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WARREN HARMON LEWIS

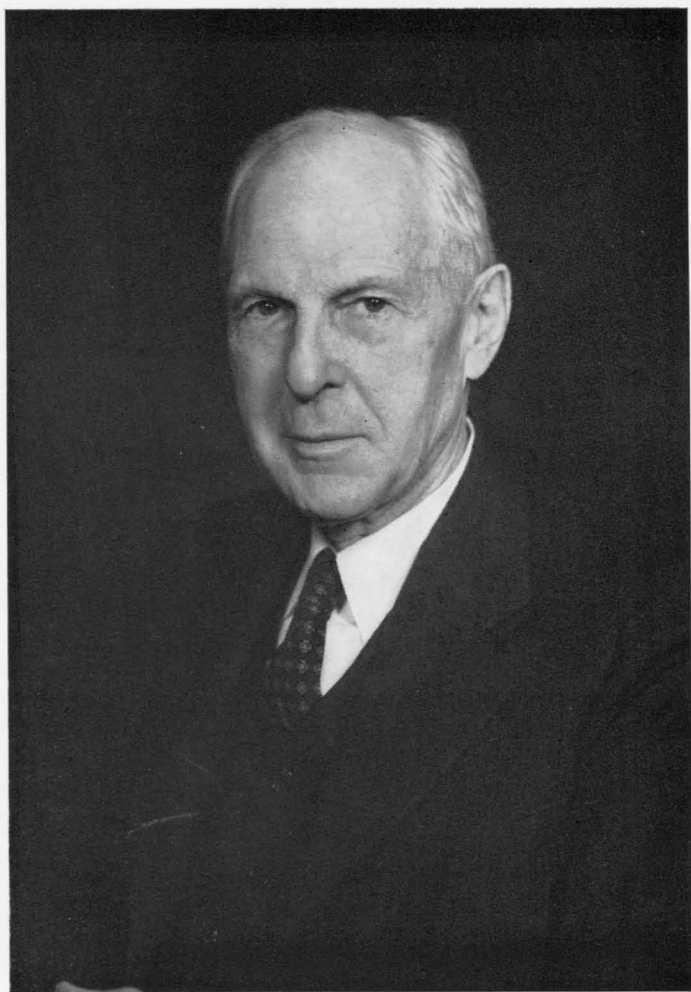
1870—1964

A Biographical Memoir by
GEORGE W. CORNER

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Biographical Memoir

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June 17, 1870–July 3, 1964

BY GEORGE W. CORNER

WARREN HARMON LEWIS was engaged for more than fifty years in continuously productive research in human anatomy, descriptive and experimental embryology, and experimental cytology. His many contributions to science include pioneering work in two fields; first, discoveries concerning the embryology of the eye, basic to the modern theory of embryonic induction; and second, fundamental study of the structure and behavior of living cells in tissue cultures, begun and carried on for more than forty years in association with his able wife, Margaret Reed Lewis.

Warren H. Lewis was born June 17, 1870, in Suffield, Connecticut, a small town fifteen miles north of Hartford near the Massachusetts border. He was the eldest child of John Lewis, Yale graduate and able lawyer, and his wife Adelaide, née Harmon. While the boy was still an infant, his parents moved to Chicago, where John Lewis practiced his profession with considerable success and took an active part in the community life of Oak Park, the suburb in which he resided.

Warren Lewis began his education in the public schools of Oak Park, and from 1886 to 1889 attended the Chicago Manual Training School. In boyhood an interest in botany was awakened by his mother's gift of a copy of one of Asa Gray's books. During his high school days he made a large collection of

plants. Throughout his life he retained this interest and could readily identify trees, shrubs, and wildflowers seen on his walks in the country. A half-brother, much younger, recalls some dissections, of a snake and a bird or two, which Warren must have made when a college student. He took his B. S. degree at the University of Michigan in 1894 and after graduation stayed there for two years as an assistant in zoology. Jacob Reighard, an accomplished naturalist and comparative anatomist, was then active in the Department of Zoology and headed it during Lewis's last year there. No doubt he was helpful to the young assistant, whose bent was strongly anatomical.

In the fall of 1896 Lewis entered the Medical School of The Johns Hopkins University, as a member of the fourth class to study at that young school which was drawing many students of great promise from all parts of the country. His professors were of the highest distinction: the famous "Four Doctors" of Sargent's painting, Welch, Halsted, Osler, and Kelly; and even more important for a student with scientific interests, John J. Abel, William H. Howell, and, in anatomy, Franklin P. Mall. Lewis was strongly attracted to Mall's department, of which Charles R. Bardeen and Ross G. Harrison were then senior members. When Lewis, immediately after his graduation in medicine, in 1900, joined the department as assistant in anatomy, his medical classmates Florence R. Sabin and John Bruce MacCallum also became assistants in the same department. All these young anatomists (Mall himself was only thirty-four years of age when Lewis became his pupil) attained renown in American science. Every one of them (except the brilliant MacCallum, who died early) became in later years presidents of the American Association of Anatomists, and four of them were elected to the National Academy of Sciences.

