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HOWARD BISHOP LEWIS

1887—1954

A Biographical Memoir by
WILLIAM C. ROSE AND MINOR J. COON

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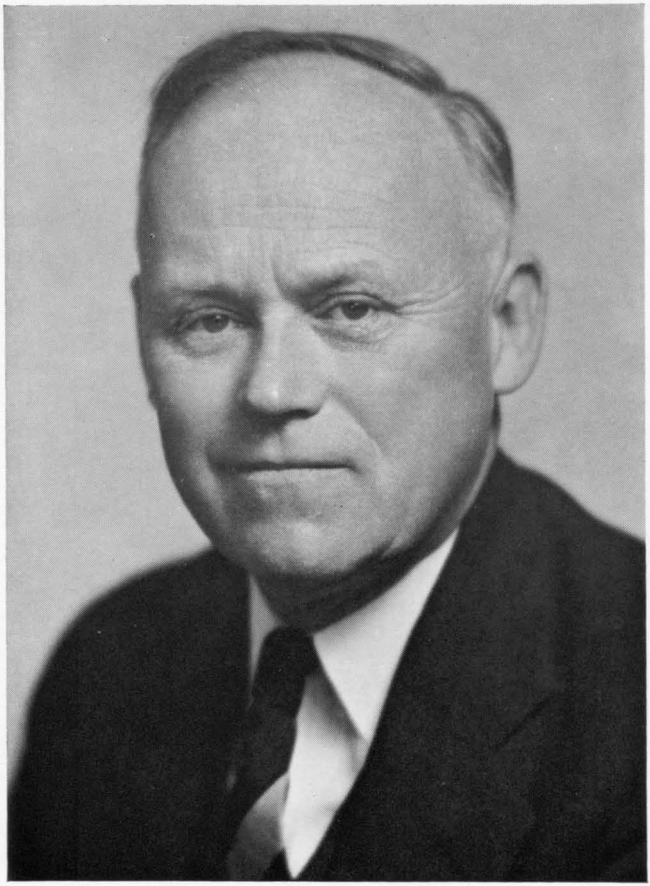

Howard B. Lewis

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November 8, 1887– March 7, 1954

BY WILLIAM C. ROSE AND MINOR J. COON

HOWARD BISHOP LEWIS died in Ann Arbor, Michigan, on March 7, 1954, after a prolonged illness. Thus ended the career of a dedicated and talented teacher, and a sound and skillful investigator. For thirty-two years he had served the University of Michigan with distinction as head of the Department of Biological Chemistry in the School of Medicine. In 1947, the University, in appreciation of his remarkable services and national reputation, conferred upon him a distinguished professorship entitled the John Jacob Abel University Professorship in Biological Chemistry. In addition to his departmental duties, Lewis was director of the College of Pharmacy from 1933 to 1947.

Lewis was born on a farm near Southington, Connecticut, on November 8, 1887, the son of Frederick A. and Charlotte R. (Parmelee) Lewis. Little information is available concerning his early life; he left no record of his boyhood, nor of the influences that motivated him in pursuing a scientific career. However, his scholarly temperament was revealed even before he entered college. Prior to his sixteenth birthday, he graduated from high school as valedictorian of his class. He had a special interest in the classics. During the year of waiting to meet the age requirement for admission to Yale, he mastered, by self-instruction, a two-year course in high school Greek. At Yale, he won the

Chamberlain Prize for the best entrance examination in the Greek language.

Lewis entered the freshman class of Yale College in 1904 and was awarded the Bachelor of Arts degree four years later. The record shows that his devotion to Greek and Latin persisted, though he graduated "with honors in physical sciences." He stood fourth in a class of three hundred and eighty. During his college years he was the recipient of prizes in Latin composition, chemistry, and calculus.

Most of the two years immediately following his graduation (1908–1910) was occupied in teaching at Hampton Institute, Hampton, Virginia, and at the Centenary Collegiate Institute, Hackettstown, New Jersey. During half of the second year, he began graduate study in chemistry at George Washington University. Apparently, Dr. Isaac K. Phelps, onetime member of the chemistry faculty at this institution, played an important role in encouraging Lewis to pursue his training in biochemistry. He, like Lewis, was a Yale graduate and a native son of Connecticut, and seems to have regarded biochemistry, a relatively new branch of chemistry at the time, as a particularly inviting field for a young scientist.

