, 1957, pp. 407–423.
[39]  Fick, 1856.
[40]  Schenck, 1902, pp. 313–336.
[41]  Loeb, 1912; reprinted 1964.
[42]  Lombard, 1916, pp. 363–375.

The paper has great scientific virtues, but it also has defects of reasoning that call into question the basis of its general conclusions.

One of the most obvious virtues is the abandonment of the unhelpful porous-membrane assumption and the espousal of a new approach to quantitative modeling. The way in which the porous membrane model was rejected was scientifically impeccable: "Only Brücke has really investigated the molecular process involved in hydro-diffusion through membranes. His theoretical ideas were later elaborated by Ludwig, and indeed they have such great mechanistic clarity and plausibility that it is difficult not to be convinced immediately that the name, first suggested by Brücke and explained in detail here, rather than the more commonly-used name "mechanical theory", since all diffusion theory must necessarily be *mechanical* to be tested by experiment..." (our emphasis).[43]

The "following conclusions" are four logical predictions, two of which Fick refuted because of inconsistency in his own experimental data, while the other two gave uncertain results.[44] This is as clear an illustration of the hypothetico-deductivist approach to science as can be found in practice. Moreover, once due allowance is made for the inevitable complexities of nineteenth century German scientific sentence-structures, the paper is strikingly lucid, in stark contrast to Graham's writings on the same theme, or even Ludwig's. Whatever criticisms we can make, Fick succeeded in placing diffusion theory on a footing that a consensus recognized as genuinely scientific, i.e. capable of systematizing a range of disparate observations, able to support quantitative predictions, and susceptible to critical testing.

Fick can scarcely be blamed for some of the paper's defects. The experimental data with which he supported his quantitative law (and refuted the Brücke-Ludwig theory) were flawed. Diffusivity estimates are seriously problematic even with modern equipment, and the home-made apparatus used by Fick gave values that varied over a range of some 30%. Such results would have been compatible with a wide range of mathematical formulations, of which the one he chose was but one example. Less forgivably, it is implicit in his studies that his concentration gradients were linear; but he made no attempt to demonstrate that this was so, merely presuming it. Apart from the experimental aspect of his paper, his Newtonian view of the interactions amongst molecules (i.e. that molecules were attracted to one another by a force akin to gravitation and mutually repelled by an equally mysterious force) was outdated even in terms of the chemistry of 1855, and would certainly have seemed quaint and eccentric by the 1880s, after the foundations of a molecular-based physical chemistry had been laid. This view of inter-

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[43] Fick, 1855, p. 74.
[44] A detailed account can found in Wheatley and Malone, 1993, pp. 1–5.

molecular forces was not crucial to Fick's argument, but it shows a style of thinking about the movements of substances in the liquid phase that was in keeping with the deduction of his law of diffusion but wholly out of step with modern beliefs. "Much has been written and debated about the difference between the forces of chemical affinity and the forces which result in the solution of a substance in a liquid; it seems to me one could use the simple atomic hypothesis, which is approved by the majority of physicists, at least as a useful aid to the overall view ... to give a mechanical explanation of it to a certain degree." Fick's idea in the 1855 paper from which this quotation is taken was that ions in solution, being of opposite charge, would attract each other and hold together firmly rather than be dispersed in aqueous solution as separate entities.

However, one distinctly defective argument in the paper is crucial to the enunciation of the law itself. Analogy plays an important part in the progress of science, so in principle there was nothing wrong with Fick's search for a comparable model in another field of research. But his choice was at best dubious. In Fourier's empirical and theoretical establishment of a mathematical relationship between heat conduction rate in a metal bar, the temperature gradient along the bar, and a constant (thermal conductivity),[45] Fick saw the pattern for an isomorphic relationship for solute diffusion rate in a cylinder of solution, the concentration gradient along the cylinder, and a constant (diffusivity). "The first task would now be to deduce the basic law for this process of diffusion from the general laws of motion ... Indeed, one will admit that from start to finish nothing may be more likely than this: that the spread of a dissolved body in a solvent, as far as it take place undisturbed under the influence of the molecular forces, proceeds according to the same law which Fourier has established for the spread of heat in a conductor; and which Ohm has transferred with such splendid success to the spread of electricity. *One need only substitute* in Fourier's law the words quantity of heat with the words quantity of dissolved body, and the word temperature with density of solution" (our emphasis). This again, on page sixty-five of his 1855 paper, shows how fickle his thought was, but the analogy was not well drawn.

Fourier had given a mathematical treatment of three-dimensional heat transfer in metal blocks. This was a generalization of the (mathematically simpler) model that he had inferred on the basis of his experiments for one-dimensional heat transfer. Fick's experiments, which as we have seen were flawed, purported to show one-dimensional diffusion in narrow cylinders of solution. He seems to have assumed that he could generalize to three dimensions just as Fourier had. Moreover, Fick presumed that mass

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[45]  Fourier, 1828; in the translation by Freeman, 1878, p. 138.

transfer in *liquids*, in which (even by his understanding) the molecules are mobile, would exhibit the same behaviour (mathematically speaking) as heat transfer in solids. Yet Fourier had been careful to point out that in fluids: "Heated molecules begin to move of their own accord … [a fact that] does not require expression in my treatise on the conductive spread of energy in solids."[46]

Even if the comparison were sound, thermal conductivity is reasonably constant only over fairly narrow temperature gradient ranges. By analogy, should diffusivity not be reasonably constant only for narrow ranges of concentration gradients? Finally, we might ask why, if Ohm's borrowing from Fourier was "not strictly correct", Fick's should be otherwise.

The fact that Fourier's model itself now appears imprecise, for reasons that Fourier himself would doubtless have expected, compounds the problems.[47] We cannot escape the conclusion that Fick's law, the foundation stone of classical diffusion theory, rests on a highly dubious and empirically weakly-supported analogy with an imprecise model in a different field of physics. His 1855 paper was a fine intellectual achievement, a positive and promising-looking responses to a very difficult scientific challenge; but we should be aware of its shortcomings and of the consequent insecurity of the law that represent its main conclusion.

## *Entrenchment of Diffusion Theory in the Physical Sciences*

The developments of thermodynamics and kinetic theory in the later nine-teenth century are peripheral to our theme and have been explored by others.[48] Suffice it to say that diffusion theory became assimilated into the emerging corpus of physical chemistry. Using Clausius' pioneering work in thermo-dynamics,[49] Kelvin derived the forms of Fourier's empirical heat-transfer equations, and might *a fortiori* have given some theoretical blessing to Fick's Law. It seems, however, that Fick and Kelvin were unaware of each other's work. In the 1880s, osmosis acquired a physical-chemical explanation in an application of van't Hoff's Law by Nernst and Ostwald.[50] It is interest-ing the such latter-day adherents of *Naturphilosophie* could reconcile their theories with a publication inspired by the severest brand of mechanistic materialism.[51] Indeed, Nernst went on to apply his account of diffusion to an

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[46] Fourier.

[47] Joseph and Preziosi, 1989, pp. 41–53; Maddox, 1989, p. 373; Malone and Wheatley, 1991, p. 373.

[48] Brush, 1967, pp. 145–183; Niven (ed.), 1890.

[49] Hasenohrl (ed.), 1909, p. 216.