Mall had assembled in his laboratory the largest collection of human embryos in America, and had made the study of

human development a principal interest of his department. In that field Lewis undertook his first research, in collaboration with Bardeen, who was studying the embryological development of the human muscular system. In 1901 Lewis published in the *Bulletin of the Johns Hopkins Hospital* his first paper, a description of the pectoralis major muscle and some of its variations. When, in the same year, the *American Journal of Anatomy* was launched from Mall's laboratory, the first article in the first number was a joint paper by Bardeen and Lewis on the development of the muscles of the limbs and trunk. Based on skillful dissections and reconstructions, and handsomely illustrated, this report was far in advance of previous work in the field and remains the classical monograph on the subject. A year later Lewis published a detailed paper of his own, of equal excellence, on the development of the musculature of the arm.

Meanwhile Lewis was turning to experimental embryology. During a summer at Woods Hole (presumably in 1901) he was fortunate enough to assist Jacques Loeb in an unusual investigation by that imaginative physiologist. Loeb, much interested in the factors controlling the span of life and the rate of life processes, was studying a seemingly paradoxical action of potassium cyanide on the eggs of sea urchins. When he immersed unfertilized eggs in very weak solutions of this deadly antioxidative poison, to his surprise their life was not terminated but prolonged; the explanation reached by Loeb and Lewis, that very dilute cyanide did not abolish but merely slowed oxidative processes in the cells, formed part of Loeb's subsequent mechanistic explanation of cell life. A summer with Jacques Loeb could not fail to open the eyes of his young associate to the exciting possibilities of experimental cytology. We may suppose also that the work imbued Lewis with Loeb's characteristically simple and direct methods of investigation,

and thus prepared him for his own notably similar approach to the problem of tissue culture which occupied him a decade later.

About 1902 Lewis visited Europe and worked for a time in the laboratory of Moritz Nussbaum at Bonn, where at the professor's suggestion he looked into the origin of the ciliary muscle of the eye. Nussbaum's recent discovery (1901) that the sphincter pupillae and retractor lentis muscles, unlike most others, originate from ectodermal epithelium rather than mesenchyme had weakened the doctrine of rigid specificity of the outer germ layer. Nussbaum suspected that the ciliary muscle also is derived from ectoderm. Lewis, working with chick embryos, found no evidence for this supposition, but in the course of his study observed that wandering pigment cells which ultimately enter the iris originate from ectodermal tissue in the optic cup. This observation, published in 1903, was completely new. As the first evidence that pigment cells in the connective tissues may have originated in ectoderm, it considerably increased the embryologists' growing doubts of the specificity of the germ layers. The great potentialities of the ectoderm, as of the other germ layers, have since been abundantly demonstrated.

Back at Baltimore, in the spring of 1903 Lewis continued his study of the development of the eye, but with a different and broader aim. The problem, he wrote in 1905, was "to determine how far the various organs and tissues are dependent or independent of the various other tissues for their origin, differentiation, and growth." He proposed to attack this problem by experiment, choosing an organ—the eye—with whose development he had become familiar through his work at Bonn.

A good clue for starting his experiments had recently been provided by Hans Spemann, then at the Kaiser Wilhelm Institute, Berlin-Dahlem. The lens of the vertebrate eye, as was then well known, is formed from the ectoderm (the skin layer)

which overlies the optic vesicle, an outgrowth of the embryonic brain. As the lens forms by conversion of ectodermal cells into primitive lens fibers, it fits into the open cup of the vesicle and thus becomes part of the eye. The skin tissue from which it developed closes over and is in turn converted into corneal tissue. Spemann found (1901), by experiments on embryos of the European newt *Triton*, that the formation of a lens from the undifferentiated ectoderm depends upon prior development of the optic cup. If the experimenter, by puncturing the early embryonic brain tissue where the optic cup is about to form, prevents its formation, then the lens will also fail to develop. In some of Spemann's experiments the future optic vesicle regenerated and grew out to touch the overlying ectoderm. In that case the ectoderm formed a lens. Spemann suggested that it would be instructive, if it were possible, either to transplant the optic vesicle to a new location in the body or else to transplant ectodermal tissue from some other region to a position immediately over the optic cup. In either case the optic cup would make contact with overlying ectoderm not originally destined to form lens tissue. Development of a lens under these conditions would constitute proof of the induction hypothesis.

