

Foreword: The ACS Division of Medicinal Chemistry - Celebrating 100 Years of Excellence.

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This Centennial Issue of the *Journal of Medicinal Chemistry* was conceived in order to commemorate the 100th anniversary of the Division of Medicinal Chemistry. The *Journal* is a fitting venue for this tribute. For the last 50 years, the *Journal* has been considered the flagship publication in our field, and a rich repository of scientific advancement in the area of drug discovery. Thus, although the *Journal* and the Division have never been formally linked, they are inextricably united by a desire to advance the practice of medicinal chemistry. It is arguably fitting for me to write this foreword, since the formation of the Division of Medicinal Chemistry occurred less than a mile from where I now sit. The changes in the world, the field of medicinal chemistry and the Division over the last 100 years have been nothing less than spectacular.

The United States in 1909. At the inception of the Division, this country was in the midst of what is now known as the Progressive Era (1890-1913), and the US was politically, demographically and scientifically very different from today. In 1909, the population of the US was 90.5 million (51% men, 11% non-white), and the average income was \$944 per year. The usual startling facts seem appropriate here (new home, \$2,650, 15.5 cents per gallon for gas, 2 cents for a first class stamp, 4 cents for a loaf of bread). The richest man in the world, Andrew Carnegie, had a net worth of \$480 million, having sold his steel business a year earlier. The world's tallest building (until 1913), the forty-two-story Metropolitan Life Insurance Tower, was completed in New York City. President William Howard Taft signed the 16th Amendment, creating a federal income tax, and the Dow Industrial Average stood at 99. All cars had cranks until the following year, and the model T Ford sold for \$850, facilitating the 1909 ratio of 1 car for every 200 people. The American death toll in horse-related accidents was 3,850-more than in motor vehicle accidents. The Indianapolis Motor Speedway, nicknamed "The Brickyard" because of the 3.2 million bricks used to pave the track, was opened, and held its first event: a hot air balloon race. New inventions in 1909 included instant coffee, Lipton's Tea, the electric toaster, the Lincoln penny, Kewpie dolls and the enclosed double-decker bus. Commander Peary reached the North Pole, and astronomers first sighted what might be a planet beyond Neptune.

Science and Health in 1909. In the spirit of the Progressive Era, numerous landmark discoveries in science occurred in the period between 1900 and 1909. In the first ten years of the 20th century, scientists were beginning to understand the basic principles of physics and chemistry: Planck's Law of black body

radiation that became the basis for quantum theory (1900); Einstein's Special Theory of Relativity (1905); Nernst's Third Law of Thermodynamics (1906). The 1909 Nobel Prize for Physics was awarded to Guglielmo Marconi and Karl Braun for their contributions to the development of wireless telegraphy. In chemistry, the first completely synthetic plastic, Bakelite, was invented by chemist Leo Baekland in 1907. The Nobel Prize for Chemistry was awarded to Wilhelm Ostwald for his work on catalysis, chemical equilibria, and reaction velocities. Niels Bohr's structure of the atom remained unknown until 1913.

Medical research in the early 1900s was focused on medical procedures, and on understanding basic human physiology. In 1901, Jokichi Takamine isolated adrenaline, which was followed in 1903 by elucidation of the role of hormones in chemical signaling by Bayliss and Starling. In 1906, English biochemist Sir Frederic Gowland Hopkins noted that certain food factors were important in human health. In 1912, Casimir Funk called these substances "vitamines", and the first vitamin (vitamin A) was isolated by McCollum and Davis. The 1909 Nobel Prize for Medicine went to Emil Kocher for his work on the physiology, pathology, and surgery of the thyroid gland.

