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THE CONTRIBUTION OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER TO THE PREVENTION OF CANCER

L. TOMATIS, M.D.

Director, International Agency for Research on Cancer, Lyon, France

The International Agency for Research on Cancer (IARC) was created in 1965 by the World Health Assembly of the World Health Organization, following an initiative of France, which originally suggested that 0.1% of the defense budget of the major industrial countries be devoted to cancer research and cancer control. Five countries responded to the initiative of France and agreed to support the creation of a specialized agency for research on cancer, within the structure of WHO, but maintaining a considerable degree of autonomy. The proposal, however, of taxing the defense budget was not accepted and the Agency was created with a fixed annual contribution from each participant State, which originally was of 150,000 US dollars. The number of countries adhering to the Agency increased progressively, first with the participation of the Soviet Union, Belgium and The Netherlands, then Japan and Australia and lately Sweden and Canada.

The Agency's main bodies are the Governing Council which is composed of the representatives of the member States and of the Director General of WHO, and which governs the general policy of the Agency and the budget; and the Scientific Council, which reviews the scientific programmes and reports to the Governing Council. The Scientific Council is composed of 12 eminent scientists, chosen because of their particular expertise in the various areas of cancer research.

The staff of the Agency is presently of 150 persons, all included, 44 of which are scientists. Although there has been a discrete turnover of scientists, the number of staff scientists has practically remained unchanged in the last three years. What instead has increased considerably, is the number of visiting scientists, fellows or scientists spending a sabbatical leave or, in any case, a temporary period at the Agency. This increase in visiting scientists has been paralleled by the increase in workshops and meetings organized by the Agency. In fact, in 1983 there were 30 workshops or meetings in Lyon, compared to 19 in 1981: an indication of the Agency's expanding activities.

The Statute of the Agency foresees a broad spectrum of activities, but early on, the decision was taken to concentrate, at least for the first period of the Agency's existence, on research in etiology, based on epidemiology and laboratory studies and with the aim of generating information useful for the primary prevention of human cancer. It should also not be forgotten that the Agency was created as, and has remained, a scientific institution, without regulatory function.

The activities of the Agency can be summarized as follows:

1) the collection, critical analysis and dissemination of information;

2) epidemiological studies on etiology and prevention;

3) studies on the mechanisms of carcinogenesis and on the development of methods for detecting carcinogens and quantifying levels of exposures;

4) education and training.

To the first group of activities pertains the collection of the data from all cancer registries in existence around the world. The information obtained from the cancer registries, many of which have initiated their activity with the assistance of the Agency, is included in a periodical publication, which is by now well known worldwide and represents a standard reference for all epidemiologists: this is *Cancer incidence in five continents* (CI5). The fourth volume of this publication has been recently published containing data from 78 registries in 32 countries [1].

Accurate information on cancer morbidity and mortality may allow an estimation of the size of the cancer problem in a given country and of changing incidence trends. At the same time, it may give an indication of which are the priorities for intervention. It can also give indirect evidence of the surfacing of a new situation or of the entrance into the environment of a new risk factor. Data from cancer regis-

tries can be used for *ad hoc* epidemiological studies, as, for instance, those that the Agency has recently coordinated, on the possible role of radiation therapy and chemotherapy in the causation of second primary tumours.

Data on cancer registries, important as they can be, do however concern a relatively limited part of the world, and in particular they refer more to industrial countries than to developing countries. For this reason, the Agency has begun, in the last two years, a programme to bring together data from areas of Africa, Asia and South America which do not have population–based registries included in CI5. At present, 55 centres in various countries of Asia, Africa and South America collaborate in this project and a new monograph on the relative frequency of cancer in developing countries will soon be available. In the meantime, the material contained in CI5 and obtained from developing countries has been used to make an estimate of the worldwide global burden of cancer [2]. It was estimated that a total of 5,870,000 new cases occurred in 1975.

Obviously the cancer burden is not equally distributed all over the world. If we look first at the most frequent cancer we see that, worldwide, stomach cancer still ranks first and lung second. While it is likely that lung will become the first target site soon, it is also important to note that breast cancer is, in absolute terms, the most frequent cancer. If we then look at which are the most frequently hit target organs, in various parts of the world, it is clear that stomach and lung do not have the same rank in priority in Europe or North America and China [2].