Lewis in 1903 undertook the more feasible of these seemingly almost impossible projects, that of substituting ordinary ectoderm for that originally overlying the optic cup. For the operative technique he had as guide the experimental work of Gustav Born of Breslau (1896-1897), who had made composite frog embryos from parts of two individuals by grafting operations. Lewis was familiar with Born's methods through his senior colleague at Baltimore, Ross Harrison, who had learned them while in Germany and had used them in spectacular experiments on growth and regeneration of the embryonic frog's tail. Born had worked with a simple head-borne magnifier (watch-

maker's loupe); Lewis availed himself of the newly perfected binocular dissecting microscope. With its superior magnification, using very delicate instruments, he could make exceedingly minute dissections of the tiny living embryo, removing or transplanting various organs. In this very considerable enrichment of the technique of experimental embryology, Lewis was an unacknowledged pioneer. Other workers besides Born and Harrison had transplanted limbs and tails, or excised accessible organs; Lewis was the first to do more refined experimental operations on amphibian embryos on a microscopic scale.

His experiments of 1903 showed beyond doubt that embryonic skin taken from the trunk region, if placed over the optic cup, would indeed be converted into a lens. This brilliantly clear result was the first experimental proof of embryonic induction, i.e., the action by which an already differentiated tissue causes a contiguous undifferentiated tissue to develop new characteristics. In 1907 Lewis reported having successfully accomplished the much more difficult reverse experiment suggested by Spemann, namely, transplantation of the embryonic optic cup to bring it under ectoderm not normally destined to form a lens. The transplanted optic cup, he found, induced lens formation as well as if it had been left at its original site. In somewhat earlier experiments he had found that differentiation of the cornea as well as the lens depends upon the inductive influence of the optic cup.

In 1907 Lewis reported another set of embryological experiments of a kind never previously attempted. Following up hints from Wilhelm Roux and Thomas Hunt Morgan that the dorsal lip of the blastopore of the amphibian gastrula constitutes in some way a center of directive influence for the differentiation of organs and special tissues, Lewis transplanted small pieces of tissue from the lips of the blastopore (in the late gastrula stage) to other parts of the embryo and found that as expected they

differentiated into structures characteristic of the embryonic axis. In one of these experiments he noted that the ectoderm under which he had placed one of the bits containing notochordal tissue was converted into the beginnings of a neural tube; but assuming, like Roux and Morgan, that the rim of the blastopore is self-differentiated, Lewis did not from this single case interpret the result as did Spemann, who from similar experiments a few years later developed the general organizer theory.

During the progress of his embryological experiments Lewis was making himself a valuable member of Mall's department. He was promoted from assistant to instructor in 1901, to associate (the Johns Hopkins equivalent of assistant professor) in 1903, and to associate professor in 1904. Harrison's departure for Yale in 1907 left Lewis as Mall's senior colleague. No doubt he too was sought by other universities, like his predecessors on Mall's staff. Records of such calls, if any came, are now lacking, but it was doubtless to hold Lewis in Baltimore that in 1914 The Johns Hopkins University took the then unusual step of creating for him a second chair in the Department of Anatomy, with the title of Professor of Physiological Anatomy.

Mall and his staff expected medical students to take the initiative in their study, not to depend upon their teachers for detailed guidance. After simple instruction in the art of dissection, they were left alone except for the daily visit of an instructor, who inspected their work, asked a few questions, and stood ready to give advice if requested. Lewis's students found him a master of gross anatomy and a willing tutor, but reserved and shy. At his daily quizzes he wore a mask of seriousness, even severity, that sometimes alarmed students who did not know his native kindness.

Although Lewis was, from 1903 on, deeply engaged in research in experimental embryology, his loyalty to Mall and

responsibility for the course in gross human anatomy recalled him from time to time to morphological work. At Mall's request he prepared for the Keibel-Mall *Handbook of Human Embryology* (1910) a compendious chapter on the development of the muscular system, based largely on the research he and Bardeen had done several years earlier. This chapter is still the best source of information on the subject.

In 1913 Mall achieved the dream of his lifetime when a grant from the Carnegie Institution of Washington enabled him to start building a research staff for the intensive study of human embryology that became the Department of Embryology of the Carnegie Institution. Lewis, anxious to support his chief's enterprise, undertook to work up a full description of a remarkably perfect human embryo 21 millimeters in length (No. 460 in Mall's collection) which by reason of its stage of development offered a rich store of information about early organogenesis. The first task in such a study was to construct, from serial sections of the embryo, a large-scale model of its external form and internal structure. In the course of this reconstruction, Lewis devised several improvements on the standard wax-plate method of modeling embryos. In place of outline drawings of each section he used enlarged photomicrographs on which, by technical means that need not be detailed here, he inscribed lines indicating reference-planes through the embryo by which the wax plates representing each section could be accurately piled. He also invented the idea of piling not the wax cutouts of the sections but, instead, the rectangular plates from which they had been cut. Thus the plates when stacked formed a block of wax containing a cavity representing the form to be modeled, into which liquid plaster of Paris was poured. After the plaster solidified, the wax was melted off, leaving a plaster model that would withstand Baltimore's summer heat. These innovations by Warren Lewis, modified only in detail by later workers, be-

came the standard procedure by which the Carnegie staff created a comprehensive series of embryological models exceeding in accuracy all previous productions of the sort.

