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Uses and Applications of Medicinal Chemistry Research in India

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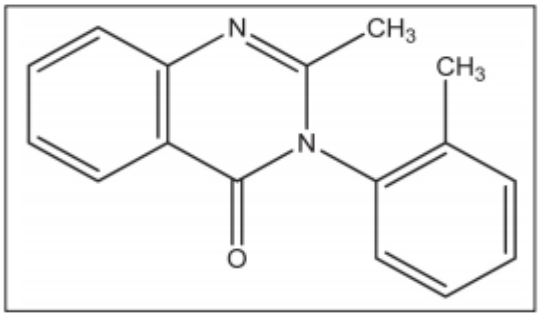
Abstract: The beginning of modern drug research in India can be traced to early part of the twentieth century. Dr Upendra Nath Brahmachari worked on drugs for kala-azar at the Campbell Medical College, Calcutta. Colonel Ram Nath Chopra organized an active centre of research on the Indian medicinal plants at the School of Tropical Medicine, Calcutta. The lead given by Chopra led to start of investigations on indigenous drug plants in various universities and colleges. By mid of the twentieth century, different institutions started getting organized for studies with systematic approach to design of new chemical entities. The credit goes to the Central Drug Research Institute, CSIR, for spreading the innovative drug research culture. The major discoveries made of the drugs through innovative drug research have been from the CDRI, Hindustan Ciba-Geigy Research Centre, and the University Institute of Pharmaceutical Sciences of the Panjab University. The other institution active was the Research Centre of the Hoechst Pharmaceuticals Limited. The Zydus Research Centre has come up of recent. There have emerged a good number of new drugs from Indian laboratories but only a few have been marketed.

Keywords: Chemistry, Medicines, drugs, colleges, Groups etc.

I. INTRODUCTION

The beginning of modern drug research in India can be traced to early part of the twentieth century. Dr Upendra Nath Brahmachari1 worked on drugs for kala-azar at the Campbell Medical College, Calcutta. Colonel Ram Nath Chopra2-4 organizedan active centre of research on the Indian medicinal plants at the School of Tropical Medicine, Calcutta. U. N. Brahmachari started working on treatment of the disease kala-azar in the second decade of the twentieth century. He examined organometallic compounds and concentrated his study on antimony derivatives. His idea of combining urea with stibanilic acid worked and led to discovery of the drug 'Urea Stibamine.' The drug was introduced for the treatment of kala-azar in 1922. The lead given by Chopra led to start of investigation on indigenous drug plants in various universities and colleges in centres such as at Calcutta, Bombay, Dacca, Patna, Allahabad, Lahore, Madras, Trivandrum etc. A particular mention may be made of the studies carried out by Dr Salimuzzaman Siddique (Tibbia College, Delhi). The earliest drug originating from India through modern drug research was the chemotherapeutic agent Urea Stibamine. Three other drug discoveries which came up later were methaqualone, peruvoside and hamycin. Out of the work initiated on the synthesis of quinazalones at the Department of Chemistry, Lucknow University, and later continued at the Regional Research Laboratory, now Indian Institute of Chemical Technology, Hyderabad, emerged the compound which was first screened at the K. G.'s Medical College, Lucknow, and later designated as methaqualone. Methaqualone came up into wide spread use as hypnotic. It has been withdrawn from the market in many countries because of its abuse. The cardiac glycoside peruvoside was isolated from Thevetia peruviana at the Pharmaceutical Laboratories of Andhra Pradesh.



