THE DEVELOPMENT OF MEDICINAL CHEMISTRY AS A DISCIPLINE: A TOPIC RIPE FOR HISTORICAL EXPLORATION

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Abstract

Although there has been a substantial amount of research and publication related to the history of the chemistry of drugs, there is a dearth of literature on the institutional and disciplinary history of medicinal chemistry. Medicinal chemistry did not become a recognized, distinct sub-field of chemistry until the twentieth century. This paper will discuss the opportunities for historians of chemistry and pharmacy in the exploration of the subject. It will delineate some of the interesting historical questions and themes and suggest possible sources and approaches that might lead to fruitful research in this area.

Although interest in the chemical aspects of drugs goes back at least to Paracelsus and the iatrochemists, it was only with the emergence of chemistry, especially organic chemistry, and pharmacology as distinct disciplines in the nineteenth century that significant progress was made in the isolation and synthesis of pure chemicals with physiological activity. And it was only in the twentieth century that significant progress was made in understanding the chemical interactions with cells that produced the specific effects of drugs. Especially important was the work of the German physician Paul Ehrlich in the early years of the century which led to the development of the receptor theory of drug action and the field of chemotherapy. Although there were some attempts to relate chemical structure to pharmacological action in the nineteenth century, it was Ehrlich who systematized and popularized this approach (1).

These advances led to the emergence of a group of chemists who focused their attention on the chemistry of drugs, founding the field of medicinal chemistry. What exactly is medicinal chemistry? In 2017, Selina Holbrook and Sylvie Garneau-Tsodikova addressed this question in *MedChemComm*. They wrote (2):

> This question still puzzles even the most experienced researchers working in this scientific discipline and generates a lot of discussion amongst those entering as well as those mature in the profession.

Andrew Coop, in the latest edition of the influential *Foye's Principle of Medicinal Chemistry*, addresses the problem of defining medicinal chemistry as follows (3):

> Medicinal chemistry has as many definitions as those doing the defining, and is complicated by the concurrent use of terms such as pharmaceutical chemistry, drug chemistry, bioorganic chemistry, chemical biology, and the list goes on.

He himself offers the very broad and somewhat vague definition of the subject as "the application of chemistry to the continuous improvement of health."

A particular complication, referred to by Coop, is that the term pharmaceutical chemistry is frequently used to refer to the same types of activities that define medicinal chemistry. A search of the literature shows that sometimes the terms medicinal chemistry and pharmaceutical chemistry are used synonymously and sometimes they are given somewhat different definitions. It is also not uncommon to find one of them described as a sub-

field of the other, with either one of them considered the broader term. For my present purposes, I will include both in my analysis, distinguishing between them only when it seems appropriate. Medicinal chemistry should also not be confused with medical chemistry, the teaching of chemistry in medical schools, which was focused more broadly on the chemical aspects of medicine in general. Medical chemistry, as Robert Kohler has shown, eventually evolved into physiological chemistry and biochemistry (4).

There is thus no one generally agreed upon definition of the field, although I believe that there is a general understanding of what medicinal chemistry involves. For my purpose here, I will use the description of what medicinal chemists do provided by the American Chemical Society on its website page on careers in the field, which I think incorporates at least most of the activities included in typical definitions of the field (5).

> Medicinal chemists apply their chemistry training to the process of synthesizing new pharmaceuticals. They also improve the processes by which existing pharmaceuticals are made.
>
> …
>
> Medicinal chemists are focused on drug discovery and development and are concerned with the isolation of medicinal agents found in plants, as well as the creation of new synthetic drug compound.

Medicinal or pharmaceutical chemistry seems to have become a recognized, distinct division or subdivision of chemistry in the twentieth century. Historians of chemistry, medicine and pharmacy, especially over the past couple of decades, have devoted substantial attention to the history of the isolation, synthesis and uses of drugs. There have also been studies of the history of structure-activity relationships, receptor theory, and drug development. However, almost no work on the institutional and disciplinary history of medicinal chemistry has been published. The purpose of this essay is to encourage the investigation of this subject by delineating interesting historical questions and themes and suggesting possible sources and approaches that might lead to fruitful research. Given the limited space available to me, I will limit my scope to the development of medicinal chemistry in the United States.

