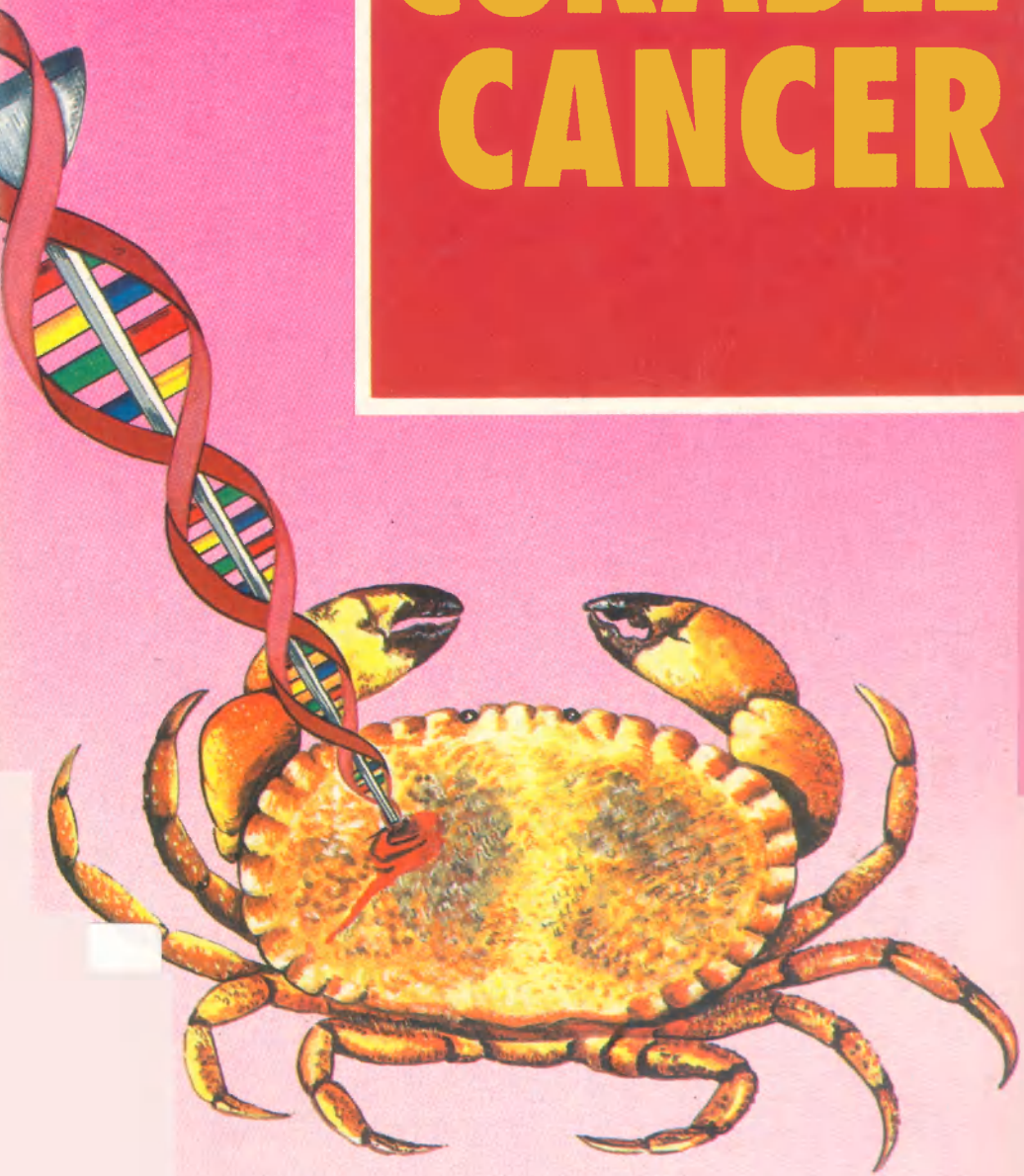
A.N.BHISEY

CURABLE CANCER



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Curable Cancer

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FOREWORD

At times human, animal and plant cells start dividing repeatedly instead of growth and differentiation that follows cell divisions in normal tissues. This unrestrained growth of cells is known as cancer. The ancient Greeks had recognized the crab like movement of the disease in the body and named it cancer The disease is widespread in humans and animals. The question what makes a normal cell cancerous has not been answered as yet, in spite of intensive research in the molecular biology of cancerous cells. It is largely believed that cancer is not a single disease and different mechanisms are involved in the transformation of a normal to a cancerous cell. The underlying mechanism is the alteration in the genetic material DNA. Thus, cancer is also regarded as a malady of genes. This can be brought about by mutations which may arise due to errors in DNA replication, exposure to radiations, and carcinogenic chemicals or tobacco smoke. Though a good mechanism to repair the genetic damage is present in living systems, at times the damage is not rectified. A single altered cell in which the regulatory mechanisms are impaired leading to uncontrolled divisions could be the origin of cancer. A number of early response genes are turned on which produce oncoproteins. Some of the oncoproteins are known to act as transcription factors and influence transcription of many other genes. Aberrant expression of nuclear oncoproteins leads to cancerous growtn.

Almost undetected, cancer spreads from its site of origin to the neighbouring organs if left unchecked. Even today, cancer remains a formidable disease. However, with spectacular advances in diagnosis and treatment, the survival rate of cancer patients has considerably improved. At the end of the 1930s, the five-year survival rate was one in five or less. Ten years later it had improved to one in four and in the mid-fifties to one in three. The improvement in survival rate is due to better awareness of the disease, early diagnosis and more effective treatment.

Cancer is curable, but prevention is better than cure and certainly many cancers are preventable. Lifestyle choices

influence the incidence of cancer. India has the world's highest rate of oral cancer which is linked to the widespread habit of chewing tobacco. Links between smoking and lung cancer have been well established. In mice, through selective breeding, strains have been developed which consistently showed high incidence of certain types of cancers. The role of heredity in several human cancers was also suspected for a long time. Now the specific genes for the cancer of the rectum and for breast cancer have been identified. Occupational and environmental exposure to carcinogenic chemicals should also be minimised to bring down the incidence in spite of the genetic potential.

Making use of the expertise available in the country, the Publications & Information Directorate (PID) is bringing out a series of popular monographs in biotechnology as a part of the project on 'Dissemination of Biotechnology Information' sponsored by the Department of Biotechnology, Government of India. These monographs would benefit school, college and university students and teachers as well as members of the public and create an awareness among them towards the newer developments in this field taking place globally and in the country. They would also create awareness of the enormous potential of biotechnology in improving our socioeconomic conditions. Both PID, which is one of the premier institutions of its type in the country engaged in dissemination of scientific information and science popularization for more than 25 years and the authors of the various monographs, who are all highly acclaimed for their scientific contribution have joined hands in this very important venture. I am confident that the readers would find the monographs informative and enlightening and this would contribute to the development of the multi-disciplinary area of biotechnology in the country.

(C.R. Bhatia)
Secretary
Department of Biotechnology
Government of India

PREFACE

The word cancer still instills great fear in the minds of people at large and in the minds of cancer patients and their relatives in particular. There is probably no other disease more misunderstood and sinned against than cancer. The misconceptions about cancer encompass a very large canvass covering its curability at one end and its etiology at the other. The question always asked is, 'when will a magic cure be found for cancer?' In this book, I have tried to address these issues in the light of present day advances of our understanding of the cellular and molecular biology of cancer and their possible impacts in preventing as well as treating cancer in future. I have attempted to make some of the scientific concepts simple without going into minute details. I hope that it will remove misconceptions and help change our attitude towards this dreaded disease.

ACKNOWLEDGEMENT

The seed for writing a book on cancer came from my long time friend Bal Phondke. However, he put himself in a very difficult position after easily convincing me into this venture. It was his great patience, perseverance and gentle prodding which finally made me complete the book. My several discussions with him also helped in the process of crystallizing some ideas.

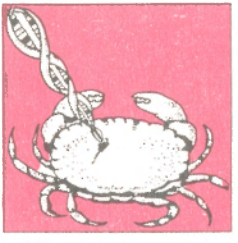
I am grateful to Dr Sukanya Datta, the editor of this book for help and suggestions. She removed several kinks and rough edges from the manuscript. I am thankful to Dr S.H. Advani and Dr K. Dinshaw of the Tata Memorial Hospital for readily providing me with some of the photographs. I am also thankful to Pradip Banerjee and Neeru Sharma for the illustrations in the book.

Dedication

This book is dedicated to my teacher
Dr (Mrs) Kamal J. Ranadive who introduced me
to the excitement of cancer research and to
Prof V.R. Khanolkar whose wide vision laid the
foundations of cancer research in India.

Contents

"*Saab pehchana* ?" The person who stood before me seemed familiar, but I could not place him immediately when he asked me if I remembered him. When I appeared uncertain, he said, he was Sanju's father and that I had helped him over ten years ago. Then it all came back to me very clearly. This gentleman had come to me with a little boy of about four. A friend of mine had asked them to see me for advice and any help they might need. The little boy Sanju, was suspected to have leukemia or blood cancer as it is generally known. Investigations were started immediately and diagnosis was made in about three days. Sanju had Acute Lymphatic Leukemia (ALL), one of the more



What, why and how

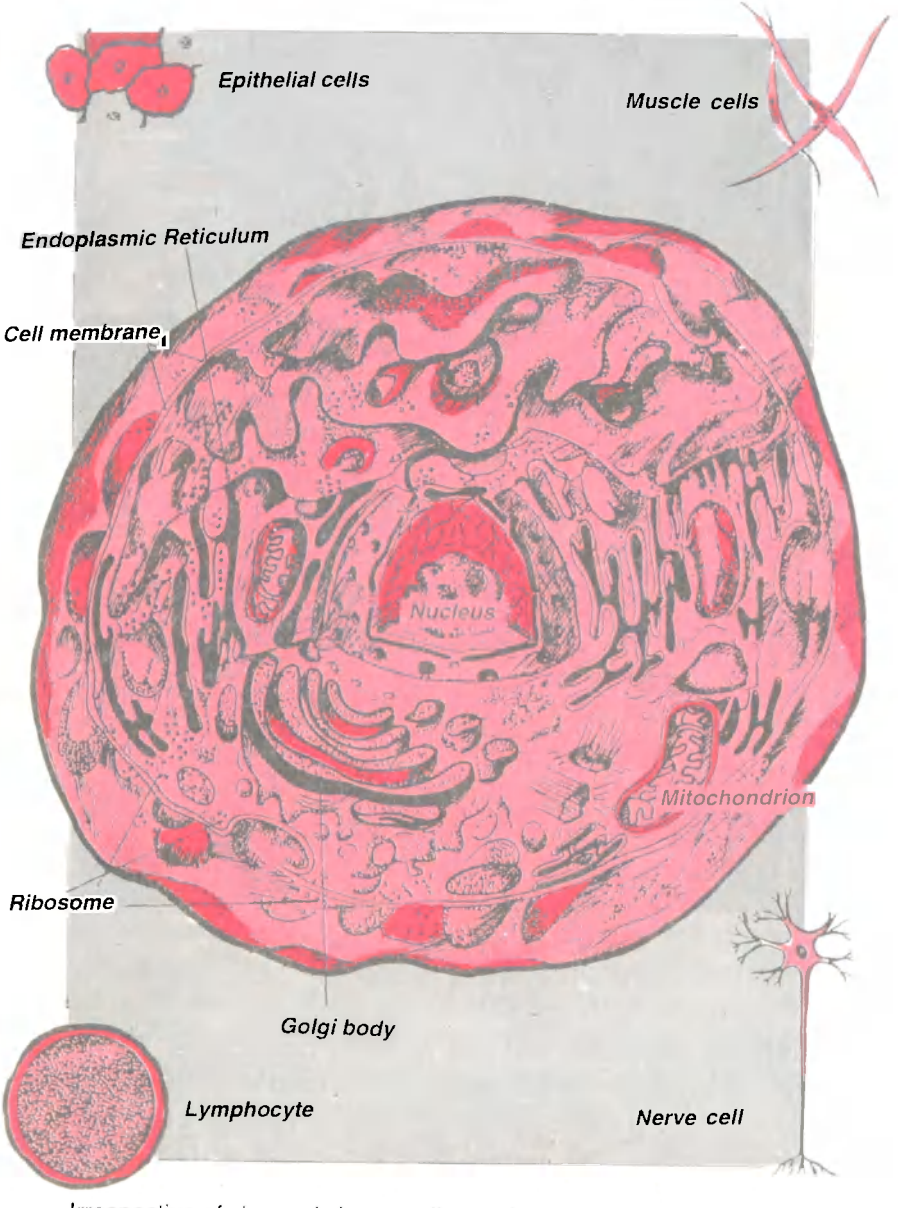
common childhood malignancies wherein excessive number of white blood cells are produced. ALL is also curable in a very large percentage of patients by using specific chemical agents to arrest and eradicate the disease. This is called chemotherapy. Sanju's father was worried. But the doctors explained to him about chemotherapy and the precautions to be taken by the patient and the family. They also told him about the importance of preventing infections and also about the very high chances of survival. The doctors advised him that chemotherapy had to be given at regular intervals and that this caused some side effects. Sanju's father agreed to follow the doctor's advice and therapy was started immediately. I used to see Sanju during the first year when he came for therapy but later lost track of him. I was surprised to see Sanju's father after such a long time and naturally inquired about Sanju. He said very happily that, Sanju was fine and working hard to appear for his secondary school certificate examination. I was really happy to hear this. Sanju is growing

into a normal adult and will live a full and normal life. This was possible due to timely diagnosis and total compliance with the doctor's advice.

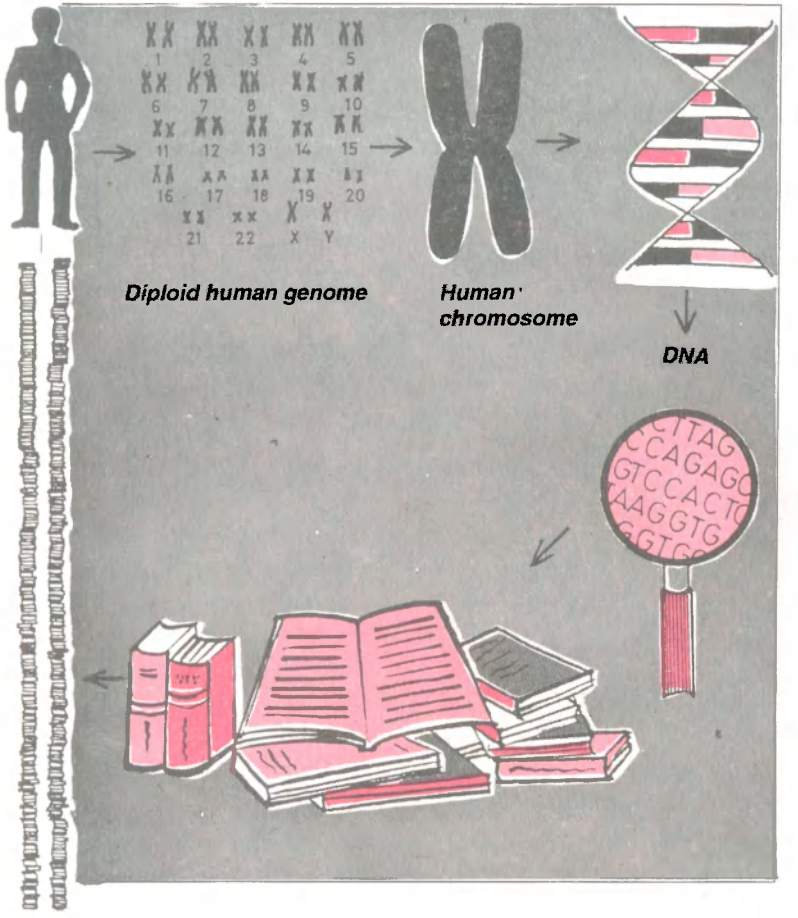
It is generally known that cancer is a problem of abnormal growth in any part of our body. It usually results in the formation of a lump or a mass. However, a number of questions still arise in the minds of people. The questions that they ask are, What is cancer? How does a cancer develop? Are all cancers curable? Will there ever be a common cure for cancer? Are cancers hereditary? Do they affect people of all ages equally? To understand the answers to some of these questions, one must first understand how our body is organized.

All living beings — plants as well as animals, are made up of a large number of basic units called cells. A cell is the structural and functional unit of living beings. There is a gradation in the complexity of organisms in terms of their organisation. Thus, some organisms such as the amoeba, or the malarial parasite, are made up of a single cell which carries out all the life functions. Such organisms are called unicellular or single celled organisms. The majority of organisms are, however, made of many cells joined together and are called multicellular organisms. In multicellular organisms such as man, the house fly, or the whale, the cells are organized into specialized tissues which come together to form organs and systems which carry out specific functions. Thus, the digestive system carries out the function of digesting the food and converting it into simpler molecules which can be absorbed and used for making energy and building up the body. The red blood cells carry oxygen to the tissues for respiration and the white blood cells fight infections. There is a division of labour in the body to carry out different functions and different types of cells become specialized to carry out these seemingly unrelated jobs.

An animal cell is a bag-like entity consisting of a nucleus and the surrounding cytoplasm. A membrane around the



Irrespective of size and shape, cells are the structural and functional units of the body

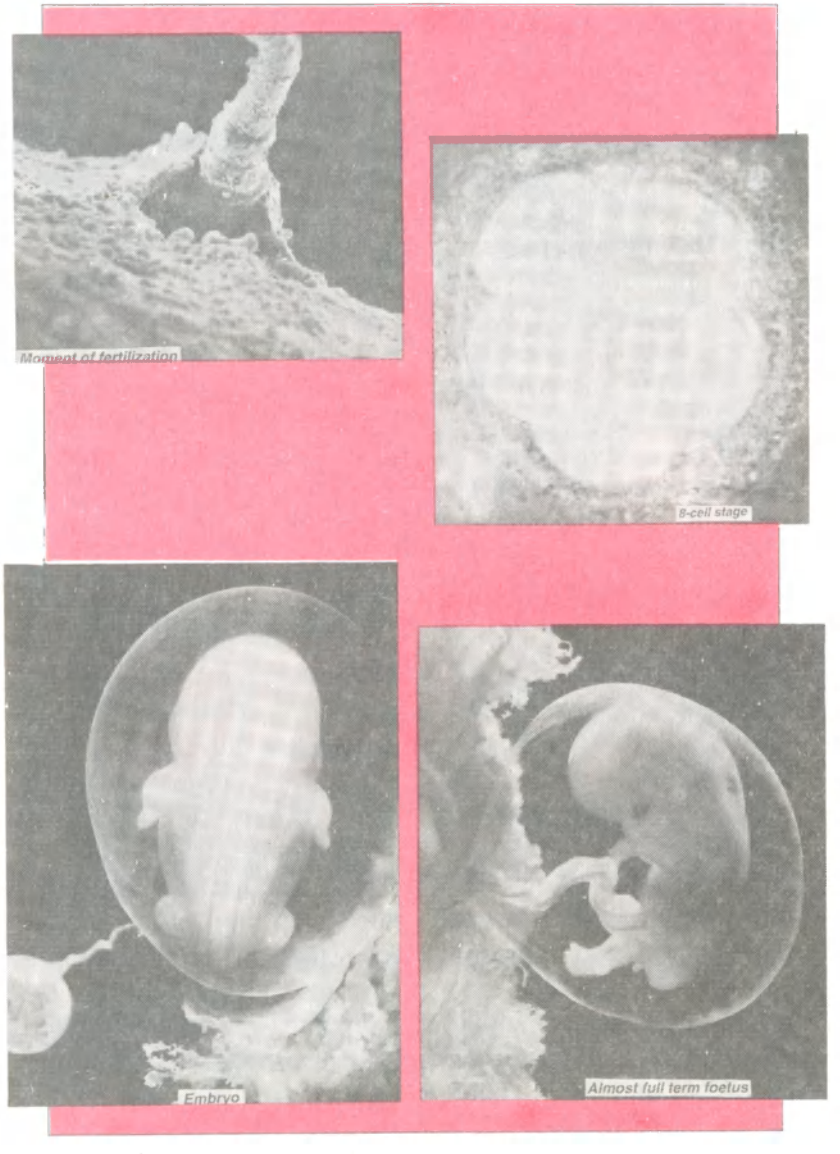


The genomic book of life

cytoplasm separates the cell from its neighbours. All the genetic information of the organism is stored in deoxyribonucleic acid (DNA) in the nucleus. The information is organized in small units — the genes, and the genes are arranged linearly in long packages — the chromosomes. Genes carry all the information about each individual such as the colour of our skin, eyes and hair. They also carry detailed informa-

tion such as whether a person will develop diabetes or heart problems. They also instruct the cells to carry out different functions by making different proteins as and when required. Genes control cell division as well. Genes are thus, also the master switches in our cells. In a normal human cell, there are 23 pairs of chromosomes. One of these pairs has dissimilar partners in the males: the larger of the two is the X chromosome and the smaller is the Y chromosome. In females there are two X chromosomes. The DNA molecule is a long double helical molecule. The total length of DNA in a single set of 23 chromosomes is about one metre but it is very efficiently packed in the chromosomes so that they ultimately fit into a cell which may have a diameter of 10 micrometres. Since a micrometre is a millionth part of a metre, nature's packaging skills merit praise.

The adult human body contains 100 trillion cells. This is one followed by fourteen zeros! These cells make up the different systems in our body. However, all these cells can trace their origins to a single cell — the fertilized egg. The fertilized egg, called zygote, is formed by the fusion of the egg contributed by the mother and the sperm donated by the father. After fusion of the two, which is an event called fertilization, the zygote passes through a period of rapid cell division. This process of cell division is called mitosis. During mitosis, one cell divides into two daughter cells which are exact copies of the parent cell, and they in turn further divide into two cells each. At each cell division the DNA is copied identically so that each daughter cell formed from the original cell contains identical sets of chromosomes and also the genes. This results in the formation of millions of cells from a single zygote. After the period of initial rapid division, some cells start undergoing changes in their size, shape and contents in preparation of the work they will undertake later. This is called differentiation. Differentiation specializes the cell and enables it to carry out specific functions. These specialized cells come together to form tissues which together form



The single zygote gives rise to the entire body

organs and these go on to form various systems in the body. Once the cells differentiate, they usually stop dividing. Thus, cell division and development of organisms are very well regulated phenomena. We still do not fully know how these controls work.

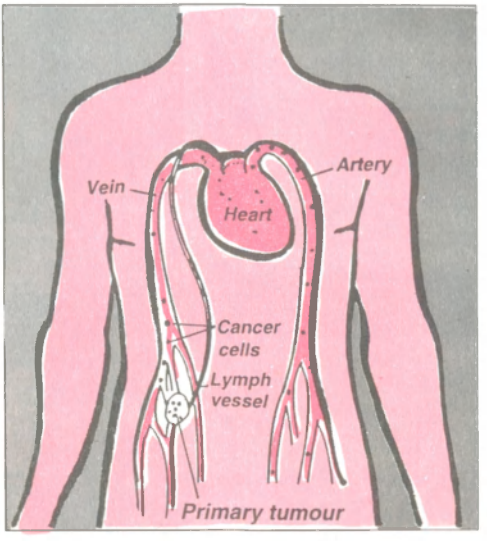
In a fully developed animal, most tissue cells do not divide. Cell division occurs only in certain tissues where continuous renewal of cells is required. Some such tissues are the skin, the lining of the intestine and the bone marrow where the red and white blood cells are formed. The red blood cell (RBC) contains the protein hemoglobin which gives our blood the red colour. Blood cells are a very good example of cell types which are continuously replaced in the body. The human adult has about 5 litres of blood which contains approximately 5 million RBC per ml of blood. The average life span of an RBC is 120 days or 10 million seconds. Therefore, 2.5×10^{13} new RBC should be produced every 10^7 seconds. This means 2.5 lakh cells need to divide every second to make new RBC. There are many more such divisions occurring in the body to replace worn out cells. All these cell divisions are well regulated and they produce cells which carry out useful functions for the body in a coordinated manner. The body is indeed a very well designed and precisely functioning machine.

However, sometimes this tight control over cell division in some cells is lost and they start dividing indiscriminately to form a mass of cells which is called a tumour. A tumour can continue to grow and increase in size at one site. They are called 'benign' tumours.Such tumours are less harmful, since they can be easily removed by surgery. However, most of the tumours we see in human beings do not stay at one site. After initial growth, the tumour cells become free, travel through the blood or **lymph** ducts and lodge themselves in other tissues. At these sites, they start 'secondary growth' or 'metastasis'. They also invade the surrounding tissue and cause its destruction. Such tumours are very dangerous and are called 'malignant' tumours. Because they spread to mul-

Cellular anarchy is like a population growing without check

tiple sites it is not possible to remove them surgically once tumours have already formed metastasis. Such tumours should ideally be diagnosed before they spread so that they can be surgically removed. Otherwise they have to be killed

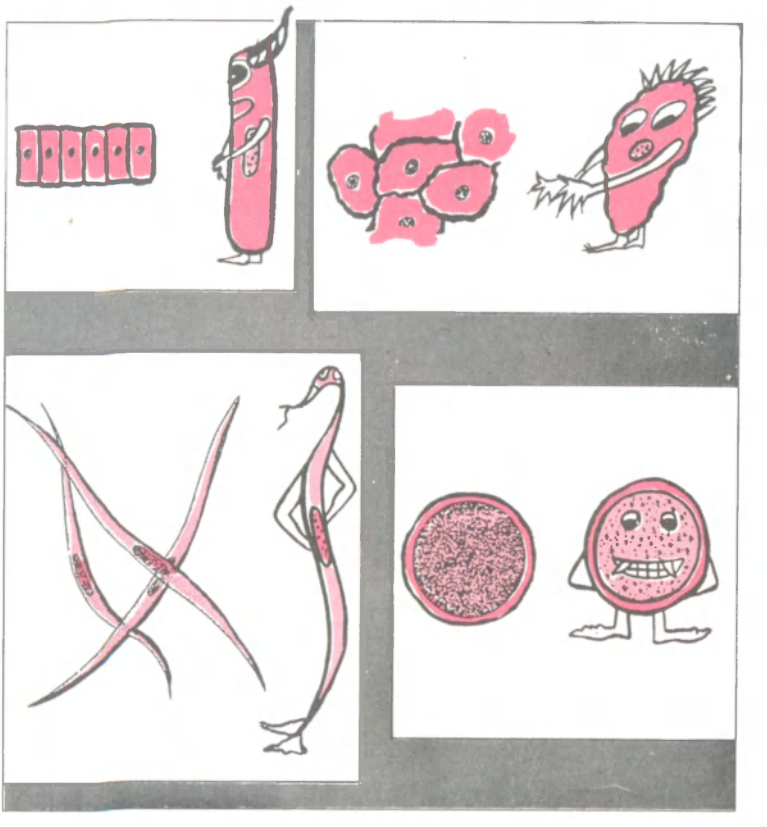
by radiations such as X-rays or γ-rays by focussing a beam of these rays on the tumour. This is called radiotherapy. The patient is also treated with anti-cancer drugs, which preferentially kill the tumour cells. Though all the tumours are generally called 'cancers', it is appropriate to call only malignant tumours, cancers.



