JACQUES LOEB.

By W. J. V. OSTERHOUT.

I.

If I venture to write of Jacques Loeb, it is not to create a portrait but only to set forth facts to aid those who would follow in his footsteps. In this I bespeak the charity of the reader. And if the writing achieve any part of its purpose it is because of many who in loving veneration gave loyal aid.

Loeb's ancestors were among those illuminati who forsook Portugal on account of the intolerance of the Inquisition: they settled at Mayen in the Rhine province several generations before he was born. His father, Benedict Loeb, was an importer, a man of simple tastes, more interested in science (especially in physics, mathematics, and geology), in literature, and in collecting books than in business. He was extremely reserved, and much of an æsthete. He married Barbara Isay and their first child, Jacques, was born April 7, 1859, and was followed by a second, Leo, some ten years later.

The father's sympathies were strongly French and thus it came about that the eager mind of Jacques absorbed French as well as German culture, all the more because he lived in a region where French influence made itself strongly felt. His father, hating Prussianism, looked longingly toward the democratic institutions of France and of the United States.

In 1873 the mother died and three years later the father followed her. Jacques, an orphan of 16, accepted a position in the bank of an uncle in Berlin. Shortly after, on the advice of an uncle, Professor Harry Bresslau, he entered the Askanische Gymnasium in Berlin. It was a purely classical school, with very little science, from which he graduated at the head of his class, with special mention for fluency in speaking Latin. At his departure his teachers gave him a copy of Zeller's "Philosophie der Griechen" with an inscription cautioning him not to become too liberal!

His teachers took it for granted that he would become a philosopher and with this in mind he entered the University of Berlin in 1880 and attended the lectures of the philosopher Paulsen. But he soon concluded that metaphysical philosophy could not give satisfactory answers to the two questions uppermost in his mind: Is there such a thing as free will? and, What are the instincts?

He seems to have conceived a distaste for metaphysics at this time and in his subsequent career the only philosopher who influenced him appears to have been Mach.

The second semester of this academic year was spent at the University of Munich: then, hoping to gain some light on the question of the will, he went to Strassburg, entering the laboratory of Goltz who was studying localization in the brain and endeavoring to refute the theories of Munk and Hitzig. Here he remained five years and on the advice of Goltz took a medical degree in 1884 and the Staatsexamen in 1885. He then spent a year with Zuntz in Berlin where he continued his work on brain physiology.

The results of his work were presented in a thesis entitled "Die Sehstörungen nach Verletzung der Grosshirnrinde" (1, 2).[1] Munk and Hitzig promptly denounced the paper and its author in no uncertain terms. There was nothing personal in this since it was merely a natural consequence of the rivalry between opposing schools at a time when bitter polemics were only too common in Germany. Nevertheless it was a severe disappointment after five years of hard labor and it was a comfort to receive a letter from William James congratulating him upon his maiden publication: for this friendly act Loeb did not cease to be grateful and throughout his life he always seemed to be on the lookout to perform similar acts of kindness for young scientists.

He was now fairly launched on the scientific career which he pursued with extraordinary success and which revealed mental powers of the highest order. His restless mind must continually find new ideas and new enthusiasms as an outlet for its energies. He had a passionate love of truth and what appeared to him to be true had to be so expressed that all could feel the inspiration and see the beauty of what

[1] The numbers refer to the numbers in the bibliography which appears in this number of the Journal.

he saw. He sought in vain for the solution of his problems in the current philosophies of the day: then came his conversion to mechanism. Faith in mechanism became the religion to which he devoted his life, and it was a religion which his love of truth forced him to test by the most rigorous scientific standards.

The ardor with which he labored cannot be understood unless we realize that to him a scientific career meant the consecration of his life to the cause of humanity. He sometimes explained his devotion to work by the whimsical remark that it was his pleasure, a kind of sport, an adventure in the unravelling of mysteries. An excellent half-truth, all very well for those who could not see beneath the surface! But at bottom was not only the drive of an active and powerful mind but a consuming desire to help suffering humanity to which his heart went out in passionate pity. He seemed continually to carry some part of the load of human sorrow. Even in his happiest moments this feeling never left him and in the latter years of his life he suffered intensely as he saw the hatred let loose by the war.

He believed that the ills of mankind spring wholly from ignorance and superstition and are curable only by the search for truth. To quote his own words: "What progress humanity has made, not only in physical welfare but also in the conquest of superstition and hatred, and in the formation of a correct view of life, it owes directly or indirectly to mechanistic science" (263). He believed that science will lead to a philosophy free from mysticism by which the human spirit may achieve a lasting harmony with itself and its surroundings: such a goal can be reached only by research, which will no doubt show less natural perversity than natural goodness and prove altruism to be an innate property of human nature, just as the tropisms and instincts are inherent in lower organisms. To establish such a conception seemed worthy of his utmost effort.

If we realize that the great driving force of his life lay not only in a powerful intellectual urge, but also in a profound emotion we may better understand his zeal and why he attacked most eagerly the subjects where mysticism was most strongly entrenched. No matter how great the difficulty he seemed determined, as far as possible, to reduce everything to mechanism and his courage was often justified by startling success. When unable to solve the problem his keen hypotheses, often startling in their audacity and beauty, and attractive for their simplicity and clarity, aroused and stimulated his readers. Often his dreams were as inspiring as his actual discoveries.

Not long after leaving Zuntz the direction of his future work began to show itself. In the fall of 1886 he became assistant to Fick, professor of physiology at Würzburg. Here the famous botanist Sachs became his friend, even going so far as to invite him to go on his walks, a condescension most unusual from an ordinarius to an assistant. And under the influence of Sachs his program commenced to assume more definite form. He had begun with the problem of the freedom of the will and his formulation of it was characteristic: if the will be free it cannot be controlled; this question must be tested experimentally. At that time it was customary to attribute volition to lower animals and it was natural to attack the problem there. The idea that behavior might be controlled by operations on the brain led to his experiments with Goltz. But these did not seem promising, and for a time he was uncertain.

It was the privilege of Sachs to lead him in the right direction, for Loeb saw that if he could control animals as Sachs controlled plants the problem of the will could be attacked scientifically. He lost no time in setting to work: the results exceeded his fondest hopes and henceforth the way was plain. He went forward so rapidly that in two years he had published his first paper on the theory of animal tropisms that was to bring him fame.

In the fall of 1888 he returned to Strassburg as assistant to Goltz and while here he did some work in collaboration with v. Korânyi of Budapest (14). The winter of 1889–90 he spent in Naples carrying on experiments on heteromorphosis and the depth migrations of animals (in the latter work collaborating with Groom (16)): and it was here that he became interested in America through his contact with Henry B. Ward and W. W. Norman.

In the spring of 1890, at the home of Professor Justus Gaule (professor of physiology in Zürich and a former assistant of Goltz), he met a young American, Miss Anne Leonard, who had just received her doctorate in philology at the University of Zürich. The acquaintance resulted in an engagement and they were married in October of the same year. After the marriage, which took place in America, they returned to Naples for the winter where he devoted himself to experiments on heteromorphosis since he was convinced that not only the "will" of the animal but also the form and function of its organs and its course of development might be controlled by the experimenter, an idea quite contrary to concepts then prevailing.

At this time he was undecided whether he should continue to live frugally on his patrimony and devote himself wholly to research or accept an academic chair, which he dreaded because of its interference with his investigations. But he deemed that his new responsibilities made it imperative to find a position. Feeling more and more irritation at the military and political conditions in Germany, and having, like his father, a hatred of militarism, his thoughts turned toward America. But there was no position in sight. At last he had an inspiration: he would earn his living as an oculist, devoting part of his time to practice and the rest to research. He began to frequent the clinic of his friend Dr. Fick, in Zürich, but after six weeks gave up in despair, saying "I cannot live unless I continue my scientific work. These problems haunt me night and day and I must go on or perish." While in this state of mind he received an offer of a position at Bryn Mawr College from Miss Thomas (then dean of Bryn Mawr) which was accepted with enthusiasm. He arrived in Bryn Mawr in November, 1891, to assume his new duties, having been delayed owing to the arrival of his first-born child, Leonard.

He was happy to be in America and he enjoyed Bryn Mawr. He had a few graduate students, among whom was Miss Ida H. Hyde. But the facilities for his work were insufficient and in January, 1892, when Dr. Whitman asked him to join his staff at the new University of Chicago, he accepted. At the same time he agreed to give the course in physiology at Woods Hole during the following summer.

At Woods Hole he was in his element. He enjoyed giving the course: he was able to work without hindrance and he met a group of men who shared his ideals and enthusiasm. He spent most of his summers in Woods Hole during the remainder of his life, except for the years spent at the University of California.

On reaching Chicago in the autumn he found things in a state of chaos. The World's Fair was in preparation and only one university building was completed. An apartment house had been leased for a year to harbor the scientific departments of the university (one department to a floor). When the first quarter opened there was not a piece of apparatus in the building. In this, as in so many other trying circumstances, Loeb's sense of humor came to his aid: it was one of his outstanding qualities and it is a great pity that this sketch cannot, from its very nature, dwell upon it. But those who seek to understand his character should not underestimate this quality which was a wonderful help in a long and difficult struggle, made doubly trying by his supersensitive nature.

The following ten years in Chicago were busy and happy ones during which he became a naturalized citizen and definitely took root in the United States. An important circumstance linking him more firmly to his new environment was the birth of two children, Robert F. and Anne, which had the greater significance because of his intense devotion to domestic life. Indeed his every moment, apart from his laboratory, was spent with his family.

After a short time the department of physiology was separated from that of biology and Loeb was placed at its head; David J. Lingle and A. P. Mathews were associated with him in the department. A physiological laboratory was dedicated in 1897. Among those who worked with him during this period (either at Chicago or Woods Hole) were C. R. Bardeen, Elizabeth E. Bickford, O. H. Brown, S. P. Budgett, Elizabeth Cooke, Martin H. Fischer, W. E. Garrey, W. J. Gies, A. W. Greeley, Irving Hardesty, W. H. Lewis, R. S. Lillie, E. P. Lyon, S. S. Maxwell, Anne Moore, C. H. Neilson, W. W. Norman, R. Burton Opitz, W. H. Packard, J. van Duyne, R. W. Webster, Jeanette C. Welch, and W. D. Zoethout.

His work was at first largely concerned with tropisms and heteromorphosis. He found that these studies involved recent discoveries in chemistry and physics. He became deeply interested in the theory of Arrhenius and thus came to write the famous series of papers on the physiological effects of ions. A direct outgrowth of this was his discovery of artificial parthenogenesis and antagonistic salt action in 1899.

The winter of 1898–99 was spent in California at Pacific Grove, where he had expected to work on marine material but since he was unable to carry out this plan he devoted his time to writing. The outcome was the "Comparative Physiology of the Brain and Comparative Psychology" (62) written in German and translated by Mrs. Loeb. This was not an isolated instance of her aid for she constantly cooperated with him in literary work.

Loeb was greatly attracted by the genial climate and the possibility of working on marine material all the year around, and when a call to the University of California came in 1902 he accepted. A laboratory was built for him at Pacific Grove not very far from the site of the Jacques Loeb Laboratory to be erected by Stanford University. The University of California Publications in Physiology began in 1903; in October of the same year the physiological laboratory at Berkeley was dedicated, the principal address being delivered by Wilhelm Ostwald. In the following year Arrhenius and de Vries spent some time at the University of California to the great delight of Loeb who had become deeply interested in their work: this acquaintance ripened into a firm friendship. This is equally true of the later visits of Boltzmann and Rutherford.