The well known crossing over of lung cancer and gastric cancer is not, therefore, a universal phenomenon. In absolute terms, cancer is more frequent in the industrial countries than in the developing countries and certainly the most intuitive explanations are, on the one side, the different importance of competing risks and, on the other, the different consistency of the age groups at highest risk for cancer which are much larger in the industrial countries than in the developing countries.

If we look at the percentage of the total cancer cases observed in various age groups, it is clear that we can expect an increase in the frequency of cancer in the developing countries, when, as it is hoped, their life expectancy will improve. Sixty percent of all cancer cases in industrialized countries do presently occur in the age group 65 and more, while in the developing countries it is only 41%. If preventive measures are not taken, one can expect that the frequency of cancer in developing countries will increase, in particular in the age group which will expand and is at highest risk, that is above 65.

A different series of projects, within the general programme of the collection, analysis and dissemination of information, concerns, on the one side, the selection and description of adequate methods for the detection and analysis of carcinogens in the environment and, on the other, the evaluation of all data related to the carcinogenicity of environmental factors. Within the first project, a series of manuals of selected methods of analysis of environmental carcinogens have been published or are planned with the objective of putting together validated methods of analysis which may allow a strict comparability of analytical data [3].

A parallel activity has been the mycotoxin check sample project which provides analytical quality assurance to laboratories involved in the detection and quantification of some of the most widely distributed environmental carcinogens; 163 laboratories in 44 countries participated last year in the analysis of aflatoxins B1, B2, G1 and G2 in corn and peanuts and of M1 in milk.

The second project is centered on the publication of the *IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans* [4].

It was in 1969 that the Agency was first requested to provide information on environmental carcinogens, in particular to provide a list of human carcinogens and a list of animal carcinogens. An attempt at preparing such a list had to be discontinued after a few months, as it appeared totally misleading or impossible to include, within a same list, chemicals for which the quantity and quality of the available information varied very considerably. Perhaps not many scientists are aware of, or, if they were, still remember today, the paucity of the available information in the late sixties, their uneven quality and, often, the total inadequacy of much of them.

It seemed, therefore, justified to postpone the preparation of lists of carcinogens and to initiate, instead, the publication of the monographs on individual chemicals. More than twelve years after the beginning of the monographs programme, a list of carcinogens, which is forcibly provisional, could be prepared. Among the over 600 chemicals or complex exposures that have been reviewed, 7 industrial processes and 23 chemicals were found to be causally associated with cancer in humans. For 14 other chemicals there is a strong possibility of such an association [5]. Within these lists, certain known human carcinogens, like tobacco smoke or alcoholic beverages, are not considered but this is certainly not because the Agency did not recognize tobacco smoke or tobacco chewing as human carcinogens, but because a monograph on them had not been prepared since it seemed that enough effort was already put on these exposures by national institutes and since the evidence of carcinogenicity of tobacco smoking was already overwhelming. The Agency has, however, now prepared a monograph on tobacco and betel chewing, and another on tobacco smoke with special emphasis on certain aspects of the risk which may not have received sufficient attention as, for instance, the effect of combined exposure and the effect of passive smoking.

Although the Agency is not involved in regulatory action, it has the role of delivering information which may have direct and indirect influence on control and regulatory decisions. The provision of qualitative information on the carcinogenicity of environmental chemicals is a typical example.

A parallel example is the information related to the mechanism of action of carcinogens. One of the questions, to which we, as well as our colleagues around the world, are trying to answer, is: to which extent is it possible to describe the mechanisms by which particular risk factors exert their carcinogenic activity? Taken up by agencies responsible for regulatory action, this same question will probably read: is it possible to categorize carcinogens according to their mechanisms of action and will this justify different preventive measures? There are, certainly, potential advantages of classifying carcinogens according to different mechanisms of action, which may eventually allow the control of carcinogens by different appropriate methods. We tried, therefore, to verify to which extent the contribution from epidemiological studies, long–term studies in experimental animals and a variety of short–term tests could help in the understanding of the mechanism of carcinogens and whether our understanding of such mechanisms has achieved a level that would make a classification according to mechanism of action possible.

