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THE STORY OF THE INDIAN CANCER RESEARCH CENTRE, PAREL, BOMBAY

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Since the days of Sir Lewis Fermor, the first President of the National Institute of Sciences of India, it is the usual practice of the President to talk on the specialized branch of science he has developed. I should, however, like to make a slight departure from tradition. Rather than talk to you about one problem, I would like to narrate briefly the development of the Indian Cancer Research Centre—and then describe some of the work done there in the newer disciplines of science under my guidance.

The Indian Cancer Research Centre was inaugurated in December 1952. Since then a number of periodical progress reports have been compiled detailing all its scientific activities. It is, however, fitting today that I should tell you about the first 10 years of life and work at the Centre. It had always been my idea that the Department of Pathology, Tata Memorial Hospital, with which I was closely associated since its inception, should form the nucleus for the establishment of the Centre for advanced basic research on cancer. In 1952 this became possible with the co-operation of the Government of India and Sir Dorabji Tata Trust, and the Indian Cancer Research Centre took the present shape.

Cancer research involves an interlocking of several disciplines in science and medicine. Accordingly the following different departments and sections have slowly developed during this decade: (1) Applied Biology, (2) Experimental Embryology, (3) Human Variation and Statistics, (4) Endocrinology, (5) Biochemistry, (6) Enzyme Chemistry, (7) Biophysics and (8) Microbiology (including Electron Microscopy). All the above departments and sections are looked after by well-trained experienced scientists. The Centre is a constituent recognized institute of the University of Bombay and is also approved by the University of Poona for post-graduate research. As such some of the best students are attracted to the laboratories for training in advanced research techniques and post-graduate degrees of Master of Science and Doctor of Philosophy. At present the total research, technical and maintenance staff is about 250, including those employed on units and schemes

sponsored by other organizations such as the Indian Council of Medical Research, the Council of Scientific and Industrial Research, etc.

The general programme of work at the Indian Cancer Research Centre is best described under three main headings: experimental and clinical studies in cancer, leprosy and physiology of reproduction. Another important activity of the Centre consists of starting new disciplines at the post-graduate level and improving the teaching of post-graduate students for M.Sc. and Ph.D. degrees.

Cancer is being studied from different aspects—its causation, mode of occurrence, biological behaviour within the host system and therapy. Different disciplines and techniques of Biology, Biochemistry and Biophysics are used, as is necessary in the investigation of malignancy in all its multiple manifestations. Biological research consists of study at two levels—systemically in laboratory animals (mice, rats and hamsters), and at the cellular level in tissue culture. In the animal experiments on the mechanism of Carcinogenesis, two main problems under investigation are (1) spontaneous and (2) chemically induced cancer of the breast and skin. In breast cancer the main attempt is to study the mode of action of intrinsic and extrinsic factors in the production of neoplasia and thereby to elucidate the steps in the process of carcinogenesis, *viz.* initiation, promotion, development and progression of tumours. Mammary cancer in mice has been induced mainly by potent carcinogens such as 20-MCA and 1, 2, 5, 6-dibenzanthracene. The skin carcinogenesis studies may be divided in three parts. In the first, chemicals are being tested for their carcinogenicity to correlate their chemical constitution with the cancer-producing activity of the substance. The hypotheses put forward by theoretical chemists for carcinogenicity of substances due to the presence of 'K' and 'L' regions are being tested in these experiments. The second part of the experiment is for testing substances for their suspected etiological role in clinical cancer, like tobacco in relation to oral cancer, chinar leaves in relation to 'kangri cancer', iron complexes in relation to induced sarcomas, and edible oils for their mutagenic effect. The carcinogens are administered at different sites: skin, subcutis and target organs like mammary glands and ovaries. The role of steroid hormones in the mechanism of experimental skin cancer is also being investigated in detail in rats and mice. Varied techniques of optical histology, histochemistry and electron microscopy are used.

Experiments in embryology are being conducted by painting virgin ovaries and studying progenies of treated mice for many generations. A series of carcinogens is under investigation for their mutagenic action in these experiments, details of which have been recently published. Another problem specific to India is the condition known as Submucous Fibrosis of the Palate observed in many ear, nose and throat clinics. It is suspected

that some irritant food additives or certain spices like chillies have some bearing on this condition. Clinical and experimental studies are in progress to investigate the etiology and pathogenesis of Submucous Fibrosis of the Palate.

In cell biology many Tissue Culture techniques have been standardized and developed. The Tissue Culture work is mainly divided in two parts: One is the continuous cultivation of stock of cell lines: (*a*) imported commercial cell lines and (*b*) those developed at the Tissue Culture laboratories of the Centre, particularly from human and mouse sarcoma. These cells are supplied to the Virus Research laboratories in India for cultivation of viruses and are used in the Centre's laboratories for various experiments like tissue interactions, nutrition of cancer cells, studies on cell transformation in continuous cultivation, etc. Various cytological and cytochemical studies are simultaneously in progress on all the 'ICRC' cell lines maintained in stock. An aspect of cell biology developed since the inception of the institute concerns subcellular organization and the fine structure of cancer cells in relation to their altered metabolism and biological behaviour. Some of the varied problems studied are differential metastasis in skin cancer, alteration in connective tissue fibroblasts in hormonal stress and neoplasia, nucleic acid metabolism in malignancy, submicroscopic cytological response to cancer chemotherapeutics and so on.

