WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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The late Professor J. H. F. Maisin

Professor Maisin died on 7 June 1971 as the result of a traffic accident that occurred when he was on his way to preside over the Seventh Session of the Scientific Council, of which he had been elected Chairman. The Director and the staff of the Agency wish to record their gratitude for his unfailing support and valuable advice.

INTRODUCTION

The permanent building of the International Agency for Research on Cancer (IARC) will be formally inaugurated in June 1972. Thus it is appropriate that the present report should not only review the work carried out in 1971, but also comment on general developments since the Agency moved to its temporary quarters in June 1967.

The activities of the Agency are described in great detail in the body of the report, but in this introduction attention is drawn to certain programmes that may serve to illustrate the Agency's method of operation.

Research policy

The basic policy of the Governing Council of IARC since its earliest meetings has been that the Agency should engage in active research of a type befitting its international role, avoiding unnecessary re-duplication of work that could be performed equally well by national research institutes. It appears worth while, at this point, to examine the Agency's present programme to ascertain how far it has succeeded in its basic objectives as an international research organization at a time when cancer research has been receiving increasing support at the national level. Many of the factors that have influenced the direction of the programme were discussed in detail in earlier Annual Reports.

From the outset, the Governing and Scientific Councils considered that, in view of its limited budget, IARC should not diffuse its resources. The Governing Council decided that the Agency should concentrate mainly on the environmental etiology of cancer in man, since, during the previous two decades, the importance of epidemiological studies in human cancer had been proven and it had been demonstrated that geographical variations in cancer incidence almost certainly reflect environmental differences. The Governing and Scientific Councils also recognized that studies in human cancer could not be divorced from recent developments in laboratory research and that a multi-disciplinary approach was indicated in view of the Agency's unique potential for carrying out geographical studies and for securing the co-operation of national laboratories in certain of its field programmes. It was accordingly important not only to recruit a group of research workers from different disciplines who would be able to keep abreast of the most recent developments in the biology of cancer, but also to install laboratories in the new building generously donated to IARC by the French authorities. Several of the Agency's member states have contributed to the equipment of these laboratories.

It was also agreed from the beginning that problems of cancer control, especially those relating to diagnosis and therapy, would remain under the aegis of the Cancer unit of WHO, with which close working liaison has always been maintained.

Methodology of the programmes

The methodology of epidemiological studies in cancer has greatly developed in the last 20 years. Early studies were largely devoted to the identification of carcinogens to which groups of industrial workers had been exposed or to investigating the association between personal habits, such as cigarette smoking, and a high cancer risk. To reveal further environmental factors, more modern, quantitative techniques are required.

The starting point in the quest for a suspected carcinogen in the environment comes when preliminary epidemiological studies or clinical reports suggest that the frequency of a given cancer is unusually high in a defined area or population. To determine the validity of the observations and to seek to relate them to factors in the local environment, more detailed studies are carried out, including an analytical study of the distribution and concentration of the suspected carcinogen combined with an epidemiological survey. Any apparent association between a suspected carcinogen and a given cancer is tested statistically and, if found to be significant, subjected to further examination. An idea of the actual research operations may be gained from some of the descriptions of individual programmes in this introduction and in the body of the report. A striking feature of these programmes is the growing importance of laboratory techniques. For example, as part of the study of mesothelioma, the form of cancer known to be caused by asbestos fibres, Dr Chang Hyun Um,[1] working under contract with the Agency, carried out microscopic examinations of several thousand sections of the lungs of people who had died in London between 1936 and 1966. He observed that the numbers of lung specimens containing asbestos bodies, which prior to 1930 were extremely rare, increased with each decade in proportion to the rate of increase of the importation of asbestos into Britain. This relatively simple application of histology thus produced important epidemiological evidence. Today, with the aid of electron microscopy and electron defraction techniques, it is possible to differentiate between the major types of asbestos and identify the exact nature of the fibres that are carcinogenic.

