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<th><strong>Title</strong></th>
<th>Molecular medicine: an overview</th>
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Applications of the natural sciences, including physics, chemistry, mathematics, and biology to the practice of medicine have been responsible for great advances in Western medicine over the past century. In 1949, Pauling et al. first demonstrated an abnormality in the haemoglobin molecule (Hb S) in sickle cell disease and subsequently, Ingram showed that a single amino acid substitution, valine instead of glutamic acid in the haemoglobin molecule, accounts for all the pathophysiology and clinical features of the disease. The era of molecular medicine had begun but progress was slow until the biological revolution of the 1970s.

Of the various molecules in the cell, deoxyribonucleic acid (DNA), which is abundant in the nucleus, is the most important. It is duplicated in cell division, is the basis for inheritance, and controls all cellular activities. It consists of only four nucleotides—two purines, adenine (A) and guanine (G), and two pyrimidines, thymine (T) and cytosine (C). The manner in which it performs its complex function was explained biochemically by the double helical structure of the molecule proposed by Watson and Crick in 1954. It consists of two helical pentose-phosphate backbones and base-pairing or complementarity of A to T and C to G in the interstices of the double helix. Separation of the double strands and the duplication of the complementary strands in cell division as well as transcription of the sense strand into the corresponding messenger RNA (where T is replaced by uridine, [U]) followed faithfully this complementarity and explained the fidelity of DNA molecular control in these important life processes.

The impact on medicine had to await development of the various DNA methods in the 1970s, which culminated in recombinant DNA technology for which a patent was awarded to Cohen and Boyer in 1980. The first application of this new technology to human disease was in the prenatal diagnosis of sickle cell disorder by Kan and Dozy who linked the Hb S defect to a DNA polymorphism detectable by the restriction enzyme, Hpa I. Since then, many genes responsible for inherited diseases have been identified and the prenatal diagnosis of severe inherited diseases can be performed early in pregnancy (9-10 weeks gestation) or even at the blastocyst stage of an in-vitro fertilised embryo, thus allowing parents and doctors the choice of healthy unaffected offspring by the early abortion of an affected foetus or the early institution of a preventive strategy.

With advances in DNA techniques, many genes have been cloned including those for known molecular disorders as well as those of unknown cause, by positional cloning or reverse genetics, examples include cystic fibrosis, Duchenne’s muscular dystrophy (DMD), and Huntington’s disease. In fact, the rate of discovery of the molecular basis of diseases has increased exponentially in the past decade. The current status of this aspect of molecular medicine is reviewed by Chan and colleagues in a Seminar paper in this issue. Besides single gene defects, recent research using DNA techniques are unravelling the causes of some common “multi-gene diseases” such as diabetes mellitus, hypertension, cardiovascular disease, stroke, and cancer by identifying in certain families the susceptibility gene that predisposes them to these illnesses. These genes interact with some environmental factors to produce the disease and the identification of such controllable factors for each particular genotype will open a new era of “individualised preventive medicine” in the future. The pitfalls of large scale genetic screening and the related ethical and philosophical issues of pre-symptomatic testing need to be addressed by the medical profession as well as the public. These issues are not discussed in this Seminar but interested readers can refer to recent reviews.

Most of the basic work in DNA was done with microbes—bacteria, viruses, bacteriophages, and plasmids. It is not surprising then that clinical
microbiologists have used this technology to improve the diagnosis of infections as well as to unravel the causes of unknown infectious diseases. Yuen and colleagues review the role of DNA technology in the modern microbiology laboratory.

Cancer, a major cause of mortality in developed countries, has been considered an enigmatic disease until the recent confirmation that carcinogenesis involves multiple alterations of cellular DNA. At last, a handle is available to study possible causes, to make accurate diagnoses, and to devise novel treatment strategies. Huang and colleagues summarise the genetic basis of cancer in the third article in this series.

One of the problems in attaining a cure for chemosensitive cancers is ascertaining when there has been complete eradication of the disease. Biochemical markers have been used, but most of them are not sensitive enough and many cancers do not have such markers. The detection of specific DNA changes in a particular cancer (gene rearrangement or translocation) can be used to monitor minimal residual disease (MRD). Liang et al review the use of MRD detection in haematological malignancies; this serves as a prototype for other chemosensitive cancers.

Many of the genes causally associated with particular diseases, such as dystrophin in DMD and huntingtin in Huntington's disease, were discovered recently by positional cloning technique and are of unknown biological function. Therefore, even with the genes isolated, the pathogenetic mechanisms of these diseases remain unknown. Using the genetic code, the translated protein sequence can be predicted but the function can only be surmised if it is homologous to a known protein. Experiments to introduce the abnormal gene (transgene) or to remove a corresponding gene (gene knockout) in an animal model serve to show the probable effect of this "new" gene and elucidate the pathogenetic mechanism in man. In addition, attempts towards correction of the molecular defect need to be performed initially in an animal model. This use of animal models is discussed by Chung and colleagues.

As for the future, the impact of DNA technology in medicine has not shown any signs of decline. With completion of the Human Genome Project and the development of effective transgenic techniques, we shall see the use of genes as drugs for the treatment of diseases and the correction of genetic defects for both inherited and acquired diseases by gene transfer. Kwong completes this Seminar by showing glimpses of this possibility and illustrates what the future of medicine may be in the 21st century.

The teaching of science to undergraduates enables them to understand the biomedical sciences and their applications to patient management in hospitals and clinics. The rapidity of current advances in molecular medicine, however, requires the continuing education and update of knowledge of medical graduates so that these new advances and novel diagnostic and treatment modalities can be used appropriately on patients. Hopefully, this Seminar will serve this purpose or at least stimulate readers to find out more about molecular medicine, which has significantly altered medical practice.

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References