Lewis entered the Graduate School of Yale University in the fall of 1910. His program of training was directed by Professor Lafayette B. Mendel, a man of remarkable charm, pedagogic skill, and research acumen. During his last two years at Yale, Lewis served as Professor Mendel's laboratory assistant. He was awarded the degree of Doctor of Philosophy in 1913.

During much of his college career Lewis found it necessary to finance his training by tutoring and other extracurricular activities. During one summer, Professor Mendel obtained employment for him in the laboratories of the Connecticut State Hospital at Middletown. This was not an unusual experience for financially needy students in Mendel's laboratory. Several in turn were privileged to engage in such employment. The

position paid a small stipend in addition to room and board. More importantly, it afforded an opportunity for the student to acquire valuable experience in clinical laboratory techniques, while leaving sufficient time for him to exercise his originality in the pursuit of an independent research project. Lewis used the occasion to study the nature of the antigen in the Wasserman reaction.

Following the completion of his training for the doctorate, Lewis accepted an instructorship in physiological chemistry in the School of Medicine of the University of Pennsylvania. He held this position for two years (1913–1915). Sometime during the latter year, he was invited to assume responsibility for the teaching and research programs of the Division of Physiological Chemistry * in the Chemistry Department of the University of Illinois. He accepted this challenge and began his new duties on the Urbana campus in the fall of 1915. There, single-handedly, except for the modicum of help received from a part-time student assistant, he organized and taught a general course in physiological chemistry and three graduate courses dealing with special topics. In addition, he attracted a number of students to work toward advanced degrees under his direction.

Between the Pennsylvania and Illinois assignments, Lewis married Mildred Lois Eaton, daughter of the late Dr. Edward Dwight Eaton, President of Beloit College from 1886 to 1917. She passed away in 1961. Two daughters, Charlotte Barber and Elizabeth Parmelee, survive.

Lewis remained at the University of Illinois until 1922, when he was called to head the Department of Physiological Chemistry † at the University of Michigan. There he continued to display his genius as a teacher, as an investigator, and as an administrator. But his influence did not stop at the borders of the campus. His wide knowledge of medical sciences and

* The name was later changed to the Division of Biochemistry.

† The name was later changed to the Department of Biological Chemistry.

medical education led many outside organizations to seek his services. For fifteen years he was a member of the National Board of Medical Examiners, a position which required an incredible amount of arduous labor. From 1936 until his final illness he was a member of the Council on Foods and Nutrition of the American Medical Association. From 1945 to 1948, he was a member of the Division of Medical Sciences of the National Research Council, and for five years he was chairman of the Michigan Nutrition Council.

As for organizations more closely associated with his specialty, Lewis was intimately involved in the activities of the American Institute of Nutrition as a councilor (1941–1942), vice president (1942–1943), and president (1943–1944). During the long period in which the American Society of Biological Chemists had no paid officials, Lewis, with rare skill and efficiency, performed the laborious task of being its secretary (1929–1933). Subsequently, he was elected to the offices of vice president (1933–1935), president (1935–1937), and councilor (1937–1940 and 1941–1942) of the Society. One of his greatest contributions to science was the dedicated manner in which, for many years, he managed the Placement Service of the Federation of American Societies for Experimental Biology. With a minimal allowance for secretarial help, he brought together many young scientists seeking employment and institutions seeking personnel. Partly because of these services, and partly because of his love of people, Howard Lewis probably knew personally more biochemists and related scientists than any other individual in this country.

At various times in his busy career, Lewis was a member of the editorial boards of five periodicals, namely, the *Journal of Biological Chemistry,* the *Journal of Nutrition, Chemical Reviews, Physiological Reviews,* and the *Proceedings of the Society for Experimental Biology and Medicine.* On several occasions he was honored by being chosen to deliver special lectures. In

1932, he was the Beaumont Lecturer of the Wayne County Medical Society; in 1941, he was Lecturer of the Harvey Society of New York; and in 1948, he was the Henry Russel Lecturer of the Research Club of the University of Michigan.

Membership in professional societies, other than those already mentioned, included the American Chemical Society, the American Physiological Society, the American Pharmaceutical Association, the American Association for the Advancement of Science (fellow), the Society for Experimental Biology and Medicine, and the American Medical Association (associate). In 1949 he was elected a member of the National Academy of Sciences. A review of Lewis's many outside activities leads one to wonder how he could have accomplished so much while successfully carrying the full-time responsibilities of a large and active department.