[50] Nernst, 1888, pp. 613–637; Nernst and Ostwald, 1889, pp. 120–130.

[51] Thiele, 1968, pp. 295–315.

explanation for the resting potential that du Bois-Reymond had discovered experimentally in nerve cells.[52]

However, the "microscopic" aspect of diffusion theory, which holds that random thermal motions of molecules in liquids are responsible for macroscopically observable time-dependent changes in concentration gradients, was provided not by classical thermodynamics but by kinetic theory. Both Smoluchowski and Einstein were motivated by a wish to find and test a specific prediction of kinetic theory,[53] in order to challenge the rejection of atomic theory by Ostwald and his followers.[54] They succeeded, ultimately, by providing an account of Brownian motion. First explicitly described in 1828 by the Scottish botanist Robert Brown, who observed in aqueous suspensions of pollen grains from *Clarkia pulchella* a rapid, continuous, short-range motion of small included particles that "...arose neither from currents in the fluid nor from its gradual evaporation, but belonged to the particle itself,[55] this phenomenon had remained something of a thorn in the flesh of nineteenth century physics and had certainly resisted explanation in terms of classical thermodynamics. The mathematical description of Brownian motion deduced by Einstein from the principles of Maxwell-Boltzmann statistics led directly, with the aid of simplifying assumptions, to Fick's Law, which Einstein dubbed "the well-known differential equation for diffusion."[56]

This completed the scientific credentials of diffusion theory. A product of experimental physiology at the outset, it had proved to be deducible from the principles of both classical thermodynamics and kinetic theory. Although no further major applications in biology had appeared in the meantime, such applications now seemed to be legitimated. Despite increasing skepticism about the possibility of underpinning physiology directly with physics,[57] here was a theory that apparently realized the dream of 1840s mechanistic materialism: a fundamental piece of physics applicable to, and indeed originally discovered through, physiology.

[52]  Nernst and Barratt, 1904, pp. 664–668.
[53]  von Smoluchowski, 1906, pp. 756–780; Einstein, 1905, pp. 549–554.
[54]  Ostwald, 1904, pp. 506–522.
[55]  Brown, Robert. A brief account of microscopical observation made in the months of June, July and August, 1827, on the particles contained in the pollen of plants; and on the general existence of active molecules in organic and inorganic bodies, Privately printed pamphlet, 1828.
[56]  Einstein, 1905, pp. 549–554.
[57]  Cranefield, 1957, pp. 407–423.

## The Entrenchment of Diffusion Theory in Modern Biology

*Two Philosophies in Biology*

So far, we have reviewed the nineteenth century origin of diffusion theory and noted its fundamental connection with mechanistic materialist philosophy. We now turn to our second question: how and why has diffusion theory persisted in twentieth century biology? This question becomes interesting when we note that although mechanistic materialism spread to the new experimental disciplines of embryology, biochemistry and genetics over the period 1880–1910, it was gradually superseded in most areas of biology by a holistic materialism.[58] Claude Bernard (1813–1878), a student of Magendie whose contributions to experimental physiology included insights into the roles of the liver and pancreas in digestion and the neural control of blood vessel dynamics, declared that "the constancy of the internal environment is a precondition for life"; the notion of what was later to be dubbed homeostasis.[59] Bernard can reasonably be regarded as one of the nineteenth century pioneers of holistic materialism.[60] By 1930, when Cannon's popular book was published,[61] the implications of the new philosophy were clear. To maintain a constant internal environment requires control mechanisms: sensors, effectors, information processing and feedback systems. These terms were imported into the language of twentieth century physiology from control engineering in the 1940s[62] – but they do not belong to the language of physics (or, indeed, of nineteenth century physiology). They are not, *ipso facto*, compatible with a mechanistic materialist perspective, according to which the (physiological) whole is *nothing but* the sum of its parts. Holistic materialism admits that a physiological whole is greater than the sum of its parts and shows less of a polarized antipathy towards vitalism than its predecessor.[63] Given that diffusion theory is so inextricably bound up with mechanistic materialism, how has it survived in this alien philosophical context?

A helpful point at which to begin this inquiry is with Bohr's research, beginning around the turn of the century, into the mechanism supplying oxygen to body tissues. Christan Bohr, one of Ludwig's most outstanding

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[58] Nagel, in Munson R. (ed.), 1970, pp. 19–32; but see also M. Beckner, 1970, pp. 54–56; Sherrington, 1906; Cannon, 1932; Fulton, 1931; Whitehead, 1926; Cornforth, 1968; Krutch, 1950; Harrington, 1996, pp. 25–29, and Chapter 2; Gregory, 1977; Allen, 1978.

[59] Olmsted, 1938; Riese, 1942, pp. 281–294.

[60] Hill, 1920.

[61] Cannon, 1932.

[62] Wiener, 1948.

[63] Nagel, in Munson R. (ed.), 1970, pp. 19–32; cannon, 1932; Krutch, 1950.

students, devoted much of his working life to the question how the mammalian body (specifically the human body) obtains an adequate supply of oxygen. His best remembered contribution to physiology was his elucidation of the oxygen carrying capacity of hemoglobin. Although Ludwig's influence is clearly apparent in his choice of research topic and his commitment to experimental science, Bohr was not an unreflecting devotee of mechanistic materialism. Bohr might have been "master of the investigation of the physical basis of physiological processes" in Denmark at the turn of the century (according to Rosenfeld),[64] but he never lost sight of the *biological* aspect of his work. *In his view, it was necessary to consider both the physical explanation for a phenomenon and its biological (functional) role at the same time*; explanations in physiology had to involve both mechanistic and teleological viewpoints, despite the frequent (apparent) incompatibility of these two perspectives.[65]

*Oxygen Transport: Secretion of Diffusion?*

Bohr's research concerned the issue of whether oxygen enters the bloodstream from the lungs, and in turn the tissues from the bloodstream, by diffusion or secretion. In the lungs, oxygen enters the blood stream from the air, while carbon dioxide leaves the blood stream and is expelled from the body. Fick argued that these processes take place by diffusion,[66] but Ludwig, apparently deviating from his original mechanistic materialism, suggested that the lungs might somehow facilitate the evolution of carbon dioxide and, perhaps by analogy, the entry of oxygen. The potential implications of this disagreement were considerable: Fick's position was consistent with mechanistic materialism, and Ludwig's was not. Perhaps these two long-standing colleagues would have settled their differences if they had been able to discuss their findings directly with one another, but at the time of the disagreement, Fick was working in Würzburg and Ludwig in Leipzig. Pflüger, a committed mechanist, saw the importance of the problem immediately and published a vitriolic rebuttal of Ludwig's position.[67] Twenty years later, Ludwig's student Christian Bohr devised an improved haemaerotonometer and obtained evidence favoring an active secretion (an active transport) of oxygen by the lungs.[68] Bohr gave Ludwig's tentative suggestion of "facilitation" a positive thrust; he implied that oxygen enters the blood not by the

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[64] Rosenfeld, 1981, Vol. I.

[65] Thompson, 1917, Chapter 1; Whitehead, 1926; Agutter and Wheatley, 1999.

[66] Fick, 1869, pp. 51–69.

[67] See some of the writings of Ludwig's disciples in Wolffberg, 1871, pp. 465–492; Strassburg, 1872, pp. 65–96; Nussbaum, 1873, pp. 296–300.

