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BIMILLENNIAL HISTORICAL REVIEW

Part V. Beyond the second millennium

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'This is not the end, nor even the beginning of the end, but it is certainly the end of the beginning.'
WINSTON S. CHURCHILL

Introduction

The final days of the 20th century are uniquely symbolic. They provide an opportunity to consider the continuing challenges in surgical oncology in a much broader context. Science and technology have come of age in the past century and they provide the tools with which we can interpret and modify the natural world to shape the future. In this commentary, we consider these challenges and opportunities in the broader economic and social context from which progress in medicine is ultimately inseparable.

After 2000 years in which the horsemen of the apocalypse have ridden roughshod over Europe, we have good reason to hope for greater stability and security than ever before. Through various supranational institutions, we have created a framework for cooperation and greater mutual interdependence in political and economic life, which we may expect to continue through the 21st century. We have witnessed the acceleration of science and technology in countries with a more liberal intellectual and social environment.

The confusion of languages continues to impair communication. The gradual extension of English as the international second language and as the *lingua franca* of technical and scientific communication seems likely to continue, thus further aiding cooperation and development. Greater opportunities for trade, transnational television media and cheap communication seem likely to erode linguistic barriers and promote greater convergence of language with time.

The intellectual climate

The territorial battles in Europe between religion and science have been broadly and amicably resolved. The scientific mind-set is soundly established, and we have adopted the insights of Galileo, of Copernicus, of Newton, of Darwin and of Einstein into our world view. We have become conditioned to an immense rate of change in science and society relative to historical patterns. Witness, for example, the growth of computing since 1940, or the political and reproductive emancipation of Western women in the 20th century. Consider that less than 70 years separated man's first powered flight and his footsteps on the moon.

How will our acclimatization to rapid change affect our attitudes in the 21st century? We may ask whether the rate of growth in scientific knowledge will be sustained. What new intellectual challenges will sustain scientific man into the distant future? Are there undiscovered realms to science in the Universe? Or will all future knowledge be a matter of degree, refining existing theories and collating more data, be it in astronomy or molecular biology? Will we exhaust the scope for meaningful new knowledge? Are our local laws of energy, of light and relativity a local cosmic aberration, or do they apply universally? Is the Universe in a state of infinite expansion, or will it eventually collapse? Is warp speed to the stars a possibility, or will the hopes of space travel of the Star Trek generation remain unfulfilled and unfulfillable?

The economic environment

The early part of the 21st century will see an ageing population in Europe. The balance of resources, population growth and economic activity suggests that growth in wealth will be modest. The centre of economic and political gravity of Europe seems likely to move eastwards as European economic cooperation expands and natural resources are developed. Economic concerns are important because the costs of health care are likely to exceed the ability of the smaller working population to sustain them at current rates of consumption. We may therefore expect to practise surgery and oncology in an environment of gradually diminishing *per capita* public financial allocations. This situation has a

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number of practical consequences. Primarily, it will constrain widespread adoption of expensive cancer treatments. It will constrain expensive schemes for population screening, for example for endoscopic survey for gastrointestinal cancers. It will also oblige clinicians to compute the economic costs and consequences of cancer treatment, and to practise within greater economic constraints than was the case during the rapid economic growth phase of post-war Europe after 1945.

The ageing of the population also has significant consequences for the pattern of disease. We will see a continuing rise in cancers of all types in parallel with this rise, and a rise in all diseases of age and degeneration. The pattern and distribution of cancers in the Western world now seems well set. Barring a dramatic change in public policies towards tobacco consumption, the morbidity of cigarette smoking seems set to continue. Conversely, a much greater public sensitivity towards environmental and technological issues makes it likely that there will be a progressive reduction in morbidity from cancers associated with other processes and products of industry, such as asbestos and organic chemicals.

The technological environment

The pattern of interaction between man and technology now seems well established in the Western world. As finite fossil fuel stocks are consumed, we may expect to see an increase in dependency upon nuclear power and electrical sources of heating and propulsion. The growing cost of fuel will change the pattern of travel and communication. This will be offset by greater use of electronic communications, greater digital bandwidth leading to more use of 'virtual presence' techniques such as video imagery and tele-conferencing.

