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正修科技大學

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102年度教師「專業課程全英語化教學」成果報告
生化工程導論
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□團體       ☑個人

單位：化妝品與時尚彩妝系

單位主管：                                          （簽章）

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中華民國 102 年 2 月 25 日
Microorganisms have been identified and exploited for more than a century. The Babylonians and Sumerians used yeast to prepare alcohol. There is a great history beyond fermentation processes, which explains the applications of microbial processes that resulted in the production of food and beverages. In the mid-nineteenth century, Louis Pasteur understood the role of microorganisms in fermented food, wine, alcohols, beverages, cheese, milk, yoghurt and other dairy products, fuels, and fine chemical industries. He identified many microbial processes and discovered the first principal role of fermentation, which was that microbes required substrate to produce primary and secondary metabolites, and end products. In the new millennium, extensive application of bioprocesses has created an environment for many engineers to expand the field of biotechnology. One of the useful applications of biotechnology is the use of microorganisms to produce alcohols and acetone, which are used in the industrial processes. The knowledge related to industrial microbiology has been revolutionised by the ability of genetically engineered cells to make many new products. Genetic engineering and gene mounting have been developed in the enhancement of industrial fermentation. Consequently, biotechnology is a new approach to making commercial products by using living organisms. Furthermore, knowledge of bioprocesses has been developed to deliver fine-quality products. Application of biological sciences in industrial processes is known as bioprocessing. Nowadays most biological and pharmaceutical products are produced in well-defined industrial bioprocesses. For instance, bacteria are able to produce most amino acids that can be used in food and medicine. There are hundreds of microbial and fungal products purely available in the biotechnology market. Microbial production of amino acids can be used to produce L-isomers; chemical production results in both D- and L-isomers. Lysine and glu-tamic acid are produced by Corynebacterium glutamicum. Another food additive is citric acid, which is produced by Aspergillus niger. Table 1.1 summarises several widespread applications of industrial microbiology to deliver a variety of products in applied industries. The growth of cells on a large scale is called industrial fermentation. Industrial fermentation is normally performed in a bioreactor, which controls aeration, pH and temperature. Microorganisms utilise an organic
source and produce primary metabolites such as ethanol, which are formed during the cells' exponential growth phase. In some bioprocesses, yeast or fungi are used to produce advanced valuable products. Those products are considered as secondary metabolites, such as penicillin, which is produced during the stationary phase. Yeasts are grown for wine- and bread-making. There are other microbes, such as Rhizobium, Bradyrhizobium and Bacillus thuringiensis, which are able to grow and utilise carbohydrates and organic sources originating from agricultural wastes. Vaccines, antibiotics and steroids are also products of microbial growth. The term 'fermentation' was obtained from the Latin verb 'fervere', which describes the action of yeast or malt on sugar or fruit extracts and grain. The 'boiling' is due to the production of carbon dioxide bubbles from the aqueous phase under the anaerobic catabolism of carbohydrates in the fermentation media. The art of fermentation is defined as the chemical transformation of organic compounds with the aid of enzymes. The ability of yeast to make alcohol was known to the Babylonians and Sumerians before 6000 BC. The Egyptians discovered the generation of carbon dioxide by brewer's yeast in the preparation of bread. The degradation of carbohydrates by microorganisms is followed by glycolytic or Embden-Meyerhof-Parnas pathways. Therefore the overall biochemical reaction mechanisms to extract energy and form products under anaerobic conditions are called fermentation processes. In the process of ethanol production, carbohydrates are reduced to pyruvate with the aid of nicotinamide adenine dinucleotide (NADH); ethanol is the end product. Other fermentation processes include the cultivation of acetic acid bacteria for the production of vinegar. Lactic acid bacteria preserve milk; the products are yoghurt and cheese. Various bacteria and mold are involved in the production of cheese. Louis Pasteur, who is known as the father of the fermentation process, in early nineteenth century defined fermentation as life without air. He proved that existing microbial life came from preexisting life. There was a strong belief that fermentation was strictly a biochemical reaction. Pasteur disproved the chemical hypothesis. In 1876, he had been called by distillers of Lille in France to investigate why the content of their fermentation product turned sour. Pasteur found under his microscope the microbial contamination of yeast broth. He discovered organic acid formation such as lactic acid before ethanol fermentation. His greatest contribution was to establish different types of fermentation by specific microorganisms, enabling work on pure
cultures to obtain pure product. In other words, fermentation is known as a process with the existence of strictly anaerobic life: that is, life in the absence of oxygen. The process is summarised in the following steps:

• Action of yeast on extracts of fruit juice or, malted grain. The biochemical reactions are related to generation of energy by catabolism of organic compounds.