The history of medicinal chemistry must be viewed within the broader context of the history of disciplines in general. Historian Suzanne Marchand pointed out in an essay in 2014 that the history of disciplines essentially emerged as a serious area of study in the late 1950s and early 1960s. She further argued that it was "practiced chiefly by North American scholars, and especially by intellectual historians and historians of science." Marchand expressed the view that the 1980s and 1990s represented the heyday of the history of disciplines, and that the field "has had its day" (6). Even if the history of disciplines is now in eclipse, as Marchand argues, there is still significant interest in the subject and I believe that this approach remains fruitful, especially with regard to fields whose disciplinary history has not been adequately examined.

An edited volume of essays published in 1972 outlined some of the issues involved in the history of scientific disciplines and discussed the development of a number of fields. The introduction in the book, titled "Problems in the Emergence of New Disciplines," provided examples of some of the general questions that scholars should be investigating. To paraphrase just a few of these questions (7):

1. Did research in the emerging discipline originate and spread within universities or other institutions?

2. Were other changes occurring within the social context (economic, political, etc.) in this period that were especially favorable or unfavorable to the exploration of the field?

3. To what extent did the introduction of technical information generated outside the research community of the new field affect scientific developments within the discipline?

This volume included case studies of two areas of chemistry, physical chemistry and agricultural chemistry (8). In his 1990 book, *Physical Chemistry from Ostwald to Pauling: The Making of a Science in America*, John Servos traced, as the subtitle implies, the emergence and growth of the discipline in the United States (9). Robert Kohler traced the development of a discipline closer to medicinal chemistry in *From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline* (1982) (4). Just recently, in 2020, Jeffrey Seeman and Guillermo Restrepo used an analysis of changes over the decades within the Nobel Prize in Chemistry program to present a convincing argument that biochemistry has evolved into a distinct discipline from chemistry (10).

These studies provide models for the type of disciplinary history of medicinal chemistry that I am proposing. I am not concerned with the question of whether medicinal chemistry is truly a distinct discipline from chemistry itself. It might be more properly viewed as a subdiscipline, but the issues involved in tracing the

history of the field are the same. I am aware of only one book devoted to the history of medicinal chemistry, William Remers' *A History of Medicinal Chemistry* (2011). While this work provides a useful and wide-ranging account of the subject, it is confined largely to chronicling the history of the development of theories, techniques and compounds, and says little about the institutional history of the discipline. Nevertheless, it is an essential reference tool. In his book, Remers clearly points out some of the complications involved in telling the story of "how medicinal chemistry fits into the formal structure of academic and research institutions," adding that "this picture is rather confusing." He goes on to correctly indicate that the "only recognized medicinal chemistry departments in American universities are located in pharmacy colleges," and that even here they may be called either medicinal chemistry or pharmaceutical chemistry. In some cases, medicinal chemistry may be merged with pharmacology or natural products chemistry into a single department (11).

Although there are few if any organized divisions of medicinal chemistry in chemistry departments, as Remers also points out, this does not mean that individuals who identify as medicinal chemists do not exist in such departments, although they may be part of a broader organic chemistry group. The presence of many key contributors to the field in chemistry departments is shown, for example, by the number of recipients of awards given by ACS Division of Medical Chemistry to individuals in these departments (12). These chemists played an important role in the development of medicinal chemistry as a discipline. For example, Alfred Burger of the University of Virginia's Department of Chemistry founded the *Journal of Medicinal and Pharmaceutical Chemistry* (now the *Journal of Medicinal Chemistry*). Although there are some medicinal chemists located in medical schools, these schools in general do not have separate departments or units of medicinal chemistry, and medicinal chemists housed in them appear to represent only a small proportion of practitioners in the field. Of course, medicinal chemists also work in non-academic institutions, most notably in pharmaceutical companies and government research laboratories.

