Role of experimental and epidemiological evidence of carcinogenicity in the primary prevention of cancer

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Summary. Experimental chemical carcinogenesis, which included long-term tests in experimental animals, had a dominating role in cancer research between the 1920s and the late 1960s. Two events marked a certain decline of confidence in the ability of experimental results to predict human risks: the incapacity of developing methods to identify agents acting on the different steps of the carcinogenesis process, and the incapacity to reproduce experimentally the strong evidence of carcinogenicity of tobacco smoke provided by epidemiological studies. It was at that time that epidemiologists and biostatisticians developed criteria for assessing the causation of chronic-degenerative diseases relying primarily on epidemiological evidence. In 1969 the International Agency for Research on Cancer (IARC) did initiate a programme for identifying the cause of cancer with the aim of promoting the primary prevention of cancer. The programme is focused on the evaluation of the carcinogenicity of environmental agents on the basis of both the experimental and epidemiological evidence and, since the 1990s, a balanced use of the new tools provided by advances in toxicology, molecular biology and genetics. A strong point of the IARC programme is that in the absence of adequate human data it is reasonable and prudent to regard agents for which there is sufficient experimental evidence of carcinogenicity as if they were carcinogenic to humans.

Key words: primary prevention, cancer, experimental carcinogenicity, epidemiology.

Riassunto. La cancerogenesi chimica sperimentale, che include test a lungo termine in animali da laboratorio, ha svolto un ruolo dominante nella ricerca sul cancro tra gli anni '20 e la fine degli anni '60. Due eventi hanno segnato un certo declino di confidenza nella capacità di risultati sperimentali di predire il rischio per l’uomo: l’incapacità di sviluppare metodi per identificare agenti che agiscono nelle diverse tappe del processo cancerogenico, e l’incapacità di riprodurre sperimentalmente la forte evidenza di carcinogenicità del fumo di tabacco fornita dagli studi epidemiologici. Fu a quel tempo che gli epidemiologi ed i bio-statistici svilupparono criteri per stabilire le cause di malattie cronico-degenerative primariamente sulla base dell’evidenza epidemiologica. Nel 1969 l’Agenzia per la Ricerca sul Cancro (IARC) iniziò un programma per identificare le cause del cancro con lo scopo di promuovere la prevenzione primaria. Il programma è focalizzato sulla valutazione della cancerogenicità di agenti ambientali sulla base dell’evidenza sperimentale che epidemiologica e, dagli anni ‘90, sull’impiego bilanciato di nuove informazioni fornite dai progressi della tossicologia, della biologia molecolare e della genetica. Un punto fondamentale del programma IARC è che in assenza di dati umani adeguati è ragionevole e prudente considerare gli agenti per i quali esiste una sufficiente evidenza sperimentale come se fossero cancerogeni per l’uomo.

Parole chiave: prevenzione primaria, tumori, evidenza sperimentale, cancerogenicità, epidemiologia.

Experimental chemical carcinogenesis which included, but was not limited to long-term tests in experimental animals, had a dominating role in cancer research between the 1920s and the late 1960s. When Passey in 1922 showed that soot extracts could induce malignant tumors in mice [1], his results were taken as the necessary definitive confirmation of the observations of Percival Pott of the occurrence of scrotal cancer in chimney sweeps. This attitude de facto implied that in order for clinical observations to be fully accepted they had to be confirmed experimentally, underlining in this way the dominating role of experimental results in cancer research.

By the late 1930s it was already clear that: a) a chemical mixture like soot could induce the same type of tumors in humans, rabbits and mice; b) the same chemical can induce cancer in different animal species, but not necessarily the same type of cancer; c) the capacity to induce cancer is not limited to a particular group of chemicals; d) carcinogens can induce cancer in organs distant from the carcinogen’s point of entry [2].
The availability by the early 1940s of spectrophotometers, the introduction of paper chromatography and the use of C14 labeled carcinogens a few years later, made possible considerable advances in biochemistry [3]. Between the 1940s and the 1950s carcinogens were identified among chemicals pertaining to a dozen chemical classes [4, 5]. At that time also long-term animal experimentation was carried out by, or under the supervision of eminent scientists, including Lacassagne, Shabad, Boyland, Shubik, Shimkin, usually combined with research aimed at a better understanding of the process of carcinogenesis. Commercial laboratories began to be involved in the performance of bioassays around the time that US President Nixon declared war on cancer. Thereafter long-term carcinogenicity tests gradually became a sort of lucrative business.

