lower Oligocene series of rocks in Wyoming, Colorado and South Dakota, where the fossilized remains of titanotheres are found, both to determine precisely their geologic succession and to close up gaps in the stages of evolution; second, it proved necessary to examine and compare the titanotheres of these geologic epochs in all the museums of this country and in several museums abroad; third, it proved necessary, in order thoroughly to understand the titanotheres, to discover and to follow many side lines of investigation that have not hitherto been followed in vertebrate paleontology.

This work has been done with the aid of many specialists, foremost among whom is my junior colleague, Professor William K. Gregory, without whose intelligent and unremitting cooperation the monograph could never have been completed.

It is, perhaps, not too much to say that this work has transformed our knowledge of the early Tertiary geology of the Rocky Mountain basin region. First, the six life periods recognized by Marsh and his no less distinguished contemporary Edward Drinker Cope may now be replaced by sixteen life periods, which may be clearly defined and separated and certain of which may be more or less precisely correlated with life periods established for western Europe. Second, a much clearer notion has been gained of the changing geographic, physiographic, climatic and volcanic conditions in Wyoming and Dakota and of their influence on the migration and succession of forms of life. Third, the wholly new method of attack on problems of vertebrate paleontology has been developed; we seek to know the entire living animal, its musculature, its mode of locomotion and its feeding habits, in order to insure the complete restoration of the body. Fourth, the study of the many branches of this group has given the most convincing demonstration that evolution, even in any one geographic region, seldom moves along a single line of descent; more frequently it moves along many lines —it is polyphyletic; in other words, it radiates, following the principles of local adaptive radiation. Finally, the history of the titanothere family in its evolution from very small and relatively weak forms into titanic quadrupeds, second in size only to the elephants, has afforded us a unique opportunity to enlarge our previous knowledge of the actual modes of evolution as well as to revise our theories as to the causes of evolution and extinction.

OBITUARY

ARTHUR S. LOEVENHART

ON April 20 the ranks of the all too small group of workers in the field of experimental therapeutics were reduced by the death of Arthur Solomon Loevenhart, and a career energetically devoted to pure science, to therapeutic advancement and to the defense and promulgation of the highest medical ideals was brought to a close.

Arthur S. Loevenhart was born in Lexington, Kentucky, December 29, 1878. He grew up in his native city, and in the course of time attended the State College of Kentucky which is located there. His early educational history is illustrative of how little the progress of science depends upon magnificent buildings or upon elaborately equipped institutes, and of how much it depends upon those rare individuals who, having caught the spirit of science, devote their lives to the pursuit of knowledge. At that time the chair of chemistry was held by Professor J. H. Kastle. The remainder of the staff of the department consisted of only one student assistant, so that it was necessary for Professor Kastle to give three or four lectures a day, supplemented by laboratory work, in order to provide instruction in the various branches of chemistry. Nevertheless, this heavy burden of routine did not prevent him from continually contributing to chemical knowledge or from presenting the subject in such a way as to inspire students to investigate its problems. Into his classes there came the young Loevenhart. Professor Kastle quickly recognized in him a keen and resourceful pupil, and Loevenhart found a wise and sympathetic teacher. The association was most fruitful. Even before Loevenhart's graduation, which occurred before his twentieth year, they had finished a joint research on "The Oxidation of Formic Aldehyde by Hydrogen Peroxide."

In the following year they started their work on lipase. In the course of this work Loevenhart made the valuable suggestion that lipase might be capable of effecting the synthesis of fats from fatty acid and glycerine, and this led to the experimental synthesis of ethyl butyrate from ethyl alcohol and butyric acid. Thus the reversibility of enzyme action was for the first time established in a clean-cut manner, there being no complication such as in the previous instance of enzyme synthesis discovered by Croft Hill in which isomaltose, not maltose, was produced under the influence of yeast maltase, the isomaltose so produced not being again hydrolyzable by the maltase.