The input of scientists of different disciplines permitted a comparison between, as well as an attempt at interpretation of, the concepts developed in the various fields of study. Scientists of different disciplines viewed the multistage process, and possible mechanisms of carcinogenesis in terms which, although similar, were certainly not equivalent because of the difference in the evidence on which each of the terms was based. For example, the sequence of early and late–stage actions identified by epidemiologists, while corresponding largely to the sequence of initiation and promotion, is not based on any of the specific mechanistic considerations implied from animal carcinogenesis studies or short–term studies. The conclusion reached was that, at present, no classification of carcinogens according to mechanisms will be exhaustive or definitive [6]. There will be definitely a follow–up to this issue, according to the availability of new information on mechanisms of action.

The pace at which discoveries have been made in recent years and months permits a certain degree of optimism. It may well be that in a short time, molecular biologists will be able to tell epidemiologists what to look for or, more likely, that, overcoming the gap that existed until recently between basic and applied research, biochemists and molecular biologists will jointly contribute to the development of a more efficient epidemiology, with a dominant public health component.

The other important branch of IARC activities is represented by the analytical epidemiology project, which, due to the shortage of time, I will only briefly mention. One concerns the multinational retrospective–prospective study on possible long–term adverse effects of man–made mineral fibres. The study which is coordinated by IARC, is carried out in 10 countries with the collaboration of national laboratories and the European office of the WHO, and probably represents the largest study of this type ever made.

The importance of verifying that substances, candidates to substitute the widely used asbestos, are not representing a hazard before they are massively introduced into our environment, is evident.

It is of some interest that the Agency has carried out a worldwide survey of the existing collections of human biological material. Of the 230 positive replies received, about a dozen, referring to collections for which certain necessary information was available, have been identified; among these, most important was the potential for following up the individuals who had donated the material. The use of such banks may become essential in the development of epidemiological surveys. One area where the case of an *ad hoc* bank will be immediately used, concerns the investigation of the role of nutritional factors in human cancer. Biological samples will be used to provide accurate measurement of a series of biochemical parameters.

Again I can only briefly mention the intervention studies that the Agency has initiated:

1) in China, an area where oesophageal cancer is particularly frequent, it has been observed by Munoz and Crespi [7, 8] that precancerous lesions of the oesophagus are particularly frequent. As they are strongly correlated with certain nutritional deficiencies, the study is aimed at verifying if the administration of certain micronutrients will contribute in preventing the precancerous lesions that, even if not caused by the same agent producing the final malignant transformation, are certainly related to the increased risk of oesophageal cancer; the essentially negative results of this study have been published recently [9];

2) another intervention study is planned in The Gambia and is addressed to the vaccination against hepatitis B of progressively all children of the country, to verify if the vaccination: *a*) provides a permanent protection against acute hepatitis; *b*) prevents the condition of carrier; *c*) prevents primary liver cancer;

3) a third intervention study is planned in an area of Uzbekistan with a high incidence of oral cancer and relatively high incidence of oesophageal cancer, related to the use of tobacco and nass: analogously to that observed in China, a deficiency in certain micronutrients has been observed and the study, therefore, will be centered on the possible effect of supplementing the diet of these groups with them [10].

Last, but certainly not in role of importance, the Agency has carried out since its inception, an educ-

ational programme aimed at the formation and training of cancer scientists. The programme has three components: fellowships, courses and publications. Fellowships are awarded for the duration of one or sometimes two years. This programme has been run in parallel and in collaboration with the UICC and a comparison of the preferred disciplines indicates that the two programmes have operated with a satisfactory degree of integration. The courses are held in various parts of the world in collaboration with the WHO Regional Offices and are mainly focused on epidemiology, although a few courses on carcinogenesis have been held. These courses, for which the faculty is in part composed of IARC staff and in part by external experts, are very well attended.

The Agency has a very active publication programme and its scientific publications series counts now over 55 titles. Certain of these volumes have become best–sellers as, for instance, the volume of *Statistical methods in cancer research* [11].

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