Man is mortal. He knows well enough that he will die some day. Still the desire to live as long as possible is always there. Diseases are our biggest enemies because they prevent us not only from enjoying a happy and healthy life but also cut short our stay on this earth.

A race has been going on between the diseases and scientific investigations. Most of the infectious diseases like tuberculosis, typhoid, malaria, infective hepatitis, tetanus, cholera, etc., which kills lacs of people every year in underdeveloped or developing countries, have been completely wiped off from the developed nations. However, these have gradually been replaced by heart disease, cancer and HIV infection which are now considered the biggest killers.

The art of medicinal chemistry - the science that strives to identify, create or modify molecules for therapeutic application - has enriched greatly from developments in the areas of organic chemistry, biology, biophysical/biochemical methods, and computational tools. While opportunities are enormous, advancing a drug candidate from bench top to clinic is associated with challenges as well, and a good understanding on both these aspects would significantly accelerate drug discovery process. Really, the unprecedented increase in human life expectancy, which has almost doubled in a hundred years, is mainly due to drugs and to those who discovered them.

History and evolution of medicinal chemistry

Medicinal chemistry's roots can be found in the fertile mix of ancient folk medicine and early natural product chemistry, and hence its name. As appreciation for the links between chemical structure and observed biological activity grew, medicinal chemistry began to emerge about 150 years ago as a distinct discipline.
intending to explore these relationships via chemical modification and structural mimicry of nature's materials, particularly with an eye toward enhancing the efficacy of substances thought to be of therapeutic value.\(^2\)

Just as in all fields of science, the history of medicinal chemistry is comprised of the ideas, knowledge, and available tools that have advanced contemporary knowledge. The spectacular advances in medicinal chemistry over the years are no exception. Burger\(^3\) stated that "the great advances of medicinal chemistry have been achieved by two types of investigators: those with the genius of prophetic logic, who have opened a new field by interpreting correctly a few well-placed experiments, whether they pertained to the design or the mechanism of action of drugs; and those who have varied patiently the chemical structures of physiologically active compounds until a useful drug could be evolved as a tool in medicine."

The nineteenth century age of innovation and chemistry

The nineteenth century saw a great expansion in the knowledge of chemistry, which greatly extended the herbal pharmacopeia that had previously been established. Building on the work of Lavoisier, chemists throughout Europe refined and extended the techniques of chemical analysis. The synthesis of acetic acid by Kolbe in 1845 and of methane by Berthelot in 1856 set the stage for organic chemistry. The emphasis was shifted from finding new medicaments from the vast world of plants to the finding of active ingredients that accounted for their pharmacologic properties. The isolation of morphine by Sertürner in 1803, of emetine from ipecacuanha by Pelletier in 1816, and his purification of caffeine, quinine, and colchicine in 1820 all contributed to the increased use of "pure" substances as therapeutic agents. The nineteenth century also contributed to the use of digitalis by William Withering, the English physician and botanist, for the treatment of dropsy. Niemann isolated cocaine in 1860 and the active ingredient, physostigmine, from the calabar bean in 1864. As a result of these discoveries and the progress made in organic chemistry, the pharmaceutical industry came into existence at the end of the nineteenth century.
The twentieth century and the pharmaceutical industry

Diseases of protozoal and spirochetal origin responded to synthetic chemotherapeutic agents. Interest in synthetic chemicals that could inhibit the rapid reproduction of pathogenic bacteria and enable the host organism to cope with invasive bacteria was dramatically increased when Domagk reported that the red dyestuff 2,4-diaminoazobenzene-4'-sulfonamide (Prontosil) dramatically cured dangerous, systemic Gram-positive bacterial infections in man and animals. The observation by Woods and Fildes in 1940 that the bacteriostatic action of sulfonamide-like drugs was antagonized by p-aminobenzoic acid, was one of the early examples in which a balance of stimulatory and inhibitory properties depended on the structural analogies of chemicals.