The years 1899–1903 were spent as a medical student at the Johns Hopkins University, but this experience did not in the least decrease Loevenhart's interest in chemical subjects. It merely served to widen his horizon; a vaster field was unfolded in

which his chemical knowledge could be put to good use. His interests and ideals naturally brought him into association with men like Professor Abel and Professor Howell, and he endeared himself to his teachers on account of his keen mind and lovable personality. During his undergraduate years he did research under their protecting encouragement and guidance, and so active was his participation that they soon came to look upon him rather as a colleague than as a student. He had his headquarters in the laboratory of Professor Abel and on graduation he was offered an assistantship in the department. There he remained for five years and his association with Professor Abel became the second great source of inspiration in his career. His teaching duties necessitated giving instruction in both physiological chemistry and pharmacology, as these two subjects were then combined in the same department, but it is apparent that his inclination turned more and more toward pharmacology because his promotion to an associate professorship was made in that subject instead of in physiological chemistry as in the previous years. His advancement was rapid and in 1908 he accepted the professorship of pharmacology at the University of Wisconsin.

When a medical student he published his now well-known theory of fat absorption, based on the reversibility of lipase action. Experimentally he found that lipase is present in the cells of the intestinal mucous membrane. Theoretically he postulated that the fat droplets found in these cells are formed by lipase synthesis from the saponified products absorbed from the intestine. Similarly, he supposed the storage and release of fats from tissue cells to be effected by the same enzyme, which is either fat-forming or fat-splitting according to the momentary concentration of the products of the reaction. The work on lipase was also continued in the following years. Further investigations were made on the remarkable inhibition of lipase by fluorides, which had been discovered by Kastle and Loevenhart; bile salts were demonstrated to have all the properties of a co-enzyme, and the ester-splitting enzymes of different organs were found to have individual peculiarities.

During his vacations as a medical student, he worked with Professor Kastle in Lexington; and the result of this collaboration was a series of papers on the mechanism of oxidation, a subject in which his interest never flagged throughout his life. His last publication, like his first, was on this subject. In one of his early independent contributions he suggested the use of benzoyl peroxide as an antiseptic.

Professor Loevenhart went to Wisconsin at the time of the organization of the first part of the Medical School and became a part of the young, enthusiastic faculty which directed the fortunes of the new institution and which provided by its close contact with the small classes an opportunity which I feel can not be equaled in the larger classes which now prevail, there, as elsewhere. The department of pharmacology was housed in an attic, but it was given a considerable number of facilities and, because of the splendid *esprit de corps* existing among the various departments, it was possible to carry on research in a most satisfactory manner.

Loevenhart's earlier scientific work at Wisconsin centered around the subject of oxidation. It was a continuation of the work started with Kastle, but from a new angle. The work with Kastle was concerned with the mechanism of oxidation, while the new work was directed toward the determination of the action of various substances and conditions on vital oxidation, and the finding of the relation of vital oxidation to functional activity.

The work on the mechanism of oxidation can be evaluated properly only against a background picturing the evolution of the ever-changing ideas on this subject, particularly as it applies to biological oxidation. It will, therefore, be possible at this time to make only a few brief statements concerning the contributions in this field. The analogy between organic peroxides and oxidases was given abundant experimental support; it was proposed that peroxidases are organic substances which react with hydrogen peroxide to form peroxides of a higher oxidation potential than the latter. Many points as to the nature and occurrence of catalase were also elucidated.

One of Loevenhart's earliest problems in the second group was that of the mechanism of stimulation of the medullary centers, particularly the respiratory center. He observed that substances which reduce oxidation cause, like anoxemia, stimulation of the center, provided the center is initially irritable and the change takes place with sufficient velocity. On the other hand, substances containing active oxygen, like sodium iodoxybenzoate, depress the center. He was therefore much impressed with the rôle played by oxidation in the control of respiration. Those who remember the notions held about respiration twenty years ago will recall that the theory which then enjoyed popularity was that respiration is controlled by carbon dioxide, and that oxygen-want affects it only secondarily through the general acidotic metabolism produced. The latter possibility Loevenhart precluded by demonstrating that the latent period of the effect of cyanides on the respiratory center corresponds with the circulation time from the point of injection to the center, there thus being no interval in which an intermediary metabolism could take place.