Genetic and epidemiological studies on cancer also form part of biological investigation of this disease process. Some of the problems specific to India are studied, such as:

(*a*) incidence of cancer and survey of habits in relation to cancer etiology;
(*b*) human genetics and cancer (blood group studies, etc.);
(*c*) hereditary anaemias.

Oral cancer forms a major part of all malignant lesions occurring in this country. Large-scale population surveys were carried out to evaluate the role of habits and other environmental factors. Statistical data are carefully collected on the high incidence of cancer of this site compiled and analysed every year. Another problem in progress in human genetics is blood group frequencies in relation to cancer.

Endocrine disorders observed in some endogamous groups in India are also under investigation. The important problems in this category are intersexuality and chromosomal investigation.

Biochemical research on cancer can be described from three viewpoints: (1) the chemistry of substances suspected to be carcinogens, (2) the basic enzymic aberrations specific to malignancy and (3) chemotherapy. Substances implicated in the etiology of cancers of different sites, such as tobacco in relation to oral cancer, chinar in skin cancer and smegma in cancer of

the penis and cervix, are being chemically investigated. Detailed fractionation studies are in progress with a view to any possible isolation of specific carcinogenic fractions from them. Some interesting observations are available on the β-Glucoronidase activity in oral cancer patients. Some of the basic studies are on the metabolism of the Sulphur-Isosters of Polycyclic Hydrocarbons that are being tested for their carcinogenicity. Enzyme studies have been on Folic Acid Metabolism and Liver Tumours and the role of Enzymes in the action of Venom. Other important problems under investigation are studies on Mitochondrial Enzymes in Tumours and Metabolism of the Antileukemic drug, Aminopterin.

The chemotherapeutic studies on the problem of cancer were started very recently. The Centre has been able to develop a new line of work on antimetabolites against the intermediates of Hexose-Mono-Phosphate (HMP) pathway. Three antimetabolites of 6-Phospho-Gluconic Acid: TDA, DICETOL and TDGA, tested for their growth-inhibiting activities, have given significantly promising results in experiments. The tumour material used for these studies was mostly Yoshida Sarcoma (Ascites) and a solid Mouse Fibrosarcoma developed at the Centre. Clinical trials of these drugs on some advanced and incurable human cancer cases are in progress.

Chemotherapeutic studies with indigenous plants have also been undertaken. Preliminary experiments on a Himalayan plant, *Hippophae salicifolia*, locally known in the Punjab as Kalabis, have shown encouraging results in regression of transplanted Yoshida sarcoma in animals.

Biophysical studies in cancer include:

(*a*) electron microscopy of Bidi and Cigarette Smoke in relation to cancer;

(*b*) a study of the effects of ionizing radiations on Amino Acids and Nucleic Acids;

(*c*) studies on the complexes of DNA and RNA with the Dye Acridine Orange.

Biophysics is a new discipline started at the Centre and has been introduced in the Bombay University curriculum at the M.Sc. and Ph.D. levels.

Another new discipline started at the Centre and introduced at the University at the M.Sc. and Ph.D. levels is that of Applied Biology. The basic disciplines of biology are considerably developed in recent years and several biological techniques are used in the investigation of medical and allied problems. It was felt, therefore, that there was enough scope for having a separate discipline of Applied Biology in which useful research work could be done. The Centre was the first institute to introduce the subject and has been recognized by the University of Bombay in the subject. There is much enthusiasm among young people for these two new disciplines.

Special mention must be made of the interesting biological material which the Centre has been able to develop during the last few years. The Centre has been using about a dozen imported strains of inbred mice for cancer investigations. It has also bred the following three strains of its own with uniquely useful genetic properties:

(1) An I.C.R.C. line of albino mouse.
(2) An inbred line of (LP) mouse.
(3) A hybrid of Paris XVII and C-57 (Bl) strains.

The I.C.R.C. mouse is a large-size mouse weighing about 50-60 gm. at six months, as compared to 25–30 gm. which is the weight of inbred American or European strains of mice. This breed has been found to be highly susceptible to spontaneous breast cancer. The inbred line of (LP) mouse was developed from a small stock imported from Paris. It is resistant to spontaneous breast cancer but is highly susceptible to chemical induction of mammary cancer. It differs characteristically from the I.C.R.C. mouse in its endocrine system and is specially useful for the study of chemical carcinogens. The third breed of mice is the hybrid of one Paris stock crossed with C-57 (Black). Both the strains are breast cancer resistant and their crossed breed also has a very low incidence of spontaneous breast cancer. This strain is particularly useful for studies on skin carcinogenesis.