Methaqualone

Medicinal chemistry and pharmaceutical chemistry are disciplines at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, where they are involved with design, chemical synthesis and development for market of pharmaceutical agents, or bio-active molecules (drugs). Compounds used as medicines are most often organic compounds, which are often divided into the broad classes of small organic molecules (e.g., atorvastatin, fluticasone, clopidogrel) and "biologics" (infliximab, erythropoietin, insulin glargine), the latter of which are most often medicinal preparations of proteins (natural and recombinant antibodies, hormones, etc.). Inorganic and organometallic compounds are also useful as drugs (e.g., lithium and platinum-based agents such as lithium carbonate and cis-platin as well as gallium). In particular, medicinal chemistry in its most common practice—focusing on small organic molecules—encompasses synthetic organic chemistry and aspects of natural products and computational chemistry in close combination with chemical biology, enzymology and structural biology, together aiming at the discovery and development of new therapeutic agents. Practically speaking, it involves chemical aspects of identification, and then systematic, thorough synthetic alteration of new chemical entities to make them suitable for therapeutic use. It includes synthetic and computational aspects of the study of existing drugs and agents in development in relation to their bioactivities (biological activities and properties), i.e., understanding their structure-activity relationships (SAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for purpose of medicinal products. At the biological interface, medicinal chemistry combines to form a set of highly interdisciplinary sciences, setting its organic, physical, and computational emphases alongside biological areas such as biochemistry, molecular biology, pharmacognosy and pharmacology, toxicology and veterinary and human medicine; these, with project management, statistics, and pharmaceutical business practices, systematically oversee altering identified chemical agents such that after pharmaceutical formulation, they are safe and efficacious, and therefore suitable for use in treatment of disease.

During the Age of Enlightenment, the 18th-century, science was held in high esteem and physicians upgraded their social status by becoming more scientific. The health field was crowded with self-trained barber-surgeons, apothecaries, midwives, drug peddlers, and charlatans. Across Europe medical schools relied primarily on lectures and readings. The final year student would have limited clinical experience by trailing the professor through the wards. Laboratory work was uncommon, and dissections were rarely done because of legal restrictions on cadavers. Most schools were small, and only Edinburgh, Scotland, with 11,000 alumni, produced large numbers of graduates.

Pharmaceutical manufacture sector

Early medical traditions include those of Babylon, China, Egypt and India. The Greeks introduced the concepts of medical diagnosis, prognosis, and advanced medical ethics. The Hippocratic Oath was written in Greece in the 5th century BCE, and is a direct inspiration for oaths of office, physicians swear upon entry into the profession today. In the medieval age, surgical practices inherited from the ancient masters were improved and then systematized in Rogerius's The Practice of Surgery. Universities began systematic training of physicians around the years 1220 in Italy. During the Renaissance, understanding of anatomy improved, and the microscope was invented. The germ theory of disease in the 19th century led to cures for many infectious diseases. Military doctors advanced the methods of trauma treatment and surgery. Public health measures were developed especially in the 19th century as the rapid growth of cities required systematic sanitary measures. Advanced research centers opened in the early 20th century, often connected with major hospitals. The mid-20th century was characterized by new biological treatments, such as antibiotics. These advancements, along with developments in chemistry, genetics, and lab technology (such as the x-ray) led to modern medicine. Medicine was heavily professionalized in the 20th century, and new careers opened to women as nurses (from the 1870s) and as physicians (especially after 1970).

A large number of Ph Ds and postgraduates are employed in pharmaceutical R&D, manufacture and custom synthesis. There is no evidence of any basic research activity or new drug discovery. As already pointed above, the number of research papers published by the pharmaceutical R&D in the industry setting is negligible. Their participation in or organizing seminars on the research too is disappointing. The pharmaceutical sector is still importing a huge quantum of chemicals from abroad. About 75% of the chemicals used in the manufacture of drugs is imported from China. Even basic chemicals like glycine, glyoxal, acetonitrile, etc. are being imported from China or other countries. There is no justification to feel proud that we export drugs to some countries while the import component of the chemicals is very high. The patents that these companies produce are by and large tweaks or polymorphs of the established procedures of well-known drugs rather than on new drug discovery. The pharmaceutical sector is receiving huge subsidies and concession from the Government. Their laboratories are also recognized as R&D centres. As such it is expected that they further their research in frontier areas and publish as is the practice in foreign countries. It is a fact that the new drugs from foreign countries emerge only from the pharmaceutical sector (like Merck, Pfizer, SKF, etc.) and they publish papers in all leading journals. The contribution of the Indian pharmaceutical sector in basic research needs to match with