The commercial production and use as a food additive of 4-dimethylaminobenzene, also known as “butter yellow”, was prohibited in the late 1930s because of evidence for its carcinogenicity in rats [6]. Similarly the results of long-term tests in 1941 demonstrating the carcinogenicity in rats of 2-acetylaminofluorene (AAF) [7] were held as sufficient warning to forestall its commercial production as an insecticide. Primary prevention was therefore implemented on the basis of the capacity of long-term experimentation in animals to predict similar effects in humans, taking into account biological plausibility but independently of the extent of understanding of the underlying mechanisms. The history of public health was teaching in fact the lesson that prevention was often efficiently implemented before a full understanding of mechanisms was attained that could confirm and explain causality.

During a large part of the last century there were quite different attitudes at the national levels concerning two categories of aetiological agents: biological agents causing contagious diseases and chemicals causing cancer. The consensus on how to deal with biological pathogens did allow a uniform approach to the primary prevention of communicable diseases throughout the world. Nobody tried hard to deny that bacteria or viruses were equally pathogenic at all latitudes. If primary prevention of infectious diseases has not been implemented with equal efficiency in poor and rich countries, is not due to a disagreement about the pathogenicity of bacteria and viruses, but to the persistent selfishness of rich countries and the equally persistent greed of pharmaceutical corporations. In contrast, primary prevention of cancer has instead stumbled from the very beginning because of the interference of powerful economic interests which perceived that any data indicating a possible cancer risk after exposure to industrial chemicals jeopardizes their profits, the protection of which being more important than the protection of human health. It happened, therefore, that chemicals were recognized as carcinogens in certain countries and not in others. Furthermore, even for chemicals that were widely recognized as carcinogenic, different levels of exposure were considered acceptable in different countries [8, 9]. It was as if the carcinogenicity of a chemical ceased to exist at certain borders or varied sharply from country to country.

The case of 4-aminobiphenyl is a pertinent example of the inconsistent attitudes of health authorities. The proposal to produce and use 4-aminobiphenyl in the United Kingdom in the early 1950s was refused because of evidence that it induced liver and bladder tumours in rodents and dogs [10, 11]. In the United States, where 4-aminobiphenyl had been produced and used since 1935, the production continued claiming that there were no published clinical or epidemiological evidence of an increased risk for cancer in humans ignoring the warning from the experimental evidence. Its production and use were finally interrupted in 1955 after the report of bladder cancer in occupationally exposed individuals [12].

The attitude of chemical corporations, which detain enormous economic power, towards results obtained with animal experimentation has been ambiguous from the start. Experimental results were generally denigrated, except in some instances when they were highly praised, with the obvious or surreptitious purpose of casting doubts on evidence for the existence of a risk provided by a clinical observation, case reports or epidemiological studies. Typical examples of this sort of negative seesaw between significance and irrelevance of epidemiological and experimental data are those associated with benzidine and 2-naphthylamine. The fact that the cancer of the bladder observed in occupationally exposed persons could not be induced experimentally in rodents, was used to cast doubts on the significance of the human observations. Once further tests produced clear evidence for the experimental induction of bladder tumors by 2-naphthylamine in dogs, doubts were raised about the significance of both the experimental results and the observations in humans with the consequence that preventive measures continued to be unduly delayed. More than half a century had to pass between the first observation of occupational bladder cancer by Rehn in 1895 and the adoption of the first measures to limit or ban the production and use of carcinogenic aromatic amines [8, 9, 13].

