The two decades between 1960 and 1980 brought about the transformation of the Department of Medicinal Chemistry beyond recognition. The department moved into new quarters once again—this time to its current home. But this pivotal era began, as it did in the country as a whole, as little more than a continuation of what had gone before in the 1950s and even earlier. Indeed, new faculty and students arriving at the College of Pharmacy in the first few years of the 1960s would have found little that might have surprised Dean Charles Rogers—or possibly even Dean Frederick Wulling.

The departments were still fashioned after the traditional pharmaceutical chemistry and pharmacognosy programs of the old school: vertically integrated and featuring almost no interdisciplinary, or even interdepartmental, collaborations beyond a continued reliance on the Chemistry Department to carry out chemical analysis of isolated products. That dependency, in turn, reflected a continuation of the relative lack of instrumentation within the department itself (Abdel-Monem, interview, 2009).

While research was a key activity for faculty in both pharmaceutical chemistry and pharmacognosy, one of the three pharmaceutical chemistry faculty members, Frank DiGangi, was not involved in research as the decade dawned: his focus was primarily on coursework for undergraduate pharmacy students (ibid.). Undergraduate students had to take credits amounting to between three and three-and-a-half years of coursework. Most of the department’s 15 graduate students were preparing themselves for a life of teaching, not research. Although it was not unusual for students to obtain an M.S. degree and leave after two years, it was also not uncommon for some students to take seven or eight years to earn their Ph.D.

Facilities and physical resources were still spartan, at least by contemporary standards. Students and faculty had access to office laboratories as well as shared
space in a community laboratory; at the time, there was no postdoctoral staff in the department. The laboratories offered microscopes and balances, but little else: learning how to use the Lloyd Extractor (now on display in Weaver-Densford Hall) was considered a rite of research passage (ibid.). On summer evenings anyone working in the un-air-conditioned laboratory had to contend with mosquitoes as well as scientific questions. Faculty and students continued to rely on the Chemistry Department—located across the street from pharmaceutical chemistry—to carry out more sophisticated analytical procedures (Kier, interview, 2009).

But the single greatest dimension of continuity in both the pharmaceutical chemistry and pharmacognosy departments was the exclusive focus on natural products, with Gisvold and Soine leading the way in the pharmaceutical chemistry program, and Earl Fischer, Herbert Jonas, and Lee Schramm, a faculty member hired in 1961 who left the department in 1968, heading up pharmacognosy investigations (ibid.). That continuity, however, was about to be broken, at least in pharmaceutical chemistry, and replaced by what would become the dominant focus for the rest of the 20th Century—synthetic medicinal chemistry.

Even before the change took place, it was heralded by a misguided announcement by Gisvold one day to faculty and graduate students working in the common laboratory. Gisvold had just learned that his application for a new National Institutes of Health grant had been turned down. Bemused, he came into the laboratory and solemnly announced that the NIH was simply not going to fund any more grant applications for natural product chemistry.

What the NIH rejection actually signaled, however, was a change already underway elsewhere in the country, if not as yet within the College of Pharmacy. Fortunately, given the department’s reputation, the College was in a position to catch that wave in its early stages, thanks to the recruitment of new faculty members—
some of whom were former graduate students at the University—who would go on to become leading researchers in their fields. One such person was Herbert Nagasawa, a research scientist at the Veterans Administration Hospital, was recruited to join the department as a research assistant professor in 1959. A 1955 Ph.D. graduate of the Chemistry Department at the University of Minnesota, Nagasawa was trained as a synthetic organic chemist. He'd started his career by investigating the bioactivation mechanisms of drugs that inhibit the metabolism of acetaldehyde; his goal was to synthesize second-generation, alcohol-deterrent drugs for the treatment of alcoholism. Nagasawa rose through the ranks and continued as a member of the department until his retirement in 2005.

In turn, it was primarily Nagasawa’s and Soine’s research interests that led to the creation of a new faculty position specifically geared toward investigating the relationship between molecular structure and biological activity at the University of Minnesota. Although Soine was interested in this area of research, he was at this time more focused on the chemistry of natural products rather than on exploring novel chemical structures to optimize biological activity.

That position was filled by Philip Portoghese, who, in 1961, became the first
departmental medicinal chemist faculty member to use synthetic organic chemistry for the specific purpose of studying the architecture of receptor binding-sites. He pursued this goal by designing, synthesizing, and biologically testing different shaped molecules.

PHILIP S. PORTOGHESE
B.Sc. 1953, Columbia University
M.Sc. 1958; Ph.D. 1961, University of Wisconsin
Assistant Professor 1961-64, Associate Professor 1964-69, Professor 1969-present, Distinguished Professor 2000; Director of Graduate Studies in Medicinal Chemistry 1974-86, University of Minnesota
Born, New York, New York, 1931.