[68] Bohr, 1891, pp. 236–268.

passive physical process of diffusion, but that it is actively secreted by the alveolar endothelial cells.

In 1903 Bohr's student, August Krogh (1874–1949), submitted his doctoral thesis on the exchange of respiratory gases in the lungs. Krogh took oxygen secretion, as opposed to pure diffusion, as his working hypothesis. To test this hypothesis he further improved the microaerotonometer for measuring oxygen levels in small compartments. From such measurements he *inferred* the alveolar oxygen levels and determined their relationship to the rate of change of oxygen concentration in the perfusing blood. He found no evidence for neural effects on oxygen movement; rather, there was a close mathematical agreement between his results and the predictions of Fick's law of diffusion. His conclusion that respiratory gases are exchanged across the lungs by diffusion, now an unchallenged article of faith in physiology textbooks, was published a year later jointly with Bohr and Hasselbalch.[69] In 1910, he wrote a series of articles confirming the value of his diffusion model in describing the oxygenation of the body; in them he established that the supply of oxygen to tissue cells from capillaries could be accounted for by diffusion alone.[70] In 1919, he published a mathematical account of tissue oxygenation; he pictured a cylinder of tissue with the oxygen-carrying capillary at the centre, and presumed radial diffusion of oxygen outwards from this central column in a completely still environment.[71]

The study of respiration initiated by Ludwig, Bohr and Krogh was taken up by J. S. Haldane (1860–1936), who graduated in medicine from Edinburgh at the time (1884) when physical chemistry was emerging on the continent as an independent discipline. He was concerned initially with respiratory diseases and later with human respiratory problems at high altitudes (pertinent to mining, mountaineering, ballooning and to the early days of aviation). In 1895, Haldane and his colleague, J. L. Smith, visited Bohr in Copenhagen and were apparently influenced both philosophically and methodologically. They devised methods for measuring the quantities of oxygen and carbon dioxide consumed and generated by the body and for determining the compositions of gas mixtures, and importantly, they invented an indirect CO method for determining the arterial blood oxygen content which would compete with Krogh's direct method.[72] This method relied on the fact that carbon monoxide competes with oxygen for hemoglobin binding. The greater the level of oxygen in the blood, the lower the capacity to bind carbon monoxide. In 1905, Haldane announced his major discovery that as the concentration of carbon

[69] Bohr et al., 1904, pp. 402–412.
[70] Krogh, 1910, pp. 248–278.
[71] Krogh, 1919, pp. 391–408.
[72] Haldane and Smith, 1896, pp. 497–517; Haldane and Smith, 1897, pp. 231–258.

dioxide in the blood increases, the rate of respiration increases concomitantly, thus expelling more of the waste gas and increasing the oxygen supply to the body. This response, controlled by the nervous system and coordinated by the respiratory centre in the brain,[73] is now considered fundamental to the physiological control of respiration. It was a typically homeostatic mechanism, of the kind upon which twentieth century physiology was soon to focus. Our remark that Bohr was probably sympathetic to Haldane's position is supported by the courteous tone of Bohr's criticism.[74] These finding seemed to conflict with Krogh's data, published almost at the same time (see above). Haldane presumed that cells and tissues should be able to *control* their activities, to organize not only themselves but also their environments. According to Krogh, however, they merely respond to general physical principles rather like passive flotsam on a physicochemical ocean. In the experimental physiology papers of Krogh and Haldane in 1904–1905, the philosophies of mechanistic and holistic/functional materialism came face to face.

Bohr had already discussed the possible implications of the apparent fact that certain Mediterranean fish appear to secrete atmospheric gases into their swim-bladders in order to maintain buoyancy.[75] Certain marine invertebrates control their orientations by forming gas bubbles, presumably by a secretory process, inside their bodies (the low density of gas bubble makes the organism orientate itself bubble-upwards). These well-established observations justified Krogh's choice of testable hypothesis and underpinned Haldane's further pursuit of the matter. If the blood carbon dioxide concentration controls breathing by a feedback mechanism, why should the passage of oxygen into the body not be controlled by cells, i.e. by a "secretory" (active transport) process? In 1911, Haldane led an expedition to Pike's Peak, Colorado, to study the physiological effects of low atmospheric pressure. He and his colleagues, using the indirect CO method, discovered that despite the reduced partial pressure of oxygen in the lungs, the blood-stream was still efficiently oxygenated; indeed, at high altitudes, the oxygen tension in the arteries exceeded that in the lungs.[76] His results convinced him that the body, autosensing its own oxygen requirement, adjusts its oxygen supply accordingly: "oxygen is secreted into the blood-stream by alveolar cells".[77] Haldane and Priestley stated that "if we seriously endeavoured to include the phenomena of life within the scope of physical science, we should require to modify drastically

[73] Haldane and Priestley, 1905, pp. 225–266; see also Allen, 1967, p. 392.
[74] Bohr, 1909, pp. 221–280.
[75] Bohr, 1893, pp. 494–500.
[76] Douglas et al., 1913, pp. 183–318.
[77] Haldane et al., 1911, pp. 181–206.

the axioms on which physical science is based".[78] It should also be noted that these authors, like Einstein, did not quote Fick's work in their discussion. With some exceptions, there seems to have been some sort of conspiracy of silence about Fick.

In his 1919 paper, Krogh, with the help of a mathematician (Ehrlang), gave a mathematical account of his cylinder model, purporting to show that diffusion *alone* could account for the supply of oxygen to the tissues.[79] Their quantitative model falters because of certain questionable assumptions, but in any case, even if diffusion *could* account for oxygen supply, it is not a necessary corollary that it *does* so. In the 1919 paper, Krogh attacked Haldane's hypothesis explicitly. Marie Krogh had already argued in 1915 that the Pike's Peak data could be recalculated to fit the diffusion model.[80]

The debate between Haldane and Krogh continued over the next decade, and is still remembered as the "Great Oxygen Secretion Controversy". The Kroghs claimed to show mathematically that all experimental data could be accounted for by diffusion alone:; Haldane and his colleagues performed more experimental studies, including indirect measurement of the lung and arterial oxygen levels in low pressure oxygen chambers, which supported the secretion concept.[81]

In the same year as the Pikes Peak study, Joseph Barcroft, a proponent of the Fick-Pflüger-Krogh position (that blood is oxygenated by diffusion alone), also led expeditions to study high-altitude respiration; these studies, at Monte Rosa and the Peak of Tenerife, were mainly concerned with the effects of work on the oxygen dissociation curve described by Bohr. The findings had little immediate bearing on the oxygen diffusion/secretion debate, though they were quoted in the discussion following Barcroft's "glass box experiment" of 1920, which finally swung the consensus opinion away from secretion to diffusion and effectively ended the controversy.[82] Barcroft, himself the subject in the experiment, was sealed in a glass room for six days, breathing an atmosphere with steadily decreasing oxygen content. Direct measurement of the $pO_2$ in his arterial blood failed to show a higher oxygen concentration than the air in his lungs. The atmosphere oxygen inside the sealed box decreased as the oxygen was used up by the occupant. Barcroft's blood oxygen level declined less rapidly because the increased breathing rate partially compensated for the lower concentration of oxygen in the air enter-

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[78] Haldane and Priestley, 1935, p. 251.
[79] Krogh, 1919, pp. 391–408.
[80] Marie Krogh, 1914/1915, pp. 271–296.
[81] Haldane et al., 1919, pp. 181–206; but see also Krogh, 1910, pp. 248–278.
[82] Barcroft et al., 1920, pp. 450–472.

ing the lungs. But crucially, the level in the blood never *exceeded* that in the lungs.