Inconsistency and ambiguity in attitudes toward environmental and occupational carcinogens have not entirely disappeared as it is shown by the case of asbestos. In spite of overwhelming longstanding evidence of its carcinogenicity in all its commercial forms no common international agreement has yet been reached the ban its production. Its use has been banned by some reach countries, but these same virtuous countries, are sending their old ships to be demolished in poor countries where occupational surveillance is minimal or non-existent [14], some poor countries still use asbestos, while a few wealthy countries still produce and export it [15].

Some of the recurrent criticisms of long term bioassays are the high doses used, use of routes of administration not necessarily corresponding to the route of exposure of humans and the lack of concordance between target organs. Two events in particular, however, marked a certain decline of confidence in the ability of experimental results to predict human risks. The first, paradoxically, was related to the widely accepted hy-
hypothesis of two-stages carcinogenesis, which opened the door to interpretation of carcinogenesis as a multi-step, multifactorial process. The pronouncement of this brilliant convincing hypothesis was unfortunately not followed by the development of adequate experimental methods to identify the different actors in the carcinogenesis process nor for evaluating their respective role. A further blow to the credibility of experimental results was the inability to reproduce in experimental animals the strong evidence for the carcinogenicity of tobacco smoke provided in the 1950s by epidemiological studies, although there was experimental evidence for the carcinogenicity of tobacco tar. It was at that time that epidemiologists and biostatisticians developed criteria for assessing the causation of chronic-degenerative diseases, taking into account biological plausibility, but relying primarily on epidemiological evidence [16]. The nine points originally proposed by Bradford Hill to distinguish between association and causation in relation to occupational exposures but then extended to all environmental agents, were possibly the strongest foundation for upgrading epidemiology in establishing a causal relationship between exposure and disease [17].

Following the acceptance that epidemiological results could by themselves alone provide evidence for a causal relationship, a further step was taken, when epidemiological evidence was considered the only acceptable proof of causality [18] relegating in this way experimental data to a subordinate role.

The International Agency for Research on Cancer (IARC) was created to initiate and coordinate an international program of primary prevention of cancer, an area that had attracted less attention and financial support than research on the diagnosis and therapy of cancer. In the late 1960s the Agency did initiate a programme for identifying the causes of cancer. At that time two incomplete, unofficial lists of human carcinogens were available, the first appearing in the well known book Chemical Carcinogenesis by Hueper & Conway [19], and the second in a WHO technical report on Primary Prevention of Cancer [20].

The IARC program was initiated in 1969 jointly by a group of IARC scientists and outside experts whose scientific background was experimental and/or human pathology, biochemistry and chemical carcinogenesis. Although the time of inception of the IARC program coincided with the growing importance of the epidemiological approach in the assessment of risks, none of the 10 externals experts of the Working Group that met in Lyon 7-11 December 1970 to draft the first IARC Internal Technical report on the Evaluation of Carcinogenic Risk of Chemicals to Man [21] was an epidemiologist, while the IARC secretariat included a biostatistician who did not, however, participate to the working sessions.

A year later, in December 1971, the first volume of the Monographs [22] was finalized in Geneva by a working group of 12 scientists, only one of whom was an epidemiologist. It had been difficult to convince him to attend, and almost equally difficult to keep him for the duration of meeting. A biostatistician was again listed among the six scientists from IARC, but he barely attended the meeting.

When an ad hoc working group was convened in 1977 after publication of the first 16 volumes of Monographs to revise the criteria for evaluating the carcinogenic risk of chemicals to humans, the situation was considerably changed as a consequence of the growing importance accorded to case reports and epidemiological data [23]. Although experts in experimental chemical carcinogenesis were still the majority in the working group, eight of the 23 members were well known epidemiologists/biostatisticians (including D. Acheson, R. Peto, P. Sartwell, and M. Schneiderman), and the IARC secretariat included N. Day, C. Muir and R. Saracci. The revised criteria became the preamble that appears at the beginning of each Monograph’s volume.

Strong points of the 1977 Monograph’s preamble were: a) the definition of the term “chemical carcinogenesis”; and b) a statement underlining the relevance of results from tests in experimental animal in predicting possible risk to humans. Chemical carcinogenesis was defined as “the induction by chemicals of neoplasms that are not usually present, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found, although fundamental differences in the mechanisms may be involved”, a definition based primarily on experimental criteria. The statement about the relevance of experimental results, anticipating what years later became the precautionary principle, was written in 1977 as follows: “In the presence of appropriate positive carcinogenicity animal data and in the absence of adequate human data, it is reasonable to regard such chemicals as if they were carcinogenic to humans.”