Cancer uses the lymph ducts as highways

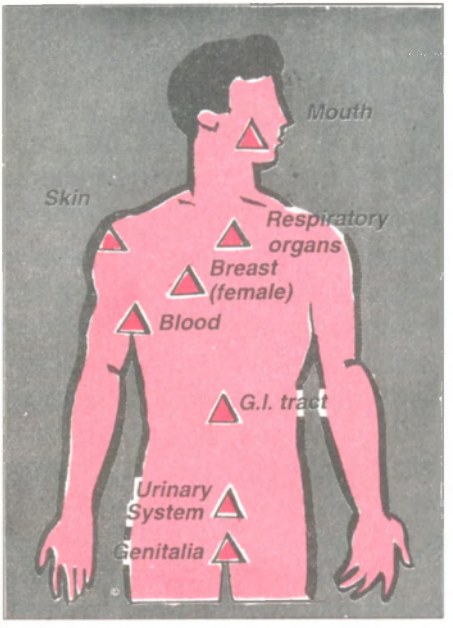
The word cancer came from the Greek word *cancrum* which means crab. The ancient Greeks had recognized tumourous growth in the body as something harmful and had realized that it spreads in the body. They felt it spreads in the body the way a crab walks. But a crab is a harmless animal and any similarity between the two is fanciful. However, the name has stuck. In our own country, description of cancers is found in — *Sushruta Samhita,* our ancient text on medicine in which different types of tumours are described.

It is apparent that any cell (or group of cells) in any of our tissues has the potential to turn cancerous or 'malignant'. Since there are many types of cells in our body, such as nerve cells, red and white blood cells, fibroblast cells, bone cells, muscle cells, and many others, therefore, there are as many types of cancers depending upon the cell type involved. Cancer is thus, not a single disease but a fairly large group of diseases. Since the various normal cell types carry out



Cancer cells have distinct identities and need different forms of treatment

different functions in the body they behave differently from each other. Their cancerous counterparts also behave differently depending on which cell type has been affected. This means that they do not grow at similar rates, they form metastasis in different tissues and they cannot be eliminated by similar anticancer drugs nor are they all equally effectively killed by radiation. They also occur in people of dissimilar age groups. It is thus clear that for such a diverse collection of diseases, there cannot be one single effective remedy.



Cancer may strike anywhere

Cancers are given a generic name depending upon the type of cell from which they develop. Thus, all cancers developing from **epithelial** cells are called 'carcinomas'. This is the single largest group of human cancers, making up almost 80% of all cancers. Tumours arising from connective tissue cells such as **fibroblast** or bone cells are called 'sarcomas'. Cancers of blood are called 'leukemias'. They are identified more specifically in accordance with the specific blood cell type. Among the leukemias, those which originate from the **lymphocytes** are called lymphatic leukemias while those arising from **neutrophilic cells** are called myeloid leukemias. In leukemias, the cancer cells are not localized but freely circulate in the blood. Lymphomas are cancers of lymphoid origin which get localized in lymph glands. There are no cancers of the red blood cells because these do not divide in the human blood stream but there are cancers of the parent or stem cells which give rise to the red blood cells. Cancers of the nervous system are named according to their cell of origin. Many different types of cells come together to form the nervous system. They also perform different functions. In the nervous system, the brain is the central organ. Messages are sent to the brain cells which

process them and send their response back to the various organs. The nerve cells carry out these functions. In addition, there are supportive cells which help them in different ways. Such supporting cells are collectively called glial cells. Tumours arising from the nerve or neural cells are called neuroblastomas. Tumours of the glial cells are called gliomas and they can also be further classified according to their cell type.

Cancer is generally considered a disease of the middle and the old ages. But certain cancers such as Acute Lymphatic Leukemia are seen mainly in children. With the advances in chemotherapy over the last twenty years, this dreaded disease is now more than 70 per cent curable. Many more cancers are now being treated successfully and are coming under the curable category. But for a cancer to be cured, it must be detected before it forms metastasis. Thus, early detection of cancer is one of our best bets in our fight against cancer, since if detected early, most cancers can be cured. Cancers are difficult to cure by treatment with drugs. In many diseases such as typhoid, tuberculosis and malaria, the causative organisms are quite different from the host's cell types. It is therefore possible to kill the germs with **antibiotics** without harming the body cells. However, cancer cells are cells of our own body. Only the regulatory mechanisms have gone haywire. Hence, it is much more difficult to prepare drugs that will selectively kill cancer cells without harming the normal cells. All anticancer drugs always have some toxic effects on normal cells. So, there are side effects on the patients while the treatment is going on. Common side effects of chemotherapy are vomitting, loss of appetite, weakness and loss of hair. The side effects disappear when the treatment is stopped. Therefore, it is important to detect the cancer early enough when it is localized and has not formed metastasis. In that case, it can be removed completely by surgery. When a cancer is at a place from where it can be removed by surgery without damaging the surrounding tissue, the

treatment of choice is surgery. Radiation therapy, which involves killing the cancers by X-rays or γ-rays and chemotherapy are considered to be treatments of second choice except in some specific cases where they are preferred.

CAUTION is our best bet in detecting cancers. The warning signals are the following:

Change in bowel or bladder habit.

Asore that does not heal.

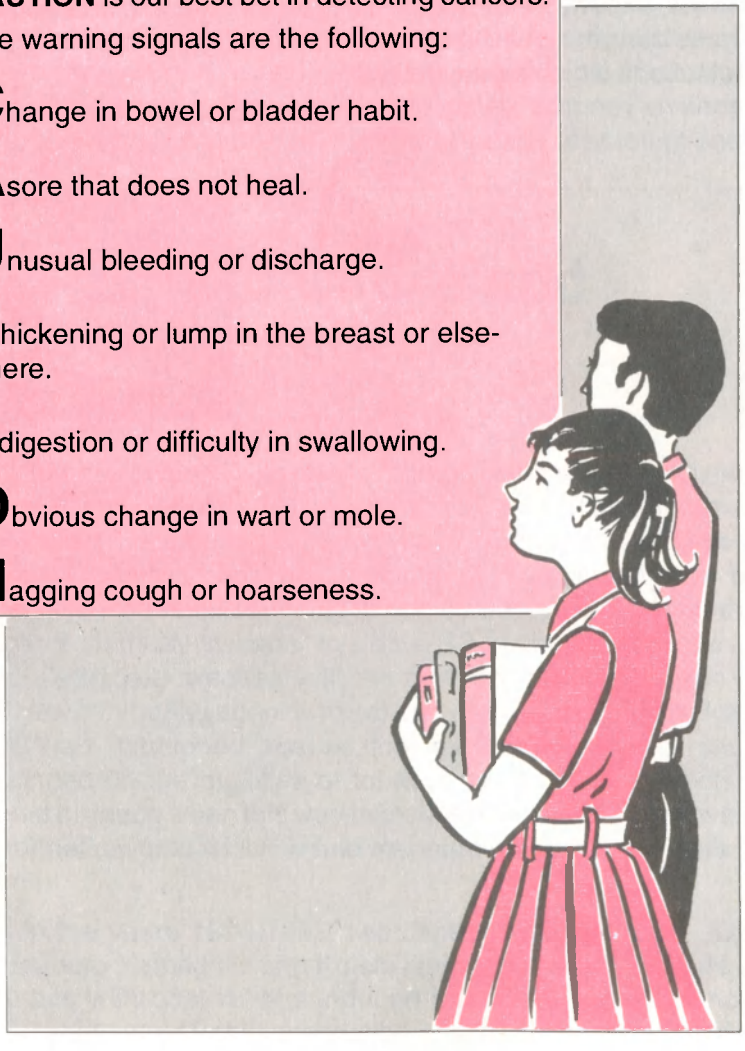
Unusual bleeding or discharge.

Thickening or lump in the breast or elsewhere.

Indigestion or difficulty in swallowing.

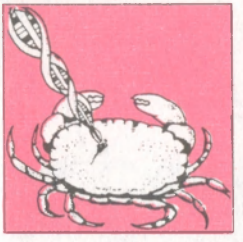
Obvious change in wart or mole.

Nagging cough or hoarseness.



There are no specific symptoms of cancer. Hence, people do not suspect that they may have cancer. When the symptoms finally appear, the cancer may be too far advanced for successful treatment. There are certain warning signals of cancers which everybody should know. If anyone senses any of these in his or her own case, or in their close relatives and friends, expert advice should be taken to clear the suspicion. These danger signals are publicized throughout the world by institutions which fight cancer.

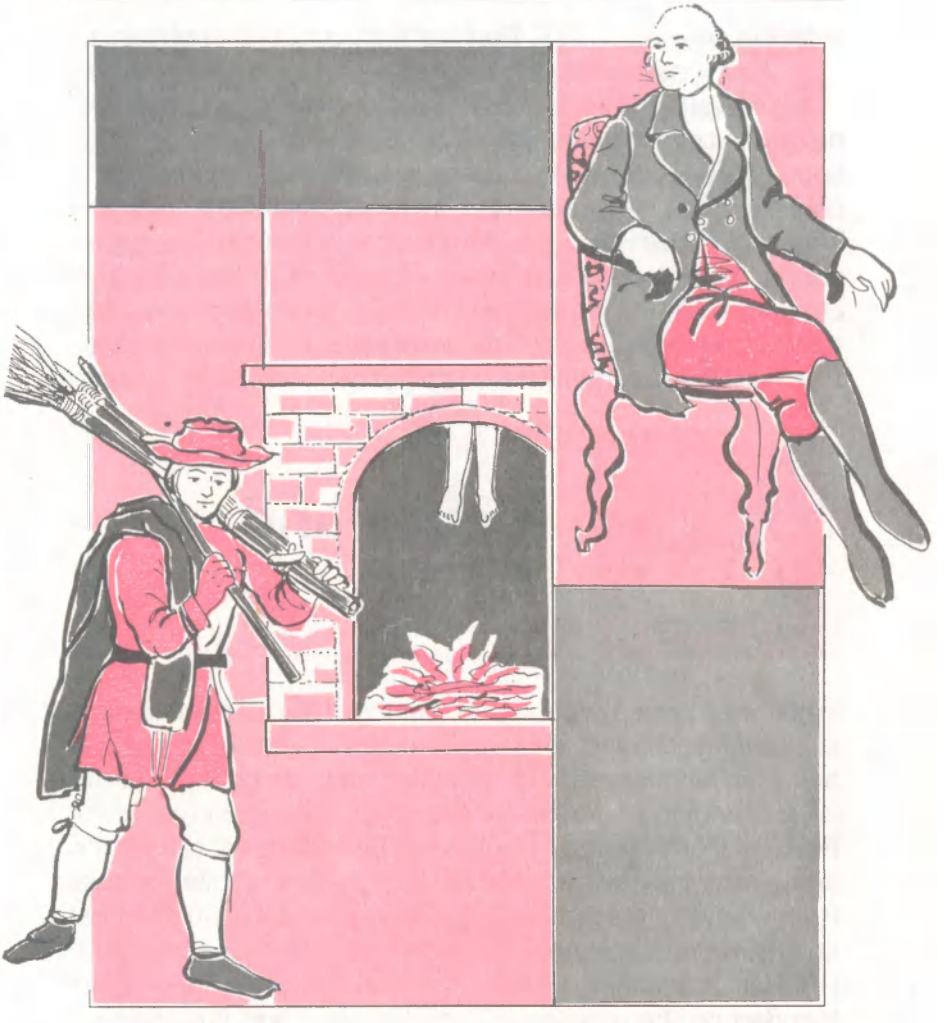
The year was 1775. Percival Pott, an English physician had made an epoch making report in '*Chirurgical observation*', that "cancer of scrotum was an occupational hazard in chimney sweeps attributable to contamination with soot". In those days the houses in England were heated by coal fires. The smoke from the fire places went up a chimney. The soot collected in the chimneys was cleaned by skinny young boys around ten years of age who climbed down chimneys without wearing any clothes which could obstruct their movements. These boys were called 'chimney sweeps'. Percival Pott accurately deduced that cancer of scrotum seen



Cause and effect

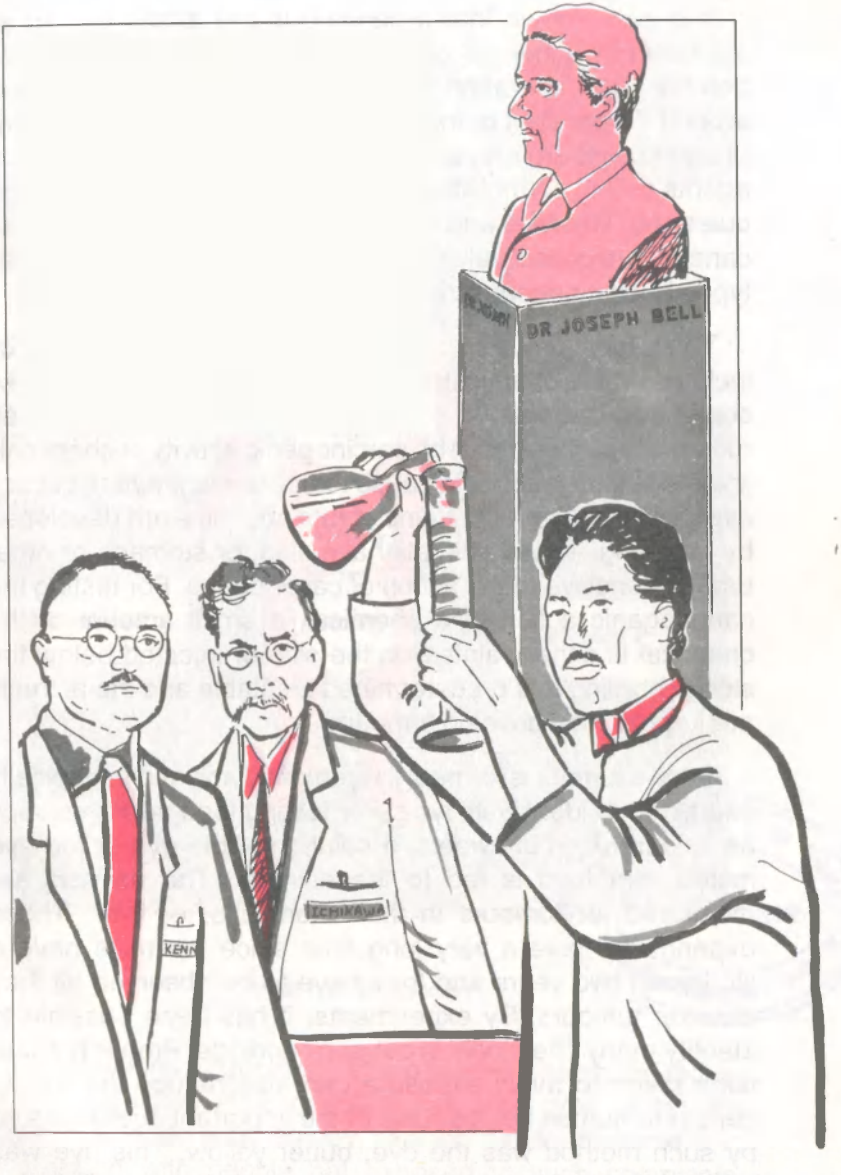
in chimney sweeps was due to rubbing of the scrotum against soot during cleaning. This was probably the first of what could be called 'undesigned experiments', which were to add to our understanding of cancer development. This observation by Percival Pott resulted in legislation by parliament raising the age of chimney sweeps to above 10 years. While Percival Pott is usually credited with the first reported association of an environmental agent with cancer, as early as in 1759, John Hill had "cautioned against the immoderate use of snuff founded on the qualities of tobacco plant and the effects it must produce when this way taken into the body" These were prophetic words which would resonate down the corridors of time.

In the years 1914-1915, two Japanese scientists — Katsusaburo Yamagiwa and Koichi Ishikawa painted the ears of rabbits with coal tar and induced tumour formation. Almost 150 years after Pott's description of scrotal cancer, Ernest L.



Sir Percival Pott was the first to appreciate occupational hazards

Kennaway in England isolated chemicals from coal tar and showed that they caused tumours when painted on mice. These studies initiated worldwide programmes on identifying chemicals which are harmful and may produce cancer.

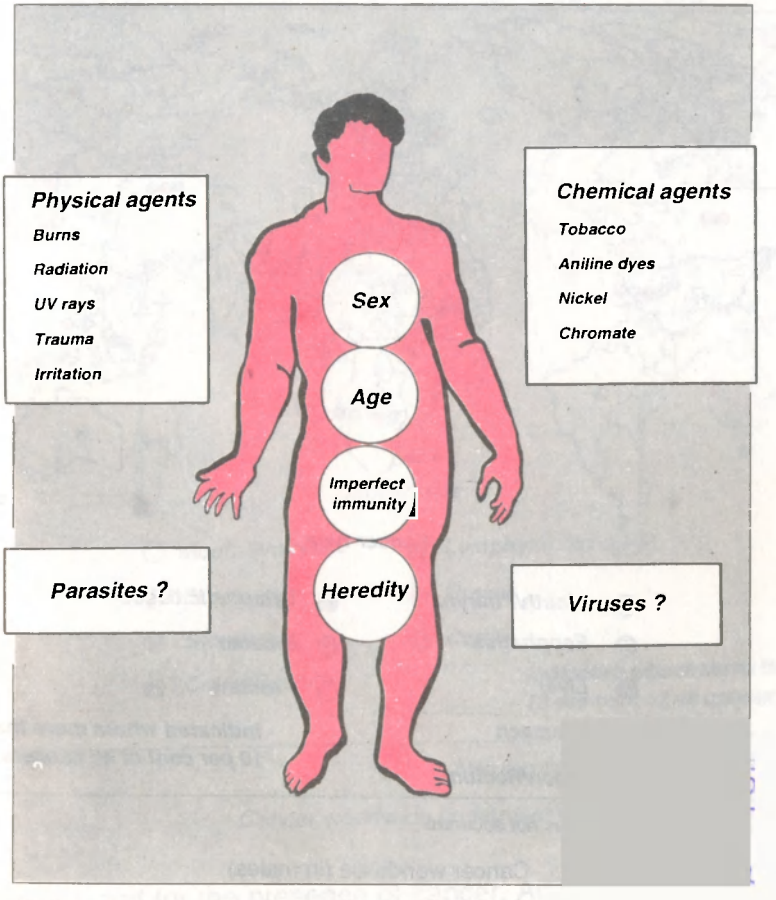


Kennaway Ichikawa and Yamagiwa, validated the observations of Bell

It is now known that a cancerous cell arises due to an alteration in a normal cell. However, many of the causes behind such alterations are still unknown. Nevertheless around 70 per cent of the cancers are due to different types of agents and are preventable. One can get exposed to such agents during normal life, either at home or at the workplace, due to our lifestyles and habits. All such agents which cause cancers are collectively called 'carcinogens'. There are three types of carcinogens: chemical, physical and biological.

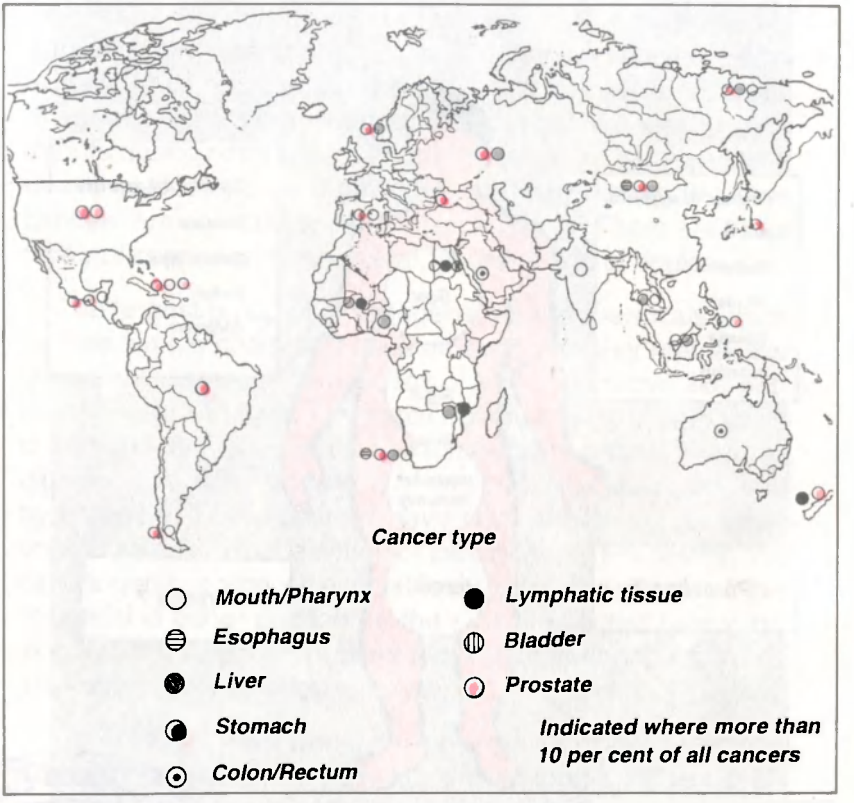
The largest group of carcinogens are the chemicals which include simple chemicals such as salts of heavy metals like cobalt and cadmium to complex organic chemicals like petrochemicals and dyes. The carcinogenic activity of chemicals is tested by their ability to cause tumours in animals. For such experiments, different strains of rats and mice are developed by breeding. These animals have skin, or stomach or other organs sensitive to the action of carcinogens. For testing the carcinogenic action of a chemical, a small amount of the chemical is either painted on the skin or injected below the skin according to a predetermined timetable and the animals are kept till they develop tumours.

Once a tumour is formed, it is removed and microscopically examined to identify its type. For testing food additives such as colours used in sweets, a solution of the dye or the dye mixed with food is fed to the animals. The animals are monitored for tumours in their stomachs, or liver. These experiments take a very long time since the mice have a lifetime of two years and they have to be observed till they develop tumours. By experiments, it has been possible to identify many chemicals in our surroundings. Proper precautions taken to avoid exposure can also reduce the risk of cancer to human beings. One of the important agents tested by such method was the dye, butter yellow. This dye was added to butter to make it look yellow and attractive. Rats fed on food containing this dye developed liver tumours and its use was banned.



What causes cancer?

Observations by doctors that, workers in a particular industry have a higher incidence of a particular type of cancer, result in a systematic survey of such exposed workers in comparison with people not exposed to such chemicals. Aniline and related compounds were identified as carcinogenic, since workers in aniline dye factories were found to have a higher incidence of cancer of the urinary bladder. Such

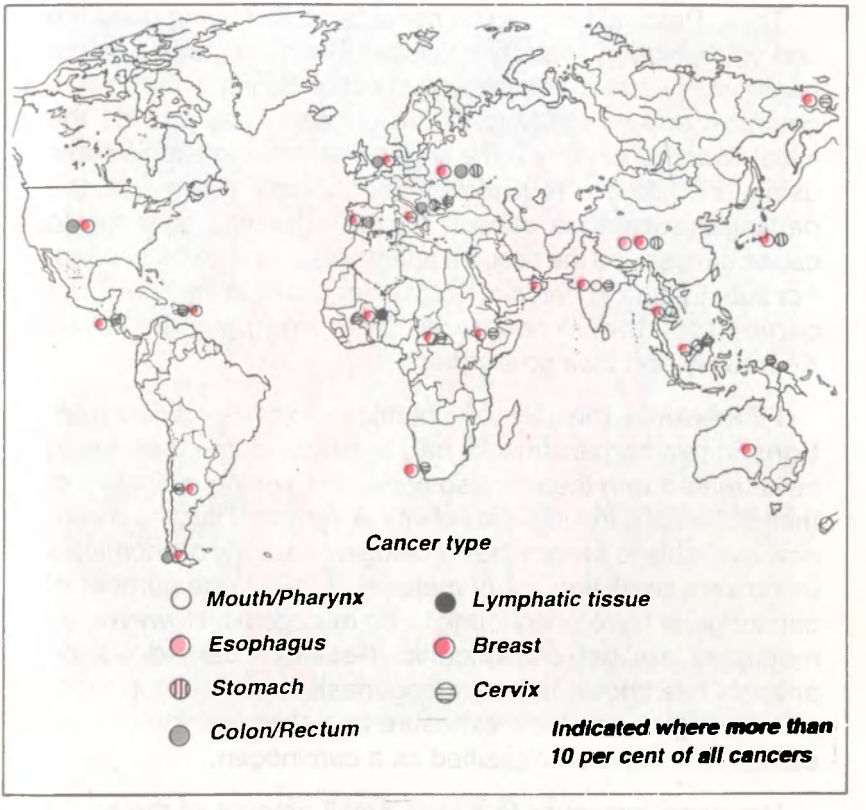


Map schematic; Boundaries not accurate

Cancer worldwide (in males)

observations can then be followed by laboratory experiments with animals to conclusively identify the carcinogen, since one can never experiment on human beings. Some of the largest of such studies on the incidence of cancer in human beings have been carried out on tobacco.

In such studies, people are questioned on tobacco usage such as smoking or chewing of tobacco, the number of cigarettes or *bidis* smoked daily, or the amount and the number of times they chew tobacco everyday. They are also



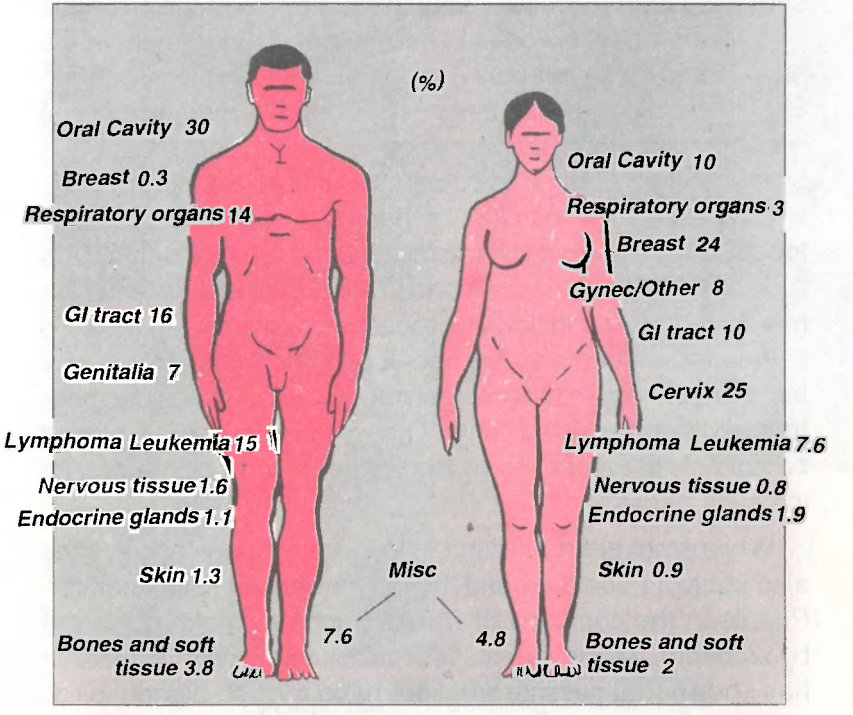
Cancer worldwide (in females)

examined for the presence of cancer. All this information is then subjected to analyses by statistical methods and then conclusions can be drawn on the risk that such substances may pose to the humans. Such studies are called 'Epidemiological studies' and give us information on the cancer patterns in the country and warn about the risk factors of cancers. These risk factors are different in different countries since they are dependent on food habits, lifestyles and environment.

Thus, Percival Pott can be considered as having done the first epidemiological study in cancer. But such studies do not conclusively prove a cause and effect relationship between a chemical and its ability to cause cancer. They provide the initial direction or point out a finger. Painstaking experiments using animals are required to conclusively prove that the particular substance causes cancer. The time it takes to cause cancer and the tissue it affects also have to be studied. For substantiating Percival Pott's observations, the final proof came from the experiments by Yamagiwa, Ichikawa Keenaway and their colleagues.

Furthermore, the ability of chemicals to cause gene **mutations** in microorganisms, or cause chromosome damage in cells treated with them is also considered being indicative of their potential carcinogenic activity. A variety of such tests are now available to predict the carcinogenic activity of chemicals using very small amount of material. A very large number of carcinogens have been found to be mutagenic. However, all mutagens are not carcinogenic. Research carried out on animals has shown that carcinogenesis is a multistep process. A single or multiple exposure to a chemical may cause cancer and it is then classified as a carcinogen.