Awards
• ACS Medicinal Chemistry Hall of Fame, 2007
• Nauta Award in Pharmacochemistry, 2006
• AHC Academy for Health Excellence in Research, 2003
• Lawrence and Delores Weaver Medal, 2001
• Alfred Burger Award in Medicinal Chemistry, 2000
• The Oak & the Tulip Medal, 1999
• Edward E. Smissman-Bristol-Myers-Squibb Award, 1991
• Nathan B. Eddy Award For Excellence in Drug Abuse Research, 1991
• Research Achievement Award in Medicinal Chemistry, AAPS, 1990
• Medicinal Chemistry Award, Division of Medicinal Chemistry, 1990
• Ernest H. Volwiler Award, AACP, 1984
• Research Achievement Award in Medicinal Chemistry, APhA 1980
• Fellow, American Chemical Society, 2010
• Fellow, American Association for the Advancement of Science, 1986
• Fellow, Academy of Pharmaceutical Sciences, 1974
Meanwhile, the sequence of events leading to his appointment provides an insight into how departmental culture—especially when it comes to hiring new faculty—has changed over the past 50 years. Portoghese’s Ph.D. thesis advisor, Professor Edward Smissman, had heard of an opening for an assistant professorship in pharmaceutical chemistry at the University of Minnesota College of Pharmacy through his friend George Hager, who was currently dean of the College. Smissman suggested Portoghese as a candidate; there were no search committees at that time. Hager then invited Portoghese to Minnesota to present a seminar on his Ph.D. research. Originally reluctant to interview at a Midwestern university because he wanted to return to his native East Coast, Portoghese was unenthusiastic about considering the University of Minnesota for a faculty position. In fact, he had already applied for a position at the University of Rhode Island. However, because of Smissman’s convincing salesmanship on the merits of Minnesota as a venue for doing research, along with his successful lobbying of Portoghese’s wife, Portoghese decided to accept the invitation to visit the University (Portoghese, interview, 2009).

After accepting Hager’s invitation, Portoghese visited Minnesota and presented his research to the pharmaceutical chemistry and organic chemistry faculty. He soon received an offer from Hager for a position as an assistant professor, which he accepted with a starting date of September 1961. The fact that he was offered the position without even having applied for it or screened by a search committee would be unusual enough today; even more unusual is that he was funded through an NIH grant for which he applied prior to arriving at the University of Minnesota. Shortly after his arrival, his grant application was funded. Since then, he has been funded continuously by the NIH.

Portoghese brought with him a keen interest in stereochemistry, which originated in an equally strong interest in graphic art. In fact, prior to enrolling in college he had to make a decision on whether to pursue a career in art or science. The connection is clear in his first funded grant, which was related to the synthesis of molecules with well-defined geometry in an effort to define the three-dimensional shape of the receptor sites for morphine and related analgesics located on nerves in the central nervous system. The area of analysis was not related to his Ph.D. research: his interest in analgesics stemmed from a seminar topic Smissman had suggested he present as a graduate student (ibid.).

After four years of research on the stereochemical requirements for opiates that produce analgesia, Portoghese had amassed a large amount of data strongly suggesting the presence of multiple opioid receptor sites in the central nervous system. This concept was counter to the prevailing dogma of the day that proposed that there was a single type of receptor that binds an analgesic molecule in a manner similar to a key that fits a lock. Ten years passed before evidence published by biologists confirmed Portoghese’s concept of multiple opioid receptor sites (Portoghese,
1965).

With more than 360 scientific publications over the past 50 years, Portoghese has made a significant impact both on the field of opioid research and medicinal chemistry research in general. A recurring theme in his research has been the utilization of novel concepts in the design of biologically active compounds. Most notably, in addition to his work relating to multiple opioid receptors, his research has included the design of highly selective opioid antagonists based on the message-address concept. Some of the compounds developed through this concept are standard research tools used in the field today. Presently, eight of his compounds are available through a number of commercial vendors and through the NIH. Through his bivalent ligand approach developed in 1982, his group first proposed the concept of opioid receptor dimers nearly two decades before they were demonstrated to exist in cultured cells. Most recently, he has led his group to design compounds that are selective for such dimers as a new approach to developing analgesics devoid of tolerance and dependence.

Portoghese’s research has been highly cited, as reflected by his listing in the “Institute for Scientific Information’s Highly Cited” database of researchers. He has been recognized both nationally and internationally with numerous awards from major scientific societies. In addition to being honored with numerous research recognitions from scientific and professional societies and the NIH, he has received honorary doctorate degrees from two universities.

Following his doctoral studies at the University of Minnesota, Dennis Larson continued working as a postdoctoral research fellow in the Department of Medicinal Chemistry on research projects involving the synthesis of radio-labeled opiate compounds and study of their pharmacokinetics in mice, and the synthesis of prostaglandin F2 derivatives. During this period he also served as an interim professor during one of Portoghese’s sabbatical leaves.

As research assistant professor, Larson continued research projects involving design and synthesis of varied unlabeled and radio-labeled opioid derivatives, as well as synthesis of substance P derivatives and synthesis of multifunctional opiate-
containing dendrimers for potential long-acting biological action. These research efforts are associated with about 10 compounds now being employed as principal pharmacological tools in research activities conducted by laboratories throughout the world. During this time, Larson also served as laboratory manager and operational adviser for Portoghese’s research group. Additionally, he served on the College safety committee and as departmental controlled substances unit registrant. He also participated in the maintenance of departmental instrumentation, such as

**DENNIS LARSON**
B.S. 1961; Ph.D. 1969, University of Minnesota
Postdoctoral Research Fellow 1970-77,
Research Assistant Professor 1978-2004,
University of Minnesota
Born, Minneapolis, Minnesota, 1939; retired, 2004.

**ROBERT VINCE**
B.Sc. 1962, University of Buffalo
Ph.D. 1966, SUNY at Buffalo
Assistant Professor 1966-67, University of Mississippi
Assistant Professor 1967-71; Associate Professor 1971-76; Professor 1976-present,
Director, Center for Drug Design 2003-present, University of Minnesota
Born, Auburn, New York, 1940.

**Awards**
- Minnesota Science and Technology Hall of Fame, 2011
- Imbach Townsend Award, 2010
- ACS Medicinal Chemistry Hall of Fame, 2007
- AHC Academy for Excellence in Health Research, 2007
- Fellow, American Association for the Advancement of Science, 2000
- Outstanding Contributions to Research and Development—Medical Alley, 1994
- Certificate of Commendation by Governor Rudy Perpich, 1989
departmental FTIR, radioactivity scanners.

