THE EVOLUTION OF MEDICINE AND THE FUTURE DIRECTION OF MEDICAL SCIENCE

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"The philosophies of one age have become the absurdities of the next, and the foolishness of yesterday has become the wisdom of tomorrow"
-Sir William Osler, 1902.

Through the years, medicine has transcended from being synonymous with magic, to the biotechnological age and the possibilities of personalized healing. The evolutionary process has been gradual, and many of the significant milestones in the art of healing were accomplished only in the last century. Global uniformity in healing practices has been achieved through the creation of pharmacopoeial standards for drugs and technological breakthroughs in medical procedures. At the core of these advances, is the development of the rational approach to the cause of disease, based on observation, analysis and sustained scientific research.

Although archeological findings unraveled the evidence of diseases in prehistoric times, we do not have much knowledge of how they were treated. The mummified remains of Oetzi the Iceman who lived 5300 years ago, found in the Alps, revealed that he had used the fungus *Piptoprus betulinus* to treat an intestinal parasite[3]. The fungus contains oils that are toxic to worms, and have antibiotic properties, indicating that ancient humans did adopt effective therapies for common ailments. However, it is believed that prehistoric humans generally attributed the occurrence of disease to the wrath of evil spirits and no symptomatic records are available, since the written word was unknown at that time.

From potions to vaccines [1,2]:

Ancient civilizations such as the Egyptians and the Greeks, attempted to provide a rational explanation for the cause of diseases. The development of the art of writing, in ancient Egypt, enabled recording symptoms and cures for various ailments. Egyptian physicians also developed expertise in medicine, surgery and anatomy. However, the diseased state was still attributed to spiritual rather than somatic causes.

A similar evolutionary pattern occurred in ancient Greece. The libraries of Alexandria carried works by philosopher scientists such as Hippocrates and Aristotle that provided rational explanations for various events and analyzed the causes and associations that precipitated disease. Hippocrates, known in

Western civilization as the “Father of Medicine” believed that diseases were not caused by demons or spirits but rather by an imbalance of the humors or fluids in the body. During the same period, the cult of Asclepios, the Greek god of healing, pioneered advances in medicine in which practical treatment was combined with spiritual and supernatural placation.

In the Roman civilization, the physician was given less importance as compared to preventive measures and public health systems to reduce the incidence of diseases. The “science” behind these systems was based on supernatural ideas, a primitive concept of “germs” and the theory of “humors” as propounded by Hippocrates. Physicians such as Galen were acclaimed for their knowledge of human anatomy and physiology and set the trend for several centuries to come. However, as no formal training in medicine was required, quacks too had a field day. To support the needs of the casualties of war, the Romans built hospitals and perfected the art of surgery. The major contribution of the Roman civilization to medical science was the concept of disease prevention.

Traditional systems of medicine such as Ayurveda and Chinese Medicine, evolving in the East, compiled treatises on diseases, their causes and symptoms, and developed healing practices based on the “mind – body” approach. The therapeutic regimen included herbs, lifestyle interventions and spiritual practices to restore the balance of forces in the diseased system.

During the Middle Ages in the West, medicine as practiced by the classical philosopher physicians largely lost its respect and was replaced by superstition, “magic potions”, the “philosopher’s stone” and elixir vitae of the alchemists. The public health and hygiene practices set by the Romans, were no longer emphasized, largely due to the indifference of the monarchs that ruled the West. Healing became the prerogative of the church, which maintained libraries and trained practitioners using Galenic concepts that were often wrong. Herbal remedies became popular, along with physical measures such as blood letting and purging.

The Renaissance period brought great advancement in science, although not much of this knowledge was applicable to medicine. For example, although the microscope was invented, it was not powerful enough to discover microorganisms as the cause of disease, and although great strides were made in the study of human anatomy, the science of chemistry was not advanced enough to enable elucidation of various processes in the human body. However, rudimentary research on herbal remedies was documented, for example, the efficacy of white willow bark in easing pain and fever.

