Eur J Cancer Clin Oncol, Vol. 23, No. 11, pp. 1571–1575, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

An Efficient Primary Prevention of Cancer Requires an Integrated Approach: Mühlbock Memorial Lecture*

LORENZO TOMATIS
International Agency for Research on Cancer, Lyon, France

Abstract—*In addition to a wide gradation of levels of exposure to man-made, naturally occurring and endogenous chemicals, to viruses and to radiation, there is a gradation of genetic susceptibility for resistance to the mutagenic and other damaging effects of noxious environmental and endogenous agents. This interplay between environmental and host factors is probably not limited to the early stage of carcinogenesis but extends over the later stages of promotion and progression.*

The risk of cancer in humans is thus increased by a wide spectrum of factors, which ranges from exposure to an identified agent, such as environmental chemicals or a virus, to culturally determined behaviour, such as age at first pregnancy. We are able today to intervene in some of these factors, while others affect risk by as yet undetermined pathways. Only progress in the understanding of the mechanisms by which these factors act can lead to specific means of cancer prevention.

New developments in molecular biology do not invalidate ipso facto *all that has been done before. While the new insights about certain aspects of the carcinogenesis process and the new techniques that have been developed in parallel demand that new approaches be explored and developed, there is little justification for downgrading long-term carcinogenicity tests, which provide proven, efficient warning about possible hazards to humans. Support for the maintenance of a programme for testing of environmental chemicals does not mean, however, that one can expect that all or even most of the agents that are carcinogenic to humans will be identified by traditional long-term testing in rodents.*

Basic and applied research, studies on the mechanisms of carcinogenesis and research on aetiology and prevention are neither opposite nor separate areas of scientific activity. They must be, and indeed are, closely interrelated. The understanding of certain stages of the carcinogenesis process is progressing side by side with the development of much more precise methods than ever existed before for monitoring low doses of exposure at the individual level. While this will be of very considerable help in the conduct of epidemiological investigations, it is clear that the efficacy of primary prevention will increase with, and indeed depend on, understanding of the mechanisms by which a factor or a series of factors contribute to the malignant transformation of cells and/or to their progression to clinical cancer.

It would be a grave error for scientists to see basic and applied research as separate or competitive. Scientists should also try not to give in to the tendency to favour the development of projects that fall in line with the preferred orientations of granting agencies and contract makers. This can result in mechanisms by which the obtaining of funds becomes a conditioning and limiting factor in the choice and design of research projects.

THERE is no compelling reason to believe that the number of carcinogenic agents to which humans can be exposed is infinite. Some of us will accept the idea that it will eventually be possible to identify most of them. What has been more difficult to accept is that an agent that has been shown to be carcinogenic at relatively high levels is also carcinogenic at much lower exposure levels, either alone or in combination with other factors, also present at very low levels. Regulatory bodies and authorities who have the duty and power to implement preventative measures can be convinced only with difficulty to take measures as obvious

*Presented at the IXth Meeting of the European Association of Cancer Research on 31 May 1987 in Helsinki, Finland.

as curbing tobacco production and advertising of tobacco, or controlling the most serious occupational risks or the most conspicuous sources of air pollution. It is no wonder, therefore, that it is difficult to convince them to take action in much less obvious situations.

There has been and still is controversy about priorities in cancer prevention. Cairns in 1981 [1] advanced the hypothesis that most human cancer may be due to gene rearrangements rather than to localized DNA changes produced by conventional mutagens. He then suggested that if this were the case then the tests most frequently used to identify human carcinogens would be inadequate, since they are tailored to detect conventional mutagens. Cairns rightly attracted attention to genetic transposition as one of the most important steps leading to cancer. However, no further substantiation has been made of his hypothesis that localized changes in DNA sequences play only a minor role in the causation of human cancer, on the basis of the observation that XP patients who have a deficient DNA repair system do not have a generalized increase of cancer at all sites [2]. Both localized mutational events and gene rearrangements may indeed be sequentially involved.

More recently, Ames *et al.* made an attempt to rank possible carcinogenic hazards for humans [3], and concluded that the carcinogenic hazard of man-made chemicals is much smaller than that of natural substances. The distinction between natural and artificial chemicals is in itself somewhat artificial, since most substances that we call natural are actually man-made, like domesticated animals, and most vegetables we presently eat. After rightly reminding us that it is totally unjustified to assume that natural is equivalent to safe, Ames questions the significance of the results obtained in long-term experimental animal tests for carcinogenicity, and in particular the use of the Maximum Tolerated Dose (MTD) as it is systematically employed within the National Toxicology Program (NTP). He further argues that perhaps the majority of chemicals would be classified as carcinogens if they were tested at the highest possible level.

