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THE ABRAHAM FLEXNER LECTURES

SERIES NUMBER TWO



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SERIES NUMBER TWO

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# TO REMIND A BIOLOGICAL ESSAY

by

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PUBLISHED FOR VANDERBILT UNIVERSITY

by

THE WILLIAMS & WILKINS COMPANY

BALTIMORE

1934

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*Made in the United States of America*

Published July, 1934



COMPOSED AND PRINTED AT THE  
WAVERLY PRESS, INC.  
FOR  
THE WILLIAMS & WILKINS COMPANY  
BALTIMORE, MD., U. S. A.



## THE ABRAHAM FLEXNER LECTURESHIP

**T**HE Abraham Flexner Lectureship was established November 22, 1927, in the School of Medicine of Vanderbilt University through the generosity of Mr. Bernard Flexner of New York City. An adequate endowment was provided, the income from which is used to secure as lecturer at intervals of two years some eminent physician or scientist who has made a definite contribution in the field of medical science or some science allied with medicine.

This Lectureship was created in recognition of the great service which Doctor Abraham Flexner, as Secretary of the General Education Board, rendered to medical education through the reorganization and development of the new School of Medicine of Vanderbilt University. Mr. Bernard Flexner wished in this way to permanently associate his brother's name with the institution which he had so generously helped to establish and improve.

The significant objective of the Flexner Lectureship was to contribute to the maintenance of those ideals and standards of scholarship in medical education and research which will bring increasing honor to Vanderbilt University and to the memory of Abraham Flexner. The Flexner Lectureship will also be of value in the develop-

ment of cultural interests in medical education and high ethical standards in medical practice.

It was thought that these purposes could be best accomplished by having some eminent physician or scientist remain in residence, biennially, for a period of two months and become associated with the teaching personnel and students of the respective departments. The first series of lectures was given during the session of 1928-1929.

The formal lectures will be published in serial volumes by the University authorities and this should afford a means of extending the influence and scientific value of the Lectureship.

JAMES H. KIRKLAND.

## FOREWORD

THE second series of the Abraham Flexner Lectures was delivered by the late Sir William Bate Hardy at the Vanderbilt University School of Medicine during the months of February and March, 1931. Sir William was a distinguished scientist whose profound insight into the fundamental nature of the phenomena he investigated gained the unquestioned recognition of scientists and scientific organizations. Although he was primarily interested in research, his vision and balanced judgment nevertheless created a demand for his services as an administrator.

In his own college, Caius College, Cambridge, England, he was Fellow, Tutor, Director of Studies, and Member of the College Council. He was appointed Demonstrator of Physiology and later University Lecturer in Physiology. He was a Fellow of the Royal Society, and served as a member of its Council and as its Secretary. During the World War the Royal Society appointed him Secretary of the Food Committee and the British government appointed him Chairman of the Food Investigation Board and Director of Food Investigation. He was also Chairman of the Advisory Board on Fishery Research. Later he organized and became Director of the Low

Temperature Research Station in Cambridge. In recognition of his scientific work he was the recipient of several prizes and received the honorary degrees of Doctor of Science and Doctor of Laws from several British Universities. Just prior to his death he was honored by election to the Presidency of the British Association.

The charm of his personality, the diversity of his general and scientific interests, his profound learning and the lucidity of his exposition combined to make Sir William an ideal choice as Abraham Flexner Lecturer. The attractiveness of his presentations rested in no small part on the fact that no written manuscript hampered the free ranging expression of his ideas. Among the topics treated in his lectures were: *The Physical Basis of Life*, *The Structure of the Cell and its Physico-chemical Constitution*, *The Chemistry of Living Processes*, *Colloidal Systems*, *The Molecular Physics at Surfaces and Boundaries*, *Physical Concepts of Lubrication* and *The Relation of Low Temperatures to the Analysis of the Dynamics of Muscular Contraction*. This variety in the fields of science, with which he showed himself profoundly familiar, represented subjects which his personal studies had enriched by contributions to their literature. Hardy's ability to make use of the wealth of illustrative allusion with which he clarified and emphasized his lectures can be understood only by a glimpse at his diverse

scientific interests. He was primarily a Zoologist but early turned his attention to Histology and Physiology, in which subjects he did research in the laboratories of Michael Foster. The contemplation of the artifacts due to histological fixation led to his studies on the relation between electrolytes and colloids, which demonstrated the existence of two types of colloidal dispersion, thus giving a new twist to the study of colloidal chemistry and placing him in the fore-front of physical chemists. Hardy's studies of blood proteins, especially the globulins, are notable. In his Low Temperature Station he carried on important investigations concerning *A Microscopic Study of the Freezing of Gel*, and developed the concept of free and bound water. His studies of the *Chemistry of Interfaces* bore fruit on the biological tree in his papers on *Molecular Orientation in Living Matter* and *Electrical Potential in the Living Cell*. These publications illustrate his unique and characteristic drive for fundamental concepts.

Illness delayed Sir William's preparation of his informal lecture notes for publication, and at his death on January 23, 1934, the manuscript of only two essays had been completed. They are presented in this little book under their author's choice of title: *To Remind*. Here Hardy reviews from a modern standpoint some older concepts of the nature of life processes which he felt were

in danger of being forgotten. The charm of style and the freshness of treatment of these topics in the two published lectures arouses the conviction that science has sustained a significant loss in the contingency which preserves his other lectures, dealing largely with his own investigations, only in the memory of those who were fortunate enough to hear them.

W. E. GARREY.

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## Chapter I

IT IS so near the date that I can almost claim to be addressing you on the hundredth anniversary of one of the half dozen greatest syntheses of knowledge. In 1835 Dujardin gave the name 'sarcode' to a kind of plastic homogeneous substance, which he had first identified in his study of the simpler microscopic types, and since convinced himself of its presence in all animals, "at any rate in the young state."

This great generalization—and there can be none greater—for every biologist since his time has built upon the unifying principle that all living things, no matter how diverse their forms, are ultimately composed of a "glutinous" substance which recognizably is the substance of life has been overshadowed by that other great generalization, the cell theory of Schleiden and Schwann. Even his word 'sarcode' has been forgotten in favour of 'protoplasm' the name which Mohl gave to the "slimy granular semi-fluid content of plant cells." The cause is not far to seek. Mohl was a botanist, and whereas botanists continued actively to occupy themselves with the structure of protoplasm, animal physiologists dropped the subject for thirty years.

Their attention was held by other things, for

in the thirties and forties, Liebig was battling with Dumas and his school for a recognition of the wider chemical potentialities of animals, and, with his life-long friend Wöhler, for the patient application of the methods of physics and chemistry to the problems of life in place of an appeal to a 'vital force'.