Why should one incident, the "glass box experiment," have terminated such a long and intricate debate? We suggest the following possible reasons. First, Barcroft's result was conclusive in terms of direct aerotonometric measurement, which was perceived as intrinsically superior to the indirect carbon monoxide method used by Haldane (perhaps unfairly, since Haldane's method remains in widespread use). Second, the conclusion supported orthodox mechanistic philosophy against Haldane's "neo-vitalism." Holistic materialism (organicism) was not yet established in physiology, but in any case Haldane's version of it was somewhat idiosyncratic. Third, the inherent danger of the experiment, in which Barcroft nearly died, projected an image of Barcroft as a hero of science and at the same time indicated that the experiment was foolish and should not be repeated. Fourth, in 1922, Barcroft capped his success by another high-altitude study at Cerro de Pasco, Peru, in which direct aerotonometric measurements again showed that arterial blood oxygen concentration is *always lower* than that in the lungs.[83] Fifth, Krogh, unlike Haldane, had help from a mathematician (Ehrlang) who gave his model a sophisticated mathematical expression. Irrespective of the philosophical approach to science, mathematically quantitative models invariably have power and influence, especially amongst those – a majority of biologists – who do not actually understand the mathematical arguments. It has more recently been shown that Krogh's mathematical model rests on fifteen challengeable (and in some cases demonstrably false) assumptions,[84] but by the time these inadequacies was exposed, the oxygen secretion controversy was long dead. Sixth, the subsequent rise of holistic materialism and the increasing focus of physiologists on homeostatic mechanisms diverted attention away from the question of how oxygen (and carbon dioxide) actually move across barriers to questions about how respiration as a whole is controlled, so that continuous tissue oxygenation at a more or less constant level is assured. And seventh, the idea of "active transport" as a physiological concept lay also in the future.

Many years later, at the age of 77, unrepentently committed to his beliefs, Haldane was to write:

> In the lungs the blood is separated from the alveolar air by tow layers of living tissue, namely the capillary endothelium and the alveolar epithelium. What part in respiratory exchange is played by these very thin layers of living tissue? Is this part purely mechanical? In other words,

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[83]  Barcroft et al., 1923, pp. 351–480.
[84]  Hoofd, 1992, pp. 197–229.

do these layers behave towards the respiratory gases as any non-living moist membrane would behave? Or may the living membranes play an active part in the process? We must now face this interesting, but also controversial subject.

There has been a tendency to assume that these membranes cannot play an active part. But, it is not long since membranes of cubical or columnar epithelial cells were supposed to play only a passive part in the separation of material: and the presumption that a thinner membrane of flattened cells cannot play an active part *has come down to us from the time, about the middle of the last century*, when physico-chemical theories became dominant in physiology, and secretion in general was supposed to be a mere mechanical process like filtration or diffusion. Another prevalent assumption is that though liquids and dissolved solids may be actively secreted, gases probably pass through living membranes by *simple diffusion* [our emphases].[85]

We might expect this argument to have competed seriously with Krogh's diffusion hypothesis, for at least the following reasons.

(a) At the time of the controversy it was known that water flows through, and is thereby exchanged between the intra- and extra-vascular compartments, the capillaries and the tissue spaces.[86] At the arterial end of a capillary, there is a net outflow of fluid, and at the venous end there is a net inflow. The alveolar surfaces do not dry out, therefore there must be fluid movement over their external aspects, and through the alveolar cytoplasm itself. These considerations imply that respiratory gases may be carried in and out by bulk flow of water, not just by pure diffusion through a stationary surface layer. The evidence for inward flow at this point is inferential and circumstantial: fluid accumulates in the lung tissue in pulmonary oedema when outflowing fluid from the blood and the tissue spaces does *not* return to the same tissue spaces. Smoke from a chimney does not "diffuse" upwind, or even (to any significant extent) orthogonally to the wind direction. Cater and others comment (re: their unexpected findings):

It was then realised that two of the basic assumptions made in classical diffusion theory were certainly not valid either *in vivo* or *in vitro. In tissues everything is designed to produce stirring*, pulsation of vessels, deformation of capillary walls by red cells, formation of tissue fluid at the arteriolar end of the capillaries and its absorption

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[85] Haldane and Priestley, 1935, p. 251.
[86] Best and Taylor, 1955, pp. 365ff; Wilson, 1968, p. 3.

at the venous end, concentration gradients which produce osmotic stirring, and fluid streaming of the cytoplasm in the cells. Hudson and Cater (1964) attempted to assess in quantitative terms what effect this stirring might have on the diffusion of oxygen in the tissues. It is equally true to say that it is impossible to abolish all stirring *in vitro* [our emphases].[87]

(The final remark in this passage refers not just to the ineluctability of Brownian motion, but to convective, seismic and other extraneous sources of movement, which can never be completely eliminated in any substantial volume of fluid.)

(b) Numerous bodily secretions of watery solutions (tears, sweat, saliva, intestinal juices, etc.) manifestly *do* depend on cellular activity and can be locally or neurally controlled. So long as "secretion" is interpreted generally (i.e. meaning only "an effect of cellular activity," not necessarily implying "creation of an uphill concentration gradient"), Haldane's findings might be explained as follows. As the oxygen demand of the body increases, so does the secretion of *water* through the alveolar cells into the tissue spaces and capillaries. The more water flows through the alveolar tissue, the more oxygen can be carried. Oxygen depletion in any tissue alters the dynamics of the blood vessels, increasing the blood flow rate through the capillaries and the permeabilities of the capillaries to water. In other words, oxygen depletion *does* enhance water movement/secretion. Increased flow through the lungs would ensure increased oxygenation of the blood, but at a lower external $pO_2$, in accordance with the Pikes Peak results. This alternative oxygen *secretion* hypothesis (oxygen secretion is entrained in water secretion) is consistent with experimental physiological data.

(c) Haldane's argument coincided with the increasingly influential holistic-materialist perspective in biology; Krogh's mechanistic materialism was already becoming old-fashioned.

More recently, Longmuir has written: "If simple diffusion is the sole mechanism of tissue oxygen transport as proposed by Krogh (1919), it is difficult to see how acclimatization could occur without a reduction in the diffusion coefficient. The kinetics of oxygen transport cannot be explained by passive diffusion alone; a search for other mechanisms led to the observation that all the kinetic data could be explained by channels in cells along which the oxygen *diffuses faster than in water*. Vanderkooi and Callis (1974) have shown that oxygen moved along membranes about six time as fast as

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[87] Cater and Silver, 1961, p. 512; see also Hudson and Cater, 1964, pp. 247–258.

through water."[88] Yet there is nothing in the symposium volume from which this passage is taken to show the effect of fluid (water) flow on gas transport, and certainly no such questioning of the diffusion concept has reached the authors of physiology textbooks. Some such works contain obviously flowed statements about the matter. For instance, Best and Taylor assert that transport of oxygen from capillaries to tissues is "the reverse" of its transport from alveoli to blood stream, neglecting the simple but crucial fact that the former process is a liquid-to-liquid transfer and the latter a gas-to-liquid.[89] Any first-year physical chemistry undergraduate would be aware that these processes must be mechanistically different. The argument implicit in some textbooks is slipshod, *viz*: (i) arterial oxygen never rises to (reliably) higher concentrations than the (estimated) alveolar levels (true); (ii) therefore blood is oxygenated from the air by diffusion (a *non sequitur*); (iii) therefore tissues are oxygenated from the blood by diffusion (very much a *non sequitur*).

