Invited Commentary

An Editor's Commentary on the Birth of a Journal

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The Editor-in-Chief of this Journal, Professor Philip S. Portoghese, has asked me to record how the *Journal of Medicinal Chemistry* came about. Thirty-four years after the groundwork for this Journal was laid, some memories have faded, some names have been forgotten, but the main circumstances surrounding its creation stand out clearly. They constitute a story of the need to find a niche for reporting researches in the emerging, developing, and mutating science of medicinal chemistry.

If the need for a periodical for the publication of characteristic papers in our science is to be understood, we have to examine the state of medicinal chemistry half a century ago and how the field advanced to the point where the demand for its own literature could no longer be ignored. We have to look at the state of education, organization, and work of medicinal chemists and at the books and periodicals available to them for the publication of their researches and for expressing their conclusions and their professional dreams. We also have to contemplate the gradual changes medicinal chemistry underwent and how the changing subject matter set these researches apart from older established fields of chemistry and experimental biology.

The concept of medicinal chemistry did not emerge suddenly among these numerous specialties. Before the 1920s, the chemistry of therapeutic agents was taught, after a fashion, in the departments of pharmaceutical chemistry of major colleges of pharmacy, and practiced in the research and development divisions of the few major research-minded units of the pharmaceutical industry. The name pharmaceutical chemistry still persists in a number of university departments whose mission is primarily the training and education of pharmacists and which depend on the good will and support of local and regional organizations of pharmacists. In the industry, the designation "pharmaceutical" justifiably covers the many R & D activities concerned with drug assays, the elaboration of drug formulations, the improvements in the preparation and manufacture of therapeutic agents, and the supplying of such chemicals in acceptable forms of administration to the distributors and retail pharmacists for filling prescriptions and over-the-counter sales to the public.

Academic departments of pharmaceutical chemistry faced an uphill struggle in their competition with other science departments. There was so little known about what makes a chemical a drug or a toxic substance that the chemistry and biology departments looked askance at pharmaceutical chemistry; it was not unusual for a department of pharmaceutical chemistry to inherit the antiquated and discarded laboratories of chemistry departments that had moved to more modern facilities. This went on all over the world and is still happening to pharmacy schools in emerging communities.

The curriculum courses in pharmaceutical chemistry reflected the frustration of the Faculty with the existing lack of knowledge of the chemistry of drugs. Undergraduate students were given a survey of analytical methods of drug assays and, if available, of synthetic pathways to structurally simple drugs. For this purpose they had to have a foundation of organic chemistry, usually a one- or two-semester course in this subject. The text books for these courses indicated how empirical organic chemistry was tied into interest in drug chemistry. Organic reactions such as addition/elimination, organic name reactions, and theoretical and synthetic methods were illustrated by examples involving biologically active substances. Walter H. Hartung's *The Chemistry of Medicinal Products* in America and Sigmund Fränkel's *Arzneimittelsynthese* on the other side of the world were typical of this approach. There were stirrings of innovation in the later editions of Fränkel's text; the author's medical background was manifested in discussions of drug action and drug metabolism here and there, providing a preview of topics of medicinal research in subsequent periods.

Graduate courses in pharmaceutical chemistry were chosen from the research interests of the Faculty. Synthetic methods used in the preparation of the few existing drugs were often taught in combination with advanced recitations of special fields of organic chemistry. The chemistry of natural products of proven or potential interest as therapeutic agents provided a standard field of graduate courses. Carbohydrates, alkaloids, flower pigments, insecticides, and alkaloid-related cholinergics and sympathomimetics formed the basis of many text books. In these books, all amines, carboxylic acids, ketones, etc. were lumped together according to functional groups, and the reader was left with a menu of diverse biological agents in each functional class without a hint about mechanisms of action.

The doctoral graduates of pharmaceutical chemistry were readily absorbed in various activities in the pharmaceutical industry, developing and manufacturing natural products and synthetic compounds of proven therapeutic value. This "proven value" was of great importance. Few pharmaceutical companies invested in researches where there was doubt whether or not they might yield a useful therapeutic agent. They wanted to have in hand a product used by the medical profession, manufacture it as expeditiously and inexpensively as the state of the art permitted, and make it available for therapy. This interest in established drug entities prompted the American Chemical Society to organize a Division of Pharmaceutical Chemistry in 1909. There was sparse activity in drug manufacture in the United States, most of the work being done in Europe, especially in England, France, and Germany. When World War I interrupted the importation of drugs, the few and primitive American facilities had to

† Editor's footnote: Dr. Burger founded the *Journal of Medicinal Chemistry*, originally named the *Journal of Medicinal and Pharmaceutical Chemistry*, together with Professor Arnold Beckett in 1958. He retired as editor in December 1971.