Besides these three inbred lines of mice, some standard mouse tumours—mammary carcinomas and induced sarcomas—have been developed and kept in serial transplantation for over five to seven years now and used as standard experimental material. Recently it has been possible to develop an ascites tumour from one of the solid mouse tumours, which could also be used in the place of Ehrlich ascites tumour. There are several strains of I.C.R.C. cell lines maintained in continuous cultivation over five years. Very few laboratories in the world are maintaining sarcoma cells in continuous cultivation. Therefore, human and mouse connective tissue cell strains, *e.g.* Human Lipogenic Sarcoma (HLS_2), Human Fibrosarcoma (HFS_9), Mouse Fibrosarcoma (MFS_8) and Mouse Skeletal Muscle (MSKM), and their sub-lines have been specially developed.

One other type of biological material developed at the Centre is an acid-fast micro-organism isolated from lepromatus leprosy designated as the 'I.C.R.C. bacillus'. It has been possible to isolate the organism successfully from six different leprosy patients and the extensive studies carried out *in vitro* have shown several points of its close similarity with *M. leprae*. This is another useful bacterial culture which several laboratories abroad (Europe, the U.S.A. and Australia) have taken from here with a view to studying the different metabolic and growth aspects of the bacillus.

The habits and usages of Indian people seem to favour the causation of

cancer at certain selective sites in the body. Similarly there seems to be a preference for varied types of endocrine disfunction among different endogamous Indian communities.

Abnormal growth of hair, or hirsutism, for which no definite cause can be found, is seen mainly in two endogamous communities in Bombay, namely, Sindhis and Parsis. Such growth of hair usually starts after the onset of puberty and continues during active reproductive life. There is very often a suggestive family history. The defect involved here appears to be of a minor degree, because these cases usually do not have any virilization and have normal menstrual function and procreative ability no less than in other members of the family without abnormal patterns of hair growth. No critical history as to the origin and evolution of the first group, *viz.* Sindhis, is available, except that the large bulk of their population has only recently migrated from West Pakistan to the West Coast of Gujarat and to Bombay City. On the other hand, the Parsis are the descendants of the people who came from Iran (Persia) after the fall of the Zoroastrian Empire at the beginning of the eighth century. Iranians have continued to migrate during the subsequent centuries to India to a limited extent and the children of Parsi fathers by alien mothers were also admitted to the Parsi fold. The total population of Parsis is 132,000 (1961 census) and a large majority of them live in Bombay. A point of equal interest is that Parsis are permitted consanguineous marriages, the incidence of marriages amongst first cousins being as high as 15 per cent, perhaps the highest in civilized population. It is, therefore, reasonable to assume that physiological peculiarities would be more common in Parsis than in Sindhis.

Adrenocortical and ovarian functions have been investigated by a series of tests in a number of cases in these two groups. Some of these cases, having normal adrenocortical and ovarian function on exploratory laparotomy in the second half of the menstrual cycle, revealed the Stein-Leventhal type of ovaries and fresh *corpora lutea.* The fluid collected from the microcystic ovaries of these patients has shown a high amount of Zimmermann positive chromogen in the ketonic fraction, as compared to that in the control group having similar morphological changes in the ovaries but having no hirsutism. The material when biologically tested for androgenicity did not reveal any activity and appears to have a structure similar to the compound Δ^4 Androstene 19-OH-3, 17-dione. It has, therefore, been postulated that in these cases there is a partial enzymatic block in the conversion of this compound to estrone, with the result that precursors like Δ^4 Androstene + dione and/or testosterone may circulate in the body and bring about hirsutism. In other words, it is probable that the hirsutism in these cases is due to the quantitative difference in the androgen and oestrogen production in the ovary. Experiments with labelled steroid compounds to find out the

turnover ratio of androgen/oestrogen in normal and in these ovaries have, therefore, been planned.

These and many other conditions are some of the clinical materials of specific interest for studies on geographical pathology that is not available on a large scale in other parts of the world. An attempt has, therefore, been made to develop extensive investigations on some of these clinical problems. To dream is given to many, but to have a vast vision and translate it into actual reality by one's own efforts is the privilege of a fortunate few. Most of us who are here today have spent many years in the pursuit of science—in its varied disciplines. You will all agree that never before has there been such basic integrated approach to the problem of the origin and maintenance of life. Our young scientists today are achieving goals that all of us have tried to work for. Many laboratories in the country with their complement of well-trained dedicated workers stand comparison with research institutions in more developed lands. That is a matter of continuing pride. We have tried to impart some of the enthusiasm for learning and the spirit of enquiry that Claude Bernard has described as the natural prerequisite of a scientist to our younger workers. They, I feel, have learnt the lessons well and it is my dearest wish that the flame of knowledge be shielded carefully by them and passed on further to future generations.