He then pointed the way directly to the solution of the matter by postulating that anoxemia, and substances affecting oxidation, modify the activity of the respiratory center through its own metabolism. He supposed that two sets of metabolic processes take place in the cells of the center, one aerobic in nature, the other anaerobic. The first type was conceived as being concerned with recuperative processes and was therefore labeled "R," while the second type was designated as an "A" process because it was believed to be immediately concerned with functional activity. Decrease of the possibility of the utilization of oxygen due to anoxemia or to drugs with a cyanide-like action would thus cause an increase of the "A" process and an increase of the cells' specialized activity; on the other hand, in the presence of plenty of oxygen the oxidative metabolism would predominate and the cells would rest. This theory has had an enormous influence in the development of the modern concepts of the respiratory center.

Much work was done on the changes which are brought about in animals kept for considerable periods of time at low oxygen pressures. The observations made in the experiments are of fundamental importance, because in showing the behavior in pure anoxemia they afford a picture which may be compared with that produced by drugs supposed to act through interference with the oxidative mechanism. Descriptions were given of the hyperplasia of the bone marrow, of the hydropic and hyaline degeneration which occurs in the parenchymatous organs, and of the metabolic changes, namely, an increased excretion of nitrogen and organic acids, and an extreme degree of acidosis which follows an initial alkalosis due to hyperventilation, and which is an important factor leading to death, as life can be prolonged by alkali administration.

Other phases of this field which were investigated were sodium cyanide as a clinical respiratory stimulant, and the decrease in the inflammatory action of mustard oil under the influence of oxidizing agents.

The entrance of the United States into the World War necessitated the immediate establishment of research units to investigate the problems of chemical warfare. The laboratories of the Medical School of the University of Wisconsin were very early turned into such a unit and Dr. Loevenhart entered into the work with his usual energy. In the early days of the investigation before the organization became perfected he, characteristically enough, took his turn in the night shifts when men were needed to watch the ventilation of the chambers and to record the symptoms of the animals.

The center of the research division of the Chemical Warfare Service was located at the American University at Washington. The organization was divided into sections and for the pharmacological section a man was sought in whom research capacity and a knowledge of medicine, physiology and toxicology was combined with the ability to cooperate with other sections and to gather together a staff of loyal coworkers. Logically enough, Dr. Loevenhart was called from Wisconsin for this purpose. Twenty-four hours after receiving the call he was in Washington.

There is no doubt that Dr. Loevenhart's experience in the Chemical Warfare Service greatly influenced his activities during the next decade. Having participated in the greatest cooperative research effort in the history of the country, he had seen the rapid progress which is attainable when chemists and pharmacologists work together, and he returned to Madison enthusiastic in his desire to utilize the benefits of such an organization in the field of therapeutics.

He outlined in considerable detail plans for the organization of a therapeutic institute. It was proposed to compensate the present marked lack of balance between the diagnostic and therapeutic aspects of medicine by directing the attention to problems which, when solved, would be capable of immediate application to the sick. An effort was to be made to bring at once into usefulness the many points now lying fallow in the immense accumulation of fundamental knowledge regarding disease. Existing therapeutic practice and the newer therapeutic researches were to be examined on a scale which would permit the gathering of statistics of real significance, so that when a result was announced it would be conclusive.

The institute was to be part of a university with a medical school and a university-controlled hospital, so that the facilities they afford would be available. It was not proposed to pile up more bricks and mortar behind which more workers could carry on research along existing lines, but rather to develop a new spirit within existing walls. The staff, made up of chemists, pharmacologists and clinicians (and at times others), was to be selected not only from the standpoint of ability but also from the standpoint of those attributes of character which would enable them to work with others in complete harmony. This staff was to cooperate with workers on the outside by providing competent men with ideas the opportunity of trying them out, and also by referring problems to those most capable of solving them, supplying them if necessary with financial and personal aid.

