From Genesis to Genes+

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Abstract

Since the beginning of time, our ancestors have been plagued by illnesses and injuries that are not too different from today's diseases. Evidence from prehistoric times and ancient civilisations have shown man's attempts at trying to understand the nature and treatment of these conditions. It was not till the early 19th century that the scientific basis of modern medicine was firmly established when micro-organisms were discovered and found to be the cause of many of these illnesses. The 20th century saw quantum leaps made in the understanding of the function of the human body and the therapeutic measures aimed at restoration of any such malfunction. The end of the last millennium was marked by historic achievements made in the Life Sciences, in particular the completion of the sequencing of the Human Genome – the code of life. The beginning of the 21st century has already seen many breakthroughs in medical sciences, especially in the fields of stem cell technology and gene therapy. The number of known illnesses directly related to genetic defects or abnormalities have increased exponentially. Many of today's scourges can be prevented or more effectively treated. Our ability to utilise this new knowledge to combat the ravages of the ageing process and its associated illnesses – degenerative diseases and cancers offer much hope for the future.

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I would like to thank the Singapore Orthopaedic Association (SOA) for inviting me to deliver this year's SOA lecture. When your President, Dr AK Mitra first asked me to deliver the lecture, I felt deeply honoured but was rather hesitant about accepting it – honoured as this annual lecture is normally reserved for an eminent international speaker and hesitant because I felt that I do not qualify as one. Having accepted the invitation, I spent several months agonising over the topic that I should speak on, knowing that I would be addressing a very distinguished audience this evening. I finally chose this title to reflect the tremendous progress Medicine in general and Orthopaedics in particular has made since the beginning of time. I therefore ask for your indulgence and would like to begin with a quotation from the Book of Genesis:

> *"So the LORD God caused a deep sleep to fall upon the man (Adam), and while he slept took one of his ribs and closed up its place with flesh; and the rib which the Lord God had taken from the man he made into a woman …… "*

Ladies and gentlemen, "live bone transplantation" has been performed since the beginning of time and under 'anaesthesia' too.

Even in prehistoric times before the appearance of modern man, diseases have plagued our ancestors. Archaeological digs have revealed evidence of diseases similar if not identical to that which is still plaguing us today. Bone tumours in Homo Erectus and tuberculosis of the spine in Neolithic man (7000 to 3000 BC) have been found in the fossilised bones of our ancestors.

Attempts at healing injuries and diseases showed that medical practice existed even in prehistoric times. Trephined skulls dating back to the Neolithic period indicated that our forefathers had probably attempted to drain blood or pus from intracranial lesions, a practice not too different from current day neurosurgical practice. That these patients survived is evidenced by the smooth rounded edges of the trephine hole.

Earliest recorded evidence of medical treatment among primitive tribes indicated that illnesses were regarded as punishments by gods, and magic spells cast by spirits. Treatment involved magic, religion and other acts and ceremonies performed to appease the spirits. The 'doctor' or medicine man administering treatment often occupies a high social position within the tribe – often the chief or priest.

The ancient civilisations of Mesopotamia, India and China have well documented treatises of diseases and their methods of treatment. Mesopotamian cultures view illnesses as a curse or punishment brought upon persons who have

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violated moral or ethical codes. Cosmology plays a central role in the interpretation and treatment of illnesses. Mesopotamian healers depended on divination to discover the "sins" committed and treatments were aimed at appeasing the gods. Methods consisted of recitations, prayers, ceremonies and sacrifices. Plants, minerals and animal products were often used. References were made to bronze instruments that indicate the use of surgical procedures. Trephined skulls found supported this.

Ayurvedic (knowledge of Life) medicine, the ancient Indian traditional art of healing was based upon sound, rational practices although not completely free of mystical, magical and religious associations and cosmology. Illnesses were thought to be retributions by nature. Their diagnostic methods include patient scrutiny and body fluids examination. They have compiled a voluminous pharmacopoeia for treatment. Some of these have found their way into modern pharmaceutical practice e.g. their use of the plant rawaulfia serpentina used to treat headache, anxiety and snake bites have found their modern counterparts using the purified extract reserpine to treat hypertension. Surgical remedies were known and procedures of amputations were part of regular practice with delicate instruments by the doctor. The practitioners were required to observe a code of ethics, very similar to the Hippocratic Oath.

