FOREWORD

It's a grand year for celebrating science

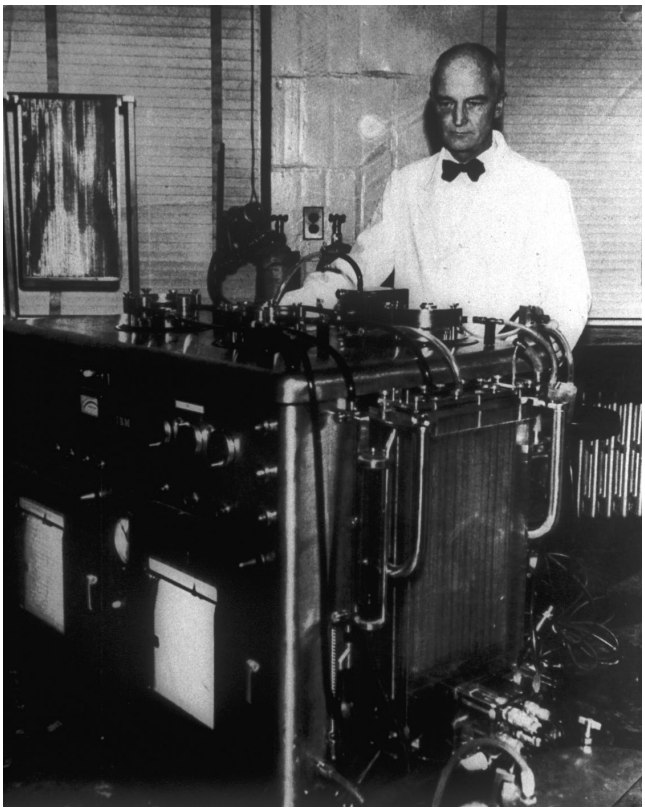
Few scientific events have been celebrated so grandiosely as this year's fiftieth anniversary of the discovery of the chemical structure of DNA. The centerpiece of Watson and Crick's one-page *Nature* paper, published on 25 April 1953, was a photo of a model of the double helix that was beautiful, revealing and tantalizing in its implications for biology and medicine. This is all history that everyone knows.

But what everyone may not remember is that several months after *Nature* published the Watson and Crick model of DNA, *Playboy* magazine appeared on the newsstands for the first time in November 1953. The maiden issue of *Playboy* featured in its centerfold a picture of a biological structure that was just as beautiful, revealing and tantalizing as the Watson-Crick structure: a voluptuous Marilyn Monroe stretching in a twisted position reminiscent of DNA (albeit left-handed DNA). One wonders whether Hugh Hefner and his photographers had seen the April issue of *Nature*!

While Marilyn Monroe was greeted by the public with thunderous enthusiasm, the initial reaction to the double helix was lukewarm at best. The general scientific community simply did not appreciate the revolutionary significance of the double helix when it first appeared. From 1953 to 1960, Watson and Crick's 1953 paper was mentioned in *Nature* only 24 times and less than 100 times in the entire scientific literature. Perhaps scientists were spending more time scrutinizing the helical structure in *Playboy* than its iconic counterpart in *Nature*. The full impact of the double helix did not hit the mainstream of biology until the early 1960s, after the triple discoveries of *in vitro* protein synthesis, messenger RNA and the genetic code.

During this year's celebratory events surrounding the fiftieth anniversary of the double helix, there has been no mention, surprisingly, of one other scientific breakthrough that also turned 50 this year, a breakthrough with ramifications that have had as profound an influence on medicine as the double helix. On 6 May 1953, John H. Gibbon, Jr. used his newly created heart-lung machine (**Fig. 1**) to perform the first successful open-heart operation on a human being, repairing a hole in the heart of an 18-year-old girl with an atrial septal defect. Gibbon experimented in animals continuously for 23 years before he perfected the device that ultimately made it possible to stop the heart during surgery without endangering the patient's life. His heart-lung machine removed the blood from the patient's veins, oxygenated it with air and then pumped the oxygenated blood back into the patient's arteries, bypassing the heart and allowing the surgeon to perform open-heart surgery.

John Gibbon's persistence for 23 years paid off royally. His invention has saved the lives of tens of millions of people over the last 50 years. Modern versions of the original heart-lung machine are used today to replace hearts with congenital defects in babies, children and adults; to repair heart valves damaged by rheumatic fever; to restore the heart's circulatory system in coronary bypass operations; and to perform heart transplants. Last year alone, more than 700,000 open-heart operations were carried out in the United States, including 610,000 coronary bypass procedures, 90,000 valve



Courtesy of the National Library of Medicine

Figure 1 The heart-lung machine—the forgotten icon of 1953. John H. Gibbon Jr., the original designer and developer of the heart-lung machine, performed the first successful open-heart surgery on a patient with congenital heart disease on 6 May 1953.

replacements and 2,500 heart transplants.