About two years ago, I had occasion to read Dujardin's papers, and I then conceived so great an admiration for him that I will ask you to let me preface these lectures by an attempt to give him his due.

He was a histologist, to use a word not invented in his time, and unlike many histologists, who perhaps as a clan have not always been as critical as might be, he questioned the reality of the appearances revealed by his microscope. "Are the 'vacuoles' " he asked, "real spaces filled with fluid or not?", and to settle the matter he studied the appearance of emulsions of oil and of air in water, the emulsifying agent being a little saliva.

The capacity for independent movement was then the index of life, and this capacity so puzzled and misled his contemporaries, amongst them the great Ehrenberg, that, like Sterne, they conceived of the simplest organisms as equipped with stomach, muscles, skin and fibres (nerves), even though these were quite imperceptible. Ehrenberg indeed urged that it was simpler to assume

the presence of organs than to account for the power of movement.

Dujardin curtly styled this an abuse of the argument by analogy. Even if the existence of such organs were accepted, the difficulty was not disposed of, for muscle, nerve, etc. must themselves be resolvable into an elementary substance with power of movement. No casuistry, he says, will avail against this "dernier terme."

I should note by the way that he had a clear idea of the presence of cells, for he speaks often of "le tissu cellulaire."

Of course his argument has its logical weakness, there will always be a dernier terme or, as du Bois Raymond put it, nearly half a century later:—to satisfy our craving for causality we have, as ultimate measure, only certain unknowns—these are the limits of our knowledge, and it is not possible to explain a limit just because it is a limit. But, "that fundamental law of human reason" as Schleiden calls, "its undeviating tendency to unify knowledge," will not even then be satisfied—indeed it is less satisfied than ever just now when our scientific philosophers are hesitating whether to be dualists with Plotinus and the Alexandrian school and try to balance two oranges on the tips of their noses, or monists with Empedocles and Haeckel and be content with one.

Dujardin left movement a mystery. "When," he says, "one comes to consider nutrition, which is another form of movement not less real and altogether incompatible with the idea of equilibrium, or the constitution and mode of aggregations of the molecule which compose the living substance, we have to admit ourselves beaten by the difficulties because the problem is that of life itself, which for us will be always insoluble." Those are memorable words.

After Dujardin came a barren period so far as the study of the living substance was concerned, indeed for the English speaking world at any rate the greatness of his generalization remained unrecognized until Huxley's great essay of 1868 on the Physical Basis of Life.

Like all barren periods it was a time of easy certainties and decisive terminology. Then were there 'proximate principles' which were 'organized' in contact with living matter. Of these principles the most important was fibrin of the blood, which was therefore sometimes called the general formative element or 'blastema'. Lecturing must have been an easy business in those days!

It was, however, a time by no means barren in other fields. Liebig, Lawes and Gilbert, Voit, Fick and Wislicenus, Subbotin—these names bear witness to the contrary.

If one were to try to follow the developments

from, say 1870 onward—and there is no time even to attempt a sketch—one would have to deal separately with structure and function. I shall have to content myself with a brief picture of what was taught in active schools of physiology in my time. The date would be roughly in the eighties, and the teacher was Michael Foster.

Living matter was then an entity which took part as a whole in the chemical cycle. For example, the energy of contraction of a muscle fibre was derived from the explosion of a substance to which Herman gave the name 'inogen', but the whole living unit partook in the explosion, not merely a non-nitrogenous part. The nitrogenous part was, however, retained in the structure of the fibre. It became irrevocably involved only when the explosion became irreversible in rigor mortis.

Metabolism—that is the whole chemical cycle—consisted, therefore, of a phase of increasing molecular complexity in which protein, fats and carbohydrates with oxygen were built up into the living substance, and a phase of decreasing chemical complexity and liberation of energy.

The picture of two operations, anabolism and katabolism—or loading and discharge—was based in the first instance on the properties of muscle, especially on its capacity for doing work when not supplied with food or even oxygen, but it received immense support when the processes

of loading and discharge of gland cells was discovered in the late eighties. It has that support still.

The gland cell is continuously engaged in forming the special chemical substances and storing them away in its substance as 'secretory granules'. At intervals, provoked thereto by nervous impulse or other form of stimulus it becomes active, two separate events happen, water and salts are passed through its substance and some of the granules are discharged and the solution so formed is the 'secretion' of the gland. There the process of loading and discharge of the muscle fibre is paralleled.

Surface forces of an unknown nature are not wanting for the secretory granule is ordinarily highly unstable in presence of water. It reacts violently with the water in the protoplasm when the internal dynamic balance of the cell is interfered with: yet in the intact living cell it is held in a medium 80% of which is water, nearly the whole of which, according to modern views, is 'free'.

If muscle fibre and gland cell seemed to function in the same way then a further step could be taken for in the mammary gland a more primitive method of forming a secretion seems to be preserved. There secretory granules are not formed but the gland cell grows and whole pieces of protoplasm slough off to contribute the special

protein and fats of the milk. The case for the participation of protoplasm as a whole, or rather of the cytoplasm seemed a pretty strong one to us in the eighties!

Two properties of living matter were stressed: its endurance only at the cost of continual chemical change and the probability that though at the apex of the chemical cycle was the complex living substance it was not always the same substance. "Since every cell and every part of a cell has its individual character stamped on it by long hereditary action, we see a reason why every bit of protoplasm should be made anew."

If we contrast this period with the modern period in which the physical and organic chemist has taken possession of biology we find that the complete participation of a living unit in metabolism has been dropped and in its place is the study—and the amazingly successful study—of special processes such as the mechanism of oxidation and reduction, of buffering, of the energy cycle of muscle, of permeability. Semipermeable membranes, highly specialized catalysts, highly specialized and complex chemical cycles have replaced the conception of a living unit. But these are only the several parts and the whole is more remote and mysterious than ever.

The position at the moment is indeed curious. The living unit we know is the cell and the body is recognized as an assemblage of cells whose

activities are coördinated—integrated is the more modern word—to a common purpose. The mechanism of integration has been analyzed with much success. We know broadly the integrating activity of the nervous system, and the method of integration by chemical agents, hormones, vitamins and the like. But of the integrating mechanism within the cell we know practically nothing. Once the cell's surface is passed our ignorance is complete; our knowledge, "a matter of gaps and guesses," to quote Foster's words.

The integrating mechanism within the cell is the little cherub which sits up aloft conducting the orchestra. We know he is there, but his features are veiled for he is the Theoria—the mystery of life itself!