The department’s growing reputation in synthetic medicinal chemistry research attracted other young research-oriented faculty, like Robert Vince, who trained under Howard Schaffer at the State University of New York in Buffalo where he worked on the design of acyclonucleosides. That work subsequently served as the basis for the development of an anti-viral drug for herpes simplex, marketed as Acyclovir. After taking a faculty position at the University of Mississippi, Vince joined the University of Minnesota in 1966 where his research continued to explore the creation of compounds that would prove effective for fighting cancer and viruses, like those that can cause herpes.

During the early 1970s Vince’s group developed the lactam, 2-azabicyclo[2.2.1] hept-5-en-2-one, dubbed “Vince’s lactam,” which has become the major intermediate for the synthesis of carbocyclic nucleotides. That work laid the groundwork for his later investigations into anti-AIDS compounds. An exciting achievement in the anti-viral area has been the successful design of a
compound called cyclaradine, which has been found to possess significant activity in treating viral infections but lack of worldwide patent coverage prevented the backing for clinical development. Ultimately, Vince’s legacy at the University will be his development of drugs effective in the treatment of cancer and a late 20th Century scourge, AIDS (Vince, interview, 2008).

In 1967, new faculty and the spirit of innovation they brought to the University, led by Portoghese, resulted in the adoption of a new departmental name that more accurately reflected the realities of the times, with the Department of Pharmaceutical Chemistry becoming the Department of Medicinal Chemistry.

Fueling the change in nomenclature was the fact that the term “pharmaceutical chemistry” did not mean quite the same thing in the pharmaceutical industry as it did at the College, giving rise to confusion. The connotation conferred on the phrase from long industry usage was of a problem-solving approach based upon pharmaceutical formulations. Nationally, the name change was catalyzed by an informal discussion of pharmaceutical chemistry participants at the 1965 AACP Teacher’s Seminar in Toronto. The name change from pharmaceutical to medicinal chemistry was also indicative of the shift that took place in the department’s research emphasis from research based on the isolation and characterization of medicinal agents from natural products to an emphasis on rational drug design based on an understanding of cell biology. The term “medicinal chemistry,” then, was much more consistent with what was actually going on in the department as well as in industry and the discipline as a whole. Within the College, there was no resistance to the name change. In the end, all faculty members in the department voted to replace the old name that had been in use since 1892 (Portoghese, interview, 2009).

Another of the young faculty members was Patrick Hanna, who began his career at the University in 1969. Hanna, who obtained his Ph.D. in medicinal chemistry from the University of Kansas, was recruited to the University as a non-tenure track
faculty member of Professor Gilbert Mannering’s Center for Drug Metabolism. Initially, his primary appointment was as an instructor in the Department of Pharmacology in the Medical School, with a joint appointment in medicinal chemistry. Although Hanna, whose background was in synthetic medicinal chemistry, initially focused his research on structure-activity relationships of histamine antagonists, he shifted his emphasis within a few years to the metabolism of carcinogens and investigations of arylamine N-acetyltransferases (NATs), which play important roles in the metabolic detoxification and activation of both arylamine drugs and arylamine carcinogens found in tobacco smoke. His early studies led to the acquisition of NIH and American Cancer Society research grants, and to his nomination by Portoghese for tenure in the College of Pharmacy. Hanna’s research on NATs and arylamine bioactivation yielded seminal contributions to the field and continued for more than three decades.

For some 25 years Hanna maintained research space in the departments of pharmacology and medicinal chemistry; he taught courses in both departments, was involved extensively in departmental and University committee service, and trained graduate students in both programs. He served as co-director of the joint pharmacology-medicinal chemistry training grant and was director of graduate studies in medicinal chemistry for nine years. Hanna was an associate editor of the Journal of Medicinal Chemistry for 18 years, and was elected chair of the Division of Medicinal Chemistry of the American Chemical Society in 1986.

Hanna has been the recipient of several teaching awards. Students in the College of Pharmacy nominated him for the Morse-Amoco Foundation (now Morse-Alumni) Award for outstanding contributions to undergraduate education, which he received in 1979. He also was inducted into the University’s Academy of Distinguished Teachers. In July 2010, after 41 years as a faculty member, Hanna began a two-year phased retirement (Hanna, interview, September 2009).
One of the most notable hires during this period was of Mahmoud Abdel-Monem, who did his graduate work at the University, obtaining his doctorate with Taito Soine serving as his mentor. After returning to Egypt for several years, Abdel-Monem came back as a postdoctoral research associate working for two years with Portoghese. He then joined the faculty of the College of Pharmacy at the University of Illinois before he was recruited to Minnesota as assistant professor and appointed to the faculty in 1971. Later, Abdel-Monem would go on to play important roles in the College’s administration.

One of his roles was to assist in revising the courses offered by the department designed to prepare graduates for the changing practice of pharmacy. Abdel-Monem modernized the two-course sequence in pharmaceutical analysis and was recognized by the students and colleagues as an exceptional teacher. In recognition of his contributions to undergraduate education he was nominated by professional pharmacy students and received the Horace H. Morse-Amoco Foundation Award in 1985.

In the research phase of his career at the University, Abdel-Monem’s program focused on drug disposition and the examination of the chemical mechanisms of the enzymatic biotransformation of biologically active substances as well as studies on the metabolism and physiological function of the polyamines. His studies led to the discovery of two potent inhibitors of the enzyme ornithine decarboxylase. One of the compounds became available and was marketed by Calbiochem and was utilized by researchers for studies on cell proliferation and the prevention of induction

MAHMOUD M. ABDEL-MONEM
B.Sc. 1959, Cairo University
Ph.D. 1966, University of Minnesota
Assistant Professor 1970-71, University of Illinois
Assistant Professor 1971-75; Associate Professor 1975-80; Professor 1980-87;
Head of Medicinal Chemistry 1983-84, University of Minnesota
Dean of Pharmacy 1987-98, Washington State University
Born, Cairo, Egypt, 1938.
Awards
• Morse-Amoco Foundation Outstanding Teaching Award, 1985
• University of Minnesota Outstanding Achievement Award, 1999
of cancer by chemical carcinogens (Abdel-Monem, interview, 2009).