In the first years of the 20th century, pneumonia and influenza were the leading causes of death in the United States, followed by tuberculosis and diarrhea. Infectious diseases took many children before they reached their teens. Of particular note in this period was the 1918-1919 pandemic of influenza, which resulted in 50 million deaths, a figure that is double the cumulative AIDS mortality of the past 20 years.¹ By 1909, infectious diseases accounted for 46.6% of deaths and cancer plus cardiovascular disease accounted for 14.8%. Today, infectious diseases (influenza, pneumonia, AIDS and septicemia) account for less than 5% of fatalities, while cancer and cardiovascular disease combined account for 31.3%.³ The average life span was 47.3 years in 1909, but has since increased by 30 years (77.6). As the Division was being formed, the opportunities to improve human health through drug discovery abounded.

The Origins of Medicinal Chemistry and the Birth of the Division of Medicinal Chemistry. The practice of modern medicinal chemistry can be traced back to the late 1800's. Most are familiar with the discovery of aspirin in 1897 as a more palatable alternative to salicylic acid, a finding credited to Felix Hoffmann³ (it is now thought that the actual discoverer of aspirin, Arthur Eichengrun, was written out of history by the Nazi regime because he was a

Jew, and credit was given to Hoffmann).⁴ However, in the period of 1900-1906, medicinal chemistry was not considered a distinct discipline, but rather was an area of concentration among organic chemists. The discovery of new medicines was greatly impacted when Theodore Roosevelt signed the Pure Food and Drug Act into law in June of 1906 (the FDA in its present form was not organized until 1927). It was in this atmosphere that Paul Ehrlich conducted what was the first organized team effort to optimize the biological activity of a lead compound through systematic chemical modifications. This approach subsequently became the basis for nearly all modern pharmaceutical research. Ehrlich set out to develop a practical treatment for African sleeping sickness. He believed that by screening many compounds, a suitable drug could be discovered with anti-microbial activity, and they began their search among chemical derivatives of the dangerously toxic drug atoxyl. The result was arsphenamine, marketed as *Salvarsan*® in 1910. It was also called *606*, because it was the 606th compound synthesized for testing. Salvarsan was the first organic anti-syphillis agent, and a great improvement over the inorganic mercury compounds that had been used previously. Ehrlich was also the first to suggest that differences in chemoreceptors between species could be exploited for therapeutic purposes.⁵ To honor his achievements, Ehrlich was awarded the Nobel Prize for Physiology and Medicine 1908.⁶

The Division of Medicinal Chemistry began as a pharmaceutical chemistry interest section of the American Chemical Society. The pharmaceutical chemistry section was organized at the 39th National ACS meeting in Baltimore (December 29, 1908 – January 1, 1909). Later that year, the 40th National ACS meeting was held in Detroit (June 29-July 2, 1909), at which 450 chemists from 5 technical divisions and two interest sections enjoyed a total of 186 presented papers.⁷ During this meeting, the section of pharmaceutical chemistry met at Detroit Central High School, in a building known as Old Main, which also housed the entirety of Wayne University (this building, built in 1894, is still in use by the University today). The only agenda item was the question of the advisability of forming the ACS Division of Pharmaceutical Chemistry. It was unanimously decided to request that the ACS council establish such a Division, and “a strong organization was formed with Professor A.B Stevens, of Ann Arbor as chairman; B.L. Murray, secretary; J.P. Remington, Edw. Kremers and J.M. Francis, executive committee”.⁷

The driving forces behind formation of the Division were Alviso Burdette Stevens and Benjamin L. Murray. Stevens, a native of Tyrone, MI, graduated from the University of Michigan in 1875 with the degree of Pharmaceutical Chemist.⁸ From 1875 to 1886 he practiced as “an analytical chemist and prescription pharmacist”. From 1879 to 1882 he taught pharmacy in the Detroit College of Medicine (later the Wayne State University School of Medicine), and in 1886 he was recruited to the University of Michigan as Instructor in Pharmacy. He