Despite his many professional duties, Lewis always seemed to find time for healthful recreation. He loved the out-of-doors. Whether his mood at the moment called for a game of tennis or a long walk in the country, he pursued the pastime with zeal and alacrity. One of his favorite hobbies was gardening. He seemed to take special delight in seeing plants grow. Perhaps this was an echo of earlier experiences as a boy on a Connecticut farm. He was an expert bridge player; and not the least important of his hobbies was his lifelong interest in philately. His knowledge of stamps is said to have amazed all who heard him talk about them. He lectured frequently to interested groups on such topics as "Pioneers in Philately"; "The Literature of Philately"; "The One Penny Black"; and "Some Early Charity Stamps." Sometimes the lectures were illustrated with slides. On one occasion he spoke on "Philately and Medicine" before the Detroit Academy of Surgeons. The next day, one of the physicians in the audience, who also was a Regent of the University, wrote in part as follows: "Your talk last night was a masterpiece. . . . I was actually thrilled. . . . It was an extremely

interesting evening . . . such a refreshing, and altogether unusual evening."

Howard's knowledge and appreciation of music continued and grew throughout his career. As a young instructor in Philadelphia, he enjoyed the symphonies, the operas, and the other musical entertainments afforded by the city. One of his associates of that period describes this quality of Howard's character as follows:

"These were the years when grand opera was being first brought to Philadelphia. Our chief, Alonzo E. Taylor, as well as the rest of the laboratory family, were all enthusiastic devotees—Howard in particular. Assembling in the laboratory a morning after an evening of opera we were plunged immediately into a vigorous discussion of the opera in some detail. Howard had an amazing memory of all the plots and in particular of the musical themes in each. I relished these occasions, for my previous laboratory contacts had suggested that art and chemistry should not be too intimately mixed." *

Later, music became a common interest of the Lewis family. Each member, except Howard, acquired a proficiency in the use of one or more instruments. Thus a trio could be assembled and a delightful concert rendered at a moment's notice. Many happy hours were spent in this way, to the edification, not only of the instrumentalists themselves, but of their many friends who were privileged to hear the concerts.

Perhaps the secret of Howard Lewis's success in so many areas of human endeavor is to be found, not only in his inherent native ability, but also in the spirit which he displayed in the performance of every undertaking. Whether work or play was the object to which he was about to devote his seemingly inexhaustible store of energy, he approached it with enthusiasm and zest, as though its doing was a new adventure never before experienced. He gave his very best to every enterprise. Not only was he a hard worker; he was a hard player as well.

* From a letter to Mrs. Lewis from the late Dr. Wm. H. Adolph.

During the forty-one years of his professional career, Lewis participated in the training of many students. Sixty-six received the Doctor of Philosophy degree under his direction, and many others were awarded the Master of Science degree. As to undergraduates, one may conservatively estimate that in excess of five thousand were privileged to take one or more of his formal courses. The effect these trainees have had, and will continue to have, upon biochemical and medical progress is incalculable. In truth, Lewis's influence "marches on."

In research, Lewis displayed both originality and ingenuity. With the collaboration of his students and colleagues, he published an impressive list of scientific articles covering a broad range of topics and requiring the application of a multiplicity of technical skills in the successful elucidation of the topics covered. During the early years of his career, he became interested in the *in vivo* formation of hippuric acid following the administration of benzoic acid. He returned to this problem from time to time as new aspects of the conjugation occurred to him. He observed in man that, after doses of 6 to 10 g of sodium benzoate, the elimination of hippuric acid takes place rapidly, 85 to 90 percent of the theoretical yield being recovered in the urine within a period of five to six hours. In these tests, the output of urea was diminished, indicating the probability that the nitrogen of the hippuric acid had its origin largely in nitrogen that normally is excreted in the form of urea. In later investigations, a quantitatively less important peculiarity was noted by the author in human subjects, for which he had no satisfactory explanation. This was a marked decrease (50 to 70 percent) in the output of uric acid during the first four hours after administering the sodium benzoate, as compared with the excretion during the corresponding periods of the fore and after days.