With a rising level in research activity and directed funding, the department also generated increased funding from federal agencies. A major example was the five-year NIH training grant submitted by Soine in 1966 and funded in 1967 to support five pre-doctoral candidates, two postdoctoral fellows and one assistant professor.

At the termination of the fourth year of the grant, College of Pharmacy Dean Lawrence Weaver, together with the chairs of medicinal chemistry, pharmacognosy and pharmaceutics, applied for and secured a five-year grant encompassing the
three basic pharmaceutical science fields (Anderson & Pennigton, 2005, 86-7).

A renewal of this grant was approved but not funded in 1976, which led the medicinal chemistry faculty to submit a proposal in 1976 as a departmental unit rather than as a coalition of the pharmaceutical sciences; this second proposal was approved for an additional five years. Soine was the principal investigator for the grant but following his untimely death in 1978, the grant was transferred to Portoghese. When time came for an additional renewal in 1981, NIH was putting pressure on both departments of medicinal chemistry and pharmacology to submit a joint application; the new NIH guidelines would limit the number of similar pre-doctoral training grants at any one institution to only one. This new training grant was submitted to establish a multidisciplinary approach that not only incorporated features of both existing programs but also included members of the Department of Pharmacognosy. Fredrick Shideman, from pharmacology, was the program director and Portoghese its co-director. Following the retirement of Shideman, Akira Takemori from pharmacology and Hanna from medicinal chemistry assumed the director/co-director positions of the training grant which continued to be funded until 1996.

Following the retirement of Gisvold in 1973, the department hired Dwight Fullerton, who at the time was doing postdoctoral research studies with Morris Kupchan at the University of Wisconsin.

Fullerton assumed Gisvold’s teaching responsibilities and carried out research on cardiac glycosides. He was expected to continue to build on the discoveries made by Gisvold. However, after three years at Minnesota he decided to accept a faculty position in 1976 at the University of Oregon.

Attempts to hire a replacement for Fullerton were not supported by the College administration. But Portoghese, who was heading the department of graduate studies in medicinal chemistry, convinced the College administration to hire a new faculty member in medicinal chemistry.

This led to the appointment of Rodney Johnson in 1978 as assistant professor to

**Dwight (Pete) Fullerton**

B.A. 1966, University of Oregon
Ph.D. 1970; Assistant Professor 1973-76, University of Minnesota
teach, among other things, nuclear pharmacy. Johnson received his Ph.D. in medicinal chemistry from the University of Kansas where he worked with Ed Smissman and Gary Grunewald. He was an assistant professor of pharmacology at the University of Kansas Medical Center prior to his position at the University of Minnesota. Although it was expected that Johnson would also do research in radiopharmacy, he started his research career by working on the design, synthesis, and pharmacological evaluation of polypeptide and peptidomimetic inhibitors of renin. This effort evolved into

RODNEY L. JOHNSON
B.Sc. 1972, University of Minnesota
Ph.D. 1976, University of Kansas
Instructor 1976-86; Assistant Professor 1978-79, University of Kansas
Assistant Professor 1979-81; Associate Professor 1981-89; Professor 1989-present; Director of Graduate Studies in Medicinal Chemistry 1986-88 and 1997-2003, University of Minnesota
a well-funded research program on the design and synthesis of peptidomimetics and constrained analogues of neuropeptides as well as excitatory amino acid related to the neurotransmitter glutamic acid. In recognition of his outstanding overall achievements as a teacher and researcher, the College appointed Johnson in 2010 as Distinguished Professor of Medicinal Chemistry (Johnson, interview, 2009).

Other faculty added to the department during these years included Thomas Holmes. Following the sudden death of Soine in 1978, the department approached Weaver for a faculty replacement, which led to the appointment in 1980 of Thomas Holmes as assistant professor of medicinal chemistry. A graduate of medicinal chemistry program at the University of Michigan, Holmes did postdoctoral research associate at the University of Chicago and then went on to become a research scientist at Ortho Pharmaceutical Corporation before coming to the University. Holmes’s research focused on synthesis of electrophilic derivatives of known anti-inflammatory and anti-tumor agents for use as affinity labels for cellular receptors and elucidation of specific molecular mechanisms of drug action. He had also great interest in teaching, which ultimately led him to take a new position at Campbell University in 1987 where he served as associate dean for 20 years.

Rodney Johnson asks Abigail Fisher to obtain a crystalline compound from an oily mixture.

**THOMAS J. HOLMES JR.**
B. Sc. 1971, Duquesne University
Ph.D. 1975, University of Michigan
Assistant Professor 1980-87, University of Minnesota

**Awards**
- Fellow, American Association for the Advancement of Science, 1985
A Time of Transition

While not as dramatic as it was for medicinal chemistry at the University, the 1960s and ’70s were also a time of transition in pharmacognosy from purely descriptive work to product extraction and the role of plant and microbial cells to product isolation.

Hired in 1958 as an associate professor of pharmacognosy to work alongside the long-time head of the department, Earl Fischer, Herb Jonas had not been trained as a pharmacognocist, but rather as a plant physiologist with extensive experience using radioisotopes in research. When Fischer, who had been ill for several years, died in 1961, Jonas took over as chair of the program. Later that year, the program added a new faculty member, Lee Schramm, who would work at the University until taking a position at the University of Georgia in 1967. During his time at the University, Schramm did research on fungi, plant cell cultures, and ergot; he and Jonas also completed an extensive revision of the pharmacognosy curriculum to reflect the changing research focus (Netz, 1971, 130). Other pharmacognosy projects investigated the effects of pesticides, insecticides, herbicides, and plant growth regulators on medicinal plants (Schramm, interview, 2009).