However, exposure to a very small amount of the same substance — a suboptimal dose will alter the exposed cells but may not make them malignant. Such cells become 'initiated' cells and have the potential to become malignant even after a very long interval. Further exposure of these 'initiated' cells to the same substance, or to another substance which in itself may not necessarily be a carcinogen can transform them into malignant cells resulting in the formation of a tumour. Substances of the second type which are themselves not carcinogenic but can convert initiated cells into cancer cells are called 'tumour promoters'. It is important to identify not only the carcinogens but also the tumour promoters in our environment since long exposure to promoters can be risky if we have been unknowingly exposed to very low amount of



Ten leading cancers in India

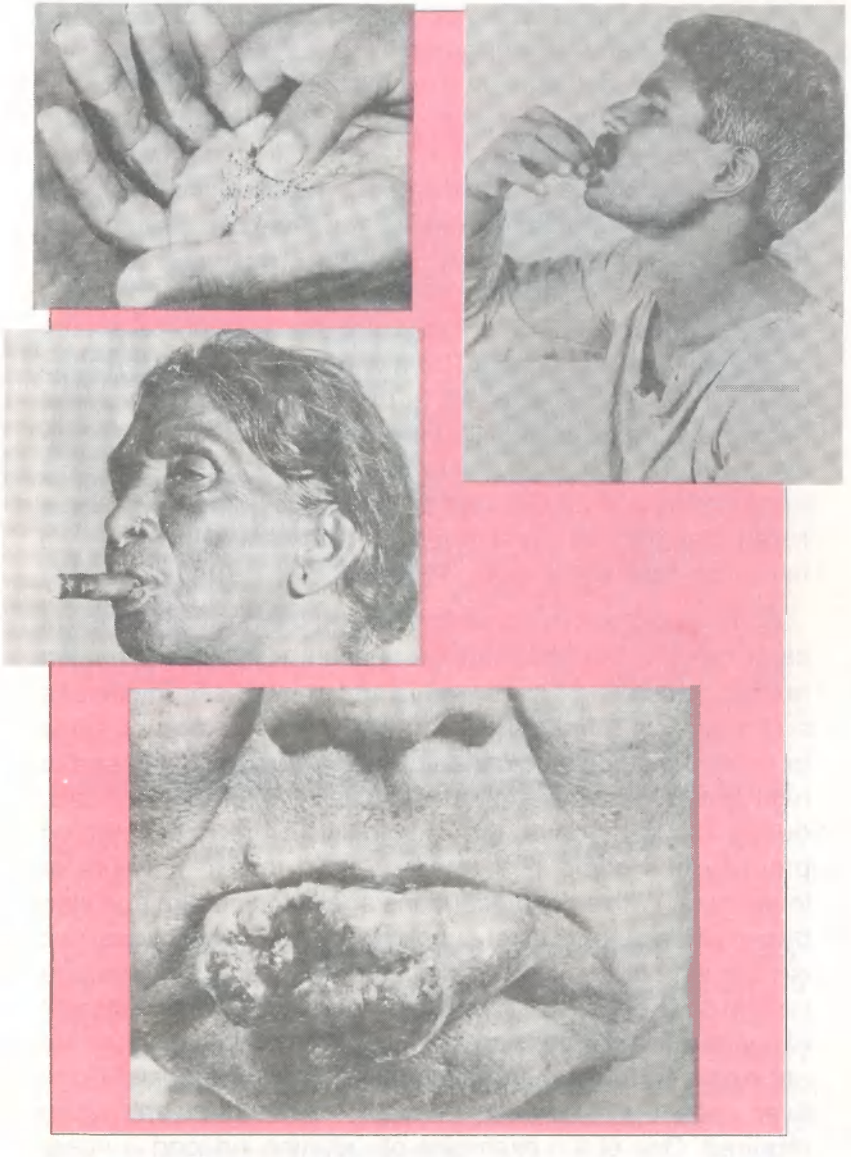
a weak carcinogen previously. The factor is of relevance to a situation that exists in our country.

In India, about 35 percent of all the cancers are in the oral cavity. Epidemiological studies have convincingly shown that these arise due to the widespread habit of chewing tobacco and smoking *bidis* and cigarettes. Tobacco contains many carcinogens and also has strong cancer promoting activity but exposure over a long period is necessary to cause cancer. Oral cancers not only cause a large number of deaths but also disfigurement. The tumours of the mouth and pharnyx-called the head and neck tumours — arise on the jaw or tongue or the **palate**. When these tumours are removed by

surgery, it becomes necessary to remove the jaw, the tongue or voice box and this causes permanent disfigurement of the face. Thus, these tumours are described as causing morbidity. These cancers also cause considerable mortality. In the western countries, the common way of using tobacco is smoking cigarettes. This causes cancer of the lung in most smokers. A large number of people in our country chew tobacco with lime and also smoke *bidis*. Smoke particles in *bidi* smoke are much larger and probably get deposited in the mouth cavity. In addition, the tobacco chewers keep tobacco in their mouth between the cheek and the gums. This is why Indians addicted to tobacco get cancers of mouth cavity more frequently than that of lung. These cancers can be almost completely prevented by giving up tobacco, or by not acquiring such habits.

While smokers run a high risk of developing cancer, they also subject people around them to increased risk of cancer. People in the company of smokers inhale smoke given out by smokers. So they are called 'passive smokers'. Research has shown that passive smokers have a much higher risk of getting cancer than people who are not exposed to smoke at all.

In some cancers, an intermediate stage between normal tissue and cancer is recognised. Such a stage is called pre-cancer. In many tobacco chewers or heavy smokers, a white patch develops in the mouth cavity: on the cheek or the tongue or below the lip. Such a white patch is called leukoplakia. With continued use of tobacco, such white patches can progress to frank cancers. Intervention studies were carried out by researchers in which patients who had leukoplakia were convinced to give up the tobacco habit. In many such patients, the patches or leukoplakia gradually disappeared, very greatly reducing the risk of cancer. Thus, for a smoker or a tobacco chewer it is never too late to give up the tobacco habit.



Indians use tobacco in many forms. Lip cancer (bottom) is common in tobacco chewers

In cancer of the **uterine cervix**, which is the number one cancer in Indian women, precancerous changes in cervical tissues can be detected by a microscopic examination of the cervical cells by the well known 'Pap' test. This test developed by Georges Pappainecolau of Cornell University was presented in 1928, as the now famous research paper, 'New cancer diagnosis' at Third race development conference. The Pap test can distinguish between normal and malignant cells and can be performed fairly easily. The test has been extensively used since 1943. It has saved the lives of thousands of women the world over. The altered cervical tissue called dysplasia takes a few years to progress into cancer and if detected early gives enough time for patients to take preventive action. Thus, in cancer of cervix, early detection can lead to prevention of cancer and the saving of many lives. It is recommended that women above 40 years should get a Pap test done once every year.

Various types of radiations make up the group of physical carcinogens. Radiations are grouped into two types, ionizing radiations such as X-rays, γ-rays and non-ionizing radiations such as Ultra Violet (UV) light. Both these radiations have been shown to be carcinogenic when people are exposed to high doses. After the introduction of X-rays for diagnosis, during the early days, the radiologists were not protected properly and some of them developed thyroid tumours or leukemias. With strict precautions against exposure and also by monitoring exposure of radiologists, such occupational risk is now almost completely eliminated. Ionizing radiations in certain doses destroy cancer cells and are used for treatment of cancer. These doses are many times higher than those we are exposed to when we take an X-ray for diagnosis. However, one must realize that X-rays should be taken only when required. One of the examples of radiation induced cancers is seen in survivors of the atomic bomb explosion in the cities of Hiroshima and Nagasaki. A large number of these survivors later developed leukemias.

Catching cancer in style

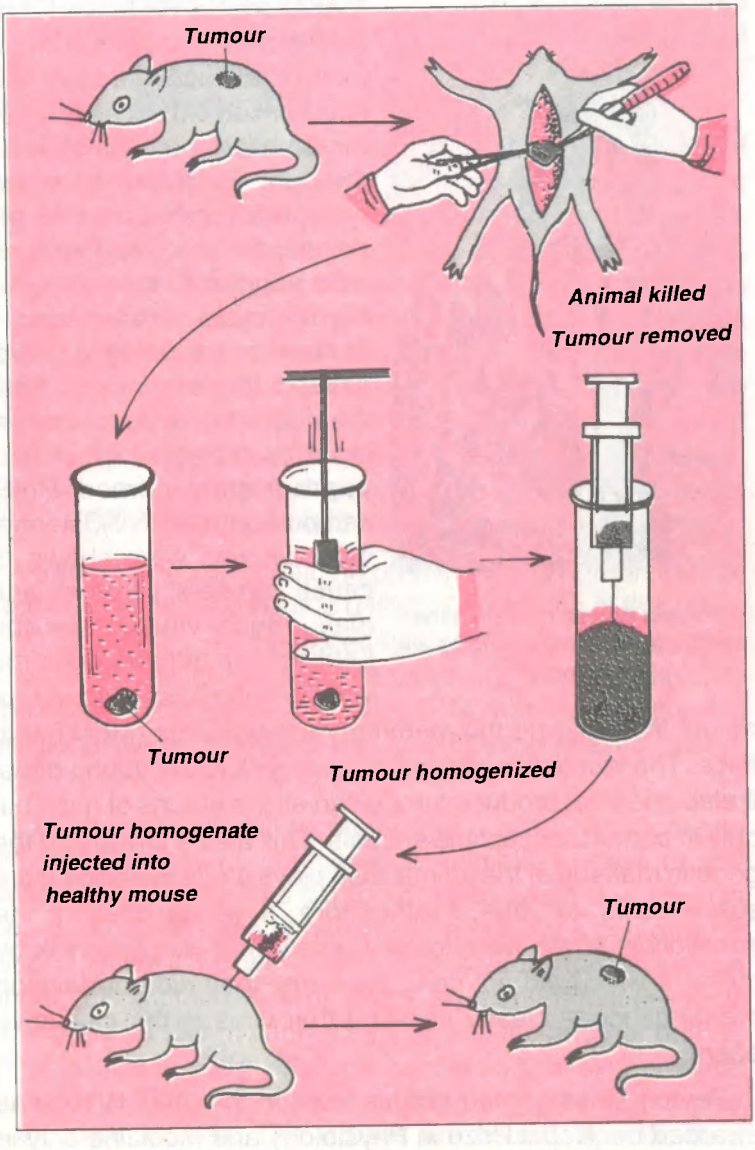
UV light is also known to induce tumours in mice. Australians, who have very little pigment in their skin are known to develop skin cancers due to overexposure to sunlight as a result of their love for tanned skins. The UV rays in sunlight are responsible for this. People with darker colour are protected from the deleterious effects of sunlight due to the presence of pigment in their skin.

Apart from these carcinogens, some biological carcinogens are also known. A large number of viruses have been

shown to produce tumours in different types of animals. A virus is a submicroscopic entity consisting of a molecule of DNA or RNA which carries its genetic information and is covered by a protective protein coat called capsid. The viruses are classified as DNA or RNA viruses depending on the nature of their genetic material.

In research work, tumours produced in animals experimentally can be continued from one generation to another by taking small pieces of tumour and injecting them below the skin of a perfectly healthy animal of the same strain. This is called transplantation of tumour. After the tumour grows to a sufficiently large size (approximately 2 cm in diameter), the animal is killed, the tumour is removed under aseptic conditions and carefully cut into very small pieces. A few small pieces put in saline solution are injected under the skin of another perfectly healthy animal. All these operations are carried out using instruments, syringes and needles which have been previously sterilized. The tumour now starts growing in the next generation and this process can be continued almost indefinitely. It is necessary to have intact living tumour cells for transplantation. By growing tumours in this way we can get a large amount of tumours to carry out different types of studies including studying the effects of different anti-cancer drugs on tumour cells. It was observed that in some tumours, injection of a cell-free extract made by **homogenization** of tumour by disrupting their cells, could still give rise to similar tumours when injected in animals. This suggested that intact cancer cells were not required and some agent may be responsible for tumour formation.

Peyton Rous working at the Rockefeller Institute in New York carried out such experiments with chicken tumours. He took tumours formed in chickens and disrupted their cells completely by homogenization and injected them into legs of other chickens, all of which subsequently developed tumours. This suggested that intact cancer cells were not required and some agent smaller than a cell was responsible for tumour



Producing cancers experimentally

Peyton Rous established the relationship between viruses and cancer

formation. So Rous went one step further. He filtered these tumour extracts through fine filters which did not allow even the smallest bacteria to pass through. To everyone's surprise, the injected chicken still developed tumours. These results suggested that some living organism smaller than a bacterium (probably a virus) caused these cancers. After the discovery of cancer causing virus in chicken which was appropriately named Rous sarcoma virus (RSV), several other viruses were shown to cause cancers in other animals. Such viruses are the Leuke frog adenocarcinoma virus which causes kidney tumours in frogs and the mammary tumour virus (MuMTV) in mice. The last one is passed through milk to the young ones. It also does not produce tumours in all the strains of mice but only in certain susceptible animals. This also showed that the genetic makeup of the animal also plays a role in deciding the susceptibility to virus. Furthermore, if young ones of the susceptible strain were foster nursed, that is, given milk by mothers which did not carry the virus, they did not develop breast cancers, clearly showing that virus is the causative agent.

Peyton Rous carried out his work in the year 1910, was awarded the Nobel Prize in Physiology and Medicine only in 1966, when he was 85. This was a very belated recognition for an epoch making discovery which changed our approach and thinking in cancer research. The RSV is a RNA virus. Its

genome has been very extensively studied and this has very greatly advanced our knowledge regarding how viruses infect cells, propagate themselves and how they convert normal cells into malignant cells.

There is no direct evidence for viruses being the cause of cancer in human beings even though certain viruses are suspected to play a role. A group of viruses called adenoviruses are suspected to be involved in human cancers. One of the best examples of association of a virus in human cancer is seen in Burkitt lymphoma, a tumour mostly seen in African children. It has been named after Dennis Burkitt who described and extensively studied it. In most of the African tumours, a strain of *Herpes* virus, a DNA virus — named Epstein-Bar virus (EBV) was found associated. However, EBV was not seen in similar tumours from USA. The exact role of EBV in causing Burkitt lymphoma is not yet clear.

Another virus that is gaining prominence in human cancer is the human papilloma virus (HPV). Two strains of this virus, HPV-16 and HPV-18, have been detected in cancer of cervix and also in cervical tissue of women with cervical dysplasia — a pre-cancerous stage. The viral DNA was detected using very sensitive technique of molecular biology called polymerase chain reaction (PCR).

It is far more difficult to prove that a given virus causes cancer in humans as compared to animals. In case of animals, direct experiments can be done to prove this, as was done by Rous. In case of humans, the evidence can only be indirect. Even if we were to isolate a virus from a human cancer, it is impossible to prove by experiment that the virus caused the cancer. It cannot be injected into another human being to see if it will produce cancer in the experimental subject. Injection in animals including monkeys may not give us the right answer. The viruses are usually specific to a particular animal and a virus which causes a disease in monkeys may not necessarily produce the same disease in man. Research work with human viruses is much more time

Why encourage cancer?

consuming. If a virus were found to be the causative agent for a human cancer, work can then be undertaken to prepare a vaccine to protect the people. If a virus showed close association with particular human cancer without being the causative agent, it could still be used as a tool for early diagnosis.

It is evident that there are a large variety of agents which can be carcinogenic. These agents are very diverse in their nature. Yet they all seem to change the cells of body in some

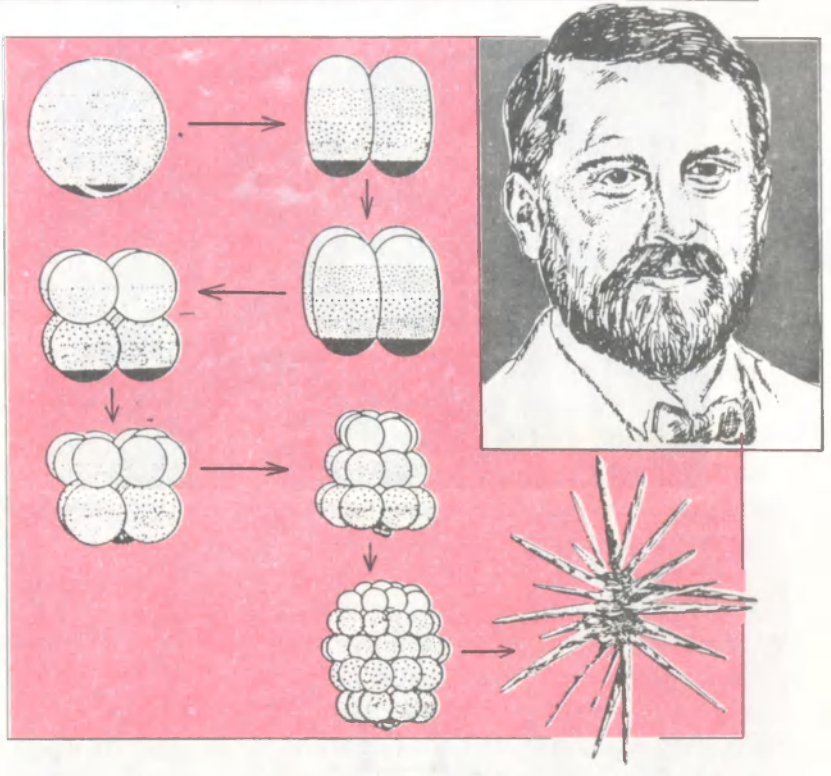
common way and convert them to cancerous cells. They should therefore be acting on some basic mechanism of the cells and affecting them. In addition to carcinogens and tumour promoters some compounds or factors which do not belong to either of these categories seem to increase the risk of cancers in human beings. Some dietary materials seem to increase such risk. Thus, an increased risk of cancer of the colon or large bowel is associated with a diet low in fibres and rich in fats and cholesterol. A diet consisting of leafy and high residue vegetables is universally recommended as being good for the body. A high fat and cholesterol diet also increases the risk of breast cancer apart from causing heart problems. Intake of Vitamin A and carotenoids are recommended. A healthy and balanced diet appears to reduce the risk of cancer though it may not prevent it. At present, a large number of scientists are doing research aimed at identifying factors in our foods which may help reduce the risk of cancer. The strategy is straightforward. Costs of treating cancers are increasing and so is the incidence of some habit related cancers — mainly tobacco associated ones. If we can educate people to develop healthier habits, we can perhaps nip the problem in the bud. Our own determination for a better life will decide our future.

In the year 1890, David von Hansemann, a pathologist, who had been looking at human cancers under the microscope reported that he frequently saw irregularities of cell division in tumours. He associated them with development of malignancy and suggested that these abnormalities could be used as criteria for diagnosing cancers. In the year 1914, a German scientist, Theodor Boveri, made some very interesting observations and predictions. He had been studying the fertilization of sea urchin eggs in his laboratory and had observed that when a single sperm fertilized an egg, the zygote developed normally. However, if an egg was fertilized by many sperms,

Clues to cancer

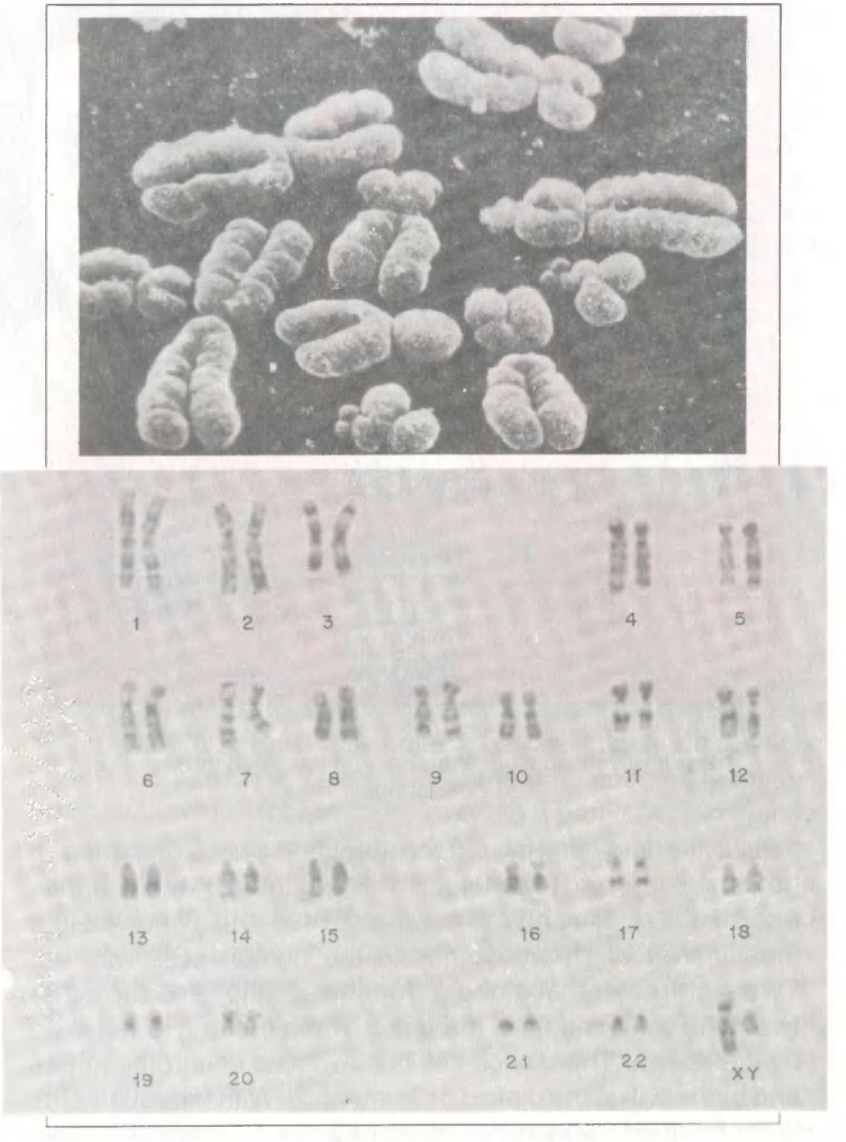
the fertilized egg had abnormal number of chromosomes. Abnormal mitoses occurred in such embryos and these usually died later. From these different observations, Boveri was convinced that "cancer cells, like the chromosomally abnormal sea urchin embryo cells, involved a particular incorrectly combined chromosome array". He proposed that alterations in the chromosomes or genome of cells result in malignancy. Genes as the basic units of heredity had not been discovered at that time. These predictions by Boveri made almost eighty years ago were prophetic and it is now known that most of the tumours show rather specific or non-random chromosome changes, some of which can now be understood at the level of individual genes.

Since Boveri, many scientists had looked very hard and for a long time at chromosomes of tumours, but had not succeeded in finding out exactly what went wrong during cancer. This was due to a variety of reasons. The first steps towards



Theodor Boveri did pioneering work on the mechanisms of cell development

this lay in knowing the exact number of chromosomes in human beings and to distinguish among them by their shapes and size. J.H. Tjio and Albert Levan in 1958, first showed that the number of chromosomes in the human cells was 46. Twenty three of these come from the mother and the other twenty three come from the father when the egg is fertilized by the sperm. Thus, each cell has two sets of chromosomes and this is called the diploid or 2n number. With improvements in techniques for staining chromosomes, it is now possible not only to identify each individual chromosome but assign genes to specific regions on them. This is done by catching the cells at the metaphase stage of cell division. The cells are

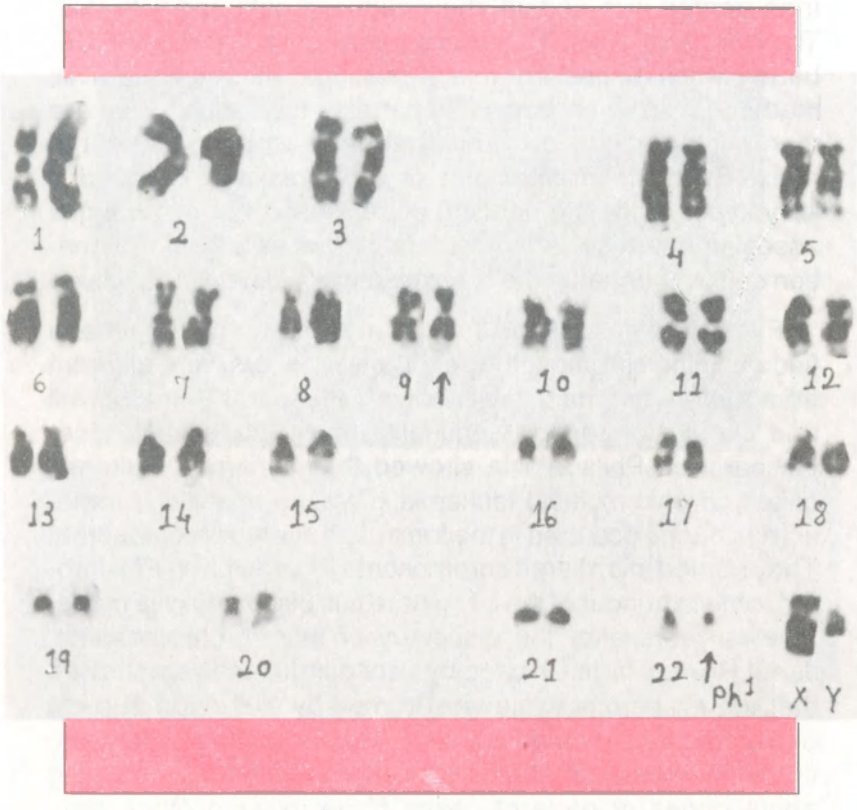


Human chromosomes as they appear under the microscope (inset) and arranged in pairs

then treated with certain chemicals and coloured with dye. They show a pattern of stained and unstained regions or bands which is specific for each individual chromosome. This method is called chromosome banding technique. They are then photographed, cut, and arranged according to a set of rules. Such an arrangement of chromosomes is called a karyotype. Since the banding pattern often shows changes associated with genetic disorders it gives us a lot of information on the changes in the chromosomes in different diseases.

Even though scientists had been trying for a long time to find out if the chromosomes of human cancers were different from those of normal, it was only in 1961, that Peter Nowell and David Hungerford working at the Institute for Cancer Research in Philadelphia showed that in human leukemia called chronic myeloid leukemia (CML), a specific chromosome change occurred in the form of an altered chromosome. They named this altered chromosome Philadelphia (*Ph*) chromosome in honour of the city where this discovery was made. Twelve years after the discovery of the *Ph* chromosome, Janet Rowley from Chicago by very careful analysis showed that the *Ph* chromosome was formed by exchange of parts between chromosomes 9 and 22. Such exchanges between chromosomes are called translocations. Translocations bring about genes or parts of genes close to each other while normally they had been far away from each other. Such a change in the location of a gene causes a change in the gene product as well. The presence of the *Ph* chromosome can not only be used for diagnosis, but it also helps us understand the changes that take place at the molecular level during malignancy. Other types of translocations have been seen in various types of leukemias and other cancers and their occurrence is used for diagnosis and also to predict the course of the disease.