Most of Lewis's experiments on the metabolic fate of benzoate were conducted on rabbits. The animals were maintained exclusively on a diet of milk, which has a very low glycine con-

tent. Despite the fact that this procedure largely deprived the subjects of exogenous glycine, the total amount of hippuric acid formed from a given dose of benzoate was not significantly diminished. Furthermore, even large doses of benzoate did not induce a noticeable increase in the output of total nitrogen. Thus the source of the glycine used in the conjugation is not to be found in an increased tissue decomposition. In a single experiment in which the bile was drained away from the intestine, the output of hippuric acid was not decreased. This appeared to exclude glycocholic acid as a significant source of the glycine. On the other hand, in all of the rabbit experiments, the distribution of nitrogen in the urine showed, as in the human subjects, a decrease in the output of urea. Evidently, in this species also, the nitrogen of the glycine used in the conjugation was derived from nitrogen that ordinarily is excreted as urea.

Studies of the *rate* of hippuric acid excretion afforded results of particular interest. The output during a six-hour period was greatly augmented when an abundant supply of glycine was given along with the benzoate. A similar, though less marked effect was induced by the simultaneous administration of DL-serine and benzoate. These results were interpreted by the author as indicating that serine can be rapidly converted into glycine for the purpose in question. Other amino acids and related compounds—alanine, cystine, leucine, aspartic acid, glycolic acid, glycolaldehyde, etc.—were found to be without effect upon the rate of synthesis of hippuric acid.

In other experiments, the administration of benzyl alcohol yielded hippuric acid at a rate only slightly less than that observed after the administration of an equivalent amount of sodium benzoate. Obviously, the alcohol is readily oxidized to the corresponding acid, at a rate which is at least as rapid as the conjugation of glycine and benzoate. That the liver may be the site of the conjugation was indicated when it was observed that animals poisoned with hydrazine, a substance known to

exert detrimental effects upon the liver, excrete much less hippuric acid in a six-hour period than do normal animals receiving comparable doses of benzoate and glycine. Under these conditions, the diminished output of hippuric acid was shown not to be due to a slower rate of absorption of the components from the intestine, nor to an injurious effect of the hydrazine upon the kidneys.

Throughout his professional career, Lewis was much interested in the metabolic behavior of the physiologically important sulfur compounds, particularly the amino acids cystine and methionine. Among his many contributions to this topic, the following may be noted.

In extension of the observations of others, in which white rats were the experimental animals, Lewis found that cystine may be a limiting factor in the nutrition of dogs receiving a low protein diet. Thus the quality of a ration, as measured by its ability to maintain nitrogen equilibrium, may be enhanced by the addition of small amounts of cystine. Furthermore, the supplementing effects of proteins of different sources, when incorporated in the basal, low protein ration, were proportional to their cystine content. These findings in adult dogs, like the earlier investigations conducted in other laboratories upon growing rats, seemed to demonstrate that cystine is an indispensable dietary component. Later, the role of methionine, and the ability of cystine to replace it in part, were recognized.

Many of Lewis's investigations were concerned with the oxidation of cystine and its derivatives as measured by the distribution in the urine of inorganic sulfate, ethereal sulfate, and the so-called "unoxidized" sulfur compounds. Rabbits usually served as the subjects. Free cystine, as its sodium salt, was found to be oxidized to inorganic sulfate without increasing significantly the output of unoxidized sulfur compounds. This occurred rather rapidly, with 60 to 85 percent of the sulfate being recovered within 24 hours. When, however, mod-

erate doses (0.5 to 1.0 g per kilogram of body weight) were administered *for several days* to either fasting or fed rabbits, renal casts and protein appeared in the urine accompanied by a diminution in the excretion of nonprotein nitrogen and creatinine. A further indication of renal injury was the marked rise in the nonprotein nitrogen of the blood. When the amino acid was administered subcutaneously, the results were variable. Oxidation largely to inorganic sulfate still occurred; but kidney damage, owing to the excretion of unchanged cystine, was observed in some cases. The degree of injury appeared to depend upon the rate at which the amino acid was absorbed from the site of injection.