Although Lewis completed his models of Carnegie No. 460, he was too much involved, after 1911, in the pioneering work on tissue culture, which will be described a little later, to publish all the findings of the reconstruction. He wrote, in fact, only one paper on this embryo, a monograph of 1920 in the *Carnegie Contributions to Embryology*, describing the cartilaginous skull, which in this embryo was at a specially instructive stage of development.

One more contribution to human morphology must be mentioned here before we revert to Lewis's experimental work. At the request of the publishers of the American edition of *Gray's Anatomy*, Lewis took over and held for twenty-four years the laborious task of editing and revising the successive editions of that famous and massive textbook. In 1918 he brought out the revised 20th edition, in which he clarified obscurities and included recent advances. At intervals of six years thereafter he produced the 21st, 22d, 23d, and 24th editions, maintaining the book's usefulness and its popularity with teachers and students, who profited by the competent revisions of an editor familiar with current research in developmental and physiological anatomy.

The year 1910 had seen an abrupt change in the direction of Lewis's experimental work and also in his personal affairs. On May 23 of that year he married Margaret Reed, an accomplished experimental biologist eleven years his junior. A graduate of Goucher College, she began her training for research as a graduate student and assistant of Thomas Hunt Morgan while he was at Bryn Mawr College and afterward at Columbia University, to which he moved in 1904. She subsequently taught physiology and biology successively at New York Medical Col-

lege, Barnard College, and Miss Chapin's School. The Lewises, like so many scientific couples, first met at the Marine Biological Laboratory, Woods Hole. Before her marriage Margaret Reed had published several papers on regeneration in the crayfish and on early amphibian embryology. After marriage she became a prolific contributor to anatomical and pathological journals, annually publishing one or more papers, jointly with her husband or other collaborators, or in her own name alone, except in those years in which the births of her three children temporarily interrupted laboratory work.

The marriage of these two able biologists initiated for both a lifetime of work in a new field of research. To understand the place of Warren and Margaret Lewis in the history of tissue culture, we must review the earliest developments in the field. In 1907 Ross G. Harrison was studying at Johns Hopkins the much-discussed question of how the long nerve filament or axon of a nerve cell is formed, whether by outgrowth from the cell or by the linking up of short strands locally developed. To answer the question, Harrison took a bit of living tissue from the central nervous system of a young frog embryo before the axons had begun to form and placed it in a drop of frog's lymph on a hollowed-out glass slide. Watching this tissue under the microscope for some days or weeks, he observed that the axons grew out from the bodies of the embryonic nerve cells. For this achievement Harrison is everywhere recognized as the originator of tissue culture.

In the following year (1908) Margaret Reed, the future Mrs. Warren H. Lewis, was in Berlin working in Max Hartmann's laboratory at the Institut für Infektions-Krankheiten. There she had an experience, important to a degree perhaps not at once appreciated, upon which her scientific career, and also that of her husband after 1910, was to be founded. While working with Dr. Rhoda Erdmann, who was cultivating

amoebae on nutrient agar, made up with physiological salt solution, Margaret Reed explanted a bit of bone marrow from a guinea pig into a tube of this medium. She observed that after a few days in the incubator the bone marrow cells formed a membrane-like growth on the surface of the agar, and that some of their nuclei exhibited mitotic figures; in other words, the cells were living and multiplying. This must have been the first *in vitro* culture of mammalian cells ever to have been made.

About the same time Harrison's experiment with the explanted nerve tissue had attracted the attention of the renowned surgical experimenter Alexis Carrel, of the Rockefeller Institute. Having himself succeeded in transplanting whole organs of laboratory animals, Carrel dreamed that some day it might be possible to grow human organs and tissues, to replace similar bodily elements removed by disease or by surgery. In 1909 Carrel sent his assistant Montrose T. Burrows to Harrison, then at Yale, to learn the latter's methods and adapt them to the tissues of warm-blooded animals. Setting up the necessary equipment at the Rockefeller Institute, Carrel and Burrows promptly succeeded in cultivating cells from chick embryos in sterile chicken blood plasma. Their first report was published in the *Journal of the American Medical Association*, October 15, 1910.