This discussion suggests four possible explanations for the persistence of diffusion theory in biological gas transport. First, individual incidents might affect the reception of ideas; the reaction to Barcroft's accident perhaps helped significantly to turn opinion against the "secretion" hypothesis. Second, diffusion theory was able to generate mathematical models and quantitative predictions. Although these were unsound in principle, they might have persuaded physiologists of the greater "scientific soundness" of the diffusion hypothesis as compared to its rival. Third, the special connotation of the word "secretion", invoking the notion that it necessarily entailed movement against a gradient, prejudiced at least some physiologists against the idea, Barcroft and his colleagues, and the Kroghs, being obvious examples. Imprecise implications in the meaning of words, including ill-chosen ones, must exert a subtle but powerful influence on the reception of ideas. Fourth, a new generation, their changing focus of scientific interest and an accompanying philosophical transition in early twentieth century physiology, diverted attention away from the issue of gas transport.

*Cell Membranes*

Another reason for the persistence of diffusion theory in twentieth century biology concerns the way in which our understanding of cell membranes developed. Ironically, it was a student of Krogh, Hans Ussing, who gave the first systematic and generally-accepted molecular level account of a "secretion" process in biology, but his concept arrived on the scene *after* the establishment of a diffusion-based model of membrane transport. Ussing

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[88] Longmuir, 1987, pp. 252–276.
[89] Best and Taylor, 1955, p. 365.

defined the term "active transport", which *does* mean the creation of a genuinely "uphill" concentration gradient.[90] [Strictly speaking, active transport moves material not against a concentration gradient but against an *electrochemical potential gradient*, i.e. energetically uphill. Usually, however, the movement is indeed against a concentration gradient. The use of radioactive tracers, crucial to Ussing's analyses, had been pioneered by Krogh.] Active transport is now an accepted part of biological knowledge, and individual active transport mechanisms are frequently the objects of research. This is another instance of the diversion of scientific attention. Ussing's work led to a virtual abandonment of the study of simple, physical, passive diffusion at the cell level (which involves no particular biological components) to complicated, *biological* active transport (which does involve such components and is therefore, in the estimation of biologists, worth investigating). The dialectic of physicochemical and biological ideas across four generations of scientists (Ludwig, Bohr, Krogh and Ussing) is an interesting topic to ponder.

Ussing's "active transport" occurs at the level of individual cells. It moves substances from the outside to the inside of the cell (or vice-versa) across the cell surface, the *membrane*. The idea that cells have membranes, regulating the passage of materials and thereby regulating cell composition, matured in the 1890s. Sir Charles Overton found that water-soluble dyes entered cells less readily than fat-soluble ones, and coined the idea of a "*lipoidal membrane*" at the cell surface.[91] Some years later, Collander and Barlund compared the rates at which substances enter cells with their relative solubilities in fat and water, and purported to show that the permeation rate increases according to fat-solubility.[92] Collander in particular had performed a number of distinguished studies on permeation rates in physical systems, but in his paper the argument is badly flawed. Their data *actually* show that relative fat solubility is only one factor, and a fairly minor one, in the determination of membrane permeation rates. The defect of interpretation was not emphasized at the time, and the Collander-Barlund study became a much-cited argument in favour of the "lipoidal" nature of the cell surface, and *a fortiori* a crucial ingredient of the first detailed model of cell membrane structure, developed by Davson, Danielli and Harvey in the early 1930s. According to this model, the membrane is essentially a two-molecule-thick layer of lipid, punctuated by narrow water-filled pores, and coated with a layer of protein to give it low surface tension and mechanical stability. The essential feature of this model is its *passivity*. Passage of materials across such a membrane by passive physical

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[90]  Ussing, 1949, pp. 43–56; Ussing, 1949, pp. 127–155.
[91]  Overton, 1899, pp. 88–135.
[92]  Collander and Barlund, 1933, pp. 1–48.

processes should correspond to the findings of Overton and of Collander and Barlund, and there is no need to posit any specific biological activity.

It was not that Danielli and his colleagues accepted classical diffusion theory uncritically. A few years later Davson and Danielli wrote, "In any real liquid . . . most of the molecules whose diffusion is studied are of the same order of magnitude as the solvent molecules, and, for reasons that were presented above, diffusion is intermittent in character. Fick's equation, therefore . . . is of approximate accuracy only. It is fortunately the case that if we measure diffusion across a solvent layer of thickness very large compared with the diameter of the diffusing molecules, Fick's equation holds within very precise limits [*sic*]. When, however, we are dealing with a thin layer or membrane . . . Fick's equation is only roughly true. . . ".[93] The "reasons presented above" were amongst those that we have discussed elsewhere and mentioned in the second main section of this article; the phrase "intermittent in character" means that Fick's *assumption of a continuous gradient is significantly inaccurate*. Nevertheless, careful and critical as Danielli was, he did not doubt that membrane transport is essentially a passive, physical process. His background was in chemistry, though his co-author Davson was a physiologist. At the beginning of this same book, Davson and Danielli stated that

> . . . substances fall into two main groups: (a) substances which diffuse according to the laws of thermodynamics, only from a region of higher to one of lower concentration (chemical potential), so that in the final equilibrium condition the substance is in the same concentration on both sides of the membrane; (b) cases where the laws of thermodynamics are apparently broken and molecules accumulate on one side of a membrane . . . we at once infer that in such cases we are concerned with the supply of energy for the transport of molecules . . . *The former group of substances is much the larger, and details of the mechanism whereby these substances pass through the cell membrane are now fairly well known* [our emphasis].[94]

It is interesting that classical thermodynamics, not kinetic theory, provides their explanatory perspective; there is no mention of the Einstein-Smoluchowski model, any more than in Krogh's work. However, Danielli and his colleagues seem to have applied Occam's Razor to the issue of membrane transport, i.e. why postulate anything more exotic than diffusion if there was no compelling *need* to do so? They had in effect predicted active transport for a minority of substances (the second class) before Ussing's work became part of our knowledge base. When Ussing published his work and the active

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[93] Davson and Danielli, 1940, p. 53.
[94] Danielli and Davson, 1935, pp. 1–2.

transport concept was established, it was assimilated into the Davson-Danielli model of the membrane without fundamentally changing that model. All that was needed was to posit that one or more the mysterious membrane proteins could "open" and "shut" a pore and suitable size at the expense of cellular energy, and the model was saved. Thus, the first experimentally demonstrated "secretion" processes in cells were pictured as mere adjuncts to a physical apparatus that operated primarily by diffusion.