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be expanded. Concomitantly, the ACS division's name was changed to Division of Medicinal Products in 1920 and to Division of Medicinal Chemistry in 1928. The term medicinal chemistry may have been a translation of the German, Medizinische Chemie, but this designation was also used abroad for analytical medical determinations in clinical chemistry.

Medicinal chemistry similar to our present concept of the field advanced in Europe through the work of Knorr,[1] Einhorn,[2] Ehrlich,[3,4] Barger and Dale,[5] and the antimalarial research teams of the German pharmaceutical industry. It was joined by the awakening of modern pharmacology and was ready for transplantation and development to leadership in the United States.

From the early work on drug discovery and drug design, as incomplete as it was, emerged two principles that still constitute the mainstream of medicinal chemical researches. One of them is the discovery of "lead" compounds, which relied in those days almost entirely on the biological evaluation of natural products, principally from the plant kingdom. A few vitamins had been isolated and used to correct nutritional deficiencies; animal gland extracts had yielded a few hormones. In most instances, few if any attempts had been made to separate multiple or toxic side effects of some of these natural products by molecular modification, with the notable exception of cocaine, the prototype of synthetic local anesthetics, and the sympathomimetic aralkylamines.

The second activity of medicinal chemistry, molecular modification, soon was to become the main preoccupation of this emerging science. Among the early synthetic drugs were the hypnotic and anticonvulsant barbiturates that invited molecular variation.[6] The pronounced depressing effects of various low-boiling general anesthetics, augmented later by other structurally unrelated compounds, convinced medicinal scientists that specific structures alone could not explain biological activity but that some physical properties might be responsible for such effects. Distribution between aqueous body fluids and lipophilic cell constituents was correctly identified as a major controlling factor.[7,8]

The first indication that drug metabolism might explain the action of some drugs and lead to more potent substances occurred in the studies of Paul Ehrlich. Ehrlich followed up the known chemotherapeutic effect of toxic inorganic arsenic compounds by incorporating pentavalent arsenic into organic analogues of nontoxic aromatic sulfonic acids. The finding that such arsonic acids are bioreduced to trivalent arsenious oxides that exhibit greater potency introduced drug metabolism into drug design. Ehrlich also groped for explanations of biological activity in general and expanded the role of drug receptors.[9] Receptors for all kinds of chemicals had been invoked by Langley,[10] and their potential functional chemistry with haptophoric and toxiphoric substituents was now being suggested. Although these early ideas, almost 100 years old, were too primitive to survive unchanged, they provided intellectual guidelines for our contemporary experimental studies of bioconversions and bioreceptors.

Thus, 65 years ago, the agenda of medicinal chemistry was set as we practice it today: to discover "lead" compounds or a leading family of chemicals, and if these cannot be used clinically directly, modify them until a therapeutic agent with acceptable specificity will be developed. The ensuing decades have added expansions, refinements, and rationalizations to these studies. Forty-five years ago, the need for collecting the bulging biochemical and biological test results of thousands of candidate compounds became necessary. After the end of World War II the *Journal of the American Chemical Society* had to add two volumes to its regular 1946 edition to accommodate the papers, mostly organic–medicinal, that had been classified and held back during the war years. Six monograph volumes devoted to systematic descriptions and listings of experimental drugs arranged according to therapeutic focus soon began to appear.[11] Entitled *Medicinal Chemistry*, they published comprehensive tables of test compounds mostly from industrial researches in the United States. Many of these research departments had by then been organized to pursue certain therapeutic goals and the medicinal chemists assigned to these teams had become experts in the chemical and biological specialties of these fields. Moreover, they had begun to plan their researches on the basis of structure–activity relationships that transgressed purely chemical considerations. The former preoccupation with certain areas of organic chemistry that had been the foundation of earlier searches for drug structures gave way to biochemical and biophysical considerations in drug design. The first monograph covering the whole field of medicinal chemistry as it existed then was published in 1951[12] and has been revised in three subsequent editions. A monumental six-volume *Comprehensive Medicinal Chemistry* has appeared in Britain in 1990.[13]