Had Dr. Loevenhart lived he would continually have strived to bring such an institution into existence, and it is a great misfortune that the realization of his ideal has been delayed by his death. During

his life the work at hand was in no way curtailed by the quest of the ideal. With outside aid received as the result of his own efforts the activity in his department was maintained on a scale far beyond that permitted by its own budget. Also, many of his researches would not have been possible without the cooperation of departments in other institutions.

Among the investigations which were carried on in the Chemical Warfare Service many were concerned with organic arsenic compounds, and it was natural that Dr. Loevenhart's interest in those substances should continue through the following years. Soon after his return to Wisconsin he started experiments on the treatment of syphilis. This is a problem which demands not only laboratory facilities but also the opportunity for the clinical testing of promising compounds. Fortunately, the latter was provided in a unique manner through a collaboration with the department of neuropsychiatry. At that time a number of new compounds had recently been synthesized at the Rockefeller Institute for Medical Research and the institute was kind enough to place a number of them at his disposal for study. One of them, tryparsamide, proved to have very striking merit in the treatment of neurosyphilis. Many of the patients treated with it were restored to their homes and to useful lives.

An intensive investigation was then started in order to determine the basis of this action. A consideration of related substances soon revealed the fact that the treatment of neurosyphilis is a very special problem in the field of therapeutics with organic arsenicals. It was found to be impossible to predict from any property revealed by experimentation whether or not a compound would be of value in the treatment of paresis. Neither the ability to penetrate into the central nervous system nor to produce symptoms referable to a toxic action upon it shed any light on the problem, nor was there any relation to the effectiveness against experimental trypanosomiasis or experimental syphilis. While the introduction of the drug was an outgrowth from the chemotherapeutic theory, its action was apparently in defiance of its tenets. The tryparsamide molecule was subjected to a most thorough analysis in the hope that its action could be connected with some part of its structure, but its remarkable therapeutic activity was lost or decreased with every change of the molecule, although strikingly enough one series of compounds, in which the side chain ended in an alcohol group instead of an amide group, had a higher chemotherapeutic index in trypanosomiasis. He therefore concluded that the therapeutic power of tryparsamide is a function of the molecule as a whole, and that its action is not to be explained primarily on the basis of its spirochaetocidal action, but rather as the result of an alteration of the response of the tissues in the presence of the spirochaete with a consequent disappearance of inflammatory infiltration and improvement of the nutrition of the cells. The destructive action on the optic tract of the group of drugs of which tryparsamide is an example was shown to be due primarily to the presence of an amino group in the para-position to the arsenic.

The other subjects which engaged his attention in recent years were the pharmacology of the nitrites, the body changes occurring in insomnia and fatigue, and the local anesthetics. In the case of the latter an investigation was made of the effectiveness of the members of two chemical series. One substance, the isopropyl homologue of procaine, was found to occupy a particularly favorable position as a surface anesthetic.

Dr. Loevenhart also kept up his interest in the subject of oxidation, and his final contribution was a remarkable observation made in some experiments suggested by his deliberations on this subject and by some observations, made a number of years previously, on the behavior of patients in psychopathic depression when stimulated by cyanide. He reasoned that substances decreasing the utilization of free oxygen should stimulate cerebral cells as well as those of the respiratory center, and by the same mechanism —the one which has been previously mentioned in connection with his work on respiration—and he planned his experiments accordingly. When sodium cyanide or, better, mixtures of carbon dioxide and oxygen in varying concentration were administered to patients in catatonic depression, there first occurred a short period of respiratory stimulation, then the catatonia passed off and for a short period the patients behaved as though a curtain which had been shutting them off from the world had been lifted. Their features became animated and conversation became possible; events which had occurred during the period of stupor were described, and replies to questions were coherent and relevant. Then, after a period of from two to twenty-five minutes, the retrograde changes began. The patients relapsed into their former mental state, inaccessible, mute and negative, and they resumed a posture identical with that which they had previously held. This observation is so new that its significance has only begun to be apparent, but its value in diagnosis and its bearing on the understanding of the nature of the psychosis is at once obvious. It gives promise of being one of his most brilliant contributions.

