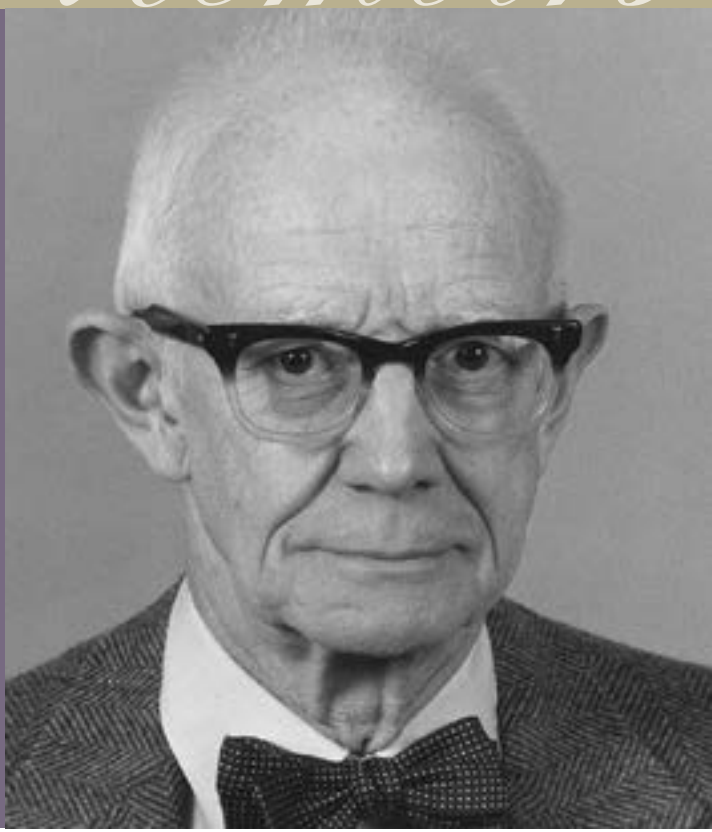
# H. Edwin Umbarger

1921–1999

BIOGRAPHICAL *Memoirs*

*A Biographical Memoir by*
*Frederick C. Neidhardt*





NATIONAL ACADEMY OF SCIENCES

# HAROLD EDWIN **UMBARGER**

*July 17, 1921–November 15, 1999*

Elected to the NAS, 1976

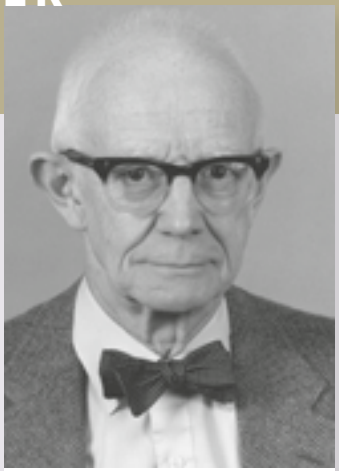


Image courtesy of Department of Biological Sciences, Purdue University.

*By Frederick C. Neidhardt*

H(arold) Edwin Umbarger had a major role in defining the pathways that living organisms employ to produce branched-chain amino acids (L-leucine, L-isoleucine, and L-valine), which are required in all proteins. He also played a pivotal role in identifying the biochemical mechanisms that bacterial and yeast cells use to modulate the synthesis of these amino acids in order to match their utilization in protein synthesis. He was a pioneer in the early days of molecular biology (mid-twentieth century), during a time when techniques from genetics, biochemistry and biophysics focused on life at the cellular level.

Ed was born in Shelby, Ohio on July 17, 1921 and he died on November 15, 1999 at a rehabilitation center near West Lafayette, Indiana where he was recuperating from surgery. His professional life was noted by his unusual accomplishments as a research scientist employing biochemistry and genetics to probe cellular metabolism. Ed was a much-loved mentor of graduate and postgraduate students.

Remarkably, he is remembered as a gifted teacher, despite his lack of oratorical skill… perhaps informed deeply by his own experiences with both brilliant and less than adequate teachers. He exuded a love of learning and of humanity. He infected others with his desire to share the wonders he saw in the living cell. Above all, he impressed his colleagues by his inordinate humility.

His first wife, Merle Abele Umbarger, whom he married while a student, preceded him in death. Together, they had three daughters, Jennifer Manson, Diana Presutti and Sharon Trachtman. He was survived by these daughters, their families, and by his second wife, Virginia Moore Abele Umbarger, whom he married in 1995.