Perhaps the earliest sign that medicinal or pharmaceutical chemistry was becoming a distinct discipline in the United States was the creation of the Division of Pharmaceutical Chemistry of the American Chemical Society in 1909. It evolved out of a special interest subgroup known as the pharmaceutical section. Most of its early members were pharmacists who were largely concerned with plant products, drug formulation and assay methods. The advent of World War I led to a change in focus. Up to that time, the United States had been almost exclusively dependent upon Germany for the importation of synthetic drugs and intermediates, but the British blockade cut off these supplies. It became necessary for the American pharmaceutical industry to produce such products and for American chemists to undertake research on drug development and synthesis. The industry exploded in the post-war period (13). A growing interest in the chemical structure of drugs and its relationship to biological activity, as well as in drug synthesis, led the Division to change its name in 1920 to the Division of Medicinal Products and again in 1928 to the Division of Medicinal Chemistry.

It was in the period following World War II that the discipline really began to flourish. The American pharmaceutical industry became a world leader in drug research, opening up many more positions for medicinal chemists. Chemistry departments developed programs to train such individuals, as did pharmacy schools, which had become much more science-based and involved in graduate education, with many establishing departments of medicinal chemistry. The first American journal in the field was founded in 1959 as the *Journal of Medicinal and Pharmaceutical Chemistry*, dropping the *Pharmaceutical* in 1963. These were all signs indicating that medicinal chemistry had become an established discipline (14).

This brief and superficial overview of the evolution of the field in the United States suggests some obvious topics for historical investigation. For example, we need to know much more about the founding of the ACS Division of Pharmaceutical Chemistry and its transformation into the Division of Medicinal Chemistry. What forces led the founders to create a special interest group and then press for it to attain Division status? Who were the individuals responsible for the change of focus of the Division from largely pharmaceutical concerns to chemical ones, and how did they bring about this change? When did members of the division begin to think of themselves specifically as medicinal chemists? How did the Division change over time? What role did it play in the development of graduate programs and publications in the field? How did the content of articles in the *Journal of Medicinal Chemistr*y differ from the content of articles in related journals such as the *Journal of Organic Chemistry*?

Other important topics in need of research include the development of teaching and graduate programs in medicinal chemistry in departments of chemistry and

schools of pharmacy and the institutionalization of research in the field in academia, the pharmaceutical industry and government laboratories. When, where and why did these developments take place, and who were the key figures involved? How did medicinal chemistry differ in each of these environments? What problems did medicinal chemists face in establishing the subject as a recognized discipline? What were the backgrounds of persons entering the field, especially in the early period when there were no graduate programs devoted specifically to medicinal chemistry?

In order for someone to develop a synthetic history of the field, there needs to be much more research on these types of questions. In addition, we need biographical studies of key individuals in the discipline and institutional histories of academic, industrial and government programs in medicinal chemistry. Work is also needed on the relationships between medicinal chemists in these different settings. John Swann's book on *Academic Scientists and the Pharmaceutical Industry. Cooperative Research in Twentieth-Century America* (1988) provides an excellent starting point for future research in this area (*15*). The history of medicinal chemistry must also be studied in relationship to related disciplines, such as organic chemistry, biochemistry and pharmacology.

There is relatively little in the historical literature addressing the types of questions raised above. For example, two histories of ACS and Remers' book devote less than a page each to the founding of the Division of Pharmaceutical Chemistry and its change of name and focus (16). A useful starting point for researching the history of the Division is Patrick Woster's article in the *Journal of Medicinal Chemistry* on the occasion of the Division's centennial in 2009. Woster has also written an article chronicling the history of *Annual Reports in Medicinal Chemistry* from its founding in 1965 up to 2015 (17). Such organizations and publications played a crucial part in the development of the discipline of medicinal chemistry.

What are some of the primary sources that historians can draw upon to tell this story? Obviously, archival and manuscript collections of individuals and institutions are a major resource crucial to the research of historians in any field. There is no specific guide to archival and manuscript collections in the history of medicinal chemistry. The Center for the History of Chemistry (now the Science History Center) published a guide to archival and manuscript collections in chemistry and chemical technology in 1987, and, although dated, it has some limited use in identifying collections related to medicinal chemistry. The publication's index, however, lists only three collections under the heading of pharmaceutical chemistry and there is no entry for medicinal chemistry. However, there may be relevant materials in collections indexed under headings such as organic chemistry and the pharmaceutical industry (18).