In 1968, Jonas transferred from pharmacognosy to the College of Biological Sciences where he accepted an appointment as an associate professor of botany. That same year, John Staba, head of the Department of Pharmacognosy at the University of Nebraska, was appointed chair of pharmacognosy at Minnesota. A nationally recognized expert in plant cell culture, Staba was brought in by the new Dean of the College of Pharmacy, Lawrence Weaver, to reinvigorate the program, in particular by strengthening research activity. Staba continued his studies on plant cell cultures where he carried out investigations to experimentally establish the environmental and biological factors necessary for aseptic higher plant cells and organ cultures to
produce and/or transform substrates into new medicinal agents. Over the years he studied cell cultures for production and transformation of digitalis, ginseng, opiates, quinine, and artemisinin. Large-scale production of the active compounds produced by the plant cells were grown in 20-gallon fermenters.

Staba held many positions in various scientific societies and was elected in 1971-72 as president of the American Society of Pharmacognosy.

Despite that ambition, it turned out that Weaver’s determination to build a clinical pharmacy program would have less than positive ramifications for both pharmacognosy and medicinal chemistry. In the absence of major increases in College funding, Weaver was forced to divert resources from medicinal chemistry and
pharmacognosy, making it difficult to accomplish the task of expanding research in those areas.

At the same time, Weaver had an interest in strengthening biological research at the University. As a result, he contacted Arthur Uhl, former dean of pharmacy at the University of Wisconsin, who arranged for a meeting with Yusuf Abul-Hajj in Madison. At the time, Abul-Hajj, who studied with Charles Sih and was involved with bioorganic research for his doctoral work, was primarily interested in pursuing a career in the pharmaceutical industry. However, Weaver explained the advantage of academia and encouraged Abul-Hajj to consider the position at Minnesota.

In 1968, Abul-Hajj was hired. Although he had no training in pharmacognosy, his ability to deepen the biological expertise of the pharmacognosy program, in particular through his work using enzymes from microbial cell systems to bring about biochemical transformations, were seen as necessary components for a strengthened program. But to work with enzymes, researchers need access to a cold room, which the College of Pharmacy did not possess. One of Abul-Hajj’s first contributions to the pro-
gram was to raise money from Smith, Kline, & French, a pharmaceutical firm that is now part of Glaxo Smith Kline, to install a cold room in the department.

This addition would prove to have far-reaching implications not just for the department or College but for the University as a whole, since it made it possible for researchers working with enzymes, like Robert Vince and others, to use this facility extensively.

Upon discovering that in the days prior to passage of the National Cancer Act it was difficult getting money to fund research in microbial transformations, Abul-Hajj shifted his focus toward cancer and steroids. His research interests involved a variety of areas related to steroid chemistry and biochemistry. The principal focus of his research in the mid-1970s was on the enzymatic mechanisms and stereochemical aspects of steroid hydroxylations and dehydrogenations in both mammalian and microbial systems. He continued throughout his career working on the design, synthesis, and evaluation of aromatase inhibitors, steroidal anti-estrogens, and estrogen-linked cytotoxic agents for the treatment of breast cancer. He also carried out extensive investigations studying the underlying mechanism(s) involved in the genotoxicity/carcinogenicity of estrogens. His laboratory was the first to show the formation of estro-
From Digitalis to Ziagen: The University of Minnesota’s Department of Medicinal Chemistry

YUSUF J. ABUL-HAJJ
B.Sc. 1962, M.Sc. 1964, American University of Beirut
Ph.D. 1968, University of Wisconsin
Assistant Professor 1968-72; Associate Professor 1972-79; Professor 1972-present;
Head of Medicinal Chemistry and Pharmacognosy 1984-87; Head of Medicinal
Chemistry 1987-94, 1996-2005; Director of Graduate Studies in Pharmacognosy, 1982-
85, University of Minnesota
Born, Jerusalem, Palestine, 1940.

Awards
• Lawrence and Delores Weaver Medal, 2005
• Fellow, American Association for the Advancement of Science, 1990

The cold room acquired in the mid-1970s was moved in the 1980s and is still currently used in Weaver-Densford Hall.

gen-nucleic acid adducts, which led his group to propose a new paradigm for the mechanism of estrogen carcinogenicity.

In 2005, Abul-Hajj was selected to receive the Lawrence and Delores Weaver Medal. Meanwhile, changes in the pharmacy curriculum necessitated hiring a faculty member in pharmacognosy who could teach immunology. As a result, the program got the green light to add Orval Mullen in 1971. Mullen stayed at the University for only three years and focused his energies exclusively on teaching. When Mullin left, he was replaced by Daniel Miller, from the University of Wisconsin, in 1976, as an assistant professor. Described as an entrepreneurial thinker, Miller initiated an ambitious research program in the area of immunological
mediators, but became frustrated by the lack of resources available to the pharmacognosy program and left in 1980 to join a group conducting similar research at Riker-3M. He subsequently held positions of vice president for research and development at Dianon Systems, a start-up company involved in perfecting the clinical use of cancer biomarkers, and president of Excorp Medical, which is engaged in the commercial development of bioartificial liver technology.

Following the departure of Daniel Miller, the College hired Thomas Shier to assume Miller’s teaching responsibilities and to embark on research in areas new to the College. Shier initially taught immunology to pharmacy students as Dan Miller had, but added the teaching of biotechnology as that field developed. When Carston R. Wagner was hired, the immunology teaching was turned over to him, and Shier continued with teaching biotechnology and added the teaching of nutrition. Shier helped found the Toxicology Graduate Program at the University of Minnesota and served as it director of graduate studies for three years.