Major breakthroughs in medical science were achieved in the nineteenth century when Pasteur established microorganisms as the cause of several diseases. Surgical techniques saw advancement due to improved capabilities to manage pain (anesthetics such as chloroform), infection (antiseptics such as phenol) and the problem of blood loss (through transfusion). Public health and hygiene were once again emphasized and Western medicine saw more advances in this single century than in the previous 2000 years. Herbal remedies were widely used and chemists began to research these herbs for active constituents with a view to develop nature-identical molecules in the laboratory and new products that would eliminate the side effects associated with certain herbal treatments. One of the major breakthroughs in this regard was Aspirin, developed as an analgesic and antipyretic in 1899. Other herbs such as the opium poppy, yielded a number of pain relievers including morphine, codeine and heroin.

The microbial theory of disease took medicine from empiricism to the era of pharmaceutical science and the development of immunologicals and vaccines to prevent infectious diseases. This development also initiated the practice of standardization and testing of therapeutic agents, to ensure safety and consistency. Life expectancy rose from 40 to 50 years

The Century of Pharmaceuticals:

The twentieth century saw the most rapid developments in medical science[1,2] and established that disease could be turned around by appropriate treatment. This was a new concept considering that from the time of the Greeks to the early 1900s, all that a physician could do was to administer palliative therapy and offer comfort to the patient till the disease completed its course. In 1909 the first "magic bullet", Salvarsan 606, was discovered as a cure for syphilis and set the stage for chemotherapy, only to be later labeled a double-edged sword on account of its toxic, arsenical nature. Sulphonamides that cured many infectious diseases including pneumonia, formed the next generation of chemotherapeutic agents in 1932. Penicillin was discovered in 1929, and by 1943 it was a commercial drug, active against a wide variety of bacteria. The antibiotic age had begun.

The quest for disease cures and longevity triggered intensive research into developing pharmaceutical drugs that addressed previously "incurable" conditions such as heart disease, cancer and diseases of neurological or genetic origin. By the end of the 1950s, medical science catapulted to the technological age with new diagnostic, analytical and production tools including chromatography, X-ray diffraction, computers, imaging techniques and tissue culture. Additionally, advances in basic scientific research facilitated a greater understanding of the human body and the life processes therein. The elucidation

of the structure and function of DNA provided vital clues to the advancement of medicine. Physiology-based medicine came to the forefront with the research on hormones and vitamins in the 1920s and 1930s. This trend continued into the antibiotics era of the 1940s, setting the platform for biotechnological advances in medical science that pervaded the last two decades of the century.

The sixties saw technological breakthroughs and the advent of several new drugs including oral contraceptives, anti-depressants and blood pressure lowering agents, along with social upheavals and the problem of drug abuse. The 1970's heralded the war on cancer, saw the eradication of a major scourge, smallpox and launched intensive global immunization campaigns against diseases such as polio, tetanus, diphtheria, whooping cough and tuberculosis. Newly emerging diseases such as AIDS, Ebola and Legionnaire's disease as well as the recurrence of old diseases attributed to antibiotic resistant strains, triggered intensive research into diagnostics and potential drug candidates. Environmental health came into focus with the discovery of the link between pollutants and certain forms of cancer. The need for better analytical tools led to further advances in biotechnological research.

A milestone in advanced analysis and separation procedures was the development of high-pressure (later called high-performance) liquid chromatography (HPLC) which enabled rapid separations of macromolecules into pharmacologically active fractions. Radioimmunoassay procedures, radiotracer techniques and advancement in tissue culture, enabled faster drug development through facilitated *in vitro* testing. The drugs developed ranged from biological molecules to sophisticated synthetic drugs including chiral compounds. Plant based anti-cancer drugs such as Paclitaxel (from the Pacific yew tree), Vincristine and Vinblastine (from the Madagascar periwinkle), and semi-synthetic derivatives from other plant chemicals came to be regarded as standard chemotherapeutic measures for a variety of cancers.