advanced to the rank of Lecturer in Pharmacy (1890), and Assistant Professor of Pharmacy (1892). During 1903-1905 he studied for the degree of Doctor of Philosophy at the University of Berne, completing a dissertation on the study of the chemical composition of the varnish on Japanese pots.⁹ He was then appointed as Junior Professor of Pharmacy at the University of Michigan in 1906. Stevens held a number of offices in national Pharmacy organizations, but was most famous for his book on the arithmetic of pharmacy.¹⁰ Benjamin L. Murray was a native of Ypsilanti, MI, and was also a graduate of the University of Michigan. He then obtained his Ph.D. degree in chemistry from Columbia University. His personal history is somewhat obscure, but it is known that he became the Vice-President of Merck and Co. during his 34-year career there, and was also Vice-President of Citizens National Bank in Rahway, NJ.¹¹ Murray is best known for a book in his area of expertise, namely, standards and tests for reagent chemicals.¹² Importantly, equal representation between academic and industrial medicinal chemists in Division leadership is a guiding principle that exists to this day.

Drug discovery underwent numerous changes in the years that followed the founding of the Division, and in response to this, Division emphasis and member demographics changed rapidly. Prior to 1920, drug discovery existed in what is known as the age of botanicals,¹³ wherein drugs were largely isolated from natural sources or used in their natural state. As such, at its inception Division members were mainly pharmacists or analytical chemists with careers in either academia or the pharmaceutical industry. Drug research in the 1920s and 1930s focused primarily on the isolation of vitamins and other natural substances. However, the discovery of penicillin extract by Fleming in 1929 ushered in the age of antibiotics, and because of significant advances in synthetic chemistry, the search for new antibiotics soon became dominated by organic chemists. By way of example, the actual substance penicillin was not identified until 1938, when it was isolated from Fleming’s crude extract by Oxford chemists Ernst Chain and Howard Florey.⁵ Their research successfully moved penicillin from the laboratory to the clinic. In response to changes in the practice of medicinal chemistry, Division membership shifted between 1920 and 1940 to include a much larger percentage of individuals with professional careers in chemistry. Subsequently, the Division underwent two name changes, becoming the Division of Chemistry of Medicinal Products in 1920, and the Division of Medicinal Chemistry in 1928. By 1940, the Division was comprised of academic and industrial chemists involved in the systematic search for new antibiotics and other new drug entities. From that time, drug discovery research has evolved significantly as a result of advances in organic chemistry, biochemistry, instrumentation, molecular biology, computing and biotechnology.

Milestones in Division History. A complete discussion of the many achievements of Division members in drug research is beyond the scope of this

short history. The reader is referred to the Division Hall of Fame, located at <http://www.acsmedchem.org>, for a more comprehensive description of these achievements. However, no history of the Division would be complete without mention of three significant milestones: the creation of the *Journal of Medicinal Chemistry*, the publication of *Annual Reports in Medicinal Chemistry* and the inception of the National Medicinal Chemistry Symposium.

Soon after the Division was formed, discussion began on the creation of a scientific journal dedicated to medicinal chemistry. Until the late 1950s, articles discussing medicinal chemistry research were published in the *Journal of Organic Chemistry*, the *Scientific Edition of the Journal of the American Pharmaceutical Association*, or one of the various US and German chemistry journals. The first journal dedicated exclusively to medicinal chemistry, *The Journal of Medicinal and Pharmaceutical Chemistry*, was published in February of 1959, edited by Arnold H. Beckett and Alfred Burger. The first issue consisted of 8 articles on topics including the pharmacology of tetravalent organophosphorus compounds, α and β -propranolols, barbiturates and Mannich bases of norepinephrine.¹⁴ The journal was initially published six times a year, and in 1962 it became an official publication of the American Chemical Society. In 1963, the title was changed to the *Journal of Medicinal Chemistry*, and Burger continued as Editor until passing this responsibility on to the current Editor-in-Chief, Phil Portoghese, in 1972. Today, the *Journal* is recognized as the premiere publication in medicinal chemistry, with an impact factor of 4.898. It is now published 24 times per year and is available electronically through the ACS Publications web site. In 2007, the *Journal* was cited more than 42,000 times, and published nearly 600 original articles.