Together with the discovery of penicillin by Fleming in 1929 and its subsequent examination by Florey and Chain in 1941 led to a water soluble powder of much higher antibacterial potency and lower toxicity than those of previously known synthetic chemotherapeutic agents. With the discovery of a variety of highly potent anti-infective agents, a significant change was introduced into medical practice.

Developments leading to various medicinal classes:

Psychiatrists have been using agents that are active in the central nervous system for hundreds of years. Stimulants and depressants were used to modify the mood and mental states of psychiatric patients. Amphetamine, sedatives, and hypnotics were used to stimulate or depress the mental states of patients. The synthesis of chlorpromazine by Charpentier ultimately caused a revolution in the treatment of schizophrenia, but who really discovered chlorpromazine? Charpentier, who first synthesized the molecule in 1950 at Rhone-Poulenc's research laboratory; Simon Courvoisier, who reported distinctive effects on animal behavior; Henri Laborit, a French military surgeon who first noticed distinctive psychotropical effects in man; or Pierre Deniker and Jean Delay, French psychiatrists who clearly outlined what has now become its accepted use in psychiatry and without whose endorsement and prestige, Rhone-Poulenc might never have
developed it further as an antipsychotic. Because of the bitter disputes over the
discovery of chlorpromazine, no Nobel Prize was awarded for what has been the
single most important break through in psychiatric treatment.

The first pure hormone to be isolated from an endocrine gland was
epinephrine, which led to further molecular modifications in the area of
sympathomimetic amines. Subsequently, norepinephrine was identified from
sympathetic nerves. The development of chromatographic techniques allowed the
isolation and characterization of a multitude of hormones from a single gland. In
1914, biochemist Edward Kendall isolated thyroxine (T4) from the thyroid gland.
He subsequently won the Nobel Prize in Physiology or Medicine in 1950 for his
discovery of the activity of cortisone. Less than 50 years after the discovery of
oxytocin in 1904 by Sir Henry Dale found that an extract from the human pituitary
gland contracted the uterus of a pregnant cat. Biochemist du Vigneud synthesized
the cyclic peptide hormone. His work resulted in the Nobel Prize in chemistry in
1955.

Frederick G. Banting and Charles H. Best, working in the laboratory of John
J. R. McLeod at the University of Toronto, isolated the polypeptide hormone
insulin and began its testing in dogs. By 1922, researchers, with the help of James
B. Collip and the pharmaceutical industry, were able to purify and produce
animal-based insulin in large quantities. Insulin soon became a major product for
Eli Lilly & Co. and Novo Nordisk, a Danish pharmaceutical company. In 1923,
McLeod and Banting were awarded Nobel Prize in Medicine or Physiology, and
after much controversy, they shared the prize with Collip and Best. For the next 60
years, cattle and pigs were the major sources of insulin. In 1978, the biotech
company Genentech and the City of Hope National Medical Center produced
human insulin in the laboratory using recombinant DNA technology. By 1982,
Lilly's Humulin became the first genetically engineered drug to be approved by
the U.S. Food and Drug Administration (FDA).
Evolving drug discovery and development process:

Working definition for medicinal chemistry

A working definition simply states that medicinal chemistry uses physical organic principles to understand the interaction of small molecular displays with the biological realm. Physical organic principles encompass overall conformational considerations, chemical properties, and molecular electrostatic potentials, as well as distinctly localized stereochemical, hydrophilic, electronic, and steric parameters. Small molecular displays should be thought of in terms of low molecular weight compounds (e.g., usually less than 1 kg) that are typically of a xenobiotic origin and thus not in terms of biotechnology-derived polymers.