Among those who worked with him at this time were F. W. Bancroft, G. Bullot, T. C. Burnett, G. C. Elder, M. H. Fischer, A. L. Hagedoorn, W. O. Redman King, E. v. Knaffl-Lenz, H. Kupelwieser, C. B. Lipman, J. B. MacCallum, S. S. Maxwell, A. R. Moore, Wolfgang Ostwald, T. B. Robertson, C. G. Rogers, Charles D. Snyder, R. Wulzen, and H. Wasteneys.

In accepting the call to California Loeb had not realized how much he would be cut off from contact with his fellow scientists. He was naturally so averse to travel that he made no attempt to attend meetings of his colleagues in the East (and it was surprising that in 1909 he attended the Darwin Centenary in Cambridge, England, went to the VIth International Congress of Psychology in Geneva, the 350th Anniversary Celebration of the University of Geneva, the 500th Anniversary Celebration of the University of Leipsic, and to the XVIth International Congress of Medicine in Budapest, and in 1911 attended the first Monist Congress in Hamburg). This isolation had much to do with his consideration of offers from Europe (especially from Budapest) and his final acceptance of a call to The Rockefeller Institute for Medical Research in 1910. He desired to be able to devote himself entirely to research and he was deeply interested in the idea of carrying on work in general physiology in connection with medicine. He thought that in this way those engaged in medical research might more easily see to what extent advance in the art of healing depends on our knowledge of the nature of the cell and how medical progress may be quickened by such fundamental principles as general physiology can supply. (See in this connection the letter reproduced on pages xvii–xix.)

He found the atmosphere of the Institute so congenial and stimulating that his activity in research became greater than ever. He delighted in meeting other workers at the noon hour when all the staff lunched together and he inspired the younger men as few could do.

In 1918 he founded the Journal of General Physiology (in collaboration with the writer) and a series of Monographs on Experimental Biology (in collaboration with T. H. Morgan and the writer), both of which met obvious needs.

Among those who worked in his laboratory (either at the Institute or at Woods Hole) were F. W. Bancroft, M. G. Banus, R. H. Beutner, McKeen Cattell, K. G. Dernby, W. F. Ewald, D. I. Hitchcock, K. v. Kőrösy, M. Kunitz, R. F. Loeb, Mrs. A. R. Moore, J. H. Northrop, H. Wasteneys, and N. Wuest. It should be added that throughout his connection with the Institute his labors were lightened by the efficiency and devotion of his secretary, Miss Nina Kobelt.

His previous studies were continued for a time and later there were new developments, such as his investigations on bioelectrical phenomena and on quantitative aspects of regeneration. He also took up anew the properties of proteins. It was a subject that had long attracted him: he had made a beginning years before but there seemed then to be no guiding principles sufficiently well established to make it possible to proceed with assurance. Nevertheless the problem was constantly in his mind and at length he discovered a way to attack it. In his earlier researches the dissociation theory of Arrhenius had furnished a clue and in the later work he found a guide in the Donnan principle. By applying this he was able to give quantitative explanations of some of the most important properties of colloids and to reduce them to simple mathematical laws.

In the midst of this important work he was persuaded to go to Bermuda for a brief holiday. A few days later he was stricken with angina pectoris, and after a short illness his death occurred, on Febru-

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ary 11, 1924. It had always been his desire to work up to the last moment and to die in one of the places whose natural beauty appealed to his imagination. It seemed therefore in accordance with his wish that the end should come during a visit to Bermuda in the midst of the most active investigations of his life.

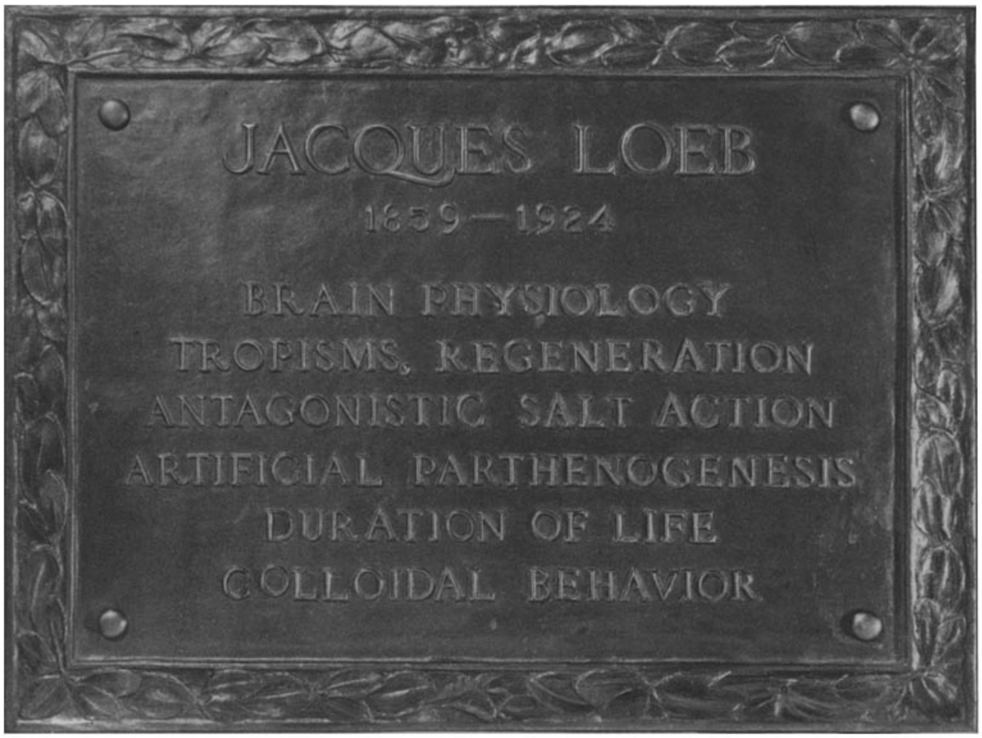
His ashes were brought to Woods Hole for interment. A memorial tablet was placed in the Marine Biological Laboratory and in The Rockefeller Institute for Medical Research. It is bordered by the leaves of *Bryophyllum*, which had served for his experiments on regeneration but which he had not known in its wild state until in Bermuda he had been delighted to see it everywhere blooming profusely.

Enshrined within this border are the chief subjects to which he devoted himself during a life time of unremitting labor. All of them represent fundamental problems of biological research. Though at first sight they may seem to present no obvious continuity it would be a great mistake to suppose that it is absent. As with all great investigators, each new question arose naturally out of the preceding. There was no running after strange gods or foreign problems. The task in hand demanded all his power of attention and it rewarded the seeker by continually unfolding new and promising leads to the very last. The end was not discernable at the start: nor did he dream when beginning with the freedom of the will that he would end by studying colloidal systems. Yet it was a transition as natural as the progress of Pasteur from crystals to microbes.

II.

Loeb's work was too diversified and extensive to permit a complete account in the limits here prescribed. The most that can be attempted is a general sketch of the evolution of his ideas, omitting all details save those which give definiteness to the picture.

To understand the development of his thought we must go back again to the start. He began with the problem of the freedom of the will and he felt that in experiment lay the only chance of progress. He turned, naturally enough, to the idea that behavior might be controlled by operations on the brain: for this reason he went to study with Goltz. Here he became acquainted with the experiments on



Marine Biological Laboratory, Woods Hole, Mass., and The Rockefeller Institute for Medical Research, New York, N.Y.

dogs which had led Munk to think that the act of vision involves a projection from the retina to a certain region of the cerebral cortex and that extirpation of certain parts of this region produces blindness in corresponding parts of the retina. Loeb carefully repeated these experiments but was unable to confirm Munk.

Many years afterward Henschen concluded from observations on human pathology that such a projection exists but not in the part of the cortex where Munk had located it and this idea was confirmed by Minkowski's experiments on dogs. Loeb then took up the discussion from an entirely new angle. He called attention to the work of investigators who had found that in the coloration of their skins certain fish reproduce a pattern, such as a checker board, forming the bottom of the aquarium. Extirpation of the eyes or of the optic ganglia in the brain or cutting the sympathetic nerve fibres which go to the pigmented cells of the skin prevents this phenomenon. Hence the path is known and Loeb suggested that what travels along this path may be an "image" in the sense that for each dark or bright point of the object there is a corresponding state of excitation first in the retina and subsequently in the optic nerves and in their terminal ganglia in the brain.

This illustrates what often happened in his work. Dropping a problem which did not seem to be leading anywhere he would nevertheless keep it always in the back of his mind so that if new facts turned up he could at once turn them to good use.

Seeing the necessity for quantitative methods in dealing with the physiology of the brain he devised a method of measuring the effects of attention and mental activity by recording the pressure exerted by the hand upon a dynamometer while the subject was engaged in reading or ciphering (5). It was found that these activities had a decided effect on the pressure imparted to the dynamometer.[2] This idea proved to be useful and suggestive.

Later Loeb returned repeatedly to the physiology of the brain and in his book on the subject (62) made useful suggestions such as those found in his discussion of the sequence of reflexes proceeding from one segmental reflex to another which he called "chain reflexes."

His early work on the brain had failed to open the experimental

[2] *Cf.* also Welch, J. C., *Am. J. Physiol.*, 1898, i, 283.

approach that he had hoped for. But fortunately he soon afterward came under the influence of Sachs who had clearly shown that plants in their responses to light and certain other stimuli behave as simple machines. Not only the brilliant experiments of Sachs but his remarkable personality, his creative imagination, and broad philosophic viewpoint inspired Loeb, who was seized with a desire to test upon animals the illuminating conceptions that Sachs had formulated in studying plants.

Loeb's method of procedure is illustrated by his experiments on the caterpillars of *Porthesia* which issue from their winter nests and climb to the tips of the branches of trees where they find the opening buds which serve them as food. It was supposed that they found the right situation, in some cases before the food was actually ready, by a marvellous instinct. To explain the origin and the heredity of such an instinct might seem to require very complicated hypotheses. But Loeb brushed all this aside by a few simple experiments showing that these animals are slaves of the light. They climb upward toward the light until they reach the tips of the branches and there they remain. They act like photochemical machines to such an extent that if food is placed behind them when they are starving they are unable to turn their heads away from the light to take nourishment. It seemed possible that this effect might be produced by a photosensitive substance reacting more strongly on the illuminated side and hence (through the medium of the nervous system) affecting unequally the symmetrical muscles on the two sides so as to turn the head toward the light. To explain the heredity of such an "instinct" we need only suppose that the parent transmits to the offspring the ability to produce the photosensitive substance under the proper conditions.

One must therefore cease to speak of the will of this animal and regard it as a matter of mechanism, completely under the control of the experimenter. "The desire of the moth for the star" began to seem less mysterious.

Thus at the very outset he came to the conclusion that certain instincts may be resolved into tropisms and it soon became evident that no hard and fast line could be drawn between instinct and intelligence. In later work he developed these ideas. Finding that the addition of carbonic acid to water may produce in an aquatic animal, ordinarily indifferent to the light, a reaction drawing it irresistibly toward a source of illumination, he raised the question whether this may help us to put certain psychological problems upon a physico-chemical basis. If behavior may be changed by the addition of an acid why not by the secretions of a gland? Might not this idea be applied to attraction between the sexes, which may involve a change from a selfish to an altruistic attitude? And why limit the consideration to glandular products? Since Pawlow and his pupils have produced a salivary secretion in dogs by means of optical or auditory signals it no longer appears strange that what we call an idea should bring about chemical changes in the body.