It may be that in the recent past the use and interpretation of results obtained in experimental animals has been exaggerated, but this should not lead to an equally or more inverse exaggerated trend. It is, of course, unfortunate that use of the MTD has been seen as a means to obtain a positive carcinogenic result at any cost, but the simplistic argument that everything could be made to seem carcinogenic just by testing it at the MTD has little justification.

DDT can produce liver tumours in several strains of mice but does not produce liver tumours in hamsters, even when the level of exposure is raised to the maximum possible. However, hamsters exposed to one of the main DDT metabolites, DDE, do develop liver tumours [4]. The NTP systematically includes the MTD in its testing procedures. The results of the first 81 chemicals tested have provided sufficient evidence of carcinogenicity for 42%. Similar proportions of positive and negative results were also found in the series of tests carried out in previous years by the NCI. For only 18 (21%) of the 81 chemicals tested by the NTP was the evidence of a carcinogenic effect obtained only at the MTD, and for half of these some carcinogenic effect was observed at a dose lower than the MTD, an effect that even if non-statistically significant was biologically meaningful [5].

Since the maximum level of exposure is inversely related to the acute and sub-acute toxicity of a chemical, chemicals with low acute and sub-acute toxicity can be administered at much higher MTDs than chemicals with a high toxicity. The main question therefore is whether the results obtained with a very high MTD can predict that a carcinogenic effect will occur following exposures to lower doses.

If humans were exposed to doses similar (or nearly similar) to the MTD, the question of the mechanism of action would be of minor importance, at least for the purposes of public health. Since the secondary toxic events which may occur following exposure to high levels are assumed not to take place at much lower levels of exposure and the lack of carcinogenic effect could therefore be related to their absence, is it legitimate to extrapolate data obtained at MTDs to the human situation? It would seem that in most instances, the logical answer in most cases would be negative. However, the existence of notable exceptions must incite us to remain very prudent about refusing the significance of results obtained at high doses. The pesticide HCB (hexachlorobenzene) induces tumours in 80% of animals exposed to 200 ppm in food, a level close to the MTD [6]. This dose level, which exceeds by far that which humans could be expected to receive, was approached in an episode that occurred a few years ago in Turkey, when several thousand individuals were intoxicated with HCB. They are now being followed up, with some difficulty, prospectively [7–9].

Laboratory animal tests still have a role to play in the detection of chemicals with carcinogenic activity and to provide a warning about possible hazards to humans. If programmes such as that of the NTP did not exist, the U.S.A. and the rest of the world would be deprived of a very important safeguard [10]. This is not equivalent to saying, however, that all or even most of the agents carcinogenic to humans will be identified by traditional long-term testing of chemicals in rodents.

Table 1. *Chemicals and exposures to complex mixtures carcinogenic to the lung in humans*

SUFFICIENT EVIDENCE	PROBABLE
Arsenic compounds	Acrylonitrile
Asbestos fibres	Aluminium production
BCME and CMME	Beryllium compounds
Chromium compounds	Cadmium compounds
Coal gasification (older process)	Chlorinated toluenes, production
Coke production	Coal-tar pitch
Mustard gas	Dimethyl sulphate
Nickel and nickel compounds	Iron and steel founding
Soots	Man-made mineral fibres (producers)
Tobacco smoke	Mineral oils (certain)
Radon (iron ore mining, uranium mining)	Rubber manufacture
	Vinyl chloride
	Welding fumes

It is important that we try to identify the major causes of human cancer among the vast number of minimal risks [3]; but it is conceivable that a vast number of so-called minimal or quasi-minimal risks collectively represent important causes of human cancer. For instance, twelve agents have been found to be carcinogenic to the lungs, while for over a dozen more there is a strong suspicion that they may increase the risk for lung cancer (Table 1). Even if tobacco remains by far the most important and asbestos the second most important lung carcinogens, this relatively long list of lung carcinogens will still permit the adoption of measures that will avoid in a number of individuals a rapidly lethal cancer. Certain exposures may generate a rather low attributable risk, but a high relative risk which it would be misleading to define as minimal.

The advances made in molecular biology and molecular genetics, the new insights that we have gained on certain aspects of the carcinogenesis process and the new techniques that have been developed in parallel, demand that new approaches be explored and expanded. However, the new developments in molecular biology do not invalidate *ipso facto* all that has been done before. The fast and successful development of what is called today molecular epidemiology clearly demonstrates this.

