Address by the Master, Academy of Medicine, Singapore at the 2000 Annual Induction Dinner—Learn the Past, Ensure the Future

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Colleagues and Friends:

I am delighted to share this celebratory occasion with you. It is a time for congratulations all round not only to our new Fellows but also to their families and friends. No specialist trains by himself. Along the way he has been helped and in turn, he has offered help to others. We will continue to learn with and from one another, our ages notwithstanding. Support from friends and families is a vital component of any person's success for no man is an island.

Tonight I wish to dwell on the topic "*learn the past, ensure the future*." We are supposedly into the 21st century and the new millennium, although some are still unsure if correctly these only commence in the year 2001. Nonetheless in the crossover from 31 December 1999 to 1 January 2000, there were big parties and celebrations worldwide and the Y2K computer bug turned out to be a non-event. We have left quite a past behind and I wish to review with you some of the medical highlights. Timesport has nominations for the top 50 sportsmen and women of Singapore. We all remember our Olympic Silver medallist, weightlifter Tan Howe Liang, and our badminton maestro, Wong Peng Soon. We also revel in our golden girls of swimming, athletics and bowling. But can we remember anything or anyone medical? I will not bore you with the top 50 but perhaps 20 is enough?

The second millennium is over. What of the astounding course of medical history over the past thousand years? What changed the face of clinical medicine? Except for some early work by the ancient Greeks, much of it wrong, there were few advances in clinical medicine until the Renaissance. Between Galen and Vesalius, over 1400 years, medicine was stagnant, dominated by the belief that illness reflected an imbalance in the four humours of the body – blood, phlegm, yellow bile and black bile. Life was nasty, brutish and short, and medical care did not help. Only with the Renaissance when scholars were thought fit to now pursue knowledge not only of god, but also of man, did humanism flower rapidly.

A comprehensive understanding of the structure and functions of the organ systems of the human body is the foundation of the life sciences. Galen did some things right but also many things wrong in anatomy and physiology, until Vesalius' anatomical treatise published in 1543 set the foundation and a new standard for the understanding of human anatomy. Then, less than 100 years later, William Harvey's work of 1628—on the motion of the heart and blood in animals—established physiologic principles that led to the understanding of blood pressure (first measured in 1733 in a horse), and much later to the clinical use of cardiac catheterisation and open heart surgery. Considered together, the work of Vesalius and Harvey provided the intellectual underpinnings for many advances in human anatomy, physiology, clinical medicine and surgery that followed.

The second discovery relates to the invention of the microscope by Dutch lens maker Antony van Leeuwenhoek (1632-1723) through which he discerned minute "animalcules". From simple single lenses, he made compound lenses and microscopes with up to 270 times magnification. These observations by him, Robert Hooke in England and others set the stage for the era of cellular biology.

Observing microscopic changes in tissues and organs led to a better understanding of disease processes. The rich substructure of cells remained hidden until 1930s when Ernst Ruska made the first electron microscope (400 times magnification). Later, with magnifications of over 10,000, the complex cell substructures like mitochondria, endoplasmic reticulum, etc were seen and their functions elucidated with histochemical and immunocytochemical methods.

The chemistry of life or biochemistry started with trying to understand the process of fermentation when crushed fruit turned to alcohol, then to vinegar. Thomas Willis (of the circle of Willis) in 1659 thought every disease acted its tragedies by the strength of some ferment. Over the next 200 years and more, enzymes were identified and quantitative physical chemistry developed. With the application of Avogadro's law for the calculation of atomic weights and the determination of molecular structure, enzymatic reactions that oxidised foodstuffs with energy liberated for cell utility were discovered. Various cycles were described e.g. citric acid and urea cycle. Sequential electron transport by mitochondria, inhibition or enhancement of the action of cellular enzymes by hormones, neurotransmitters and cytokines meant that cells could communicate with each other. Organic and inorganic chemistry of cells (sodium, potassium, acid base) became important in the basic knowledge required by doctors for the delivery of good medical care.

On a different plane, the fourth advance relates to the application of statistics to medicine. Indian and Arabic mathematics and numbering were introduced to Europe in 1202; allowing bookkeeping and modern computation to evolve. In the 16th and 17th centuries, probability theory developed and ideas of relative frequency surfaced. Inference and induction, together with regression analysis, came in the 18th century and in 1747, a clinical trial took place when James Lind treated 12 scorbutic ship passengers with oranges and lemons. Lime juice for all sailors was an edict of the British Admiralty that led to the elimination of scurvy from the navy. Modern epidemiology was born in 1854 when John Snow demonstrated cholera spread from contaminated water by analysing disease rates among citizens served by the Broad Street Pump in London's golden square. Sir Ronald Fisher (1890-1962), the most important figure in modern statistics, developed the analysis of variance and multivariate analysis. He also introduced the principle of randomization as a method to avoid bias in experimental studies. Randomised clinical trials emerged in the 1950s and were adopted by the National Institutes of Health in the United States in the early 1960s. And now we have computer support, essential to empirical investigation and statistical inferences.