CSIR institutions and universities. The planners and policy makers need to think aloud as to why a study of SAR studies of a series of compounds or discovery of new drugs are not forthcoming in India and plan steps to ameliorate the research in India. The publication of research papers in the Journal of Medicinal Chemistry is a mirror to indicate our efforts on new drug discovery. This aspect was neglected by national institutes/laboratories and private pharma. It is a fact that state universities have no infrastructure for new drug discovery Although our universities have expertise in heterocyclic synthesis, they fail to adopt new methodologies like C–H activation, metal-mediated C–C bond formation and metal-free approaches to construct heterocyclic and enhance the impact of the work. One observation to be noted is that almost all the journals mentioned here are not being subscribed even by CSIR laboratories. Of course, many CSIR laboratories have on-line subscription to these journals, but these are not accessible to junior scientists. What is published by one researcher in a big laboratory is not known his co-scientists. In universities, except Indian journals, no international journals or internet subscriptions are available. That is the reason why IJC(B) is favored by state universities and PG colleges. Internet subscription, however, is not a substitute to a library with journals and books.

The number of purely Indian pharma companies is fairly low. Indian pharma industry is mainly operated as well as controlled by dominant foreign companies having subsidiaries in India due to availability of cheap labor in India at low cost. In 2002, over 20,000 registered drug manufacturers in India sold $9 billion worth of formulations and bulk drugs. 85% of these formulations were sold in India while over 60% of the bulk drugs were exported, mostly to the United States and Russia. Most of the players in the market are small-to-medium enterprises; 250 of the largest companies control 70% of the Indian market. Thanks to the 1970 Patent Act, multinationals represent only 35% of the market, down from 70% thirty years ago. Most pharmacy companies operating in India, even the multinationals, employ Indians almost exclusively from the lowest ranks to high level management. Homegrown pharmaceuticals, like many other businesses in India, are often a mix of public and private enterprise. In terms of the global market, India currently holds a modest 1–2% share, but it has been growing at approximately 10% per year. India gained its foothold on the global scene with its innovatively engineered generic drugs and active pharmaceutical ingredients (API), and it is now seeking to become a major player in outsourced clinical research as well as contract manufacturing and research. There are 74 US FDA-approved manufacturing facilities in India, more than in any other country outside the U.S, and in 2005, almost 20% of all Abbreviated New Drug Applications (ANDA) to the FDA are expected to be filed by Indian companies. Growths in other fields notwithstanding, generics are still a large part of the picture. London research company Global Insight estimates that India's share of the global generics market will have risen from 4% to 33% by 2007. The Indian pharmaceutical industry has become the third largest producer in the world and is poised to grow into an industry of $20 billion in 2015 from the current turnover of $12 billion.

Process chemistry and development

The final synthetic chemistry stages involve the production of a lead compound in suitable quantity and quality to allow large scale animal testing, and then human clinical trials. This involves the optimization of the synthetic route for bulk industrial production, and discovery of the most suitable drug formulation. The former of these is still the bailiwick of medicinal chemistry, the latter brings in the specialization of formulation science (with its components of physical and polymer chemistry and materials science). The synthetic chemistry specialization in medicinal chemistry aimed at adaptation and optimization of the synthetic route for industrial scale syntheses of hundreds of kilograms or more is termed process synthesis, and involves thorough knowledge of acceptable synthetic practice in the context of large scale reactions (reaction thermodynamics, economics, safety, etc.). Critical at this stage is the transition to more stringent GMP requirements for material sourcing, handling, and chemistry.