Though cystine undergoes oxidation with considerable ease in the animal body, this is not true of certain derivatives of this amino acid. Thus, phenyluraminocystine is oxidized to a very limited extent, and increases markedly the output of unoxidized sulfur. This behavior of the compound was interpreted by Lewis as indicating the probability that deamination ordinarily precedes the oxidation of the amino acid. Furthermore, since phenyluraminocysteine was excreted after feeding phenyluraminocystine, the author suggests that perhaps the first step in the catabolism of cystine may be its conversion into cysteine. In line with this suggestion are the observations that thiolactic and thioglycolic acids are readily oxidized when fed to rabbits, or injected subcutaneously, whereas dithiodiglycolic acid is not. Perhaps, he says, only mercapto compounds, or substances readily converted into them, are oxidized with ease in the animal body. Lewis points out that such a generalization, if true, applies only to aliphatic compounds, since neither thiophenol nor thiocresol, in which, of course, the sulfhydryl group is attached directly to the benzene ring, is oxidized in the animal organism.

The fate of several other compounds related chemically to cystine was tested by Lewis and his colleagues. Definite, but

variable, increases in the output of inorganic sulfate were observed following the oral administration of cysteic acid or taurine. Insofar as oxidation of these compounds occurred, it is believed to have been associated with the activity of the intestinal microflora. The accuracy of this conclusion is attested by the fact that, following the subcutaneous introduction of either cysteic acid or taurine, all extra sulfur appeared in the organic sulfur fraction of the urine. The excretion and distribution of the extra sulfur after the oral or subcutaneous administration of peptides containing glycine and either cysteic acid or taurine did not differ significantly from the findings with the free sulfonic acid. Neither *S*-carboxymethylcysteine, isocysteine, nor thiourea underwent oxidation when injected subcutaneously into rabbits. After the oral administration of *S*-carboxymethylcysteine, a slight increase in urinary sulfate was observed, which again is believed to have been due to activities of the intestinal flora. *S*-Benzyl derivatives of homocysteine and cysteine were not oxidized significantly. However, deamination probably occurred as shown by an increase in α-keto acids in the urines. Thus, deamination may take place even though further catabolic change is blocked by the presence of a nonlabile group.

In growth studies involving the use of young white rats, Lewis confirmed the observations made elsewhere, that taurine is not capable of improving the quality of rations known to be deficient in cystine and methionine. Also, cysteic acid, dibenzoylcystine, and the betaine of cystine are incapable of promoting the growth of animals upon such diets. On the other hand, diglycylcystine and dialanylcystine are readily utilized for growth purposes, while the dianhydride of dialanylcystine is not.

Lewis investigated the cystine content of hair from several species, and conducted experiments designed to determine the relationship of the sulfur-containing amino acids to the growth

and composition of hair. It was observed that, within certain limits, the cystine and total sulfur content of the hair of white rats tended to vary with the content of the sulfur-containing amino acids in the diet, and to some extent with the age of the rats. Hair from young rats had a significantly lower cystine and total sulfur content than hair from adult animals. Hair from rats receiving a diet known to be deficient in cystine and methionine resembled in composition hair from young animals. However, retardation of growth per se, as illustrated by a lysine deficiency, did not produce hair low in cystine and total sulfur. In general, the cystine and methionine requirements for body growth seem to take precedence over the requirements for the production of hair. Later experiments demonstrated, as was to have been expected, that methionine is just as effective a supplement as cystine in inducing the growth and a normal cystine content of hair.

One would expect that the curious metabolic anomaly known as cystinuria would be of very special interest to one who had devoted so much time and energy in elucidating the biochemical behavior of sulfur compounds. And so it was. First, Lewis and his colleagues presented evidence indicating that cystinuria probably is not so rare a condition as had previously been thought. This conclusion was based upon the results of tests upon urine samples obtained from about 11,000 healthy young men and women. For the most part, the samples were procured in connection with the medical examinations given to entering students at the University of Michigan and at two neighboring institutions. The tests revealed four students whose urines regularly contained cystine crystals, and hence were intensely cystinuric. Samples from twenty-five additional individuals, though devoid of cystine crystals, consistently responded positively, in varying intensity, to color tests for the amino acid. Several individuals were subjected to extended investigation. The data obtained with one young man, who seemingly was in

excellent health except for the excretion of cystine, showed that the output of cystine varied rather closely with the total nitrogen content of the urine, and not with the cystine content of the diet. Indeed, the subject could completely oxidize to sulfate doses of 2 to 3 g of cystine. Obviously, the excreted cystine must have been derived from endogenous sources.