Finding out the differences between normal and cancer cells is one of the major goals of cancer research. If clear cut differences can be found between a normal cell and its



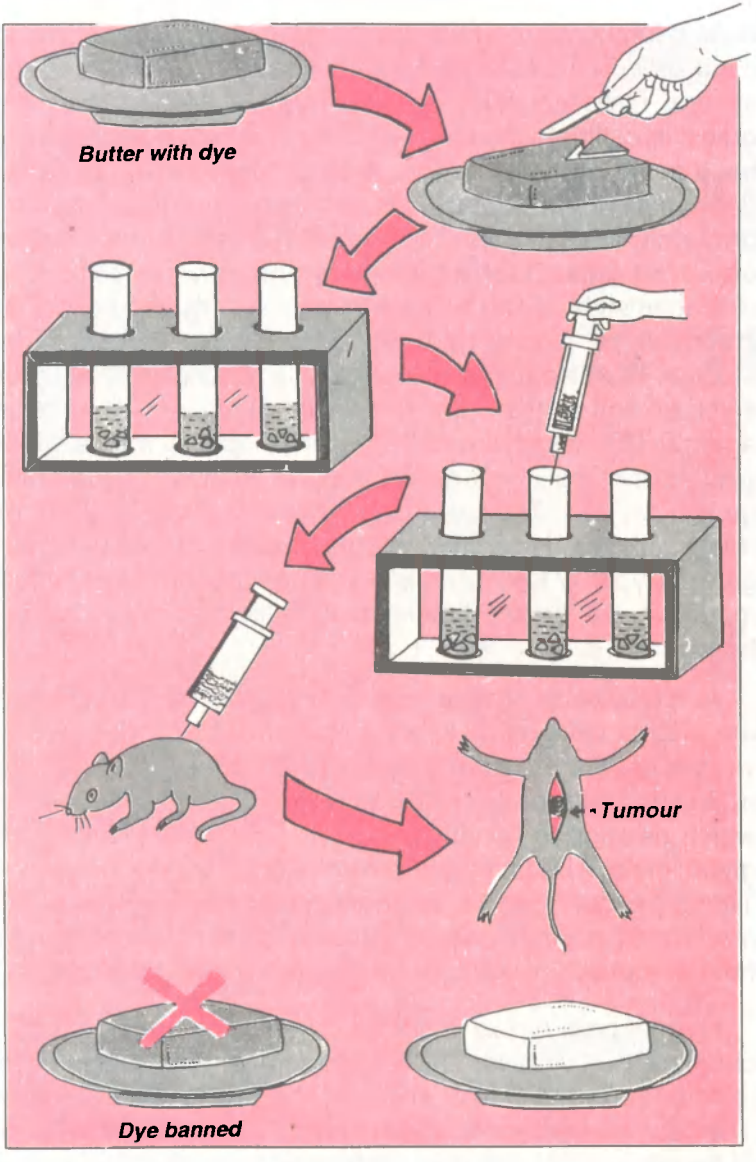
Chromosomes of a person with chronic myeloid leukemia

cancerous counterpart, such information can be used to detect cancer and to diagnose it at an early stage. In addition, if such differences were in the metabolic capabilities of the two cell types, then they could be exploited to selectively kill the cancer cells without harming the normal ones. However, such clear differences between the two are rarely found. It is even more difficult to find differences between human tumours and normal human cells since one cannot experiment with human beings. A way to overcome this problem is to grow

human tumours outside the body either under artificial conditions or in animals. The former technique is called tissue culture. Cells obtained from different human tumours are grown in culture where they multiply indefinitely and seem to have an infinite lifetime. This is an exceptional quality since, under similar conditions, cells obtained from normal tissues grow only for a finite time, age and die. This is particularly true of human cells. Once a tumour can be grown in culture, its characteristics, such as growth rate and its regulation, its chromosome picture and metabolic characters can all be studied. It is also possible to study the susceptibility of these cells to anti-cancer drugs, growth regulators, and other agents. The cells have to be grown in special media which contain salt solutions, amino acids, vitamins, serum and growth factors. The cells are grown in glass or specially treated plastic bottles and dishes. It is still not very easy to grow all types of tumour cells in culture but such tissue culture models have greatly helped the understanding of tumour biology.

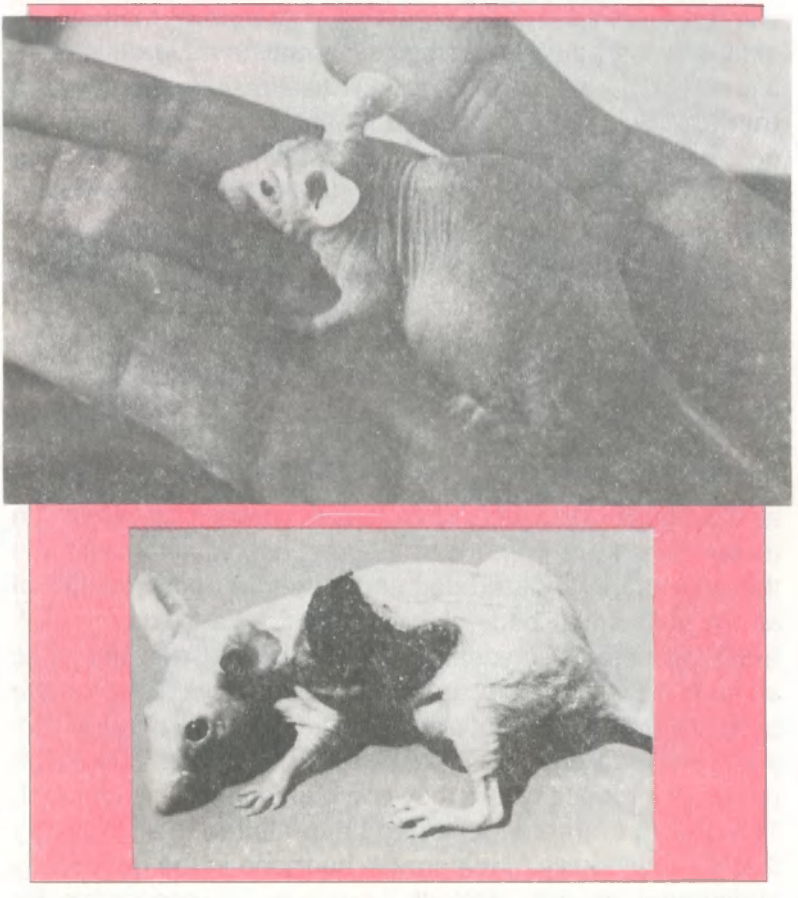
Animal cancer models similar to different human tumours are also developed by treating animals with carcinogens or viruses at different sites on the body. The tumours produced at these sites are then studied and compared with cancers which develop in human beings at similar sites. If rats are given, the dye butter yellow, they develop tumours in the liver. These tumours can be compared with liver cancers of humans and if such animal tumours show similarities with human cancers, we can use them as a model for studies.

Normal cells grown in culture can also be transformed by chemicals or viruses. Once transformed, they are later injected into experimental animals where they form tumours. They can be used for studying effects of drugs or other forms of treatment. One can also study how the cancer develops in animals after treatment with the carcinogen and understand the different steps in development of cancers. Thus, rat, mouse or hamster tumour models for different organs such



Safety of food additives and colours are tested on animals

as prostate, lung, skin, liver and leukemias are now available. These show similarities to the respective human cancers and are extensively used in studies.

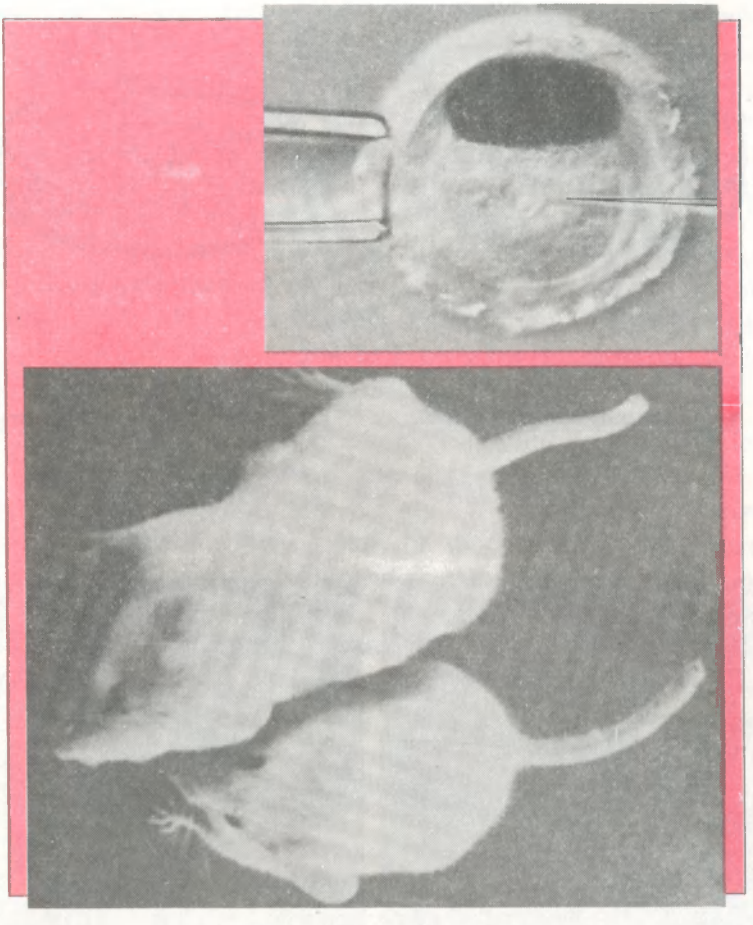


Normal hairless mouse (top) develops skin tumour (bottom) when painted with chemical carcinogen

Another approach is to grow human tumours in animals such as mice. However, these cells cannot be maintained over long periods since the immune system of the host

recognizes the tumour as foreign or non-self and kills it. The mechanism is the same that the body uses in rejecting a tissue grafted from another animal. By treating the host animal with drugs which suppress the immunity, the transplanted tumours can be grown for a couple of months. By extensive breeding experiments, scientists have developed a strain of mouse called, 'nude'. These mice do not have the **thymus**. Such animals cannot mount an immune response against the grafted tumour and it is now possible to grow many more human tumours in 'nude' mice and study their biological properties than had been previously possible.

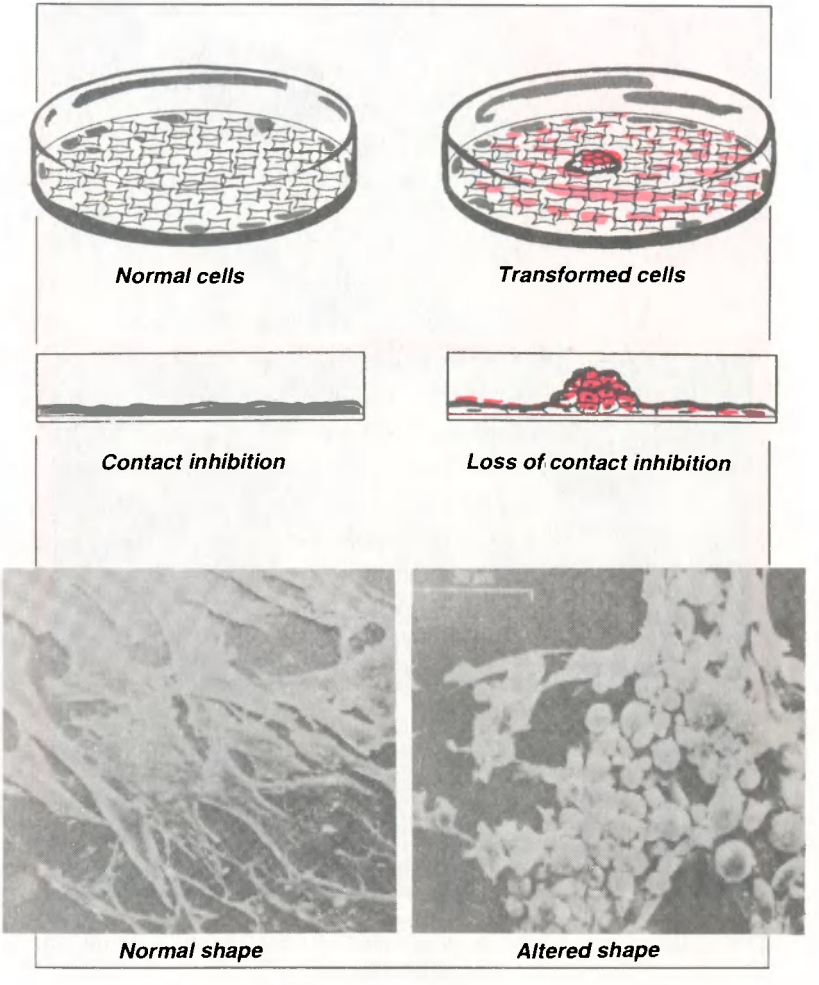
Animals can now also be genetically engineered to have unique characters. One of the best examples of such an engineered mouse is the so called, 'supermouse'. It is now possible to inject many copies of a particular gene in the egg of a mouse by a very fine needle. The manipulation is carried out under a microscope by means of an instrument called a micromanipulator. The egg is then fertilized by sperm in a dish and put back in the uterus of a female where it develops into a complete mouse. The injected gene gets incorporated into the DNA of the fertilized egg and therefore becomes part of all the cells in the body of the mouse that develops from it. Such genetically engineered animals are called transgenic animals. In case of the 'supermouse', scientists injected the gene for growth hormone in some eggs while they did not inject anything in others. All these eggs were put back in the uterus of a mouse where they completed their development. The growth hormone gene had been altered in such a way that it continuously made growth hormone in the genetically engineered animals. Growth hormone is responsible for increase in size of the animals but during normal development the body does not make the hormone continuously. Therefore, the transgenic mice grew many times bigger than their siblings which developed from eggs that had not been injected with this gene. One can inject even unknown genes, that is, genes whose functions we do not know, into model



The supermouse created by microinjection (inset) is much larger than its normal sibling

animals and make them transgenic to find out what these genes do in our body.

A comparison of normal and cancer cells grown in culture is made under similar experimental conditions to understand the differences between the two. One can study movements of cells grown in culture by attaching a movie camera to the



Behaviour differs in normal and malignant cells

microscope. In the year 1958, Michael Abercrombie and Jack Ambrose, in UK, studied the movements of normal and cancer cells in culture. They found that when normal cells get crowded together in culture, they inhibit further movement of

each other when they meet. However, under similar conditions, the tumour cells do not stop each other's movements and continue to travel further. The phenomenon shown by normal cells was called, 'contact inhibition'. This phenomenon or rather, the loss of it, was then related to the ability of tumours to form metastasis. It was felt that normal cells send signals to each other and also receive them. Tumour cells seem to lose such ability. When normal cells are maintained in culture they may grow close to each other but do not overlap. The tumour cells grow on top of each other or pile up. This is also due to the loss of contact inhibition. This behaviour helps identify tumour cells in culture.

One of the main aims of research in cancer has been to understand how cells divide and also, what stops their division. It is understood that during early development, the embryo consists of only rapidly dividing cells. This division gradually stops so that after birth, mitosis is seen mainly in renewing tissues such as bone marrow and skin. Cells growing in tissue culture provide an excellent system for such studies since these cells are continuously dividing. Normal cells growing in culture send signals to their neighbouring cells to stop dividing through contact between their membranes when they become tightly packed. Hence, multiplication of normal cells stops when they completely fill the vessel in which they are growing. This is called, density dependent inhibition of growth. Multiplication of tumour cells is not affected by such crowding and they continue to multiply.

When a cell divides, it forms two identical daughter cells. It has to distribute its genetic material equally to the daughters. Hence, while preparing for cells division the DNA is doubled. Thus, before the process of mitosis starts, the cell has to double the amount of DNA it had at the resting stage. In other words, the number of chromosomes is doubled. They are divided equally between the two daughter cells. The process of replication of DNA is not only very important but has to be carried out with great precision. Any mistake at this

Stages of mitosis with cell cycle (inset)

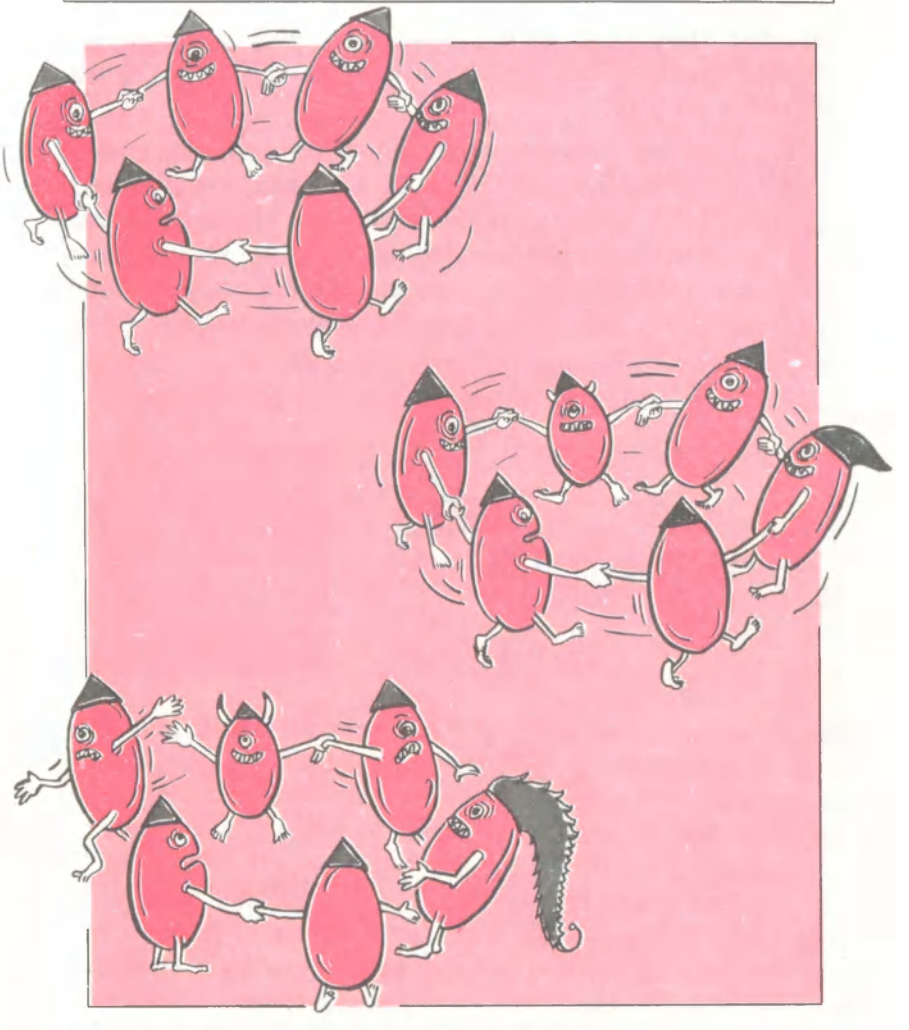
stage will result in mutations and may cause a genetic anomaly. Similarly, the distribution of chromosomes must be equal to the two daughter cells. If a mistake is made during distribution, they will receive an unequal number of chromosomes. Aberration at any or all of these stages may lead to the development of cancer.

Scientists all over the world have been trying to understand the secrets of cell division but these are being revealed in bits and pieces. When cells multiply continuously, the period between two successive cell division is called the cell cycle. The cell cycle has two stages which can be clearly studied under the microscope. These are interphase and mitosis. Mitosis is the actual cell division in which the chromosomes become visible and get distributed into two daughter cells. Mitosis is divided into four stages: prophase, during which the chromosomes condense and the nuclear membrane disappears; metaphase, when the chromosomes get arranged in the centre of the **spindle** which is responsible for the distribution of the chromosomes equally to the daughter cells; anaphas, when the chromosomes move to opposite ends of the cell; and telophase, in which the two daughter cells separate from each other.

During the remaining period of the cycle the cell shows a well developed nucleus and carries out all its functions. This stage is called, interphase. Synthesis of DNA for the next division starts some time after completion of the previous division. The period during which DNA synthesis occurs is called the 'S' phase. There is a long gap of time between completion of telophase and beginning of S phase. This gap is termed as G1. After the DNA is completely duplicated, the cell enters prophase after a short gap of time called G2. Thus, the complete cell cycle is made up of G1+S+G2+M (mitosis). Differences are found in the time taken for completion of one cell cycle by normal and tumour cells. Information on the cell cycle time and the duration of different phases of the cell cycle tells us whether a tumour is fast growing or slow growing and

this knowledge can be used for planning the treatment with radiations and drugs.

There are other properties of tumour cells which help us distinguish them from normal cells or other disease conditions. Just as criminals usually leave some evidence at the scene of the crime, some cancers also leave their signature. Some tumour cells show similarities to embryonic cells. During embryonic development, certain tissues make some particular protein which are not made after birth. The best example is hemoglobin, which gives red colour to our blood. During the growth of the foetus in the mother, the foetus makes a variety of hemoglobin called foetal hemoglobin which is different from the hemoglobin present in children and adults. As the foetus grows, the formation of foetal hemoglobin is reduced and more and more adult type hemoglobin is made, so that after birth most of the hemoglobin is of the adult type. Some tumours seem to make many proteins which were made during embryonic development. The occurrence of such proteins in the patient's blood is used to diagnose cancers or their re-appearance after the patient has been treated and the tumour has disappeared. A protein called alpha-feto protein made by the foetal liver is also made by liver cancers and is a good diagnostic test for liver cancers. A protein called carcino-embryonic antigen (CEA) is made by cancers of the large bowel, liver, stomach, and pancreas, and also some breast and lung cancers. Another protein called PSA is made by prostate cancer. These proteins are made in extremely small amounts and find their way into the patient's blood. Even a very small quantity of blood taken from the patient is sufficient to detect the presence of these proteins. Such tell-tale marks of tumours are called 'tumour markers', as they suggest the presence of particular type or group of tumours. The first such tumour marker was described in 1847, by Henry Bence-Jones at Guy's hospital in London. In the urine of patients with multiple myeloma — a cancer of **antibody** making cells, he found an abnormal



protein. This was shown by Gerald Edelman and J.A. Gally, to be incomplete antibody molecules made by the tumour cells and its detection became an important test for the diagnosis of this type of cancer.

All these markers are for the cells that have become cancerous. Most of the proteins are made in very small quantities so that to detect them, very sensitive methods are

needed. They have use in diagnosis but they cannot have a predictive value. They cannot tell us if a person will get cancer a year or so later.

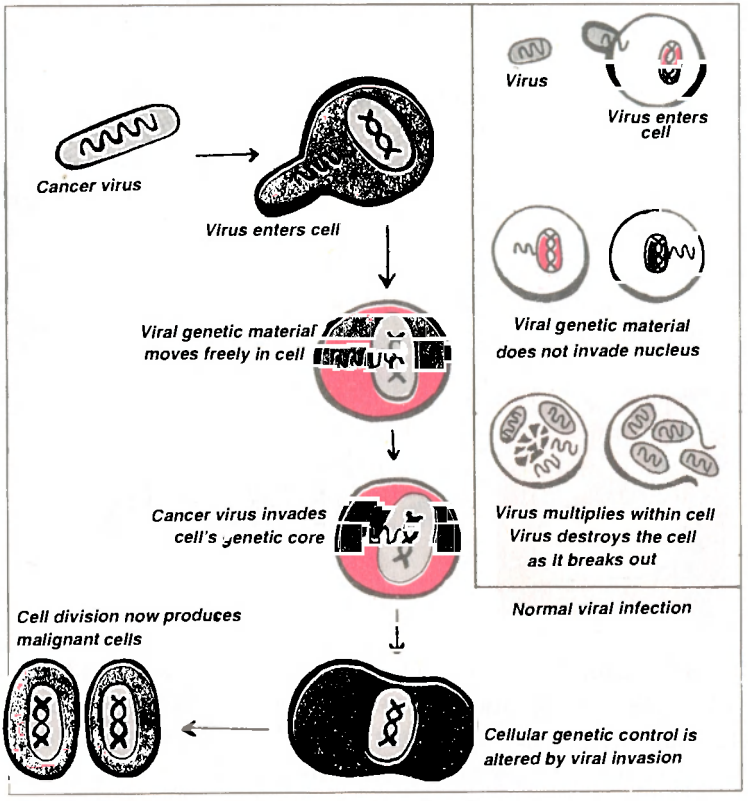
Some cancer cells may wear these altered proteins on their surface to show them off. Thus, CEA is seen on the surface of cells of the tumours mentioned above. These molecules are called tumour associated antigens (TAA). They not only help detect the tumours but may also be the cause of doom for the tumour. One can use such molecules to target drugs that may kill them.

The family members of Barbara Garvey who lives in Yorkshire, UK. have an unusual problem. Her three daughters and five granddaughters know that they are likely to get cancer of the breast or of the ovary because these cancers have occurred in many members of their family. While cancer is not an inherited disease, some families have been found to have a very high incidence of these two types of cancers. Breast cancers seen as isolated cases in the families are called 'sporadic' cancers. Among all the breast cancer cases, only 5 per cent may develop in the early thirties while in the others, it develops much later,usually in the fifties.

Split identity

Young patients tend to have a family history of breast cancer which means that some close relatives of these patients, such as mother, grandmother, sisters, or aunts have had breast cancer. These types of cancer are called 'familial' cancers. Mary-Claire King and her colleagues at the University of California, Berkeley, USA, have been studying such families for the last 18 years. They have found that the inheritance patterns of cancer in the members of these families are very similar to that of some DNA sequences located on their chromosome 17, and that these cancers may be caused by a gene(s) situated in this part of chromosome. This gene was named BRCA-1, though nothing else was known about this gene.

These observations raise several questions. Is some particular gene in our genome responsible for causing a particular cancer? If so, how does it do so ? Is there more than one such gene? Do they also increase the risk of some other



How cancer virus act

cancers? Answers to some of these questions may ultimately help, in detecting, treating even preventing cancers and in alleviating suffering. The BRCA-1 gene has now been isolated, and it is expected that a lot of information on the protein it makes and the way it works will be known in the next couple of years.

A few viruses have also been shown to cause cancers in animals. *Polyoma* virus is one such virus which when injected into different animals such as mice, rats and hamsters pro-

duces tumors. These tumour cells can be grown in culture. Marguiret Vogt and Renato Dulbecco from California Institute of Technology, USA, did some very interesting experiments on such tumour cells. They knew that when hamster cells grown in culture are infected with *Polyoma* virus, they become malignant, and look very similar to cells from hamster tumours grown in culture. If such cells converted to malignant cells in culture are injected in hamsters, the animals develop large tumours. It was not known what causes this change. To find out whether the gene(s) of *Polyoma* virus caused this change, Vogt and Dulbecco treated the cells with *Polyoma* virus DNA and sure enough the cells were transformed. These and many more experiments clearly showed that the genes of the virus were responsible for changing a normal cell into a malignant one. If the viral genes were removed from these cells by experimental means, the cells lost their malignant properties proving that these genes are necessary for continuation of the malignant state. *Polyoma* virus has extremely small amounts of DNA (as compared to the human cells) and therefore very few genes. Hence, it was comparatively easy for scientists to look among these few genes to find out the cancer causing ones.

