In this issue

Cancer

Cancer is a dreaded disease and its incidence is on the rise. This is particularly alarming in developing countries like India where life expectancy is increasing rapidly. It has been estimated that the incidence and death rate from cancer in India will rise by a factor of 3 between the years 1991 and 2025 simply as a function of ageing (Ramarao, pers. commun.). The incidence of cancer shows global variations, suggesting that different risk factors operate in different parts of the world (see Notani, **page 465**). These risk factors are largely related to lifestyle and diet but infectious agents such as viruses and parasites may also be causative agents. For example, hepatitis B virus infection is responsible for hepatocellular cancer prevalent in China and other south Asian countries, whereas Epstein Barr virus is associated with Burkitt's lymphoma prevalent in Africa. Infestation by the schistosoma parasite is responsible for the very high incidence of urinary bladder cancer in Egypt and other North African countries. In women, cancer of the cervix and breast are the commonest. The former is strongly associated with human papilloma virus which is likely to be the causative agent. The incidence of breast cancer is rising rapidly with increasing trend towards an urban lifestyle which results in late age at first childbirth, fewer pregnancies, shorter duration of lactation, etc., all of which are well-established risk factors for breast cancer. Nonetheless, tobacco remains the single most important cause of cancer worldwide (see Gupta, **page 475**). In India, over a third of all cancers are in the head and neck region, especially the oral cavity, consequent to the popular custom of tobacco chewing.

Cancer occurs in two waves during the human lifespan: a smaller wave of childhood cancers which usually occur during the first decade of life followed by several decades when cancer is rare to rise again in the 5th or 6th decades when the incidence rises exponentially. The childhood cancers are probably initiated *in utero* while the adult cancers are distinctly related to ageing and superimposed with lifestyle factors. Cancer is thought to be caused by mutations in the DNA. An initiating mutation produces a clone of cells, one of which is further mutated to produce a second clone which on mutation of one of its cells produces a third clone and so on until the eventual production of a clone of cells with a malignant phenotype. Further, genetic changes produce clones which are invasive and/or have metastatic potential. A small proportion of cancers (5%) are due to germline mutations in one allele of a gene, which are inherited predisposing the individual to a specific type of cancer. The loss of the other allele at a later age precipitates the disease. The remaining large burden of sporadic cancers is caused either by spontaneous mutations or external agents such as radiation, chemicals or carcinogens such as tobacco.

Mutations in the DNA that produce cancer afflict either the genes that safeguard the integrity of the genome called 'caretakers' such as mismatch repair genes, nucleotide excision repair genes, etc. or cell cycle check-point genes called 'gate-keepers' which prevent cell cycle progression until the damaged DNA is repaired. The latter category of genes include *p53*, *Rb* (retinoblastoma gene), *APC* (adenomatous polyposis coli gene), etc. (see Anderson, **page 501**). In inherited cancers one allele of either the caretaker or the gatekeeper genes is mutated in the germline. Examples of inherited cancers due to mutations in caretaker genes are xeroderma pigmentosum, atexia telangiectasia, hereditary non-polyposis colorectal cancer, etc. while those due to mutations in gatekeeper genes include Li–Fraumeni syndrome, Wilms tumour, etc. Although the genetic lesions in heritable cancers are well understood, the genetic changes in the vast majority of sporadic cancers which occur due to somatic mutations remain largely obscure.

Two types of cancer genes whose mutations can cause either gain or loss of function are known (see Zingde, **page 508**). Oncogenes belong to the first category and are capable of transforming predisposed cultured cells *in vitro* in their mutated forms. Normal cellular oncogenes in their physiological capacity are usually concerned with normal cellular proliferation or signal transduction. Some of these oncogenes code for growth factors or growth factor receptors (see Rajkumar, **page 535**). They are abnormally activated by point mutations, translocation to abnormal sites to produce fusion proteins or by amplification. Interestingly, during evolution retroviruses appear to have incorporated these oncogenes into their own RNA genome during infection of animal cells. Several oncogenic viruses have been isolated, which are capable of causing cancer in the animal kingdom as a result of overexpression of the viral oncogenes driven by the strong viral promoter. RNA virus-induced cancers are common in animals but are surprisingly rare in humans (see Weiss, **page 528**). DNA viruses are more common in causing human cancers and they do so by incorporating their DNA genome into the host nucleus. Examples are: human papilloma virus causing cervical cancer, hepatitis B virus causing liver cancer and Epstein Barr virus causing nasopharyngeal cancer and Burkitt's lymphomas (see Zur Hausen, **page 523**). Loss of function genes or tumour-suppressor genes seems to be more important in human cancers; their mutation leads to the accumulation of other mutations, including those in oncogenes, due to loss of cell cycle check-point function. The subject of cell cycle control in relation to cancer is discussed by Michelle Garrett (**page 515**). Loss of function genes are also involved in DNA repair and their mutations may lead to genomic instability. Although numerous mutations in diverse genes have been described, so far not a single gene has been found that is mutated in all sporadic cancers, or all sporadic cancers of the same type or organ, or even all cells of the same cancer. Many oncogenes and tumour-suppressor genes seem to be involved in every cancer but the same genes are not found to be mutated to all cancers. A global view of how gene mutations may result in cancer has eluded us. Major mutations in the form of chromosomal aberrations and aneuploidy as the cause of cancer was described nearly 100 years ago. Virtually all sporadic cancers show varying degrees of large chromosomal changes. It is being increasingly realized that chromosomal instability and aneuploidy may be extremely important in the development of cancer. An interesting debate on the competing theories of

cancer involving gene mutation and aneuploidy is presented by Peter Duesberg *et al.* (**page 490**). Genomic instability, both at the level of nucleotide sequence and chromosomes, is the hallmark of cancer and the surprising extent to which the cancer genome is unstable is discussed by Garth Anderson (**page 501**). Anderson shows that chromosomal instability precedes malignant transformation and may be the cause and not the result of malignancy.