Like results were obtained with other subjects. Invariably, the administration of cystine, whether isolated from hair, or derived from the patient's own urine, was without effect upon the cystine excretion, but induced a large increase in the sulfate content of the urine. A similar experiment in which cysteine hydrochloride was ingested led to increases in the output of both cystine and sulfate. When DL-methionine was given, much extra cystine appeared in the urine, accompanied by a moderate rise in sulfate. Strangely, less extra cystine was excreted after a given dose of methionine when the subject was consuming a high protein diet (124 g daily) than when he was ingesting a moderate protein intake (55–60 g daily). This suggested to Lewis the possibility that the utilization of the precursor of urinary cystine in cystinuria occurs more readily under conditions of a high level of protein metabolism. No evidence was obtained for the presence in the urine of a complex containing cystine. Furthermore, both in children and in adults, the loss of cystine in the urine did not alter the cystine content of the hair and nails. No cystine could be detected in the sweat of a patient with pronounced cystinuria.

Lewis's interest in amino acids was not restricted to cystine and methionine, though they seem to have been uppermost in his thoughts. His scientific curiosity included the origin, functions, and metabolic deportment of many amino acids. Extensive experiments were devised to determine the relative rates at which amino acids are absorbed from the alimentary tract, their influence on blood composition, and their effectiveness in the formation of glycogen. In studying absorption, use was

made of the well-known technique devised by Cori. For this purpose, the amino acids, as their sodium salts, were administered by stomach tube to white rats. The extent of the absorption was measured in each case at the end of a period of three hours by killing the animal, removing its alimentary tract, and determining the amount of unabsorbed amino acid remaining in the tract. Incidentally, Lewis confirmed Cori's statement that the rate of absorption is independent of the absolute quantity and the concentration of the amino acid in the intestine.

The results obtained with each amino acid were expressed in terms of the "absorption coefficient" of the compound, which, by definition, is the milliequivalents absorbed per 100 g of body weight per hour. The figures are not reproduced here; it is sufficient to state that the absorption coefficients of the amino acids tested may be arranged in the following *descending* order: glycine, alanine, cystine (expressed as cysteine), glutamic acid, valine, methionine, leucine, isoleucine, and isovaline. Thus, of the above, glycine was absorbed most rapidly and isovaline least rapidly. No significant difference could be detected in the absorption coefficient of the natural L-form of an amino acid and that of its DL-counterpart.

In later experiments, attention was directed to the effects of structural changes on the rates of absorption of several amino acids, all of which were derivatives of propionic acid. The data revealed that α-alanine (natural L-alanine) is absorbed more rapidly than is β-alanine, and serine more rapidly than isoserine. These findings led Lewis to postulate that the rate of absorption is decreased as the amino group of a compound is moved away from the carboxyl. In like manner, a comparison of the absorption rates of alanine and serine on the one hand, and of β-alanine and isoserine on the other, seemed to indicate that the replacement of a hydrogen atom by a hydroxyl group diminished the rate of absorption. It would be interesting to

know whether a similar relationship exists between structure and alimentary absorption in amino acids other than those derived from propionic acid.

Changes in the distribution of nonprotein nitrogenous constituents of the blood were determined following the administration of a number of amino acids. Rabbits were the experimental animals. The amino acids investigated were glycine; the L-forms of alanine, glutamic acid, arginine, and lysine; and the DL-forms of alanine and aspartic acid. Each amino acid was administered, usually orally, in an amount equivalent to 0.182 g of amino nitrogen per kilo of body weight. Blood samples were taken before the amino acid was given, and at intervals of 3, 6, 12, and usually 30 hours thereafter. Each sample was analyzed for nonprotein nitrogen, urea nitrogen, and amino acid nitrogen. From the nitrogen distribution values, it was evident that glycine and L-alanine are absorbed very rapidly, but that glycine undergoes deamination less rapidly than any of the other amino acids.

In studies of glycogen formation, the oral administration of either L- or DL-alanine to white rats which had been deprived of food for 24 hours resulted in a rapid deposition of glycogen in the liver. On the contrary, after administration of glycine or L-leucine, the hepatic glycogen values were similar to those of control animals. The monosodium salt of L-glutamic acid induced a slight increase in liver glycogen. In later experiments, the glycogenic effects of certain amino acids, after three-hour absorption periods, were found to proceed in the following *descending* order: DL- and L-alanine (essentially the same), DL-serine, D-alanine, and DL-isoserine. No glycogen formation could be detected after the administration of β-alanine.