New bioanalytical methods, novel separation procedures, and rapid spectroscopic identification of increasingly complex bioactive compounds opened the study of many metabolites that occur in minute amounts and could not be isolated previously. Some of these hormonal or otherwise biocatalytic metabolites, as well as fragments of proteins and nucleic acids, were chosen as "lead" structures for the subsequent design of metabolite analogues, both agonists and more often antagonists. Also, experimental biologists contributed importantly to "lead" compound discovery by observations of potentially interesting side effects while screening test compounds for a given biological activity. In several instances, these side effects could be promoted to a principal activity in an unrelated therapeutic area by molecular modification.

The first stirrings of rationality in molecular modification occurred by the application of bioisosteric exchanges from 1932 onward.[14] Bioisosterism involved comparisons of chemical, physical, and biological properties, and this yielded some satisfactory results in the design of useful drugs. A great impetus was given to drug design by the

(1) Knorr, L. *Chem. Ber.* **1883**, *16*, 2597; **1884**, *17*, 2037; *Ann. Chem.* **1887**, *238*, 137, 160, 203.
(2) Einhorn, E.; Uhlfelder, E. *Ann. Chem.* **1909**, *371*, 131.
(3) Ehrlich, P. *Chem. Ber.* **1909**, *42*, 17; *Lancet* **1913**, II, 445.
(4) Ehrlich, P.; Bertheim, A. *Chem. Ber.* **1907**, *40*, 3292.
(5) Barger, G.; Dale, H. H. *J. Physiol.* **1910**, *41*, 54.
(6) Shonle, H. A.; Moment, A. *J. Am. Chem. Soc.* **1923**, *45*, 243.
(7) Meyer, H. H. *Arch. Exp. Pathol. Pharmakol.* **1899**, *42*, 109; **1901**, *46*, 338.
(8) Overton, E. *Pflüger's Arch. Ges. Physiol.* **1902**, *92*, 115.
(9) Ehrlich, P. For references, see: Burger, A. *Chem. Eng. News* **1954**, *32*, 4172.
(10) Langley, J. N. *J. Physiol. (London)* **1905**, *33*, 374.
(11) *Medicinal Chemistry*. Vols. 1–6. A Series of Reviews Prepared under the Auspices of the Division of Medicinal Chemsitry of the American Chemical Society. Wiley: New York; 1951–1963.
(12) Burger, A. *Medicinal Chemistry*; Interscience: New York, 1951.
(13) *Comprehensive Medicinal Chemistry*; Hansch, C., Ed.; Pergamon: Oxford, 1990.
(14) Burger, A. *A Guide to the Chemical Basis of Drug Design*, Wiley: New York, 1983; pp 28–29.

realization that the transport of a drug to its receptor can be gauged to a large extent by log P, a constant measuring hydrophobicity.[15] Other attempts to predict biological potency do not require a priori physical measurements[16] but use them once they have been determined.

Receptors are now recognized as conjugated proteins; they may span membranes and facilitate the transport of small molecules across membranes, or they may be dispersed in the cytoplasm. Some nucleic acids can also function as receptors. Active sites of enzymes are often included in receptor classification. A few X-ray diffraction spectra of drug–receptor complexes have been obtained and serve as welcome aids for those who study molecular modeling. This procedure might lead to totally new prototype compounds. All these researches demand suitable media of scientific communication.

Medicinal Chemical Publications

In Europe, a number of chemical journals opened their pages to record chemical–biological relationships at an early date. *Helvetica Chimica Acta* published such papers from the 1930s on, implementing careful chemical data with reports of qualitative and sometimes quantitative biological tests. *Angewandte Chemie* carried similar articles, and *Arzneimittel-Forschung* became one of the leading journals in the field. *Progress in Drug Research* is a review organ that has appeared once a year for over three decades. The *Bulletins* of the chemical and biological societies of France carried occasional papers on medicinal research, and the *Bulletin de l'Institut Pasteur*, published in Paris, and *Il Farmaco* (Italy) also were repositories of medicinal chemical papers. In this country, the *Journal of Pharmaceutical Sciences* contains a section devoted to such articles.