Another example of the application of laboratory techniques to epidemiology is provided by work on human liver cancer. The relationship between this form of cancer and viral hepatitis had long been a subject of speculation, but it was only with the development of sensitive techniques that it was possible to test the serum of hepatitis patients and cancer patients and show the presence of what is now known as Australia antigen. Studies are now in progress to determine the precise degree of correlation between the presence of Australia antigen in a patient's serum and the occurrence of liver cancer.

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 34.

International collaboration

From the examples just given, it is clear that laboratory research and epidemiological studies are both vital links in the chain of research aimed at uncovering the causal agents in human cancer. These examples also happen to illustrate the way that collaboration has developed between the Agency and a number of national laboratories. This collaboration, which has been extremely important in, for example, the testing of pesticides as well as in the development of sophisticated analytical techniques, has grown tremendously in the last five years, and there are at present more than 70 Collaborative Research Agreements between the Agency and national laboratories in many different countries. The Agency's own laboratories provide a focal point for these extended collaborative projects and enable IARC, through its different units, to maintain its authoritative position in multidisciplinary studies of human cancer. It is noteworthy that, in 1971, the Agency's own laboratory operations accounted for approximately 11% of the overall budget. By the system of research agreements, the Agency has been able to draw on the expertise and resources of many national laboratories, often making only limited financial contributions towards the project cost, the rest being borne by the national laboratories.

Research training

The Agency has also been concerned with developing manpower for cancer research, especially in the environmental field, and its fellowships programme lays particular stress on the training of young scientists interested in developing their competence in epidemiology, biostatistics, and chemical carcinogenesis. Some former Fellows are now members of the Agency's staff, and others maintain contact with the Agency's programme, continuing research they originally started during the period of their fellowships.

Examples of research methodology

(*a*) *Oesophageal cancer*

The incidence of cancer of the oesophagus shows very wide geographical variations. It is also increasing significantly in certain population groups such as the black community in the USA. A unique situation has been discovered in Iran along the southern shore of the Caspian Sea and is being investigated by the Agency in association with the Institute for Public Health Research in Teheran. In this area, the incidence of oesophageal cancer changes from an exceptionally high level in the east to a very much lower level in the west; this situation offers an opportunity of identifying environmental factors present in the east and absent, or less concentrated, in the west, which may be related to the variations in the frequency of oesophageal cancer. A detailed epidemiological survey is accordingly being carried out in conjunction with a systematic sampling of food constituents and prepared meals from selected households in the area. These will be analysed for potential carcinogens in the Agency's own laboratories and elsewhere. A case-control study in Normandy,

FIG. 1. NEWLY ELECTED MEMBERS OF THE SCIENTIFIC COUNCIL OF THE IARC

Dr Z. Bacq (1972-1973)

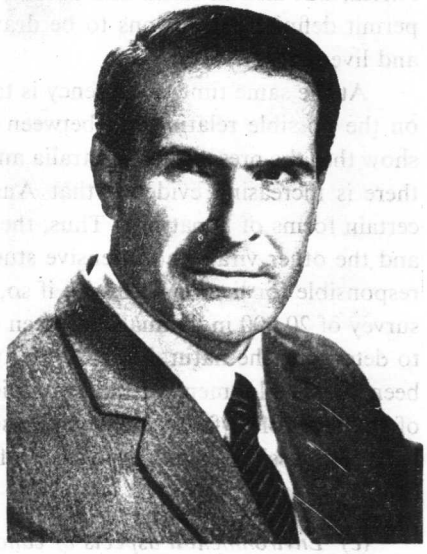
Professor Th. M. Fliedner (1972-1975)

Dr B. E. Gustafsson (1972-1975)

Dr F. J. Rauscher (1972-1975)

FIG. 1. NEWLY ELECTED MEMBERS OF THE SCIENTIFIC COUNCIL OF THE IARC *(concluded)*

Professor N. N. Trapeznikov (1972-1974)



Professor U. Veronesi (1972-1975)

France, where there is also an unusually high incidence of oesophageal cancer, may give important data for cross-comparison. These studies may provide clues to the etiology of this type of cancer and resolve the question whether or not it is associated with a high consumption of alcohol.