Have I exaggerated the mystery? If any one doubt, let him consider the hepatic cell. There is no evidence of specialization in the mammalian liver—indeed the evidence is definitely against it. Any or every cell seems capable of synthesizing glycogen from sugar or from lactic acid, of solving the chemical conundrum:—how to pass directly from carbohydrates to fats and back or proteins to fats, of dealing with metallic poisons, of controlling the chemical cycle of haemoglobin, of synthesizing uric acid, so on and so on. Has the biologist any picture even of the vaguest kind, of how so diverse a chemical factory can operate in a fluid mass, say  $10^{-8}$  cubic millimetres in volume?



Some day it will be necessary to return to the standpoint of the eighties, and to realize that there is some master process, some integrating principle now vaguely but truly spoken of as 'structure' which subdues a galaxy of catalysts to its purpose, and deserves the title 'living'.

I confess when I think of the task of discovering it, I become as pessimistic as Dujardin. Think of the chemical potentialities. Oxidation, reduction, desaturation, alkylation, acylation, condensation, any or all of these processes are carried on, and "any or all of these processes may be brought *de novo* into play as the result of the intrusion of a new molecule" to convert that molecule into something less harmful to the machine. Think of the range of the potencies of living matter—which enables the same portion to become brain or skin according to the impulse it receives from its surroundings, and above all, lay hold of the fact that though the living cell has these powers and has a righting moment which resists change, it often seems helpless to carry on without external guidance.

Putting aside 'biogen', and biological molecules as the extravagances of the enthusiasts, "eccentricities of genius" was Mr. Pickwick's phrase, the view of the eighties was essentially sound. It helped to keep the real end in view.

I am inclined to think the main difficulty the biologist feels in seeing the wood for the trees,

lies in the fact that he is trying to decipher a palimpsest written and cross-written by countless ages, until, like a modern news-sheet, it is all head lines. I don't mean merely that there has been specialization, but something more so that what appears to be primitive and actually is universal, may after all be merely secondary. I can think of no real illustrative analogy, but take a ship, a modern liner with the special complexity of a motor liner with its main and subordinate machinery, and think of the ecstasy of organology an inhabitant from another planet would indulge in before he arrived at the essential unity of the whole, and a ship is a relatively simple thing because it will stay put when it ceases to work, and that is the last thing the living cell will do.

One way of proceeding is to search for properties which are common to all forms of living matter, and assume that they are fundamental and archaic. The process is something like the search for those roots common to different languages from which the parent language might be recovered.

Of course the attempt has been made before, though not perhaps with the same object. In the eighties the list of fundamental properties, and it would not be altered now, ran "contractile, irritable and automatic, respiratory, receptive, assimilative, metabolic, and reproductive."

Now the curious thing about this list is that the one feature which is undeniably archaic, and which is perhaps the only quality for which that claim can be made with certainty is missing. It is the property of defying the laws of probability by producing in an orderly universe asymmetrical molecules.

That, to quote Pasteur, is "the only distinct line of demarcation which we can draw today between dead and living matter." Someone, I cannot recapture the passage, has put it in another way—"two worlds stand side by side, the asymmetric and the symmetric, the world of the quick and the world of the dead."

The presence of asymmetric molecules in a fluid or to be more exact of an excess of right or left handed forms can be detected by the capacity of the fluid to rotate the plane of polarized light. The right and left handed isomerides have the same chemical properties, they differ only in that they possess equal and opposite rotatory power. The existence of a right handed isomeride implies the possibility of the existence of its opposite, the left handed isomeride, just as the presence of a right handed screw implies the possible existence of a screw of exactly similar dimensions which differs only in having a left handed twist.

These *obiter dicta* are justified in a later lecture; for the moment they suffice with one addition that, since right and left handedness leaves the

chemical and physical attributes the same the chances are that right and left handed molecules will be formed in equal quantities when there were present initially only symmetrical bodies and when no asymmetric force acted during the reaction.

“No fortuitous concourse of atoms, even with all eternity for them to clash and combine in, could compass the feat of the formation of the first optically active organic compound. Coincidence is excluded, and every purely mechanical explanation of the phenomenon must necessarily fail.”<sup>1</sup>

That is an extreme statement, the doctrine, shall I say, of the extreme left. I quote it here because it is in the main true, because I want to bring home to you the greatest of the many improbabilities of living matter and because I want to draw from it a momentous inference.

Living matter is still the sole source of optically active compounds. It has within itself asymmetric powers which enable it to produce freely from the symmetric substances, carbon dioxide, water, and ammonia, optically active substances. It seems able to evade an enormous mathematical improbability.

Now if that be true the inference is that the beginning of life was an unique event at any rate

<sup>1</sup> Professor Japp.

in world history. There must have been a definite creative period whose duration does not concern us and whose character in three dimensional chemistry is a mathematical impossibility.

Let me illustrate this by a trivial but actual episode. I recollect how on a stormy morning a boy came late to a certain preparatory school. The boy made excuse that the way was slippery and for each step he took forward he slipped back two. "Then how did you get here?" asked the master, and the boy, having more wit than wisdom replied, "I turned round, Sir, and tried to walk home."

Now that feat is not mathematically impossible but it needs a nice adjustment of effort, of gradients, of coefficients of friction which the fortuitous clash of circumstances is unlikely to produce. It is, in short, an event of such a high degree of improbability that were it to occur one might safely claim the fact as unique.

There follows a second inference. Once the creative period ended what is now called survival value must have begun to operate, and with it three properties; individuality, adaptability and growth or reproduction.

The complement of individuality is semipermeability, of adaptability is metabolism, for it is a moving system which is both capable of change and yet has a righting moment. Living matter could not have appeared simply as a phase sepa-

rating out which might disappear to reappear again. It was an unique production which once lost would be lost forever. To avoid that it must have acquired the capacity to endure in changing states of temperature, radiation, and chemical composition.

Countless workers have explored the phenomenon of optical rotation. Since Pasteur, the whole doctrine of stereochemistry has been founded on it.

“Our knowledge of that aristocracy of chemical compounds which possess, in addition to all the commonplace and vulgar physical attributes, the distinctive seal of nobleness—optical activity”—has been vastly enlarged yet “there still remains a deep gulf between” natural and artificial synthesis. The plant, that mysterious and highly complicated laboratory, produces from the simple inactive constituents of the atmosphere and the soil within a very limited range of temperatures moreover, the necessary carbohydrates, proteins, etc. in their optically active form.