![Fig. 1: Nonlinear relationship of medicinal chemistry to basic and applied research](image)

The technologies that can be deployed as tools to study these interactions at medicinal chemistry's fundamental level of understanding are, by intent, dissociated from medicinal chemistry's definition. Presently, such tools include biotechnology-related methods such as site-directed mutagenesis, combinatorial chemistry methods, provided that the latter are coupled with knowledge generating structural databases, and long-standing synthetic chemistry manipulations that can be conducted in a systematic manner on either one of the interacting species in order to explore SARs. Finally, it should be appreciated that
this definition merges both the basic and applied natures of medicinal chemistry's scientific activities into a key mix of endeavors for which a new research paradigm (Fig. 1) has also been recently proposed as being a significant trend, even if potentially "dangerous" in that it could compromise the longer-term pursuit of fundamental knowledge by bringing applied science decision criteria into the funding programs that have previously supported pure, basic science.

The process of drug discovery

Inventing and developing a new medicine is a long, complex, costly and highly risky process that has few peers in the commercial world. Research and development (R&D) for most of the medicines available today has required 12-24 years for a single new medicine, from starting a project to the launch of a drug product (Fig. 2). In addition, many expensive, long-term research projects completely fail to produce a marketable medicine. The cost for this overall process has escalated sharply to an estimated US $1.4 billion for a single new drug. The funds to support this research usually come from the income of the private pharmaceutical company that sponsors the work. In research ('R'; discovery) phase, only a fraction of the scientific hypotheses that form the basis for a project actually yield a drug candidate for development. In the drug development ('D') phase, experience has shown that only approximately 1 out of 15-25 drug candidates survives the detailed safety and efficacy testing (in animals and humans) required for it to become a marketed product. And for the few drug candidates that successfully become marketed products, some will not recover their costs of development in the competitive marketplace, and only approximately one in three will become a major commercial product. Clearly, this is a high-stake, long-term and risky activity, but the potential benefits to the millions of patients with serious diseases provide a constant motivating force. At virtually every phase – from project initiation to discovery, development and planning for marketing for a new drug – modern medicinal chemist can have a role.
Stages in the drug discovery process

The drug discovery process begins with the identification of a medical need, including a judgement on the adequacy of existing therapies (if there are any). From this analysis, together with an appraisal of the current knowledge about the target disease, will come hypotheses on how to possibly improve therapy — that is, what efficacy, safety or mechanistically novel improvements will advance the method of drug treatment for patients with the target disease. On the basis of these hypotheses, specific objectives will be set for the project. Then, testing selected chemicals in appropriate biological tests can begin. Key subsequent steps in the process include detecting relevant biological activity (a 'hit') for a structurally novel compound \textit{in vitro}, then finding a related compound with \textit{in vivo} activity in an appropriate animal model, followed by maximizing this activity through the preparation of analogous structures, and finally selecting one compound as the drug development candidate. This drug candidate then undergoes toxicological testing in animals, as required by law. If the compound passes all these tests, all
the accumulated research data are assembled and submitted as an Investigational
New Drug Application (IND) to the Food and Drug Administration (FDA) in the
United States (or comparable agency in other countries) before clinical trials are
initiated. In the clinic, there is sequential evaluation in normal human volunteers
of toleration (Phase I), efficacy and dose range in patients (Phase II), followed by
widespread trials in thousands of appropriate patients to develop a broad
database of efficacy and safety. For the few (4-7%) drug candidates that survive
this series of development trials, a New Drug Application (NDA) that contains all
the accumulated research data is filed for thorough review by the experts at the
FDA. Only with their approval can the new drug be offered to doctors and their
patients to treat the disease for which it was designed.

**Drug metabolism:**

The human body is an example of an exquisitely designed, extremely
complex machine that functions day-in and day-out to allow for survival of the
organism in response to a never-ending onslaught of external challenges. When
one considers the enormous variety of environmental stressors to which the body
is continually subjected, it is not surprising to anticipate the existence of a
multitude of checks and balances associated with its physiological and
biochemical systems.