In the tradition of Watson and Crick (who received the Lasker Basic Award in 1960) and John Gibbon (who received the Lasker Clinical Award in 1968), this year's Lasker Awards celebrate pioneering achievements that have opened new fields of biomedical science.

The recipient of this year's Lasker Award in Basic Medical Research is Robert G. Roeder of The Rockefeller University, who is honored for his pioneering studies on gene transcription in eukaryotic organisms. Roeder's discovery of multiple RNA polymerases and the general transcriptional machinery opened the field of gene expression in animal cells to biochemical analysis. His research on transcription began in 1965 when he was a graduate student with William J. Rutter at the University of Washington in Seattle. With Rutter, Roeder discovered the three eukaryotic RNA polymerases and identified the nuclear products of each polymerase (Pol I, which forms ribosomal RNA; Pol II, which forms messenger RNA; and Pol III, which forms transfer RNA). As an independent scientist, first at Washington University and then at The Rockefeller University, he purified each of the three polymerases and identified their different subunit compositions.

With pure polymerases in hand, Roeder developed the first cell-free test-tube reactions in which eukaryotic genes could be transcribed in a faithful manner outside of cells. This accomplishment in the late 1970s opened the field of RNA transcription in much the same way that Arthur Kornberg opened the field of DNA replication by synthesizing DNA in the test tube. Roeder's classic papers in 1979 and 1980 provided the basic system that hundreds of scientists have used for biochemical studies of gene transcription. From many studies over the last 25 years, we now know that regulated gene transcription in eukaryotes requires an immensely complex multisubunit assemblage of more than 60 proteins, involving the following multilayered components: the general transcription machinery, consisting of RNA polymerase and multiple general transcription factors; thousands of different gene-specific transcription activators and repressors; and several multiprotein coactivator complexes that link the activators and repressors to the general transcription machinery. Understanding the biochemical basis for transcription provides the conceptual framework for understanding how biological information is retrieved from the genome, and is thus of great importance to all aspects of biomedical research.

The Lasker Award in Clinical Medical Research is given each year to honor a scientific contribution that has improved the treatment of patients by alleviating or eliminating a major medical disease. This year's award is given to Marc Feldmann and Ravinder Maini of the Kennedy Institute of Rheumatology at Imperial College School of Medicine in London for their discovery of anti–tumor necrosis factor (TNF) therapy as an effective treatment for rheumatoid arthritis and other autoimmune diseases.

In 1984, when the cytokine field was relatively new, Feldmann (a basic immunologist) and Maini (a clinical rheumatologist) initiated a collaboration to investigate the hypothesis that cytokines were important in the pathogenesis of rheumatoid arthritis, a disease that occurs in 0.5–1% of the adult population. By examining cytokine production in synovial explants obtained from the joints of rheumatoid patients, they uncovered a cytokine cascade of inflammation in which TNF is the master cytokine that stimulates the production of other inflammatory cytokines (such as interleukin-1, interleukin-6 and granulocyte-macrophage colony-stimulating factor), which in turn stimulate production of TNF itself. Feldmann and Maini tested their hypothesis in experimental animals and showed that inhibition of TNF blocked collagen-induced arthritis.

With these preclinical data in hand, they persuaded the biotechnology company Centocor Inc. to provide them with a chimeric mouse-human antibody to TNF, which had been developed by Centocor for use against sepsis, to test in patients with rheumatoid arthritis. A remarkably successful initial clinical trial in 1992 was followed by the development of a clinical program, leading in 1998 to the approval of TNF blockade for treatment of rheumatoid arthritis.

Today, three drugs that inhibit TNF—Remicade, Enbrel and Humira—are licensed in the United States and Europe. These three TNF blockers (Remicade and Humira are antibodies to TNF and Enbrel is a TNF receptor–IgG fusion protein) have benefited more than 350,000 people with rheumatoid arthritis. Notably, in about 50% of treated patients, the drugs have arrested the destruction of cartilage and bone in affected joints, a beneficial effect that has not hitherto been observed with other types of anti-inflammatory therapy. This success in rheumatoid arthritis led to clinical trials for other autoimmune diseases, and TNF blockers have recently been approved for use in patients with juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn disease (an inflammatory condition of the small intestine).

The work of Feldmann and Maini is a classic example of the 'bench-to-bedside' clinical investigation that produced the first targeted therapy for autoimmune diseases. At each step in the clinical development of TNF blockers—from the initial cytokine assays of synovial explants from rheumatoid patients, to the preclinical studies in animal models, to the first clinical trials in patients—Feldmann and Maini had the central role.

Joseph L Goldstein
Chair, Lasker Awards Jury

Lasker Award recipients receive an honorarium, a citation highlighting their achievements and an inscribed statuette of the Winged Victory of Samothrace, which is the Lasker Foundation's symbol of humankind's victory over disability, disease and death.

To read the formal remarks of speakers at the Lasker ceremony, as well as detailed information on this year's awardees, please refer to the Lasker web site at: http://www.laskerfoundation.org/.