In the search for cancer causing genes, many answers were provided by the Rous sarcoma virus which was first discovered by Peyton Rous in 1910 and forgotten by the scientific community for a very long time. This virus, which produces sarcomas, when injected in chickens can also convert normal chicken cells growing in culture into cancerous cells. This virus has RNA as its genetic material unlike most of the living beings where DNA is the genetic material. Molecular biologists using very fine techniques showed that when this virus infects a cell it first copies its RNA molecule into a DNA molecule which is the normal genetic material of the cell in which it enters. An enzyme called reverse transcriptase makes a DNA copy of the RNA molecule. This DNA copy now gets attached to the cell's DNA so that it now becomes

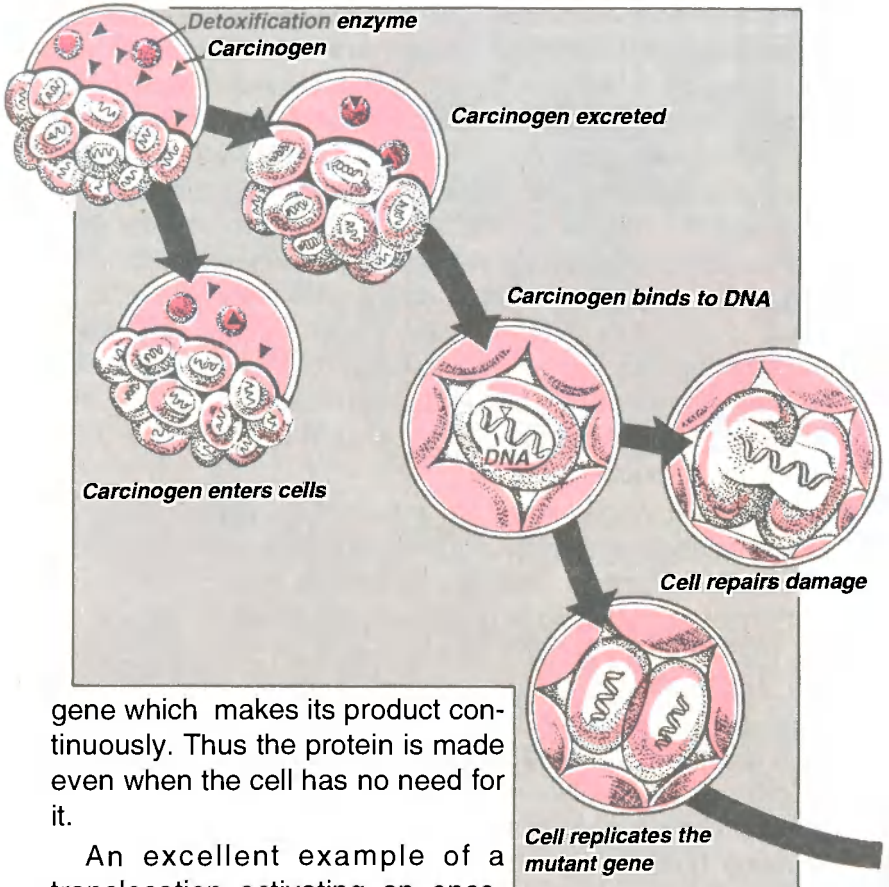
a part and parcel of that cell. Thus, when this cell multiplies, the viral genes also multiply along with the cellular genes and get distributed equally into the daughter cells. Scientists found that the Rous sarcoma virus too had very few genes—four, of which three were required for making virus particles in the host cell. The fourth gene was found to be responsible for making the cells cancerous and its removal from the infected cells caused the malignant cells to become non-malignant. If a changed or mutated fourth gene was put in cells, the cells did not get transformed. This gene was named *src* or *sarc* since it caused sarcomas in the chickens. Genes that caused cancers were named 'Oncogenes' or cancer causing genes. Several such oncogenes were discovered in RNA viruses that cause cancers in different animals. The RNA viruses causing cancers are called retroviruses as the direction of copying genetic information is reversed in these viruses.

Michael Bishop and Harold Varmus worked on viral oncogenes

A bigger surprise awaited the scientists. Michael Bishop and Harold Varmus of the University of California (USA), showed that genes almost identical to the viral oncogenes were present in the cells of different animals including man, forming part of the genetic make-up. The questions then are, what are they doing in our cells and how do they cause development of cancer? It is now agreed that under normal conditions, the oncogenes are useful and have specific func-

tions during development. The oncogenes in the cells are called cellular oncogenes (*c-onc*) and their counterparts in the viruses are called viral oncogenes (*v-onc*). From all the information available on oncogenes in different animal cells, Robert Hubner and George Todaro proposed a hypothesis. They proposed that the cellular oncogenes get converted to changed oncogenes by interaction with carcinogens, mutagens and undergo different types of changes. This is why cellular oncogenes are also called protooncogenes. It is these changed oncogenes which cause cancer. More than thirty oncogenes have been identified until now. They make different proteins which are unrelated to each other. Thus, the different oncogenes convert normal cells to cancerous cells by different mechanisms.

The cellular oncogenes are activated by different means. In some cases, a mutation in the gene results in the formation of an altered protein. This slightly altered protein now loses its normal function and begins to act like a cellular version of Mr. Hyde. A change of this type is seen in an oncogene called *ras*. The mutation always occurs at **codon** 12, 13 or 61 and changes the amino acid glycine to valine in the *ras* protein. This causes the normal cell to become malignant. Treatment of cells with chemical carcinogens frequently causes this mutation and such a mutation has also been found to occur in many human tumours. Some times, an oncogene gets amplified. Normally, there are two copies of a cellular oncogene, one each on a particular chromosome contributed by each parent. However, in amplification, a large number of copies of the same gene are formed at these sites. It is not very clear as to how this happens. Such amplified oncogenes are also seen in many tumours. Sometimes, translocation of an oncogene from one chromosome to another may make it active at all times instead of intermittently. This happens in a cancer called Burkitt lymphoma. An active regulatory element on chromosome 14 is brought close to the *myc* oncogene on chromosome 8 by a translocation. This activates the *myc*

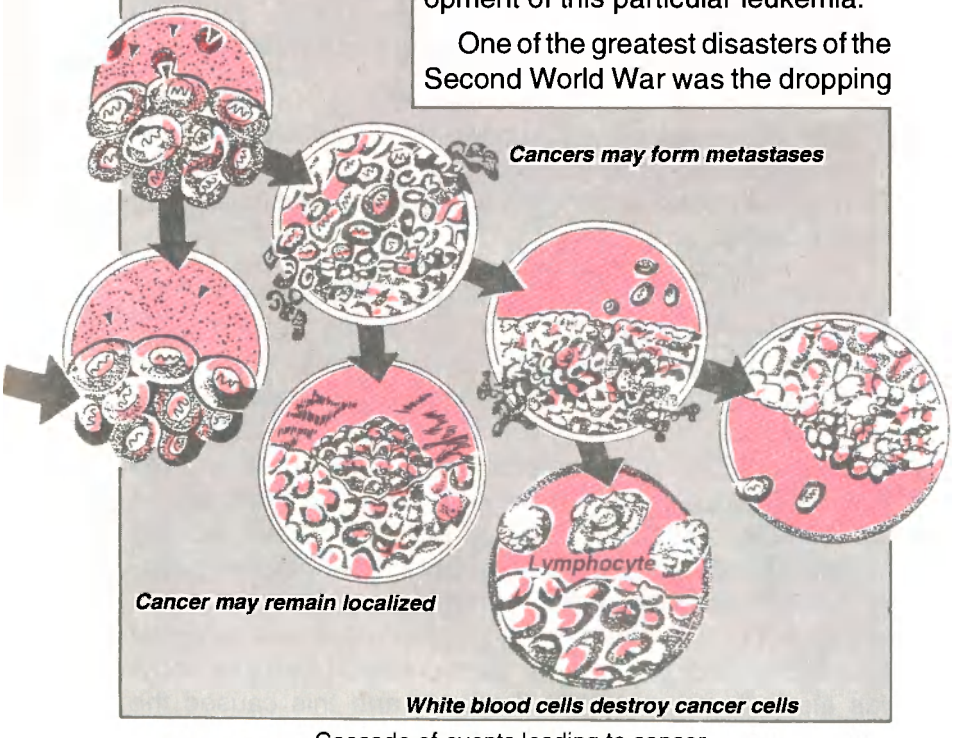


gene which makes its product continuously. Thus the protein is made even when the cell has no need for it.

An excellent example of a translocation activating an oncogene is seen in the *Ph* chromosome in human chronic myeloid leukemia, which was the first observed consistent chromosome change in a human cancer. In the formation of the *Ph* chromosome, the *abl* cellular oncogene on chromosome 9 is joined to a gene called *bcr* on chromosome 22. This shift causes activation of the *abl* oncogene and it now makes

a large hybrid protein of *bcr* and *abl*. David Baltimore and his colleagues at Massachusetts Institute of Technology, USA injected the *bcr-abl* hybrid gene in mice eggs to make transgenic mice. The mice which develop from these eggs carry the *bcr-abl* gene in all their cells. These mice, when they grow up, develop a disease similar to human chronic myeloid leukemia. This indicates that activation of the *abl* oncogene is probably the main event in the development of this particular leukemia.

One of the greatest disasters of the Second World War was the dropping

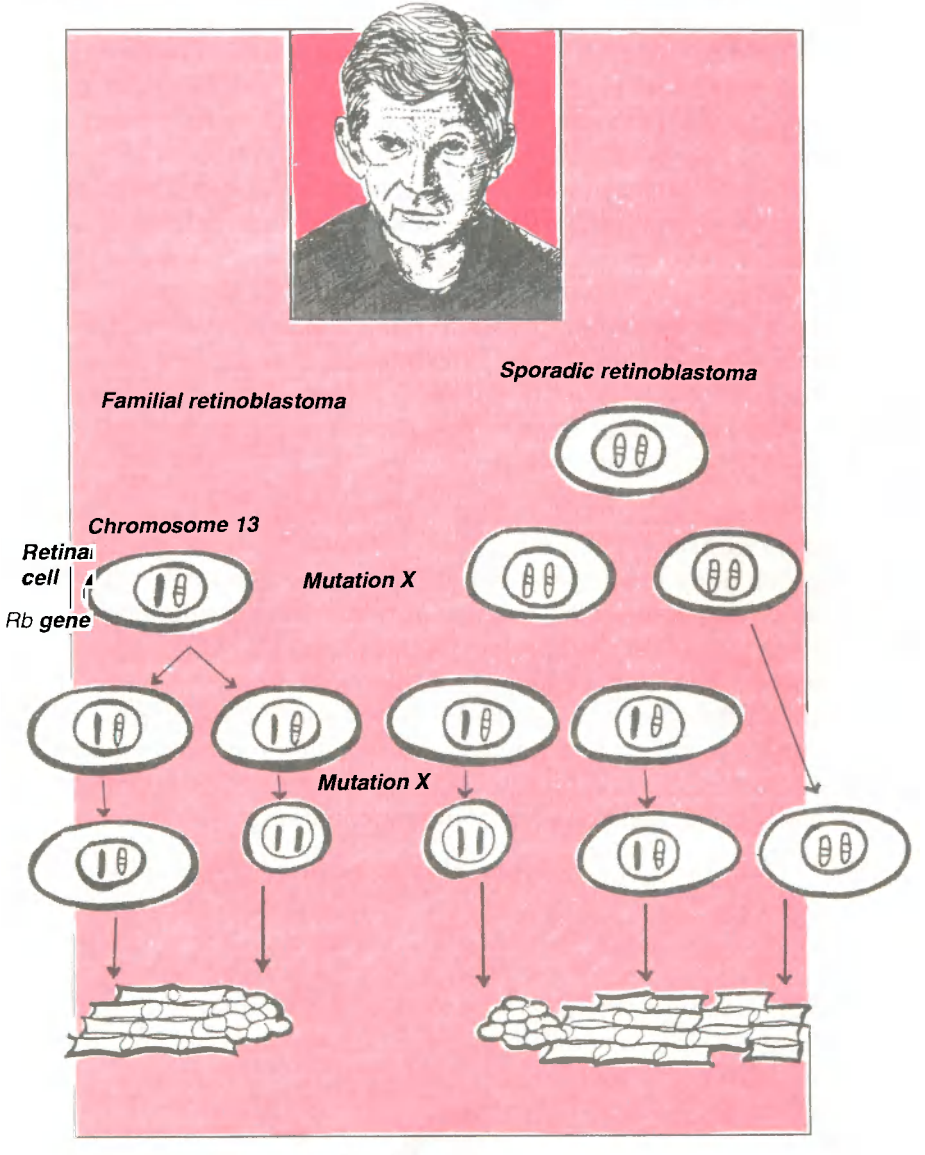


Cascade of events leading to cancer

of atom bombs on Hiroshima and Nagasaki in Japan. Thousands of people died but many people survived the holocaust despite exposure to high levels of radiation. These survivors have been very carefully monitored for years to study the long term effects of radiation. A large number of medical tests have been carried out on them. Scientists also studied their chromosomes to see if these were damaged and whether radiation damage was specific to any particular chromosome. In some of these survivors, the *Ph* chromosome was seen. Evidently, this was one of the effects of radiation. However, these people did not develop leukemia when the *Ph* chromosome was first seen in their bone marrow cells. They developed leukemia 7-8 years later which means these altered cells existed in their body for many years without manifesting malignancy. It is possible that they may have undergone further changes during this period and then finally become leukemic.

Different oncogenes have been shown to be altered in different types of human cancers and sometimes, more than three to four altered oncogenes have been found in a type of human cancer.

Retinoblastoma is a rare childhood tumour affecting the eye. It shows two types of patterns. In some families, more than one child may be affected by this tumour, and these tumours appear early in life. These are the hereditary type tumours and may affect both the eyes. In the 'sporadic' type, only a single child in the family may be affected and the tumour develops in only one eye. In 1971, Alfred Knudson after an extensive statistical analysis of the disease patterns in these families postulated that a mutation in both the paternal and maternal copies of a particular gene caused this cancer. This meant that the child had inherited one defective gene from one of the parents. Its counterpart (another copy) was also altered or lost in the eyes and this caused the cancer. Jorge Yunis of the University of Minnesota (USA) showed that a small part of chromosome 13 was lost in some



Alfred Knudson postulated the 'two-hit' theory about retinoblastoma

of these patients. Scientists also had a lucky break. They found that gene for an enzyme called esterase D was also lost with this piece of chromosome. This loss could be detected by biochemical techniques. Thus, a change and a loss of that gene seemed to cause the cell to become cancerous. Scientists predicted that this particular gene must be preventing a change from normal to cancerous and that when it was not active or lost, its shielding effect was gone and the result was development of cancer. This gene was named *Rb* as its affect was first shown in retinoblastoma patients, and this new group of genes which seemed to prevent cancer development by their normal action were given the general name 'suppressor genes' as against the oncogenes which cause cancer when active.

Another important gene in this group is called *p53*. This gene is involved in the regulation of cell division. A mutation in this gene results in the making of a modified *p53* protein which competes with normal *p53* protein. The mutated protein has a longer life. This protein therefore neutralizes the normal *p53* protein and inhibits its suppressor action. Molecular biologists have now studied this gene in different types of human tumours and have found mutations in a very large number of them. A mutation in the *p53* gene is an important event in the development of human cancers.

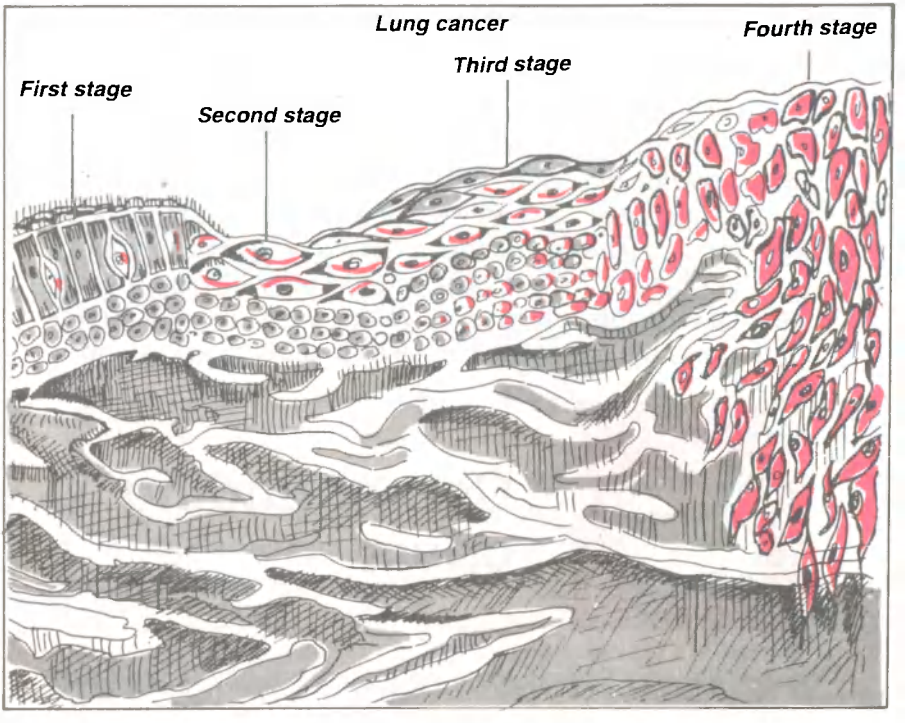
The connection between alterations or activation of oncogenes and development of cancers is fairly well established. Most of the human tumours show altered oncogene(s) and some in addition, show change in a suppressor gene. Can this information help us in detecting the cancer at an early stage? This is a question that doctors who treat patients and scientists who wish to go to the roots of oncogenesis are asking.

I have a friend who smokes heavily. My best efforts to make him give up smoking have failed. This is probably my only defeat in convincing people to give up smoking. When I argue with my friend, he always cites the example of Winston Churchill, former British prime minister, statesman and writer who smoked cigars. Churchill lived a long life and never developed cancer. My friend argues that he will probably be like Winston Churchill and never develop cancer. Any argument on the risk he subjects himself to, are futile, mainly because he wants to close his eyes to reality. However, if we ponder over his argument we realise that every smoker does

Compounding crisis

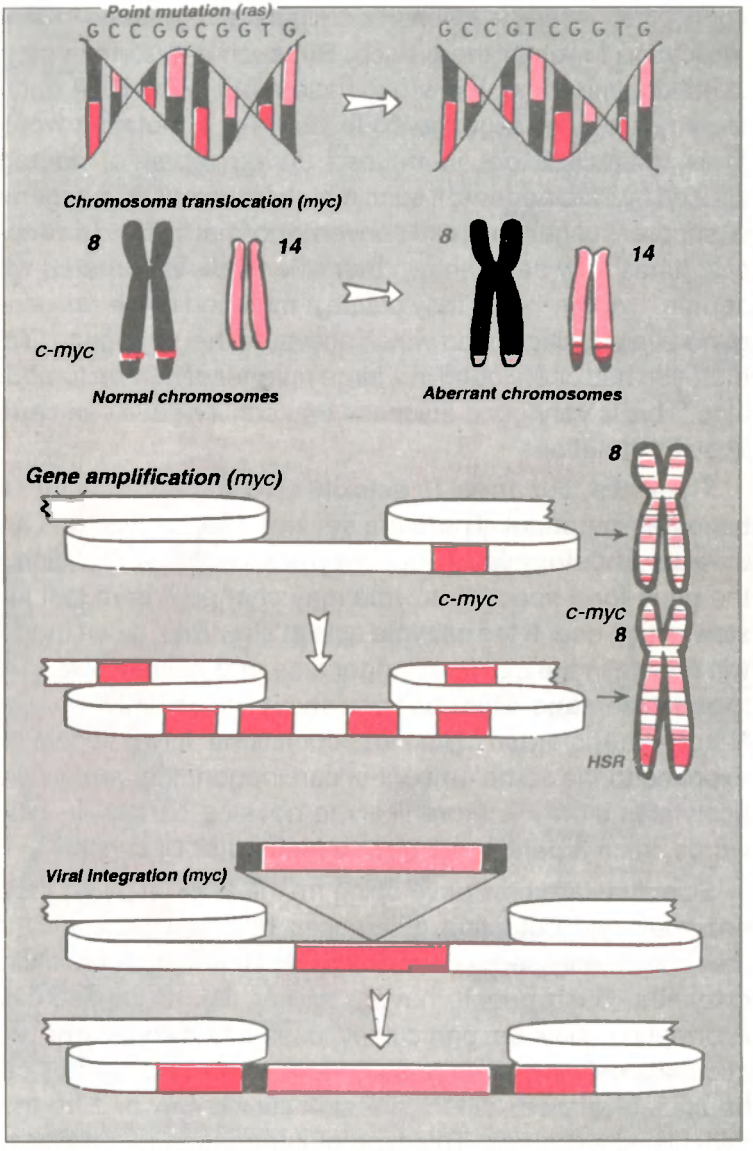
not get cancer. The question we may ask is who gets it and why?

To find an answer to this question, we have to understand how chemical carcinogens change a normal cell into cancerous one. When harmful chemicals enter our cells, the cellular response is to try to change them into harmless substances and eliminate them from the body. The chemicals which are highly poisonous or toxic are very reactive and immediately react with the key molecules in the cell causing death of the cell. This may damage the organ and perhaps kill the person as well. The amount of any carcinogen we are exposed to at a given time, is too small to cause such a drastic effect. The cells then try to convert the tiny amounts of these chemicals, in a stepwise manner to less harmful substances. A number of enzymes called detoxifying enzymes, carry out this job. A substance entering the cells may be carcinogenic by itself and react with the molecules in the cells. It is also possible that



How lung cancer develops

this substance may not be a carcinogen but may be converted into a carcinogen by detoxifying enzymes before it is made harmless. If this reaction occurs slowly, the carcinogenic substance will remain in the cell for a longer time and will have better chance to react with cellular molecules. In a large number of cases, these carcinogens react with the cell's DNA and get attached to it. These molecules attached to the DNA form, what are called, 'DNA adducts' and damage the DNA. The cells normally have machinary to repair damage to DNA. There are a number of repair systems which carry out this work. Some remove the adducts. The repair system also removes a part of that strand of DNA which has been dam-

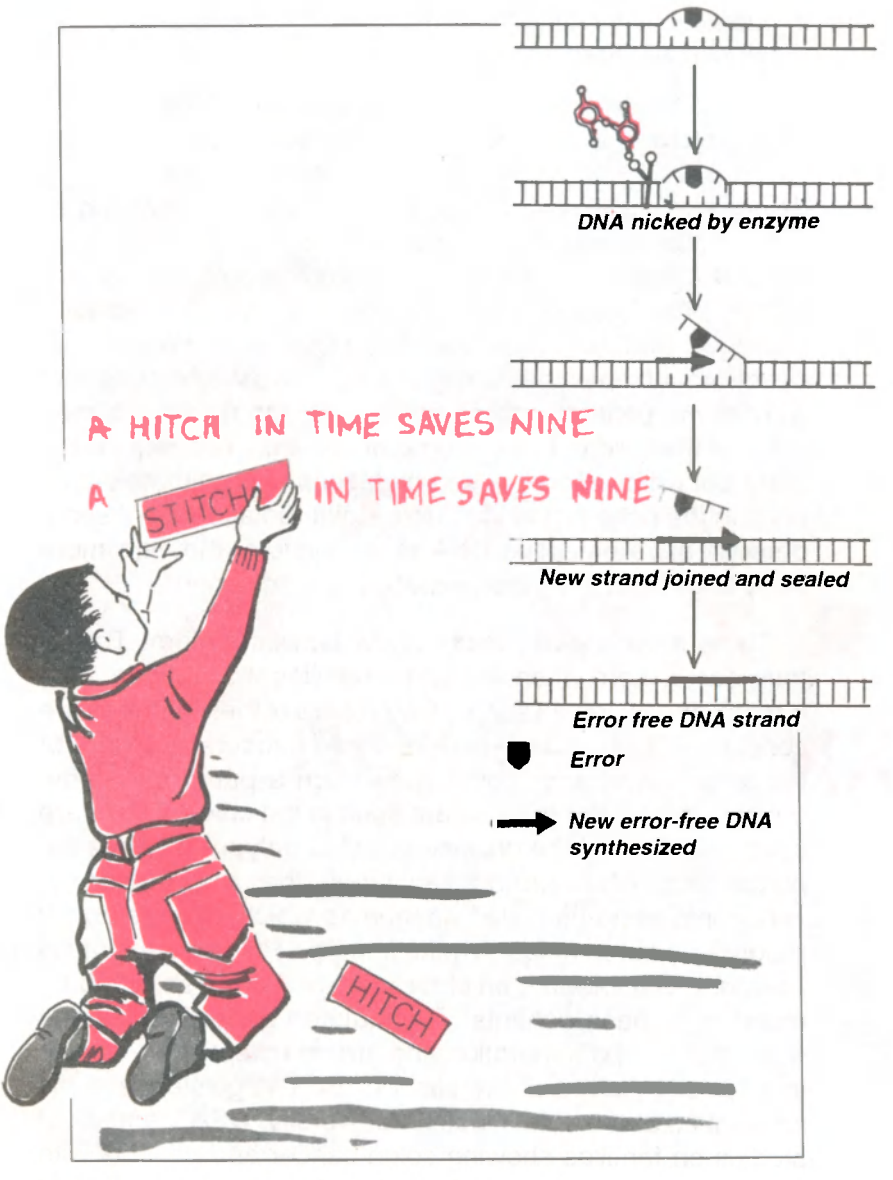


How oncogenes may be activated

aged. Then it uses a mechanism similar to that used in DNA replication to repair the breach. But such a system is prone to making mistakes. If a wrong base is put in the DNA during repair , it may change the code just like a mutation would. Thus, mutations get introduced during repair of damage caused by carcinogens. If such mutations occur in oncogenes or suppressor genes, it can convert a normal cell into a cancer cell. It has now been shown that when cells are treated with certain hydrocarbons, they cause a mutation in the *ras* oncogene at a specific codon which activates this oncogene. This mutation has been found in a large number of human tumours also. This is very good evidence that carcinogens can cause specific mutations.

Therefore, our ability to detoxify carcinogenic substances becomes important. There are several enzyme systems and the rate of detoxification by enzymes varies. A mutation in the gene for a specific enzyme may change it from fast to a slow acting one. If the enzyme acts at slow rate, a carcinogen will remain in the cell for a longer time and will be more likely to cause damage. This has been shown for an enzyme called N-acetyl-transferase in human populations. If two people are exposed to the same amount of carcinogen, the person who acetylates slowly is more likely to develop cancer. In other words, such a person will have a higher risk of cancer.

Scientists are now developing methods of studying these enzymes and detecting differences between them so that they can identify people with deficient or inefficient detoxifying enzymes. Such people have a higher risk of cancer. This information may be particularly useful to people who are occupationally exposed to hazardous chemicals as they can be shifted to areas where the exposure is low or zero thus minimising extra risk. This type of information is now being collected on a small scale in populations working in industry. It marks the beginning of a new discipline called 'molecular epidemiology'. Such studies can reduce the risk of cancers

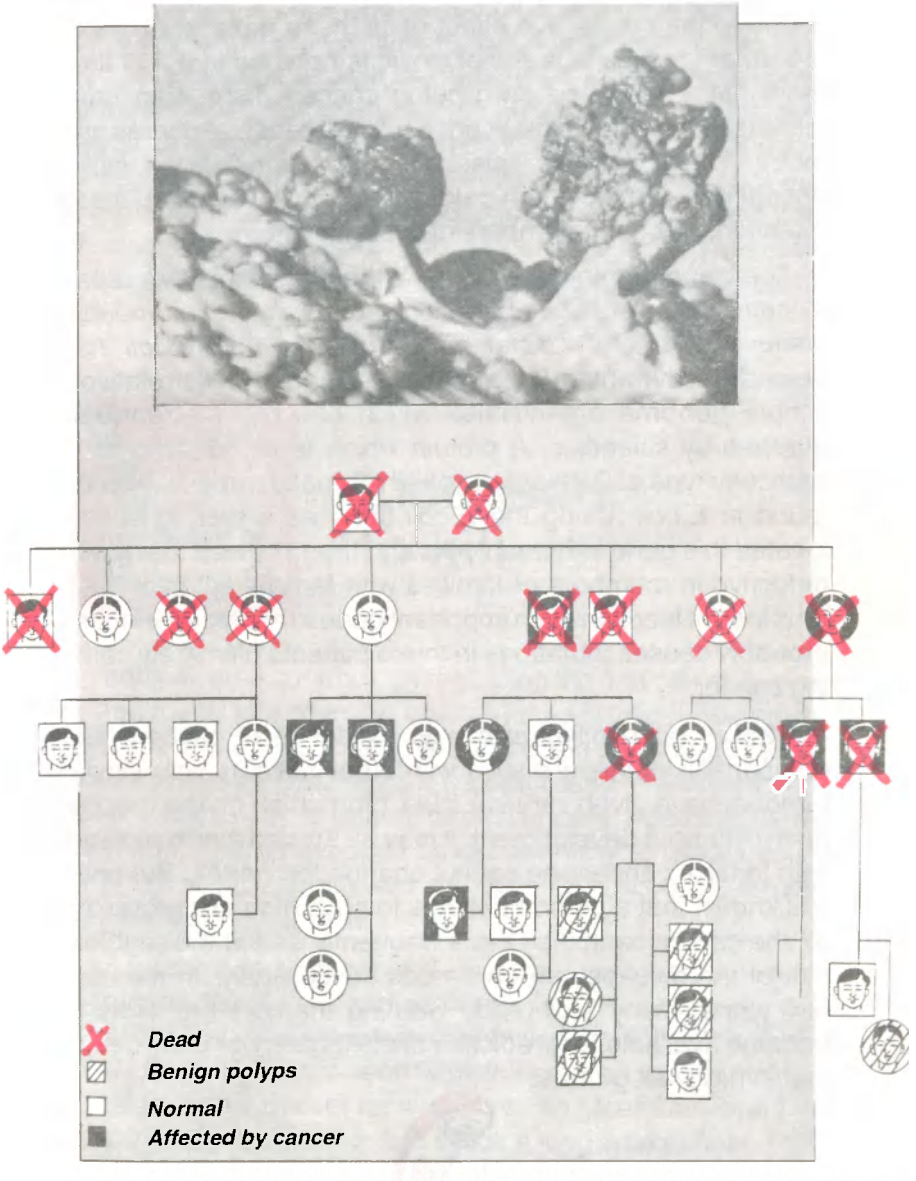


DNA repair is necessary to maintain genomic integrity

in populations occupationally exposed to carcinogens or due to chosen lifestyles.