• Biomass or mass of living matter, living cells in a liquid solution with essential nutrients at suitable temperature and pH leads to cell growth. As a result, the content of biomass increases with time. In World War I, Germany was desperate to manufacture explosives, and glycerol was needed for this. They had identified glycerol in alcohol fermentation. Neuberg discovered that the addition of sodium bisulphate in the fermentation broth favored glycerol production with the utilization of ethanol. Germany quickly developed industrial-scale fermentation, with production capacity of about 35 tons per day.3 In Great Britain, acetone was in great demand; it was obtained by anaerobic fermentation of acetone-butanol using Clostridium acetobutylicum. In large-scale fermentation production, contamination was major problem. Microorganisms are capable of a wide range of metabolic reactions, using various sources of nutrients. That makes fermentation processes suitable for industrial applications with inexpensive nutrients. Molasses, corn syrup, waste products from crystallisation of sugar industries and the wet milling of corn are valuable broth for production of antibiotics and fine chemicals. We will discuss many industrial fermentation processes in the coming chapters. It is best to focus first on the fundamental concepts of biochemical engineering rather than the applications. There are various industries using biological processes to produce new products, such as antibiotics, chemicals, alcohols, lipid, fatty acids and proteins. Deep understanding of bio-processing may require actual knowledge of biology and microbiology in the applications of the above processes. It is very interesting to demonstrate bench-scale experiments and make use of large-scale advanced technology. However, application of the bioprocess in large-scale control of microorganisms in 100,000 litres of media may not be quite so simple to manage. Therefore trained engineers are essential and highly in demand; this can be achieved by knowledge enhancement in the sheathe bioprocesses. To achieve such objectives we may need to explain the whole process to the skilled labour and trained staff to implement bioprocess knowhow in biotechnology.
Unit 2. Fleming and Discovery of Penicillin

In September 1928, Alexander Fleming at St. Mary's Hospital in London was trying to isolate the bacterium, \textit{Staphylococcus aureus}, which causes boils. The technique in use was to grow the bacterium on the surface of a nutrient solution. One of the dishes had been contaminated inadvertently with a foreign particle. Normally, such a contaminated plate would be tossed out. However, Fleming noticed that no bacteria grew near the invading substance.

Fleming's genius was to realize that this observation was meaningful and not a "failed" experiment. Fleming recognized that the cell killing must be due to an antibacterial agent. He recovered the foreign particle and found that it was a common mold of the \textit{Penicillium} genus (later identified as \textit{Penicillium notatum}). Fleming nurtured the mold to grow and, using the crude extraction methods then available, managed to obtain a tiny quantity of secreted material. He then demonstrated that this material had powerful antimicrobial properties and named the product penicillin. Fleming carefully preserved the culture, but the discovery lay essentially dormant for over a decade.

World War II provided the impetus to resurrect the discovery. Sulfa drugs have a rather restricted range of activity, and an antibiotic with minimal side effects and broader applicability was desperately needed. Howard Florey and Ernst Chain of Oxford decided to build on Fleming's observations. Norman Heatley played the key role in producing sufficient material for Chain and Florey to test the effectiveness of penicillin. Heatley, trained as a biochemist, performed as a bioprocess engineer. He developed an assay to monitor the amount of penicillin made so as to determine the kinetics of the fermentation, developed a culture technique that could be implemented easily, and devised a novel back-extraction process to recover the very delicate product. After months of immense effort, they produced enough penicillin to treat some laboratory animals.

Eighteen months after starting on the project, they began to treat a London bobby for a blood infection. The penicillin worked wonders initially and brought the patient to the point of recovery. Most unfortunately, the supply of penicillin was exhausted and the man
relapsed and died. Nonetheless, Florey and Chain had demonstrated the
great potential for penicillin, if it could be made in sufficient amount. To
make large amounts of penicillin would require a process, and for such a
process development, engineers would be needed, in addition to
microbial physiologists and other life scientists.