“I know of no more profound difference than this between common substances and those produced under the influence of life’, Pasteur wrote again in 1860 and he was justified.”<sup>2</sup>

Looking at life in its broadest aspect the most

<sup>2</sup> F. M. Jaeger. *The Principle of Symmetry*. 1917.

striking feature is its improbability. What after all is Dujardin's sarcode but a slime, containing 80 per cent of water, the rest composed of highly unstable chemical substances? Once the unknown principle we call life is lost the slime is rapidly dispersed into its elements, yet this weak formless matter has seen the hills themselves come and go!

How it contrives to endure now is easily seen. Sarcode covers its nakedness with a coat as stable as it itself is unstable of wood, horn, silica, or lime salts and, so withdrawn, it fashions for itself a stable environment of buffered solutions, even of stable temperatures. In suitable surroundings it persists as tiny units each sheltered by a cunningly contrived film of semipermeable matter and multiplies in its countless millions and even then it has the capacity to shift its form to even smaller units, each armour clad and produced in even greater numbers. But these chemical and physical shifts, to escape what would appear to be an obvious fate, must be secondary devices. Living matter cannot have come into being with them at its command. We can argue the uniqueness of the creative period from the primitive defenselessness as well as from the improbability of the synthesizing of the asymmetric molecule which is its characteristic possession.

That it exists at all is the great improbability

but there are minor ones. The very foundation of life as we know it now is an improbability of the first order for in the first photo-synthesis of carbon dioxide and water to formaldehyde the chloroplast contrives to catch and hold three quanta at once and in this it is unique for no known endothermic photo-chemical reaction involves more than one quantum. The chances of even two quanta being absorbed simultaneously by the same molecule are so small as to be negligible.

Having come into being, how 'in the dark backward and abyss of time' did it contrive to commit its future to the keeping of those few substances of no outstanding chemical significance which we call vitamins?

It is indeed a strange type of the things which out of weakness are made strong which can catch the trick of the diffractive grating to fit the birds in a tropic forest with dresses literally of the colours of the rainbow.

If the beginning of life is bound up with molecular asymmetry it is no less indissolubly connected in a strange way with amino acids—a unique chemical group with singular relations to acids, to bases and to salts. It might be argued that the relation of asymmetry, at one time all-important, has lost such overwhelming significance and is now vestigial. The same cannot be said of the amino acid. Bacteria to trees, mon-



ads to mammals, protoplasm is composed of those highly specialized and complex derivatives, the proteins, and the analysis of function throws an increasingly important biological burden upon them. We have only to think of the myosin of muscle, of respiratory pigments or of enzymes to realize this.

I am inclined still to stick to an old heresy of mine which can be put in another way; that with the amino acid group comes in the capacity of living matter to form with electrolytes those complex dynamical systems which are all-important in the living cell. It is at least significant that even in bacteria the proteins fall into two main classes distinguished by their reaction with water and electrolytes, the albumins and the globulins.

The type forms are found where perhaps one might expect to find them in that simplest of body fluids, blood and serum. If I may be excused a personal memory I recollect vividly how, after years spent in the study of blood serum, to change to blood plasma was to move to a world of incredibly greater complexity where any or every reagent produced changes which bewildered analysis. It is of course possible to break down the molecular architecture into classifiable and stable blocks, but it is of the complete structure I speak.

Has not the clotting of plasma been studied



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with some intensity for just on a century—but an acceptable and complete doctrine seems yet a-wanting.

Serum has its curious problems to which I, at any rate, do not know the solution. It is a high grade solution in that it will pass freely through a porcelain filter. Yet it contains a set of substances of obstinate insolubility in water—the lipoids. They are easily separable and are soluble in boiling alcohol but I could never make a beginning of resolving them in serum. It is curious too in the fact that the proteins into which it is separable are usually electrically charged when dissolved but the whole serum seems to be unchanged so long as its internal equilibrium is not disturbed by dilution.

Plasma and serum are however being studied now in a fashion not possible in my time. The patient and beautiful work of Adair has fixed the molecular weight of some proteins with precision—more power to his elbow and those others, his fellow workers in the field.

Proteins are the raw material of protoplasm, the bricks and mortar of which it is actually built up and if we ask how it can fulfil this function the answer in the main is two-fold, on the chemical side it lies in the capacity for building huge molecules with an indefinite number of active polar groups. We know now that the countless different forms of life on the earth base their

differences on the chemistry of the proteins. If we try to follow this up we shall find that it needs as a rough computation twelve digits to express the different kinds of proteins needed to make up the differences in the human race alone. On the chemical side, therefore, this chain of amino acids with its side-chains must be capable of practically an infinite number of chemical variants. With that aspect of the question I am not competent to deal, my interest lies in another direction, the relation to electrolytes, that is the physical side of the question. I leave the chemical side with just one word—the extraordinary stability of living matter. Generation after generation through untold repetitions in the form of successive generations these small structural chemical differences are reproduced and that in spite of the complex cycle from ovum to the completed type.

## Chapter II

"I have in fact set up a theory of molecular asymmetry, one of the most important and wholly surprising chapters of the science, which opens up a now distant but definite horizon for physiology."

LOUIS PASTEUR (1860)

LET us first get certain dates clear for I find I can grasp a subject the more easily if its several stages stand in a framework of time. The dates I take from Pasteur's Lectures of 1860.

In 1808 Malus found reflected light possessed of new and surprising properties which distinguished it from light proceeding directly from a source. He called the change which the light suffered by reflection *polarization* and distinguished the *plane of polarization* of the rays. Malus also proved that the change produced by double refraction when a ray of light is divided into two rays passing through a crystal of Iceland spar was the same as that due to reflection.

Arago in 1811 noticed that, though in general polarized light passed unchanged along the axis of a uniaxial crystal, in some crystals the plane of polarization was rotated. Crystals of quartz had this property and in 1813 Biot described how some crystals turned the plane to the right, others to the left.

It had been known for some time that right

and left handed crystals of quartz could be distinguished and that though the two varieties were symmetrical in a certain sense they were not superposable, just as right and left handed screws cannot be made to coincide.

Herschel in 1820 made the fruitful suggestion that all right handed crystals would rotate polarized light to the right and all left handed crystals to the left.

The step which next concerns us was the great discovery by Biot (1815) that certain natural organic substances rotated the plane of polarization. Such, for example, were turpentine, solutions of sugar, of camphor and of tartaric acid. These substances differed from quartz in a most important particular for quartz to be optically active must be crystallized; in solution or in the solid uncrystallized condition it was without action. The natural organic substances on the other hand were active in solution from which Biot concluded that the optical activity of such bodies was due to the individual constitution of their molecules. It is this molecular asymmetry which concerns us.