The idea of a National Medicinal Chemistry Symposium was conceived in the years following World War II, and in 1948, the first National Medicinal Chemistry Symposium was held at the University of Michigan. The symposium was chaired by medicinal chemists F.F. Blicke of the University of Michigan and Glenn E. Ulliyot of the SmithKline French company. It was agreed that the meeting would be held every other year, always on a University campus, and always co-organized as a collaboration between academic and industrial medicinal chemists. Since 1966, this meeting has been the venue for the presentation of the Division of Medicinal Chemistry award. The winners of this award include a Who's Who of the most accomplished and successful medicinal chemists; in 1982, the recipient was Bengt L. Samuelson of the Karolinska Institute, who was awarded the Nobel Prize for Physiology and Medicine later that year. The 32nd National Medicinal Chemistry Symposium will be held at the University of Minnesota in June of 2010.

The publication of *Annual Reports in Medicinal Chemistry* began in 1966 as a means to provide concise updates on the progress in medicinal chemistry research in various therapeutic areas. This series was initiated largely due to the efforts of

Cornelius K. Cain, who served as the editor for Volumes 1-6. In addition to the Cain, the section editors of volume 1 included John Biel, Sydney Archer, Edwin Flynn, Richard Heinzelman, Irving Tabachnick and Edward Smissman. It contained "31 concise reviews concerned chiefly with very recent pharmacological developments in central nervous system agents (including analgetics and anorexigenics), renocardiovascular agents (antihypertensives, diuretics, antirhythmics), pulmonary agents, gastrointestinal agents, antimicrobials (antibiotics, antivirals, antiparasitics) and metabolic agents (antidiabetics, steroids). Other reviews consider the fate, distribution and receptor interactions of drugs, regulation of cell metabolism, and drug-enzyme effects". Volume 1 contained 341 pages, and sold for \$7.50. *Annual Reports* was published by Academic Press until volume 37, and thereafter has been published by Elsevier. Volumes 34-43 are currently available in electronic format.

Table 1. Revolutionary Drug Products by Decade

Drug	Trade name	Year Marketed	Use
1900s			
epinephrine	adrenaline	1901	hormone ¹⁵
1910s			
arsphenamine	Salvarsan®	1910	antisyphilitic ¹⁶
phenobarbital	Luminal®	1912	sedative/hypnotic ¹⁷
1920s			
insulin	--	1922	hormone ¹⁸
1930s			
sulfanilamide	Prontosil®	1935	antiinfective ¹⁹
1940s			
penicillin	--	1942	antiinfective ²⁰
1950s			
chlorpromazine	Thorazine®	1957	antipsychotic ²¹
1960s			
norethynodrel/mestranol	Enovid®	1960	birth control ²²
propranolol	Inderal®	1967	β -receptor antagonist ²³
1970s			
cimetidine	Tagamet®	1976	H ₂ -receptor antagonist ²⁴
1980s			
captopril	Capoten®	1981	antihypertensive ²⁵
fluoxetine	Prozac®	1987	antidepressant ²⁶
1990s			
topotecan	Hytamin®	1996	antitumor ²⁷
atorvastatin	Lipitor®	1997	cholesterol reduction ²⁸
saquinavir	Fortovase®	1997	HIV protease inhibitor ²⁹
sildenafil	Viagra®	1998	erectile dysfunction ³⁰
etanercept	Enbrel®	1998	rheumatoid arthritis ³¹
trastuzumab	Herceptin®	1998	breast cancer ³²
2000s			
imatinib	Gleevec®	2001	antitumor ³³

In many cases, Division members played key roles in the discovery and development of drugs that changed the face of modern pharmacology and drug therapy. It would be a daunting task to provide a complete list of these discoveries here, but a sampling of these revolutionary agents appears in Table 1, along with references to the original publications outlining their discovery. Of particular interest is the partial shift in the emphasis of drug discovery research from antiinfectives (1900-1942) to other maladies such as cardiovascular disease, depression and cancer. The reader should also note the involvement of members of the Division of Medicinal Chemistry Hall of Fame in the research described in references 24, 25, 27 and 30.

