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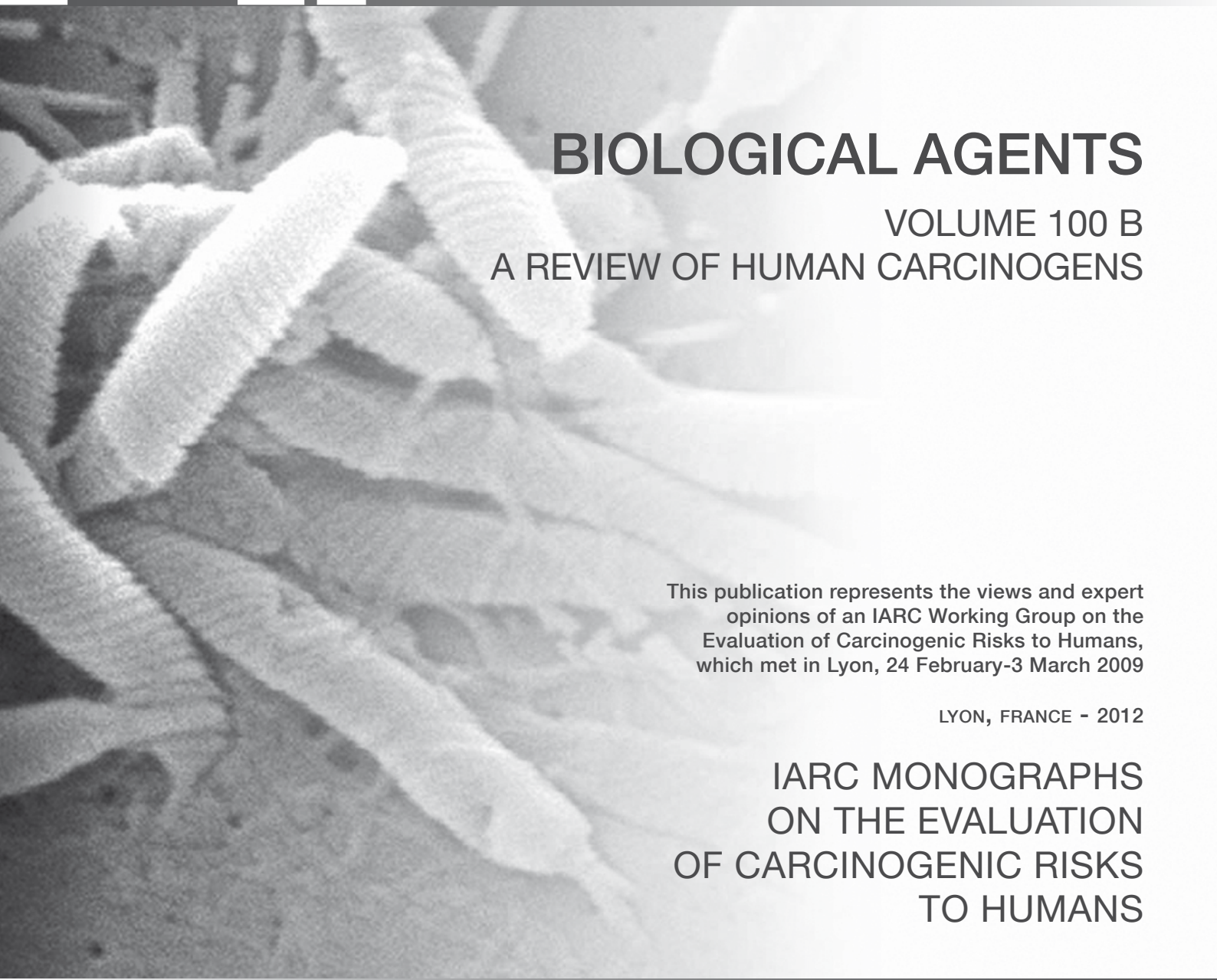

BIOLOGICAL AGENTS

VOLUME 100 B
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 24 February-3 March 2009

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IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

GENERAL REMARKS

Part B of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* considers 11 biological agents that were first classified in Volumes 1–99: seven viruses, three worms, and one bacterium.