Table 2. *The most frequent cancers world-wide, both sexes combined, in* 1980

		no. (1000)	%
1.	Stomach	669.4	(10.5%)
2.	Lung	660.5	(10.4%)
3.	Breast	572.1	(9.0%)
4.	Colon/Rectum	572.1	(9.0%)
5.	Cervix	465.6	(7.3%)
6.	Mouth/Pharynx	378.5	(6.0%)
7.	Oesophagus	310.4	(4.9%)
8.	Liver	251.2	(4.0%)
9.	Lymphoma	237.9	(3.7%)
10.	Prostate	235.8	(3.7%)
11.	Bladder	219.4	(3.5%)
12.	Leukaemia	188.2	(3.0%)

From Parkin *et al.* [11].

Three considerations merit particular attention: (1) The marked differences in the main cancer target sites in different regions of the world probably result from the prevailing role played by different aetiological agents and may therefore indicate the need for different types and levels of intervention, as well as different priorities; at the global world level, the most frequent cancer in females is breast cancer (which is also the most frequent cancer in absolute, if the two sexes are considered separately); in males it is lung cancer. For both sexes combined the most frequent cancer in 1980 was still gastric cancer, immediately followed, and possibly by now surpassed by lung cancer (Table 2) [11]. (2) The risk of cancer in humans is increased by a wide spectrum of factors, which ranges from exposure to an identified agent such as an environmental chemical or a virus, to a culturally determined behaviour, such as age at first pregnancy, and to genetic predisposition. On some of these factors we are able today to intervene, while others affect risk by as yet undetermined pathways. Only the knowledge of the mechanisms by which these factors act may lead to specific means of cancer prevention [12]. (3) While the highest potential for cancer prevention varies between different populations, the proportion of cases which can actually be prevented will practically depend on our knowledge of the factors that cause cancer, of their mechanism of action and finally on the applicability of our knowledge to preventive measures in given populations.

Table 3. Relative risks for cancer associated with certain exposures

Organ affected	Factor	High Risk level	Low Risk level	Reported relative risk
Breast	Ionizing radiations	100 rads	No exposure	3.0
Bladder	Cigarette smoking	25 cigs./day	Non-smokers	5.0
Lung	Asbestos	Occupational exposure	No occupational exposure	5.0
Lung	Nickel refining	Occupational exposure	No occupational exposure	5.0
Leukaemia	Benzene	Occupational exposure	No occupational exposure	5.6
Lung	BCME/CMME	Occupational exposure	No occupational exposure	9.2
Oesophagus	Alcohol consumption	120 gms ethanol/day	40 gms ethanol/day	23
Lung	Cigarette smoking	25 cigs./day	Non-smokers	30
Liver	Hepatitis B virus	Chronic carriers	Non-carriers	100
Liver (angio-sarcoma)	Vinyl-chloride	Occupational exposure (high concentrations)	No occupational exposure	400
Pleura, peritoneum	Asbestos	Occupational exposure (mainly crocidolite)	No occupational exposure	500
Bladder	Benzidine and/or 2-naphthylamine	Occupational exposure	No occupational exposure	500

From IARC [13], modified.

In attempting an evaluation of the possible impact that preventive measures might have, among the various factors to be considered are the number of individuals at risk and the intensity of the risk. From Table 3, it is possible to realize the reduction in risk from which exposed individuals might benefit [13]. These measures of the relative risks, however, do not provide a means to calculate the population effect, that is, the overall reduction in population rates of the disease, since this will depend on the proportion of the population that is exposed. The variations in relative risks, as well as in the proportion of the population actually exposed, should induce great caution before a risk can be justifiably called minimal.

The three considerations mentioned above indicate that the only reasonable approach to cancer prevention cannot but be multidisciplinary, with as close as possible an interaction between basic and aetiological research. The efficacy of primary prevention obviously will increase with, and in certain instances totally depends upon, the understanding of the mechanisms by which a factor contributes to the malignant transformation of cells and/or to their progression to clinical cancer.

We are periodically reminded that funds for research are limited and that priorities must be established. Given the budgetary limitations that most of us are experiencing at present, this is often a very painful operation which also has a semi-hazardous component and contains an unavoidable bias. The semi-hazardous component is that we have a limited capacity to predict accurately which of several projects among which we are asked to make a choice will succeed in producing meaningful results.

The unavoidable bias is that projects which fall in line with the preferred orientations of granting agencies and contract makers are favoured. An equally unavoidable consequence is that some scientists, consciously or unconsciously, bend part of their intellectual capacity to satisfying requirements which guarantee the availability of funds. If pushed to an extreme, this may result in a mechanism by which the obtaining of funds will be a conditioning and limiting factor *per se* in the design and development of research projects.