For the most part, however, medicinal chemists submitted their reports to the major organs of the respective national chemical societies. In Britain, the *Journal of the Chemical Society*, and in the United States the *Journal of the American Chemical Society* accepted papers that contained, almost as an afterthought, brief summaries of the biological evaluation of compounds described chemically in the main body of the paper. Almost universally, the details of biological tests had to be placed in such organs as the *Journal of Pharmacology and Experimental Therapeutics* and similar periodicals. The *Journal of Organic Chemistry* followed the lead of the *Journal of the American Chemical Society* and quite frankly discouraged details of biological tests beyond a brief summary. Biological journals are not read routinely by chemists. Moreover, the biological journals do not carry chemical experimentation, such as the syntheses of test compounds, or the chemical and physical reasoning of molecular modification. That held not only for American biological journals but also for such periodicals as the *British Journal of Pharmacology and Chemotherapy*. That meant that the whole story of a medicinal chemical investigation had to be divided up and could not be followed in one reading.

The post-World War II years witnessed an unprecedented expansion of chemical, biochemical, and medicinal chemical researches. Journals that had published 2000 pages per year grew and mushroomed to 5000 or 6000 pages and, unless their subscription prices could rise at the same rate, faced grave economic difficulties. The first to meet this challenge was the *Journal of the American Chemical Society*, which hitherto had accepted the increasing bulk of papers in medicinal chemistry. At a national meeting of the American Chemical Society in New York, the editor of the *Journal of the American Chemical Society*, Professor Marshall Gates, announced to a standing-room-only audience that the journal had been ordered by the Publication Board of the Society to restrict the number of annual pages. Therefore, papers concerned with studies in topics other than classical confines of chemistry could no longer be considered by the journal. He specifically singled out medicinal chemical manuscripts as victims of this changed policy.

This announcement was greeted with dismay by the medicinal chemists in the audience but with hidden pleasure by the editors of the *Journal of Organic Chemistry*. This journal had not encountered insuperable growth problems as yet and let it be known that it would only too gladly consider suitable studies in medicinal chemistry provided that biological test results would be held to a brief summary. With so many medicinal chemists involved in synthetic or degradative work, i.e. essentially in organic chemistry, the offer by the *Journal of Organic Chemistry* was appreciated and most submissions turned to this outlet. Inevitably, the *Journal of Organic Chemistry* grew, especially since the 1950s saw a proliferation of physical–organic and spectroscopic and mechanistic studies. Within a few years, there were rumors that the *Journal of Organic Chemistry* would be forced to follow the example of the *Journal of the American Chemical Society* and restrict page numbers. This would be an across-the-board cut and not be aimed at any subspecialty of chemistry in particular. Medicinal chemists, like chemists in other areas involving organic chemistry, could expect increasing difficulties in getting their papers accepted.

There was, however, also another reason for this apprehension. Pharmacological testing of series of related compounds by established test methods was not regarded as innovative science by biological journals, and the best of these journals let it be known that such routine test reports would no longer be accepted. Medicinal chemists and their pharmacological colleagues thus found themselves between a rock and a hard place. Where should they submit their manuscripts? As an illustration, a history of medicinal chemistry from the middle of the 19th century to 1950 had to appear in *Industrial and Engineering Chemistry*.[17]

When I was chairman of the Division of Medicinal Chemistry of the American Chemical Society in 1954, I suggested that the time had come for the Division to sponsor or promote a journal in its own field. This suggestion was voted down almost unanimously at a business meeting of the Division. The majority of those present—to be sure only a small fraction of the membership—felt that we might as well struggle along with the existing situation of the *Journal of Organic Chemistry* rather than risk the uncertainties of a new journal. After that meeting, there was no further official discussion about this subject.