For many years chemists had been puzzled by the existence of two forms of tartaric acid, the ordinary form which was dextro-rotatory and a form called paratartaric acid or racemic acid which was optically inactive. Pasteur, whilst still a scholar at the *École Normale* was in his

spare time, as he says, studying the molecular constitution of bodies with the object of finding experimental support for Herschel's suggested connection between crystallized asymmetry and optical activity. He examined the crystal form of racemic acid and found no signs of asymmetry.

At this juncture, in 1844 when Pasteur was in his twenty-second year, Mitscherlich, a Berlin chemist and crystallographer restated the puzzle as follows:—The two forms, tartaric acid and racemic acid have the same chemical composition, the same crystal form, the same specific gravity—in short the same physical features. From these similarities it follows that the nature, the number, the arrangement and the distance of the atoms from one another are the same and yet one is optically active, the other inactive.

This completely upset Pasteur's ideas. How could bodies be other than identical if the nature, the proportion and the arrangement of their atoms are the same? So he decided to investigate the crystal forms afresh, taking, as Mitscherlich had done, the sodium ammonium double salts for the purpose. He set his solution to evaporate slowly in the laboratory and when some grams of crystals had separated he found to his surprise that the crystals of the tartrates were all right handed and the crystals of the racemates were of two kinds, some right handed and some left handed. He carefully separated the right

handed crystals from the left and observed the solution of each in the polariscope and saw "with as much surprise as joy that the solution of the right hemihedral crystals turned the plane of polarization towards the right and the solution of the left hemihedral crystals turned it towards the left."

He went a stage further by showing that when solutions of the same strength, one of the new laevo-rotatory acid and the other of the ordinary dextro-rotatory acid were mixed, they reacted with evolution of heat and a mass of crystals of the inactive racemic acid was deposited.

Here was proof that the optically inactive racemic form was a compound of both acids equivalent with equivalent, and that the atoms of the two optically active acids were arranged in their molecules in an asymmetrical way like that of an object and its reflected image. "Are the atoms of the dextro acid arranged in the molecule as a right handed spiral or are they at an angle of an irregular tetrahedron, or do they have some other asymmetrical grouping?" he asks, and replies—"This we do not know. It is certain, however, that the atoms of the laevo acid possess exactly the opposite grouping. Finally we know that racemic acid arises from the union of two asymmetric groups whose atoms are arranged in inverse order."

This experiment may be ranked as one of the

half-dozen crucial experiments of history—it founded the vast science of stereo-chemistry.

Those who like to toy with the "Ifs" of history have here an opportunity for there was a big element of luck in Pasteur's discovery. The spontaneous fission of a racemate into its unit bodies is a function of temperature and only a limited number of examples has since been discovered. Below  $27^{\circ}\text{C}$ . the sodium ammonium racemate undergoes spontaneous fission: above  $27^{\circ}\text{C}$ ., however, the racemate itself crystallizes out. The transition temperature is, however,  $-6^{\circ}\text{C}$ . What if Pasteur had missed the dissociation as he probably would have done had it not been his habit as he tells us to allow his solutions slowly to evaporate at room temperature?

Symmetry, dissymmetry and superposability need a word of explanation. Standing in front of a vertical mirror if the image of one's body could be rotated through  $180^{\circ}$  and brought forward it would completely coincide with the actual body. The mirror image of a cube or sphere or cone can be made to coincide by simple motion forwards without rotation. But there are geometrical forms which cannot be made to coincide with their mirror image, a right or left handed screw, or an irregular tetrahedron are examples. Such bodies are different from their mirror images. Therefore, and this is the important fact to grasp, the existence of one such means the



possible existence of another which is its mirror image. The existence of a right handed screw means the possible existence of a left handed screw.

It may seem a slight thing whether the atoms of a molecule are on a right or left handed screw or at the angles of a right or left handed tetrahedron. It is, so long as only scalar properties are concerned—so long, that is, as no asymmetrical forces are acting.

Right or left handedness of the molecule does not affect the physical properties of the enantiomorphs (or antipodes—both terms are used). Their specific gravity, melting or boiling points, etc. are identical; they differ only in the fact that they rotate the plane of polarization in opposite directions, and to the same extent, they are endowed with equal but oppositely directed rotatory powers. But when they react with other asymmetrical bodies the influence of asymmetry is profound. Pasteur used a vivid illustration. The two tartaric acids behave in exactly the same way with potash which is symmetric but not with the base quinine which is asymmetric—for example, the solubilities of the two salts, dextro and laevo, are then different. Molecular asymmetry here alters the chemical affinity. “Let us attempt to make this similarity and dissimilarity clear by means of an illustration. We may think of a right handed screw and a left handed screw

as being driven into exactly similar, straight-grained blocks of wood. All the mechanical conditions of the two systems are the same; this is instantly changed when the same two screws are driven into a block in which the fibres themselves have a right or left spiral arrangement."

In the effort to make the position clear I have perhaps given the impression that the effect of asymmetry on the course of chemical change is casual and episodic. It is not; it is quite general. There is a theorem based on the principles of symmetry stated by Jaeger as follows:

When two stereo-chemical arrangements which are non-superposable mirror images  $A$  and  $A'$  of each other are combined in a corresponding way with another stereo-chemical complex  $f$ , also different from its mirror image  $f'$ , the two figures  $Af$  and  $A'f$  thus produced will no longer be mirror images of each other.

The solubility of optically active antipodes and of their inactive racemic compounds is not abnormal, they behave like double salts. When solutions of antipodes are mixed the formation of the racemate occurs with liberation of heat but the phase diagram is peculiar in that it is symmetrical about a line passing through the origin and at  $45^\circ$  to either axis (Bakhius Roozeboom).<sup>1</sup>

When, however, an asymmetric body  $f$  reacts

<sup>1</sup> Zeitschr. f. Physikalische Chem., v. 28, 494, 1899.

with a racemate the diagram no longer has this extreme simplicity.

The ground is now sufficiently cleared for a return to the biological problem—the significance of the asymmetry of living matter.

Protoplasm is not merely asymmetric, its asymmetry is specific. It grows and reproduces generation after generation and its proteins remain laevo-rotatory. The plant cell produces, generation after generation, only dextro-glucose and dextro-fructose.

In the course of a certain disease a pentose appears. It is racemic and the fact is rightly hailed as a portent because racemates in biology are rare.

Bile acids are dextro-rotatory, plants produce alkaloids generation after generation, strychnine, nicotine, etc. with the same optical activity. Lactic acid is one of the most important substances in the chemistry of life, it is a stage in carbohydrate metabolism and in the conversion of proteins to carbohydrate. The biological form is always dextro-rotatory—indeed the laevo-rotatory form is toxic and is excreted for the most part unchanged. When the racemic form is injected into a rabbit it is asymmetrically attacked, some of the laevo-rotatory forms being excreted. Glucose or fructose perfused through the liver is turned into right handed lactic acid.