When Shier came to the College he had 10 years of research experience at the Salk Institute where he worked on mechanisms of cell killing by phospholipase

---

**ORVAL L. MULLIN**  
Ph.D. 1971, The Ohio State University  
Assistant Professor 1971-74, University of Minnesota
activation, but his greatest research achievement was as a graduate student when he developed mutasynthesis, a novel way for making new antibiotics. In Minnesota he continued his studies on cell killing mechanisms including studies on cell killing in ischemic disease such as myocardial infarction and stroke using mammalian cell culture systems and explored the use of ionophores and chelators as tools to study mechanisms of cell killing.

The skills he brought in the use of mammalian cell cultures as a research tool was something new for the department. Mammalian cell culture techniques provide important tools for understanding cellular mechanisms, as well as in vitro evaluation of drug candidates early in the drug discovery process. Shier quickly set up his laboratory and established the technique in the department. After a few
years working with cell cultures, the techniques of mammalian cell culture became an important research tool in medicinal chemistry. Shier’s research program has subsequently developed into several related areas. The largest part of the program has been devoted to studies on mycotoxins, which cause cancer, carried out in collaboration with scientists at U.S. Department of Agriculture laboratories. These studies have focused mainly on mycotoxins with significant commercial and health impacts, aflatoxins, fumonisins, and botryodiplodin. Other areas studied have included cryopreservation, single cell protein and most recently the development of novel approaches to drug delivery for human gene therapy.

Some of the major accomplishments of these studies were the first determination of the complete chemical structure of fumonisin B1; elucidating the role of phospholipase activation in cell killing mechanisms; determining the mechanism of action of fumonisins; the discovery of novel inhibitors of tyrosine-specific protein kinases; the discovery of novel food processing-induced structural alterations in contaminating mycotoxins, some of which increased their toxicity; and the discovery that the toxin which facilitates infection of plants by fungi in soil is botryodiplodin, not phaseolinone, as had been widely believed. Shier has also edited, authored, or co-authored three books as a faculty member, one on the study of toxins, one on mammalian cell culture methods, and one on the education system of the Philippines. He is the founding editor of the journal *Toxin Reviews*, which he established in 1980 and has continued to edit for more than 30 years. A co-editor has been added to help with manuscript flow, but the main base of editorial activities has remained housed in the Department of Medicinal Chemistry.

The changes that took place in faculty hires in the 1960s and 1970s in both medicinal chemistry and pharmacognosy led to decreased emphasis on natural product research resulting in an erosion and lack of interest for support of the medicinal plant garden and the greenhouse. At that time, the College had two gardeners, Onie Benson and Clarence Stoltman, who spent many years working with Professors Fischer and Gisvold to maintain a state-of-the-art
From Digitalis to Ziagen: The University of Minnesota’s Department of Medicinal Chemistry

medicinal plant garden. With the decreased emphasis in teaching and research on natural products coupled with the emerging clinical pharmacy education to pharmacy students provided the opportunity for the College of Pharmacy administration to phase out its support for the green house and the medicinal plant garden. Following the retirement of Onie Benson, Clarence Stoltman left the University two years later. Both positions were not replaced, and their salaries were redirected to support the expanding programs in clinical pharmacy.

The period between 1960 and 1980 had many advances. However, during the same two decades, Dean Lawrence Weaver continued to drain resources from the program, a move accelerated by his decision to de-departmentalize the College in 1974. As part of that move, for the first time in the history of the College, he initiated efforts to merge pharmacognosy into medicinal chemistry. Following the consolidation of the departments, both continued to operate as individual graduate programs, although there was some overlap between the two, particularly in the training of graduate students. Weaver’s aim was to eliminate faculty lines in one or both programs, and to open up lines for clinical pharmacy. As it turned out, the merger did not occur until late in the 1980s, by which time the College had moved into new quarters, and Weaver had been replaced by a new dean.

Developments in Publishing & Community

Medicinal chemistry’s growing renown as a research-oriented department helped usher in two other significant developments at the College during this time.

In 1972 the department became the new home of the Journal of Medicinal Chemistry. The publication began life in 1959 as the Journal of Medicinal and Pharmaceutical Chemistry. In 1962, it was acquired by the American Chemical Society with its name shortened to the Journal of Medicinal Chemistry.

For the first decade of its life, the journal was edited by co-founder Alfred Burger, a faculty member at the University of Virginia. When Burger retired in 1971, the ACS selected Philip Portoghese to become editor-in-chief. Portoghese immediately instituted structural changes that helped turn the journal into the field’s leading publication. Setting up offices in the basement of Appleby Hall (the journal is now
housed in Weaver-Densford Hall), he expanded the editorial staff, enlisting associate editors Patrick Hanna (1972-89), Mahmoud Abdel-Monem (1972-83), and Herbert Nagasawa (1972-2004). Over the years, several other faculty members from the department served as associate or senior editors including Rodney Johnson (1984-88) and Yusuf Abul-Hajj (1995-present) (Portoghese, interview, October 2009). As of January 2012, Gunda Georg from the University of Minnesota and Shoameng Wang from the University of Michigan have been selected as the new editors-in-chief of the *Journal of Medicinal Chemistry*.

Ultimately, the journal has helped not only the discipline, but also the department by making it more visible to researchers around the world. In turn, this has possibly had an impact on grant funding, increasing the likelihood of success in grant applications and the recruitment of both new faculty and top-quality graduate students.

The second development that came out of the critical period of transition was the establishment of close relationships with four other universities to foster graduate studies in medicinal chemistry.