The inadequacy of the Davson-Danielli model in descriptive terms was certainly offset by its *heuristic* value. It had served as an explanatory device in cell physiology for about thirty years, though recognition of its shortcomings steadily grew throughout this time, and it was the inspiration (or the target) for many informative experiments. Given this deficiency, and at the same time recognizing the importance of "secretion" (as opposed to "diffusion") processes in regulating cell composition, why were these problems not recognized earlier than 1930? But in a sense, they had been. For example, the observation that intracellular potassium concentrations are generally much higher than extracellular ones evoked some remarkable attempts at physico-chemical, as opposed to specifically biological, explanations; the intellectual gymnastics involved sometimes bordered on the grotesque: "If only osmosis and thin cell membrane permeability were involved the sodium contents of living matter would greatly exceed in amount the potassium . . . [Therefore] permeability and osmotic pressure are considerably affected by ionic mobility, which plays an important role in determining the inorganic composition of living matter."[95] "Ionic mobility" is a "measure" of how fast a particular ion can move in a particular medium; but there is no unequivocal way of measuring it, and the supposition that two such closely similar ions as sodium and potassium would move at vastly different rates in the same medium is, to say the least, unlikely. At the time this remark was made (1930), there was simply no coherent way of explaining the divergent ion contents of the compartments of living matter They were noted, but the automatic response to them was to find some sort (indeed, any sort) or physicochemical explanation. As it turned out, they could not be assimilated into a body of theory until Ussing's achievement reached public notice; however, by then the Davson-Danielli model of the membrane was firmly entrenched.

The modern conception of the membrane retains the lipid bilayer proposed by Danielli and his colleagues, but gives the protein components a more organized structure and a more dynamic role.[96] The earliest version of this *fluid-mosaic model* dates from around 1970. It emphasizes the capacity of the proteins to fulfil *specific* transport (and other) functions, but does not deny the

[95]   Burton, 1930, p. 677.
[96]   Singer and Nicolson, 1972, p. 720.

reality of diffusion processes. It was presented as an updating of the Davson-Danielli model made in the light of improved understanding of membrane protein organization. This presentation acknowledges the vulgar belief that science progresses by the gradual accretion of knowledge: "The fluid mosaic model has evolved by a series of stages from earlier versions. Thermodynamic considerations about membranes and membrane components initiated, and are still central to, these developments."[97]

In fact, the Singer-Nicolson model is fundamentally different in spirit from its earlier counterpart, despite same superficial similarities. It is a "secretion" model, in which the membrane proteins are accorded specific dynamic roles, whereas the Davson-Danielli model was a diffusion model, a contrast was rendered almost invisible by the assumption that the later model was no more than an update of the earlier one. But this discussion suggests further reasons for the persistence of diffusion theory in biology:

(a) Occam's Razor – sometimes a blunt and potentially dangerous instrument rather than a fine dissecting tool – would lead us to prefer a simple (e.g. physical) explanation over a more complex (e.g. biological) explanation for a phenomenon in which both are possible.

(b) Scientists too infrequently concern themselves with the history of science. If they also continue to believe, and teach, the old positivist notion that science progresses only by the accumulation of facts (which occasionally requires and adjustment of perspective and of inherent assumptions), then we may see why once the Davson-Danielli idea that membranes are primarily passive diffusion sites was established, it could not easily be uprooted. More elaborate information was simply superimposed by Singer and Nicolson on an existing, basic framework of explanation. After this, the original idea might be modified, but here *it was never explicitly repudiated*. Any substitute (innovative) model would have required a massively persuasive body of supporting evidence.

(c) An accident of history aggravated the situation. The Collander-Barlund studies and the Davson-Danielli model were published before Ussing had demonstrated the reality of active transport. If the order of events had been reversed, then the notion that membranes are influenced primarily by diffusion rather than by biological processes might never have been established; but this is surmise.

A few years ago, the lipid layers of the membrane were regarded as functionally homogeneous, and indeed passive, entities. It is now clear that they are no such thing: the sorting and placing of lipids is a highly elaborate and

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[97]  Singer and Nicolson, 1972, p. 720.

as yet incompletely understood process.[98] Each protein associated with the cell membrane has a distinct function appropriate to its location in space. The activities of structures so information-rich as these cannot be described adequately, and thus even thought of, in terms of a simple physical process such as diffusion.

*Cell Structure and Metabolism*

Perhaps the "accident of history" by virtue of which Collander-Barlund studies and the Davson-Danielli model predated Ussing's description of active transport was not entirely "accidental." Ussing could not have performed his studies until some idea of the source of "cellular energy" had been established, and this was achieved only through the painstaking work by which our knowledge of intermediary metabolism was constructed. It would go beyond our remit here to enter into a detailed account of the history of metabolism. Suffice it to say that it occupied most leading biochemists for the first half of the twentieth century, and involved the application of organic-chemical concepts and techniques to extracts of cells or slices of tissue. In general, this colossal research effort showed that energy is derived from foodstuffs by means of their step-by-step conversion to carbon dioxide and other waste products. Initially, most of this energy is liberated, again step-by-step, in the form of "energetic electrons." Subsequently, these electrons are transferred to oxygen molecules, forming water as a further waste product. In the process the energy from the electrons is "trapped" by the attachment of phosphate to the compound adenosine diphosphate, making adenosine triphosphate (ATP). ATP, in turn, becomes the source of energy for cellular activities: contraction of muscles, cell movement, heat production, synthesis of the cell's chemical compounds, luminescence in animals such as fireflies and glowworms, *and active transport*. But since this picture did not *start* to become clear until the 1930s, Ussing could not have established the mechanism of active transport much earlier than he did.

However, the study of metabolism had more direct effects on the entrenchment of diffusion theory in biology. The entire exercise was predicated on the necessary presumption that the internum of the cell was largely unstructured. This point was seldom made explicitly; cell structure was simply ignored (with a few exceptions) because the interest of researchers was focused on chemical reaction sequences. However tacit the presumption, it was inescapable. The concepts and techniques of organic chemistry, indispensable in studying metabolism, related exclusively to homogeneous solutions, not to multiphasic, structured systems. If the cell were other than a "bag of solution,"

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[98]   Jacobson and Dietrich, 1999, pp. 87–91.

organic chemical approaches could not be applied to it and metabolism could not be elucidated. Many details of intracellular structure had already been seen by light microscopists in the late nineteenth century, which should have established that the cell was not an unstructured bag of solution.[99] However, the pioneers of biochemistry at the turn of the century seem to have turned their backs on this evidence. The so-called internal structures of the cell were seen as artefacts caused by fixing, drying and staining material for microscopy, and were not parts of the living material itself.[100] The compromise notion that the interior of the cell was a "colloidal solution," i.e. a solution of large molecules and molecular complexes that could sometimes take on the characteristics of a gel, quickly became established.[101]

The effect of colloidal solutes on the distribution of water and electrolytes was analyzed by Donnan on the basis of classical thermodynamics. Because of the net charge on the totality of intracellular colloids, Donnan predicted from theory that small positive ions such as potassium will equilibrate to higher concentrations inside than outside the cell. This prediction matched experimental findings, and accounted for the electrical potential gradient across the cell membrane that is essential for the conduction of electrical impulses in nerves and other excitable tissues.