At a different level, priorities are defined according to criteria in which science and politics as well as human wisdom and hypocrisy are deeply intermingled. The most powerful individuals on the planet can preach that they care about their fellow man, but at the same time provide thousands of times more money for killing each other than for alleviating illness or misery or for preventing disease.

The limited funds available, coupled with a certain parochialism, established a sort of vicious circle

that strengthened the false assumption that basic and applied research are two separate and almost independent branches of research. Thus, funds which, for instance, were attributed to research on aetiology and prevention, were seen by basic scientists as being withheld from basic research. As all areas of biomedical research, with the exception of those with obvious immediate economic advantages, are experiencing various degrees of financial restriction, the same charge could be made by any scientists whose grant or contract has not been approved.

It should be clear therefore that: (1) basic and applied research, studies on the mechanisms of carcinogenesis and research on aetiology and prevention are neither opposite nor separate areas of scientific activity; they must be, and indeed are, closely interrelated; (2) the assumption that only basic research is 'true' science, and that all other approaches to the primary prevention of cancer are not, is not justified and perhaps reflects a certain level of intellectual snobbery. There is no solution of continuity between the studies of the mechanisms of diseases, the epidemiological and laboratory based investigations on aetiology, and the implementation of primary prevention. The understanding of certain stages of the carcinogenesis process is actually progressing side by side with the development of much finer and more precise methods than ever existed before for monitoring low doses of exposure at the individual level. This will be of very considerable help in the conduct of epidemiological investigations [14–18]. To see, therefore, basic and applied research as separate and in competition is a grave error and can only serve the purpose of preventing scientists from forming a common front for spending the available resources rationally and efficiently and perhaps for obtaining more of them.

REFERENCES

1. Cairns J. The origin of human cancers. *Nature* 1981, **289**, 353–357.
2. Kraemer KH, Lee MY, Scotto J. DNA repair protects against cutaneous and internal neoplasia: evidence from xeroderma pigmentosum. *Carcinogenesis* 1984, **5**, 511–514.
3. Ames BN, Magaw R, Gold LS. Ranking possible carcinogenic hazards. *Science* 1987, **236**, 271–280.
4. Cabral JRP, Hall RK, Rossi L, Bronczyk SA, Shubik P. Lack of carcinogenicity of DDT in hamsters. *Tumori* 1982, **68**, 11–17.
5. Haseman JK. Issues in carcinogenicity testing: dose selection. *Fund Appl Toxicol* 1985, **5**, 66–78.
6. Cabral JRP, Shubik P, Mollner T, Raitano F. Carcinogenic activity of hexachlorobenzene in hamsters. *Nature* 1977, **259**, 510–511.
7. Cabral JRP, Mollner T, Raitano F, Shubik P. Carcinogenesis of hexachlorobenzene in mice. *Int J Cancer* 1979, **23**, 47–51.
8. Peters HA. Hexachlorobenzene poisoning in Turkey. *Fed Proc* 1976, **35**, 2400–2403.
9. IARC. *Hexachlorobenzene: Proceedings of an International Symposium.* Morris CR, Cabral JRP, eds. IARC Scientific Publications No. 77, International Agency for Research on Cancer, Lyon, 1987.
10. Huff JE, McConnell EE, Haseman *et al.* Carcinogenesis studies: results of 398 experiments on 104 chemicals from the U.S. National Toxicology Program. *Ann NY Acad Sci* (in press).
11. Parkin DM, Laara E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int J Cancer* (in press).
12. IARC. Approaches to Classifying Chemical Carcinogens According to Mechanism of Action. IARC International Technical Report No. 83/001, Lyon, 1983.
13. *Cancer: Occurrence, Causes and Control.* IARC Scientific Publications, International Agency for Research on Cancer, Lyon (in press).
14. Harris CC, Weston A, Willey JC, Trivers GE, Mann DL. Biochemical and molecular epidemiology of human cancer: indicators of carcinogen exposure, DNA damage, and genetic predisposition. *Envir Health Persp* (in press).
15. Harris CC. Human tissues and cells in carcinogenesis research. *Cancer Res* 1987, **47**, 1–10.
16. Weinstein IB. The origins of human cancer: molecular mechanisms of carcinogenesis and their implications for cancer prevention and treatment. *Proc Am Assoc Cancer Res* 1987, **28**, 465–466 (abstract).
17. Dragstad LO, Autrup H. Detection of aflatoxin-like substances in the general Danish population. In: Proceedings of the IXth EACR Congress, Helsinki, June 1987.
18. Umbenhauer D, Wild CP, Montesano R *et al.* O^6-Methyldeoxyguanosine in oesophageal DNA among individuals at high risk of oesophageal cancer. *Int J Cancer* 1985, **36**, 661–665.