In 1962, the universities of Minnesota, Iowa, Kansas, and Illinois—all institutions with strong medicinal chemistry programs—created the “Medicinal Chemistry Meeting in Miniature,” or MIKI for short, to provide a forum for graduate students in medicinal chemistry to present papers and to network with faculty and graduate students from other institutions.

Joseph Cannon, a faculty member at the University of Iowa, proposed and hosted the first MIKI meeting. The faculty who oversaw the Iowa graduate students and who helped put together the first MIKI meeting at the University of Iowa in 1963 included: Ole Gisvold, Taito Soine, and Philip Portoghese from Minnesota; Edward Smissman, Matt Mertes, and Robert Wiley from Kansas; John Gearian, Ludvig Bauer, R. Coviello, and Ralph Daniels from Illinois; and Joseph Cannon and Donald Witiak from Iowa.

In 1966, the host university (the site...
for the weekend meeting rotates among the four participating schools) began inviting an eminent researcher—who may or may not be associated with one of the four founding universities—to deliver a keynote address, giving students the chance to meet and socialize with a top scientist in medicinal chemistry (Hanna, interview, November 2009). Over the decades, graduate students have been given increasing responsibility for organizing and managing the event, from arranging accommodations, choosing the venue for the scientific program and selecting the keynote speaker to arranging the opening night reception and a banquet that takes place the second day of the event. Graduate students now also bear the burden of fundraising money to support MIKI meetings. So important is MIKI to graduate education that medicinal chemistry graduate students at the University of Minnesota are required to attend at least four MIKI meetings before taking their Ph.Ds. The MIKI meeting served as a model for similar meetings elsewhere in the United States (MIKI, 2009).

Raising the Research Profile

The transformation between 1960 and 1980 of the department from classically-oriented, natural products research into a medicinal chemistry department supported by state-of-the-art instrumentation and increased federal funding was dramatic and played an important role in raising the research profile of the department both nationally and internationally.

These two decades also saw dramatic changes in the College’s administrative structure. The change got underway with the resignation of Dean George Hager at the end of 1965 and his replacement by Lawrence Weaver in March 1966, after a brief interim when faculty member Charles Netz served as acting dean.

The new dean of the College of Pharmacy would go on to serve two terms in that capacity, totaling nearly 20 years. In the end, his policies would have an impact on the College second only to Frederick Wulling. Unlike every previous pharmacy dean, Weaver came to the University not from academia but from industry, and he brought with him a spirit of innovation and visionary leadership designed to place the College at the top of the pharmacy profession.

For his first eight years as dean, however, Weaver didn’t make many dramatic changes to the existing administrative structure, which had changed little over the decades; his predecessor as dean, for example, operated with just one assistant dean for support. By 1974, Weaver continued to rely on just one assistant dean, augmented by a single new staff position reporting to him: assistant to the dean and director of continuing education.

Early that year, though, he took the first real steps toward altering the College’s administrative structure, creating three new assistant deanships to join the already extant job of dean of student affairs, to which he appointed Frank DiGangi after Charles Netz retired in 1966. Hugh Kabat, a faculty member in pharmacy administration, became assistant dean for administration. Taito Soine was appointed assistant dean for research and graduate studies, and John Staba as assistant dean for professional education.

Not long after, Dean Weaver initiated even more far-reaching administrative changes designed to advance his goal of putting the College at the forefront of pharmacy education.

Weaver was convinced that clinical pharmacy was the wave of the future. But the path forward was challenging, to say the least. Since money to expand the number of faculty in clinical pharmacy was not available from the University’s central administration, the only option was to reallocate resources from other departments within the College. At the time, medicinal chemistry commanded the most resources, but faculty in both that department and in pharmacognosy resisted the idea of diverting any of their resources in order to fund a beefed-up clinical pharmacy undertaking.
Until 1974, Weaver had administered the College with the help of a faculty council, later called the Administrative Advisory Committee. The council consisted of the assistant deans and the chairs of the College’s four departments: medicinal chemistry, pharmaceutics, pharmacognosy, and pharmacy administration.

In order to free up resources—in which allocations were tied to the departments—Weaver made the bold move of dissolving the departments. He replaced them with an administrative structure of four units organized along functional lines. There was now a Drug Action Unit, which included medicinal chemistry and pharmacognosy; a Drug Delivery Unit, which included pharmaceutics; a Professional Practice Unit, which encompassed clinical pharmacy and related activities; and a Continuing Education Unit. Operating alongside these units was the College’s graduate program, which continued to function like a department (Anderson & Pennigton, 2005, 98-104).

To head up these new units, Weaver bypassed the former departments and appointed other faculty members, some of whom, like Abdel-Monem, were relatively new to the College. Dissolving the departments was a way of reducing perceived resistance to change by department members while at the same time uncoupling the undergraduate curriculum (and resources to underwrite that curriculum) from departmental control (Abdel-Monem, interview, 2009).

Within medicinal chemistry, de-departmentalization brought about dramatic changes in undergraduate curriculum. For example, prior to the transition the department had two large laboratories designated for exclusive use for undergraduate courses. By the end of the transition to the new functional unit structure, those laboratories were gone. In addition, the department moved from a chemistry-based focus to a focus on therapeutic applications—a shift that brought medicinal chemistry more into synch with the pharmacology unit. As director of the Drug Action
Unit, Abdel-Monem spearheaded a faculty effort to develop an integrated multidisciplinary course sequence with faculty in medicinal chemistry (Hanna), pharmacognosy (Abul-Hajj), and pharmacology (Dunham). The main objective of these courses was to avoid duplication and provide a better way of integrating the course content. This innovative approach continued throughout the years spanning from 1975 through 2012.