The first efforts with fermentation were modest. A large effort went into
attempts to chemically synthesize penicillin. This effort involved
hundreds of chemists. Consequently, many companies were at first
reluctant to commit to the fermentation process, beyond the pilot-plant
stage. It was thought that the pilot-plant fermentation system could
produce sufficient penicillin to meet the needs of clinical testing, but
large-scale production would soon be done by chemical synthesis. At that
time, U.S. companies had achieved a great deal of success with chemical
synthesis of other drugs, which gave the companies a great deal of control
over the drug's production. The chemical synthesis of penicillin proved to
be exceedingly difficult. (It was accomplished in the 1950s, and the
synthesis route is still not competitive with fermentation.) However, in
1940 fermentation for the production of a pharmaceutical was an
unproved approach, and most companies were betting on chemical
synthesis to ultimately dominate.

The early clinical successes were so dramatic that in 1943 the War
Production Board appointed A. L. Elder to coordinate the activities of
producers to greatly increase the supply of penicillin. The fermentation
route was chosen. As Elder recalls, "I was ridiculed by some of my
closest scientific friends for allowing myself to become associated with
what obviously was to be a flop—namely, the commercial production of
penicillin by a fermentation process" (from Elder, 1970). The problems
facing the fermentation process were indeed very formidable.

The problem was typical of most new fermentation processes: a valuable
product made at very low levels. The low rate of production per unit
volume would necessitate very large and inefficient reactors, and the low
concentration (titer) made product recovery and purification very difficult.
In 1939 the final concentration in a typical penicillin fermentation broth
was one part per million (ca. 0.001 g/l); gold is more plentiful in sea
water. Furthermore, penicillin is a fragile and unstable product, which
places significant constraints on the approaches used for recovery and purification.

Life scientists at the Northern Regional Research Laboratory made many major contributions to the penicillin program. One was the development of a corn steep liquor-lactose based medium. This medium increased productivity about tenfold. A worldwide search by the laboratory for better producer strains of *Penicillium* led to the isolation of a *Penicillium chrysogenum* strain. This strain, isolated from a moldy cantaloupe at a Peoria fruit market, proved superior to hundreds of other isolates tested. Its progeny have been used in almost all commercial penicillin fermentations.

The other hurdle was to decide on a manufacturing process. One method involved the growth of the mold on the surface of moist bran. This bran method was discarded because of difficulties in temperature control, sterilization, and equipment size. The surface method involved growth of the mold on top of a quiescent medium. The surface method used a variety of containers, including milk bottles, and the term "bottle plant" indicated such a manufacturing technique. The surface method gave relatively high yields, but had a long growing cycle and was very labor intensive. The first manufacturing plants were bottle plants because the method worked and could be implemented quickly.

However, it was clear that the surface method would not meet the full need for penicillin. If the goal of the War Production Board was met by bottle plants, it was estimated that the necessary bottles would fill a row stretching from New York City to San Francisco. Engineers generally favored a submerged tank process. The submerged process presented challenges in terms of both mold physiology and in tank design and operation. Large volumes of absolutely clean, oil- and dirt-free sterile air were required. What were then very large agitators were required, and the mechanical seal for the agitator shaft had to be designed to prevent the entry of organisms. Even today, problems of oxygen supply and heat removal are important constraints on antibiotic fermenter design. Contamination by foreign organisms could degrade the product as fast as it was formed, consume nutrients before they were converted to penicillin, or produce toxins.
In addition to these challenges in reactor design, there were similar hurdles in product recovery and purification. The very fragile nature of penicillin required the development of special techniques. A combination of pH shifts and rapid liquid-liquid extraction proved useful. Soon processes using tanks of about 10,000 gal were built. Pfizer completed in less than six months the first plant for commercial production of penicillin by submerged fermentation (Hobby, 1985). The plant had 14 tanks each of 7000-gal capacity. By a combination of good luck and hard work, the United States had the capacity by the end of World War II to produce enough penicillin for almost 100,000 patients per year.

This accomplishment required a high level of multidisciplinary work. For example, Merck realized that men who understood both engineering and biology were not available. Merck assigned a chemical engineer and microbiologist together to each aspect of the problem. They planned, executed, and analyzed the experimental program jointly, "almost as if they were one man" (see the chapter by Silcox in Elder, 1970). Progress with penicillin fermentation has continued, as has the need for the interaction of biologists and engineers. From 1939 to now, the yield of penicillin has gone from 0.001 g/l to over 50 g/l of fermentation broth. Progress has involved better understanding of mold physiology, metabolic pathways, penicillin structure, methods of mutation and selection of mold genetics, process control, and reactor design.