The computer revolution and applications such as the Internet still have a long way to run to maturity, changing patterns of employment and information use. The surgeon's craft may be secure from robotics for a long time to come, but the knowledge-based professions will undergo significant changes as access to information and expert-based systems becomes much easier for the public.

Space exploration will continue to expand our intellectual horizons. The technology of astronomy and of unmanned spacecraft will provide new interest and challenges. Of all the bodies in the solar system, Jupiter's oceanic moon Europa is a compelling draw for planetary probes. Questions of interplanetary colonization with simple, rugged DNA-based life forms will offer new horizons for environmental debate now that exportable, non-aerophilic life forms have been discovered around geothermal vents in the deep cold oceans and hot sulphurous springs on Earth.

The life sciences

Classification and genetics

We have seen the trend of the past 2000 years to consolidate and unify scientific theory, in mathematics, physics, astronomy, biology and chemistry. The past 200 years have been the period of biological and medical classification. In the 19th century, the broad classifications of disease were recognized. In the 20th century, this classification has been extended to the cellular and genetic levels. Genetic sequencing has allowed the identification of gene homologies and variations between species, and has characterized the sequence of species diversification, the molecular clock of evolution. The 21st century will see a continuation of this trend, to the exquisite definition of individual tumours according to their genetic components and irregularities.

The human genome project is one embodiment of this process of genetic classification down to the base nucleotide sequence. With this information, we may hope to understand the most subtle workings of the human cell, the tissue and the organism; of the processes of embryogenesis and differentiation; to devise more specific and effective treatments for a variety of diseases; and to understand precisely the mechanisms of cancer. This molecular deconstruction and reconstruction will pre-occupy molecular biologists for years to come. We may expect to see experimentation with the human genome and with reproductive biology, including cloning of parts of the genome for therapeutic experimentation. The prospect of encoding each individual's genome on a silicon chip is now at hand.

Within the field of cancer, genetic markers may find applications in the detection of minimal residual disease, the characterization of a source of recurrence, and the monitoring of bone marrow purging and differential display PCR (DD-PCR), the latter which allows catalogues of gene expression to be prepared for individual tumours.

Infectious disease

Sooner or later, we will be obliged to confront the failure of antibiotic practice through widespread resistance and microbial evolution. The antibiotic era may be short-lived and we may be obliged to fall back on other strategies of surgical antisepsis without the confidence of antibiotic 'bail-out' if serious sepsis intervenes. Conversely, molecular biology and immunology may find new strategies for systemic antisepsis, such, for example, as genetically engineered clonal immunoglobulins.

Old diseases will pose new problems. Tuberculosis seems likely to re-emerge as a significant problem in non-immunized populations. Malarial resistance is now widespread and morbidity is growing again. Climatic change, whether man-made or through natural meteorological variation, may bring the disease northwards into Europe. The plague and cholera may become epidemic again in some of the more crowded and destitute cities around the world. Continued vigilence remains essential against viral diseases, including influenza. While AIDS has been contained in developed countries, latent diseases such as the haemorrhagic fever viruses can emerge rapidly. A more sinister aspect of infectious disease is their deliberate use in human conflict. Biological agents, the 'poor man's atom bomb', are accessible to states which do not occupy common political, economic or religious ground with European nations.

Malignant disease

The detailed mechanisms of cancer development and progression have so far eluded understanding. The greater the detail of the genetic, signalling and regulatory mechanisms of cancer cells, the more the similarity with normal cells, the complexity and the power of homeostatic defence mechanisms (DNA repair, drug exclusion pumps) becomes apparent. We may come to view cancer as primarily a disease of human ageing and of genomic degeneration. Many cancers may be an inevitable epidemiological consequence of the longer life-span. The development of more effective cancer therapies, while offering considerable hope to individuals, may not have a significant effect on population dynamics nor global life expectancy.