Dunham joined the University as an instructor in the School of Medicine, teaching and coordinating the pharmacology courses to pharmacy students. He played a key role in the integration of medicinal chemistry, pharmacognosy, and pharmacology courses and continues in this regard. He joined the Department of Medicinal Chemistry in 1982 as an associate professor. His research has focused on the biosynthesis and pharmacology of endogenous vasoactive mediators and their role in hemodynamics and hypertension. During the 1970s, he instructed several medicinal chemistry graduate students in the application of methods for biological evaluation of their target compounds and has participated in collaborative research with Professors Portoghese, Vince, and Nagasawa.
Weaver continued to evolve the administrative structure, eventually adding a layer of assistant deans to oversee the four functional units. But budgetary decisions lay firmly in the hands of the dean. Under the new administrative structure, then, the fight for resources became a matter of individual faculty dealing directly with the dean without the intermediary of a departmental head (Anderson & Pennigton, 2005, 98-104).

But in medicinal chemistry, faculty found a novel way to band together and sustain a departmental identity, even in the face of de-departmentalization. During the transition, Portoghese was named director of graduate studies in medicinal chemistry. In that position, he rallied his colleagues by creating a “shadow” department of graduate studies in medicinal chemistry, complete with its own letterhead and regular departmental meetings but devoid of any budgetary support by the College administration. Such was the esteem Portoghese enjoyed in the eyes of the University’s central administration that the dean’s office simply turned a blind eye toward this small, but nonetheless critical act of defiance (Hanna, interview, 2009).

Finding A Home on Campus

The College’s move from Wulling Hall to Appleby Hall in 1960 brought new laboratory and office space to the department. The change, however, was barely three years old before discussion got underway about a larger, comprehensive change in University facilities that would eventually see medicinal chemistry move again, into its present headquarters.

In 1964, University President Charles O. Wilson created the Committee for the Study of Physical Facilities for the Health Sciences, to take a comprehensive look into the facilities needs not just of the College of Pharmacy, but of all the health sciences at the University. At the time the University’s five-year facilities plan called for a modest expansion of Appleby Hall.

Then in 1966, Dean Lawrence Weaver was added to the facilities committee and given the task of canvassing the faculty and administrators in the College of
Pharmacy on whether or not the College should be included in a larger comprehensive health sciences complex of facilities (Netz, 1971, 148).

Early in 1967, Weaver submitted his report to the committee. In it, he said that the College had determined that it must be part of the integrated health care complex because of a number of critical issues, including the prospect of steadily rising undergraduate enrollment and additional space needed for faculty and research facilities. At that time, the College of Pharmacy had some 31,000 square feet of space but was projected to need more than four times that much—133,000 square feet—by the middle of the 1980s.

As a result Weaver soon let faculty members know that the College was now part of the planning process for the proposed health sciences center. In 1969, the Legislature appropriated $14 million for construction, with most of that money devoted to dentistry and the basic sciences. The University also requested federal matching funds. At this stage, neither the Legislature’s appropriation nor the request for matching grants included funding for a new facility to house pharmacy (College of Pharmacy, 1977).

Dean Weaver now took the initiative in appointing a task force to prepare a direct College of Pharmacy request to the Minnesota Legislature. Although that request was withdrawn, the Legislature did approve additional funding that included money to initiate planning and purchase land for “Unit F,” a part of the health sciences facility that would house both pharmacy and the School of Nursing (ibid.).

Groundbreaking on the first of the buildings took place in 1971. It would house the School of Dentistry and the School of Public Health, along with parts of the School of Medicine. Three years later, by which time work had also begun on a second building that would become the Phillips Wangensteen Building, funding for the pharmacy and nursing complex was still no closer to hand.

But Weaver was undaunted. He and the dean of the School of Nursing resubmitted the request for federal funding, proposing in return a big jump in the number of students enrolled each year into the pharmacy program even though projections of employment trends didn’t really justify that kind of increase. In any case, the federal government went ahead and appropriated almost half of the projected $21 million cost of the pharmacy/nursing building in 1975.

Next, Dean Weaver was faced with the need to raise matching funds from the state, which he coupled with a drive to raise money from private sources. In approaching the state he combined direct lobbying with legislators by himself and other officials at the College with pressure from the Minnesota State Pharmaceutical Association.

The efforts proved to be of little avail, at least in the short-run. Instead of matching the $8.7 million federal grant, state legislators offered up a meager $300,000 to pay for a study of ways to answer the needs of nursing and pharmacy for more space
without constructing a new building. Despite the rejection, Weaver pushed on. He fought suggestions that Appleby Hall be upgraded and expanded to meet pharmacy’s space needs, and continued lobbying hard at the Legislature.

In 1977, he won a breather when the federal government granted an extension on the time limit to raise a matching grant. Together, the Regents, Dean Weaver, and the dean of School of Nursing returned to the state capitol to try again.

This time, Dean Weaver succeeded. After a spring visit to the campus by members of the Senate Finance Committee and a change of heart on the part of Gov. Rudy Perpich—who had initially opposed the idea of putting state money into a new pharmacy/nursing facility—the Minnesota Legislature passed a measure on the last day of the session approving money to help move the College and build a new facility to house it.

Groundbreaking on what would become, fittingly enough, Weaver-Densford Hall, took place in fall, 1977, and the new building was ready for its new tenants by the end of the summer in 1980 (Anderson & Pennigton, 2005, 94-8). Not only did the move greatly increase and modernize the space...
available for the College, but for the first time in the school's history, it fully integrated the College into the University's multi-departmental college Academic Health Center. Although most faculty members in medicinal chemistry and pharmacognosy were not in favor of the move, in retrospect, this change was the best thing that happened to the department as it provided an avenue with increased research collaborations with researchers in the medical school (ibid., 94-8). §