Most of these agents were evaluated more than 15 years ago, and were classified by IARC as *carcinogenic to humans (Group 1)* with two exceptions: Kaposi sarcoma-associated herpesvirus (KSHV), and the worm *Clonorchis sinensis*, both previously classified as *probably carcinogenic to humans (Group 2A)*. KSHV was last assessed ten years ago and, in view of the extensive scientific literature published since, needed to be re-evaluated. *Clonorchis sinensis* was also included because its biology and epidemiology of infection are very similar to those of *Opisthorchis viverrini*, another worm reviewed in this volume.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected *A Review of Human Carcinogens* to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical

overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the toxicokinetic properties of the agent, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results appear in the printed version of Volume 100, and more extensive tables that include all studies appear on the website of the *IARC Monographs* programme (http://monographs.iarc.fr). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise; then all sections of each *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, *Tumour Site Concordance between Humans and Experimental Animals*, will analyse the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, *Mechanisms Involved in Human Carcinogenesis*, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could render future research more informative. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the review of biological agents in this volume

1. Historical aspects*

Current knowledge linking infection with some biological agents and carcinogenesis in humans is the result of a long and laborious but exciting succession of scientific discoveries, which started more than a century ago. These important historical steps have been thoroughly retraced by Dr Harald Zur Hausen in his recent book "Infections Causing Human Cancer" (2006) from which this paragraph has extracted some highlights.

At the end of the 19th century, the first suspicions arose that infectious agents (initially parasites, liver flukes and *Schistosoma* infections) could cause specific human cancers: in 1900 Askanazy reported a link between infection by a liver fluke and liver cancer in former East Prussia (Askanazy, 1900). Five years later, another report described a case of chronic infection with bilharzia (*schistosomiasis*) and

* Part of this text has been adapted from zur Hausen (2006): Infections Causing Human Cancers, 2006. Copyright Wiley-VCH Verlag GmbH & Co. KGaA (reproduced with permission).

bladder cancer (Goebel, 1905). It took more than 50 additional years before further evidence emerged of an involvement of infectious agents in human cancers.

In 1958, a British surgeon, Dennis Burkitt, described a specific childhood lymphoma in equatorial Africa occurring only in specific geographic regions: it was subsequently called *Burkitt lymphoma*. Because these regions coincided with areas of holoendemic malaria, Burkitt speculated that this tumour should have an infectious etiology, most likely vectored by an arthropod, possibly by a mosquito (Burkitt, 1962). In a small fraction of cultured Burkitt lymphoma cells Epstein and colleagues (1964) noticed herpesvirus-like particles: a new member of the Herpesvirus family was discovered and later named Epstein-Barr virus (EBV).

The development of immunofluorescence allowed the detection of highly elevated antibody titres against EBV viral antigens in patients with Burkitt lymphoma (Henle & Henle, 1966, Henle et al., 1969), and subsequently also in a second human cancer, nasopharyngeal carcinoma (Old et al., 1966). EBV was also identified as the causative agent of infectious mononucleosis (Henle et al., 1968). Besides, the Henles' laboratory first demonstrated that latent EBV infection was widespread in all human populations.

The first hints of an oncogenic potential of EBV originated from the establishment of lymphoblastoid lines of cord-blood origin when co-cultivated with lethally X-irradiated Burkitt lymphoma cells in culture (Henle et al., 1967). This was further underlined by the discovery of persisting EBV DNA in "virus-negative" Burkitt lymphoma cells (zur Hausen & Schulte-Holthausen, 1970), as well as in primary biopsies from Burkitt lymphomas and nasopharyngeal cancer (zur Hausen et al., 1970; Wolf et al., 1973). The induction of lymphoproliferative disease after inoculation of EBV into cottontop marmosets (Shope et al., 1973) or owl monkeys (Epstein et al., 1973) added to the evidence in this early phase.

In the 1970s, more infectious agents were considered as potential human carcinogens. Three independent findings contributed to this development: the discovery of a role of hepatitis B virus (HBV) in liver cancer, the identification of a retrovirus in a rare form of human leukaemia, and the characterization of novel types of papillomaviruses causing the second most frequent cancer in women, i.e. cancer of the cervix.