Otto Warburg, one of biochemistry's great pioneers, was the first to address the question of how the cell uses oxygen. Warburg and his colleagues ultimately characterized the system to which we have alluded (the transfer of energized electrons to oxygen and the concomitant production of ATP). In 1912, however, early in his research, Warburg published a disturbing discovery: oxygen utilization requires structural elements in the cell – a solid phase.[102] (We now recognize these structures as *mitochondria*, which had been described by light microscopists two decades before Warburg's publication.) This finding did nothing to prevent the application of physicochemical concepts to cellular activities. In 1930, for example, the Nobel Prize-winning muscle physiologist A. V. Hill wrote, "so long ... as membranes are not present to interfere with the free play of molecules and ions ... electrolytes will ionize, buffer substances will react, reversible reactions will proceed to equilibrium, just as they do *in vitro* ... ."[103] Twenty-six years later, Hill had transmuted his mechanistic persuasion into something akin to Bohr's (and Haldane's) view of the correct approach to biological explanations.[104]

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[99]  Porter, 1984, pp. 3s–12s.
[100]  Fisher, 1899; Hardy, 1900, pp. 158–210; see also Ostwald, 1909; translated 1912.
[101]  Donnan, 1911, pp. 572–558; Hardy, 1912, pp. 601–610; Kruyt and Overbeek, 1962.
[102]  Warburg, 1912, pp. 277–291.
[103]  Hill, 1930, p. 672.
[104]  Hill, 1956, pp. 1233–1237.

By implication, the cell is a simple physicochemical system in which processes such as diffusion account for movements of molecules and ions from place to place. [The caveat about membranes entered by Hill refers specifically to Warburg's finding; in a continuation of the same passage, Hill remarks, citing Warburg's paper, that "it is only when solid structural elements are present that biological oxidations occur."] Significantly, and in contrast to earlier findings, Hill claimed that practically all the water inside the cell was "free" rather than "bound," i.e. available to act as a solvent and as a medium for diffusion.[105] But Balcar and his colleagues had found much intracellular water was in a bound state,[106] and had discussed the possible biological implications of this; and in this context the writings of Gortner should be consulted.[107]

Since the implication of these ideas was that the cell internum does, at least in part, behave as a gel, then diffusion through gels became an important subject of study, and was duly studied by Bigwood.[108] He noted that not only is diffusion in gels highly dependent on the absolute concentration of diffusing substance (in contrast to the prediction of classical diffusion theory that diffusion rates depend only on concentration *gradients*), but that it is both slow and unpredictable, particularly when the gel is made of protein, as the gel state of the cell interum must be: "The diffusion of ions in gelatin gels is always a very slow phenomenon when the concentration of diffusing ion in different regions of the gel ... the gel swells reversibly, altering concentration or activity gradients ...."[109] And this was a study of diffusion of simple electrolyte solutions! However, such historical notes of caution went largely unheard. Metabolism required enzymes in solution. To reach its enzyme, any substance to be metabolized had to diffuse through the cell. After the reaction, the product had to diffuse away again to encounter the next enzyme. This indispensable perspective in the study of metabolism allowed no space for studies such as Bigwood's; implicitly, the cell internum *could not* resemble a gelatin gel in its physical properties. Oddly, there seems to be no citation of Bigwood's work in the biochemical or physiological literature of the 1930s.

In this discussion, we have seen yet more aspects of the entrenchment of diffusion theory in biology. There was a genuine urgency about the investigation of metabolism. The new discipline, biochemistry, was designed to answer some of the most pressing questions of experimental physiology, agri-

[105] Hill, 1930, pp. 9–22.
[106] Balcar et al., 1919, pp. 116–128.
[107] Gortner, 1929, Chapter 8.
[108] Bigwood, 1930, pp. 700–719.
[109] Reiner Peters, 1986, pp. 305–359.

culture, and the brewing industry. The investigation of metabolism required the concepts and methods of organic chemistry. These could only be applied to unstructured solutions. The cell had therefore, historically, to be portrayed as an unstructured solution. That being so, all elementary physicochemical processes that occur in unstructured solutions – including diffusion – were presumed to take place in the cell in order to maintain the validity of the model.

The logic was inescapable; and because we, in more recent times, benefit from the contribution to the understanding of metabolism that those early biochemists achieved, we accept, along with that understanding, their presumption that diffusion occurs in the cell internum. It is fascinating to observe how the organic-chemical perspective of the biochemists successfully excluded all uncongenial findings: they dubbed the light microscopic studies as artefacts; the requirement for solid structures in biological oxidations was reduced to a parenthetic acknowledgement (Warburg's work being far too important to ignore); they ignored evidence for bound intracellular water, and likewise ignored studies on diffusion through gels (and the difficulties to which they gave rise). Such selectivity imposed by their theoretical perspective proved, as it so often does, a key factor in the historical development of scientific beliefs about diffusion. There is indeed a "veil of theory over the face of nature." This is further seen in, for example, the long-held view that diffusion constraints limit the size of cells, which we have specifically dealt with elsewhere.[110]

## The Survival of Diffusion Theory in Biology

We consider that the three issues we have selected and analyzed (the secretion/diffusion controversy in oxygen transport, the model of cell membranes, and the assumed character of the cell internum developed during the pioneering studies of metabolism) suffice to show some of the main reasons why diffusion theory became entrenched in modern biological thought and survived the philosophical transition from mechanistic to holistic materialism. However, this tells us very little about the extent to which the idea of diffusion survives in biology today, or *why* it is that it still survives (although a considerable change has occurred in the general attitude towards diffusion since we have been writing on the subject, i.e. over the last 10 years). Nor does it put the history of diffusion theory in biology into a contemporary context: what alternative approaches to molecule transport inside cells are now promising to provide more satisfactory explanations? To end, we will briefly consider these two topics.

[110]   Agutter and Wheatley (in press).

*The Attractions of the Diffusion Concept*

Although some modern textbooks still seek to apply classical diffusion the-
ory to biological systems, others seem to use the word "diffusion" merely
to denote undirected molecule movements that (apparently) do not involve
any specific biological machinery. In other words, they are using the term
in a commonplace (vernacular) sense without connoting the applicability
of Fick's Law or any modification thereof. It seems to us that although
the word "diffusion" is harmless in principle when used in a qualitative
sense, it has deeply entrenched quantitative overtones that render it always
at least potentially misleading, as we have mentioned earlier. As a thorough
review of the intracellular transport field in the 1980s showed,[111] calculations
of "diffusivities" and "intracellular viscosities" from experimental data are
commonplace. Such calculations do *presume a quantitative understanding of
diffusion rather than the qualitative use of the word*, so mathematical theory
still survives in cell biological practice.

This brings us back to the problem we delineated in the introduction to this
paper, the problem that motivated our historical investigation. Why do we still
continue to teach (and use in research) an explanatory idea which is inapplic-
able to the cell internum? While we cannot offer a definite answer, some of the
following comments based on discussions with many professional colleagues
might be considered reasonable, but their status is anecdotal. First, diffusion
theory is intuitively plausible, little more than a mathematical formalisation
of common sense. Second, as remarked earlier, it has enjoyed striking success
in a number of scientific fields, so it has a good track record. Third, because
it involves no explicit assumptions other than those of statistical mechanics,
it is immediately attractive as the "default option" when there is no obvi-
ous specific or "biologically interesting" explanation for the movement of a
molecule in a biological system. Fourth, for those whose experimental work
involves dilute aqueous solutions of substances of biological origin, diffu-
sion is indeed a phenomenon encountered daily in the laboratory (although
many effects attributed to diffusion can be largely convective movements and
vibrations).[112] Fifth and not least, it is easy to teach and it forms an attractive
pedagogical basis on which to erect a study of biological processes, such as
active transport.

