10th Seah Cheng Siang Memorial Lecture: Going Places—A Rheumatological Odyssey

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Madam Chairperson, Dr Chng Hiok Hee; Mrs Margaret Seah; Members of the Academy of Medicine and Members of the Seah Family; Distinguished Guests; Friends and Colleagues.

Introduction

I am greatly honoured to deliver the 10th Seah Cheng Siang memorial lecture. I came into direct contact with Professor Seah in January 1965 when I joined the then Thomson Road General Hospital as his senior registrar. Of course even before then, I and everyone in the medical profession knew Professor Seah. I was his student, then his "tukang" and finally his friend. Many of the prominent doctors today were also his "tukang"—among them Dr John Tambyah, Dr Tay Chong Hai, Dr Loong Si Chin, Dr Evelyn Mah, Dr Chua Kit Leng and Dr Lee Boon Teik. All of us have very fond memories when we were there and the annual Christmas Party was one of the highlights.

I will now share with you for the next 45 minutes or so the topic of my presentation "Going Places—A Rheumatological Odyssey".

Arthritis Timeline

Arthritis is an ancient disease. Among the fossilized remains of early man (Neanderthal man), and even in the fossilised dinosaur remains, there are signs of arthritic disease. Paleopathologists using computed tomographic (CT) scans also found arthritis in mummies in ancient Egypt around 1500 BC. Indeed in the earliest medical textbook, the Ebers Papyrus around 1550 BC, rheumatism was described and ointments were recommended to make the joints limber.

Although now we know there are more than 100 forms of arthritis, the term gout was used to describe all forms of arthritis until very recently. Arthritis was such a frustrating condition to treat that William Osler once said "When an arthritic walks in the front door, I walk out the back door".

Coming of Age

Two events in the early 1990s marked the coming of age of rheumatic diseases. In 1926, the Ministry of Health in England noted "nearly one-sixth of the industrial invalidity of this country was due to diseases classified as rheumatism". As a result, in 1929, the British Red Cross built the first Clinic for Rheumatism in Peto Place, Maryleborne Road in London. In the US, organisation of the specialty of rheumatology began in 1928 when the American Committee for the Control of Rheumatism was founded. This was the forerunner of the American Rheumatology Association (1937) and the American College of Rheumatology (1988). In Singapore, the first Department of Rheumatology was established at the Tan Tock Seng Hospital in 1994.

A Brave New World

On Monday, 26 June 2000, President Clinton and Prime Minister Tony Blair announced simultaneously in Washington and London that scientists have completed a rough map of the genetic make-up of a human being and are only a few years away from a complete map. The project which started in 1988 is expected to take 15 years at a cost of 3 billion in US dollars. Sixteen laboratories around the world in the US, UK, France, Germany, China and Japan together with 1200 scientists are working on the project. This project of truly biblical proportions and probably the most important scientific effort mankind has ever undertaken, promises to revolutionalise medicine including rheumatology in the coming years.

Since arthritis is essentially a disease of old age, genes that control ageing are obviously an important target. It is estimated that out of the 80 to 100,000 genes in the human genome, as many as 7000 might modulate ageing. Even if only 1% were truly important in ageing, a total of 70 genes would merit detailed study. Scientists believe that within the next 10 to 20 years, it will be possible to slow the ageing process in humans. This will have great impact on

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degenerative diseases like arthritis, in particular, osteoarthritis. Indeed, if you are still around in the next 10 to 20 years, your chances of reaching 100 years, and a healthy 100 years at that, is good. I am sure centenarians will be common in your children's time.

The other important scientific discovery is the stem cell and stem cell technology. Stem cell technology has been touted by the journal *Nature* as the top scientific discovery in the year 1999, although scientists have been working with this technique a number of years before.

Stem cells can come from a fertilised egg or from the bone marrow, peripheral blood and umbilical cord blood. These stem cells have the amazing potential to turn themselves into any cell of the body. For example, stem cells introduced into a diseased kidney becomes much more like kidney cells. The other kidney cells "educate" and "integrate" the new cells until the organ effectively is regenerated. In Pittsburgh, doctors are using stem cells to treat patients whose brains have been damaged by strokes. Other potential areas in which such technology can apply are spinal cord injuries, macular degeneration, pancreatic stem cells in diabetes, liver diseases and heart failure. Talking to a well-known rheumatologist from Sydney recently, he believes that we can grow new hips and knees within the next 5 to 10 years—so orthopaedic surgeons beware!