With some minor editorial changes this statement, formulated when experimental carcinogenesis data were still considered somewhat superior to or at least on a par with epidemiological data, has remained the corner stone of the program.

In January 1979 after the publication of 20 volumes of Monographs the epidemiological and experimental degrees of evidence of carcinogenicity were systematically categorized as sufficient, limited or inadequate and the agents were placed into one of three groups: group 1, carcinogenic to humans; group 2, possibly carcinogenic to humans and group 3, not classifiable as to its carcinogenicity to humans. Group 2 was subdivided in subgroups 2A and 2B to reflect higher and lower degree of evidence. Assignment to group 1, symbolizing definitely carcinogenic to humans, was exclusively on the basis of human data, while experimental data continued to play a key role in the assignment to group 2A and 2B [24].

Experimental data regained relevance in the evaluation of risks to humans when the inclusion of mechanistic considerations changed the criteria for admission to the various groups. A first attempt to classify chemicals according to mechanism of action was made...
in 1983. On that occasion, while it was agreed that such a classification could represent an important contribution to the prevention of human cancer, it was concluded that “at present no classification of carcinogens according to mechanisms could be exhaustive and definitive” [25].

It was in 1991 that an ad hoc working group advised the IARC that data on mechanisms thought to be relevant to an evaluation of the carcinogenic risk of an agent to humans should be used in making the overall evaluation, together with the combined evidence from studies in experimental animals and humans [26, 27]. The changes in the criteria do not necessarily lead, however, to better protection of public health. They may provide additional elements for placing an agent or exposure in group 1 even if the epidemiological evidence is less than sufficient (as was the case for ethylene oxide and TCDD). The criteria can also be used, however, to claim that, in spite of sufficient experimental evidence of carcinogenicity, the mechanism of carcinogenicity in experimental animals does not operate in humans, therefore lowering the category of agents assigned to group 2A or 2B to group 3 [28].

On the basis of generalized but largely unconfirmed mechanistic considerations, the induction of tumors in the urinary bladder and thyroid in rats, fore-stomach in rats and mice, the lung after inhalation of particles in rats, and the liver in mice, would be disregarded in evaluating carcinogenicity. If this proposal were to be adopted many chemicals would no longer be considered carcinogens and the degree of confidence in the evidence for carcinogenicity of an additional number of chemical would be reduced [29, 30].

Although results of studies in experimental animals have drawbacks, their primary role being to provide qualitative evidence of carcinogenicity, it is a fundamental premise of toxicological research that results of such tests are applicable to humans. Furthermore all human carcinogens that can be submitted to long-term carcinogenicity tests have been shown to be carcinogenic in at least one animal species, and in many instances experimental evidence of carcinogenicity has preceded the human evidence and could have allowed an earlier adoption of preventive measures. Assessment of the carcinogenicity of an agent to humans formulated on the basis of both the epidemiological and experimental evidence, with balanced use of the new tools provided by advances in toxicology, molecular biology and genetics, as done by IARC, appears therefore to be the best possible approach to evaluating of possible risks to humans.

Given the general paucity of epidemiological data and the low probability that agents listed in group 2B and even in group 2A are attractive subjects for epidemiological studies, indiscriminate downgrading of the results of tests in experimental animal would result in elimination of the only indication of potential hazard for humans for a considerable number of environmental chemicals and chemical mixtures.

It is not uninteresting that the campaign against the significance of experimental carcinogenesis in particular of long-term animal tests, initiated long ago, has surfaced again recently with renewed virulence. Scientific and economic arguments are vigorously and often disingenuously used to belittle or deny relevance and the value of long-term animals tests in predicting human effects [31, 32]. One may wonder whether it is a pure coincidence that this campaign has been intensified during the discussion of the European Union project for the Regulation, Evaluation, and Authorization of Chemicals (REACH).

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References