In clinical medicine, I would like to recollect the following landmarks. The first is the development of anaesthesia, analgesia and amnesia to allow modern surgery to take place. It was in 1799 that laughing gas was recognised as an analgesic agent by Sir Humphey Davy who inhaled it to relieve his toothache. In 1844, Horace Wells a dentist used the same gas to anaesthetise 15 patients and with his friend William Morton arranged a public exhibition of nitrous oxide anaesthesia for a dental extraction at the Massachusetts General Hospital. It was a disaster. However, Morton in 1846 at MGH successfully demonstrated publicly the use of ether anaesthesia. In 1847, a Scottish obstetrician, James Simpson, used chloroform to aid childbirth. But modern anaesthesia only began in 1942 when routine use of muscle relaxants were used first by Harold Griffith in Montreal.

The second is the discovery of genes in chromosomes. It was Charles Darwin's 1858 theory of evolution followed by Gregor Mendel's treatise on the segregation of traits in peas in 1865 that foundations were laid but left buried in time. Walter Fleming in 1875 discovered the chromosome as the key to genetic segregation and by 1890s, it was established as the structural unit of genetic heritage. Early 20th century saw Archibald Garrod start medical genetics with the proposal that inborn errors of metabolism were inherited according to Mendel's laws. Linear gene maps of the fruit fly surfaced in 1911 using the same principles applied today for mapping human genetic diseases. In 1943, genetic transmission was demonstrated by DNA and 6 years later, the DNA molecule was described as having 4 bases with definite pairing rules. Watson and Crick elucidated the double helix of DNA and 10 years later, messenger RNA was discovered. In the 1970s, reverse transcriptase was found; allowing the birth of genetic engineering. Genetically engineered insulin was marketed in 1982, and in 1986 genetically engineered hepatitis B vaccine went on sale. Soon the human genome would be completely mapped out.

The third important advance is the development of body imaging that has made possible diagnostic radiology as a specialty. Roentgen, a German physicist, discovered X-rays in 1895 and duly received the first Nobel Prize for physics in 1901. There are 3 phases in the developments. The first aimed at developing technologies to define the morphologic features and function of the internal organs. Ultrasound, radionuclide tracers and contrast agents all greatly contributed to enhance visualisation of disease processes, enhance precision of therapies and improve understanding of pathophysiology. The second phase was access to the vascular tree (contrast angiography) and improved tissue characterisation in CT and MRI thus permitting resolution of very small structures throughout the body. This permitted new treatments for cancer, vascular and cardiac diseases. Today in the third phase, imaging methods are used to guide therapy directly, including on-line guidance of minimally invasive surgery.

The fourth breakthrough encompasses the discovery of the relation of microbes to disease, knowledge of the immune system and the discovery of antimicrobials. Epidemics were thought to be due to bad air till Pasteur (19th century) established bacteriology as a science and himself as the father of fermentation. Pasteursation is the use of heat treatment to destroy microorganisms. He also isolated the toxin from *Bacillus anthracis* which stimulated greatly the field of immunology. Attenuation was a process he discovered and then used to prevent rabies by immunisation of a young boy bitten by a rabid dog. Koch developed the techniques of culturing on solid media, staining bacteria and dry heat sterilisation. Medical bacteriology was born as bacterial pathogens were isolated and identified. Koch's bacillus is of course the tuberculosis germ; Koch's postulates his criteria to distinguish a bacterial pathogen from a nonpathogen and Koch's phenomenon, the basis of the tuberculin test. Lister established antiseptic principles, which make it safe today to perform extensive surgical operations without septic complications.

Immunology emerged towards the end of the 19th century, founded by Jenner of cowpox-smallpox fame. It was in 1890 when Emil Behring and Kitasato Shibasaburo developed their diphtheria antitoxin and in the process, discovered antibodies. Metchnikoff identified the phagocyte and cellular immunity. Within 20 years, the main elements of clinical immunology, allergy, autoimmunity and

transplantation immunology were described. Immunochemistry became a quantitative science. It was not till the 1950s when focus shifted from sera to cells. The study of immune cells and molecular biology influenced powerfully our detailed understanding of the immune response and made possible effective transplantation surgery. Vaccines against infectious diseases helped protect us and our children so much so that longevity is today an issue. A landmark in the history of vaccines is the hepatitis B vaccine, the first vaccine produced by DNA technology. On the other side of the coin was the discovery of antibiotics and antimicrobials. Paul Ehrlich founded the field of chemotherapy for infections when in 1910 he discovered salvarsan for the treatment of syphilis. In 1928 Alexander Fleming discovered penicillin. This was followed in 1935 by Domak's discovery of Prontosil, a red dye, whose breakdown product, sulphanilide, was as effective as the parent drug in curing streptococcal infections. The rest is history.