Before the penicillin process, almost no chemical engineers sought specialized training in the life sciences. With the advent of modern antibiotics, the concept of a bio-process engineer was born. The penicillin process also established a paradigm for bio-process development and biochemical engineering. This paradigm still guides much of our profession's thinking. The mind set of bioprocess engineers was cast with the penicillin experience. It is for this reason that we have focused on the penicillin story, rather than on an example for production of a protein from a genetically engineered organism. Although many parallels can be made between the penicillin process and our efforts to use recombinant DNA, no similar paradigm has yet emerged from our experience with genetically engineered cells. We must continually reexamine the prejudices the field has inherited from the penicillin experience. It is you,
the student, who will best be able to challenge these prejudices.

To understand the mind set of a bioprocess engineer you must understand the regulatory climate in which many bioprocess engineers work. The U.S. PDA (Food and Drug Administration) and its equivalents in other countries must insure the safety and efficacy of medicines. For bioprocess engineers working in the pharmaceutical or biotechnology industry the primary concern is not reduction of manufacturing cost (although that is still a very desirable goal), but the production of a product of consistently high quality in amounts to satisfy the medical needs of the population.

Consider briefly the process by which a drug obtains PDA approval. A typical drug undergoes 6.5 years of development from the discovery stage through preclinical testing in animals. Human clinical trials are conducted in three phases. Phase 1 clinical trials (about 1 year) are used to test safety; typically 20 to 80 volunteers are used. Phase II clinical trials (about 2 years) use 100 to 300 patients and the emphasis is on efficacy (i.e., does it help the patient) as well as further determining which side effects exist. Compounds that are still promising enter phase III clinical trials (about 3 years) with 1000 to 3000 patients. Since individuals vary in body chemistry, it is important to test the range of responses in terms of both side effects and efficacy by using a representative cross section of the population. Data from clinical trials is presented to the PDA for review (about 18 months). If the clinical trials are well designed and demonstrate statistically significant improvements in health with acceptable side effects, the drug is likely to be approved. Even after this point, there is continued monitoring of the drug for adverse effects. The whole drug discovery-through-approval process takes 15 years on the average and costs about $400 million (in 1996). Only one in ten drugs that enter human clinical trials receives approval. Recent PDA reforms have decreased the time to obtain approval for life-saving drugs in treatment of diseases such as cancer and AIDS, but the overall process is still lengthy.

This process greatly affects a bioprocess engineer. PDA approval is for the product and the process together. There have been tragic examples where a small process change has allowed a toxic trace compound to form or become incorporated in the final product, resulting in severe side
effects, including death. Thus, process changes may require new clinical trials to test the safety of the resulting product. Since clinical trials are very expensive, process improvements are made under a limited set of circumstances. Even during clinical trials it is difficult to make major process changes.

Drugs sold on the market or used in clinical trials must come from facilities that are certified as GMP. GMP stands for good manufacturing practice. GMP concerns the actual manufacturing facility design and layout, the equipment and procedures, training of production personnel, control of process inputs (e.g., raw materials and cultures), and handling of product. The plant layout and design must prevent contamination of the product and dictates the flow of material, personnel, and air. Equipment and procedures must be validated. Procedures include not only operation of a piece of equipment, but also cleaning and sterilization. Computer software used to monitor and control the process must be validated. Off-line assays done in laboratories must satisfy good laboratory practices (GLP). Procedures are documented by SOPs (standard operating procedures). The GMP guidelines stress the need for documented procedures to validate performance. "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics" and "There shall be written procedures for production and process-control to assure that products have the identity, strength, quality, and purity they purport or are represented to possess."
Unit 3 Marshall and *H. pylori*

Around the world, millions of people have suffered from chronic stomach ailments, including ulcers and gastritis. For generations, medical science taught that these painful and often disabling conditions were caused by emotional stress and dietary factors. Patients receiving conventional treatment might experience temporary relief, only to have the symptoms recur year after year. In Western Australia, a young doctor, working in relative isolation, pursued another hypothesis, the possibility that these chronic stomach ailments were caused by a microscopic corkscrew-shaped organism called *Helicobacter pylori*.