It is evident that these considerations may throw some light on the nature of ethics. Loeb put the matter as follows (214, page 31):

> "If our existence is based on the play of blind forces and only a matter of chance; if we ourselves are only chemical mechanisms—how can there be an ethics for us? The answer is, that our instincts are the root of our ethics and that the instincts are just as hereditary as is the form of our body. We eat, drink, and reproduce not because mankind has reached an agreement that this is desirable, but because, machine-like, we are compelled to do so. We are active, because we are compelled to be so by processes in our central nervous system; and as long as human beings are not economic slaves the instinct of successful work or of workmanship determines the direction of their action. The mother loves and cares for her children, not because metaphysicians had the idea that this was desirable, but because the instinct of taking care of the young is inherited just as distinctly as the morphological characters of the female body. We seek and enjoy the fellowship of human beings because hereditary conditions compel us to do so. We struggle for justice and truth since we are instinctively compelled to see our fellow beings happy. Economic, social, and political conditions or ignorance and superstition may warp and inhibit the inherited instincts and thus create a civilization with a faulty or low development of ethics. Individual mutants may arise in which one or the other desirable instinct is lost, just as individual mutants without pigment may arise in animals; and the offspring of such mutants may, if numerous enough, lower the ethical status of a community. Not only is the mechanistic conception of life compatible with ethics: it seems the only conception of life which can lead to an understanding of the source of ethics."

He therefore regarded the study of tropisms as of fundamental importance not only for biology but likewise for psychology and for philosophy and he endeavored to place it upon a sound scientific basis.

He tried to find quantitative relations and he was able to show in some cases that animals obey the Bunsen-Roscoe law which states that equal amounts of energy in the form of light produce equal results (*i.e.* that for equal effects intensity multiplied by time of exposure equals a constant) as had already been shown for plants by Blaauw.

The tropism theory would lead us to expect that when light comes from two different directions an animal will place itself so that the eyes will be equally illuminated on both sides. If the relative intensity of the lights be changed the animal should change its position accordingly. If in addition the animal obeys the Bunsen-Roscoe law varying the time of exposure to the light should have the same effect as a proportionate change in the intensity. Ewald, working in Loeb's laboratory, found that the eye of *Daphnia* takes up a position in accordance with this law. Loeb then showed in collaboration with Ewald (240) and later with Wasteneys (291) that the heliotropic curvature of the stems of the polyp *Eudendrium* obeys this law. In collaboration with Northrop (300) he showed that the larvæ of the barnacle when exposed to two sources of light move at an angle which agrees with this law: they also showed that when the horseshoe crab is tethered by a string attached to its tail and allowed to orient itself between two sources of light the position it assumes is in accordance with expectation (389). These results together with those of other observers served to establish the principle on a firm basis.

As the result of Loeb's work the motions of animals came to be explained more and more on the basis of tropisms rather than of single reflexes: few movements exemplify simple reflexes and in many cases they represent groups of reflexes which are better described as tropisms.

The study of tropisms led him to question some current notions regarding the function of the central nervous system. The flight of the moth into the flame, which had been regarded as a typical reflex, he explained as a simple tropism like the turning of a plant to the light. In the case of the plant the mechanism consists of an apparatus for receiving the stimulus and for transmitting it to the place where the motion takes place. He therefore asks, Why is it necessary to assume anything else in this animal: why postulate that the central nervous system does anything more than transmit the stimulus? And why not explain other reflexes on the same basis? This would indicate that the problem of coordinated movements needs a fresh attack and that the cause of coordination may, in some cases at least, be found outside the central nervous system.

It was a natural thing for him to pass on from the study of reflexes and tropisms to attack the problem of consciousness by seeking to resolve it into the simpler elements which compose it. He defined consciousness as the phenomena determined by associative memory the presence of which can be experimentally determined by ascertaining whether the animal is capable of learning: where this is lacking consciousness cannot exist. The fundamental problem of psychology is the mechanism of associative memory and the manner in which stimuli are transmitted; the method of attack is to try to discover what properties of colloids make such phenomena possible. For the solution of these problems we must use the methods of physical chemistry, particularly as employed in the study of protoplasm.

Many of these views are summarized in his "Comparative Physiology of the Brain and Comparative Psychology" (62) which had a strong influence, at a time when it was much needed, in replacing anthropomorphic speculation by sound experiment.

It may be added that although his attention was chiefly devoted to heliotropism where he could work quantitatively, he fully realized the importance of the other tropisms on which he made so many important observations. He pointed out very clearly the fundamental significance of tropisms in the struggle for existence, their importance in relation to adaptation, and their rôle in developmental mechanics. His writings gave an enormous impetus to the experimental study of animal behavior and encouraged the expectation that it might be brought under the control of the experimenter and his suggestions influenced both psychology and philosophy.

For him nothing was more natural than to go further and inquire: If we can control the behavior of the animal why not seek to determine also its form and development? This led to his experiments in the field which he called physiological morphology. He found it possible to control regeneration so that, for example, certain hydroids can be made to produce "roots" in place of "stems," just as botanists had previously found for plants. This he called heteromorphosis.

He accepted the explanation given by the botanists (and especially by Sachs) that the organs are determined by "organ-forming materials" so that where these materials collect the appropriate organs will be formed.

The impression made by these studies is well rendered by Herbst (whose opinion derives especial weight from his critical scientific attitude).

"Wirkten sie doch wie ein heller Sonnenstrahl, der plötzlich in das Dunkel der Morphologie fiel, die damals ganz im Banne phylogenetischer Forschung stand, welche wegen ihrer nicht zu beseitigenden Unsicherheit, ja mitunter Willkür, uns jüngere Forscher nicht mehr befriedigen konnte. Hier aber schienen einem Tatsachen gegeben zu sein, die in einem die Hoffnung erweckten, dermaleinst auch das tierische Gestaltungsgeschehen kontrollieren zu können. Freilich um die Entwicklung des Organismus aus dem Ei handelte es sich in diesen Arbeiten nicht, sondern nur um die Regeneration verlorengegangener Teile und um ähnliche Erscheinungen. Die Wirkung dieser Schriften war so gross, dass man sie nur mit derjenigen der Arbeiten von Trembley, Bonnet und Spallanzani auf Forscher und Laien der zweiten Hälfte des 18. Jahrhunderts vergleichen kann, denn wie damals die erste Hochflut in der Erforschung der Regenerationserscheinungen einsetzte, so wälzte sich nach dem Erscheinen der Beiträge Loebs die zweite heran, befruchtend und reichen Ertrag erbringend für die biologische Wissenschaft."[3]

He later produced such monstrosities as Siamese twins, triplets, or quadruplets in the egg of the sea urchin by diluting the sea water and causing the egg to burst and extrude one or more rounded masses of protoplasm. On replacing the egg in ordinary sea water each extruded portion gave rise to an embryo, as did also the main body of the egg to which it was attached, the attachment persisting as the embryos developed.

By such experiments he hoped to analyze the forces which control development, believing that the biologist should aim at as complete control of living matter as the physicist and chemist have over their material, and that the best hope of success lay in applying their methods to biology. He made brilliant use of this conception. He became especially interested in the dissociation theory and as one of the first results he published the well known series of papers on the physiological effects of ions. He thought that the specific effects of

[3] Herbst, C., *Die Naturwissenschaften*, 1924, xii, 400.

salts on the organism might be due to the combination of ions with substances in the protoplasm whose properties might thereby be altered. He found an analogy in the case of soaps where potassium makes a soft soap, sodium a harder one, calcium one that is still harder, and so on (63).

To test these ideas he exposed organisms to salts in varying concentrations. Fertilized eggs placed in sea water whose osmotic pressure had been increased by the addition of sodium chloride could not segment but if replaced in ordinary sea water after two hours they passed rapidly into a many-celled stage. His explanation was that in the more concentrated solution the nucleus divides but the cytoplasm is unable to do so; on replacing the eggs in ordinary sea water the division of the cytoplasm follows at once. Four years later Norman repeated this work, adding magnesium chloride to the sea water. Still later Morgan made similar experiments on unfertilized eggs and found on replacing them in ordinary sea water that they began to segment but this soon stopped and no larvæ were formed. About the same time Mead observed that the addition of a little potassium chloride to the sea water caused the unfertilized eggs of the marine worm *Chætopterus* to expel their polar bodies.[4]

Loeb found in 1899 (68, 69) that unfertilized eggs of the sea urchin which had remained for two hours in a mixture of equal volumes of sea water and two and a half molar magnesium chloride would develop into plutei when replaced in ordinary sea water. The announcement of this fact was received by his scientific colleagues with a degree of incredulity which bordered almost on indignation and there was a general feeling that his results must be due to contamination by sperm, which are widely dispersed throughout the sea water during the spawn-

[4] Prior to all of these observations was that of O. and R. Hertwig (1887) that eggs treated with strychnine occasionally segment a few times. Still earlier Greeff (1876) had observed that parthenogenesis sometimes occurs in the starfish *Asteracanthion* (the development did not proceed beyond the blastula stage) and O. Hertwig (1890) had confirmed this for *Asterias* and *Astropecten* but neither of these authors had determined the conditions under which this rare phenomenon took place. It was also known that eggs of arthropods, echinoderms, and annelids might begin to segment after lying for some hours in sea water. There also exist in the literature other reports of the beginning of cleavage under various conditions (122, pages 83 and 84, also 157).

ing season. There was, however, a difference in the appearance of eggs which were fertilized by sperm and those which were caused to develop by the treatment with magnesium chloride since in the latter the fertilization membrane is not as evident as in the former (indeed it was supposed for a long time that the latter had no membrane at all). Doubt presently disappeared and throughout the civilized world went a stir such as a scientific announcement seldom makes.

It was soon found that the action of magnesium chloride consisted merely in raising the osmotic pressure and that equally good results could be obtained by the addition of other neutral salts or even of sugar, as well as by the use of sea water concentrated by evaporation. This was therefore known as the osmotic method of artificial parthenogenesis.

Loeb stated that the importance of this discovery consisted in transferring the problem of fertilization from the domain of morphology to that of physical chemistry and he undertook to discover what physical and chemical changes cause the egg to develop. He first tried to imitate the formation of the typical fertilization membrane which is produced by the entrance of the sperm. He succeeded in this by exposing the eggs to certain fatty acids and then replacing them in sea water, but the development was not normal unless this treatment was followed by exposure to sea water of increased osmotic pressure or to sea water deprived of oxygen or containing a little potassium cyanide. In this case the plutei often appeared perfectly normal. Later Delage succeeded in carrying larvæ produced by artificial parthenogenesis to the stage of sexual maturity. It may be added that Loeb, using the method of Guyer and of Bataillon, later produced parthenogenetic frogs and raised them to sexual maturity (277, 354).

It is of interest to note that the sea urchins raised by Delage were males. The frogs raised by Loeb were of both sexes: the chromosome number was regarded by Goldschmidt as diploid and this was later confirmed by Parmenter.[5]

Two questions presented themselves, What are the physical and chemical changes which produce the fertilization membrane, and,

[5] Parmenter, C. L., *J. Gen. Physiol.*, 1925-28, viii, 1.