Ancient Chinese Medicine dates back to many thousands of years. It stresses the importance of health maintenance and disease prevention and involves the interplay of the basic duality of *Ying* (cold and negative) and *Yang* (warm and positive). The objective of treatment is to try and achieve a balance of these 2 forces – a harmonisation of natural forces to maintain health and to bring patients back to health from illnesses. Early Chinese medical writings and documentation were impressive. Examples are a 30-volume pharmacopoeia known as *Chien Chin Yao Fang* (a thousand remedies), *Nei Ching* (Canon of Medicine) and a 50-volume codification of Pathology often referred to in Medical jurisprudence during the Sung Dynasty.

Although surgery was not known to be used commonly in ancient Chinese medical practice, records have shown that physicians do use surgical techniques in their practice. The famous surgical extraction of an arrow and the subsequent debridement of the underlying bone of the humerus from the arm of a general by the famous physician Hua T'o whilst the general drank wine and played chess bears testimony to their surgical skills. Perhaps the Chinese have also discovered the anaesthetic effects of alcohol. In addition, traditional Chinese manipulations for the treatment of fractures, dislocations and sprains were widespread even before the advent of modern orthopaedics.

Perhaps the best known name in modern Medicine, both by the profession and the lay public, is that of Hippocrates. Hippocrates lived from 460 BC to 370 BC. He is best known for laying down an ethical code of practice – the Hippocratic Oath for physicians. His lesser known writing is perhaps more important – the Corpus Hippocraticum or the Hippocratic Collection. The most famous and thorough portion in this Collection is the surgical part. Amongst its various surgical prescription is the part on the treatment and reductions of dislocations and fractures of bones and joints. Many of us will still remember and occasionally employ the Hippocratic method of reduction of the dislocated shoulder.

The scientific basis of Modern Medicine was established in the early 19th century. This was brought about by 2 important developments – the use of anaesthesia and the discovery of micro-organisms as the causation of many illnesses. Other developments, which helped to put this on a firm basis, included understanding the structure of and function of the living organism, the science of physiology and the introduction of new diagnostic tools into clinical methods.

The birth of orthopaedic surgery as a distinct specialty can be traced to the mid 18th century, although treatment of musculoskeletal diseases and injuries were undertaken by general physicians and surgeons long before this. The term "Orthopaedics" takes its origin from the Greek words "orthos" which means straight or to straighten and "paidea" – the rearing of children. Nicholas Andre, Professor of Medicine at the University of Paris coined this in 1741 when he attempted to treat children's deformities by trying to 'straighten' them. These were conditions like scoliosis, tuberculosis of spine and joints, poliomyelitis and other childhood deformities. The illustration of his treatment methods by the use of a staff to straighten a bent growing sapling is now the international insignia of orthopaedic societies. It was not until the dawn of the 20th century that significant progress was made in this specialty, helped by the discovery of X-rays by Wilhem Konrad Roentgen. Up till then, most orthopaedic treatments were mechanical using splints, braces, plaster casts and manipulations. Fractures of the hip were considered untreatable. Many of you may be interested to know that the first cadaveric total knee transplantation was done by Erich Lextor in 1908, although it never really took off because of the complications associated.

Modern medicine came to Singapore 2 years after Raffles landed. The British East India Company established a medical outpost in 1821 in a wooden shed situated at Bras Basah Road to treat their own soldiers as well as locals – this is the humble beginning of modern medicine in Singapore. Within a short space of just over 180 years, modern medicine in general has made quantum leaps towards improved patient care and outcomes. We are proud of these achievements.

Orthopaedic Surgery in Singapore dates back to the pre-war era. Then it was practised as part of General Surgery dealing mainly with fractures and other limb injuries. As experience and interest grew, many were encouraged to take up the specialty and work was extended to other prevalent conditions like spinal and joint tuberculosis, pyogenic osteomyelities, poliomyelitis, scurvy and ricketts. As interest and work expanded, young surgeons were sent overseas for training.