The MEDI Hall of Fame. A complete account of all of the achievements of Division members from 1930 to the present would take up much more space than is prudent here. In 2006, Division officers Dave Rotella and Patrick Woster (acting on a suggestion from past chair Dan Flynn) created the MEDI Hall of Fame Award to provide a permanent archive of these achievements. To date, 58 medicinal chemists have been inducted into the Hall of Fame, either by winning one of the major Division Awards, or by being selected from nominations submitted by the membership. A new class of inductees is welcomed into the Hall of Fame at each Fall National ACS meeting.

ACS provides Division membership information dating back to 1970, although a number of current members joined prior to that date. The Division roster lists 172 scientists with continuous membership since 1970. It is of interest to note that this "class of 1970" includes 13 of the 58 members of the Hall of Fame, many of whom are still involved in the field today, and is replete with the names of internationally recognized medicinal chemists.

Division Electronic Services. By 1994, Division membership grew to 7,108 regular members. The Division Chair in that year, Gary Grunewald, approached Membership Committee member Patrick Woster to discuss creation of a web site for the Division. The Division of Medicinal Chemistry homepage first appeared in August of 1994, and featured a small amount of Division news, a membership application and a form to sign up for the Division listserv and email roster. At that time, ACS did not have a web presence, and the Division web site was the first published by any ACS division. The Division web page was housed on a server at Wayne State, where it remains today, and a listserv was populated with those Division members who had access to email. Almost immediately, the Division listserv, which was intended to communicate news to members, was used to post "non-chemistry" items, including ads for Christmas trees, bottled water, and a catalogue of Russian brides. The listserv was discontinued after 3 years, but the web page continued to grow in content as Division membership ballooned to 10,540 in 2006. In that year, the Division became the second largest technical division in ACS. By 2000, the office of Secretary was divided to create 2 new positions on the Executive Committee, a

Program Chair responsible for organizing Division programming at national ACS meetings, and a Secretary responsible for the web site, newsletters, elections, public relations and other communication functions.

The costs associated with mailing newsletters, election ballots and abstracts to all members exceeded \$100,000 in the year 2000. In 2001, the Division newsletter was renamed the *Reaction Times*, and was distributed electronically through the Division web page. In 2005, mailing of Division abstracts for national ACS meetings was discontinued in favor of an electronic version, and Division elections were converted to an online format in 2005. An RSS feed was added in 2006 that was the first for any technical division. Today, all Division publications except *Annual Reports in Medicinal Chemistry* are distributed through the Division web page. The resultant cost savings have assured that Division dues have not been raised for the past 10 years.

Division Awards. As early as 1966, the Division began administering awards to honor members who made outstanding contributions to the field of medicinal chemistry. The first of these awards was the Division of Medicinal Chemistry award, which has been given at every National Medicinal Chemistry symposium since 1966 (see above). The inaugural recipient was Bernard R. Baker. The Division Award is open to any scientist here or abroad, whose research has directly or indirectly had a significant effect on medicinal chemistry. In 1975, Corwin Hansch was the recipient of the first Bristol-Myers Squibb Smissman Award in Medicinal Chemistry. The Smissman Award is open to a living scientist whose teaching, research or service has had a substantial impact on the intellectual and theoretical development of the field of medicinal chemistry. Until recently, these were the only two awards administered by the Division. However, between 1980 and 2008, numerous Division members have received one of two prestigious ACS awards, the GlaxoSmithKline Alfred Burger Award or the E.B. Hershberg Award for Important Discoveries in Medicinally Active Substances.