And finally, the development of molecular pharmacotherapy has permitted rational identification of targets for drugs. Active constituents of drugs binding to specific macromolecules or receptors resulted in therapeutic effectiveness. Chemotherapy for cancer began in 1946 when nitrogen mustard – the mustard gas of World War I – was shown to cause regression of lymphomas. In 1949, methotrexate was used successfully in treating childhood leukaemia. In 1965, cisplatinum's effectiveness against epithelial cancer was shown. Betablockers, H_2 blockers, as well as agonist drugs like levodopa for Parkinson's disease, are now widely used in everyday practice.

Before I leave the past, I wish to mention a few famous names and their contributions to medicine. Sigmund Freud, an Austrian neurologist, is considered the founder of psychoanalysis. Karl Landsteiner, an Austrian pathologist, is called the "father of blood grouping" and he received the Nobel Prize in 1930. He made possible safe blood transfusion. Marie Curie discovered radium. Her discovery of radioactivity is the basis of radiation therapy and the Nobel Prize was hers in 1903 (physics) and again in 1911 (chemistry). I have not been comprehensive but that is not possible tonight.

What of the future? Life expectancy has lengthened. Methuselah mice have had one third more life through gene manipulation and for man, we can expect to reach 130 years old routinely soon. We will look forward to more and more old people with arthritis, heart disease, stroke and cancers. Familiar enemies but new settings. There will be more designer drugs like Prozac and Viagra of 1990s. The Human Genome Project is a biological revolution whose impact and implication are far-reaching and limitless.

Can we live longer, more healthily? What about a glimpse of the coming future? Imagine this. You are worried that you might have heart disease. You e-mail your doctor who arranges a videoconference with you. He takes down your medical history over the Internet and makes an appointment to see you. As you walk into the clinic, you notice that it resembles the flight deck of the Starship Enterprise. Ceiling vents monitor you for infections that you might be carrying. If you are, a robot will enter the room and use electronic sensors to instantly identify the microorganism and recommend treatment.

Another robot greets and ushers you through to your doctor. You hand over your health record, which is held on a credit card with a unique microchip. The microchip contains details of your full gene map as well as a complete account of all your health problems. Your credit card also reveals your father died of a heart attack and that you have diabetes. But your diabetes is well controlled because several years ago, you had a glucose monitor implanted under the skin of your wrist. The monitor automatically adjusts insulin doses from an internal reservoir. You have also had your toilet upgraded so that it automatically analyses urine samples for signs of long-term effects of diabetes. These samples are passed automatically to your doctor's clinic for analysis. All seems well.

Most crucially, your credit card confirms that you have enough funds to pay for the procedures that your doctor is about to recommend. Fearful of litigation, he explains to you the latest research on heart disease. Naturally there is too much information for him to carry in his head, so he calls it up on a two-way computer screen and takes you through all the possible diagnostic tests, the possible treatments and carefully explains the risks attached. He does not insist you have the procedure, but gives you all the information you need to make a decision.

You decide to proceed. On screen you fill in a questionnaire that assesses your mental capacity. You are of sound mind and you next complete the consent form on the computer terminal. Your credit card acts as your electronic signature and the computer screen performs a quick retinal scan to confirm your identity. The forms that you have completed are sent to your lawyer, the doctor's lawyer and to a central health database. You are finally ready for the procedure.

The procedure is quick. An ultra high resolution MRI scanner looks at your heart and the blood vessels supplying it, instantly building a 3-D image of your heart which is pumping strongly although one coronary artery is partially blocked. Your doctor has never come across a narrowing at this site before. He decides to ring the world's premier cardiology unit and on video links, he talks over your problem with a current professor of cardiology, whose grandfather incidentally was Singaporean. The professor can view your coronary arteries and talks over your

symptoms with you. He decides that because of your father's death, your symptoms and your genetic makeup, the artery should be cleared at once. He recommends external laser therapy. You electronically sign another consent form and you have the treatment. You don't feel a thing. A repeat scan shows that the blockage is gone. Within an hour you are heading home, glad you decided to see a doctor, but sad to have been made several thousand dollars poorer. You feel you have had a lucky escape.

Is this fantasy? No. Designer man or not, 21st century health care is coming upon us and hopefully you can afford it when it arrives. Singapore sees the potential and the possibilities in the life sciences industry, which is more than biotechnology. It comprises the research, development and manufacture of pharmaceuticals and medical devices. The Chairman of the Economic Development Board (EDB), at the inaugural life sciences investment seminar on 9 December 1999 said, "The life sciences industry is poised for rapid growth and we expect this cluster to become a significant contributor of growth in Singapore's manufacturing sector, continuing its double digit growth over the next few years."

My challenge to you, to us, is not to be onlookers but partakers and participants in this brave new world dawning upon us. The world is one big village. Let us draw strength and inspiration from the history of medicine so as to grasp the opportunities coming our way in the future. A bright future is not by accident; we should strive to ensure it.