Why is the after-treatment necessary? To answer the first he sought to discover whether other means could cause the formation of the typical membrane. It was produced by certain cytolytic agents, particularly those which markedly affect surface tension, such as saponin, bile salts, and soap. It could also be produced by lipoid solvents, such as benzene and toluene (as Herbst and Hertwig had already observed), by alcohols and ethers, by certain bases, by ultraviolet light, and by other means. These agents are destructive and kill the egg unless it be removed in time and given an appropriate after-treatment.

Loeb concluded that all of these agents act on a substance, probably a lipoid, at the surface of the protoplasm causing certain colloids to swell and thereby lift up a delicate membrane from the surface (the question whether this membrane is preformed or is produced during the treatment is not essential). This could be brought about, for example, if the protoplasm at the surface consisted of an emulsion, the inner phase consisting of particles surrounded by a film of lipoid which might be removed by solution or precipitation or even by mechanical agitation so as to bring the particles into direct contact with the outer phase and cause them to swell and to lift up the fertilization membrane.

The question arose, How can an alteration of the surface of the sea urchin egg cause development? Perhaps by its effect on oxidation: Warburg had stated that oxidations occur chiefly at the surface, hence a change in the condition of the catalysts at the surface or an increase of permeability might increase oxidation.

When the membrane is formed in artificial parthenogenesis of the sea urchin there is a great increase in oxidation (as Warburg found) and the egg quickly dies if there is no additional treatment. But if oxidation is suppressed for a time (by depriving the eggs of oxygen or by adding a trace of potassium cyanide to the sea water) they live and can afterward develop normally. Temporary suppression of oxidation is evidently not the sole factor involved, since increased osmotic pressure is even more effective and certain narcotics act in much the same way without diminishing oxidation. All of these agents stop development for a time and this would seem to be the essential thing: during this period the egg has a chance to recover from the effects of the treatment which produces the membrane and if the suppression does not last too long normal segmentation occurs when the egg is replaced in ordinary sea water.

His general conclusion was that the sperm brings to the egg two substances, one of which acts on the surface of the protoplasm in such a way as to form a fertilization membrane, the other factor having a corrective action which prevents any harmful results of the processes immediately following membrane formation.

Evidence in favor of this idea was obtained on placing unfertilized eggs of certain species of sea urchin in hyperalkaline sea water and adding starfish sperm. The results seemed to indicate that the sperm bears at its surface a substance which can cause membrane formation by mere contact with the egg but that the substance bearing the corrective factor lies deeper in the sperm and produces no effect unless the sperm actually penetrates the egg. At any rate many cases were found in which the sperm produced membrane formation but the eggs did not develop unless treated with hypertonic sea water and it was assumed that in these cases the sperm did not penetrate but merely induced membrane formation by coming in contact with the surface of the egg and that the membrane thus formed prevented the sperm from penetrating. In other cases where the egg went on developing it was assumed that the sperm had penetrated.

With some species of sea urchins it was possible to produce membrane formation with an aqueous extract of starfish sperm which had been killed by heating to 60°C. Such eggs behave like those treated with a fatty acid and it is necessary to give them the after-treatment with hypertonic sea water to make them develop normally, as was also the case if such eggs are subjected to the action of living sperm of the shark or the rooster which do not penetrate but only give to the egg the substance which causes membrane formation. If this substance were like the so called lysins of blood it would seem possible to produce membrane formation with the blood of various foreign species. This proved to be the case with the blood of ox, sheep, pig, and rabbit, and certain invertebrates. In some cases it was necessary to sensitize the eggs by preliminary treatment with strontium or barium. In all cases the eggs perish unless given the after-treatment.

Lysins of the sea urchin have no effect on eggs of the same species, just as the lysins of sheep's blood cannot affect the corpuscles of sheep though they quickly destroy those of other animals. Is this because the lysins cannot penetrate cells of their own species or because antibodies protect the cells even if the lysins penetrate them? Loeb's answer was that if the egg of the sea urchin contained an antibody the sperm could not produce a membrane and it therefore seemed probable that the immunity of blood corpuscles to their own lysins may be due to the fact that the lysins cannot penetrate.

Other possible explanations have been suggested for many of the phenomena of artificial parthenogenesis, but those given here seemed to him on the whole the most probable. Later work brought to light new facts, as, for example, that the corrective treatment could precede as well as follow the treatment which produced the membrane, but these did not essentially change his viewpoint.

What has been said relates especially to the sea urchin. Other forms show divergencies: for example, in the starfish egg fertilization produces no increase in oxidation and other differences exist. But his main conceptions were developed from the experiments with sea urchin eggs and it has therefore seemed better to confine the account chiefly to these.

This brief outline of his method of analyzing the problem of fertilization says nothing of the many disappointments, the frequent failures, the long and tedious groping in the dark which preceded success. Nor does it touch on the wealth of new problems that came with each discovery. An example is seen in the experiments in which sea urchin eggs were treated with the sperm of the starfish. Under ordinary conditions no result is obtained but Loeb discovered that if the sea water were made slightly more alkaline fertilization took place and a normal development followed.

He found that fertilization could be brought about by the sperm of ophiurans, holothurians, or even of molluscs. But the employment of such foreign sperm did not affect the character of the larvæ which had the same appearance as if fertilization had been effected by sea urchin sperm of the same species.

Since development could be so easily started the question arose whether it could also be stopped and reversed at the will of the experimenter. The question of reversibility of development had first been raised by Loeb in 1900 (75, 78) when he observed the transformation of a hydroid polyp into the less differentiated material of the stolon which can in turn give rise to a new polyp. Since that time a number of instances of reversibility have been described by other observers.

He found that the artificial parthenogenesis of the sea urchin egg induced by alkali was reversible. Eggs treated with the alkaline solution followed by a hypertonic solution would develop in sea water but if, after removal from the hypertonic solution, they were placed for a short time in sea water containing sodium cyanide or chloral hydrate they would not develop when replaced in sea water but acted as if no treatment had been given them (237, 239, 264). The initiation of development by butyric acid also proved to be reversible.

Another suggestion arising from the study of the developing egg concerns the mechanics of growth. During the first period of division the nuclear material of the egg increases in a manner which indicates that cytoplasmic materials are transformed into nuclear substance. Nuclear division may occur at fairly regular intervals and at each division the nuclear material is approximately doubled. It follows that the mass of nuclear material produced at each division is proportional to the mass already present which might mean that the reaction which produces nuclear material is catalyzed by some constituent of the nucleus so that the greater the amount of nuclear material already on hand the more rapid the rate of the reaction. This, as he pointed out, is the case with an autocatalytic reaction (125, 139, 168). This suggested to T. B. Robertson the possibility that the growth of the entire organism might agree with the curve of autocatalysis and an examination of the available data convinced him that this was the case. About the same time Wolfgang Ostwald reached the same conclusion.

The experiments on artificial parthenogenesis called his attention to the problem of natural death. This interested him profoundly, partly because of its bearing on ethical problems. Is death a necessary consequence of the process of growth and development, or is it something superimposed, capable of being postponed or eliminated? He expressed his views as follows:

"The writer showed in 1902 that the problem of fertilization is intimately connected with the problem of the prolongation of the life of the egg cell. The unfertilized mature egg dies in a comparatively short time, which may vary from a few hours to a few weeks according to the species or the conditions under which the egg lives. The fertilized egg, however, lives indefinitely, inasmuch as it gives rise, not only to a new individual, but, theoretically at least, to an endless series of generations. The death of the unfertilized egg is possibly the only clear case of natural death of a cell, i.e., of death which is not caused by external injuries, and the act of fertilization is thus far the only known means by which the natural death of a cell can be prevented. The two problems, fertilization and prolongation of life, are thus interwoven, and the experiments on the mechanism of fertilization become at the same time studies on the problem of natural death and prolongation of the life of the egg cell." (157, English edition, page 1.)

He pointed out that while the fertilization of the egg by sperm of the same species prolongs the life of the egg indefinitely its span of life may be very brief if the sperm of certain other species is employed.

He found that the sensitiveness of the sea urchin to the effect of abnormal solutions increased as development proceeded so that when certain unfavorable solutions are improved by the addition of sea water the eggs die more quickly because they rapidly develop to a stage in which they are much more sensitive than before (245).

The discovery of artificial parthenogenesis made it possible to analyze the factors which prolong the life of the egg. The usual treatment of the sea urchin egg consists in first causing membrane formation in the unfertilized egg but eggs so treated die much more quickly than untreated eggs. It might therefore seem that the "corrective treatment" usually applied after membrane formation is responsible for prolonging the life of the egg. But when the corrective treatment is applied before membrane formation the eggs live no longer than untreated eggs: if the membrane formation is subsequently induced they live and develop. Hence it would appear as if both treatments are needed.

Membrane formation in the sea urchin egg appears to be followed by deleterious processes and only if the development of the egg be temporarily suppressed by the "corrective treatment" can it live. Under these circumstances we arrive at the paradoxical result that the life of the egg may be prolonged by the temporary application of potassium cyanide or by depriving it of oxygen or by subjecting it to the action of narcotics.

Another method of attacking the problem of death was by studying temperature coefficients. He believed that this method had great importance for biology and workers in his laboratory had been pioneers in applying it to such life phenomena as the heart beat (Snyder, Robertson) and to nervous conduction (Maxwell, Snyder).

Experiments on the sea urchin egg (made at high temperatures) showed that lowering the temperature 1°C. doubled the length of life although it had been shown by the work of other investigators (with which his own agreed) that at lower temperatures it was necessary to raise the temperature 10°C. to double the speed of development. This might be regarded as an indication that development and death are not due to the same chemical processes for in that case no such difference in the effect of temperature would exist and this might explain the extraordinary richness of life in the colder parts of the ocean where the low temperature would have a much greater effect in prolonging the life of the developed organism than in retarding development.

But the question assumed a different aspect when experiments were made on vinegar flies (in collaboration with Northrop). They are so short-lived that the experiments can be carried on without raising the temperature to an abnormal level so that the normal duration of life is studied rather than the rate of killing by abnormally high temperature. They worked with vinegar flies free from microorganisms so that there could be no suspicion that death was brought about, as Metchnikoff had suggested, by toxic substances produced in the intestinal tract by the action of bacteria.

The experiments showed that the effect of temperature was practically the same on development and on length of life and this was interpreted to mean that the duration of life depends on the time required to complete a chemical reaction (or series of reactions). The nature of this reaction could not be defined but many of the cells of the body when removed from the influence of the rest can go on dividing indefinitely as shown by Leo Loeb, Harrison, and others, and especially by the experiments of Carrel. This is also true of cancer cells, as shown by Leo Loeb. Such cells are potentially immortal like the unicellular organism.

Closely connected with these subjects is that of oxidation which early occupied his attention and led him to suggest that the nucleus is the center of oxidation in the cell. Later Warburg concluded that oxidation is largely confined to the surface of the sea urchin egg but the experiments of Loeb and Wasteneys did not confirm this view. They also made experiments on the effect of narcotics on the sea urchin egg and came to the conclusion that, contrary to the theory of Verworn, certain substances can produce narcosis with little or no diminution in the rate of oxidation.