Recombinant DNA technology made it possible to produce biotechnology-based drugs such as human insulin and DNA vaccines. Novel drug delivery systems including liposomes, transdermal patches and controlled drug delivery systems enabled targeted drug delivery with enhanced bioavailability. The drug discovery process was further enriched technologically by advancements in techniques such as Fourier-transform ion cyclotron resonance (FT-IR-MS) and multidimensional spectroscopy. Advances in computer technology enabled viewing protein structures three-dimensionally, thereby helping to discover safe and effective molecules that would bind to specific target proteins, for example, substances inducing apoptosis (cell death) in cancer cells.

Life expectancy rose to 80 years in the developed countries, by the end of the century. Along with the improved quality of life, the problem of obesity and its related complications such as diabetes and heart disease also came into focus. The final decade of the century saw renewed interest in traditional therapies and the concept of "integrated medicine" wherein several Allopathic medical practitioners also offered some form of complementary therapy. These included herbal remedies, techniques such as acupuncture, relaxation regimens and homeopathic medicines. A growing interest in preventive medicine provided greater impetus to scientific research on alternative therapies, particularly with regard to herbal remedies. A revolutionary trend was the increased acceptance of the concept of "food as medicine", which had been enunciated by Hippocrates centuries earlier.

Phytonutrients, minerals and vitamins with proven beneficial pharmacological effects termed "nutraceuticals" gained popularity in recent years. Formulated as dietary supplements and functional food products, these ingredients have scientifically validated health benefits. Dietary supplements can claim effects on the structure or function of the body, but they cannot claim to diagnose, treat, cure or prevent a disease. Common health conditions addressed by supplements include joint health, digestive problems, cholesterol levels, skeletal strength, hormonal imbalance, body fat, optimal vision, emotional problems, breast and prostate health and gender specific problems.

The Century of Biotechnology :

Advances in biotechnology are beginning to increasingly influence the course of medical science. Just as the microchip in the last century transformed the way we live, the mapping of genes is set to revolutionize medical science in the 21st century. In the words of the 1996 Nobel Prize-winning chemist Robert F. Curl of Rice University, the 20th century was "the century of physics and chemistry, but it is clear that the next century will be the century of biology."

The human genome project which aims at mapping over 100,000 genes, signified the first step in understanding humans at the molecular level. This set the trend for the development of the next generation of novel therapeutics, wherein an individual's genetic profile could be used to generate personalized medical treatment. Individuals respond differently to therapeutic modalities on account of genetic differences. Disconcerting evidence to this fact is provided by the fatalities associated with standard drug therapies, on account of individual variations in drug metabolism.

The pharmacokinetic and pharmacodynamic profiles of drugs are subject to individual variations. Pharmacokinetics pertains to the biological fate of drugs in

the body over a period of time, including the processes of absorption, distribution, concentration in various tissues, biotransformation and excretion; while pharmacodynamics describes the biochemical and physiological action of drugs in the body. Both processes are based on a series of events that are linked to the genetic framework, including the expression of specific metabolic enzymes and hormones, release or suppression of neurotransmitters and modulation of the physiological or psychological response.

Pharmacogenetics is essentially the convergence of the fields of pharmacology and genetics in relation to genetically determined responses to drugs. For instance, a patient administered a "safe" muscle relaxant during surgery could suddenly develop breathing difficulties, sometimes with a fatal outcome, due to inherent genetically determined differences in the way he metabolizes the drug. Pharmacogenomics has emerged as a sub-discipline that would help to develop new drugs to target a particular disease or provide the desired pharmacological action, while simultaneously reducing the likelihood of such adverse effects.