Ideally, historians would be able to consult the archival records (correspondence, minutes, etc.) of key institutions such as the Division of Medicinal Chemistry. My searches of the literature and contacts with the Division itself, however, have not turned up any substantial cache of historical records for the Division. There might be a limited amount of useful material in the five boxes of Records of the American Chemical Society Committee on Divisional Activities in the Othmer Library of Chemical History at the Science History Institute in Philadelphia (https://www.sciencehistory.org/othmer-library). This committee is responsible for the oversight and coordination of the activities of the various divisions, and the Division of Medicinal Chemistry is among those represented. The catalog record, however, indicates that the bulk of this collection dates from the period 1960-1982, so there would appear to be little material relating to the early decades of the Division. The Othmer Library also contains records from several of the ACS Divisions, but the Division of Medicinal Chemistry is not among them, and it is possible that no significant archives for the Division exist. Unfortunately, I have also not been able to locate an archive of historical records for the *Journal of Medicinal Chemistry* in my search of the literature and contacts with the editors of the publication.

It would be instructive to understand the development of interest and expertise in medicinal chemistry in the pharmaceutical industry, and large American firms such as Eli Lilly and Merck do maintain archival collections. I used some of these materials many years ago in the research for my book on the history of American pharmacology (19). In my discussions with other historians in more recent times, however, I have learned that it has become increasingly more difficult to obtain access to these company archives. These archives represent a potentially rich source of information on the history of medicinal chemistry within the commercial sphere, and I encourage historians to continue to make efforts to gain access to them. The personal papers of scientists who worked in industry (see examples below) can be another source of relevant information.

For those interested in the development of the field within the federal government, the voluminous records at the National Archives and Records Administration

(NARA) are a potential resource, especially the records of agencies such as the National Institutes of Health (NIH) and the Food and Drug Administration. Searching NARA's catalog on its website (https://www.archives.gov) is the logical place to start, but there is a large amount of material and it is not generally described in enough detail to make it easy to focus in on the desired items. One first needs to research the history of these agencies to identify which of their divisions/units were the principal homes for medicinal chemists and their work. Examples of areas where medicinal chemists have worked at NIH are the Division (later Laboratory) of Chemistry, now incorporated into the Laboratory of Bioorganic Chemistry of the National Institute of Diabetes and Digestive and Kidney Diseases, the Unit of Chemotherapy established during World War II (which concentrated on antimalarial drugs), research programs on drug addiction (which were eventually incorporated into the National Institute on Drug Abuse), and cancer chemotherapy programs within the National Cancer Institute (20). It would also be profitable to look at the funding of research in medicinal chemistry by government agencies such as NIH to shed light on changes in research trends in the field. When delving into any of these types of records, it is advisable to consult with an archivist at NARA before planning a visit.

Tracing the development of medicinal chemistry in academia is another important part of the story, and this occurred, as mentioned above, largely in departments of chemistry and schools of pharmacy. University catalogs are a useful resource for tracing the evolution of courses and graduate programs in medicinal chemistry. In the case of pharmacy, it is fortunate that there is a large collection of school of pharmacy catalogs in the Kremers Reference Files (https://aihp.org/collections/kremers-reference-files/) of the American Institute of the History of Pharmacy (AIHP) at the University of Wisconsin-Madison. The collection consists of catalogs from well over a hundred schools of pharmacy, some now defunct, from some 40 states, as well as a number of catalogs from foreign schools. A list of the catalog holdings is available from the AIHP (contact aihp@aihp.org). This resource would be valuable for understanding the development of medicinal chemistry in American schools of pharmacy.

Chemistry departments do not generally issue separate catalogs of their programs, so information on medicinal chemistry in these departments would have to be gleaned from more general university or college catalogs. I am not aware of any single significant collection of catalogs from different universities, and relatively few such catalogs appear to be available online in digital form. Researchers would have to consult these documents in individual university libraries and archives. In addition to the catalogs, an important source for investigating the development of medicinal chemistry graduate programs in chemistry departments is the ACS Directory of Graduate Research, issued biennially from 1953. This publication, which eventually evolved into an online version (DGRweb) was discontinued in 2016. Unfortunately, the online database is no longer available. The Othmer Library, however, has print copies of the majority of the directories issued between 1955 and 1979.