Training

Medicinal chemistry is by nature an interdisciplinary science, and practitioners have a strong background in organic chemistry, which must eventually be coupled with a broad understanding of biological concepts related to cellular drug targets. Scientists in medicinal chemistry work are principally industrial scientists (but see following), working as part of an interdisciplinary team that uses their chemistry abilities, especially, their synthetic abilities, to use chemical principles to design effective therapeutic agents. The length of training is intense with practitioners often required to attain a 4-year bachelor's followed by a 4-6 year Ph.D. in organic chemistry. Most training regimens include a postdoctoral fellowship period of 2 or more years after receiving a Ph.D. in chemistry making the length of training ranging from 10-12 years of college education. However, employment opportunities at the Master's level also exist in the pharmaceutical industry, and at that and the Ph.D. level there are further opportunities for employment in academia and government. Many medicinal chemists, particularly in academia and research, also earn a Pharm.D (doctor of pharmacy). Some of these PharmD/PhD researchers are RPhs (Registered Pharmacists). Graduate level programs in medicinal chemistry can be found in traditional medicinal chemistry or pharmaceutical sciences departments, both of which are traditionally associated with schools of pharmacy, and in some chemistry departments. However, the majority of working medicinal chemists have graduate degrees (MS, but especially Ph.D.) in organic chemistry, rather than medicinal chemistry, and the

preponderance of positions are in discovery, where the net is necessarily cast widest, and most broad synthetic activity occurs.

In discovery of small molecule therapeutics, an emphasis on training that provides for breadth of synthetic experience and "pace" of bench operations is clearly present (e.g., for individuals with pure synthetic organic and natural products synthesis in Ph.D. and post-doctoral positions, ibid.). In the medicinal chemistry specialty areas associated with the design and synthesis of chemical libraries or the execution of process chemistry aimed at viable commercial syntheses (areas generally with fewer opportunities), training paths are often much more varied (e.g., including focused training in physical organic chemistry, library-related syntheses, etc.). As such, most entry-level workers in medicinal chemistry, especially in the U.S., do not have formal training in medicinal chemistry but receive the necessary medicinal chemistry and pharmacologic background after employment—at entry into their work in a pharmaceutical company, where the company provides its particular understanding or model of "medichem" training through active involvement in practical synthesis on therapeutic projects.

Public health

Public health measures became particular important during the 1918 flu pandemic, which killed at least 50 million people around the world. It became an important case study in epidemiology. Bristow shows there was a gendered response of health caregivers to the pandemic in the United States. Male doctors were unable to cure the patients, and they felt like failures. Women nurses also saw their patients die, but they took pride in their success in fulfilling their professional role of caring for, ministering, comforting, and easing the last hours of their patients, and helping the families of the patients cope as well. From 1917 to 1923, the American Red Cross moved into Europe with a battery of long-term child health projects. It built and operated hospitals and clinics, and organized ant tuberculosis and ant typhus campaigns. A high priority involved child health programs such as clinics, better baby shows, playgrounds, fresh air camps, and courses for women on infant hygiene. Hundreds of U.S. doctors, nurses, and welfare professionals administered these programs, which aimed to reform the health of European youth and to reshape European public health and welfare along American lines.

Government Support

The Indian government established the Department of Biotechnology in 1986 under the Ministry of Science and Technology. Since then, there have been a number of dispensations offered by both the central government and various states to encourage the growth of the industry. India’s science minister launched a program that provides tax incentives and grants for biotech start-ups and firms seeking to expand and establishes the Biotechnology Parks Society of India to support ten biotech parks by 2010. Previously limited to rodents, animal testing was expanded to include large animals as part of the minister’s initiative. States have started to vie with one another for biotech business, and they are offering such goodies as exemption from VAT and other fees, financial assistance with patents and subsidies on everything ranging from investment to land to utilities. The biotechnology sector faces some major challenges in its quest for growth. Chief among them is a lack of funding, particularly for firms that are just starting out. The most likely sources of funds are government grants and venture capital, which is a relatively young industry in India. Government grants are difficult to secure, and due to the expensive and uncertain nature of biotech research, venture capitalists are reluctant to invest in firms that have not yet developed a commercially viable product. The government has addressed the problem of educated but unqualified candidates in its Draft National Biotech Development Strategy. This plan included a proposal to create a National Task Force that will work with the biotech industry to revise the curriculum for undergraduate and graduate study in life sciences and biotechnology. The government’s strategy also stated intentions to increase the number of PhD Fellowships awarded by the Department of Biotechnology to 200 per year. These human resources will be further leveraged with a "Bio-Edu-Grid" that will knit together the resources of the academic and scientific industrial communities, much as they are in the US.