1951 marks a watershed year in the history of orthopaedic surgery in Singapore. The chair of Clinical Surgery in the then University of Malaya (the predecessor of the current NUS) was converted into the chair of Orthopaedic Surgery. Prof JAP Cameron was appointed as the first Professor of Orthopaedic Surgery. The importance of Orthopaedic Surgery in the healthcare scene of Singapore was reflected by the rapid development of the specialty. The second department – the government department of Orthopaedic Surgery was established in 1956 with the appointment of Mr DWR Gawne at the helm. Those of you who are of my vintage will fondly remember this as the “O” unit of the Outram Road General Hospital.

The 2 departments were in the throes of trying to manage and contain 3 major groups of illnesses that account for a significant amount of morbidity and mortality – infection, severe congenital musculoskeletal deformities and trauma.

Poliomyelitis was rife and many unfortunate children were afflicted with it – maiming them for life. Even today, you can still see the scars of this group who are now in their 50s and 60s. We can be justly proud of the bold step taken by our predecessors in wiping out the disease through mass vaccination with the Sabin vaccine against conventional wisdom of the West then. In retrospect, this is a right move.

Pyogenic osteomyelitis, septic arthritis and tuberculosis of bones and joints especially in children were rife and widespread from neglect of open wounds, inadequate treatment and complications arising from treatment by unqualified practitioners and poor housing, nutrition and sanitation. Wards at the Singapore General Hospital (the only hospital in those days to have an orthopaedic service) were filled with such patients. Severe congenital conditions like osteogenesis imperfecta, congenital bands and other skeletal deformities were common. Such conditions were well recognised clinical entities but not much could be done in the way effective treatment nor prevention as their genetic basis were not well understood.. The introduction of modern surgical techniques, effective antimicrobials and other prophylactic measures as well as improved nutrition, housing and sanitation also helped to reduce and control such conditions from assuming epidermic proportions. These conditions are fortunately rarely seen today.

The rapid industrialisation of the 60s and 70s and the marked increase in the number of motor vehicles on our roads and highways saw a dramatic rise in the incidence and severity of musculoskeletal injuries. Limb amputations, fractures and severe crushing injuries were common and often sustained at the workplace, on the roads and at home. Many of the factories and other workplaces in the early years of our industrialisation programme had no proper safeguards to protect workers against mutilating injuries. Such severe injuries often caused workers to be maimed and crippled for life.

1962 also marked a significant milestone in the history of Orthopaedic Surgery. Sir John Charnley and his team at Wrightington in the UK introduced the use of low friction total hip arthroplasty for the treatment of crippling osteoarthritis of the hip. This has changed the prognosis and the outcome of treatment for such conditions dramatically. The quality of lives for these patients have improved significantly. These principles were also applied to total knee arthroplasty with comparable excellent outcomes.

Another milestone was made in the early 70s, especially in hand surgery. The introduction of the operating microscope in orthopaedic practice has enabled successful replantation of amputated fingers and hands. This was subsequently applied to reconstructive procedures following major tissue resection. It has not only enhanced functional outcomes for such patients but has also opened up an entire new front in the field of reconstructive surgery. Major tumour resection with limb salvage enables many patients to achieve cures with good functional preservation, enabling them to live a near normal lifestyle and quality of life. This is the gold standard treatment today for early osteosarcomas and other limb malignancies.

The 80s and early 90s also saw rapid advancement in the field of spine arthroscopic surgery. Better understanding of the biomechanics and functional requirements of the spine, together with new and better implants, have resulted in excellent treatment outcomes in severe scoliosis, unstable degenerative spondylosis and spinal trauma. The use of fibreoptic and imaging technology allowed surgeons to view, diagnosed and treat intra-articular injuries and other joint derangement endoscopically without having to resort to open surgery. Patients have less postoperative pain and morbidity and often these are done on an ambulatory basis.

Towards the end of the 20th century, the rapid progress made in the fields of Cell and Molecular Biology and Biomedical engineering began to impact the practice of Orthopaedic Surgery. The discovery and isolation of chemical mediators in the causation of and perpetuation of diseases marked turning points in our relentless fight against debilitating diseases. The finding of the association between autoantibodies and complement and mast cells in the pathogeneis of severe arthritis in rats has significant implications in our ability to prevent or control disabling arthritis. Similarly, the astute observation by *Marshall Urist* on the catalytic effect of bone marrow elements on fracture healing has led to the discovery, isolation and synthesis of BMP7. This has helped surgeons in treating problematic fractures. How this worked was not known until recently when it was established that BMP7 attracts and differentiate stem cells (found mainly in bone marrow and cancellous bone) into osteoblasts and osteoctyes, aiding the healing of fractures. Another important implication of the discovery of BMP was the observation that BMP2 is found to be associated with osteosarcomas and this can be used as a tumour marker in monitoring results of treatment of this malignancy.