Hopefully, the following account (written without benefit of a complete curriculum vitae fourteen years after Ed's death) captures something of his legacy.

## Early life and influences

Ed grew up in Mansfield, Ohio, where he attended public schools, graduating from Mansfield Senior High School in 1939. The oldest (by 7 years) of three sons, Ed grew up in an economically modest home. His parents had not attended college, but were supportive of a child who in early grade school became fascinated by geography, then history, and then archaeology. His interest in archaeology persisted through high school, and he planned to major in Latin and Greek in preparation for his dream of a Ph.D. in archeology. That dream ended when his high school Latin teacher forced him to take biology, followed by chemistry and physics. In Ed's words: "…it was only in biology and chemistry that I received A's." Ed went on to make an observation that is somewhat startling and provocative. (I quote from a document entitled "Autobiographical facts of a more personal nature," submitted to the National Academy of Sciences by Ed after his election to membership.)

At Harvard, Ed came to grips with the fact that he was ill prepared for a first-rate graduate program in biological science geared to educating first-order researchers.

> *I was markedly stimulated in biology by a lazy teacher who had mimeographed work sheets with blanks to fill in from verbatim passages in any of 3 different biology texts. He conducted each class by a recitation procedure while recording the previous class's work sheet or quiz results. Quizzes and work sheets were graded in class by the class itself. While his effort was minimal, it was an open-ended affair that allowed the inquisitive student ample time and opportunity to learn more than was minimally required.(1)*

He graduated from Ohio University in 1943 with a B.S. degree in chemistry, and in the following year was awarded an M.S. in Zoology from the same school. Service in the U.S. Navy as a hospital corpsman occupied the next two years, after which he was admitted for graduate work at Harvard University.

## Preparation for discovery

At Harvard, Ed came to grips with the fact that he was ill prepared for a first-rate graduate program in biological science geared to educating first-order researchers. His introduction was a shock, providing in Ed's words "…a pretty rude awakening process for an unsophisticated, small town boy from Ohio." Before Professor George Wald

"sent him packing", Ed had experienced three inspiring courses: genetics from Sheldon Reed, bacterial physiology from Kenneth Thimann, and physical chemistry from Jeffries Wyman and John Edsell. Ed considered the year he spent in Wald's laboratory "… important to my personal development."(1)

Across the Charles River, Ed found the atmosphere in J. Howard Mueller's Department of Bacteriology and Immunology at Harvard Medical School conducive to blossoming as an independent thinker and experimenter. Mueller was noted for letting people develop in their own ways, and he apparently saw much promise in Ed.

A visit to that department by a very young Bernard D. Davis in the late 1940's revealed to Ed the potential usefulness of employing penicillin selection to collect auxotrophic mutants (i.e., those requiring new growth factors) in bacteria to learn how vital building blocks of protoplasm were made. Mueller endorsed Ed's idea to use the Davis penicillin enrichment procedure to isolate mutants blocked in the biosynthesis of valine and isoleucine. That encouragement sent Ed along a path from which he never deviated.

Following the award of his Ph.D. in 1950, Ed remained at Harvard for the next decade, eventually becoming an assistant professor. Mueller's department provided much intellectual nourishment. Years later Ed credited the many interactions he enjoyed with Boris Magasanik, Harris Moyed, Arnold Brodie, and Harold Amos as fortunate happenstances contributing to the development of his own ideas. And, in characteristic Umbarger fashion, Ed was quick to point out the germinal effect of a small paper (2) by the timely visitor, Bernard D. Davis. Davis's musings in 1950 on how certain small molecules might serve as "substrate for one enzyme and governor for another" is credited by Ed as leading to his own first notable discovery: end-product inhibition.

The groundwork for Ed Umbarger's major contributions to molecular biology clearly were laid at Harvard, and it was there that the crucial first experimental evidence was obtained that led him to elucidate how order and regulation can be brought about in the tangled biochemical pathways of metabolism. This story follows.

## New ideas in cellular metabolism

### Background

At mid-twentieth century, a race began to ascertain how the main constituents of living cells were made. For many microorganisms, such as *Escherichia coli*, all that cell growth required was a sugar plus inorganic salts, with the latter providing nitrogen, phosphorus,

sulfur and small amounts of iron, magnesium, and other minerals. When it became possible to combine biochemistry with genetic analysis in microbes, the task of defining metabolic processes of biosynthesis became eminently feasible, and in a few decades the metabolic maps showing the paths to protoplasm from sugar were close to complete.