Before this paper appeared, the Lewises had independently begun in the fall of 1910 to cultivate bone marrow cells from guinea pig embryos, in the blood plasma of older embryos. They were evidently following up Mrs. Lewis's observation of 1908, utilizing Harrison's method except that the culture medium was mammalian blood plasma instead of frog's lymph. Their first results were inconclusive, but the report of Carrel and Burrows encouraged them to renew their effort, this time using tissue from embryonic chicks and explanting discrete bits of tissue instead of a few cells as before. The outcome exceeded expecta-

tions. They obtained growth and multiplication of cells from many organs. With more insight than Carrel at first possessed, they recognized that most, if not all, of the proliferating cells were of kinds common to all organs, namely, connective tissue cells and the endothelium of blood vessels. The much more difficult cultivation of glandular epithelium and other highly differentiated cells was for future decades to achieve.

From 1910 to the early 1920s all tissue culture workers—the Lewises, Alexis Carrel and his colleagues, and others elsewhere who attempted to grow animal cells *in vitro*—were chiefly occupied in exploratory efforts to discover what kinds of cells could be grown and what were the best culture media. The aims, and hence the methods, of the two pioneer groups were somewhat different. Carrel's long-range hope was to grow organs or at least masses of tissue, and his group therefore sought the media most effective for growth, however complicated they might have to be. The Lewises, desiring chiefly to study the microscopic structure of individual cells, needed optically clear media. Having been successful with a simple mixture of Locke's salt solution, agar, and bouillon, they proceeded to try the clear salt solution alone and found that connective tissue cells, endothelium, and nerve fibers would spread out into the fluid from the explanted bits. This earliest attempt by any investigator to grow cells in a solution containing only chemically definable constituents was premature; as yet too little was known about such factors in the regulation of vital processes as vitamins, trace elements, and pH (acid-alkalinity balance). What little multiplication of cells occurred in these salt-solution cultures depended, we now know, on nutritive materials released from the explants. For long-continued growth and extensive cell multiplication organic supplements were necessary, and almost a half century was to pass before culture media of fully defined chemical constitution were achieved.

For the time being, while Carrel's group were using embryo juice and other complex supplements to ensure active growth, the Lewises worked with salt solutions, at the most supplemented with bouillon and dextrose (Locke-Lewis solution). They put their bits of tissue (as Harrison had done) in a hanging drop on the underside of a thin glass slip which served as the transparent lid of a small moist chamber on a microscope slide. Such a preparation became known as "the Lewis culture." Later the Lewises for special purposes also used Petri dishes and the roller tube method which their co-worker George O. Gey had developed by improving upon Carrel's roller tubes; and when their experiments called for long maintenance of living cells they used plasma or other media nutritively richer than the Locke-Lewis fluid.

In Locke-Lewis solution, with or without the supplement of bouillon or plasma, cells of the hardier types, notably fibroblasts and macrophages, migrated out from the explant and flattened themselves on the under surface of the cover slip, and thus could be readily observed under high magnifications. The method was ideal for the study of cytological details. Even if, for lack of complete nutrition, the cells thus studied were shortly to degenerate, they survived for some days, displaying the appearance and behavior during life of microscopic elements hitherto observed only after the drastic procedures of fixation (i.e., killing and coagulation of the protoplasm) and staining with dyes.

By 1915 the Lewises were able to present a comprehensive description of the living cell and its nucleus and cytoplasm, of mitochondria, and of the segregation vacuoles which the cell forms around phagocytized particles. At first their observations were chiefly morphological, although as early as 1917 they could describe various physiological activities—the locomotion of leucocytes, the contraction of smooth muscle cells, and the

budding of striated muscle fibers. Degenerative changes such as widespread vacuolization of the cytoplasm and the formation of giant cells (in lymphoid tissue) could of course be readily studied in these simple cultures.

In 1917 Franklin P. Mall died after an acute surgical illness, leaving vacant the two posts which he had concurrently occupied. To succeed him as director of the Department of Embryology of the Carnegie Institution, the Institution promoted Mall's senior associate in the embryological laboratory, George L. Streeter. As for the headship of the Department of Anatomy at Johns Hopkins, Warren Lewis was not greatly interested in the post; he was too deeply immersed in his own researches and did not care for the tasks of administration and teaching. When one of his juniors, Lewis H. Weed, was appointed to succeed Mall in the anatomical chair, Streeter invited both the Lewises to join the Carnegie laboratory. Enjoying the services of the skilled Carnegie technical staff, they continued their joint and individual projects without the distractions and time-consuming routine of administrative work—an outcome of great advantage, as the sequel shows, to biological science as a whole. Warren Lewis retained, by courtesy of the University, his professorial rank and title.