For over a decade, Dr. Barry Marshall endured the hostility and ridicule of a medical establishment deeply invested in the received wisdom that peptic ulcers were a chronic condition requiring a lifetime of treatment. A pharmaceutical industry earning billions of dollars every year from the sale of prescription ulcer medications was particularly unreceptive to the notion that the ailment could be permanently cured by a short course of antibiotics. When animal testing of his theory proved inconclusive, Dr. Marshall took the courageous step of experimenting on himself, deliberately infecting himself with *helicobacter* to prove it was the cause of these common ailments. Dr. Marshall proved he had discovered not only the cause but the cure for most stomach ulcers and gastritis.

Today his discovery is recognized as one of the greatest breakthroughs in medicine since the polio vaccine. He continues his struggle against *helicobacter*, the most common chronic infection in the world. Barry Marshall's vision and courage have been recognized with the greatest honors in the world of science, including the 2005 Nobel Prize in Medicine.

Barry James Marshall was born in Kalgoorlie, a mining town in the interior of Western Australia. His father was a welder, his mother a nurse. When he was eight years old, the family moved to the outskirts of Perth, the large coastal city that is the capital of Western Australia. The oldest child in the family, he was an irrepressibly curious boy, fascinated by the natural world and all things mechanical. Marshall excelled in school and won a scholarship to study at the University of Western Australia (UWA),
where he completed medical studies in 1974. He interned in general medicine at the Queen Elizabeth II Medical Center in Perth, and carried out his residency at Royal Perth Hospital, where he explored a number of specialties, including gastroenterology.

As a resident physician, Marshall saw a great many patients with bleeding stomach ulcers. A staff pathologist at the hospital, Dr. J. Robin Warren, had found mysterious bacteria in the stomachs of many of these patients, near the site of their ulcers. He had found the same organism in patients with chronic inflammation of the stomach lining (gastritis), but could not find it in patients who lacked these symptoms. Warren's observations were anomalous for a number of reasons. Generations of medical scholars had taught that stomach ulcers were caused by an excess of stomach acid generated by stress and dietary factors. It was also believed that bacteria could not survive for any length of time in the acid environment of the human stomach.

Fascinated by the novelty of this mysterious spiral-shaped organism, eventually named Helicobacter pylori, Marshall decided to specialize in gastroenterology, with the specific intent of studying these bacteria, and pursuing the possibility that they were in fact causing the stomach ulcers in his patients. Taking advantage of the body of literature becoming available through the computer networks that were the precursors of the Internet, he found references to this bacteria dating back nearly a century. It was now possible for the first time to compare these unrelated observations and compile a body of data implying a clear correlation between the presence of helicobacter and the occurrence of both gastritis and peptic ulcers. Marshall also found instances of ulcer patients experiencing temporary relief from treatment with the chemical element bismuth, the active ingredient in over-the-counter remedies such as Pepto-Bismol. After initial setbacks, Marshall succeeded in growing helicobacter in the laboratory in 1982, and determined that bismuth could destroy the bacteria in the petri dish. Warren and Marshall published their findings jointly in the British medical journal The Lancet, but their article received little attention. Over the next two years, Marshall's clinical trials of bismuth with human patients enjoyed initial success, but the patients' symptoms invariably returned.
In September 1983, Marshall presented his findings at an international conference in Brussels, Belgium, but his unrestrained enthusiasm, combined with his youthful appearance and informal manner, apparently fed the skepticism of his audience. Marshall's critics contended that the presence of Helicobacter in the stomachs of patients with gastric diseases was coincidental, and that the bacteria were probably harmless.

Practitioners of gastroenterology and the pharmaceutical industry were both heavily invested in the theory that peptic ulcers were caused by emotional stress and stomach acids, and could only be treated with repeated courses of antacid medication. While the reduction of stomach acid often alleviated the existing ulcer, inflammation of the stomach lining usually persisted, and most patients found themselves returning in a year or two with another ulcer. Patients were routinely advised to seek psychiatric counseling, find less demanding employment or make other drastic lifestyle changes to address the purported cause of their disease. Volumes were published detailing the alleged psychological causes of gastric ailments, and ulcers remained a frequently cited example of psychosomatic illness.

In this environment, the possibility that the ailment was directly caused by a single microorganism that could be completely eliminated with a two-week course of antibiotics was a threat to the status quo. While many of Marshall's critics had serious scientific questions about his hypothesis, others may have had economic motives in disputing his findings, and Marshall was not shy about saying so. The targets of his criticism soon sought to discredit him and his research. One prominent gastroenterologist dismissed him as "a crazy guy saying crazy things."