Several of Lewis's papers dealt with the metabolism of phenylalanine. After the oral or subcutaneous administration of this amino acid to rabbits, significant amounts of phenyl-

pyruvic acid appeared in the urine. However, no phenylpyruvic acid was excreted when the amino group was blocked by the formation of the ureido derivative of the amino acid. This observation was interpreted as indicating that oxidative deamination is a necessary step in the metabolism of phenylalanine and must occur prior to the opening of the benzene ring. No evidence was obtained for the excretion of *p*-hydroxyphenylpyruvic acid. In some experiments, after relatively large doses of phenylalanine, slight increases in the output of phenaceturic acid were observed. Apparently, under such conditions, part of the phenylpyruvic acid may be oxidized to phenylacetic acid, which is then conjugated with glycine and excreted without undergoing further oxidation.

Of particular interest was the observation that the daily administration of phenylalanine to white rats in doses exceeding 0.3 g per 100 g of body weight per day, and for considerable periods of time, led to the excretion of homogentisic acid. This appears to have been the first time that alcaptonuria has been consistently produced experimentally. The observation was interpreted by Lewis as lending support to a concept, which was controversial at the time but now is generally accepted, namely, that homogentisic acid is a normal intermediate in the metabolism of phenylalanine.

In experiments of a different kind, Lewis observed that *N*-methylglycine (carnosine) can undergo demethylation in the animal body, and thereby serve as a source of glycine for hippuric acid formation. On the other hand, a comparable reaction with *N*-ethylglycine does not occur.

In studies of histidine metabolism, five of eight rabbits that received large doses of this amino acid by mouth responded by excreting urocanic acid. However, no urocanic acid was excreted after the subcutaneous administration of like doses of histidine. Severe toxic manifestations were exhibited by every animal that excreted detectable amounts of urocanic acid, while

those that failed to show the presence of this acid in the urine displayed no signs of intoxication. These findings led Lewis to question the assumption that urocanic acid is quantitatively an important intermediate in the normal metabolism of histidine. Doubtless he would have altered this opinion in the light of currently accumulated evidence.

Lewis verified the strange report in the literature that pregnant women frequently excrete histidine. Of the urine samples obtained from 169 pregnant females, 85 percent showed the presence of histidine in excess of the normal traces. In contrast, of the urine samples collected from 59 nonpregnant women and 50 men, only 9 percent showed the presence of excess histidine. No logical explanation is available to account for the excretion of this amino acid. The phenomenon does not occur until the third month of pregnancy, and consequently cannot be used as an early diagnostic aid.

Lewis and his colleagues were among the first to attempt the dietary replacement of an essential amino acid by a related compound for purposes of growth. As is well known, a diet containing 18 percent of gliadin as the chief source of nitrogen is incapable of supporting normal growth in young white rats. The factor limiting growth under such conditions is the low lysine content of the food. The addition of this amino acid to the basal ration greatly increases the rate of gain in body weight. It seemed reasonable to assume that some compound closely related to lysine might be transformed into the amino acid, and thereby improve the quality of the basal diet. With this possibility in mind, growth tests were made with several caproic acid derivatives as dietary supplements, namely, norleucine, α-hydroxycaproic acid, ϵ-hydroxycaproic acid, ϵ-aminocaproic acid, and α-hydroxy-ϵ-aminocaproic acid. All proved to be totally incapable of serving in place of the missing lysine, and consequently are not convertible into it. In the light of more recent investigations in other laboratories, in which the α-hy-

droxy analogues of several amino acids have been shown to be capable of serving in place of the corresponding amino acid, it seems very odd that α-hydroxy-ε-aminocaproic acid was not converted into lysine. The most likely explanation of the negative results is the probability that the test compound underwent catabolic changes, possibly involving the ε-amino group, before oxidation and amination could occur in the α-position.

Toward the end of his career, Lewis became interested in a toxemia known as lathyrism. This condition is associated with the prolonged consumption of large amounts of legumes of the genus *Lathyrus.* The toxemia is said to be rather common in India, in northern Africa, and in other areas where legumes of this genus constitute a high percentage of the daily diet. Those afflicted with the malady experience muscular weakness, lameness, and paralysis of the extremities. Lewis was able to induce the disease in young white rats (adult rats are more resistant) by feeding diets containing 50 percent of a finely ground meal prepared from decorticated sweet peas *(Lathyrus odoratus),* or from the seeds of certain other varieties of *Lathyrus.* Pathological examinations of the long bones of the leg revealed lesions similar to those observed in acute scurvy. However, the administration of ascorbic acid, which normally is synthesized by the rat, exerted no preventive effect.