As the Lewises went on with the tissue cultures in their new quarters, they found that not all the experiments were equally successful. They could at first only attribute the variation in survival and growth to unknown differences in the media or in the environment of the culture chambers. The chief difficulty was, however, soon overcome. Biologists were beginning to appreciate the physiological importance of hydrogen ion concentration. Mrs. Lewis and a young co-worker, Lloyd D. Felton, using W. Mansfield Clark's newly available indicators, studied the pH of growing tissue cultures (1922) and thereafter routinely adjusted the medium to the optimum pH value.

With this improvement, the two indefatigable investigators were better equipped to study the physiological behavior of living cells. They could follow, for example, the transformation of fibroblasts into flattened mesothelial layers like those which line the peritoneal cavity and other body spaces, and could watch the formation of macrophages, epithelioid cells, and giant cells from mononuclear white blood cells. Warren Lewis demonstrated the similarity of cells thus formed to those which the pathologists observe in the lesions of tuberculosis. He described also the behavior of macrophages in inflammatory processes.

These numerous and varied observations greatly helped to clear up the confusing phylogeny of the monocyte-macrophage-epithelioid cell-giant cell series. Against the view of their colleague and friend Florence R. Sabin, the Lewises showed that the monocytes and macrophages are not two distinctive cell types; on the contrary, they represent different physiological states of the same cell. Monocytes, when they take up fluid, cell debris, or microorganisms from the tissues by phagocytosis or by the process of pinocytosis (to be discussed later), develop a "segregation apparatus" of cytoplasmic vacuoles and assume the aspect of macrophages. Implicit in this finding was a further conclusion, against the view of F. B. Mallory and N. C. Foot, that macrophages are by no means solely derived from the endothelial lining of blood vessels, many of them being activated monocytes from the blood and connective tissues. As to the pre-history of the monocytes themselves, however, Lewis never arrived at a firm conclusion with regard to the much-debated hypothesis that they are derived from lymphocytes, representing in fact an intermediate stage in the conversion of lymphocytes to macrophages.

From all this intensive study of the cells of connective tissue and the blood came a by-product of considerable interest to

obstetricians, the discovery by Warren Lewis (1924) that the formerly mysterious "Hofbauer cells" of the human placenta are macrophages. Another important finding was that the fibroblasts of areolar connective tissue do not (as some believed) constitute a syncytium. They have that appearance because the living cytoplasm of two such cells can come into such close contact that even with the best optical equipment no boundary between the cells can be seen, yet they may subsequently separate along the same line of contact. This observation proved significant in connection with another case of apparent cytoplasmic fusion, namely, synaptic junctions in the nervous system. Having so many leads for the use of their tissue-culture techniques in solving difficult cytological problems, Warren and Margaret Lewis after the early 1920s tended more and more to work individually, but always side by side in the laboratory and in close consultation. It is almost as difficult to draw a line between their respective ideas and accomplishments as between two contiguous fibroblasts, but it may be said that Warren Lewis continued to think and work chiefly on problems of descriptive morphology and cell mechanics, while his wife gave a greater share of her attention to microbiological problems, for example, pH changes in cultures, the reversible gelation of living cytoplasm, and the cultivation of viruses in living cells.

In 1923 Warren Lewis began to apply his knowledge of living cytology to the cells of malignant tumors, which for a dozen years Alexis Carrel and others had been growing in tissue cultures. Lewis's first venture into the field of cancer was made with a young colleague, George O. Gey, studying certain cells which abound among the spindle cells of a mouse sarcoma and which Carrel had taken to be the malignant elements. Lewis and Gey found them to be macrophages, the spindle cells being in fact the malignant elements. For more than twenty years after their first cultivation of cancer cells, the Lewises and various

co-workers made cultures of many sarcomas of the rat and mouse, and a few also from human tumors. Warren Lewis showed that the tumor cells are permanently altered from the normal state, retaining the malignant pattern of growth through many successive cultures. In more than a dozen papers, lectures, and brief talks from 1923 to 1948 he described in detail certain cytological features (size of the cell and its elements, appearance of the nuclear plasm and cytoplasm) by which, taken as a whole, the living malignant cell of connective-tissue origin differs from its normal counterpart, the fibroblast. No present-day monograph on cancer cytology fails to quote from this treasury of expert observations.

About 1929 Warren Lewis began to use motion pictures to record his microscopic observations. With Paul W. Gregory he studied and pictured the earliest development of the rabbit embryo from the first cleavage of the fertilized ovum to the blastocyst stage. With Elsie Starr Wright (1931, 1935) he made similarly enlightening films of segmenting ova and blastocysts of the mouse. These studies of rabbit and mouse embryos were apparently the first motion pictures of early mammalian development and the first time-lapse films of cells in tissue culture.