Humans are exposed throughout their lifetime to a large variety of drugs
and nonessential exogenous (foreign) compounds (collectively termed
“xenobiotics”) that may pose health hazards. Most drugs and other xenobiotics are
metabolized by enzymes normally associated with the metabolism of endogenous
constituents (e.g., steroids and biogenic amines). The liver is the major site of drug
metabolism, although other xenobiotic-metabolizing enzymes are found in
nervous tissue, kidney, lung, plasma, and the gastrointestinal tract.

Among the more active extrahepatic tissues capable of metabolizing drugs
are the intestinal mucosa, kidney, and lung. The ability of the liver and
extrahepatic tissues to metabolize substances to either pharmacologically inactive
or bioactive metabolites before reaching systemic blood levels is termed “first-pass
metabolism". Other metabolism reactions occurring in the gastrointestinal tract are associated with bacteria and other microflora of the tract. The bacterial flora can affect metabolism through the production of toxic metabolites, formation of carcinogens from inactive precursors, detoxication, exhibition of species differences in drug metabolism, exhibition of individual differences in drug metabolism, production of pharmacologically active metabolites from inactive precursors, and production of metabolites not formed by animal tissues. The pathways of xenobiotic metabolism are divided into two major categories.

**Phase I reactions (Biotransformations)**

This type includes oxidation, hydroxylation, reduction, and hydrolysis. In these enzymatic reactions, a new functional group is introduced into the substrate molecule, an existing functional group is modified, or a functional group or acceptor site for Phase II transfer reactions is exposed, making the xenobiotic more polar and, therefore, more readily excreted.

**Phase II reactions (Conjugation)**

These reactions are enzymatic syntheses whereby a functional group, such as alcohol, phenol, or amine, is masked by the addition of a new group, such as acetyl, sulfate, glucuronic acid, or certain amino acids, which further increases the polarity of the drug or xenobiotic. Most substances undergo both Phase I and Phase II reactions sequentially.

**New drugs for neglected diseases: From pipeline to patients:**

In wealthy countries, state-funded research has yielded breakthroughs in molecular biology, chemistry, and engineering. These advances have been taken up by the pharmaceutical industry and applied to drug development for a growing range of illnesses and conditions. As a result, patients have access to new drugs that are better tolerated, more specific, and more effective than old ones. In poor countries, however, millions of people have yet to experience the benefits wrought by science.
The deadly infectious diseases that plague them, such as sickness, Chagas disease, and visceral leishmaniasis, failed to arouse the interest of drug developers. The Drugs for Neglected Diseases Initiative (DNDi) is a new, Not-for-Profit organization set up to correct this fatal imbalance by developing new drugs for these forgotten patients.

Dropped off the radar screen

Most of the drugs still used to treat 'neglected diseases' were developed in colonial times. These are often expensive, difficult to administer, and hard to tolerate; several of them are also becoming ineffective because of increasing parasite resistance. Very few new alternatives have been developed in the past decades: between 1975 and 1999, 1,393 new drugs were made available to the public, but only 16 of these were meant for neglected diseases.7

The wealth of knowledge generated in this field could easily be used for drug development if the treatment of neglected diseases were perceived as
financially attractive. But populations affected by neglected diseases have no purchasing power, so there is no financial incentive for drug companies to develop the drugs. The basic mechanics of the market-driven system are failing to help these populations. So most scientific research stops at the publication stage or falls through the gaps at different stages of the drug development pipeline (Fig. 3). In the pipeline three gaps can be seen.

   **Gap 1:** Basic research is published but preclinical research is not considered worthwhile.

   **Gap 2:** Validated candidate drugs don't enter clinical development because of profit-based company choices.

   **Gap 3:** Drugs never reach the patient (registration problems, lack of production, high prices or drugs poorly adapted to local conditions).

**Practice of medicinal chemistry (MC) in the new millennium:**

The most striking differences from the longstanding practice of MC are:

(i) Data reduction of huge amounts of rapidly derived HTS biological results,

(ii) Greater emphasis upon multitechnique chemical structure considerations, and most importantly,

(iii) The simultaneous attention given to all of the ADMET-related parameters along with efficacy and efficacy-related selectivity (E/S) during lead compound selection and further design or enhancement coupled with an expanding knowledge base that offers the possibility for achieving synergistic benefits by taking advantage of various combinations of multi-agent, prodrug, soft drug, and/or multivalent drug strategies.