Post-World War II

A cochlear implant is a common kind of neural prosthesis, a device replacing part of the human nervous system

Smallpox vaccination in Niger, 1969. A decadelater, this was the first infectious disease to be eradicated.

The World Health Organization was founded in 1948 as a United Nations agency to improve global health. In most of the world, life expectancy has improved since then, and was about 67 years as of 2010, and well above 80 years in some countries. Eradication of infectious diseases is an international effort, and several new vaccines have been developed during the post-war years, against infections such as measles, mumps, several strains of influenza and human papilloma virus. The long-known vaccine against Smallpox finally eradicated the disease in the 1970s, and Rinderpest was wiped out in 2011. Eradication of polio is underway. Tissue culture is important for development of vaccines. Though the early success of antiviral vaccines and antibacterial drugs, antiviral drugs were not introduced until the 1970s. Through the WHO, the international community has developed a response protocol against epidemics, displayed during the SARS epidemic in 2003, the Influenza A virus subtype H5N1from 2004, the Ebola virus epidemic in West Africa and onwards.

As infectious diseases have become less lethal, and the most common causes of death in developed countries are now tumors and cardiovascular diseases, these conditions have received increased attention in medical research. Tobacco smoking as a cause of lung cancer was first researched in the 1920s, but was not widely supported by publications until the 1950s. Cancer treatment has been developed with radiotherapy, chemotherapy and surgical oncology. Oral rehydration therapy has been extensively used since the 1970s to treat cholera and other diarrhea-inducing infections. The sexual revolution included taboo-breaking research in human sexuality such as the 1948 and 1953 Kinsey reports, invention of hormonal contraception, and the normalization of abortion and homosexuality in many countries. Family planning has promoted a demographic transition in most of the world. With threatening sexually transmitted infections, not least HIV, use of barrier contraception has become imperative. The struggle against HIV has improved antiretroviral treatments, and in the late 2000s (decade), male circumcision was cited to diminish infection risk (see circumcision and HIV).

X-ray imaging was the first kind of medical imaging, and later ultrasonic imaging, CT scanning, MR scanning and other imaging methods became available. Genetics have advanced with the discovery of the DNA molecule, genetic mapping and gene therapy. Stem cell research took off in the 2000s (decade), with stem cell therapy as a promising method. Evidence-based medicine is a modern concept, not introduced to literature until the 1990s. Prosthetics have improved. In 1958, Arne Larsson in Sweden became the first patient to depend on an artificial cardiac pacemaker. He died in 2001 at age 86, having outlived its inventor, the surgeon, and 26 pacemakers. Lightweight materials as well as neural prosthetics emerged in the end of the 20th century.

Modern surgery

Cardiac surgery was revolutionized in the 1948 as open-heart surgery was introduced for the first time since 1925.
In 1954 Joseph Murray, J. Hartwell Harrison and others accomplished the first kidney transplantation. Transplantations of other organs, such as heart, liver and pancreas, were also introduced during the later 20th century. The first partial face transplant was performed in 2005, and the first full one in 2010. By the end of the 20th century, microtechnology had been used to create tiny robotic devices to assist microsurgery using micro-video and fiber-optic cameras to view internal tissues during surgery with minimally invasive practices.
Laparoscopic surgery was broadly introduced in the 1990s. Natural orifice surgery has followed. Remote surgery is another recent development, with the Lindbergh operation in 2001 as a groundbreaking example.

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