Yeast ferments only dextro-hexoses, not the

left handed varieties; on the other hand the pancreatic lipases hydrolyze left handed more rapidly than right handed esters. Microorganisms attack right handed and left handed amino acids at different rates; sometimes one kind alone is hydrolyzed.

To follow the chemistry of life is like treading a maze where the paths twist and turn but the twists and turns stay put year after year, generation after generation. The pattern is, so far as human experience goes, fixed for all time. The fundamental synthesis of living matter as we know it—the production of carbohydrates by the green plant—has a right handed twist only dextro-hexoses being formed. Generation after generation adrenaline is left handed and the left handed form has thirteen times the physiological efficiency of the right handed variety. Left handed thyroxine is three times as active as the right handed form.

It is an odd thing that this maze is scarcely mentioned in modern textbooks. I have picked up volume after volume but found the heading 'asymmetry' absent from the index, yet the steadiness of the course, now right now left, unchanged by time, shows that asymmetry is something basic in life.

It cannot be easy to track the maze to whatever may be at its centre for it means an attempt to unravel the tangle of slow adjustments which

practically infinite time has made. "Call on the lazy leaden stepping hours, whose speed is but the heavy plummet's pace!"—the burden is borne slowly by the long procession of years but the end is gained.

Obviously there are two problems, quite distinct, but frequently confused. I am inclined to think that Pasteur himself confused them when in 1860 he said: "I hold the existence of an asymmetric force acting at the origin of natural organic compounds as proven"<sup>2</sup> and in 1871 he wrote: "I believe that there is a cosmic dissymmetric influence which presides constantly and naturally over the molecular organization of principles immediately essential to life."<sup>3</sup>

The first problem is the continued production of optically active compounds in the living cell and the second is the production of the first enantiomorph.

The continuous intervention of an *external* asymmetric force in the one sided synthesis of the living is not needed for the one sided influence is inside the cell in the form of enzymes some of which at any rate are dissymmetric and of asymmetric compounds.

Oddly enough Pasteur himself discovered the process when he gave the first example of split-

<sup>2</sup> Lectures, see Richardson, Foundations of Stereo-chem., p. 31, 1901.

<sup>3</sup> Life of René Vallery Radot. P. 198, London, 1920.

ting a racemate by combining it with an asymmetric body. He allowed racemic acid to react with the dextro-rotatory base cinchonine. Both laevo- and dextro-cinchonine tartrate were formed but the left handed salt was the less soluble and could be separated by fractional crystallization.

Here the presence of an asymmetric body guided the reaction and the discovery suggested to him that the mould absorbed and metabolized the dextro-rotatory tartaric acid and left the laevo-rotatory behind because of a dissimilar reaction of the two antipodes with an asymmetric substance in the living plant.

“There cannot be the slightest doubt that the only and exclusive cause of this difference in the fermentation of the two tartaric acids is the opposite molecular arrangement of the laevo-tartaric acid” and that in spite of the absolute identity of the physical and chemical properties of both “*so long as they are exposed to non-asymmetric influences.*”

Pasteur discovered the process and applied it to a special case, but it was left to Emil Fischer to make it perfectly general.

The theorem quoted on page 26 is the formal answer to the first problem. By its aid we can dimly understand and feebly imitate the manner in which the living cell resolves racemic compounds and even synthesises optically active

bodies from simple materials just as we can dimly understand and feebly imitate the device by which the living cell selects material and controls diffusion into or out of its interior.

Natural synthesis is one-sided because it occurs under the guidance of asymmetric molecules. Fischer supposed that in the most profound synthesis of living matter, asymmetric bodies in the chloroplast combine with carbon dioxide or formaldehyde with the result that the further condensation to sugars proceeds in an asymmetric way. There is something analogous to heredity in the "further progress of dissymmetrical configuration in a series of successive reactions."

Chemical reactions in the living cell do not go to completion; "a state of completed reaction equilibrium is never reached, only a kind of apparent 'dynamical constancy,'" so Jaeger puts it. What this means and the part dissymmetry plays in it can again be dimly perceived.

Enzymes can react at different rates with antipodes in vitro. Zymase ferments only d-glucose, not l-glucose and pancreatic lipase hydrolyzes l-mandelate more rapidly than its antipodes. Hence to explain the preferential attack of yeasts on right handed tartaric acid or hexoses, or the higher nutritive value of polypeptide it is enough to refer it to a twist in the enzymes concerned.

The remarkable thing is that ordinary catalysts can do the trick *provided they are themselves asymmetric.*

Marckwald and Mackenzie<sup>4</sup> saponified the ester of racemic mandelic acid with l-menthol and when the saponification was complete the free acid obtained was the optically inactive racemic form. But if the reaction were stopped after one hour the d-mandelic acid was obtained in excess, therefore the velocity of reaction of l-mandelic acid was less than that of the dextro-rotatory acid.

Bredig and Farjans<sup>5</sup> found that when laevo- or dextro-campho-carboxylic acid was dissolved in the neutral solvent acetophenone with some laevo-nicotine added, the dextro-acid was decomposed 13 per cent faster than the laevo-acid, the products being camphor and carbon dioxide. "The speed of reaction of racemic acid was just intermediate between the values obtained for the optically active components." The same general result was obtained with quinidine as a catalyst, the ratio of the velocity constants being 1.46. In these reactions the bases were not destroyed in detectable quantity nor was there a mass relation between the quantity of the base added and of the acid attacked. There was merely acceleration and the specificity was remarkable. If the bromo-campho-carboxylic acids were used the right handed form was more rapidly decomposed

<sup>4</sup> Ber. d. deutsch. Chem. Gesellsch., v. 41, 752, 1908.

<sup>5</sup> Ibid., v. 34, 469, 1901.



when quinidine was the catalyst and the left handed form when it was quinine.

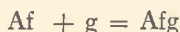
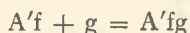
There is again a general theorem which covers these cases. According to it there must be a difference in the velocity of reaction between antipodes when the catalyst is asymmetric, therefore "as soon as a molecule of lower symmetry different from its mirror image has been created in the living cell the (characteristic) one-sidedness of further synthesis is not only fully conceivable but it is even a necessity."<sup>6</sup>

In the living cell reactions occur in series. Take only two steps; the first:



The ratio  $Af/A'f$  that is the relative masses, depends upon time, temperature and concentration. The reaction also occurs in a space with semi-permeable walls whose selective action we are free to assume is also guided by its own molecular asymmetry.