Progress was also made in the field of material science, in particular bio-materials used in human organ and tissue replacement. Together with better understanding of the complex function of human joints and kinematics, we are witnessing quantum improvements in adult reconstructive joint surgery – new prostheses giving such crippled patients a new lease of quality life and the ability to survive longer. With improved surgical technique and introduction of new technology, results have been greatly enhanced. An example is that of computer aided minimally invasive surgery for knee and hip replacements. This not only allows to the surgeon to accurately align the prosthesis without too much eyeballing, but is also less traumatic to the patient and hence less associated morbidity. Hopefully, this will translate into shorter hospital stay.

The 20th century ended with orthopaedic surgery well positioned to take a quantum leap into the new millennium. However, the scenario for surgeons has also changed. Changing population demographics, disease trends and patient expectations required them to accept paradigm shifts in orthopaedic practice. We are dealing with an increasingly ageing population who will be exposed to increased risks to their musculoskeletal system. Easy access to information and their better educational background will also mean much higher (and sometimes unreasonable) expectation from their doctors. The cost of treating this will continue to escalate.

Realising this, the United Nations has endorsed the motion to designate the decade of 2000 to 2010 as the Bone and Joint Decade and the WHO formally launched this at its headquarters in Geneva on 13 January 2000. Its mission is to improve the quality of life for people with musculoskeletal conditions and to advance the understanding and treatment of those conditions through research, prevention and education. Though seldom realised, as heart diseases and cancers tend to overshadow them, musculoskeletal conditions are the greatest cause of severe disability worldwide. They consume a very large part of every nation's health budget. In the US, arthritis affects 50% of people over 65 and 40% of all women above the age of 50 are expected to suffer from at least 1 osteoporotic fracture. Treatment of these accounts for over US$215 billion. in healthcare costs and loss of productivity. With most countries' population ageing rapidly, this problem will only deteriorate. In addition, road traffic and other accidents contribute to this. It is estimated that by the year 2010, it will account for about 25% of all healthcare expenditure in developing countries.

On the other hand, the quantum leaps made in technology and the life sciences holds promise of hope and a better life for these patients. The unraveling of the code of life – the *Human Genome* in June 2000 has and will continue to revolutionise the practice of Medicine. We are barely 2 years into the 21st century, but already there are signs and indications that this millennium will see a totally different world from that of the last century. The frontiers of medicine have never looked more promising. What was once deemed to be in the realms of science fiction is now not only possible but probably within reach over the next few years.

The association of abnormal genes and diseases has long been recognised but its significance is still not fully realised. The mere presence of an abnormal gene does not necessarily confer a disease state on that person. Even the definition of the term disease is still not universally agreed upon. Writing in the *Science* journal, Larissa and Gallinger from Toronto define disease as a state that places individuals at increased risk of adverse consequences. Genetic variation (genotype) plays an important but not absolute role in translating such variations into visible characteristics (phenotype).

Nevertheless, the number of diseases shown to be associated with genes had increased markedly over the years and will continue to do so in the post-genomic era. It is thought that a large number of diseases can be traced to specific locations on the DNA chain of the human chromosome. The environment influences their phenotypic expressions. This has implication on the diagnosis, treatment and prognosis for these diseases.

A recent discovery at the Stanford University School of Medicine has excited many orthopaedic surgeons and rheumatologists. A team of researchers in the Department of Developmental Biology found that in a mutant strain of mice known as ank, a mutation in chromosome 15 led to the development of a form of ankylosis, fairly similar to the severe debilitating human form of ankylosing spondylitis. On further probing, they zeroed it down to a 150000-base pair stretch of the DNA in chromosome 15, containing 11 genes (called progressive ankylosis ank locus).