In 2005, the David W. Robertson Award for Excellence in Medicinal Chemistry was created, and is administered by the Division. This annual award, conceived by Bharat K. Trivedi and supported by an endowment from Pfizer, is intended to recognize seminal contributions to medicinal chemistry by young scientists. A second new Division award, the Robert M. Scarborough Award for Excellence in Medicinal Chemistry, was initiated in 2007 through a supporting donation from Portola Pharmaceuticals. This award is intended to recognize individuals who have had primary, leading roles in the discovery of novel therapeutic agents, or who have otherwise made scientific discoveries that enhance the field of medicinal chemistry. A complete list of Division award winners can be found on the Division Hall of Fame web site. Beginning in 2010, the Division, in cooperation with ACS Publications, will offer the Philip S. Portoghese Journal of Medicinal Chemistry/Division of Medicinal Chemistry

Lectureship. The object of this named lectureship is to enhance the visibility of the *Journal*, and to strengthen relationship between the *Journal of Medicinal Chemistry* and the Division. The annual award will honor the accomplishments of an individual who has had a major impact on medicinal chemistry research.

Since 1991, the Division, through the generosity of sponsors from the pharmaceutical industry, has awarded Pre-Doctoral Fellowships on a competitive basis to graduate students in medicinal chemistry. In 1991, four such fellowships were awarded to support graduate students in their 3rd or 4th year of study. In 1997, an additional award was added, and by 2008 the Division was able to offer 9 fellowships annually. For 2009-2010, each fellowship will provide \$24,000 in support to those selected. Current sponsors include Bristol-Myers Squibb, Pfizer, Novartis, Lilly, Amgen, Sanofi-Aventis, and Wyeth. Two additional awards are funded by the Division.

Division Demographics. When it was formed, the makeup of the Division paralleled that of the profession of chemistry, in that there were few female members. The first woman involved in Division leadership was Barbara Roth, who served as Secretary in 1975-76, and as Division chair in 1977. Since that time, 3 women have served as Division chair, and 4 have served in other officer positions. This is perhaps reflective of the composition of the discipline, and of Division membership. In 2008, the Division membership was 18.7% female, 5.5% African American, Hispanic or native American, and 23.4% Asian. Nearly 22% of our members reside outside the U.S., and 60% of our membership is between the ages of 31 and 55. The majority of Division members (53.4%) have doctoral degrees in chemistry or medicinal chemistry. Half of our members are employed in industry, and the rest are academic or government scientists, or are involved in sales or marketing.

Globalization of the Division. As was mentioned above, 22% of current Division members reside outside of the US. This trend began in earnest in 1994, when an electronic application form became available on the Division web site. In response to this trend, globalization was a major topic at the Division's first strategic planning meeting, held in Detroit in June of 2006. The emphasis on globalization is apparent in the Vision Statement developed at that meeting: *The Division is a global authority and advocate for the practice of medicinal chemistry, with the goal of improving human health through drug discovery research and education.* MEDI now has established relationships with the European Federation for Medicinal Chemistry and the Asian Federation for Medicinal Chemistry, largely through the efforts of Tom Perun, who has served as the Division Foreign Societies Liaison for several years. We have also begun to establish relationships with the Brazilian Chemical Society and medicinal chemists in China through an exchange of scientific symposia, and a delegation from the Division attended the AIMECS09 meeting in Cairns, Australia in August of 2009.

Future Directions. It should be clear to the reader that the Division of Medicinal Chemistry and its members have been driving forces behind the discovery of revolutionary new medicinal agents, and thus have had a major impact on human health. The age of genomics has facilitated the identification of new targets for chemotherapeutic intervention, and as such, the role of the medicinal chemist in the maintenance of human health will continue to expand. As the premier organization dedicated to the advancement of medicinal chemistry, the ACS Division of Medicinal Chemistry and its membership will play a critical role in drug discovery through support for medicinal chemistry research, education and public service.

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