At the moment Christopher Reeves a.k.a. Superman may not be able to fly again—that may take another 10 to 20 years. Most scientists believe that by the year 2050, man will be able to replace many body parts at the cellular level using such technology.

A Look at the Future—Treatment of Common Rheumatological Diseases

Osteoarthritis

Osteoarthritis (OA), particularly of the knee and hip, is by far the commonest of the rheumatic diseases. It is a major cause of early retirement, the second most common disability in the United States and it has major, often underappreciated impact on functional and social activities, relationships, socioeconomic status, emotional well-being and body image. Presently, it is estimated that arthritis affects approximately 15% of the total US population or approximately 40 million adults, and of these, 16 million (43%) are affected by osteoarthritis.

Optimal management of OA involve primary and secondary prevention. Primary prevention includes education, joint protection from injury, exercise, weight reduction and avoidance of repetitive motion occupation. Most current OA therapy is targeted toward secondary prevention and is primarily palliative. Non-pharmacologic therapeutic modalities include education, exercise, rehabilitation, physical therapy, braces and bandages, canes and other walking aids, shoe modification and orthotics. Pharmacologic therapies can be administered topically, orally or into joints directly. The major oral agents currently in use are the analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), especially the new selective COX-2 inhibitors. Several new potential therapeutic modalities have emerged in recent years. These include the use of intraarticular hyaluronic acid injections, acupuncture and the possible beneficial effects of oral glucosamine and chondroitin. Surgical interventions like arthroplasty of the knee or hip, joint lavage, osteotomy, and appropriate repair of torn ligament or menisci have been used with considerable success.

The recent identification of specific genes associated with rare hereditary forms of osteoarthritis in a few families offers the possibility of specific treatment in the future for some of these individuals. Delivering therapeutic reagents to joints in the form of genes is an alternative future prospect but this is probably many years away. Meanwhile, widespread interest has been generated concerning the prospect of autologous chondrocyte implantation for repairing cartilage defects thus halting the progression of the disease. One can look forward to an exciting future in the therapy of OA.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common disease that affects between 0.5% and 1% of the population worldwide. It is one of the commonest causes of disability. After 12 years of disease, more than 80% of patients are partially disabled and 16% are completely disabled. Life expectancy is shortened by an average of 7 years in men and 3 years in women, an outcome equivalent to the increased mortality of patients with Hodgkin's disease, diabetes and stroke.

Over the past few years, treatment of RA has made significant progress. Apart from the introduction of selective COX-2 inhibitors and the earlier use of combination of established disease modifying anti-rheumatic drugs (DMARDs), several novel concepts and therapeutic strategies have emerged. These are the TNF-α antagonists, etanercept (Enbrel) and infliximab (Remicade), that have powerful anti-inflammatory effects in patients with RA. These agents need to be given parenterally and are extremely expensive. Another new drug is leflunomide (Arava) which is a pyramidine synthesis inhibitor with clinical efficacy generally equivalent to methotrexate. Finally, the identification of target genes for gene therapy has been a matter of continuous interest for many researchers but this is probably many years away.

Systemic Lupus Erythematosus

Many of you consider Professor Seah as a gastroenterologist, in particular a hepatologist. In fact, he published the first paper in the world on the use of intravenous bolus cyclophosphamide in patients with severe lupus.[1] Following his lead, I continued the work and published our further experience.[2] Since then, hundreds of papers have been published on the subject and intravenous pulse cyclophosphamide is now standard treatment for severe lupus nephritis round the world.

Therapeutic prospects for the upcoming millennium include new drugs (DHEA, mycophenolate, tacrolimus, intravenous immunoglobulin) and new attempts to achieve immunological reconstitution using near-ablative chemotherapy (with or without bone marrow or stem-cell rescue). A variety of other agents currently in development include LJP 394 (a β-cell toleragen), anti-CD40 ligand, various monoclonal antibodies, immunoadsorption, vaccination and autoimmunisation.

The feasibility of gene therapy in SLE will depend on further definition of lupus-promoting genes, availability of methods to establish stable expression of potentially corrective genes and search for a safe vector.

Some Things However Must Never Change

With the beginning of a new millennium, the medical profession faces unprecedent pressures and challenges that jeopardise our ability to care for patients. To be effective, physicians must work together. We must be vigilant about threats to high standards, research, education and ethics and seize opportunities for improvement. We need to ensure that relationships with patients, students, colleagues and other healthcare professionals are marked by trust and mutual respect. The pursuit of excellence, caring for our patients with compassion and a sturdy resolve to retain the valued fundamentals of our profession must never change. Our patients and Professor Seah expect nothing less.

REFERENCES

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