Single nucleotide polymorphisms (SNPs), a direct outcome of the Human Genome Project, are instrumental in the development of "smart drugs". More than 85% of genetic variability is estimated to occur due to single nucleotide base substitutions in gene sequences. These variants are known as single nucleotide polymorphisms, or SNPs. Pharmacogenomics assesses the link between SNPs and the therapeutic response in individuals, thereby leading to a better understanding of pharmacokinetics and pharmacodynamics, a reduction in adverse events related to pharmacotherapy and enabling the design of appropriate dose regimens.

Clinical pharmacogenomics imparts the required diagnostic elements that can be potentially applied to discover drug response markers, reduce the size and cost of clinical trials and provide a new tool for addressing drug approval issues. DNA microarray (DNA chip) technologies provide rapid and cost-effective methods of identifying gene expression and genetic variations. Such approaches enable the development of genotype-phenotype correlations (gene-disease, disease-drug and gene-drug). For instance, the antileukemia drug 6-mercaptopurine is known to have adverse effects at normal doses in some individuals with lower efficiency of the naturally occurring enzyme thiopurine methyltransferase, linked to genetic causes[4]. A blood test now enables the identification of this genetic variation, facilitating proper dosing of the drug to the susceptible individuals. Similarly, clinical studies on a number of anticancer drugs, active against a variety of cancers, including head and neck cancer, pancreatic cancer and solid tumors, based on genetic markers, are currently underway[4].

Toxicogenomics is a sub-discipline that assesses the safety of potential drug candidates at the gene level, using DNA microarray technologies.

Functional genomics encompasses a range of technologies aimed at establishing a functional relationship between a particular genotype and a given disease state. These technologies enable the identification of gene patterns that are up or down regulated in certain disease states and characterize the interaction of proteins in specific disease conditions.

Proteomics is the technological field that elucidates the functions of proteins expressed by genes, for application to drug discovery and pharmaceutical product development. The research tools used in proteomics include model organisms that are used to understand the role of specific genes and their products in disease onset and progression. The model organisms used include microorganisms, insects and animal models in which the effects of gene mutations (transgenesis) on normal development and health, and the expression of proteins can be determined. The study of protein expression, as well as protein structure and function, provides a broader perspective to understanding biology than the study of gene sequence or gene expression alone. Recent advances in the study of protein-protein interactions, quantification and comparisons of protein expression, the creation of proteomic databases for human and other cells, and the elucidation of protein functions, promise to accelerate the development of effective diagnostic and therapeutic products.

Bioinformatics is the discipline that provides computational tools required to Process genomic data. The flood of genomic information, from sequences and gene expression, to SNPs and protein structures, would be of limited value in the development of smart drugs without Bioinformatics. Bioinformatics includes computing platforms and data management systems that handle gene sequences and related information. Advances in the field of computing have yielded powerful software that enables rapid interpretation and comparison of such data, providing valuable tools to the drug discovery and development process.

Thus in the last decade of the century, biotechnology revolutionized the concept of diagnosis and treatment of disease through enabling the identification of novel drug targets that could be addressed with small molecules and antibody therapeutics.

Harnessing the future:

The immense significance of biotechnology is evident, in light of the morbidity and mortality currently associated with pharmacotherapy. Pharmaceutical drugs are reported to be the sixth largest cause of death in the USA[5]. Pharmacogenomics opens new avenues to removing the limitations inherent in

conventional pharmaceutical research and in standard clinical diagnosis and treatment practices. Conventional treatment strategies involve the trial-and-error approach, wherein "blind" chemical agents that do not target patients according to variations in genotype, which in turn affects drug response, are prescribed. A number of dose regimens therefore need to be evaluated before the optimal balance of therapeutic efficacy and safety is achieved. The doctor examines the patient, prescribes medication, then waits to see if there is an improvement. In 60% of the cases, no improvement may result, necessitating hospitalization of the patient due to side effects of the medication or inefficacy of the drug, both scenarios being attributable to genetic causes[6].