Important as these problems were Loeb did not allow himself to be diverted from his basic program, out of which had sprung the experiments on artificial parthenogenesis. This program dealt with the fundamental properties of protoplasm as affected by ions. In order to ascertain the effects of individual ions it is desirable to employ an organism which can live either in distilled water or in fairly concentrated salt solutions. This is the case with the fish *Fundulus* whose eggs develop equally well in distilled water or sea water. Loeb was surprised to find that on adding to distilled water as much sodium chloride as is contained in sea water the eggs could not develop: in other words the sodium chloride is toxic and it was evident that the other salts found in sea water must somehow overcome this toxicity. The announcement of this fact was received with genuine astonishment.

He found that the addition of all sorts of salts with bivalent or trivalent cations in the right proportions could more or less completely remove the toxicity due to salts with monovalent cations. He spoke of this as antagonistic salt action and he called solutions such as sea water, in which the toxicity is suppressed by the admixture of salts in the proper proportions, a physiologically balanced solution. In order to have antagonistic salt action toxic salts must be present in sufficient concentration to produce injurious effects and these injurious effects must be overcome by other salts which have a protective action.

Botanists had long before found that plants (which can live for some time in distilled water) grow much better when certain salts are added. Very often such salts have only a nutritive function since there are no toxic effects to be overcome because the solutions are too dilute (just as *Fundulus* requires no addition of protective salts in a solution of sodium chloride having a concentration of 0.125 M or less). When

Herbst found that all the salts of sea water were needed to raise marine animals he worked from the same viewpoint. There was nothing to suggest that sodium chloride was toxic because his animals died very quickly in distilled water. But in the case of *Fundulus* eggs Loeb showed that the toxicity of sodium chloride could be largely overcome by adding salts without nutritive value; some, indeed, were very toxic when used alone, such as the salts of lead and zinc: it was evident that the action of such salts must be purely protective.

The striking fact that monovalent cations are antagonized by bivalent and still more by trivalent cations led Loeb to suggest that the sign and valence of the ion may in many cases be far more important than its chemical nature, as had already been found to be the case in certain experiments on colloids. This suggestion proved to be a highly stimulating one.

Ringer had found long before this that when the heart of a frog is perfused with a solution of sodium chloride the beats gradually diminish and ultimately cease: the addition of either calcium or potassium makes possible a resumption of activity but the beats are not normal unless both calcium and potassium are added in the proper proportions. Ringer concluded that there exists between calcium and potassium an antagonism analogous to that which exists between certain poisons of the heart, for example between atropine and muscarine: but for Ringer sodium chloride was an indifferent substance whereas Loeb regarded it as toxic. It may be added that Oscar Loew had shown that the toxicity of magnesium for certain plants largely disappears if sufficient calcium is added. But these workers arrived at no such far-reaching conclusions as Loeb. The experiments on *Fundulus* opened up a new point of view: had not this been the case they could not have created so much interest. In this connection we may quote the remarks of Höber:

"Loeb fand, dass das Ca nicht bloss durch die chemisch verwandten Mg, Sr und Ba ersetzt werden kann, sondern auch durch die Protoplasmagifte Ni, Mn, Zn, Pb, Cr u.a. Dies war ein so unerhörter Befund, dass im Hinblick darauf ein so ausgezeichneter Kenner der Salzwirkungen wie Overton damals den Satz schrieb: 'Dass die Calciumsalze durch Bariumsalze oder die Salze der zweiwertigen Schwermetalle in keiner Weise ersetzt werden können, müsste jedem toxikologisch gebildeten Physiologen von vornherein klar sein.' Heute haben wir eine Reihe von Beweisen dafür, dass in der Tat—mehr oder weniger gut—die zwei- und dreifach positiv elektrisch geladenen Ionen einander vertreten können, und obwohl Loeb, wie gesagt, aus seiner Entdeckung mit weitreichendem Blick sofort die Konsequenz auf die Kolloidchemie zog, so hat diese doch erst in neuester Zeit, in unmittelbarer Anknüpfung an die physiologischen Vorbilder, besonders durch Studien von Freundlich, das richtige Nachbild schaffen können; es gibt anorganische Kolloidsysteme, die das physiologische Kolloidsystem recht getreu imitieren. Loebs Entdeckung war der wichtigste Anstoss, das Interesse an dem Studium der physiologischen Bedeutung der Salze neu zu beleben und zugleich durch rein theoretische Untersuchungen zu vertiefen, und wieviel das besagen will, das lehrt ein Blick in die physiologische, pharmakologische und klinische Literatur unserer Tage. Sie strotzt von Untersuchungen über Ionenwirkungen; um kleinsten Schwankungen in den Normalkonzentrationen der Ionen nachgehen zu können, wurden vorzügliche Mikromethoden ersonnen; die Wirksamkeit der normalerweise anwesenden Kationen, besonders der mehrwertigen Ca und Mg, wurde von den verschiedensten Seiten beleuchtet, ihr Verhältnis zu den Protoplasmakolloiden, insbesondere zum Eiweiss, und ihr Verhältnis zu den Ionen des Wassers vielseitig durchforscht, wobei auch wichtige klinische Interessen und das Interesse am Ausbau der Theorie ihrer Wirkungen gewichtig mitsprachen; die Erforschung der bioelektrischen Phänomene trat in ein neues Stadium ein. Bei diesem ganzen Neubau hat Loeb selber an den verschiedensten Stellen mitgewirkt."[6]

When an organism can live in distilled water the question of antagonism is perfectly clear, but when this is not the case there may be difficulty in distinguishing between the nutrient and the protective effects of salts. *Fundulus* in its early stages develops as well in distilled water as in sea water but this cannot continue indefinitely since, for example, calcium is necessary for the formation of bones. When *Fundulus* develops in sea water the function of calcium may be purely protective at the start; later it becomes nutritive also.

But notwithstanding the complications due to nutritive functions, the importance of the protective action of salts is clearly evident in such solutions as sea water. This is also true of the blood of mammals and in this connection Loeb experimented on muscles, finding for example that in the absence of calcium they undergo rhythmical contractions, and he suggested that this might account for tetany under certain conditions. This suggestion has since found practical application in medicine.

The important question arose, What is the mechanism of the pro-

[6] Höber, R., *Klin. Woch.*, 1924, iii, 511.

tective action of salts? Loeb found that as soon as the embryo escaped from the egg membrane the whole picture changed and it was no longer possible, for example, to diminish the toxicity of sodium chloride by the addition of salts of lead or of zinc. Nor did calcium alone suffice to remove toxicity since the addition of potassium was also necessary (282).

He therefore concluded that the membrane plays an important rôle and that in a balanced solution the salts probably acted on it (or perhaps on the micropyle, which is regarded as especially permeable) in such fashion as to make it less permeable than in a solution containing a single salt. Hence it would appear necessary that the salts should act simultaneously in protective action: this is not the case with nutrient action where the salts can be given in succession.

The recent work of Bodine[7] and of Armstrong[8] indicating that dissecting off the membrane makes no essential change in certain reactions of the embryo, appears to mean that the seat of action is in these cases at the surface of the embryo.

Loeb also found that when eggs are placed in sufficiently concentrated sea water they float for several days. In a solution of pure sodium chloride they quickly sink and since he regarded the egg as normally almost impermeable to water he believed that this result indicated that salt had entered. Addition of a small amount of calcium chloride to the solution of sodium chloride enabled them to float for days, indicating that it inhibited the entrance of salt.

But it is also possible to assume that in certain cases penetration occurs and that the antagonistic action takes place in the protoplasm, especially in those cases where acids are antagonized by salts and the experiments show that the acid is absorbed by the organism (270).

He also considered the possibility that certain salts penetrate more rapidly because they attach themselves to the surface so as to form a more concentrated layer which increases the concentration gradient. If some of the salt in this layer is displaced by another salt the entrance of the first salt will be somewhat inhibited (and its exit facilitated) producing an antagonistic effect (266). In this connection he made

[7] Bodine, J. H., *Proc. Nat. Acad. Sc.*, 1927, xiii, 698; *Biol. Bull.*, 1928, liv, 396.
[8] Armstrong, P. B., *J. Gen. Physiol.*, 1927–28, xi, 515.

some very striking experiments with the dye neutral red: *Fundulus* eggs stain more rapidly in distilled water than in solutions containing salt or acid and lose the dye more rapidly in solutions containing salt or acid (without dye) than in distilled water.

The question of permeability began to assume an increasing importance as a factor which controls all the activities of the cell, but it was evident that for satisfactory progress methods must be found of determining exactly how fast substances can penetrate. He tried to test the hypothesis of Overton that the surface of the cell is lipoid and allows only substances soluble in lipoid to enter the cell. This seemed improbable because water passes rapidly into the cell and the substances normally taken up by the cell are in general insoluble in lipoid but are soluble in water. It seemed to him more probable that the surface of the cell is a protein film, such as forms spontaneously on the surfaces of aqueous solutions of protein. At the same time he thought that lipoids are present in or close to the surface of the egg and that they play an important rôle in the formation of the fertilization membrane.

Since as a rule salts are almost or quite insoluble in lipoid they could not be expected to penetrate a lipoid film, unless very slowly. But Loeb found evidence for the penetration of salts: for example, after the heart has begun to beat in the embryo of *Fundulus* (while still enclosed in the egg membrane) it can be brought to a standstill by the penetration of potassium salts. It was found (266, 269, 286, 287, 288, 289) that the membrane was almost impermeable to potassium salts in very dilute solutions but that the addition of more potassium salt (or certain other salts) made it more permeable: he called this "the general salt effect." If too much salt was added it again became impermeable (antagonistic effect).

He pointed out the analogy to globulins which are insoluble in low concentrations of salts, become soluble when the concentration increases sufficiently, but again become insoluble when the concentration becomes too great. He was therefore inclined to think that the increase of permeability was due to the solubility of a constituent of the membrane which behaves like globulin. On this basis one might expect that the addition of a neutral salt would increase the diffusion of alkali into the egg (and augment its toxicity) but would have the opposite effect on the diffusion of acid since analogous effects are observed on the solubility of globulins (303). The experiment showed that this expectation was justified.

Loeb found that to a certain extent the behavior of potassium in entering the cell is paralleled by that of acids (270). He observed that weak acids and bases appear to penetrate much more rapidly than strong ones, indicating that the protoplasm is not readily permeable to ions.

As part of his studies on the physiological effects of ions he desired to take up bioelectrical effects but his distrust of all but the simplest apparatus led him to postpone it until the advent of Beutner, whose training fitted him especially for the task. Together they studied the very interesting phenomenon of the "concentration effect," that is, the potential difference observed in leading off from two places in contact with different concentrations of the same salt. Employing mostly such plant tissues as apples and leaves of the India rubber tree they found that in dilute solutions they obtained the maximum values which were theoretically to be expected. The results indicated that the organism acts as a reversible electrode for all sorts of cations but the effects due to protoplasm are difficult to separate from those due to the dead cell wall.

Somewhat similar results had previously been obtained by MacDonald but their theoretical significance had not been understood and the work had been largely overlooked.

Loeb and Beutner endeavored to find non-living models which would act similarly and this undertaking (subsequently continued by Beutner) led to the discovery that many organic substances immiscible with water not only give the concentration effect but also act somewhat like living tissue when brought in contact with a series of different salts of the same concentration (chemical effect). Thus the way was opened up for the study of bioelectrical phenomena on a new basis.