The records of pharmacy schools and chemistry departments housed in university archives are another resource for tracing the development of the field in academia. Most major university archives have online catalogs that would assist historians in identifying these sources. Historians could narrow this task of selecting which pharmacy schools and chemistry departments to focus on by using secondary sources on the history of medicinal chemistry and other published works to identify institutions that have played an obviously significant role in the development of medicinal chemistry in this country. Identifying key academic leaders in the field, as discussed below, could also assist in deciding where to concentrate one's efforts.

Published histories of schools of pharmacy, departments of chemistry and universities can also provide information on the development of medicinal chemistry and help identify the most influential departments in advancing the field in academic institutions in the United States. A good place to start in identifying histories of schools and colleges of pharmacy is the section on "Education" in *The History of Pharmacy: A Selected Annotated Bibliography* (21). There are published histories of the medicinal chemistry departments at the Colleges of Pharmacy of the University of Minnesota and Ohio State University, the only ones of their kind that I know of (22). A relatively few histories of departments of chemistry, such as those of the universities of Wisconsin, Tennessee and Arizona, have been published and these may be a source of relevant information (23). Histories of many major universities also exist, although these are not likely to provide much information specifically on medicinal chemistry programs.

Another potential resource for researching the evolution of medicinal chemistry in the United States is the personal papers of practitioners of the discipline. In addition to providing information on the careers of these individuals, these records could also shed light on

relevant developments within the institutions in which they worked and the professional organizations with which they were affiliated. Sources for identifying key individuals who influenced the discipline include the lists of award winners (12) and the Hall of Fame of the ACS Division of Medicinal Chemistry (24), available on the Division's website (https://www.acsmedchem.org/), and a list of the Chairs of the Division through 1976 in a book on the history of ACS (25). Obituaries and biographical and autobiographical sketches can also serve as starting points for research in this area. A number of useful autobiographical essays by medicinal chemists can be found in the pages of *Annual Reports in Medicinal Chemistry* and *Medicinal Chemistry Reviews*.

For academic chemists, any surviving papers will often be housed in the archival collections of the universities with which they were most closely identified. For example, the papers of Sidney Riegelman, a pharmaceutical chemist who was a pioneer in pharmacokinetics and biopharmaceutics, are in the University of California, San Francisco Archives (26). The Othmer Library also houses several collections of papers of prominent medicinal chemists, including some who worked in the pharmaceutical industry such as Max Tishler and Lloyd Conover.

Oral histories of medicinal chemists can also be a valuable source of information. The Center for Oral History at the Science History Institute (27) includes in its collection interviews with a number of individuals who have worked in the field of pharmaceutical and medicinal chemistry, such as Ernest Volwiler and Paul Anderson. Transcripts of the interviews are available for consultation at the Institute or copies may be ordered from the Center for Oral History. Although the earliest pioneers of medicinal chemistry are now deceased, the fact that the field has developed significantly in the past half a century means that many important figures who have helped shape the discipline are still living. This provides historians with an opportunity to conduct oral histories with these chemists to preserve their recollections and insights, although time is of the essence here because many of them are advanced in years. A couple of examples of those who should be interviewed are Philip Portoghese, Editor-in-Chief of the *Journal of Medicinal Chemistry* from 1972 to 2011, and Kenner Rice, longtime Chief of the Drug Design and Synthesis Section of the National Institute on Drug Abuse.

Lastly, I would cite as another source of potential information on the history of medicinal chemistry databases such as SciFinder and Web of Science. For example, one can use them to track the number of papers published in medicinal chemistry by years or decades in order to chart the growth of the field. I have utilized this technique myself in other contexts using Science Citation Index (included in Web of Science). Citation indexes can also be used in the tracing of networks of researchers in the field.

I hope that this brief survey of issues and sources related to the history of medicinal chemistry as a discipline will serve to stimulate further research on the subject. Studies on the science of medicinal chemistry (e.g., theories, drug discovery) will and should continue, but these must be complemented by research on the development of the subject as a distinct discipline in order to paint a more complete picture of the history of the field. The histories of the science and discipline of medicinal chemistry are of course not totally separate fields. Each influences the other and both are needed for a comprehensive picture. To give just one example, how has the life of a medicinal chemist changed over the past century with respect to such factors as areas and methods of research, types of institution worked at, sources of research support, and perception of the field by participants and outsiders? Obviously both scientific and institutional factors have influenced changes in what it means to be a medicinal chemist.

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References and Notes

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