The second reaction is of the form:



in which the ratio  $A'fg/Afg$  can approach unity.

The net result is already too complex to be

<sup>6</sup> Jaeger, l. c., p. 299.

stated in simple terms but it has certain obvious biological features. Within a certain chemical framework defined by the atomic configurations A, A', f, g, the course of change is completely flexible in response to external physical conditions and it is a process which, by reason of the different velocities of left and right handed reactions lends itself to, indeed invites, the accumulation of asymmetrical reserves to be drawn upon when mass ratios reach certain values. It is indeed possible now, as it was not in Pasteur's time, dimly to perceive the dynamical structure of the series of events which confirm dissymmetry as a quality of protoplasm.

Dissymmetry is, according to Pasteur, the one property which distinguishes the organic from the inorganic world; an equally decisive difference, however, or so it seems to me, is the capacity for growth by intussusception. Is it possible to place these properties in the relation of cause and effect?

It is possible that in the dissymmetry of its reactions lies the clue to, but by no means the explanation of, the confused blend in living matter of stability with apparently limitless variability. According to Keilin the yeast plant will lose the whole complex enzymic mechanism of the cytochrome reaction if the need for its use be withdrawn. Every part atrophies save the pyrrol ring from which, when needed, the whole

can be entirely reconstructed. Is this an example of the heredity of asymmetry?

That brings us at once to the second and most difficult problem. Given that the chemistry of life consists in a series of events in which asymmetry is inextricably involved how did the series start? How was the first asymmetric molecule created?

The difficulty centres in the fact already mentioned that when only symmetrical substances are involved and when no asymmetrical force is acting the reaction will yield only symmetrical products or, if asymmetrical molecules are formed the chances of formation of right and left handed molecules is even. The result then is an optically inactive, internally balanced racemate.

It is a question of probability which Le Bel<sup>7</sup> in 1874 stated in his well-known theorem as follows:

“When any phenomenon whatever can take place in two ways only, and there is no reason why it should take place in one of the ways in preference to the other, if the phenomenon has taken place,  $m$  times in one manner and  $m'$  times in the other manner the ratio  $\frac{m'}{m}$ , approaches unity as the sum  $m + m'$  approaches infinity.

<sup>7</sup> J. A. Le Bel. Bull. d. l. Societé Chimique de Paris, v. 24, 337, 1874. Translated in the Foundations of Stereo Chemistry where also will be found translated the Lectures of Pasteur, and papers by Van't Hoff and Wislicenus, New York, 1901.

“When an asymmetric body is formed in a reaction where there are present originally only symmetrical bodies the two isomers of inverse symmetry will be formed in equal quantities.

“This is not necessarily true of asymmetric bodies formed in the presence of other active bodies, or traversed by circularly polarized light, or, in short, when submitted to any cause whatever which favors the formation of one of the asymmetric isomers. Such conditions are exceptional. . . .

“We have a striking example of this in tartaric acid, for neither the dextro- nor the laevo- tartaric acid has ever been obtained directly by synthesis, but the inactive racemic acid which is a combination of equal parts of the dextro- and laevo-acids is always obtained.”

The chemist now is well supplied with optically active compounds, they are on his shelves or can be on his shelves by the hundreds if not by the thousands, but living matter has intervened directly or indirectly in the production of every one of them.

Asymmetric molecules are produced in the laboratory but, in agreement with Le Bell's theorem right and left handed forms appear in equal numbers and the result is an internally balanced racemate which is optically inactive.

There are, however, three methods of resolving a racemate, all due to Pasteur. In rare instances

and, as we have seen between narrow limits of temperature the racemate undergoes spontaneous fission, right and left handed crystals being deposited. Man can then play the part of Maxwell's demon by sorting the two kinds into separate heaps. When that is not possible the part of the demon can more frequently be taken by some fungus or yeast or dissymmetric enzyme which attacks one antipode more rapidly than the other. Examples have been given earlier. The plant need not be living.

Lastly and as the third method the racemate can be combined with an asymmetric acid or base when the salts of the antipodes have different solubilities and can be separated by fractional crystallization. But the bases usually employed are all the products of the activities of living cells. Life intervenes at first or second hand in each of the three methods.

There is, however, a fourth method not usually employed because of its ill success namely the introduction of an external asymmetric influence which can warp the reaction so as to give it the desired twist.

For many years Pasteur tried this method and failed. The literature of later and equally fruitless attempts is large. Some slight success has been gained with circularly polarized light. Reactions which should produce optically active compounds have been carried out under the in-

fluence of such light. This method was suggested by both Van't Hoff and Le Bel.<sup>8</sup> It has uniformly failed.

Cotton tried a variant. He attempted to destroy one of a pair of dissymmetrical substances which synthetic chemical processes produce<sup>9</sup> and chose for the experiments those solutions of copper racemate which rapidly change in sunlight. It failed.

More recently a slight measure of success has been got by the use of ultra-violet rays. The principle is simple. A dextro-polarized ray is more strongly absorbed when passing through a mixture by the dextro-rotatory component, it ought, therefore, to destroy more of it.

W. Kuhn and Braun exposed the ethereal solution of the racemic ester of  $\alpha$ -bromo-propionic acid in sealed vessels of quartz to both dextro- and laevo-polarized light. The result was slight the greatest rotation observed of either sign being 0.05.<sup>10</sup>

W. Kuhn and Knopf were a little more successful with the racemate dissolved in hexanes. They exposed to light of a wavelength corresponding to the absorption band of the racemate and exposure was continued until 40 per cent was

<sup>8</sup> Van't Hoff-Le Bel. Bull. Soc. Chim. Paris, v. 24, 337, 1874.

<sup>9</sup> Cotton. J. Chem. Physique, v. 7, 81, 1909. Trans. Far. Soc., April, 1930, p. 379.

<sup>10</sup> Naturwiss., v. 17, 227, 1929.

destroyed and readings of  $+0.78^{\circ}$  to  $-1.04^{\circ}$  were got.<sup>11</sup>

What is the probability of the first optically active substance being separated, by the fortuitous clash of circumstance, as Japp put it? That it must be remembered is our problem, not the production under human guidance.

Japp took the extreme view "not with all eternity to act," which means that the probability of the origin of life has always been infinitely small. There are, however, different orders of infinity. Kinetic theory is a statistical theory and the probability that heat will flow down a gradient of temperature is enormous, but Kelvin pointed out that the mathematical theory showed that, given enough trials, an occasion must come on which the water in a kettle will freeze when it is put on the fire.<sup>12</sup>

In the case we are considering the degree of infinity is much lower, or, to put it the other way round, the probability is much higher: let us try to estimate it.