As an illustration of his courage in attacking difficult problems we may consider his treatment of organization and adaptation. He was led to this problem by his experiments on the development of the egg. His general attitude may be stated in his own words:

"It is generally admitted that the individual physiological processes, such as digestion, metabolism, the production of heat or of electricity, are of a purely physicochemical character; and it is also conceded that the functions of individual organs, such as the eye or the ear, are to be analysed from the viewpoint of the physicist. When, however, the biologist is confronted with the fact that in the organism the parts are so adapted to each other as to give rise to a harmonious whole; and that the organisms are endowed with structures and instincts calculated to prolong their life and perpetuate their race, doubts as to the adequacy of a purely physicochemical viewpoint in biology may arise. The difficulties besetting the biologist in this problem have been rather increased than diminished by the discovery of Mendelian heredity, according to which each character is transmitted independently of any other character. Since the number of Mendelian characters in each organism is large, the possibility must be faced that the organism is merely a mosaic of independent hereditary characters. If this be the case the question arises: What moulds these independent characters into a harmonious whole?

"The vitalist settles this question by assuming the existence of a pre-established design for each organism and of a guiding 'force' or 'principle' which directs the working out of this design. Such assumptions remove the problem of accounting for the harmonious character of the organism from the field of physics or chemistry. The theory of natural selection invokes neither design nor purpose, but it is incomplete since it disregards the physicochemical constitution of living matter about which little was known until recently." (290, pages v-vi.)

The question therefore is, What ensures the integrity of the organism? He suggested that the unity of the organism might be largely determined at the outset by the structure of the protoplasm. In some eggs a definite structure is indicated by regions differing in appearance: from each of these certain organs arise. In these cases the egg might be regarded as a rough model of the future embryo. The harmonious correlation of the parts of the embryo might therefore be determined by the arrangement of the parts of the egg.

The fact that the structure of the egg is important might possibly be related to the fact that the size of the egg cannot be artificially diminished beyond a certain point without interfering with development. He undertook experiments like those performed on infusoria by Nussbaum and, employing different methods, caused the egg of the sea urchin to break up into small fragments. He concluded that only those fragments develop into plutei which contain in addition to the nucleus a sufficient amount of certain constituents of the cytoplasm.

Loeb felt that those who thought it impossible to account for development on a physicochemical basis might have been misled by the assumption that the cytoplasm of the egg is more homogeneous than is actually the case. He believed that proper recognition of the importance of the structure of the egg might change this point of view.

There are other things to consider, such as the mutual influence of the various parts, a factor which is capable in many cases of a mechanistic explanation. Thus he observed that in the yolk sac of *Fundulus* the pigment cells have at first no definite arrangement "but that they gradually are compelled to creep entirely on the blood vessels and form a sheath around them with the result that the yolk sac assumes a tiger-like marking." He regarded this as a tropistic reaction and believed that such reactions play an important part in development.

An analysis of the mechanics of development must include a study of regeneration. It had been assumed by some that when a missing part of the organism is replaced there must be a directive force which ensures that the regenerated part shall be just what is needed to complete the organism and enable it to perform its functions. Loeb found many cases where this is not so; for example, under some conditions a hydroid instead of regenerating a lost stolon produces a polyp "so that we have an animal terminating at both ends of its body in a head." Such cases of heteromorphosis are difficult to explain on the basis of a directive force which operates to supply the needs of the animal. They become more intelligible if we assume that the formation of organs is due to specific substances (as had been postulated by Sachs and others in the case of plants) and that where these substances accumulate the organ in question will be formed. This accumulation can be controlled to a certain extent by the experimenter. Loeb discussed this in connection with such cases as the development of legs in tadpoles. Young tadpoles have no legs but the mesenchyme cells from which the legs are to develop are present at an early stage. Ordinarily no growth occurs during a long period (from four months to a year or more) but Gudernatsch found that legs can be made to grow even in very young specimens by feeding them the thyroid glands of various animals. The mechanism of this process is not clear but Loeb suggested (257) that the stimulation of the growth of body cells might be analogous to the process by which the egg is caused to develop, *i.e.* by changes at the surface of the cell.

Another way in which one part can influence another is illustrated in plants: it seemed clear from the work of previous experimenters, as well as from his own, that one part can inhibit another by diverting the flow of formative material. Thus a bud at the top of the stem takes the material away from one lower down but if the terminal bud be removed the other begins to develop.

These facts made him feel that a mechanistic approach to the problem was possible. He went on to examine the equally important question of adaptation. He showed that many characteristics of the organism which are regarded as adaptive may be explained on a mechanistic basis. The reactions of animals to light depend on a photochemical substance which may arise without reference to adaptation and occur in animals which pass their lives in total darkness in the mud or under the bark of trees. One is no more under the logical necessity of supposing that heliotropism can arise only in response to a need or under the guidance of a "directive force" than in the case of galvanotropism where no one would dream of invoking such conceptions. The reactions of a galvanotropic animal are as beautifully developed as any tropism although in nature such animals are never exposed to electric currents. Since a mechanistic explanation appears possible here why not in the case of other tropisms?

He emphasized the fact that many cases of "adaptation" may very well be the "preadaptations" of Cuénot, *i.e.* "adaptations" which arise before they can be of any use, which would seem to rule out a directive force. Thus many marine organisms die when placed in concentrated sea water but the fish *Fundulus* is an exception. If a portion of the ocean became landlocked so that the concentration of salts increased and all the fish except *Fundulus* died an observer might easily suppose that these fish had gradually become adapted to the more concentrated sea water.

Curiously enough his attempts to increase the natural resistance of *Fundulus* by placing it in sea water which gradually became concentrated by evaporation had little result.

He stressed the fact that in many other instances, including the famous case of blind fish in caves, there is evidence in favor of the idea that the supposed "adaptation" may have been a "preadaptation."

When adaptation really exists it appears in many cases as if it could be explained on a mechanistic basis without invoking a directive force, as, for example, when (in collaboration with Wasteneys) he brought about an adaptation of *Fundulus* to life at higher temperatures, a change which has many physicochemical analogues.

These examples may suffice to illustrate his point of view. He felt, however, that here as elsewhere quantitative experiments are a necessity and he therefore determined to undertake such experiments in studying regeneration. He proposed to ascertain whether in this field, long a stronghold of vitalism, careful measurements would reveal the rule of mechanism or the reverse.

Obliged to put the problem aside until he could discover suitable material he eventually found what he needed in the life plant of Bermuda (*Bryophyllum calycinum*). Its large leaves have numerous marginal indentations in which new plants arise when a leaf is separated from the stem and placed in a moist atmosphere. He made numerous experiments with this plant. He employed as a criterion of growth the dry weights of the parts studied. The result was not doubtful; whenever measurements could be made a machine-like regularity became apparent; for example, not only did two leaves detached from the same point on the stem produce the same dry weight of new buds and roots, but when a leaf was removed, a small piece of the stem being left attached to it, and the new growth was confined to the attached piece of stem, it was equal to the growth of new buds and roots on a similar leaf deprived of stem. He began a program of research on this basis but the work progressed slowly because a single experiment might require weeks and he would not have more going on than he could observe with minute care. Hence it happened that at the time of his death the program was only begun. He had, however, arrived at some tentative conclusions which, even when they were not novel, were of interest on account of their quantitative basis.

He concluded that the production of buds at one end of the stem and roots at the other was not due to differences in the "ascending" and "descending" materials, as Sachs and others had supposed; also that the formative material moves more readily toward organs where the most rapid growth occurs, which explains why those organs inhibit others which are growing more slowly; also that gravity may cause sap to sink and so promote growth on the lower side. He likewise concluded that no "wound hormone" exists.

It is characteristic that he should so courageously attempt to place this difficult subject on a quantitative basis and to formulate it in mathematical terms.

An important episode which throws light on his habits of thought is his work upon the properties of proteins. His studies on the effects of ions had resulted in a series of articles in which he developed the idea (simultaneously with Pauli) that ions combine with proteins to form ion-protein compounds (70, 308). He also made the suggestion that pepsin owes its activity to its ionic state and that it is a weak base which becomes more ionized in acid solution and hence more active (trypsin being considered a weak acid). The idea had been published before, though without Loeb's knowledge. The suggestion was stimulating and led others to investigate the subject with the result that pepsin later came to be regarded as an amphoteric electrolyte (Michaelis) or as a monovalent anion (Northrop), trypsin being a monovalent cation (Northrop).

Carrying his studies on proteins as far as he thought that existing methods could give clear-cut results he turned aside to pursue certain other problems growing directly out of his work on ions, such as artificial parthenogenesis and antagonistic salt action.

But the fact that he laid them aside did not mean that they were out of mind. For nearly twenty years they remained in the background awaiting the opportunity which only a new method could furnish. One day, washing some eggs of *Fundulus* on a filter to free them from adhering salt solution, the idea occurred to him that he might treat proteins in the same way to get rid of the excess of substances which did not combine with them. He thereupon placed powdered gelatin in solutions of acids and bases, rinsed off the excess of solution on a filter, and determined how much remained in the gelatin, his preliminary assumption being that this represented the amount in actual combination with the protein. Thus a way seemed to be opened to determine whether proteins combined with these substances in definite proportions. Although he subsequently abandoned this method the fact remains that this idea was the starting point of his renewed activity in this field of work.

His experiments soon convinced him that the subject had fallen into confusion because of insufficient attention to the hydrogen ion concentration: methods of measuring and of controlling this had been developed since he had first attacked the subject and he now made good use of them, availing himself at the start of the assistance of Dr. K. G. Dernby. He had now found the needed clue and he set to work with characteristic energy.

The importance of the hydrogen ion concentration lies in the fact that in alkaline solutions the protein acts like an anion but in sufficiently acid solutions it behaves as a cation. At a certain hydrogenion concentration (the isoelectric point) these two actions are approximately equal. He found that gelatin at its isoelectric point (pH 4.7) is almost inert. Its combining power is so small that it can easily be freed from salts by bringing it to this point (a matter which certain industries later found to be of great practical importance). At this point its osmotic pressure, viscosity, power of swelling, and some other properties are at a minimum. On addition of acid or alkali these properties increase and by plotting them against the pH values characteristic curves are obtained.

The explanation of these curves came about in a very natural way. In order to measure the osmotic pressure of the solutions they were placed in bags of collodion, impermeable to gelatin but permeable to water and to salts. This created the condition necessary for a Donnan equilibrium and it became necessary to study the principle set forth by Donnan, particularly as previously applied by Procter and Wilson to the swelling of proteins. It was found that by means of the Donnan principle all these curves received a quantitative explanation: this was so complete that Loeb felt justified in saying that until an equally satisfactory theory could be found his explanation seemed bound to stand.

The Donnan principle (more properly called the Gibbs-Donnan principle) states that ions inside a membrane which are unable to pass through it affect the behavior of those that do, acting as if they attracted those of opposite sign (thereby increasing their concentration inside the membrane) and repelled those of the same sign (thus decreasing their concentration inside). It may be expressed by the equation:

$$C_i \, A_i = C_o \, A_o$$

in which C_i and A_i represent the concentrations inside the membrane of the cation and the anion respectively of a diffusible salt: C_o and A_o are the corresponding concentrations outside.