Two years later I met Professor Arnold Beckett of the Chelsea School of Pharmacy of the University of London, who was on leave in the United States. During discussions of our publication problems, he mentioned his difficulties in placing his manuscripts in the *British Journal of Pharmacology*, and expressed a wish for a journal in which both the chemical and biological results of a medicinal chemical investigation could be reported, either in the same paper or in consecutive papers in the same issue. I told

(15) Hansch, C.; Fujita, T. *J. Am. Chem. Soc.* **1964**, *86*, 1616.
(16) Free, S. M.; Wilson, J. W. *J. Med. Chem.* **1964**, *7*, 395.
(17) Moore, M. L. *Ind. Eng. Chem.* **1951**, *43*, 577.

him about the negative response of the Division of Medicinal Chemistry of the American Chemical Society, which had closed the door to further approaches. Therefore we decided to ask a private publisher about our problem.

Interscience had published my two-volume *Medicinal Chemistry* in 1951, and I was in the midst of assembling a second edition. There had been a difficulty with the title of my book. Mr. Maurice Dekker, the president of Interscience, had wanted to call it *Medicinal and Pharmaceutical Chemistry* to distinguish it from medical, i.e. clinical chemistry, which he felt might be confusing to readers abroad. It took persuasion and the help of the Interscience editor Eric Proskauer to salvage the title *Medicinal Chemistry*. But by now the Firm could be expected to be reconciled with this description of our field, and I asked them whether they would be interested in publishing a journal with the same title. Beckett and I met Messrs. Dekker and Proskauer at luncheon under the Christmas tree in Rockefeller Center in New York in December 1957. The two officers of Interscience expressed high enthusiasm for our program. It would be a journal with an international editorial board to distinguish it from an ACS-sponsored publication, since the ACS Division of Medicinal Chemistry had turned down my inquiry. Professor Beckett and I would be co-editors to whom manuscripts could be submitted. Only on one point Mr. Dekker was adamant: as 8 years earlier, he insisted the journal should be called *Medicinal and Pharmaceutical Chemistry*, and no pleas to delete the "*and Pharmaceutical*" could sway him. Perhaps he felt that Arnold Beckett, who hailed from a British college of pharmacy, would not care as deeply as I did about this addition to the name of the journal.

Interscience provided me with an IBM typewriter, one office chair, the salary of a half-time secretary, and stationery. Buoyed by this munificent support, we wrote to several dozens of prominent medicinal chemists and pharmacologists in the United States, Europe, India, Japan, and USSR, inviting them to join our editorial board. The response was spotty, but we ended up with an adequate number of medicinal scientists. In the 3 years of the Interscience-supported journal, we never met our board members, and not once received comments, advice, or consent from them. What was worse, our pleas that they send us manuscripts and encourage their colleagues to do the same received only a very limited response. Only three board members ever sent us a paper for publication, and not about their best work. Our referees could barely recommend acceptance.

The response to the journal in Europe was slow. Professor Beckett did not receive but a handful of manuscripts, and I had to work doubly hard to get enough papers ready for the next issue. A few good papers started to arrive from American academic and industrial laboratories after about 2 years of mediocre performance. We hoped that the need for a medicinal–chemical journal would be greater than had been admitted.

In 1960, I received a letter from Professor A. C. Cope, Chairman of the Publication Board of the American Chemical Society. It stated that the Society—not its Division of Medicinal Chemistry—planned to issue its own journal in the field of medicinal chemistry, and added a warning that this would become harmful to our small journal. The ACS would be willing to acquire our journal if Interscience would sell it to them. I forwarded the letter to Interscience, who replied to Professor Cope. They told him it was unfair for a tax-exempt organization to interfere with the program of a commercial publisher, but since Interscience with their more limited resources could not compete with the powerful ACS, they would be amenable to an offer for our journal. The ACS dispatched Mr. Richard Belknap, their publications manager, to New York, and the ACS bought the *Journal of Medicinal and Pharmaceutical Chemistry* from Interscience, at a great financial sacrifice by the private company.

It now became necessary for the editors and the editorial board to resign since the ACS chose their editorial staffs with the advice of expert Divisional officers. At a national meeting in Cleveland, the officers of the Division of Medicinal Chemistry invited me to meet with them to discuss the changeover. At the last moment they could not secure a meeting room, and all of us—Drs. Biel and Smissman and about eight others—piled into a dimly lighted walk-in coat closet to settle our question. Dr. Biel offered me the editorship of the new ACS journal, and I accepted, but asked what would be done about Professor Beckett. The officers felt they could not include a foreign editor, especially since Beckett was not a member of the ACS. They left it up to me to choose an assistant editor; Everette L. May at the NIH accepted the assignment.