Collectively, these comments amount to the claim that the only funda-
mental fault with diffusion theory in biology is that it is an oversimplified
account of cellular transport processes; an idealisation analogous to, say,
the "frictionless surface" of mechanics. We must emphasize that this is not

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[111]   Agutter et al., 1995, pp. 261–272.
[112]   Robinson and Stokes, 1956.

our view. The idealized frictionless surface is a mathematically manageable model; it has heuristic value for understanding the behavior of ballbearings rolling down a smooth inclined plane; just consider in contrast, however, its heuristic value in understanding the movement of an irregular piece of polystyrene over a rough convoluted surface in a draughty room. Idealized models have scientific value, but only *within reasonable limits*. Similarly, diffusion is mathematically manageable; it has heuristic value for understanding transport processes in the cell internum, unless perhaps we are looking at a dead cell. Any such application lies well outside the limits of diffusion theory and is simply misleading.

*Alternative Perspectives*

Granting that "diffusion" is not an acceptable way of explaining intracellular molecule movement, let us briefly consider alternatives. This is a scientific issue rather than a historical one, but to ignore it altogether would suggest that our paper was wholly negative. We re-emphasize that our concern is not with *specific* transport processes in cells; membrane transport systems, the movements of materials by the cytoskeleton, exocytosis and endocytosis (the processes of bulk export of material from and import of material to a cell), the partitioning of proteins to different subcellular compartments, events at the nuclear pore and so on, are all currently productive fields of research. Our concern is rather with the movements of molecules in cells that occur without the involvement of any specific mechanisms, movements traditionally ascribed to "diffusion."

A convenient point of departure, because the publication was more or less contemporaneous with many of the event discussed in Part II, is a 1930 lecture by Sir Rudolph Peters. "Extreme order has to be reconciled with a fluid anatomy ... this cannot be done adequately without borrowing conceptions from physiology, and especially from neurology. The cell must be considered as a reflex entity, structurally organized so far as even its chemistry is concerned, with chains of chemical substances acting as it were as reflex arcs ...."[113]

Notice the recognition that this outstanding biochemist gives to earlier (and generally-neglected) microscopic studies, and his willingness to apply a holistic-materialist perspective on the cellular and subcellular levels of organization. He pictures the cell as an integrated assembly of fluid and solid parts, *a sensitive mosaic*. Later in the same article, Peters says: "Our mosaic may radiate its effect throughout the cell. It is ... perfectly possible to appreciate how a coordinate structure may be maintained in a medium which is apparently liquid. This theory is all that is needed to enable us to

[113] Rudolph Peters, 1930, pp. 797–807.

understand how substances can reach a special site in the cell. Between our chains of molecules, fixed by their radiating webs, there will exist paths from the external to the internal surface, the *capillaries* of the cell."[114] Implicit in the remarkable words of Peters is the possibility of two kinds of intracellular transport: one along the solid structures, the "chains of molecules, fixed in their radiating webs"; and one through the liquid paths defined by this web, through which liquid can flow, the "capillaries of the cell." We believe, as Peters implies, that two models of intracellular transport are needed: a solid-state model, which accounts for the movements of macromolecules and assemblies thereof; and a perfusion/flow model, which will account for the movements of small molecules and ions. We have already published outlines of these ideas, and work on the development of quantitative models continues.[115] The structured nature of the cell internum is apparent from any modern cell biology textbook; some impression of the history of our understanding of its structure can be gleaned from Porter and some of our own writings.[116] As for the ubiquity of fluid flow in living systems, it is well attested, and there are very few biological barriers that are impermeable to water.[117]

Physicochemical data can be obtained from living systems, but the whole corpus of modern cell and molecular biology makes it clear that such data can seldom, if ever, be interpreted in the same way as in non-living systems.[118] Yet the temptation of reductionism persists. The dream of the mechanistic materialists, that physicochemical data can and should be interpreted in precisely the same way irrespective of whether the system is living or non-living, remains seductive. And it is in the context of that dream that diffusion theory still survives in biology. Perhaps we have yet to fully appreciate the message of J. Z. Young: "the more we come to know of the flux of chemical changes in the body, the more one great weakness of the machine analogy stands out. The concept of a dynamic organization, such as that of a whirlpool, demands a consideration of time – of before and after and of gradual development and change of pattern, but the machine models of physiology allow no place for this element."[119] In the tissue spaces, as well as inside the cell, there is fluid circulation amongst solid-state elements. There is no reason to suppose that the alternative models we are elaborating should not be applied generally in biology.

[114] Rudolph Peters, 1930, p. 806 (authors' emphasis).
[115] Wheatley, 1993, pp. 181–188; Agutter and Taylor, 1996, pp. 21–52.
[116] Porter, 1984, pp. 3s–12s; Malone, 1981, pp. 1477–1488; Malone, 1981, pp. 1489–1502; Wheatley, 1985, pp. 299–307; Agutter, 1991; Agutter, 1994, pp. 849–858; Clegg and Wheatley, 1991, pp. 504–513.
[117] Wheatley and Clegg, 1994, pp. 83–92.
[118] Polyani, 1986, pp. 1308–1312.
[119] Young, 195, p. 146.

In Haldane's late work, the following passage, like that from Peters (above), provides a precedent of our way of thinking:

> When we take a broad general view of the phenomena of life, one of the most fundamental facts that appears is that the composition of each organism is distinctly specific. ...substances must be present in some kind of combination in the living "substance"; *and if so the living substance cannot be regarded as a mere solution of free molecules.* The molecules are in some sense bound, as they are in a solid; and in so far as this is the case the living substance must in certain respects behave as a solid, *impervious to the free passage of material by diffusion* ... But, consider how a gas could not pass "forward" through an ordinary solid without "diffusion backwards" at the same time ... evidently a living cell does not behave like an ordinary solid: or it is constantly taking up and giving off material, not merely during secretion, but at every moment of its existence ... In the secretion of oxygen and many other substances such as water, sugar, urea, salts, etc., the substance taken up in one form at one side of a cell is given off in the same form at the other side. We have no reason to believe that there is any fundamental distinction between the taking up and giving off during respiration and during secretion. Müller (1830) regarded secretion as akin to growth, a theory bound up with his vitalist physiology: *the clue at which he was grasping was swept from the hands of physiologists by the wave of mechanistic speculation which passed over physiology about the middle of the last century* ... [our emphases].[120]

Though this passage relates to issues that were particular to Haldane's interest, his rejection of mechanistic materialism, total and wholehearted, coincides so closely with modern biological thought that it seems strange that theoretical biologists have allowed diffusion theory to survive unchallenged for so long. Considering the criticisms in our analysis in this article and elsewhere, there is certainly no reason to suppose that classical diffusion theory, or any of its offspring, will play a significant role in our understanding of biology in the future.

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[120] Haldane and Priestley, 1935, p. 251.

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