The fact that the Donnan principle applies indicates that the protein is present as ions (or charged particles acting as ions). At the isoelectric point the number of ions is at a minimum. When the solution is made more alkaline they increase in number just as if the protein were a weak acid: they also increase if acid is added instead of alkali, as if the protein were a weak base. The gelatin therefore acts as an amphoteric electrolyte, behaving as a cation below pH 4.7 and as an anion above this point. Assuming for convenience that the molecule has one acid and one basic group we should have at the isoelectric point $NH_2 - R - COOH$. On the addition of NaOH this would behave like a weak acid such as acetic acid and give sodium gelatinate, $NH_2 - R - COO^- + Na^+$ (which may be written $G^- + Na^+$). But if HCl were added the gelatin would behave like a weak base such as ammonia, giving gelatin chloride, $Cl^- + NH_3^+ - R - COOH$ (which may be written $Cl^- + G^+$).

It is therefore clear that the behavior of gelatin depends on its degree of ionization. The properties mentioned above have a minimum value at the isoelectric point because the ionization is at a minimum, and these values increase when acid or alkali is added because the ionization increases.

The Donnan principle leads us to expect that when protein is placed in a collodion sack which is permeable to water and to ordinary salts but not to the protein there will be a difference of potential between the inside and outside of the membrane (membrane potential). No one had succeeded in finding this but Loeb was able to demonstrate that it is present and that its magnitude is in accordance with the theory.

These facts are in harmony with the idea of Procter and Wilson that in the swelling of a gel each particle of protein acts very much like a collodion sack filled with a solution of protein and that the amount of swelling is proportional to the amount of pressure which would be produced in such a sack. In one case the molecules and ions of protein are kept together by the walls of the sack and in the other by their mutual coherence.

He concluded that the Donnan principle explains quantitatively some of the most puzzling peculiarities of proteins, such as the fact that, starting with the isoelectric point and adding acid or alkali, the osmotic pressure, viscosity, and swelling power increase up to a certain point and then begin to decrease. This depends on the sign and the charge of the cation of the alkali and on the anion of the acid which is added. These effects are diminished by neutral salts, the influence of the salt depending on the charge of the ion whose sign is opposite to that of the protein.

The presence in the solution of submicroscopic particles in addition to the gelatin ions and molecules introduces a complication but it is one which can be controlled and studied. It is evident that in so far as the gelatin forms particles it will behave as a colloid but in so far as it is in the form of molecules or ions it will behave as a crystalloid. But these molecules or ions will behave as colloids if prevented from diffusing (*e.g.* by means of a collodion membrane) and Loeb emphasized the fact that colloidal properties cannot be manifested unless diffusion is restricted by semipermeable membranes or by the coherence of the molecules to form particles. In this connection the semipermeable membranes of the living cell assume great importance.

He studied many other questions, such as the cataphoretic charge on proteins, which cannot be fully discussed here.

In view of his results Loeb felt obliged to reject many of the current conceptions regarding proteins, as, for example, the idea that the effect of acids, bases, and salts is due to adsorption and the theory that viscosity depends on the hydration of protein ions. He also concluded that under the conditions of these experiments the Hofmeister series did not apply. He pointed out the importance of the idea that proteins are amphoteric electrolytes and stressed the importance of quantitative methods of study, with careful control of the hydrogen ion concentration. He clearly indicated the significance of these facts and concepts for physiology.

His work was a powerful stimulus to research and is widely regarded as an immense simplification and clarification of the whole subject. He himself declared that his work was only a first approximation leaving much to be done to complete the picture.

It is of interest to note that just as the early distinction between colloids and crystalloids had been replaced by the idea that the same substance may be in a colloidal or a crystalloidal state, depending on the size of the particle, so Loeb substituted for this another conception, that of colloidal behavior, *i.e.* the same particles may behave as colloids or crystalloids depending on the presence or absence of semipermeable membranes.

In the course of this work Loeb was struck with the fact that a collodion bag full of salt solution placed in contact with pure water may show a movement of water outward, instead of the inward movement which would be expected on a purely osmotic basis. This phenomenon (which is known as anomalous osmosis) had been previously explained as due to a difference in potential on the two sides of the membrane, the latter charged by the adsorption of ions. To Loeb however this explanation was not satisfactory and he began in characteristic fashion to resolve this complex problem into its component parts by setting up experiments in which each factor could be studied separately.

He recognized the fact that anomalous osmosis is much more marked in dilute solutions and that it makes a great difference whether the experiment is made with an ordinary collodion membrane or one which has been treated with protein. He summed up his observations in the following rules:

"1. Solutions of neutral salts possessing a univalent or bivalent cation influence the rate of diffusion of water through a collodion membrane, as if the water particles were charged positively and were attracted by the anion and repelled by the cation of the electrolyte; the attractive and repulsive action increasing with the number of charges of the ion and diminishing inversely with a quantity which we will designate arbitrarily as the 'radius' of the ion. The same rule applies to solutions of alkalies.

"2. Solutions of neutral or acid salts possessing a trivalent or tetravalent cation influence the rate of diffusion of water through a collodion membrane as if the particles of water were charged negatively and were attracted by the cation and repelled by the anion of the electrolyte. Solutions of acids obey the same rule, the high electrostatic effect of the hydrogen ion being probably due to its small 'ionic radius'" (328).

He showed experimentally that Rule 1 was valid whether the collodion membranes were treated with proteins or not but that Rule 2 did not apply to untreated membranes. Thus when solutions of salts with a trivalent cation were separated from pure water by a protein-treated collodion membrane, water diffused rapidly from the solvent into the solution while no water diffused into the solution when untreated membranes were employed. Negative osmosis could be shown with acids only when the electrolyte was separated from pure water by a protein-treated membrane.

These seemingly paradoxical phenomena were explained by Loeb as due to the behavior of the proteins towards acids and alkalies. Untreated collodion membranes are always negatively charged in contact with pure water whether hydrogen ions or trivalent cations are present or not. Treated collodion membranes are also negatively charged on the alkaline side of the isoelectric point of the protein employed but positively charged when the protein is acid. This might be expected since in alkaline solutions the protein functions as the anion and in acid solutions as the cation. The anomalous behavior of trivalent ions was shown to be due to the formation of complex ions between the trivalent metal and the protein used to coat the collodion membrane. Salts with trivalent cations, such as $LaCl_3$, form with proteins complex ions which are positively charged but tetravalent anions, such as Na_4FeCN_6, yield complex ions which are negatively charged.

He further showed from experiments at different pH values that, due to the presence of protein in the membrane, a Donnan equilibrium was set up with the result that some of the acid is forced from the salt solution into the outer liquid which originally contained no salt. The difference in hydrogen ion concentration inside and outside of the membrane creates a potential difference.

A contributing factor is the diffusion potential (which would exist even though no membrane were present): this is apparently responsible for the fact that when the pH value is the same on both sides of the membrane (and lies on the acid side of the isoelectric point of the protein contained in the membrane) the rate of diffusion of negatively charged water into salt solution increases with the valency of the cation and diminishes with the valency of the anion of the salt. In the case of monovalent cations the diffusion of water into the salt solution was found to vary inversely as the relative mobility of the cations employed.

The distinct contribution of Loeb in the field of anomalous osmosis lies in the fact that his explanation does not involve adsorption.

In the midst of his research on proteins he was stricken down. Death came when he was actively engaged in what he regarded as the most fundamental investigation of his life. He himself said that it was the work with which he should have begun, since it was more logical to commence with the simpler systems found in colloids than with such conditions as exist in protoplasm. But indeed none could know better than he that the ways of research are not to be regarded as mere matters of logic.

III.

This brief sketch may serve to outline the development of his ideas. But since the man was greater than his work his achievement cannot be properly understood without some notion of his personality.

We must recognize that he was above all an idealist. Protected by academic life, and by a devoted wife who knew how to aid him in times of stress and encourage him during his hours of depression, he lived largely apart in a world of ideals. They wrought in him so powerfully that he spoke to his followers with prophetic fire. Their inspiration lured him on, dominating his life. He embodied Pasteur's profession of faith before the Academy, in the words now graven on his tomb: "Heureux celui qui porte en soi un dieu, un idéal de beauté, et qui lui obéit."

The austerity which goes naturally with high ideals, the temper of the aristocrat in the finest sense of the word, was his, but he had also a tender heart which felt the sorrows of all who suffered and his sympathy was always with the masses who struggle against oppression whether economic or spiritual.

We must also realize that he had the temperament of an artist, running the gamut of the creative imagination, its brooding depression, its rare exaltation. He knew the heights and the depths but not the happy mean of mediocrity. That nobility of soul which accompanies this temperament at its best was also his: a fine scorn of injustice, grossness, and all unbeautiful things.

The outstanding feature of his intellectual equipment was his creative imagination, implying prophetic vision, the intuitive and emotional urge of ideas which we call divination, the qualities that raise the seer above the common run.

With such a temperament intense mental effort may result in exhilaration rather than exhaustion. If this be called capacity for work we should realize that it is quite different from the capacity for doing disagreeable work. To him research was a joyous adventure, however much it involved that might be called drudgery.

It is no exaggeration to say that he lived in his work as do few men. It seemed as though his mind were continually occupied with his problems not only when awake but even during sleep when subconscious processes seemed to carry on with troublesome questions which might yield him a solution in the morning. When he reached a point where he was making no progress he turned to something else until these processes were readjusted and he could make a fresh start. He often found it advantageous to keep two or more pieces of work going on so that he could rest by turning from one to the other, as when he found recreation in working with *Bryophyllum* during his researches on proteins. His career illustrates the fact that continual concentration of mind (purely spontaneous, and very different from a forced concentration which cannot be long sustained) can produce an astonishing quickness of judgment, the ability to proceed with confidence when others find themselves at loss.

Fortunately his poetic imagination was associated with a keen critical sense. The more audacious the conception the more rigorous must be the proof. He would test and retest his conceptions and repeat his experiments over and over again. It is remarkable that so few of his observations of fact had subsequently to be modified. He published only a small part of his experimental work, and of the many suggestions that occurred to him few found their way into print. His students were often amused when he began to think aloud in the midst of a lecture, making and discarding one hypothesis after another for he had the rare gift of thinking while he spoke. He was wont to say "Nothing is so cheap as an idea." Indeed ideas came so rapidly that often he did not know which to follow. But when one had been selected he was not satisfied until he had thoroughly tested it.

He rarely published an observation without formulating a working hypothesis regarding the underlying causes. But he regarded such working hypotheses merely as temporary tools to be discarded when better could be found and he never hesitated to reject his own hypotheses when he could replace them by juster conceptions.

With this critical attitude toward his own work, which developed more and more as he grew older, it was natural that he should be as critical of others: but he shrank from giving pain and always hesitated a long time before publishing his criticisms. If attacked he proved himself a doughty antagonist.

The questions he put to nature were never dull and in consequence the answers he received were always interesting, sometimes startlingly so. He did not begin to work until he felt that he had framed the question properly. He assumed that in order to put an intelligent question to nature there must be a clear guiding principle. He did not believe in plunging blindly into the labyrinth. He was not satisfied until he had pondered on all the possibilities, both of attack and of interpretation, knowing that a bizarre suggestion is often the one that leads to discoveries. His method of approach was seldom conventional and the result was apt to be surprising. His colleagues were often astonished when he seized upon a subject from an entirely new angle. A scientist who had devoted much time and thought to formulating certain rules of scientific discovery exclaimed in disgust "He has no right to make such discoveries."