The achievements just recorded also represent the labors of many young workers starting on scientific careers. Dr. Loevenhart was ever on the alert for

signs of research ability among his students and when this was once detected it was most carefully nourished. Workers were attracted to him by the spell of his personality. They were admitted to his laboratory as part of the scientific family and given an independence which was limited only by the consciousness that they were harmoniously working together toward a common end.

The only dominating force in the laboratory was the intelligence and ready knowledge of its chief. Hours were spent by him in the elucidation of ways and means, more hours were spent in the meticulous preparation of statements for publication, yet in the end his claims for personal credit were extraordinarily modest. How much these years of association with Dr. Loevenhart were appreciated has been very touchingly expressed in letters written by his collaborators since his death.

Dr. Loevenhart was truly an apostle of the spirit of science, of science for its own sake and science for what it could contribute to the welfare of mankind. He was never so happy as when he could arouse or quicken the same spirit in others, and the extent to which he did so was one of his most conspicuous successes. Many of his former associates now occupy positions of responsibility in other schools, and the roster of the Pharmacological Society contains the names of ten members who have actively engaged in research in collaboration with him.

The high regard held for Dr. Loevenhart by his colleagues was shown by his position on many important committees and by the fact that he was twice made president of the Pharmacological Society. He had an enormous circle of friends, and at the dinners or smokers during any scientific gathering he could always be found surrounded by a group of them, who had gathered to listen to his witty and inspiring conversations enlivened by his inexhaustible supply of stories which always seemed to have such a pointed connection with the topic of the moment. His friends afforded one of the greatest pleasures in his life, and loyalty to a friend was one of his outstanding characteristics. The last years of his life were burdened by ill health, but they did not prepare his friends for his premature death at the age of fifty-one years. Throughout his ill health his cheerfulness never failed. Instead of diminishing his activity his illness seemed to spur him on to search more actively for means more immediately useful for the relief of the suffering of sick people. His last years were the most productive of his life, and his laboratory was one of the most active in the country.

The world at large will remember him as a scientist and a humanitarian, and a smaller group will remember him also as an inspiring teacher, but those who worked with him and played with him will remember him too as a lovable human being endowed with an indefinable charm.

H. S. GASSER

RECENT DEATHS

DR. CHARLES RANOLD MACINNES, associate professor of mathematics at Princeton University, died on September 29 at the age of fifty-three years.

DR. GEORGE F. WHITE, professor of chemical engineering in Clarkson College of Technology at Potsdam, New York, fell down a flight of stairs and was instantly killed on September 18. Dr. White for the last five years had been chemical engineer and director of the science department of Bauer and Black, of Chicago.

DR. WILLIAM FAIRFIELD MERCER met with almost instant death on July 29 at his summer home, Otto, N. Y. While Dr. Mercer was oiling his car it rolled backward crushing him underneath. Dr. Mercer had been head of the department of biology at Ohio University, Athens, since 1900.

DR. CHARLES AUGUSTUS BROWN, radiologist and founder of the Brooklyn Cancer Institute, died on September 27. He was fifty-six years old.

DR. GEORGE F. GAUMER, of Izamel, Yucatan, discoverer of several new mammals and author of a monograph of the mammals of Yucatan, died on September 2.

WALTER HEAPE, the English embryologist, died on September 10 at Tunbridge Wells at the age of seventy-four years.

THE death is announced of Dr. Richard Zsigmondy, professor of inorganic chemistry at the University of Göttingen. He was awarded the Nobel prize in 1928 in recognition of his work during the previous year in the field of colloidal research.

DR. MARIE, of the Pasteur Institute, Paris, has died from botulism contracted in the course of his researches on the disease.

SCIENTIFIC EVENTS

THE ROOSEVELT MEMORIAL OF THE AMERICAN MUSEUM OF NATURAL HISTORY

IT is announced that construction will soon begin on the great memorial to Theodore Roosevelt in New York City. On September 24 the bids were opened by Colonel Frederick Stuart Greene, of the State Department of Public Works at Albany for the foundation of this structure. At a luncheon given by Dr. Osborn, chairman, to Colonel Greene and the trustees