As soon as Lewis began to film cells in tissue culture he realized that by repeated screening of his films he could learn much more about cell mobility and other physiological changes than by direct observation. Furthermore, time-lapse cinephotography enabled him to speed up, on the screen, activities far too slow to be comprehended by direct vision. An immediate result was the discovery (1931) of a previously unknown kind of cell activity which Lewis called "pinocytosis" (drinking by cells). Certain cells (macrophages, fibroblasts, sarcoma cells) are seen in cultures to possess wavy marginal ruffles or veil-like pseudopodial membranes. Filming such cells at one-minute intervals, Lewis observed them to actively enfold and engulf

droplets of fluid from the surrounding medium. In this way a cell may take up relatively large amounts of fluid, as much as a third of its volume in one hour. Lewis conjectured that this means of admitting fluid, with whatever dissolved substances and finely particulate matter it may contain, may be a physiologically important source of nutritive materials. As he stated with a rare flash of humor (1931), "It seems probable that, instead of sitting around doing nothing much of the time, they [the macrophages] are always actively engaged in drinking tissues' juices, digesting them, and passing the fluid and digestive products back into the tissue fluids." This conclusion is now generally accepted.

Another vital activity whose study was much facilitated by motion pictures was the locomotion of cells. The nature of the forces by which cells move has long been a puzzle. It has been said that there are few biological problems for which so many hypotheses have been advanced to explain so few data. Watching leucocytes and lymphocytes moving through his cultures, Lewis was struck by the similarity of their progression to that of the amoeba. He was thus led to base his own theory of cell movement on the ideas of Samuel O. Mast, who described the amoeba as having a surface layer of jelled protoplasm (plasmagel) surrounding a fluid mass (plasmasol). The flow of plasmasol into the pseudopodia, Mast believed, results from imbibition of fluid by the plasmasol, causing it to stretch the plasmagel layer, which in turn contracts, exerting pressure upon the fluid plasmasol and forcing it to flow. To this concept Lewis added the idea that the plasmagel, like inorganic colloidal gels, possesses inherent contractibility. Flow of the plasmasol and consequent amoeboid movement could therefore be produced by local gelation of the surface layer. On this assumption he based a plausible theoretical explanation of cell locomotion. Later Lewis used the same basic hypothesis to

explain the cleavage of segmenting ova, and also the overgrowth of the yolk by the blastoderm during the development of the bony fish. Although today's students of these obscure forces no longer fully accept Lewis's analysis, his assumption that inherent contractibility of the plasmagel is in some way involved in amoeboid movement is retained in more recent theories.

Lewis's motion pictures of living cells of higher animals in physiological activity, of mammalian ova in the process of division and blastocyst formation, and of the development of the zebra-fish egg won keen attention and admiration when he exhibited them at meetings of anatomists, zoologists, and cancer investigators. There was so much demand for them from teachers that Lewis had to arrange for their systematic distribution by purchase or rental, himself carrying on the necessary correspondence from his own office. To thousands of students of zoology, embryology, and histology all over the world, they have given a vivid impression of the structure of living normal and malignant cells of the blood and connective tissues, of cell division, phagocytosis, pinocytosis, the locomotion of leucocytes and macrophages, and the earliest stages of mammalian development.

Dr. Lewis was a man of somewhat more than average height and of spare build. He was always athletic. There is a family story that at the age of three he rode a tricycle from his home in Oak Park to his father's law office in the city of Chicago. In Baltimore, when the season permitted, he kept up the sport of ice skating learned in his youth in Illinois, and in summer at the seashore he enjoyed swimming and sailing.

The reserved manner and thoughtful conversation Warren Lewis displayed to those of his general acquaintance—reflecting a temperament more like that of his New England ancestors than of the Midwesterners among whom he grew up—were lightened by occasional flashes of quiet amusement or a gentle

chuckle at another's humor or a jest of his own. Fellow scientists and students who went to him for technical advice were always kindly and helpfully received. As his publications reveal, such consultations frequently led to joint research to which he generously contributed his time and technical skill. Speaking before scientific audiences he was serious, cautious, a little hesitant. His uniformly lucid and informative publications are expressed in excellent English and effectively illustrated. The all too few formal lectures in which he summed up large portions of his work are characterized by a dignified style and calm judgment on controversial questions; an excellent example is the presidential address, at the 1935 meeting of the American Association of Anatomists, on "Normal and Malignant Cells."