The human AS equivalent form is about 98% identical to this in chromosome 15. What is more interesting is that this locus is absent in invertebrates, i.e. animals that do not have a bony skeleton (hence no joints). Translated this at the cell and molecular level, it was discovered that such mice exhibit a reduced ability of the chondrocytes in the articular cartilage of the joints to pump pyrophosphate into the extra-cellular compartment. This resulted in cartilage reduction, stiffening of the joints and formation of bony spurs known as osteophytes – all classical manifestation of arthritis and ankylosing spondylitis in man. Such discovery surely offers hope to human sufferers; as the next step forward would be to genetically mainpulate this locus in chromosome 15.

The rapid advancement made in stem and progenitor cell technology has opened up vast new possibilities and opportunities for the orthopaedic surgeons of the 21st century. A biological autograft grown from ones' own stem cell onto a customised computer aided and designed joint scaffolding will allow joint replacement without its current associated complications. Recent developments in third generation biomaterials that are cell- and gene-activating materials, designed not only to be bio-absorbable but are able to attract and stimulate progenitor cells to grow on them, holds great promise in this direction. Work on this by *Gough* from the Imperial College have shown that such materials (e.g. 45S5 monolith and 58S foam) are able to genetically control and activate osteoblasts to grow rapidly on them.

Recent work on co-axing stem cells, to differentiate into neurons in vivo in laboratories and on experimental animals, has produced results which appear most promising. In other laboratory experiments, researchers working with growth inhibitors blockers manage to make paralysed rats walk. Extrapolated, all these offers much hope for crippled and paralysed patients stricken with debilitating neurological disorders like Alzheimer's disease, Parkinson's disease and spinal cord injuries.

The discovery that a number of cancers are associated with genomic instability, telomere dysfunction and p53 gene inactivation also offers hope for musculoskeletal cancers like osteosarcomas. Our future ability to control such conditions through genetic manipulation and gene therapy will mean more effective treatment without the mutilating and debilitating effects of surgery and chemotherapy of today. In an interesting experiment, Jain et al from Stanford University School of Medicine engineered a conditional transgenic mouse to over-express the *myc* oncogene (a multiple oncogene) which induced the formation of a highly malignant osteosarcoma. By briefly suppressing one of the oncogene, they are able to cause the tumour cells to differentiate into mature osteocytes, forming histologically normal bones or apoptosis (cell death). Subsequent reactivation of the oncogene does not reactivate the malignant process but also induces apoptosis (cell death).

Conclusion

Orthopaedic surgery in the 21st century will see significant changes brought about by scientific discovery and advancement in technology. The quantum leaps made in the life sciences, research and developments in biotechnology and information technology have changed the entire scenario. I believe that many of today's musculoskeletal diseases can be prevented or more effectively treated, as we understand better the cellular and genetic basis of these diseases. The surgeon of tomorrow must not only be a master of surgical skills but a scientist, engineer and, most important of all, a compassionate doctor.

We have come a long way from our humble beginnings. Many of the concepts, beliefs and treatment methodologies of our forefathers may appear to us as crude or even ludicrous in view of present day knowledge and understanding of the science of life. However, it will serve us well to remember that:

> *"We enter the future facing backwards, seeing only the road on which we have just traveled. We will do well to view today's Medicine as merely a marker between the past and the future"*
>
> Lyons Petrucelli

I am certain that what we do and believe in today will be viewed equally with amusement by tomorrow's generations of surgeons.

However, lest we forget, no matter what and how much changes Medicine has and will undergo the most important thing that should not and must not change is that of the interests and wellbeing of our patients. I would like to end by quoting a verse from Moses Maimonides, a 16th Century physician from his Prayer of a Physician:

Endow me with the strength of Heart and Mind
So that both may be ready to serve
The rich and poor, the good and wicked
Friend and enemy
And may I never see in the patient
Anything else but a fellow creature in pain
Moses Maimonides

In closing, I would like to pay tribute to a man who has contributed much to the development of Orthopaedic Surgery in Singapore. The late Professor N Balachandran has been instrumental in nurturing and building up a whole generation of orthopaedic surgeons who are now leading the various departments and institutions to the next stage of development. His vision and outstanding leadership has benefited patients, the profession and specialty. He has been teacher, mentor, friend and confidante to many of us.