(*b*) *Liver cancer*

In many parts of the world liver cancer is a problem of great importance, but its etiology is as yet unknown. A fungal contaminant called aflatoxin, often found in protein supplements used for treating malnutrition, is among the agents suspected. It has long since been shown that it can produce liver cancer in many animal species but it is important to determine whether or not it is carcinogenic in man. Since the withdrawal of aflatoxin-contaminated protein supplements would hinder the treatment of children suffering from malnutrition, this question is of considerable socio-economic significance.

Sensitive chemical techniques are being used to determine the level of aflatoxin in food samples collected in areas of high and low cancer incidence. Preliminary studies carried out in the Murang'a district of Kenya by the IARC Regional Centre, Nairobi, have suggested a significant association between aflatoxin ingestion and the incidence of liver cancer,

but the findings need to be confirmed in other geographical areas. Studies on the distribution of aflatoxin and liver cancer are therefore being conducted not only in other parts of Africa, but also in India and south-east Asia, and it is hoped that the resulting data will permit definite conclusions to be drawn about the degree of association between aflatoxin and liver cancer.

At the same time the Agency is taking an active interest in the studies now in progress on the possible relationship between viral hepatitis and liver cancer. Serological studies show that the presence of Australia antigen is associated with liver cancer; at the same time, there is increasing evidence that Australia antigen itself may be the infective agent in certain forms of hepatitis. Thus, there are two suspected etiological agents, one chemical and the other viral, and intensive study is expected to show whether they are both in fact responsible for liver cancer and, if so, whether they operate independently or together. A survey of 20 000 individuals has been carried out over a period of two years in West Africa to determine the natural history of Australia-antigen positivity. An important aspect has been the development of the serological diagnostic technique based on the determination of the level of α_1-fetoprotein in the sera obtained from blood samples. With this test it has been possible to diagnose cases of liver cancer before they were recognizable clinically.

(c) *Environmental aspects of cancer in industrialized countries*

The studies of oesophageal and of liver cancer illustrate the type of situation that may be found in non-industrialized countries, where, once a suspected factor has been identified, its association with the incidence of cancer in the area concerned may be demonstrated fairly directly. In industrialized countries, too, this relatively simple approach is sometimes possible, an example being a study of the high risk of bladder cancer in a group of chemical workers, which showed a direct association between exposure to β-naphthylamine and the incidence of the disease. More usually, however, the environmental situation in the industrialized countries is liable to be complicated by the operation of a number of etiological factors at the same time. During the last three years, the Agency has therefore attempted to co-ordinate and standardize analytical techniques capable of measuring the actual carcinogenic load to which a population is subjected. This work is being carried out in the Agency's own laboratories and, by contract and agreement, in many other laboratories throughout the world. The carcinogens considered to be particularly important for study are the polycyclic aromatic hydrocarbons, certain forms of asbestos, and the nitrosamines. All these substances are known to be highly carcinogenic in experimental animals, and asbestos has been shown to be carcinogenic for man. They are all known to be present in the human environment, but the development of analytical techniques for the quantitative determination of the very small amounts present in foodstuffs or in polluted air has proved extremely difficult. Once these methods have been perfected and standardized, it will be possible to determine the overall carcinogenic load and to ascertain whether or not these substances must be considered serious hazards as human carcinogens.

A growing number of chemical substances have been shown to be carcinogenic when administered to experimental animals, but very few of them have been proved by epidemiological studies to be carcinogenic in man. β-naphthylamine, known to be a bladder carcinogen in man, does not produce bladder tumours in rodents. Evidence of the carcinogenicity of a given substance, even in several animal species, cannot in fact automatically be taken as proof that the substance is carcinogenic in humans. Exposure of any section of the population to a potential carcinogenic hazard must be avoided, yet the results of the animal experiments cannot be directly extrapolated to man. Under the guidance of a working group of experts in chemical carcinogenesis, the Agency is assembling all the established experimental and, where available, epidemiological data on each of a series of chemicals, so that the potential carcinogenic hazard of each chemical for man may be evaluated. The collected data will be published in a series of monographs which will be available to governments, industrial undertakings, and other agencies that may be called upon to take decisions about the acceptance or elimination of any given substance in the human environment.