Dr. and Mrs. Lewis led a quiet life of devotion to work in their laboratory. They were seldom seen apart. Their vacations were generally spent at Woods Hole, later at the Mt. Desert Island Biological Laboratory, where they varied their work by observations and experiments on marine organisms. They regularly attended the annual meetings of the American Association of Anatomists, where each of them usually presented a paper or showed a motion-picture film.

The social life of the Lewises centered warmly around their family, colleagues, and research students, with whom picnics, hikes, and sailing parties took place almost every weekend. In sociable Baltimore there were frequent exchanges of hospitality with University and Carnegie Institution friends.

Warren Lewis was much interested in prehistory and archaeology. He visited, with his wife, many of the caves in southern Europe, particularly that of Les Eyzies. In his later years they made several trips to the Mayan excavations of the Carnegie Institution of Washington in Yucatan and Guatemala.

When Warren Lewis reached the age of retirement, in 1940, he accepted an invitation to join the Wistar Institute in Phila-

delphia, and was accompanied in this move by Mrs. Lewis, who, however, retained for some years her connection with the Carnegie Institution of Washington. At the Wistar Institute, where they were greatly respected and appreciated by the younger scientists about them, they both continued their investigations at a gradually diminishing pace.

Warren Lewis was elected a member of the National Academy of Sciences in 1936 and of the American Philosophical Society in 1943. He was president of the American Association of Anatomists, 1934-1936, and of the Mt. Desert Island Biological Laboratory, 1933-1937. The Pathological Society of Philadelphia in 1958 awarded to Warren and Margaret Lewis jointly its William Wood Gerhard Gold Medal for contributions to pathology. Foreign recognition came to Warren Lewis in the form of honorary membership or fellowship in the Royal Microscopical Society of London, the Société de Médecine of Ghent, and the Academia Nazionale dei Lincei, Rome. The International Society for Experimental Cytology put him at its head, as president, in 1939 and kept him there until 1947.

At Warren Lewis's eighty-fifth birthday, in 1955, he was in good health and alert of mind, as indeed he remained for years thereafter. Among those who sent greetings to a dinner held later that year in Baltimore to honor him and his wife, Alfred Newton Richards, ex-President of the National Academy of Sciences, wrote of Warren Lewis's quiet, never-ceasing thoroughness, his endless reliance upon his own hands and mind, his seeming disdain of applause and public recognition. Another lifelong friend wrote of Margaret Reed Lewis's rich accomplishments as a productive research worker, devoted wife and mother, friend and counselor of students and colleagues. An experienced tissue-culture worker declared that the Lewises' laboratory had done more than any other, over the years, to demonstrate the relative ease with which cells and tissues, in culture,

may be used to advantage in a wide variety of undertakings, in many fields of experimental biology and medicine.

In September 1960 the Lewises journeyed to Paris, where they had spent their honeymoon fifty years earlier, to attend a congress of cytologists at which Warren Lewis was awarded the Triennial Ross G. Harrison Prize of the International Society of Cell Biology—an honor doubly pleasing because it linked his name with that of his old friend and fellow-pioneer in tissue-culture research.

Dr. Lewis died in Philadelphia, at the age of ninety-four, on July 3, 1964, after a short illness following an accidental fall. He is survived by Mrs. Lewis and their three children—Dr. Margaret Nast Lewis, physicist at Harvard University; Warren R. Lewis, engineer and atomic physicist, Richland, Washington; and Dr. Jessica H. Lewis (Mrs. Jack Myers), Associate Research Professor, Department of Medicine, University of Pittsburgh.

Only a few months before his final illness, he and Mrs. Lewis received a special tribute when the Wistar Institute held a symposium in their honor, on a most appropriate topic, "The Retention of Functional Differentiation of Cultured Cells." On this occasion his friends presented to the Wistar Institute a portrait of Dr. Lewis by the eminent painter Franklin Watkins. The presence of many scientists who had worked with him, or benefited by his counsel, was ample testimony to the value of a lifetime of original and fruitful research on some of Nature's deepest questions.

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KEY TO ABBREVIATIONS

- Am. J. Anat. = American Journal of Anatomy
 Am. J. Cancer = American Journal of Cancer
 Am. J. Physiol. = American Journal of Physiology
 Anat. Record = Anatomical Record
 Arch. exp. Zellforsch. bes. Gewebezücht. = Archiv für experimentelle Zellforschung besonders Gewebezüchtung
 Biol. Bull. = Biological Bulletin
 Bull. Johns Hopkins Hosp. = Bulletin of the Johns Hopkins Hospital
 Carnegie Inst. Wash. Contrib. Embryol. = Carnegie Institution of Washington Contributions to Embryology
 Carnegie Inst. Wash. News Service Bull. = Carnegie Institution of Washington News Service Bulletin
 J. Exp. Med. = Journal of Experimental Medicine

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