The active principle was found to be readily extractable with cold water or 30 percent ethyl alcohol. From meal prepared from *Lathyrus sylvestris Wagneri,* the species having the greatest toxicity of the ten varieties tested, Lewis succeeded in concentrating the active agent about forty times. Since then, the possibility has been suggested that more than one deleterious compound may be present in *Lathyrus* legumes. One such component has been isolated and identified as β-(γ-L-glutamyl)-aminopropionitrile.

The above outline of some of Lewis's publications, though very incomplete, may give the reader an idea of the breadth

of his research activities. Many aspects of protein metabolism, other than those described, were explored by him, as may be seen by examining his extensive bibliography. In addition, his interests included problems in carbohydrate metabolism, as illustrated by papers on the behavior of certain pentoses, mannose, and inulin in the animal organism. He investigated the metabolism of a number of branched-chain aliphatic acids, described new examples of β-oxidation, and conducted a series of studies on the hydrolysis of esters of dicarboxylic acids by liver lipase. Even the physiological effects and the metabolic fate of several toxic agents, notably hydrazine and its derivatives and selenium compounds, did not escape his attention. A multitude of miscellaneous topics, too numerous to be described in detail, came under his scientific scrutiny. Among the strikingly unique contributions may be mentioned a comparative biochemical study of the urine of the horned lizard, the nitrogenous components of the blood and urine of the turtle, and the nitrogenous metabolism of the earthworm. Truly, his versatility knew no bounds.

Shortly after his death, the Executive Faculty of the School of Medicine at the University of Michigan paid its respects to Howard Bishop Lewis by approving unanimously an appropriate testimonial to be recorded in its minutes and transmitted to his family. Excerpts from that expression of esteem, as phrased by his colleagues, may serve as a fitting conclusion to this survey of his life and work. It reads in part as follows:

"It is difficult to appraise the inspired work of Dr. Lewis, and to make a true evaluation of his vital years of service to the medical profession. To understand the magnitude of his influence, it is necessary to comprehend his remarkable ability and unusual skill in dealing with the training of his students and the administrative functions of his offices. . . . He taught the value of ideals and high standards of accomplishment, and gave to his pupils many guiding principles which have contributed

to their enduring happiness and success in the profession of medicine and allied fields of science. . . .

"Dr. Lewis was as great and as honorable and as respected as the University he loved so much. May his students and colleagues reap the full benefit of the inspiration which he has left with us."

THE AUTHORS are deeply grateful to the late Mrs. H. B. Lewis for supplying much of the information herein recorded concerning her husband's early life and nonprofessional interests, and for permitting us to see and make use of the contents of letters written to her by close friends following Howard's death.

We are also indebted to Dr. A. A. Christman, a former student, friend, and colleague of Dr. Lewis, for supplying many of the scientific facts not otherwise available, and for rendering very substantial assistance in the preparation of the bibliography.

BIBLIOGRAPHY

KEY TO ABBREVIATIONS

Am. J. Pharm. Educ. = American Journal of Pharmaceutical Education
Am. J. Physiol. = American Journal of Physiology
Ann. Internal Med. = Annals of Internal Medicine
Ann. Rev. Biochem. = Annual Review of Biochemistry
Cyclo. Med., Surg., Specialties = Cyclopedia of Medicine, Surgery, and Specialties
J. Am. Chem. Soc. = Journal of the American Chemical Society
J. Am. Dietetic Assoc. = Journal of the American Dietetic Association
J. Am. Med. Assoc. = Journal of the American Medical Association
J. Biol. Chem. = Journal of Biological Chemistry
J. Mich. State Med. Soc. = Journal of the Michigan State Medical Society
J. Nutrition = Journal of Nutrition
J. Pharmacol. Exp. Therap. = Journal of Pharmacology and Experimental Therapeutics
Oral Surg., Oral Med., Oral Pathol. = Oral Surgery, Oral Medicine, and Oral Pathology
Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental Biology and Medicine

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