The recognition of complexity of tumours and of the similarity rather than the differences between normal and malignant cells will condition our approach to cancer therapy in the 21st century. We have become accustomed and conditioned to specific treatments in medicine, where the mechanisms of a disease have been clarified. Thus, for example, antibiotics target specific molecular architecture of microbial cells, while receptor blockers modify heart rate, neurotransmission and gastric secretion. Cancer may demand a more complex approach, in which surgical excision of the established, morbid lesion remains the mainstay of therapy. New and subtle, multifacetted adjuvant strategies may need to be tailored to individual patients and tumours to optimize survival and quality of life.

Screening and early detection

Satisfactory and cost-effective screening strategies for most forms of cancer remain elusive. Prostate cancers may be amenable to detection by screening tests such as serum antigens. An effective tool for colorectal cancer screening is fibre-optic endoscopy, but total population screening is constrained by the huge cost of implementation and the balance of morbidity.

Genetic testing for solid tumours is in part constrained by our lack of understanding of the natural history of tumours. At what stage does a normal cell become malignant? To what extent does the individual's normal genotype contribute to the malignant genotype and phenotype later in life? Can such variations be reliably and predictively assessed? These are questions for the molecular geneticists in the 21st century.

New, non-invasive imaging technologies combined with computer databases and algorithms may also aid cost-effective screening for malignant disease. In this regard, the full potential of magnetic resonance imaging has yet to be explored. New forms of non-invasive blood analysis based on optical technology are also promised.

Instrumentation for cancer research

The technology of cell and subcellular analysis continued to advance at a prodigious rate in the 1990s. Many of these technologies will bear fruit well into the 21st century. Computers have transformed the capabilities of instrumentation, while lasers, fluorochromatic dyes and monoclonal antibodies will advance our understanding of cell and genetic structure and function. The confocal laser microscope will allow us to interrogate dynamic cell function in great detail. Quantitative laser cytometry will allow more precise predictive classification of human tumours according to their expression of moieties relevant to treatment, such as DNA repair enzymes and energy dependent multi-drug resistance pumps. This may be the key to more specific targeting of drugs to individual tumours, among other applications. Fluorescence-based comparative genomic hybridization (CGH) will allow rapid comparisons of the genetic composition of normal and abnormal cells. Fluorescence *in situ* hybridization will allow the rapid and detailed characterization of chromosomal abnormalities in malignant cells.

The human genome project has been accelerated by new technologies. For example, capillary array electrophoresis allows rapid gene sequencing when used in combination with base specific fluorochromes and laser light excitation. Such developments are allowing rapid progress to be made in the human genome project, which in turn will be the basis of substantial progress in the biological and clinical sciences.

The technology of drug development and screening will continue to advance in tandem with computer and laser technology. For example, light-directed chemical synthesis of oligonucleotide arrays is now possible on a silicon chip. This allows hybridization sequencing of genes and fragments on a single sliver of glass upon which up to 256 000 different but precisely defined oligonucleotides, each up to 20 bases long, are bound. This matrix of defined DNA or RNA sequences has so far facilitated the study of mycobacterium variants, of HIV drug resistance, of the *p53*, *MSH1* and *MLH1* genes in the colorectal cancer cascade, and of the *BRCA1* familial breast cancer gene. Future developments may see up to 5000 genes encoded on a single 'oncochip', for rapid and accurate assessment of mutations in cancer studies.

Prospects for cancer treatment

Surgeons have explored the full range of therapeutic options with conventional instrumentation, from the conservative (lumpectomy) to the ultraradical (hemicorporectomy) in the search for surgical control of aggressive cancer. The existing patterns of therapy seem well established, and surgery will continue to play a major role in the treatment of cancer unless dramatic advances in tumour lysing adjuvant therapy emerge. Surgical extirpation of the primary lesion, wherever possible, seems likely to remain the mainstay of eradicational therapy for cancer. We may see further refinement in technique, for example in relation to clearance margins, and in the surgical resection of metastatic disease, particularly of the liver, which shows promise. However, in overall biological and strategic terms, such refinements are likely only to show marginal benefits in subcategories of cancer.