Marshall persevered, methodically testing his hypothesis with laboratory animals, but could not cultivate the bacteria in either rats or pigs. By 1984, he had experienced considerable success in treating human ulcer patients with the combination of bismuth and antibiotics, but he had not proved that introducing the Helicobacter into a human subject would, in fact, cause gastric illness.

Lacking other human subjects, Marshall resolved to try the experiment on himself. To the horror of his assistant, he ingested a turbid, foul-tasting
solution of Helicobacter pylori. After a week, he began to display a number of symptoms, vomiting copious amounts of clear liquid, and appearing increasingly drawn and fatigued. On examination by endoscopy, it was found that the lining of his stomach, previously normal, had become seriously inflamed. Marshall's symptoms soon abated, but he had demonstrated that the bacteria could cause illness in humans. Although he was rebuffed by the Australian medical establishment, interest in his work was spreading. When he was invited to attend a medical conference in Dallas, Texas in 1985, he repeated his assertions of the bacterial cause of gastric illness and challenged the audience of medical scientists to prove him wrong. Before long, experiments in the United States and elsewhere, many designed to refute his hypothesis, were in fact confirming it.

In 1986, Marshall was invited to the United States to serve as a Research Fellow and Professor of Medicine at the University of Virginia. He taught and carried out his research in Virginia for over a decade, establishing the International Research Foundation for Helicobacter and Intestinal Immunology in Charlottesville, Virginia.

By 1994, Marshall's theory of the bacterial cause of peptic ulcers had been largely accepted by the international scientific community and Marshall's work was showered with honors, beginning with the prestigious Warren Alpert Prize. After receiving the Australian Medical Association Award, along with his old colleague, Dr. Warren, Barry Marshall received the most coveted honor in American medicine, the Albert Lasker Clinical Medical Research Award. In the words of the Lasker jury, "Rarely do the discoveries of a single individual change the lives of countless millions within the span of a decade. The revolutionary research of Barry J. Marshall into the causes and treatment of peptic ulcer disease has accomplished just that, and in so doing he has dispelled the darkness surrounding a painful chronic disease and lighted the pathway to a cure." The citation added, "With brilliant insight, personal courage and boundless conviction, Dr. Marshall altered the world's view of peptic ulcer disease."

In 1996, Marshall was named Professor of Research in Internal Medicine at Virginia, and the United States Food and Drug Administration
officially approved a course of treatment for peptic ulcer disease consistent with Marshall's findings. The following year, he returned to Australia, accepting an appointment as Clinical Professor of Medicine at the University of Western Australia. In 1999, he was given the added position of Clinical Professor of Microbiology.

Marshall's views had now gained acceptance around the world. In rapid succession, he received Canada's Gairdner International Award, Germany's Paul Ehrlich Prize, the Netherlands' Heineken Prize, Australia's Florey Medal, the Buchanan Medal of Britain's Royal Society, the Benjamin Franklin Medal for Life Sciences and Japan's Keio Medical Science Prize.

For over a decade, Marshall had been mentioned as a contender for the Nobel Prize in Physiology or Medicine. Almost every autumn, around the time of the Nobel announcements, Marshall and his old friend Dr. Warren would meet for a beer at a favorite pub in Perth and joke about winning the Nobel Prize. At the time of his interview with the Academy of Achievement in 1998, Dr. Marshall was already dismissing the possibility of adding the Nobel medal to his honors as a chance that had passed him by, but in the Autumn of 2005 he received word that he and Dr. Warren would indeed share that year's Prize. In the words of the Nobel Committee, they were honored "for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease." The Committee added, "Thanks to the pioneering discovery by Marshall and Warren, peptic ulcer disease is no longer a chronic, frequently disabling condition, but a disease that can be cured by a short regimen of antibiotics and acid secretion inhibitors." Barry Marshall accepted this crowning honor with characteristic good humor. As much as his pioneering studies of Helicobacter pylori, he sees his work as an educator of young medical scientists as being among his most important achievements.