When the question had been formulated he recognized that the chance of a successful answer lay largely in the choice of material. In this respect he displayed great sagacity. It is said that when he began his work on tropisms he was found among the cases of the museum looking for animals that most resembled plants. True or not, the story illustrates his habit of mind.

His notion of biological research was simple: all the observed phenomena should be expressed in the form of equations containing no arbitrary constants. Anything short of this is to be regarded as merely preliminary. In attempting such a program the success of the investigator must depend on his capacity and courage, his choice of material, and the state of science, particularly on the state of physics and chemistry. He must know enough about organisms to be able to make a wise choice of material and thoroughly to understand the behavior of the form which he selects. He must be preparèd to assist in clearing up the particular field of physics or chemistry which he needs to use as a tool, as Loeb himself illustrated in his work on colloids.

He felt that the biologist should aim at the same sort of control over living matter that the physicist and chemist have over their material and that the best prospect of success lies in applying their methods to biology. His attitude may be illustrated by a quotation.

"Facts of this character should dispose of the idea that the organism as a whole does not react with that degree of machine-like precision which we find in the realm of physics and chemistry. Such an idea could only arise from the fact that biologists have not been in the habit of looking for quantitative laws, chiefly, perhaps, because the difficulties due to disturbing secondary factors were too great. The worker in physics knows that in order to discover the laws of a phenomenon all the disturbing factors which might influence the result must first be removed. When the biologist works with an organism as a whole he is rarely able to accomplish this since the various disturbing influences, being inseparable from the life of the organism, can often not be entirely removed. In this case the biologist must look for an organism in which by chance this elimination of secondary conditions is possible. The following example may serve as an illustration of this rather important point in biological work. Although all normal human beings have about the same temperature, yet if the heart-beats of a large number of healthy human beings are measured the rate is found to vary enormously. Thus v. Kőrösy found among soldiers under the most favourable and most constant conditions of observations —the soldiers were examined early in the morning before rising—variations in the rate of heart-beat between 42 and 108. In view of this fact, those opposed to the idea that the organism as a whole obeys purely physico-chemical laws might find it preposterous to imagine that the rate of heart-beat could be used as a thermometer. Yet if we observe the influence of temperature on the rate of the heart-beat of a large number of embryos of the fish *Fundulus*, while the embryos are still in the egg, we find that at the same temperature each heart beats at the same rate, the deviations being only slight and such as the fluctuating variations would demand.[9] This constancy is so great that the rate of heart-beat of these embryos could in fact be used as a rough thermometer. . . . .

"Why does each embryo have the same rate of heart-beat at the same temperature in contradistinction to the enormous variability of the same rate in man? The answer is, on account of the elimination of all secondary disturbing factors. In the embryo of *Fundulus* the heart-beat is a function almost if not exclusively of two variables, the mass of enzymes for the chemical reactions underlying the heart-beat and the temperature. By inheritance the mass of enzymes is approximately the same and in this way all the embryos beat at the same rate (within the limits of the fluctuating variation) at the same temperature. This identity exists, however, only as long as the embryo is relatively quiet in the egg. As soon as the embryo begins to move this equality disappears since the motion influences the heart-beat and the motility of different embryos differs.

[9] Loeb, J., and Ewald, W. F., *Biochem. Z.*, 1913–14, lviii, 179.

"In man the number of disturbing factors is so great that no equality of the rate for the same temperature can be expected. Differences in emotions or the internal secretions following the emotions, differences in previous diseases and their after-effects, differences in metabolism, differences in the use of narcotics or drugs, and differences in activity are only some of the number of variables which enter." (290, pages 299–302.)

The urge of his mind was to see each subject simply and as a whole. He was not content to pursue a special part of a problem without considering its relation to all the rest. Processes in particular animals must be compared with those of other animals, of plants, and of inorganic nature. Nor was he satisfied to find that they had something in common but he must work until its real nature was evident, until his idea of it was so clear and simple as to become a tool of precision and power. To achieve this it was necessary both to simplify and to generalize and these powers he possessed to an extraordinary degree.

It was sometimes said that he pictured his problems too simply and was satisfied with explanations too simple to correspond to reality. But this was an important factor in his success for it encouraged him to attack complicated problems and proceed as far as possible. If the point at which he stopped was not always as near to the ultimate solution as he himself thought this can in no way detract from the value of what he actually contributed.

All his experimentation bore the hall-mark of austere simplicity. It was a part of his temperament to distrust complicated apparatus. Few could devise such simple and decisive means of testing their hypotheses. He eliminated errors due to the variation in organisms by performing great numbers of experiments with innumerable controls, repeating again and again until the possibility of error seemed to be eliminated. He showed remarkable sagacity in choosing the material where life processes could be studied in a clear and simple way by using the methods of physics and chemistry and he had great skill in finding the procedure which would bring out the essentials of the phenomenon in question. He wasted no time in unprofitable experiments. If he could not find an organism which would give an unequivocal answer to the question he put the problem aside until a suitable organism should be found. Though he might wait for years he was prompt to act when the right material presented itself.

Courage played a great part in his success. He did not select problems because they were easy but because of their importance. That at the very outset he attempted to investigate the freedom of the will on an experimental basis illustrates this. With him one felt the power of a mind which gloried in difficult problems, with a confidence in its power to conquer that came from a long series of triumphs. It was a mind always alert, poised to turn easily in any direction, and operating with bewildering speed and certainty.

His courage sprang largely from his faith in the cause to which he consecrated his life: a conviction that mechanism could explain the most baffling mysteries. It almost approached a dogma and his zeal knew no limits. It was a militant faith calculated to move mountains and it grew firmer with each new discovery. If a philosophy be judged by its fruits his convictions justified themselves for they inspired him to attack apparently impossible problems with an audacity that was often justified by important discoveries. Can any one suppose that he would have discovered more if he had been a vitalist?

This magnificent faith and enthusiasm seemed at times to transfigure him so that it was not strange that young men followed him gladly. He always encouraged their efforts and was eager to help them. He had a truly lovable and sympathetic personality that drew men irresistibly. His teaching was inspiring and unforgettable. It was free from pedantry and pose because they were utterly foreign to his nature. He detested sham: and the ways of the politician were anathema to him. One felt instinctively that he cared only for truth and that in its quest he would spare no labor or sacrifice.

The eager, impatient student found in him a spirit zealous, quick, and full of youthful fire: and indeed his enthusiasm kept him always young. He lectured with a dramatic intensity which sprang from deep feeling. To an interested student he would pour forth his soul but he was little inclined to lure or drive an unwilling pupil. He could not sympathize with the idea that pedagogy consists in subduing the class to a state in which it can no longer resist instruction.

His intimate talks in the laboratory were at once the joy and despair of fellow workers. His mobile features, his expressive, eager eyes, alight with enthusiasm, were a fascinating study as he flashed from mood to mood, smiles and frowns following in rapid succession.

Quick to wrath, he was also quick to feel the folly of anger and in the midst of a tempest he would suddenly stop, then smile, and at length burst into laughter as the incongruity of the situation dawned upon him. And his laughter was without after-trace of anger, open, whole hearted, and reassuring

His sense of humor was extraordinary: he dearly loved a joke even at his own expense. When in the mood he was unsurpassable both for wit and humor. At such times he relaxed completely, and indeed these moments were almost his only relaxation. But they seemed to suffice and after them he would resume his toil wholly refreshed.

In conversation the emotional character of his thought, with its sudden flashes, might sometimes prove exhausting or even bewildering to more phlegmatic natures. A visitor to his laboratory was quite apt to leave in a somewhat breathless state. The rapidity with which ideas were suggested, examined, and rejected was often astonishing. But conceptions that survived were treasured, to be thought through, dreamed over, and worked at, under an emotional stress which is often evident in his writing.

This emotional urge seemed to be capable of lifting him above personal considerations to levels of objectivity not always realized by those who did not come into personal contact with him. And this seemed to him the true scientific attitude: it was not surprising that in dedicating one of his books (290) to Diderot he should quote the words of John Morley: "He was one of those simple, disinterested, and intellectually sterling workers to whom their own personality is as nothing in the presence of the vast subjects that engage the thoughts of their lives."

Often dogmatic in expressing his views, he was always open to conviction and would at once admit the correctness of an opposing view if the evidence offered were sufficient. His criticism of opponents involved no personal malice and if they were in trouble none could be readier with assistance and sympathy. Indeed he was continually going out of his way to help people who were almost unknown to him. This quality greatly endeared him to his students, who felt for him gratitude and trust as well as admiration.

It is difficult to understand how one absorbed in such great tasks could find time for so many acts of thoughtfulness: could allow himself to be so continually interrupted by those seeking help. It is no wonder that all who knew him testify to his immeasurable kindness. What Roux said of Pasteur applies also to Loeb: "L'œuvre . . . . est admirable, elle montre son génie, mais il faut avoir vécu dans son intimité pour connaître toute la bonté de son coeur."

The range of his reading was indeed a continual marvel. Scientific books and periodicals of all kinds were eagerly devoured and with unflagging interest he followed the newer developments of sociology, politics, and belles lettres. He could get the gist of an article very quickly and his astonishing memory seemed never to let anything slip. He sometimes quoted a remark of Sachs: "All originality comes from reading," meaning that it is necessary to be familiar with what is known in order to strike out in new directions.

This breadth of knowledge made it natural for him to utilize in his work recent advances in other fields of science. Thus he took the idea of tropisms and of heteromorphosis from botany: he applied to biology the theories of dissociation and osmotic pressure which resulted in the discovery of artificial parthenogenesis and antagonistic salt action. And to the very end of his life he kept in touch with recent progress in physics and chemistry and found application for much of it in his own studies. In his hands this cross-pollination of the sciences produced excellent fruit.

His multiplicity of learning was correlated by a synthetic imagination, an instinctive ability to unite harmoniously the diverse elements of different disciplines. He seemed at home in many fields and passed without effort or hesitation from one to another. He mingled the best elements of French and German culture; he successfully combined physical and chemical methods in the solution of his problems; he used in a masterly way the methods of the exact sciences to deal with vague and mystical biological concepts.

In all this he was aided by circumstances. His youth was a time of "Sturm und Drang" in the physiological sciences, when new wine was being put into old bottles, and the great impetus given to physiology by Claude Bernard and Johannes Müller was felt by a host of keen young workers of unusual ability and enthusiasm. At that time, too, the youthful science of physical chemistry was making extraordinary strides. Loeb appeared at the right moment to take advantage of these remarkable circumstances and he utilized them with astonishing skill.

Such are some obvious aspects of this many-sided man, superficial features easy to recognize: but indeed to know his mind and heart is another matter.

Here we may perhaps pause to ask ourselves, How are we to remember him? He was an idealist, sympathizing keenly with all suffering, consecrating his gifts to humanity, finding in every discovery a weapon against superstition: a scientist with an artist's soul, emotional, intuitive, creative: a thinker, strangely original, born to blaze fresh trails and teach new doctrines with a prophet's zeal: and a dreamer, regarding the world of life with the poetic insight of a seer, and seeking, with creative imagination rarely equalled, to sweep aside its mystery and set free the mind of man.

"And he being dead yet speaketh." His visions that have made others see visions, his ideals that quicken the heart of youth, cannot but continue to shed inspiration, in circles that widen more and more; and in shaping the soul of the future he may serve humanity more than he dared to dream.