At the same time, microbial physiologists recognized that knowing the enzymatically catalyzed biochemical pathways of metabolism provided merely the groundwork for understanding cell growth. How the many hundreds of reactions were coordinated remained a daunting puzzle. The radioactive isotope studies of the Biophysics Group at the Carnegie Institution of Washington (3) had demonstrated that the processes of metabolism were remarkably systematic and flexibly coordinated. *E. coli* cells growing in a glucose minimal medium no longer made the amino acid isoleucine if this amino acid was added as a supplement to the medium. And there were many other indications of complex behavior as well.

Ed Umbarger is celebrated for his contributions to both these twentieth century endeavors. Beginning in the 1950s he helped elucidate the fascinatingly complex biochemical pathways leading to leucine, isoleucine and valine. Important as this work on pathway elucidation was, some would say that the most significant and unique contributions of Ed concerned the second problem – how the operation of these pathways was regulated in the living cell.

**Umbarger's contributions to the molecular biology of regulation**

1. End-Product Inhibition. By the mid-1950s, Ed had in his grasp several novel observations regarding the biosynthesis of valine, isoleucine and leucine. He knew from his own work and that of others that these amino acids shared biochemical steps; the pathways were not discrete. He knew from research conducted by biophysicists working in the Department of Terrestrial Magnetism (!) of the Carnegie Institution of Washington (3) (as well as from his own studies with mutants blocked at various enzymatic steps) that cells seemed to know how much of these amino acids to make. They never overproduced these amino acids even though mutants blocked at intermediate steps could overproduce the products before the blocked reaction). Also he recalled the speculation by Bernard D. Davis (2), that some small molecules in metabolism may possibly be substrates in one reaction and governors of other seemingly unrelated reactions. Here in his own words is Umbarger's description of a fateful day at Harvard Medical School (1):

"It was known from the work of the Biophysics Group at Carnegie Institution of Washington that the flow of carbon from glucose to isoleucine was blocked by isoleucine.

It was also known that isoleucine spared the utilization of threonine by organisms requiring threonine for growth. In reviewing these facts one afternoon with Harold Amos, it became clear that both facts could be explained if isoleucine inhibited threonine deaminase. A simple three-tube experiment by Barbara Brown, who had been assaying threonine deaminase activity in extracts earlier that day, showed the predicted inhibition to be so."

That day a major part of the solution of physiological regulation of biosynthesis was found. End-product inhibition of the first enzyme (in this case, threonine deaminase) in a biosynthetic pathway by its ultimate product (isoleucine) opened a tremendous conceptual door.

2. Multiple duplicate enzymes under separate control. A corollary prediction can be made from the discovery that isoleucine inhibits threonine deaminase. Ed asked how this property can be useful when the deamination of threonine is also a required step for cells growing in an energetically challenging but otherwise rich environment (i.e., one devoid of sugar). In such a case, the deamination of threonine to produce the corresponding keto-acid available for catabolic metabolism would be senselessly impeded by isoleucine in the environment. Ed reasoned that since *E. coli* can indeed deaminate threonine under these conditions, the reaction must be catalyzed by a separate threonine deaminase, one immune to inhibition by isoleucine. His prediction proved correct. *E. coli* does invest extra DNA to encode a threonine deaminase unaffected by isoleucine (Umbarger, 1957).

This knowledge was just the beginning of understanding the implications for metaboli pathways. For example: Umbarger (with others) had established that four of the five steps in isoleucine formation are each catalyzed by an enzyme performing homologous steps in the pathway leading to valine (cf. Umbarger with B. D. Davis, 1962). If pathway flow is to be regulated by the end product inhibiting the first enzyme of the path, how could the synthesis of isoleucine and valine ever separately be controlled? The first enzyme in the valine path (acetohydroxy acid synthase) is the second enzyme in the isoleucine path. If the presence of excess valine were to inhibit acetohydroxy acid synthase, the cells would become starved for isoleucine. The answer was presaged by the threonine deaminase story, but in a fascinatingly byzantine manner. Ed and others were able to show that there are not one but three different enzymes catalyzing the formation of hydroxyacids during this step. The three isozymes are highly similar in structure and in catalytic properties, and each of them can make the two hydroxyacids: acetohydroxybutyrate (leading to isoleucine) and acetolactate (leading to valine). The isozymes differ in their sensitivity to inhibition by isoleucine and valine. Thus, as in the case of threonine deaminase,

evolution has led to additional genes that produce functionally identical catalysts that differ in their regulation (summarized in Umbarger, 1996).