Pharmacogenomics enables matching drugs with specific "genetic handles" to the appropriate patient, from the beginning of the treatment process. A comprehensive database of genetically targeted drugs along with personalized medical cards that carry the patient's genetic information and medical history, provide the necessary tools for diagnosis and treatment. A futuristic "Physician's Desk Reference" would therefore contain information on the genetic match of those individuals best equipped to receive the treatment, in addition to the usual data on the chemistry, pharmacological action and side effects of the medication[6].

According to researchers, pharmacogenomics technology could begin to benefit patients as early as in the next five to six years. A newly developed technology helps to identify unique haplotypes (patterns of SNPs present in the DNA of every patient). A "genetic bar code" is produced by 13 to 15 of these haplotypes. This technology was validated in a recent study of asthma patients, in which the researchers found a clear correlation between clinical response to albuterol and haplotypes associated with the beta-2-adrenergic receptors expressed in bronchial smooth muscle. In another study, markers in multiple genes were shown to be responsible for 50% of the variability in drug response to commonly prescribed statins (HMG-CoA reductase inhibitors), which are used to lower elevated blood cholesterol levels. Genetic information which has much more predictive capabilities than conventional medical information, would therefore permit the development of a patient's response profile to a particular statin drug[6].

The promise of effective and safe treatments for conditions such as Parkinson's disease and the identification of specific drug targets for commonly encountered diseases such as atherosclerosis and diabetes appears to be tangible. For example, gene therapy using the gene that encodes aromatic amino acid decarboxylase (AADC), has been shown to effect significant recovery from Parkinson's disease[7]. MMP-8 (matrix-metalloprotein 8) a collagenase enzyme

expressed in atherosclerotic plaques, is being researched as a likely target for the treatment of cardiovascular disease[8].

Recent studies point towards genetic predisposition to diabetes, which is more widely prevalent in certain ethnic groups including Native Americans, Hispanics, African Americans and Asian Americans in the US. A study on Mexican –Americans revealed that the presence of specific variations in one gene resulted in a three fold increase in the risk of diabetes. Calpain-10, a protein associated with this gene has been shown to be involved in glucose regulation[9]. More recent studies provide the link between obesity and the development of Type 2 diabetes. Researchers identified a mechanism that helps explain how the hormone leptin (originally termed the "satiety signal"), is involved in the metabolism of fatty acids in muscle. A novel molecular link between obesity and diabetes is thus indicated, suggesting the possibility of a new target for the development of drugs that would help manage both conditions[10].

Advances in the fields of molecular biology, combinatorial chemistry and robotics have revolutionized the process of drug discovery. In traditional pharmaceutical research, compounds were prepared and screened one by one for efficacy. Current advances in technology make it possible to screen several potential drug candidates simultaneously. In the field of antibiotics for example, the classical approach involved testing large libraries of potential antibacterial compounds for efficacy against various infective agents. Due to the uncontrolled use of antibiotics, the problem of encountering resistant strains looms large. The current approach is to identify specific bacterial targets such as enzymes that pose a requirement for, or contribute to susceptibility *in vitro*. The bacterial metalloenzyme PDF (polypeptide deformylase), an enzyme involved in bacterial protein biosynthesis is one such example. The gene encoding this enzyme is present in all sequenced pathogenic bacterial genomes and protein synthesis in eukaryotic organisms does not involve the formylation-deformylation reaction. Based on this, PDF is a potential target in the discovery of novel broad-spectrum antibacterial agents that are free from established resistance mechanisms[11].

"The same object will both wound and cure me", a 2000 year old quote from Ovid, is often applied to prescription medicines. Medical science in the 21st century is all set to dispel this notion. The promise of personalized medicine that predictively addresses the genetic roots of conditions such as Alzheimer's disease, Huntingdon's disease, multiple sclerosis, a wide range of cancers and other debilitating diseases appears to be close at hand. Such an approach would help eliminate the possibility of negative individual response to specific therapeutic regimens. Additionally, technological advances such as tissue regeneration techniques and stem cell research have made rejuvenative and

regenerative therapies a biological reality. Perhaps the quest for the fountain of youth is no longer a pipe dream.

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