Today, Barry Marshall is the National Health Medical Research Council (NHMRC) Senior Principal Research Fellow at the University of Western Australia. In recent years, his research has illuminated the patterns of helicobacter infection in different populations around the world. In more developed countries, with adequate supplies of clean drinking water, the rate of infection is declining, but it persists in less developed countries,
and among recent immigrants from those countries. It is probably the most widespread chronic infection in the world, and is nearly universal in the world's poorest countries. Thanks to Dr. Marshall's work, helicobacter is now recognized as a major factor in the development of stomach cancer. Once the most common of cancers, stomach cancer has declined precipitously in the developed world, while remaining prevalent everywhere else. Dr. Marshall hopes to see the insidious corkscrew organism controlled to the point where it can no longer pose a threat to the life and health of men, women and children anywhere in the world. His discoveries have already freed millions from unnecessary suffering.
James Dewey Watson was born and raised in Chicago, Illinois. He was a precocious student, and entered the University of Chicago when he was only 15. He received his Bachelor of Science degree in Zoology four years later, and went on to earn a Ph.D. in the same subject at Indiana University. He was engaged in research at the University of Copenhagen in Denmark when he first learned of the biomolecular research underway at the Cavendish Laboratory of Cambridge University in England. Watson joined Francis Crick in this work at Cambridge in 1951.

Together, Watson and Crick attempted to determine the chemical structure of living matter. When their initial research failed to produce results, the directors of the laboratory ordered them to end their investigation, but they continued their work in secret and, on February 28, 1953, they made a momentous discovery.

The two scientists had determined the structure of the molecule deoxyribonucleic acid (DNA), of which all living matter is made. In June they published their findings in the British science journal Nature. The article created a sensation. The DNA molecule, Watson and Crick had found, is shaped like a double helix, or "gently twisted ladder." The two chains of the helix unlink "like a zipper," and reproduce their missing halves. In this way, each molecule of DNA is able to create two identical copies of itself.

The initials DNA and the elegant model of the double helix, became known around the world. So did Watson and Crick. Their discovery revolutionized the study of biology and genetics, making possible the recombinant DNA techniques used by today's biotechnology industry.

James Watson became a Senior Research Fellow in Biology at the California Institute of Technology, before returning to Cambridge in 1955. The following year he moved to Harvard University, where he became Professor of Biology, a post he held until 1976.

In recognition of their discovery, Francis Crick and James Watson shared the 1962 Nobel Prize for Physiology and Medicine with Maurice Wilkins.
In 1968 Watson published his account of the DNA discovery, The Double Helix. The book became an international best-seller, but some in the scientific community were scandalized by Watson's less-than-flattering portrayal of his own colleagues. Throughout the ensuing controversy, Watson insisted that devotion to the truth was as essential in writing for the general public as it is in scientific research.

In the same year, James Watson married the former Elizabeth Lewis. They have two sons: Rufus and Duncan.

While continuing his duties at Harvard, James Watson became Director of the Cold Spring Harbor Laboratory on Long Island. At the time, this institution was in serious financial difficulty but, under Watson's vigorous leadership, it became financially sound and is now an international leader in genetic research. Scientists working under Watson at Cold Spring Harbor uncovered the molecular nature of cancer and identified cancer genes for the first time. Every year over 4,000 scientists from around the world come to Cold Spring Harbor to study; the Institute's influence over international genetic research is profound.

In 1988, Watson accepted an invitation from the National Institute of Health to become Associate Director of the Human Genome Project. The following year, Watson became Director of the project and guided it skillfully through the storm of controversy surrounding genetic research. This undertaking has applied the kind of resources usually associated with military and aerospace research to creating a complete directory of the genetic code of the human species. To do this, researchers must determine the location, chemical composition and function of 50,000 to 100,000 separate genes. This will permit the development of tests, and possibly cures, for thousands of hereditary disorders or diseases which have some genetic component.

Watson left the Genome project in 1992, having seen it off to a successful start. He continued his work at Cold Spring Harbor Laboratory throughout this period, and in 1994 became President of that institution, and later served as its Chancellor.

Universities and governments around the world have honored James

Over the years, James Watson occasionally attracted controversy with his uninhibited remarks on a variety of topics. In 2007, he apologized publicly after an interview in which he speculated that Africa's progress might be hindered by genetic inheritance. He retracted the statement and regretted any offense caused by his remarks. Shortly thereafter, he retired as Chancellor of Cold Spring Harbor Laboratory and resigned from the Laboratory's Board of Directors, after 43 years of service. In his resignation statement, he offered the hope that genetic science would soon conquer cancer and mental illness. "Final victory is within our grasp," he said. "I wish to be among those at the victory line."

Deoxyribonucleic acid is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms and some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints or a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

Chemically, DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.
Within cells, DNA is organized into long structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in organelles, such as mitochondria or chloroplasts.[1] In contrast, prokaryotes (bacteria and archaea) store their DNA only in the cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.