Faulty DNA repair as a possible cause of cancer was suggested by J.E. Cleaver in 1968, in patients with a disease called *Xeroderma pigmentosum.* Patients with this disease develop multiple skin cancers when they are exposed to sunlight.These cancers occur on arms or the face. Cells from several *Xeroderma* patients and normal people were grown in culture by scientists and exposed to UV light. This radiation damages the DNA. It was found that while cells from normal people could repair the damage caused by UV light, cells from *Xeroderma* patients could not carry out the repair. It turned out that they did not have some of the enzymes required to carry out repair. This caused mutations and ultimately cancers, in the cells exposed to ultra violet radiation. So if some persons have defective DNA repair system, they are more likely to get cancers when exposed to carcinogens.

There are cancers which show familial pattern. That is they occur more often in certain families than normal incidence patterns would suggest. Members of these families are considered to be susceptible to these cancers. Cancers of the large bowel and colon show such a pattern. In some families, grape-like growths are seen in the colon. These are called polyps and the disease is called polyposis. While the polyps themselves are not cancerous, they may further advance into tumours called adenomas which if not removed progress to carcinomas. A gene named APC (*Adrenomatous polyposis coli*)present on chromosome 5, was shown to be mutated in these patients. The mutated genes are passed down to the next generation and are manifest. This results in a familial pattern of the cancer. Bert Vogelstein and his colleagues at the John'Hopkins University, USA, carried out studies on families showing colon cancer and patients with sporadic colon cancer and came to the conclusion that at least four to five oncogenes — one of which is p53 — show mutations in this type of cancer. The development of cancer



Polyposis (inset) seems to run in families

is due to the cumulative effect of all these mutations. There are other families where polyposis is not manifest but they have many members with colon cancer. They also have increased susceptibility to cancer of the breast, pancreas and ovary. These patients also show mutations in the same oncogenes. The question naturally arises is why do so many mutations occur in members of these families?

The culprit again appears to be the inefficient DNA repair system. Scientists have been looking at DNA repair mechanisms in the colon bacterium *Escherichia coli*. *E.coli* has helped uncover many secrets of life, thanks to its relatively simple **genome** organisation which has been extensively mapped by scientists. A protein which is responsible for a particular type of DNA repair called mismatch repair has been found in *E.coli*. Using the *E.coli* gene as a tool, scientists located this gene in human cells and then showed that it was defective in members of families with familial colon cancer. This loss of function of an important gene in the repair process probably causes mutations in these patients ultimately causing cancer.

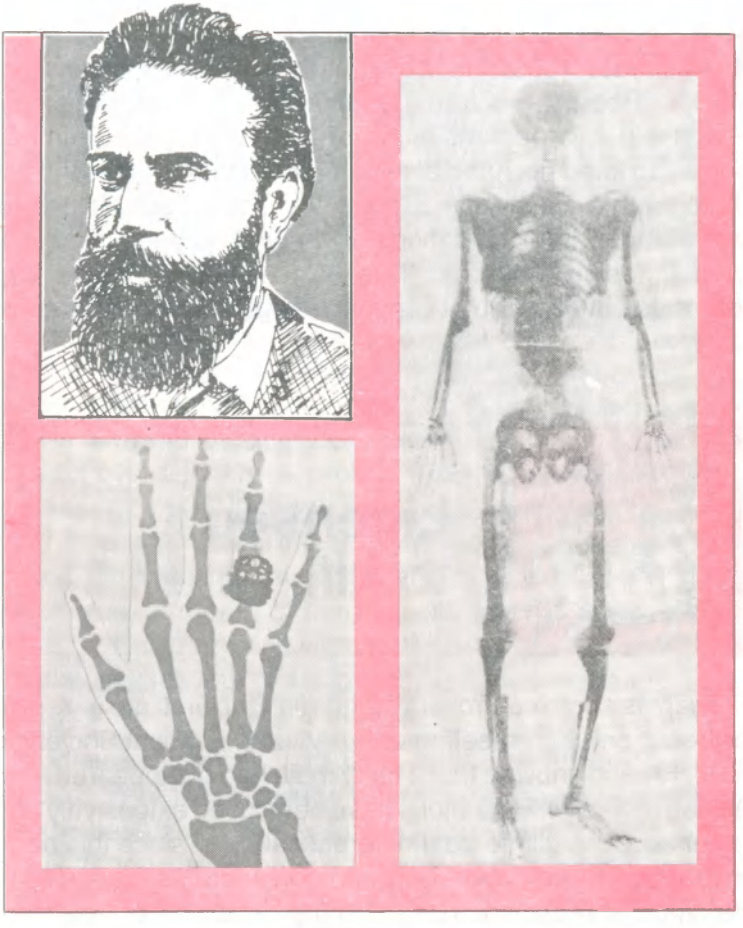
Studies on families with high incidence of cancers and comparison of these results with other patients with similar tumours have given very valuable information on the mechanism of tumour development. It may be argued that in patients with familial cancer one cannot change the genes. But once it is known that a person belongs to such high risk group, he or she can be examined more frequently and at the slightest hint of the disease can be treated successfully. In the next few years, many such early warning markers are likely to become available for prediction of malignancy or early detection in high risk groups.

Wilhelm Conrad Roentgen discovered X-rays in the year 1895. However, it is not as well known that Roentgen is also the father of diagnostic radiology. During a public demonstration of X-rays, he asked his colleague to keep his hand between the X-ray machine and the photographic film and made the first radiograph of bones. One of the major applications of X-rays has been their use for diagnosing diseases. This is possible as X-rays can penetrate our bodies and can form images on a photographic plate.

Licensed to kill

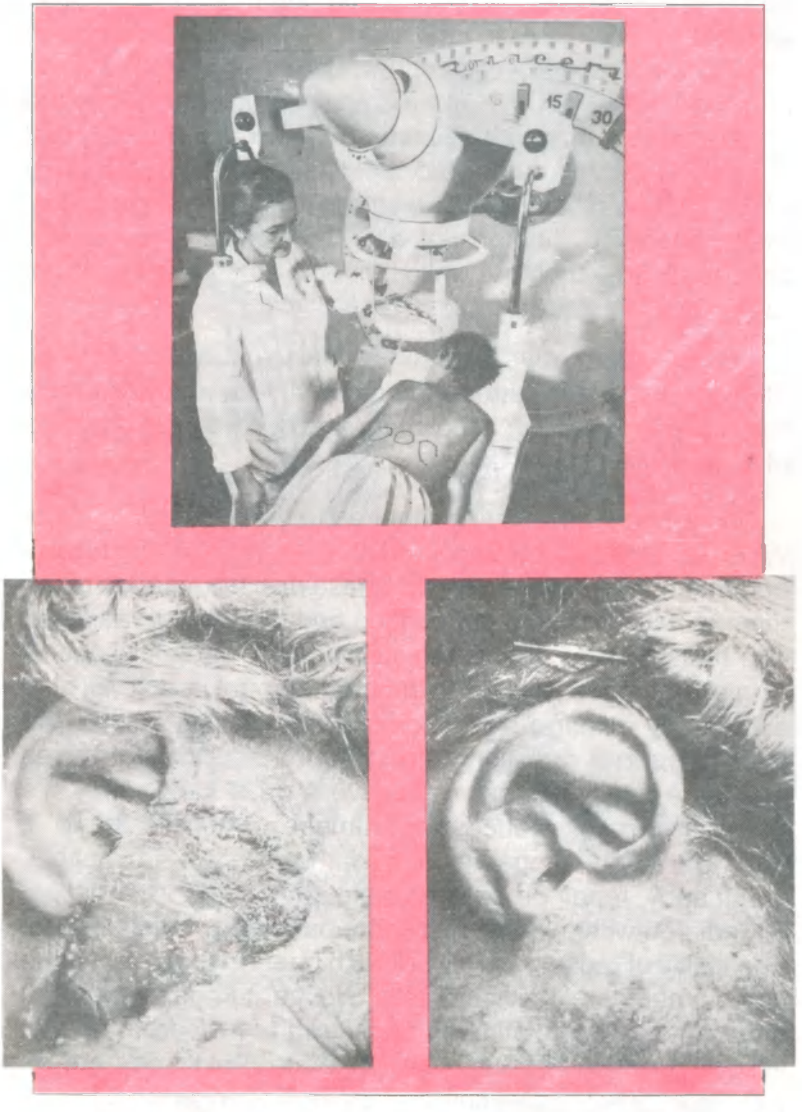
There is some controversy regarding the first use of X-rays for treatment. In a meeting of the Vienna Medical Society in 1897, Freund showed that a hairy mole had disappeared after the use of X-rays. Radiations have been used extensively and rather successfully to treat different cancers since this demonstration. There have also been considerable advances in the types of radiations used and the methods of treatment over the last many years.

About the same time that X-rays were discovered, Henry Becquerel discovered **radioactivity**. He also probably did one of the first experiments in radiobiology which is the study of the effects of radiations on living things. He kept a container of radium in his pocket for six hours. An ulcer developed in the skin under the pocket and it took a long time to heal. This showed the damaging effects of radiations on the body. Today, therapeutic doses of radiations are used to kill cancer cells. This is called radiotherapy.



Wilhelm Conrad Roentgen (inset) took the first ever X-rays

Radiations used for the treatment of cancer are mainly the X-rays and gamma rays. These are called ionizing radiations since they cause ionization of atoms or molecules through which they pass. These **photons** have high energy. This energy is absorbed by electrons of atoms through which they pass. These electrons now reach higher energy levels or are excited. If the radiation energy is sufficiently high, one (or



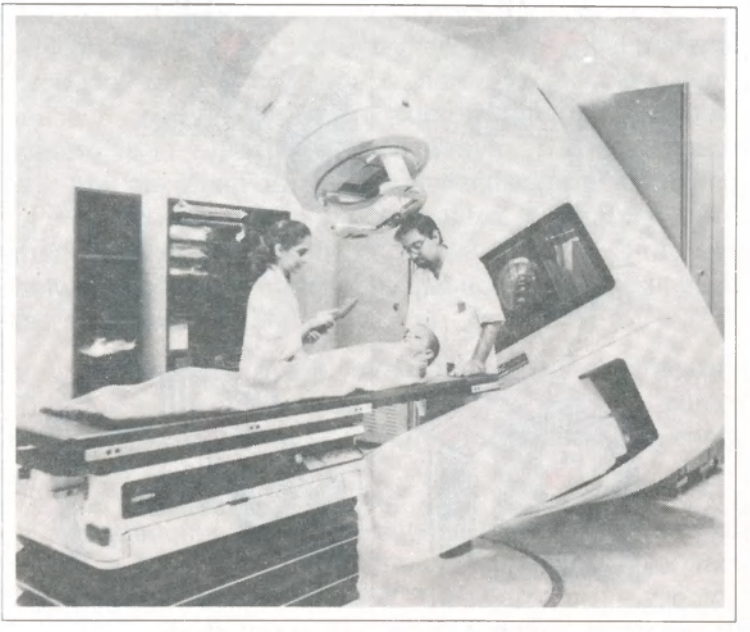
Radiotherapy machines allow millions of electron volts to be targeted deep into the body. Squamous cell carcinoma before (left) and after (right) radiotherapy

more) orbital electron is ejected from the molecules through which they pass. This is ionization. In biological material, it produces considerable effect and damage even if this release is localised. X-rays are extranuclear in origin. They are generated in a machine. Gamma rays are intranuclear, that is, they are given out by radioactive **isotopes**. The energy of the gamma rays depends on the isotope that emits it. The mean energy of photons of a 150-440 kVp X-ray unit is between 0.06-0.14 MeV; while that from a 60 Cobalt gamma ray source is 1.25 MeV.

In addition to X-rays, electrons are also used for treatment. These can be accelerated to high energy and to extremely high speeds in a linear accelerator and can achieve energies of 1.3-6.2 MeV.

The amount of radiation required to kill a tumour is large. When a tumour is being irradiated, a number of factors determine the total dose given. These are: the location of the tumour, its depth from the surface and the type of radiation. The radiation also affects the surrounding normal tissues. A single large dose will kill the tumour no doubt , but it will also extensively damage surrounding normal tissue. Hence, the total amount of radiation is fractionated into smaller doses which are given once a day for several days. However, while this considerably reduces the damage to normal tissue, it does not stop it altogether. This damage is not irrevocable. In our body, repair processes operate and the normal tissue, if irradiated within limits, can come back to its original state. The ability of radiation to kill cells is highest in tissues with the highest number of dividing cells. Hence, tumours are killed more readily by radiation as compared to cells from normal tissues because tumour cells proliferate rapidly and are always in a state of active cell division. However, all the tumours are not equally sensitive to radiation. Certain types of cancers such as those of the food pipe, testicular tumours, some brain tumours are more sensitive to radiation and are treated by radiotherapy.


BLAST



Linear accelerator

High energy electrons generated in a linear accelerator are also very effective. They can be focussed in a small area so that damage to surrounding tissue can be minimised. They also have much higher energies. Hence, in many advanced centres, X-ray machines have been completely replaced and cobalt machines, partially replaced by linear accelerators.

With the help of the CT or CAT scan machines, it is now possible to very accurately locate the tumour as these machines produce three dimensional images of the body. This makes it easy to diagnose as well as precisely locate a tumour. Before radiation is given to a part of the body, fiberglass moulds are made to fit that part in such a way that the surrounding normal area receives very little radiation. The treatment is planned accurately by using computers such

CAT scans of tumours in the brain

that the tumour is killed but damage to surrounding tissue is minimised.

The action of radiations on cells is modified by certain factors. The most important among these is molecular oxygen. Cells irradiated in the presence of oxygen are more sensitive to radiation. Certain chemicals mimic this action of oxygen. Such chemicals are called radiosensitizers as they enhance radiation damage. The drug misonidazole is used as a sensitizer in the treatment of human cancer. There are other types of chemicals too, which help the cells to repair the damage caused by radiation. Such substances are called radioprotectors.

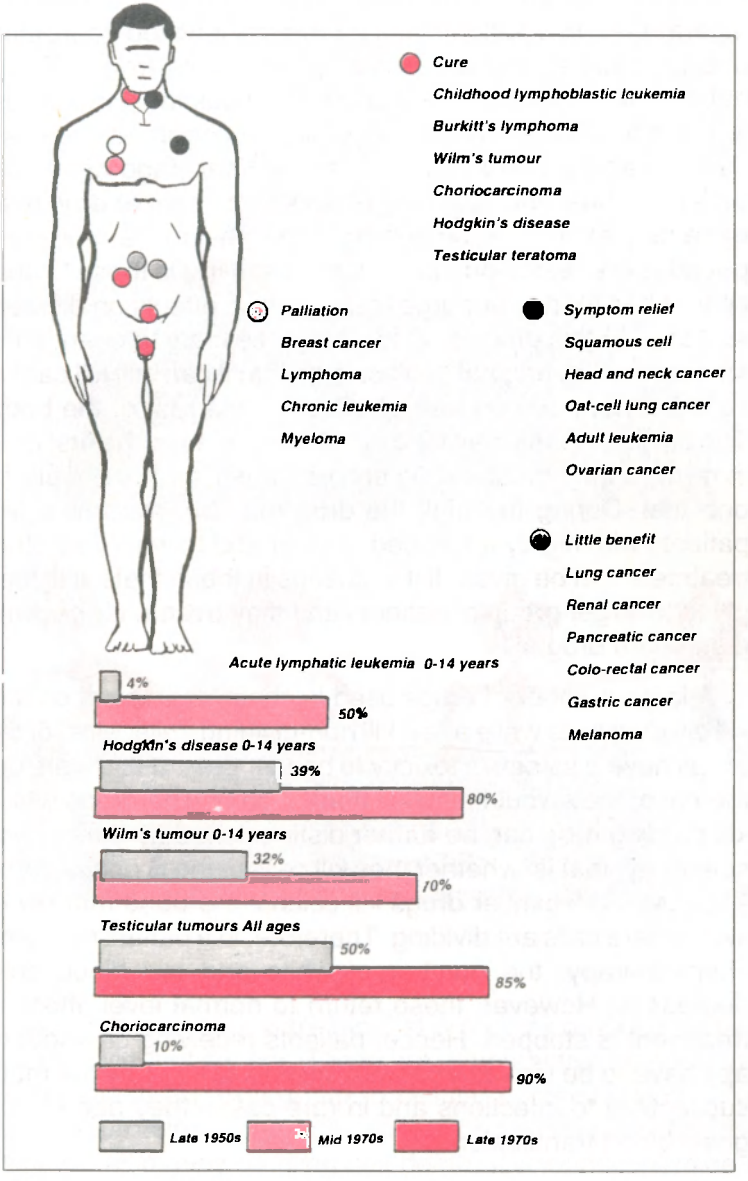
There are at least three types of cells in a tumour: dividing or multiplying cells, dying cells and dormant cells . The third

group of cells are neither dead nor dividing. The dividing cells may be in any one of the four phases of cell cycle. The dormant cells are those that have decided to stop multiplying and to go out of cell cycle. Cells which are dividing are sensitive to radiation but dormant cells escape death even after receiving radiation. Some time later, they get back into the cell cycle and give rise to many more cancerous cells. These then again form a tumour at the same site, after the original tumour had disappeared due to radiation. Such a growth is called a "recurrence".

Radiations cause side effects in the patient. One of these is depression of peripheral blood count. This means that there is perceptible drop in the number of blood cells in the circulatory system. Nausea, and vomitting also occur, particularly in patients who receive radiation in the area of the food pipe, stomach or intestine. However, these side effects disappear after the treatment is over.

Chemotherapy is the treatment of choice when surgery is not possible. In case of leukemias, the cancerous white blood cells are not localised but are circulating in the blood, and surgery is impossible. If radiations cannot kill such cancers, chemotherapy is the only answer.

The history of chemotherapy is rather unusual. Sulphur mustard, a toxic chemical was developed during World War-I for use by the army on the battlefield. It caused burns in the eyes, on the skin and in the respiratory tract of the soldiers exposed to it and incapacitated them. Other effects of this compound were studied after the war. It was found to reduce the number of blood cells and it also affected the bone marrow where these cells are made. It therefore seemed to affect dividing cells. A derivative of this compound, nitrogen mustard, was made later. It had anti-tumour properties. Its first trial on patients was done in 1942. Since then hundreds of thousands of chemicals have been synthesised and tested for anti-cancer action. The type of chemicals tested seem to come from every possible source. Most are synthesized in

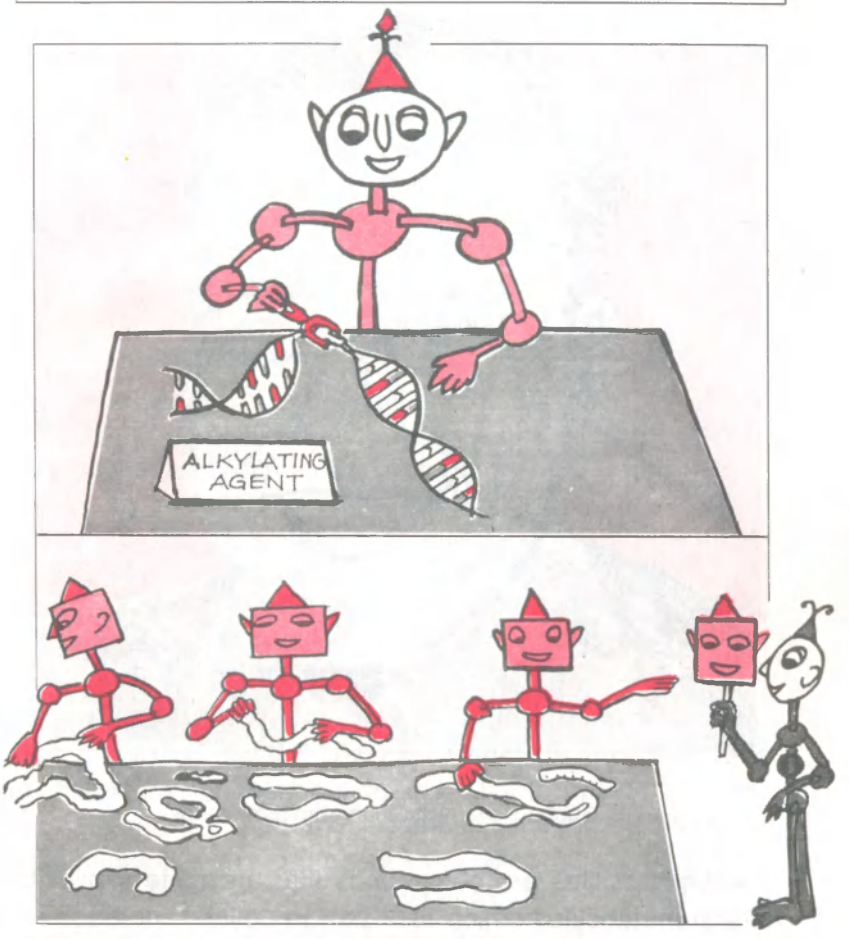


Chemotherapy against cancer — encouraging trends

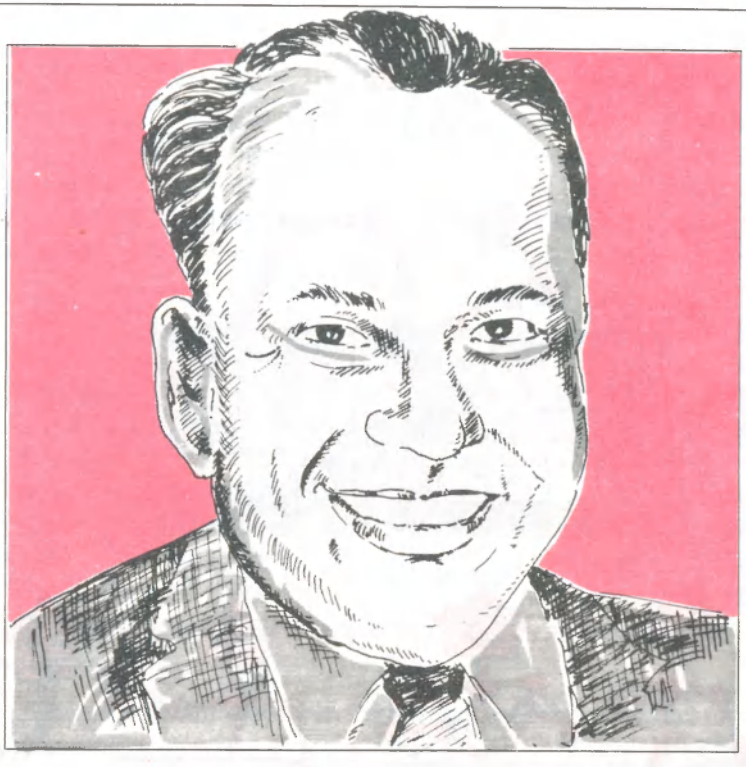
laboratories. In addition, natural products isolated from plants and animals, antibiotics made by organisms from different habitats and products mentioned in various indigenous systems of medicine undergo rigorous testing in laboratories. Only a handful of them make it to the final stage of treating patients. Thus, finding a new effective anti-cancer drug is an extremely expensive proposition. The effect of a new compound is first tested on mouse tumours. If it kills these tumour cells, it has then to undergo tests for toxic effects on different systems. In this process, it is often necessary to change the structure of the original molecule so that it can still kill cancer cells but not have undesired effect on the rest of the body. The entire process may take upto ten years from the first tests in mice to the time the drug comes for what is called, phase one trial. During the trial, the drug may be given to a few patients with highly advanced cancer and to whom no other treatment can be given. If it succeeds in these trials, it is then given to larger group of patients and may eventually become a standard drug.

A large number of drugs used in chemotherapy of cancer kill dividing cells while a few kill non-dividing cells. Most of the drugs have a selective toxicity to cancer cells. If this were not the case, they would also kill normal cells. The drugs which kill dividing cells can be further distinguished by their phase specificity, that is, whether they kill cells in the S phase or the M phase. Anti-cancer drugs kill cells of the bone marrow or skin, where cells are dividing. Therefore, in a patient receiving chemotherapy, the number of white and red blood cells decreases. However, these return to normal level after the treatment is stopped. Hence, patients receiving chemotherapy have to be looked after with special care. They are more susceptible to infections and in rare cases they need to be given blood transfusion.

The anti-cancer drugs are classified under different groups according to their mode of action. The more important of these groups are alkylating agents and antimetabolites.



Alkylating agents were the first group of compounds used for treatment of cancer. These are very reactive compounds. They attach an alkyl group to cellular constituents such as DNA or proteins. They also cause crosslinking between DNA strands ultimately causing cell death. Cyclophosphamide is one of the most frequently used alkylating agents in the treatment of different cancers such as those of breast, lung, ovary and leukemias.