3. Multivalent regulation of enzymes with multiple functions. While Ed was delving into the world of control of enzyme activity, a major interest of molecular biologists was the regulation of gene function, i.e., control of how much of an enzyme is made from a gene. How the genes encoding the enzymes of the valineisoleucine leucine pathways are controlled is a related, and no less interesting, story.

It is summarized by the statement that regulation of the shared valine-isoleucine enzymes is controlled by (negative feedback) repression of the transcription of the genes for the pathway enzymes (summarized in Umbarger et al., 1996). In general, as shown by Ed and his several former students, the regulation is multivalent: i.e., repression (inhibition of enzyme synthesis) requires all three acids to be in excess; when any one of them is limiting, derepression (synthesis) of the biosynthetic enzymes occurs. The principal mechanism of gene regulation of the branched-chain amino acid pathway is by the process called attenuation, discovered by Charles Yanofsky (cf., 4) for the tryptophan pathway.

## Career advancement and recognition

Ed, untenured, left Harvard in 1959. After a year working at several laboratories in England, he returned to the U.S. in 1960 with an appointment as Senior Staff Investigator at the Cold Spring Harbor Biological Laboratory, Long Island, New York. In 1964 he was offered and accepted a full professorship at Purdue University, where he remained for the rest of his illustrious career. In 1970 he was named Wright Distinguished Professor of Biological Sciences at Purdue.

Ed's continuing contributions to science were recognized over the next two decades: election to the National Academy of Sciences in 1976; election to the American Academy of Arts and Sciences; a Guggenheim Memorial Fellowship; a Medallion from the Ben Gurion University of the Negev in Israel; the Pasteur Award from the Illinois Branch of the American Society for Microbiology; the Rosenstiel Award in Basic Medical Sciences from Brandeis University; the McCoy Award for Contributions to Science and an honorary degree from Purdue University; and the Ohio University Alumni Certificate of Merit. An annual award in Ed's name in the Department of Biological Sciences recognizes outstanding graduate research. (Note: this list of honors awarded during Ed's Purdue years was gleaned from a Memorial Resolution (5) prepared by Ed's Purdue associates.)

In 1992 former associates and students at a symposium at Purdue honoring his lifetime of achievement celebrated Ed's contributions as a scholar. In a final tribute, Purdue University established the Umbarger Distinguished Professorship of Biological Sciences in 1999.

## Personal qualities and attributes

Some desirable attributes of a great scientist are easily identified and acknowledged. One hopes to find in a scientific academician such qualities as brilliance, erudition, creativity, and the ability to communicate and influence others, especially the young. Not always are such hopes realized. But Ed Umbarger's colleagues, and the institution in which he served for most of his career, recognized all these attributes in Ed, and rewarded him accordingly.

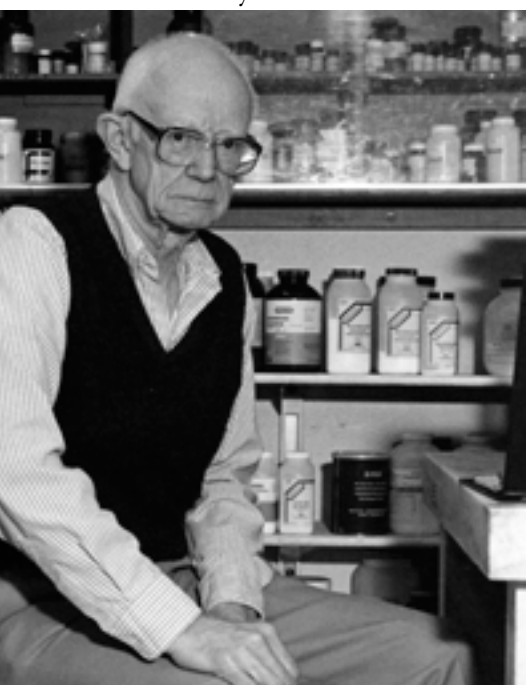


Image courtesy of Department of Biological Sciences, Purdue University.

But there were other facets to Ed that transcended these traditional qualities of academicians. I know I speak for many of his close colleagues when I describe the other parts of Ed's personality.

