GENERAL REMARKS

Several biological agents have been implicated in the development of human cancers. Following recomendations made by an advisory group which met in 1991 (IARC, 1991), the *IARC Monographs* programme was expanded to include consideration of exposure to or infection with biological agents such as viruses, bacteria and helminths. The fifty-ninth volume of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* evaluated human infections with hepatitis B virus, hepatitis C virus and hepatitis D virus. This sixty-first volume considers certain helminthic infections with schistosomes and liver flukes and bacterial infection with *Helicobacter pylori*.

Helminths are parasitic worms which differ from all other infectious agents in that they are larger and multicellular and are always located extracellularly in the mammalian host; they do not multiply in humans. The worms are highly aggregated in their distribution within infected communities, with a majority of worms being harboured by a minority of the infected population. It is this segment of the population that is at considerable risk of developing severe disease.

Schistosomiasis, which is considered in this volume, is widespread: it is estimated that 200 million people in at least 74 countries are infected (WHO, 1993). Five species of the *Schistosoma* trematodes cause disease globally: *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum*. Only the first three, which account for the vast majority of schistosomal disease in humans, are considered here. A causal association between infection by *S. haematobium* and squamous-cell carcinoma of the urinary bladder was first postulated towards the beginning of this century (Goebel, 1905), and concern has been raised more recently about an association between infection with *S. mansoni* or *S. japonicum* and increased risk for cancers of the gastrointestinal tract (Inaba *et al.*, 1984; Chen & Mott, 1989).

About 17 million people in Europe and Asia are infected with certain liver flukes: with *Chlonorchis sinensis* in China, the Korean peninsula and Viet Nam; with *Opisthorchis viverrini* in Thailand and Laos; and with *O. felineus* in the Russian Federation and eastern Europe. Liver cancers were first described in association with infection with *O. felineus* and *C. sinensis* in clinical series nearly a century ago (Askanazy, 1900; Katsurada, 1900) and in association with *O. viverrini* 50 years later (Viranuvatti & Mettiyawongse, 1953).

The bacterium, *H. pylori*, first characterized and cultured in 1982 (Marshall, 1983; Warren, 1983), is the cause of most cases of chronic gastritis and duodenal ulcer. More than half of the world's population may be infected with *H. pylori*. The demonstration that atrophic gastritis is a precursor condition for gastric cancer led to the suggestion that this bacterium may be involved in the development of this cancer (Correa, 1992).

Chronic infection and inflammation contribute to the multistage carcinogenesis process by many different mechanisms. Several hypotheses have been proposed, which are briefly summarized below.

In response to infectious or inflammatory agents, inflammatory cells are activated to produce reactive oxygen and nitrogen species, which kill invading pathogens. These radicals can also damage macromolecules, including DNA, in adjacent normal tissues, resulting in the induction of mutations, DNA strand breaks and chromosomal aberrations. The increased rate of cell division and the decrease in efficiency of DNA repair in infected tissues may increase the rate of fixation of mutations. Inflammatory cells secrete various cytokines and enzymes, which may stimulate the growth of tumour cells (Ames & Gold, 1990; Cohen & Ellwein, 1990; Preston-Martin *et al.*, 1990).

A further mechanism by which bacteria and other parasites may contribute to carcinogenesis is the production of toxins and carcinogens. Bacteria and activated inflammatory cells can generate nitrosating agents from nitric oxide. Methylation damage to DNA has been reported in the urinary bladders of people infected with *S. haematobium* and in the livers of mice infected with *S. mansoni*. Alteration of the metabolism of carcinogens and endogenous substrates in the host may also play a role in the carcinogenic process.

In the evaluation of the biological agents considered in this volume, the same principles were used as in previous *Monographs* (see Preamble). Inferences on the role of these agents in the induction of neoplasia are based on the same criteria as those used for chemical compounds in the *Monographs* series. There are, however, minor differences in the nature of the evidence available for the assessment of the role played by infectious agents in the genesis of cancer. Unlike chemical exposures, for which the only available measure usually derives from memory or imperfect records, human exposure can be measured objectively, by the laboratory evaluation of biological specimens. Measures of exposure to infectious agents commonly have no time reference, however, and recent exposure cannot always be easily distinguished from exposure in the distant past. Moreover, the sensitivity and specificity of measures of exposure depend on the uniqueness of the agent and the host response.

In addition, with specific reference to helminthic infections, descriptive epidemiology assumes a rather more important role than it usually does. This is because exposure to helminths is sharply circumscribed geographically and demographically. Moreover, the malignancies suspected of originating with helminthic infection are in several cases rare. Thus, if the occurrence of an otherwise rare tumour is well circumscribed in terms of age, sex and geographical unit, it can be more easily compared to the analogous distribution of infection.

Studies of carcinogenesis in animals also assume a somewhat different role in the assessment of infectious agents than that of chemicals. While infected animals do develop tumours which are histologically very similar to those in infected humans, the 'dose' delivered is more difficult to control, since growth and, in the case of bacteria, replication occur in the host. Moreover, since the process of carcinogenesis may be dependent on the host reaction, the relationship between latency and the life span of the experimental animal becomes an important issue.

Various animal models have been used to study the carcinogenicity of these organisms and to explore their mechanisms of action. Although, as might have been expected for infectious biological agents, there were detectable differences in susceptibility to them among species and strains, what was truly remarkable was the extent to which the biological effects produced in the experimental animals occurred at the same sites and produced the same type of lesions as those seen in humans infected with these organisms. This target organ specificity was also observed in experiments in which tumour induction was produced by infection plus exposure to low doses of several chemical carcinogens. It may not be possible to expose animals to levels of infection that exceed human exposures to the degree that can often be done with chemicals. Therefore, it may not be possible with infectious agents like these to maximize their tumour response to a level that is detectable in bioassays of conventional size or to foreshorten the period to tumour occurrence, as is commonly done with chemical carcinogens. Even if the infection is an important factor in the development of tumours in people, these biological agents may not take all of the required steps in multistep carcinogenesis to yield neoplasms efficiently. Instead, they may be very effective in causing persistent injury and stimulating progressive cell proliferation at the site of infection. This process may efficiently achieve the first or several steps in transformation; later steps are traversed inefficiently with the organisms alone but with notable effectiveness when they are combined with known carcinogens.

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