Y. Subba Row — the man of miracle drugs

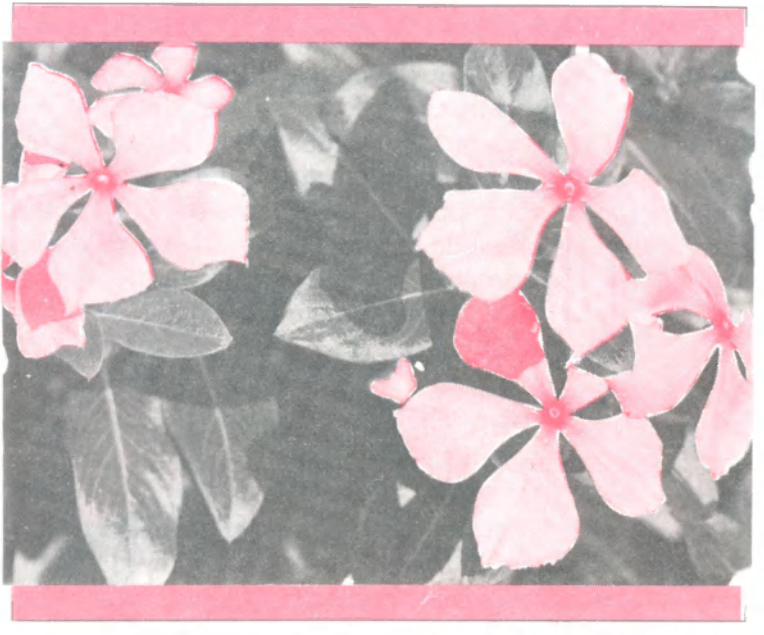
Antimetabolites are compounds that are quite similar to natural metabolites which take part in cellular metabolism. They mimic the natural metabolites and occupy their position in a reaction. Since they are not the actual molecules, the particular reaction stops at this step. When antimetabolites block a vital reaction, the cell dies. Folic acid plays an important role in reactions involved in DNA, RNA and protein synthesis. One of the first antimetabolites made was a folic acid analog. The antifolates, as these compounds are called, have for many years been important weapons in therapeutic anticancer armoury. One of the pioneers in this field was the Indian scientist Yellapragada Subba Row — the man of

miracle drugs. It has been said of him that, "Yet because he lived you may be alive and well today. Because he lived you may live longer." Subba Row produced folic acid antagonists in his laboratory and these proved to be real growth inhibitors of cancer cells. One of them, aminopterin, brought about almost miraculous recovery of children suffering from acute leukemia. The most important antifolate is methotrexate or amethopterin which binds to and inhibits an enzyme called dihydrofolate reductase. It is used against breast cancer, acute lymphatic leukemia and tumours of mouth cavity.

Other important members of this family are analogs of purines and pyrimidines which are one of the basic components of DNA and RNA. 6-Mercaptopurine is a purine analog used in the treatment of acute leukemias. Other alkylating agents are BCNU, CCNU and Busulphan. 5-Fluorouracil (5-FU) is a very effective pyrimidine analog. It is used for the treatment of cancers of breast, pancreas and liver. Another extensively used pyrimidine analog is Cytosine arabinocide or Ara-C used in the treatment of myeloid leukemia.

Antibiotics which act against various bacteria have become a part of our life. Almost everybody has heard of antibiotics like penicillin, ampicillin and tetracycline. But not everyone is aware that antibiotics can kill cancers. Many of these antibiotics are produced by organisms called *Streptomyces*. Anti-cancer antibiotics such as adriamycin, daunomycin, rubidomycin are called anthracycline antibiotics. Their cellular toxicity is probably due to their capacity to attach very tightly to DNA. These antibiotics are used in the treatment of leukemias, sarcomas, and cancer of the urinary bladder. Other anti-cancer antibiotics are mitomycin and bleomycin.

Many **alkaloids** isolated from plants have anticancer activity. Two alkaloids isolated from *Catharanthus rosea* (previously *Vinca*) — a common flowering plant are very effective against leukemia. These are vincristine and vinblastin. They disrupt the mitotic spindle and cause mitotic arrest. Another



The common *Sadabahar* is a treasure house of anticancer compounds.

compound with similar action is podophyllotoxin isolated from the plant *Podophyllum peltatum*. Taxol isolated from the Pacific yew has quite a different mode of action. While *Vinca* alkaloids and podophyllotoxin break down into smaller sub-units the cytoskeletal organelles called microtubules, taxol stabilizes them by crosslinking them to each other. This interferes with normal cellular activity and blocks cell division. Taxol crosslinks the microtubules. The effect is that the cells appear almost frozen and their activity stops. The two group of compounds affect the microtubules in different fashions but their end-effect is to block cellular activity resulting in cellular death.

Taxol was originally isolated from the bark of the Pacific yew (*Taxus brewifolia*) by Indian born scientist Mansukh Wani and his colleague Monroe Wall. However, the amount of taxol

Taxol, the new anticancer compound in another gift of nature

that could be produced from the yew tree was limited. A kilogram of bark could, at the best, yield only 50-150 milligram of taxol. Producing a kilogram of taxol meant stripping three or four mature trees (sixty years old) totally. This restricted the total availability of taxol for research purposes to only three kilograms in the last twenty years. But in 1994, taxol was successfully synthesized in the laboratory by two teams of American scientists. The first team was led by K.C. Nicalaou at the Scripps Research Institute, La Jolla, California and the other by Robert Holton of Florida State University. The synthesis of taxol in the laboratory will not only provide a steady supply of the drug at a reasonable cost but will also lay to rest fears of ecological disturbances brought on by large scale logging of the slow growing adult yew trees.

Steroid hormones which regulate many functions in our body are also used for fighting cancers. Their use in the treatment of cancer was triggered by the experiments of Charles Huggins and his colleague who showed that enlargement of prostate could be reduced by treatment with estrogen. Castrating the animals and thereby stopping the supply of male hormones also had a similar effect. This, and many other experiments, established the relationship between hormones and cancer. Later, it was found that some breast tumours require estrogen for their growth. Removal of the ovary stops the growth of such tumours. At present an anti-estrogen compound called Tamoxifen is used for treating breast cancer effectively. Several anticancer drugs may be independently active against the particular type of cancer. Does it mean that they act as alternatives to each other? Or does it mean that they are given as a cocktail or multiple drug therapy?

Both these possibilities exist but at present, multiple drugs are routinely used to treat a patient. The cancerous cells in a tumour are in different phases of the cell cycle at any given time. Just as a crowd coming out of a stadium exits from different gates at different speeds and in different directions

so too, cancer cells are in different stages of the cell cycle at any given time. Such cells are called asynchronous cells as compared to synchronous cells which can be considered to be like soldiers marching in step one behind the other. Anti-cancer drugs have to take this lack of synchronicity into account. A drug which kills cells in the S phase will not harm

cells in G1 or in M. Thus, a large fraction of cells will be left unharmed. If two drugs–one acting on S phase cells and another on G1 and G2 cells are combined, then a very large—fraction of the tumour cells can be killed simultaneously. Hence, combinations of drugs acting on different phases of cell cycle are used to kill maximum number of tumour cells. These combinations are not randomly made but are thought out carefully, taking into consideration the phase specificity of drugs, their toxicity and sensitivity of the tumour. Depending upon the type of cancer, combination treatment is repeated at intervals of 3-4 weeks. Such combination therapies have greatly increased the success rate of cancer treatment.

Like bacteria that become resistant to antibiotics, cancer cells too are known to become resistant to drugs so that when a drug is repeated, the cancer continues to grow. It is important to find out how the cancer cells become resistant to drugs. Once we understand how the cells escape the action of a drug, we can develop strategies to overcome it. To understand this we must understand how a drug kills the cancer cells.

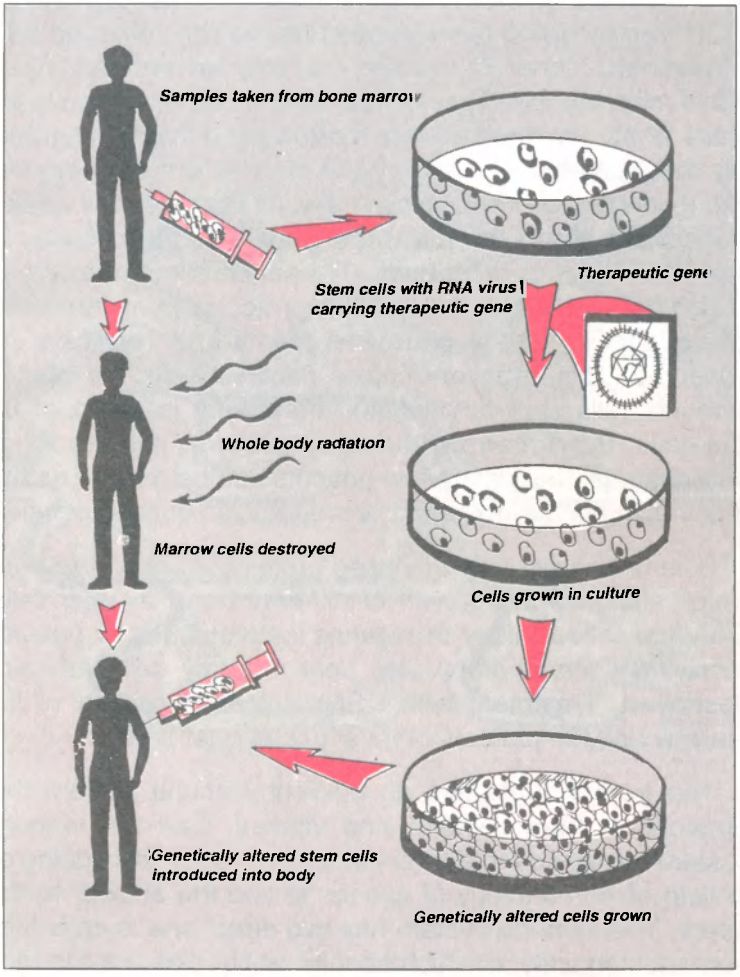
Methotrexate (MTX) is an anti-metabolite used in chemotherapy of cancer. When this drug gets into a cancer cell it attaches to a molecule of the enzyme dihydrofolate reductase (DHFR) and stops the production of the metabolically important folic acid in cancer cells. To understand how the cancer cells overcome the action of this drug, scientists grew these cells in culture and studied them. In cells which are killed by MTX there is one pair of genes for DHFR. In these cells MTX completely neutralizes the DHFR made by these genes since their amount is small. It was found that in MTX resistant cells, about 2000-3000 copies of the DHFR gene were made by the cells. These genes produced such a lot of the enzyme that the MTX molecules could not neutralize the excess of DHFR molecules produced and the cells survived. Such an increase in the number of genes is called 'gene amplification'. Resistance to other drugs also occurs through such amplification.

Many tumours show very unusual resistance. Normally, when a tumour becomes resistant to a particular drug, other drugs with different modes to action are still effective against it. Doctors treating some patients found that some tumours showed resistant to drugs which were totally unrelated to each other and had different mechanisms of action. This type of resistance was called multi-drug resistance (MDR). MDR is seen in many tumours. The way it works is rather unusual. Cells have pump-like mechanism by which chemicals and nutrients enter/exit the cells. In MDR, the cells produce excess of this pump protein named P-glycoprotein, and it starts throwing out the drugs which have gone inside the cells. The drugs do not stay inside the cells long enough for them to act and kill the cell. The pump seems to throw out different drugs equally efficiently and thus make the cells resistant to many drugs at the same time. Scientists have to carry out experiments to understand how the cancer cells become resistant to different groups of drugs and try to work out strategies to combat them.

Patients with leukemia are given chemotherapy with three or four different drugs. However, in spite of these drugs, the disease recurs in certain types of leukemias. The leukemic cells are produced in the bone marrow and it is not possible to kill all the leukemic cells without harming the normal cells. However, all is not lost. Doctors have found an alternative to chemotherapy which is transplanting the diseased bone marrow with marrow taken from a very close relative, a brother or sister, after completely destroying the patient's bone marrow. The body's immune system normally kills cells or organs transplanted from another person since it identifies the transplanted tissue as foreign or non-self. This reaction is called the graft versus host reaction and is due to specific proteins on our cells which signal 'self' or non-self as the case may be, enabling the immune system to differentiate between the two. In case of identical twins such antigens are similar and transplants between them are always successful. Trans-

Vandana Kadam — messenger of hope

plants can also be done between brothers and sisters, if they have similar antigens. If such similarity is found, it is called a 'match'. About twelve years ago, young Vandana Kadam became the recipient of India's first bone marrow transplant.



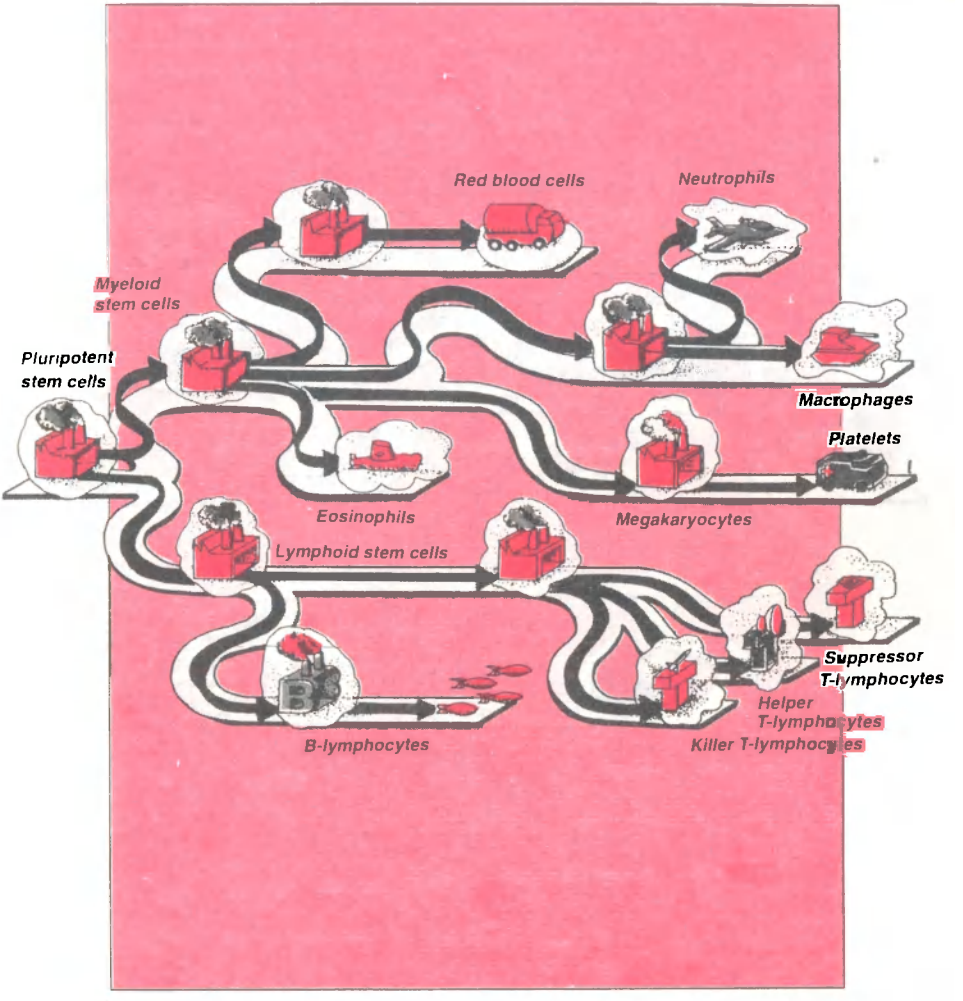
New genes for old

Her brother donated the requisite tissue. Today the leukemia that threatened to cut short her life has been vanquished and Vandana is training to be a nurse specially to attend to cancer patients.

The bone marrow of leukemic patient is then completely destroyed by giving radiation and the marrow removed from a matched donor is injected the way an ordinary blood transfusion is given. The injected bone marrow cells go to the place where the original bone marrow used to be and gradually the different cells of the bone marrow start dividing and make new red and white blood cells. All this takes 2-4 weeks. During this period the patient is given blood transfusion to meet the demands of his body. The patient's immune system is also not functional and has to be protected from infections. The patient is kept in germ free rooms and very carefully observed. This is a very critical period. Once, the grafted immune cells start functioning, the patient is cured of his leukemia. Bone marrow transplant has now achieved high success rates but only a few patients can be treated as this requires special wards and the treatment is quite expensive.

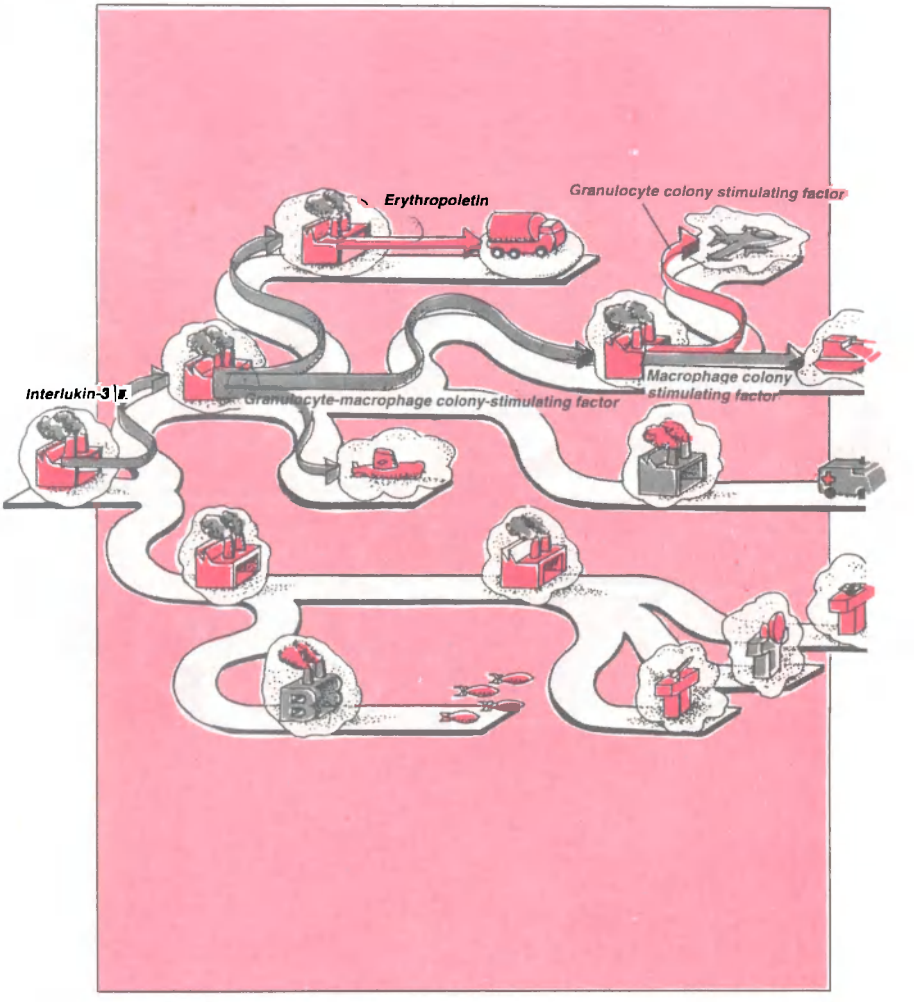
Scientists have now identified proteins made in the body which stimulate the growth of different bone marrow cells. They are called colony stimulating factors (CSF). In patients receiving chemotherapy, the bone marrow cells are also destroyed. Treatment with CSFs helps restoration of the marrow and the patients recover in a shorter time.

The human body has an efficient immune system that protects us from bacteria and viruses. Can the immune system not fight cancer? Very extensive research is going on in field of 'immunology of cancer' to find the answer to this query. The immune system has two arms: one is called the humoral immunity in which specific antibodies are made to fight germs, viruses and other toxic molecules. The other arm of immunity is the cell mediated immunity in which, different types of lymphocytes kill the bacteria and other agents physically or by secreting toxic chemicals. Cell mediated immunity is the main arm that operates against cancers. Scientists have been studying the different types of lymphocytes taking part in the killing of cancer cells, and on the basis of these studies have tried to enhance the immune response against



The body's defense system provides immunity against many infections

a particular type of tumour. There are different types of cells such as natural killer (NK) cells, cytotoxic T cells (CTL) and lymphokine activated killer (LAK) cells which kill cancer cells. These are called effector cells. Some of these depend on an



Provoking the immune system to fight better

antibody made against a protein specific to the tumour cells to kill tumour cells, while others kill directly. The former type of killing is called antibody dependent cell cytotoxicity (ADCC). The number and activity of these cells can be

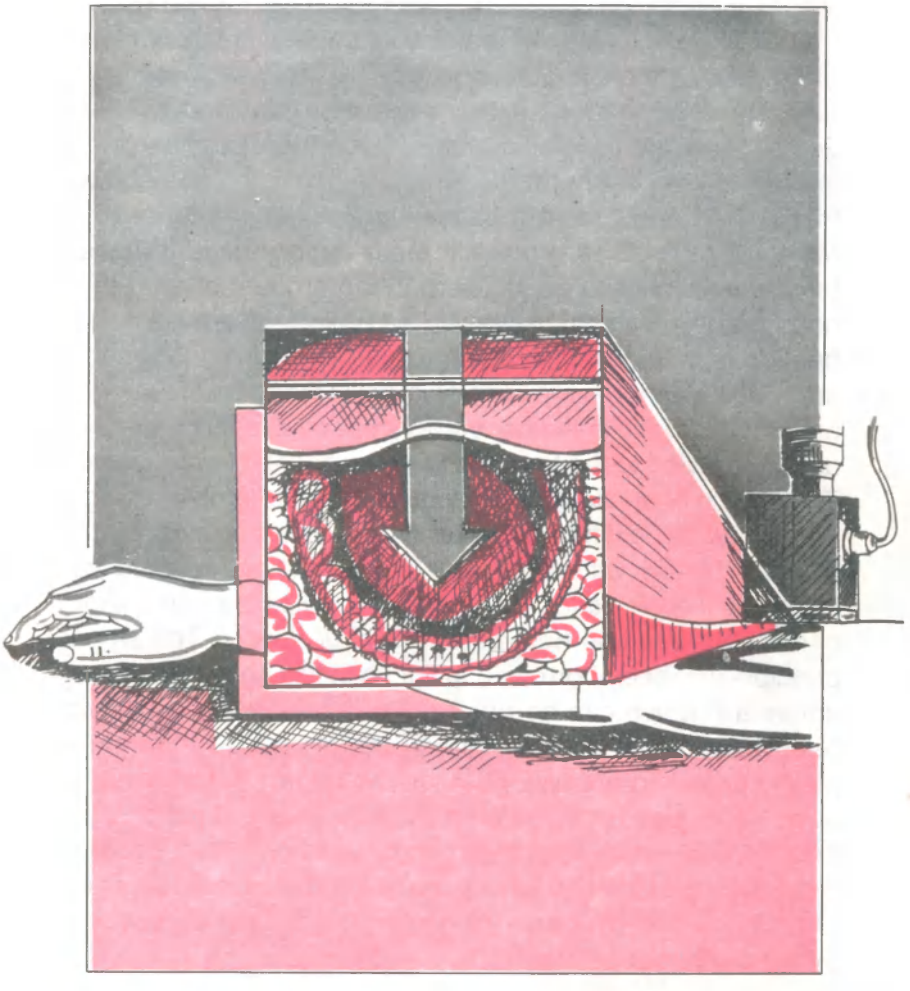
increased by factors produced by some of these cells. These factors are called lymphokines. There are several lymphokines, prominent among them are the Interleukines and interferons. There are at least 15 interleukines numbered IL-1-15. They stimulate different effector cells. IL-2 increases T lymphocytes and can be used for improving immune response. Research work is being carried out all over the world to manipulate these factors so that the effector cells can kill maximum number of tumour cells. However, immunotherapy is still in it experimental stage and is not yet a standard mode of treatment like chemotherapy and radiotherapy.

Scientists, doctors and radiologists are constantly making efforts to discover new drugs and design better treatment protocols for chemotherapy. They are committed to finding ways of overcoming resistance and increasing rate of cell killing by radiations. Efforts are also being made to find ways of taming cancer cells and activating the body's immune system to eliminate the tumours. But how successful have these efforts been and what does the future hold ? Can genetic engineering find a solutions to cancer? Will we be able to cure every cancer patient? Anti-cancer drugs kill the cancer cells but they also harm the normal

Tomorrow's therapies

dividing cells. Can we not direct them only to the cancer cells?

Before a drug kills cancer cells, it must enter the cells. Some drugs are designed to use small differences between normal and cancer cells so that they can enter the cancer cells more easily than the normal cells. But normal cells cannot totally exclude them. If we can design the drugs to act like ballistic missiles and send them into cancer cells, the battle can be won. Such 'magic bullets' can then kill the tumours without harming other cells, but this is easier said than done. Can we use other 'tricks' to kill cancer cells more efficiently with the existing drugs? These are difficult questions no doubt, but determined human effort is slowly yet confidently finding answers. Doctors and scientists are trying out new strategies on selected patients. We can call these therapies of tomorrow.

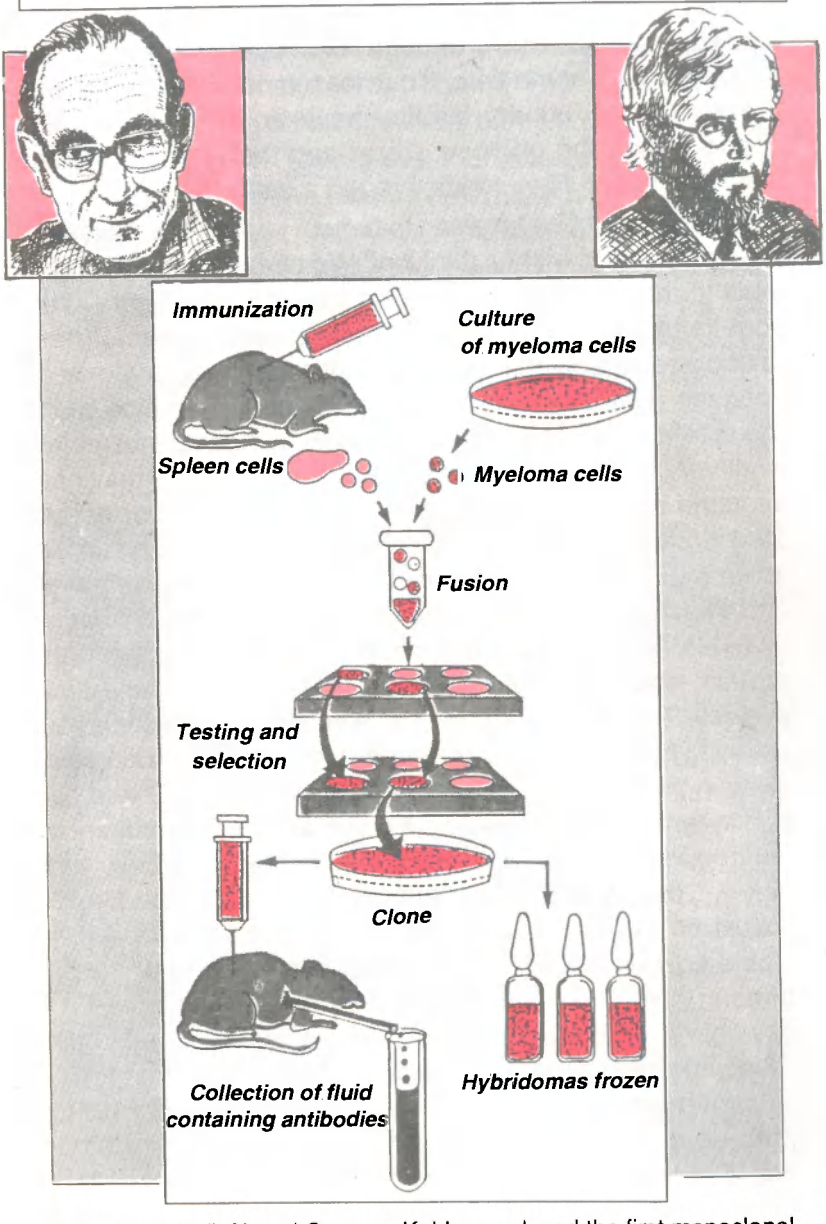


Microwaves can be used for localized deep penetration to treat tumours

Improvements in our arms and ammunition for radiation therapy will come from the use of fast neutrons and proton beams. Effect of radiation therapy can also be increased by hyperbaric oxygen and hyperthermia. Hyperbaric oxygen

means increasing the molecular oxygen in the tumour tissue. Higher oxygen tension in the tumour causes death of many more cells when radiation is given. This may be possible by using new chemicals which not only cause this effect but also get concentrated in the tumour. Hyperthermia means an increase in the temperature. Extensive research has shown that if the tumour is at a slightly higher temperature, both radiation as well as drugs kill more tumour cells. Higher temperature causes an increase in the amount of drug that goes inside a tumour. However, the main problem is how to heat up a tumour without heating up its normal neighbouring area. Some tumours are superficial while many other tumours are situated deep in the body. Devices called applicators are usually applied to the tumours to increase their temperature. The design of applicators present a technical problem since these have to be different for tumours at different sites. Many of us are familiar with microwave ovens that have entered the kitchens. These cook the food in minutes because they penetrate deep and heat up the food uniformly. The same principle has been borrowed to fight cancer. Thin microwave antennae, which can be arranged around the tumour have been developed. Others that can be introduced through a plastic tube into a cavity such as the urinary bladder have been developed and tried on a limited number of patients. If they become successful, they can be used on a larger scale. Scientists are literally turning on the 'heat'. Resistance of tumours to two drugs — cis-platin and MTX— has been overcome by hyperthermia.