Doll and Peto have estimated that approximately 70% of human cancers are preventable either by quitting tobacco or a change in diet and lifestyle. However, such a goal is not easily achievable. Early detection of cancer by screening is a complex issue and has been successful only in cervical cancer and, to some extent, in breast cancer. Identifying populations with genetic predisposition to cancer is currently being extensively pursued (see Mohandas, **page 482**). If such populations are identified then screening and prevention approaches can be directed to such predisposed groups. On the other hand, it has been argued that those who test negative may take such a carefree approach to life that there will be more deaths from their indulgence than by the prevention of cancer in the predisposed groups. Of the common cancers, 5% of breast cancers are caused by the inheritance of mutated *BRCA1* and *BRCA2* genes and their recent identification has opened up prospects of counseling and prevention but has at the same time raised many ethical and legal issues concerning genetic testing. The human genome project opens up the prospect of identifying more subtle forms of genetic predisposition in the population which may be related to specific DNA polymorphisms. However, how predictive, either singly or in combination, these polymorphisms will prove to be, will be a question for the future.

As we all know, treatment of cancer has not been the greatest success story of modern medicine. Apart from some haematogenous cancers, childhood cancers and lymphomas where chemotherapy has had considerable success, the common solid tumours – the real killers have been refractory to treatment. Surgery forms the mainstay of treatment of solid tumours but is successful only when the tumour is detected in early stages. The addition of chemotherapy and radiotherapy provides only marginal improvement on the survival figures. The future trend of treatment of cancer is going to be more targeted than the blunderbuss approach of chemotherapy which kills cancer cells indiscriminantly. Gene therapy is one such approach and many clinical trials using different methods are in progress (see Mulherkar, **page 555**). These include the use of replication-deficient retroviruses or adenoviruses as vectors to deliver the gene in question; the use of synthetic antisense DNA molecules; immunemodulation by the introduction of genes *ex-vivo* into T-lymphocytes or dendridic cells; the use of modified tumour infiltrating lymphocytes as adoptive immunotherapy; use of suicide genes which produce enzymes that convert the antiviral drug ganciclovir into toxic products, or DNA vaccines in which DNA coding for tumour-specific antigens are injected intramuscularly as naked plasmid DNA. However, it is not yet clear as to how successful gene therapy will be in the long run in our battle against cancer.

On a more futuristic note, new drug development based on knowledge emanating from the human genome project has caught the pharmaceutical industry in a tizzy (see Sikora, **page 549**). It is hoped that many new targets for the cancer therapy will be discovered and huge investments are being made and the future challenge is not only to find new targets but also to decide which target is likely to be most fruitful, given the fact that millions of dollars are required before a drug can be eventually marketed. But the real question is, given the molecular complexity of cancer, whether targeting one (or more) molecule will be sufficient to eliminate cancer cells.

Personally, I feel that killing of cancer cells may not be the final answer to the cure of cancer. This has been amply demonstrated in common solid tumours in which chemotherapy, albeit with its blunderbuss approach, has fared poorly. While there have been dramatic responses to chemotherapy in these cancers in terms of tumour shrinkage, these have not led to a commensurate increase in cure rates. The classic example is high dose chemotherapy in metastatic breast cancer. Several studies have shown that although high dose chemotherapy with bone marrow rescue can lead to disappearance of all disease (often up to half a kilogram of tumour tissue) in upwards of 50% of the patients, compared to in only 10% of those given conventional chemotherapy, the survival curves are identical. What makes us believe that when the blunderbuss approach of high dose chemotherapy, which kills cells indiscriminately, fails to cure cancer that therapies specifically targeted at genes, enzymes or receptors will achieve a cure? After all, the goal of treatment in both cases is the same – to induce apoptosis!

It is unlikely that there is going to be a dramatic cure for cancer in the near future in spite of all the hype of pharmacogenomics, gene therapy or other novel anti-cancer agents. To my mind the cure of cancer is still a distant dream because we are far from understanding the real nature of our enemy. Nevertheless, progress will certainly be made but these will take place in small increments through treatment (both molecular and traditional), early detection and prevention. And to measure these small increments in survival or cure we need precise scientific instruments. Included in this issue is an article by Badwe (**page 561**) on the importance of randomized clinical trials which is the only instrument capable of measuring small clinical benefits reliably. Finally, lest we forget the cancer patient who continues to suffer from pain and misery in spite of the excitement of the emerging science, I have included a chapter on psychosocial research so that we can determine how best to assess the patients' woes in order that we can deal with them with compassion and understanding (see Watson, **page 566**).

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