It should be clear that in order to effectively play this key, central role, medicinal chemist of the new millennium (Fig. 4) will have to remain well versed in physical organic principles and conformational considerations while also becoming even more adept at applying them within the contexts of each of the ADMET areas as has previously been done during medicinal chemistry's pursuit of distinct efficacy-related biochemical scenarios.
STUDIES ON CLINICALLY IMPORTANT HETEROCYCLIC COMPOUNDS

Biological information
- Pharmacological/Physiological
- Genomics, proteomic and molecular biology
- Biochemistry

Chemical structures
- Real and virtual compound libraries
- Wild and elicited natural products
- Random and directed combinatorial chemistry
* Rationally designed molecules (from below)

HTS Biological activity
Functional groups and physicochemical properties

X-Ray analysis/docking studies whenever amenable

Molecular conformation considerations based upon composite of techniques

Site directed mutagenesis studies
Computational analysis
Spectroscopic analysis, e.g. NMR, MS

SAR hypotheses or rationales encompassing:
- E/S pharmacophores
- Absorption, distribution and elimination patterns
- Metabophores
- Toxirnophores

Lead selection or drug design/enhancement and synthesis *

Decisions about single versus multi-agent therapeutic strategies including Prodrug, Soft drug and Multi-valent drug considerations for each participant

[Fig. 4: Practice of medicinal chemistry (MC) in the new millennium]
This central role for medicinal chemistry may become even more critical in long term, i.e., for the next 50 to 75 years of the new millennium. Speculating that the new drug discovery paradigm will indeed mature within the next 25 years into a synergistic merger of efficacy and thorough ADMET-HTS systems that allows for an effective multi-parameter survey to be conducted at the onset of the discovery process, the accompanying, validated predictive data that will have been generated over this initial period should be statistically adequate to actually realize today's dream of "virtual" or "in silico screening" through virtual compound and virtual informational libraries (not just for identifying potential efficacy leads to synthesize as is already being attempted, but across the entire preclinical portion of the new paradigm wherein the best overall preclinical candidate compound is selected with high precession for synthesis at the outset of a new therapeutic program).

The changing landscape of the pharmaceutical industry with respect to globalization:

Some basic questions about the new technologies and procedures now used for drug research, compared with the dwindling supply of new drugs approved in recent years, have been raised in recent news articles.\textsuperscript{9-12} For example, has the introduction of major changes in the drug discovery process caused the obvious drop in new drug output? Is this drop temporary, to last only until the new technologies begin to yield some products? Have the changes produced a decrease in output by stifling the creativity of the scientists (including the medicinal chemists) involved in drug discovery? Has the role of serendipity, so important to drug discovery in the past, been supplanted by robots? What has happened to the role of the medicinal chemist's intuition and creativity in producing quality drugs? How many of today's most successful drugs could have been made through the limited chemical pathways offered by combichem techniques? Making millions of new chemicals robotically does not, apparently, lead to more new drugs.
Today, the rapidly expanding knowledge base concerning diseases, their causes, symptoms and their effects on the human body holds great promise for the discovery of important new medicines. Sequencing the human genome also offers an opportunity for finding many more novel and selective therapies. Such discoveries will probably come from teams of scientists, including medicinal chemists, whose careers are devoted to this one task. The enormous cost of this task will be borne mainly by those pharmaceutical companies that can successfully generate the required research funds from the sale of their existing drugs.

Medicinal chemists today live in exciting times. They are key participants in the effort to produce more selective, more effective, and safer medicines to treat the diseases of mankind. Their work can have a beneficial effect on millions of suffering patients — surely an important motivating factor for any scientist.