Humbleness. Some might say that Ed's humbleness grew from his academically humble background. This would be a grave error. Ed's approach to science was colored not so much by his awe of the practitioners of science (which we know he had) as by his wonderment of the nature of the biological universe. Always the first to acknowledge a colleague for an idea… or a distant researcher for inspiration, Ed taught many of us the proper use of "Credits" at the end of scientific papers. To the very end, he credited colleagues, students, former students, and strangers as his sources of inspiration.

Science as a Continuous Endeavor. Living in decades in which the knowledge imparted to him as a student was swiftly surpassed by new discovery every year, Ed recognized the

need to impart to students both the thrill of the chase and the recognition that the chase depended on advancing the baton handed on by a predecessor.

Science as a Global Human Exploration. Every academic and mentoring activity in Ed's lifetime was an expression of his deeply-held belief that science was a pursuit that should be open to all. His career-long efforts to bring people of diverse ethnicity, color and social status into science, and into leadership roles in science, was an example for all his colleagues. Ed was a staunch supporter of affirmative action in both academic admissions and hiring policies. His conviction — and his determination to follow that conviction— were evident to a generation of young scientists.

## Science education

Ed believed that science was what one learned in the laboratory. Many of his colleagues were aware that he was not an electrifying lecturer. Ed stammered, particularly in unrehearsed settings. His lectures (and scientific presentations) were thus not well received (at first) and no one nominated him as Science Educator of the Year. Possibly, Ed's halting speech when expressing profound thoughts was partly responsible for his early wanderings to find an academic home. Yet, oddly, Ed had an enormous (though little recognized) impact on education regarding the molecular biology and physiology of bacterial cells. This impact is described in the next section.

Conceptualization of Science. While never applauded as a lecturer, Ed Umbarger is one of the preeminent microbial biochemists in the field of education in the twentieth century. He made metabolism come alive to students and senior scientists alike. Here is how this came about.

In 1960 Ed read an appendix to a Ph.D. thesis presented by Dan G. Frankel to Harvard Medical School. Dan had calculated the energy costs of metabolism for growth on different substrates. Ed was struck by the utility of such a global approach to metabolism. He saw immediately its value, and encouraged others to develop this analysis further. Ed followed his own advice, and developed and presented a noteworthy course in global metabolism at Purdue.

Years later, Ole Maaløe, John Ingraham and I wrote a textbook on microbial physiology (7). We incorporated the quantitative approach Ed had developed for his bacterial physiology course at Purdue. We adopted his concept of functional classes of metabolic reactions, renaming them fueling reactions (producing 13 precursor molecules, ATP and reducing power); biosynthetic pathways (using the products of the fueling reactions to

build precursor components for protoplasm), and polymerization (using the dozens of building blocks to form macromolecules), followed by assembly (of macromolecules into cellular structures). Further, we built upon Ed's concept of a cost-accounting approach to cell metabolism. The success of that textbook rested in some degree on its presentation of what may be called the Umbarger Synthesis.

This aspect of Ed's theoretical formulation of metabolism led his longtime Purdue colleagues to write as follows (5):

> *...Umbarger's contributions to education are remarkable. His global conceptualization of metabolism, which organized reactions tions into functional classes, found its way into major textbooks, facilitated the immersion of students into the subject of metabolism, and paved the way for a flux analysis of metabolite flow during growth.*

When it came time to assemble the information available about Escherichia coli ("everybody's cell") it was a given that Ed Umbarger would be chosen not only to contribute to the section on amino acid biosynthesis and its regulation, but also to help edit the entire tome (Umbarger et al. 1987, and the second edition in 1996).

## Outreach for education

Some of us involved in science education hold in great reverence an article published by H. E. Umbarger (1977) entitled "A one-semester project for the immersion of graduate students in metabolic pathways."

Microbial molecular biologists are not, as a population, avid readers of educational journals. But this article served a pivotal role among writers of textbooks. It is worthwhile to read the abstract:

> *For several years I have been employing a learning exercise that requires the student to look with care at each reaction in a metabolic pathway and to consider the consequences of the reaction in terms of the investment or yield of energy, reducing power, or carbon...It can become a semester-long exercise if it applies to Escherichia coli growing in a glucose-mineral salts medium. The student accumulates yield or investment values, represented as positive or negative values, respectively, for each step in the catabolic routes (Class I reactions). The resulting values are used later when considering the Class II reactions in which the key*

> *intermediates of the Class I reactions are drained away as initial substrates in pathways leading to the small molecule building blocks. When these values have been obtained, it is possible to estimate the cost of synthesis of E. coli cell material using a rather simple but reasonably idealized composition of E. coli...*

This approach to cellular metabolism not only educated generations of students, but also served as the organizing principle for multiple textbooks, as well as for the presentation of the major summary of information about *E. coli* first published in 1987 (Umbarger et al. 1987) and updated nine years later (Umbarger et al. 1996).