The Agency has organized international studies of the carcinogenicity of the long-acting pesticide DDT in experimental animals; these have shown that, at very high doses, liver tumours are produced in mice. In other studies, the levels of DDT stored in human fat tissues, sampled from different populations, are being measured; although these levels are often very high there is as yet no epidemiological evidence of any modification of the cancer pattern in any of the populations studied.

The importance attached by the Governing Council to these environmental studies is illustrated by a resolution, adopted at its last meeting in October 1971, on the Agency's advisory role in the field of environmental carcinogenesis.

The Governing Council considered it important that responsible authorities should be able to call on the competent and independent scientific opinions of the Agency and endorsed the preparation of the series of monographs on the evaluation of the carcinogenic risk of chemicals to man. The Agency should also be prepared to make available to governments all documentation in its possession on substances on which they might in future seek advice. Such advice would be based on the Agency's own studies of experimental methods and the epidemiology of human cancer, as well as on the literature.

(*d*) *Viruses and cancer*

The possible role of viruses in human cancer is receiving considerable attention in laboratories in many parts of the world. The Agency's interest in studies of Australia antigen has been already mentioned. Even more important, perhaps, are the studies being carried out in association with the US National Cancer Institute, Bethesda, Md., USA, and the East African Virus Research Institute, Entebbe, Uganda. A large body of evidence has accumulated suggesting that certain human cancers may in fact be of viral origin. The Agency has been studying, in particular, nasopharyngeal carcinoma in Asia, which is

serologically associated with herpesvirus, and Burkitt's lymphoma in Africa, which is likewise associated with a herpesvirus. A mass survey has been organized which will follow a population of approximately 35 000 individuals in Africa over a sufficient period of time to see whether the development of Burkitt's lymphoma in that population is in fact linked with the immunological changes associated with herpesvirus infection. The logistic problems are considerable, but no laboratory study could possibly provide the results that it is believed will be obtained from this survey.

Priorities

The selection of priorities in cancer research is exceedingly difficult. On the one hand, it may be considered more important to try to identify the etiology of a cancer because it happens to be frequent; on the other, it may be more profitable both scientifically and, ultimately, from the public health point of view to study a form of cancer that, though relatively rare, may serve to identify principles on which the control of more frequent types of cancer can be based. It is not possible to say either from a scientific or a public health point of view that concentration on any single type of cancer is justifiable. It is believed that the current programmes of the Agency represent a reasonable balance between concentration on certain limited areas and a more general frontal attack on the problems of human cancer epidemiology. It is certainly important that the staff of the Agency should remain aware of recent developments in cancer research so that new information can be applied with the least possible delay to the problems in hand and the fullest advantage can be taken of new laboratory techniques at the earliest opportunity. Recently, for example, the discovery of an enzyme described as a reverse transcriptase was announced. This discovery, which at first may have appeared to be simply a novelty in the field of molecular biology, soon took on a much greater significance when the enzyme was found in virtually all tumour viruses and thus might be considered as a marker for a transforming RNA virus. If, in fact, reverse transcriptase proves to be specific for RNA oncogenic viruses, it may very well play a valuable part in cancer epidemiology as a means of identifying the existence of infection by oncogenic viruses. While the Agency may not be in a position to take immediate advantage of this or similar discoveries, the staff must certainly be equipped to explore the potentialities of such developments in so far as they have a bearing on the programme of the Agency, taking into account the limited means at its disposal. The Scientific Council of course performs an extremely valuable role in drawing the attention of the staff to such promising developments when they occur. Moreover, once the Agency is installed in its own building, the presence of visiting scientists spending their sabbatical years or shorter periods of time at the Agency will serve to bring the staff into contact with ideas current in other national institutes and to ensure that, in its work, the Agency keeps abreast of the latest developments in different countries. If the staff are to remain responsible for the co-ordination and development of the research programmes they must not work in scientific isolation.