Lasers are another potential weapon in our armoury. Lasers deliver a coherent beam of light to a very small area and can kill tissue by heating. A new form of therapy called photodynamic therapy is being tried on tumours. Certain chemicals called photosensitizers, absorb light of particular wavelength and later release this energy. Release of this energy in cells can kill them. Photosensitizers concentrated in the tumour if they are injected into blood. If we now

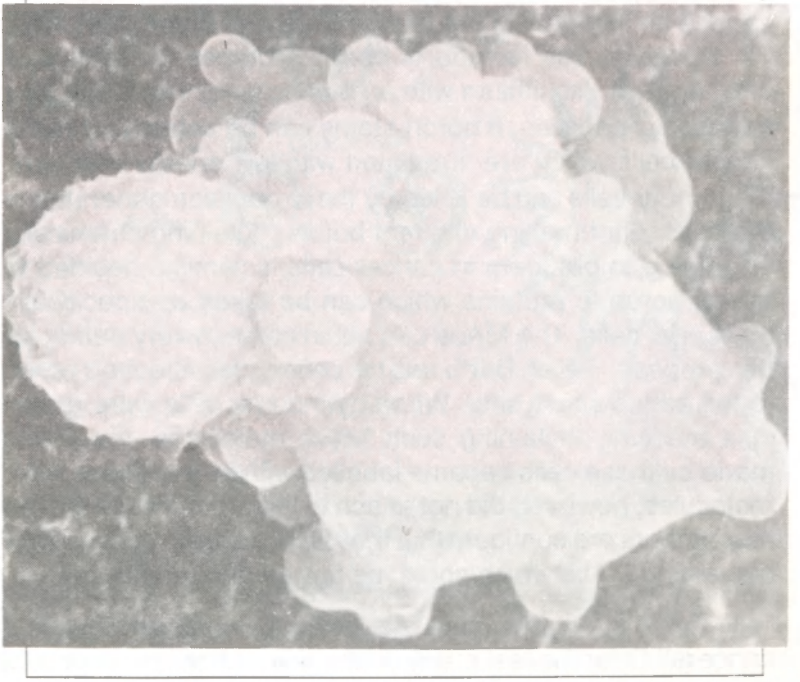


Cesar Milstein (left) and Georges Kohler produced the first monoclonal antibodies

introduce a laser beam through **fiber optics** in the tumour and shine it for some time, it can kill tumour cells. Over 5000 tumours of the urinary bladder have been treated by first concentrating the photosensitizer and then introducing the laser beam with fiber optics through a catheter.

Can drugs not be targeted to tumour cells? Or is it only our imagination and wishful thinking? We already have the basic tools to make magic bullets. One way the body fights infections is by making specific antibodies against them. These antibodies attach themselves to the bacterial material or antigens against which they were formed. This type of immune response called the humoral immunity does not usually work very well with tumour cells. But some tumours may have acquired new proteins on their cells. These tumour associated antigens(TAA) can be used in our fight and to our advantage. Normally, antibodies are made by taking a protein and injecting it in very small quantities into an animal at intervals. The animal starts making antibodies against this protein which can be harvested from its blood. It is now possible to get very specific antibodies using a technique called hybridoma technique where the antibody making cells grow in tissue culture and continuously produce these high quality antibodies. These antibodies are called monoclonal antibodies (MAbs). The scientists who developed this technique, Cesar Milstein and Georges Kohler from the Medical Research Council laboratories in London were awarded the Noble prize in Physiology and Medicine in the year 1985. If tumour cells make unique TAAs on their cell surface it is possible to make several MAbs against different parts of the TAA molecules. One can then select the best one in terms of its strong reaction with the tumour cells. With the help of this MAb we can deliver drugs or toxic substances to the tumour cell. The MAb injected into the patient will attach itself to the tumour cells but not to the normal cells as the normal cells do not show this antigen. This antibody can help a group of T cells (CTL) in killing tumour cells. Another way to target

tumour cells is to attach a molecule of anti-cancer drug, or a toxin molecule to this MAb. These will be delivered directly to the tumour cells so that the drug can get concentrated in the tumour. This will reduce the ill effects on the normal cells. Some plants like the castor plant make chemicals which are poisonous to cells. This poison or toxin molecule is made up of two parts. The first part attaches to a cell while the second part kills the cell. Now, this second part can be cut and attached to the MAb which will deliver it to the cancer cells. Treatment with MAbs is being tried in different hospitals. They have shown limited success. It is possible that they will not be effective when the tumour is large. Doctors in Germany

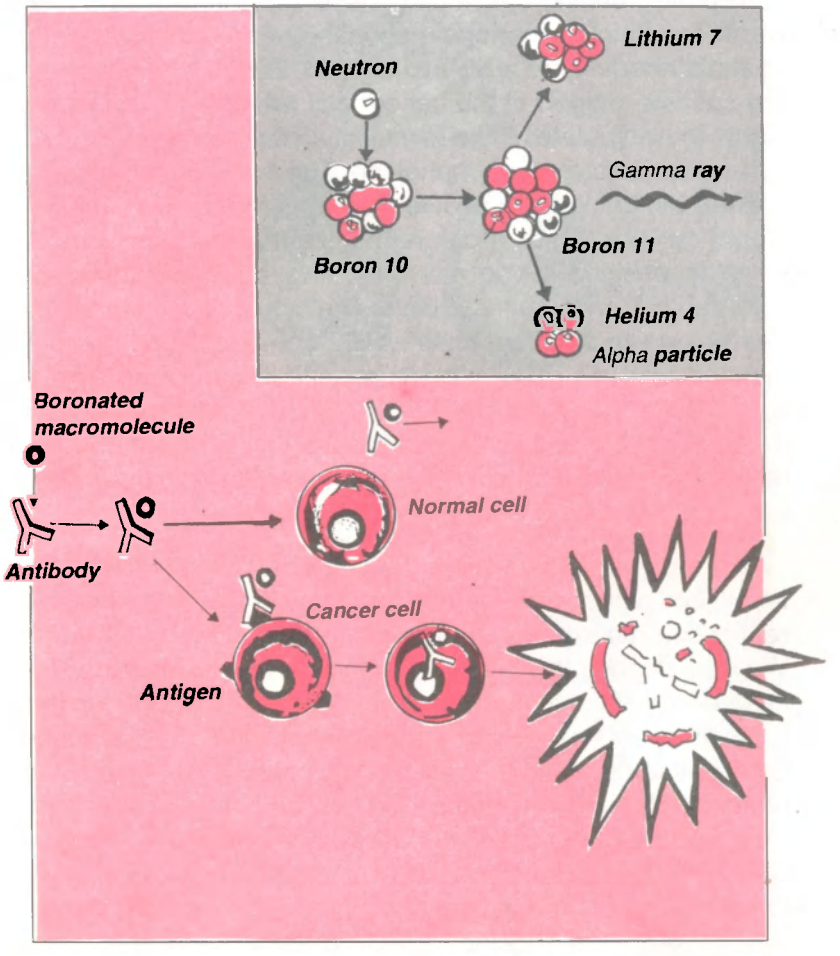


A white blood cell in the process of destroying the much larger cancer cell

have devised a different strategy for certain cancers. They remove the tumour by surgery. However it is difficult to make sure that there are no stray tumour cells left in the patient's body. So after the operation, the surgeons use a sensitive method to see if there are any cells in the bone marrow. If they get a positive answer they inject a specific MAb which helps the cytotoxic T lymphocytes (CTL) to kill these remaining tumour cells. These methods are being used on a limited scale at present but if the success rate is found to be high could soon be saving thousands of lives.

The MAb can also be used to literally 'bomb' the tumour as suggested by Gordon Locher over 50 years ago. This is based on property of the element boron which can absorb low energy neutrons called slow or thermal neutrons. This causes an increase in the atomic weight of boron from 10 to 11. However, this isotope of boron becomes unstable and disintegrates into lithium with an atomic weight of 7 and also releases α-particles. If boron atoms can be selectively put in cancer cells which are irradiated with low energy neutrons, the tumour cells can be killed by the α-particles generated in the cells. After making different boron containing chemicals, and trying to put them in cancer cells, scientists decided to attach boron to proteins which can be taken up specifically by cancer cells. The MAbs can again come in very handy for this purpose. Ralph Barth and his colleagues attached boron to the amino acid lysine. When hybridoma cells were grown in a medium containing such lysine molecules, the MAbs made by these cells became labelled with boron.These MAb molecules, however, did not attach to the tumour cells but the researchers are confident that they will be able to make boron containing MAbs which could be targeted to tumour cells.

If there are TAAs, can we develop a vaccine against cancers? Over the last many years, several cancer vaccines have come and gone. Some appeared promising initially but did not show consistency. Most of the earlier vaccines aimed at producing antibodies against tumour cells. It has been



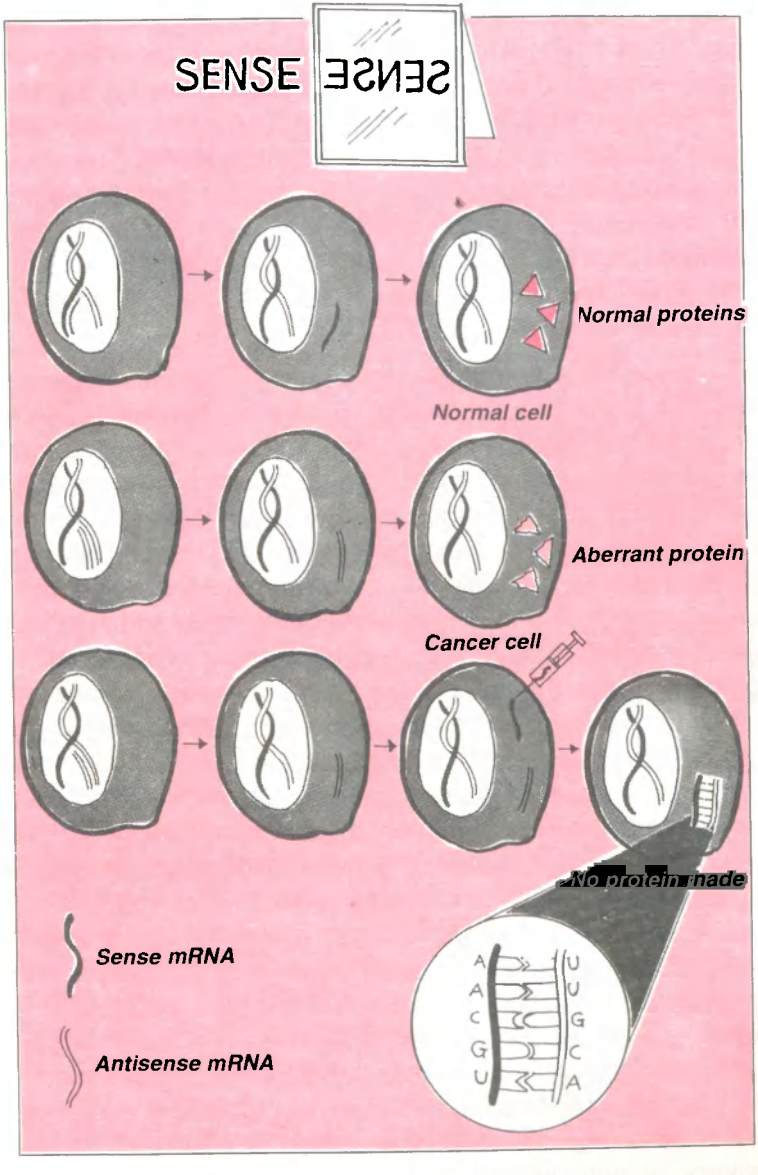
Bomb the tumour

realized that the more effective immune response against cancer is through cell mediated immunity, and efforts for making vaccines are directed at making more effective CTL. Techniques of molecular biology, genetic engineering and immunology are being combined to develop this new generation of vaccines which are undergoing limited clinical trials.

The logic behind developing these vaccines is straightforward. To mount an immune response, the immune cells need to simultaneously receive two signals: the first depends on the specific antigen of the cancer cell, while the second is a signal that stimulates them to multiply. This second signal can be a growth factor or a lymphokine. The antibody molecule is a three dimensional molecule and it fits into a three dimensional antigen. Thus, it can recognize molecules which are three dimensional but not a simple string of amino acids which is thread-like or linear instructive. The cytotoxic T lymphocyte can recognize small proteins which are linear. If a patient is injected with a small tumour specific protein and also a lymphokine, then the patient's CTLs will constantly recognize the tumour cells and will also be activated by the lymphokine to kill them. Do we have the technology to engineer such vaccines? The answer is yes.

A great deal is known about the genome of *Vaccinia* or the small pox virus. The genes responsible for infection and replication have been identified. The viral genome is large. We can remove the genes responsible for causing the disease and replace them with gene(s) for a tumour antigen like CEA and inject them into the patients. The virus will make CEA and release it in the blood of the patients. Ultimately the patient's CTL will recognize it on tumour cells and kill them. This vaccine developed by Jeffrey Schlom of the National Cancer Institute, Bethesda, USA, is undergoing phase I trials. Olivera Finn of the University of Pittsburgh Medical Centre has developed a vaccine based on mucin — a substance found on the surface of cells from cancers of large bowel, breast and pancreas. Mucin is combined with BCG (Bacilli Calmette Guerin) and injected in patients with these cancers. A large amount of information is coming out from basic research and many innovative approaches are being tried.

New tools have emerged with our ability to manipulate genes. One such possibility is anti-sense therapy. To understand this therapy it is necessary to understand how genes



Anti-sense makes good sense when it comes to cancer therapy

function. DNA is a double stranded molecule which carries the information about the sequence of amino acids in the form of a triplet codor. A sequence of three nucleotides represents a particular amino acid. One strand of DNA which carries this sequence is called the coding or anti-sense strand. The other strand which is complementary to the coding strand is called the non-coding or sense strand. The information on the coding strand is copied to make the messenger RNA or m-RNA, which is similar to the sense DNA strand barring the substitution of thymine by uracil.

If an m-RNA was made by the sense DNA strand it would be similar to the anti-sense DNA. Such an anti-sense m-RNA can react with the normal m-RNA the same way as two complementary strands of DNA react. Introducing such anti-sense mRNA in a cell stops the synthesis of that particular protein. It has been shown that if the multiple drug resistance (MDR-1) anti-sense RNA is put in drug resistant breast cancer cells in culture, the MDR protein is not made and the cells become sensitive to drugs. A large amount of information obtained about the effectiveness of anti-sense treatment comes from the use of tissue culture cells. Mutations in and amplification of some oncogenes have been observed in a very large number of human tumours. Mutations in tumour suppressor genes such as retinoblastoma and the p53 gene are known to make an altered gene product which is responsible for multiplication of these cells. In theory, we can shut these mutant genes off with anti-sense m-RNA and stop cell growth. Such specific anti-sense molecules can be synthesized in the laboratory if we know the exact mutation in a tumour cell. These are called anti-sense oligos. However, most of the tumours show changes in more than one oncogene or suppressor gene. This can complicate the picture. There are a large number of unsolved problems about the delivery of anti- sense RNA to tumours, their stability in humans and many others. However, these will not be insurmountable considering the overall progress of research in

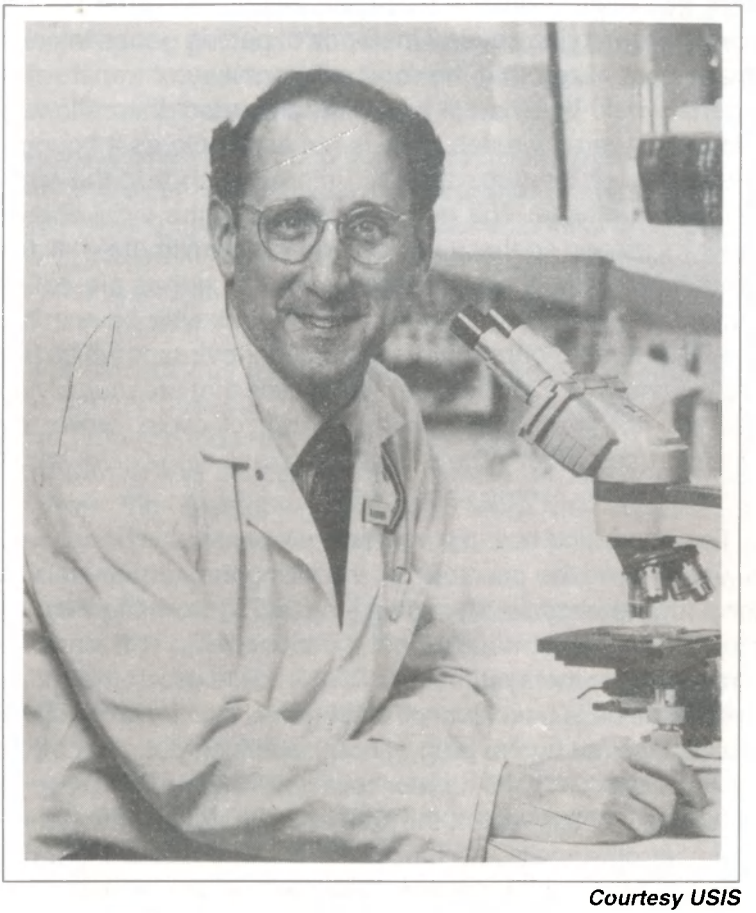
these different fields. Anti-sense therapy for the *ras* oncogene is being tried. It was also found that anti-sense oligos to the *bcr-abl* junction sequence stopped the growth of leukemic bone marrow cells but did not affect normal bone marrow cells in culture. Anti-sense therapy may become a reality in future.

David, a little boy in the United States of America had made headlines in the seventies as the 'bubble boy'. He suffered from a disease called severe combined immuno-deficiency (SCID). This is a very rare disease where the patient's immune system is barely functional. Such patients are very susceptible to even ordinary infections. They have to be kept in germ free chambers or bubbles, where they would be restricted all their life as otherwise they would succumb to infections. SCID is caused by mutations in both the sets of gene making an enzyme called adenine deaminase (ADA). A totally revolutionary therapy by which a normal ADA gene is put in the patient's lymphocytes has been devised. This is 'Gene therapy' in which the defect due to a faulty gene is corrected by transferring a normal functional gene in the target cells. In case of SCID, it is put in lymphocytes, but they can also be put in muscle cells from where they will release their product for normal functioning of the cells. Children who have been given gene therapy with ADA gene are now leading normal lives. They do not have to live in isolation any more, can go to school and play with other children. Gene therapy is also being tried on patients who have hereditary diseases as a result of mutation in both the paternal and maternal copies of one particular gene. Some examples of such genetic diseases being treated by gene therapy are SCID, **hemophilia**, **cystic fibrosis** and **hypercholesteremia**. Cancer is not a genetic disease where a pair of genes has to be replaced but can some form of gene therapy be used to treat cancer?

One of the first doctors to carry out gene therapy for cancer was Steven Rosenberg of the National Institutes of Health, USA. His approach was based on the following logic. In any

tumour, there are always lymphocytes. These are called tumour infiltrating lymphocytes(TIL). One can remove TIL from a piece of tumour, multiply them in culture by treating them with a factor like IL-2 and inject them back into the body. It is found that many of these TIL go back to the tumour. Rosenberg and his colleagues collected such TIL from tumours, put the gene for tumour necrosis factor(TNF) in them, multiplied them in culture and injected them back into patients. TNF is a cytokine which kills tumour cells. By putting

David lived out his brief life inside a sterile plastic bubble. Ashanthi (left) and Cynthia (right) can lead near normal lives, thanks to gene therapy



Courtesy USIS

Steven Rosenberg was one of the first to carry out gene therapy for cancer.

TNF gene in TIL, the TNF was directly delivered to tumour cells where it could be effective. These experiments showed that gene therapy could be carried out in human tumours.

Scientists have been experimenting extensively to make these systems foolproof. Naturally enough, initially these experiments have to be done on animals to show that they

work and also to ensure that there is no risk to the human beings. After trying several methods of putting genes in cells, scientists realized that the most efficient way of transferring a gene would be to put it in a virus and infect the cells with such engineered viruses. This is not as simple as it sounds. The genes of the virus are first altered such that the virus loses its virulence. The gene introduced in the virus should make its protein so that it can be active and ultimately kill the tumour cells. Such viruses which carry the genes are called vectors. At present, two types of virus vectors are being tried. The RNA tumour or retroviruses and adenoviruses which are DNA viruses. The retroviruses infect cells that are multiplying and will not infect cells which are out of cycle, while the adenoviruses infect all cells. But both these types have some advantages and some shortcomings.

To understand how the vector is prepared, it is necessary to understand the principle behind killing the tumour cells. A gene for the enzyme thymidine kinase(TK) from the *Herpes simplex* virus is introduced in the cancer cells. This enzyme is required for the synthesis of DNA in cells which are multiplying. The cells have their own TK gene. The TK gene of the virus is blocked by the drug ganciclovir which does not block the cells' own TK. If the tumour cells have the *herpes* TK gene transferred by the vector, they die after treatment with ganciclovir but other cells like those in the bone marrow are not affected. The virus is not directly put in the cancer cells. The retroviral genes are divided into two separate sets. One set has the genes required for making a virus particle. Other viral genes such as the oncogene are removed and discarded and in their place the *Herpes* TK gene is inserted. These two sets of genes are inserted in cells called 'packaging' cells. The packaging cells make virus particles which have the *herpes* TK gene. The packaging cells are injected directly in the tumour. When genetically engineered virus particles made by the injected packaging cells infect cancer cells, they only make the *herpes* TK enzyme. Two weeks later the patient is

treated with ganciclovir. This kills all the tumour cells because they have the *herpes* TK. The results obtained with a few patients are encouraging and selected clinics are now trying this method to treat different types of tumours.

Gene therapy is not only an experimental technique but it also needs specialized laboratories and at present can only be given to a handful of patients. But scientists are making newer vectors which are more efficient and effective. They are finding alternate ways of killing cancer cells. So the future is definitely bright.

It is evident that newer methods are being developed to treat cancer patients to achieve higher rate of cure. At the same time the total number patients with cancer is rising. A large part of this increase in the number of cancer patients are from the developing countries which are overcoming infectious diseases, improving the standard of living and also rapidly industrializing. They are the ones who will be most affected. The costs of treating these patients will be enormous. Cancer is becoming more and more curable with advances in medical sciences. But many cancers are preventable since they are caused by our habits and lifestyles. These can be prevented by educating people about cancer and making them change their habits. There is light at the end of what was once considered a tunnel. Let's shed our ignorance and go towards that star.

On being told that he has cancer, J.B.S. Haldane, the famous scientist, gave free play to the muse in him and expressed his feelings in a poem called, 'Cancer's Funny Thing'. The opening lines aptly sum up the truth about cancer and its therapy and remain valid even today. I quote,

*

"I wish I had the voice of Homer
To sing of rectal carcinoma,
which kills a lot more chaps, in fact
Then were bumped off when Troy was
sacked.

Yet, thanks to modern surgeons' skills,
It can be killed before it kills
Upon a scientific basis
In nineteen out of twenty cases.

Glossary

Alkaloids: Water insoluble crystalline chemicals produced by plants and animals. These are usually the nitrogen containing salts of organic acids.

Antibiotics: Substances produced by a microorganism which inhibit the growth of other microorganisms.

Antibody: Type of protein synthesized by the immune system in response to the introduction of a foreign protein or antigen. Antibodies are highly specific and bind strongly only to those antigens in response to which they are formed.

Codon : Sequence of three bases in DNA or mRNA, that codes for a particular aminoacid.

Cystic fibrosis: A disorder of the pancreas because of a recessive gene mutation which affects one child in 2,500 live births. In another form of the disease the narrow airways of the lungs are clogged by heavy sticky mucus. Repeated infections make the lung weak and major blood vessels rupture during bouts of coughing.

Epithelial: Pertaining to the surface or lining layer of cells.

Fiber Optics: The use of very fine transparent fibres of glass to transmit light. The light passes along the fibres by a series of total internal reflections.

Fibroblast: A flattened, irregular shaped connective tissue cell.

Genome: The complete set of chromosomes found in each nucleus of a given species. It represents the entire genetic material of the organism.

Hemophilia: An inherited disorder in which the blood fails to clot.

Homogenization: The breaking down of a tissue so that it has uniform nature throughout. A form of maceration or pulping.

Hypercholesterimia: A condition characterized by excessive cholesterol in the blood.

Isotopes: Atoms of the same element which have the same atomic number but different atomic weights as they contain different numbers of neutrons in their nuclei.

Lymph: A clear fluid containing white blood cells drained from the body tissues into the blood stream by lymphatic vessels.

Lymphocytes: White blood cells found in the lymph nodes, thymus, tonsils and spleen. They have a large spherical nucleus surrounded by a thin layer of clear cytoplasm. They play an important role in the body's defense against infections.

Mutations: A random inheritable change in the genetic material of the cell.

Neutrophilic cells: A type of white blood cell. Also known as neutrophils.

Palate: The roof of the mouth.

Photon: The quantum of electromagnetic radiation. It has zero mass and no charge.

Radioactivity: The process of spontaneous disintegration of unstable atomic nuclei accompanied by the simultaneous release of energy in the form of ionizing radiation.

Spindle: A structure formed during cell division. It is responsible for the correct distribution of chromosomes to the daughter cells.

Thymus: Bilobed organ sitting astride the heart in vetebrates. It plays a significant role in the development of mature lymphocytes which are responsible for imparting immunity to the body.

Uterine cervix: The neck of the uterus or womb.

SIGNIFICANT milestones have been crossed in cancer research. From being a term coined by the Greeks in fanciful recognition of its crab-like movements in the body, cancer is today recognized as a condition of extreme cellular anarchy. Relentless research into the hows and whys of carcinogenesis has resulted in an awesome arsenal of medical weapons against cancer. Survival rates for a disease, once considered synonymous with certain death, have risen sharply over the last few decades.

This lucidly written and profusely illustrated book tells us how cellular control mechanisms break down in cells which then become rebellious. It highlights the fact that many cancers may be prevented by sensible lifestyle choices and that, thanks to modern medicine, yet others are Curable Cancers.

About the Author

Dr Avinash N.Bhisey (b.1938) did his Ph.D. in Applied Biology from Bombay University in 1966. As a Wellcome Trust Fellow, he worked at the Chester Beatty Research Institute, London and later as Research Associate in the Institute for Cancer Research, Philadelphia, USA. Dr Bhisey is the Head of the Cell Biology Division of the Cancer Research Institute in Bombay. His research interests are cancer cytogenetics and regulation of cytoskeletal interactions in normal and cancer cells. He is a fellow of the Indian National Science Academy and former Vice-President of the Asia-Pacific Organisation of the Cell Biology.

Dr Bhisey has published over 70 papers in national and international journals, organised several workshops and participated in many international conferences. This is his maiden effort at popular science writing.

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