## NOTES

1. Excerpted from H. E. Umbarger. Autobiographical facts of a more personal nature. 1976. Written for inclusion in the files of the National Academy of Sciences, Washington, D.C.
2. B. D. Davis. 1950. Competitive inhibition of metabolites: a mechanism for integration of biosynthesis. *J. Clinical Investigation* 29:808.
3. R. B. Roberts, P. H. Abelson, D. B. Cowie, E. T. Bolton, and R. J. Britten. 1963. *Studies of Biosynthesis in Escherichia coli.* Washington, D.C.: Carnegie Institution of Washington Publication 607.
4. C. Yanofsky. 1981. Attenuation in the control of synthesis of bacterial operons. *Nature* 289:751-758.
5. A. I. Aronson, G. Kohlhaw, and I. Tessman. 2000. Memorial Resolution for H. Edwin Umbarger. Purdue University records.
6. D. G. Frankel. Ph.D. Thesis. 1989. Harvard University.
7. J. L. Ingraham, O. Maaløe, and F. C. Neidhardt. 1983. *Growth of the Bacterial Cell.* Sunderland, MA: Sinauer Associates, Inc.

## SELECTED BIBLIOGRAPHY

1951 With J. H. Mueller. Isoleucine and valine metabolism of *Escherichia coli.* I. Growth studies on amino acid-deficient mutants. *J. Biol. Chem.* 189:277-285.

1955 With B. Brown. Isoleucine and valine metabolism in *Escherichia coli.* VI. Antagonism between isoleucine and valine. *J. Bacteriol.* 70:443-449.

1956 Evidence for a negative-feedback mechanism in the biosynthesis of isoleucine. *Science* 123:848.

1957 With B. Brown. Threonine deamination in *Escherichia coli.* II. Evidence for two L-threonine deaminases. *J. Bacteriol.* 73:105-112.

1958 With B. Brown. Isoleucine and valine metabolism in *Escherichia coli.* VII. A negative feedback mechanism controlling isoleucine biosynthesis. *J. Biol. Chem.* 233:415-420.

1961 Feedback control by endproduct inhibition. Cold Spring Harbor Symposia *Quant. Biol.* 26:301-312.

Endproduct inhibition of the initial enzyme in a biosynthetic sequence as a mechanism of feedback control. In *Control Mechanisms in Cellular Processes.* D. M. Bonner, ed. pp. 67-86. New York: Ronald Press.

1975 With C. S. Brown and E. L. Kline. Single reactions with multiple functions: multiple enzymes as one of three patterns in microorganisms. In *Isozymes II; Physiological Function*, pp. 249-273. New York: Academic Press.

With S. C. Quay, D. L. Oxender, and S. Tsuyumu. Separate regulation of transport and biosynthesis of leucine, isoleucine, and valine in bacteria. *J. Bacteriol.* 122:994-1000.

1977 A one-semester project for the immersion of graduate students in metabolic pathways. *Biochemical Education* 5:67-41.

1981 Regulation of amino acid metabolism. In *Comprehensive Biochemistry.* Vol. 19a. N. Paskin, ed. pp. 1-49. Amsterdam: Elsevier/North Holland.

1987 Biosynthesis of the branched-chain amino acids. In *Escherichia coli and Salmonella typhimurium: Cellular and Molecular Biology.* F. C. Neidhardt, J. L. Ingraham, K. Brooks Low, B. Magasanik, M. Schaechter, and H. E. Umbarger eds. pp. 352-367. Washington DC: American Society for Microbiology.

1996 Biosynthesis of the branched-chain amino acids. In *Escherichia coli and Salmonella: Cellular and Molecular Biology*, 2nd Edition, F. C. Neidhardt, R. Curtiss III, J. L. Ingraham, E. C. C. Lin, K. B. Low, B. Magasanik, W. S. Reznikoff, M. Riley, M. Schaechter, and H. E. Umbarger eds. pp. 442-457. Washington DC: ASM Press.