The conventional instrumentation of the general surgeon seems likely to remain the mainstay of surgical practice. Laparoscopic instrumentation seems unlikely to succeed steel instruments and open surgery, because of the

phenomenon of metastatic port site seeding, because of cost, and because of technical constraints on the radicality of laparoscopic surgery in reasonable operating time. Other forms of minimally invasive therapy, such as angiographic placement of perfusion catheters, may find a useful adjuvant role.

Adjuvant therapy

New forms of administration radiation therapy such as continuous, hyperfractionated courses (CHART), or radiotherapy combined with synergistic drugs, may improve treatment. We do not seem at present well placed to make more than incremental gains with the existing range of drugs for cancer therapy. The search will continue for more specific cytotoxic agents and strategies with a broader therapeutic index. We are obliged to continue the search for effective treatment strategies along two routes: firstly, to seek out the distinctive features of cancer cells so as to specify new and effective therapies, and secondly, to develop existing treatment strategies to minimize morbidity and to improve the therapeutic ratio. We may expect to see further development of photoactivated drugs in the next few years, particularly for the treatment of light accessible tumours such as those of the urinary tract, and the development of new regional perfusion strategies, particularly for liver metastases.

Gene therapy (GT) has attracted considerable interest and resources. It may offer potential in cancer treatment. Gene therapy may be targeted at somatic or germ line cells. The criteria which justify research into gene therapy for any disease are that the disease process should be life threatening but potentially reversible, that the gene should have been cloned, that a delivery system should be feasible and that there should be a measurable end point to demonstrate therapeutic gain. Candidate diseases include immune deficiency syndromes, cystic fibrosis, the haemoglobinopathies and rare metabolic disorders. A variety of GT techniques have been considered, including immune enhancement, the vectoring of biological agents such as tissue-specific viruses, selective drug activation by specific genes (genetic prodrug activation therapy, GPAT) and the correction of somatic defects.

Gene therapy has yet to find proven applications in cancer therapy. A particular problem lies in the effective delivery of therapeutic vectors to all tumour cells. Human solid tumours are very heterogenous with regard to vascularization and perfusion, such that it is not possible to guarantee delivery of conventional agents to all areas of a target lesion. This problem may also apply to viral vectors. Nevertheless, early clinical studies are now in progress. One approach is to stimulate endogenous immunity to tumour antigens, using specific cytotoxic T cells and recombinant vaccines.

Concluding comments

The professional status and role of surgeons has been in continual evolution for many centuries. It may well be that the 20th century represents the zenith of autonomous practice for oncological surgeons. New patterns of oncology team working, centralization of cancer services and technical specialization will change our working practices. Clinical data collection, audit and outcome analysis will assume greater importance, aided by better computer software and data networking. The nature of the doctor–patient relationship will continue to change under the pressures from the legal systems and from rising public expectations and intolerances. The professional values of skill, judgement, character and manner will nevertheless remain at the core of surgical practice regardless of fashion and technology.

Optimism for advances in early cancer diagnosis and more effective adjuvant treatment in the next century must be tempered by realism. Cancer surgery has been exploited to its limits, and offers the prospect of cure to many patients. However, the inadequacies of cancer treatment still compromise huge numbers of patients with aggressive and advanced disease, for which we must seek new treatment modalities. If the 19th century was the century of classification, then the 20th century was the century of technical progress in surgery and its many associated disciplines. The principles of excellence in technique and judgement will remain central to the cancer surgeon's craft, but we must hope and strive for the 21st century to be the century of effective adjuvant treatment.

In the broader context, there is much to be done to advance the greater good of mankind. We may reflect upon the appalling life expectancy rates in many parts of the world, which far outweigh the epidemiological consequences of cancer. The balance of human happiness and human misery is now largely under man's control. We have the technical means if not yet the political will to harness war, pestilence and famine. Clinicians and scientists can influence the larger social, economic and political context in which we live and work. We must build upon the example of our predecessors who have had the moral courage to challenge accepted wisdoms in the past. There is much work still to be done for the betterment of mankind in the 21st century.