Mr. Belknap decided not to change the name and format of the journal for 1 year. At the end of that time, the page size was enlarged to that featured by the *Journal of the American Chemical Society*, the *Journal of Organic Chemistry*, and other major ACS journals, with two columns of text for better readability. One of my students who was gifted artistically, Dr. Stuart Zimmerman, designed the new cover. The name was changed, finally, to the *Journal of Medicinal Chemistry* upon my request since we no longer had to heed the sales objections of our previous publishers.

The ACS still could not provide expanded office help and facilities, and this imposed considerable stress on the editor's office. But once the *Journal of Medicinal Chemistry* had been launched in this manner, it was on its way to grow and increase in stature.

Like all other new journals, the *Journal of Medicinal Chemistry* had to overcome a number of "childhood diseases". The majority of medicinal chemists was accustomed to publish in the older, established periodicals and had to be convinced that the new journal would provide a long-lasting and dignified outlet for their papers. Today, when publication in the *Journal of Medicinal Chemistry* is regarded as a privilege, it is difficult to reconstruct the hesitancy with which medicinal scientists regarded early issues. Repeated personal appeals to potential authors were necessary to persuade them to submit a manuscript. The singular is employed on purpose; the extraction of a wisdom tooth was easier than soliciting manuscripts. The first few issues of the Journal, even though page size had not yet been enlarged, were thin pamphlets, much to the despair of ACS headquarters, who had counted on an early solid volume with appeal to subscribers. It took 2 or 3 years for the realization to sink in that the *Journal of Medicinal Chemistry* represented an equal-opportunity extension of the *Journal of the American Chemical Society* with concentrated specialization in drug research.

In the late 1960s, the ACS encountered new financial strictures. With more NIH grant funds available for medicinal studies and industrial drug research expanding at an unprecedented rate, even the mushrooming new journals of the Society began to strain the resources of the ACS Publication Board to the limit. The Board proposed savings of journal space by recommending short-hand abbreviations of common words, deleting vowels, using

contractions, and other objectionable devices. Most authors rebelled, and rightly so, but as editor I had to play ball with the Publication Board. For a while the journal looked as if it had been wrought through a faulty word processor. Objections to this nonsensical procedure became louder, and the Publication Board had to retreat. By and by the text of papers resumed their normal, readable, and dignified format. Nevertheless, a cap was put on the number of pages the journal could publish per year. At the semiannual meetings of the Division of Medicinal Chemistry, the Editor reported these repeated restrictions and appealed to authors to condense their background introductions, descriptions, and discussions in their papers.

Scientific productivity ultimately depends on the drive and ingenuity of an individual and can overcome arbitrary restrictions on reports of the results in journal pages. The unrivalled champion in publishing medicinal chemical research of great originality in the 1960s was Professor B. R. Baker, particularly during his tenure at the University of California at Santa Barbara. Year after year Baker submitted 35 long, detailed, and letter-perfect manuscripts to the *Journal of Medicinal Chemistry* per year. It was often barely necessary to get these papers refereed since they incorporated all the stylistic format recommended to authors and offered classical contemporary medicinal thought to the readers. Another prolific contributor of high-quality and exciting papers was Karl Folkers, a master of medicinal–biochemical research. As the fields of antibiotics, CNS-active agents, and pharmacodynamic drugs unfolded, many other ingenious authors appeared on the scene and enriched the pages of the Journal. A widely acclaimed suggestion for QSAR[16] appeared in this Journal.

The review of books is a common feature of many scientific publications. Dozens of books on bioorganic, medicinal, pharmacological, and related topics are submitted to editors for review. To begin with, books were assigned to experts but many of these reviewers delayed their work for months, even years, or never replied. I found that reading almost any book semicritically could be accomplished in a few days, and thus I began to review many books myself for the Journal. The copies of the books were then donated to the departmental library of my university.

In 1971, on my first retirement—there have been three more since—the editorship of the *Journal of Medicinal Chemistry* was handed over to Professor Portoghese, who soon, with renewed energy and vigor, doubled the annual pages and introduced several new features such as Perspectives. The Journal has continued to grow and increase in stature; it represents now the most honored organ for drug design and allied activities in the world.