The experiments quoted above show that an effective external influence actually exists in circularly polarized light; more than that it is continuously in operation at the surface of the sea where the sun's rays are polarized by reflec-

<sup>11</sup> Naturwiss., v. 18, 183, 1930.

<sup>12</sup> Encyc. Britt. 11th edition, article: Heat.

tion and get a right or left handed twist owing to the rotation of the earth. There is, therefore, a finite probability but it is a very small one because the rotation is too slow compared with the speed of molecular reaction to affect photo-synthesis and it is right handed in the one hemisphere, left handed in the other so that, on the average, equal numbers of antipodes would be formed and the units of living matter would have on the whole equal right and left handed bias. In the panmixia of life they would cancel out. But living matter has by no means equal bias. Carbohydrates, proteins, alkaloids of natural origin have consistently a right or a left handed bias. The asymmetry of living matter is specific and consistent.

The importance of Kuhn and Knopf's results must not be exaggerated. The circumstances were highly selective and artificial. Living matter, man himself, again played the part of Maxwell's demon in much the same way as he did when Pasteur sorted the left and right handed crystals of sodium ammonium tartrate into two groups.

We can as little imagine either process, the selection by light of a particular wavelength or selection by sorting crystal enantiomorphs, acting in that first gift of asymmetry in the living cell. Both, however, are possible operations in an inorganic world but with an exceedingly low order of probability.



There is another character of such operations; the antipodes produced were carefully sheltered from destruction; in the world as we know it there is prodigious wastage.

For a long tract of geological time, ever since living matter appeared the flux of matter from the asymmetric world to the symmetric world has continued but there has been no accumulation. Living matter has become dead matter and its asymmetry has been lost because the inorganic world tends always to the higher stability of symmetry.

The asymmetric force which produced the first enantiomorphs must therefore have had sufficient intensity to produce asymmetric molecules faster than the normal wastage.

I think enough has been said to prove that the probability of the production of optically active substances is finite but of an exceedingly low order, low enough to justify classing the origin of life as unique.

From Pasteur's experiments and surmises came the whole of stereo-chemistry, that branch of the science in which not only is atomic composition taken account of but also the relative position of the atoms in space. Chemists were slow to accord molecules a third dimension, they did not indeed rest content with plane structural formulas but believed that a knowledge of the actual arrangement of the atoms was beyond discovery by experiment.

To the question: When has a chemical molecule dissymmetry? They gave only a general answer, namely, that the atomic configuration shall be non-superposable with its mirror image and mentioned the spiral and the angles of an irregular tetrahedron as examples.

The first precise answer came in 1874 from Van't Hoff and Le Bel who independently but almost simultaneously introduced the idea of the asymmetric carbon atom and so founded the science of stereochemistry. The four valencies of the carbon atom are vectorial quantities determined by magnitude and direction and are directed like the lines which join the centre of a regular tetrahedron to its corners. If the four radicles linked to the carbon atom are all different the arrangement has no axis of symmetry and to it Van't Hoff gave the name "asymmetric carbon atom." Since their time the chemistry of optical activity has been practically confined to the chemistry of the asymmetric carbon atom though Van't Hoff himself discussed cases of optical activity with no asymmetric carbon atom but with an enantiomorphic configuration of the whole molecule, e.g., styrene and some diphenyl derivatives.

These ideas were not received gladly. Kolbe, then professor at Leipzig and one of the leading chemists, criticized these speculations in an article which might have come from the pages of the *Eatonswill Gazette!*

“If anyone supposes that I exaggerate this evil” (the decay of chemical research owing to the growth of ‘a miserable speculative philosophy’) “I recommend him to read, if he has the patience, the recent fanciful speculation of Messrs. Van’t Hoff and Herman on the arrangement of atoms in space.” It is the voice of Mr. Potts which is speaking.

I should have taken no notice of this matter had not Wislicenus oddly enough prefaced the pamphlet and, not by way of a joke but in all seriousness, warmly recommended it.”

When Kolbe died Wislicenus took his place at the University of Leipzig.

Recently there has been a return to Pasteur's more general position. It is now recognized, for example, that molecular asymmetry may depend upon the configuration of the combining electrons rather than the atoms. It is now known that rotatory power is definitely related to the electric moments of the group attached to the carbon atom and that the power is lost when the electric moment of the molecule vanishes. Knowledge, however, has not progressed far in these directions and the chemistry of optical rotation is still practically in its infancy, and that despite nearly a century of intensive study. It is no more possible now than in the time of Pasteur to predict from the known structure of a molecule the amount or even the sign of the rotation. Indeed

the application of the wave theory reduces right and left handed enantiomorphs from the position of static non-superposable configuration to being the extreme limits of a change of phase.

To take a simpler problem which yet must have enormous biological implications and is still completely enigmatic. Why should a super-saturated solution of a racemic form deposit only d- or l- forms when seeded with a d- or l-crystal?

The influence of the solvent is also a puzzle—a substance may be laevo-rotatory when crystalline but dextro-rotatory when dissolved in water.

Pasteur has been called a vitalist. I doubt whether he would have accepted the label. He was a fighter all his life, always in hot water, and no one was more likely to resent being tagged with any such ticket. It was probably to be rid of it that he wrote in 1884 "not only have I not set up as absolute the existence of a barrier between the products of the laboratory and those of life, but I was the first to prove that it was merely an artificial barrier and I indicated the general procedure necessary to remove it by knowing that it would be necessary to have recourse to those forces of dissymmetry which you have never employed in your laboratories."

And yet the hypothesis of a special vital force and the search for it is as likely to lead to our goal as any other. I would even go further and say that the physical and chemical improbabili-

ties of living matter are so great as to make a hypothesis of special creations more restful and almost as valid as that of continuous evolution.

Is there any guess which comes within whooping distance of the shifts and tricks by which the primordial slime clothed itself in diffraction gratings to give the birds the colour they need in a tropical forest?

I am not shocked by vitalism but I am afraid of it as a dangerous flag to fight under. The biologist's job is to take the findings of physics and chemistry and faithfully to apply them to the riddle of this impossible elusive living slime in its coat of many colours. As a biologist I resent the temptation of the physicist when he advises us to seek new principles and as a biologist I would say to my brother biologists let them keep their imagination unclouded by the lure of arithmetical coincidences in tables of calculated and observed values. These have their use but for the present in the inner court of biology opportunities are scanty. One does not need to go far in molecular physics to find how dangerous a guide they may be.

















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