The frequent coincidence between infectious hepatitis and hepatocellular carcinoma (HCC) was noted early in Africa in the 1950s by British and French pathologists (reviewed in Szmuness, 1978). While investigating a potential role of human genetic polymorphisms in relation to inherited susceptibility to disease, Blumberg et al. (1965) described a "new" antigen in the blood of an Australian aborigine (the "Au" antigen), which was shortly thereafter recognized to be the surface antigen of HBV, termed today HBsAg (Blumberg et al., 1967; Blumberg, 1997). In this case, basic research initially remote from studies on infectious agents led to the discovery of HBV, to diagnostic methods for viral detection efficiently used for donor blood testing, and finally to a vaccine. Several epidemiological studies followed this discovery and stressed a role of chronic infection with HBV in HCC development. A key contribution was presented in 1981 by Beasley et al. with a prospective study in Taiwan (China) showing that HBV carriers had a more than 200-fold elevated risk for developing HCC than virus-negative individuals. Vaccination studies today underline the importance of this viral infection for hepatocellular carcinoma. Indeed, the world's first universal HBV vaccination program launched in Taiwan (China) in July 1984 has resulted in a reduction of the original prevalence of HBV infection to approximately one-tenth, and a clear prevention for HCC by the vaccine was recently reported in childhood and early adulthood (Chang, 2011).

The discovery of the first human retrovirus, human T-cell lymphotropic retrovirus (HTLV-1) and its association with human cancer originated from rather independent studies in Japan and in the USA. In 1977, a new type of leukaemia called adult-T-cell leukaemia/lymphoma (ATLL) was described by Takatsuki and colleagues in the coastal regions of southern and western Japan (Takatsuki et al., 1977; Uchiyama et al., 1977). The first isolation of HTLV-1 from a cutaneous T-cell lymphoma was reported in the USA (Poiesz et al., 1980). One year later, Japanese researchers identified the same virus from an ATLL cell line (Miyoshi et al., 1981), and could link this infection to this specific leukaemia (Hinuma et al., 1981).

Shortly later, when the acquired immunodeficiency syndrome (AIDS) epidemic just started in the USA, the human immunodeficiency virus type 1 (HIV-1) was discovered as a new T-cell lymphotropic human retrovirus, first isolated from a patient with lymphadenopathy (Barré-Sinoussi et al., 1983). The following year, the virus was firmly associated with AIDS (Gallo et al., 1984).

The initial link between human papillomavirus and cancer became clear as a result of research on a rare hereditary condition, *epidermodysplasia verruciformis*, described in 1922 by Lewandowsky and Lutz in Basel, and characterized by an extensive verrucosis. At sun-exposed sites of the body of these patients, some of the papillomatous lesions of the skin converted into squamous cell carcinomas. In Lutz (1946) and later Jablonska & Milewski (1957) proved the viral etiology of these warts in autoinoculation experiments. Then, in the late 1970s, novel types of papillomaviruses, most frequently HPV 5, were isolated within *epidermodysplasia verruciformis* lesions and biopsies of squamous cell carcinomas of those patients. (Orth et al., 1978, 1979).

Another track of papillomavirus research resulted in the identification of specific HPV types as causative agents for cancer of the cervix, other anogenital cancers, and a subset of oropharyngeal carcinomas. By the end of the 1960s and during the 1970s, serological studies suggested a role of herpes simplex virus type 2 (HSV 2) in cervical cancer (Rawls et al., 1968, Naib et al., 1969). However, a possible causal role of papillomavirus infections for cervical cancer was only postulated when several anecdotal reports had shown malignant conversion of genital warts (*condylomata acuminata*). Attempts to characterize the viral DNA in genital warts started (zur Hausen et al., 1974, 1975, zur Hausen, 1976, 1977) leading initially to the discovery of the heterogeneity of the papillomavirus family (Gissmann & zur Hausen, 1976; Orth et al., 1977; Gissmann et al., 1977), which today comprises 120 fully sequenced genotypes (Bernard et al., 2010). The use of hybridization experiments, performed under conditions of reduced stringency with the DNA of the already isolated HPV types 6 and 11 as probes permitted the subsequent cloning of HPV 16 (Dürst et al., 1983) and of HPV 18 (Boshart et al., 1984), the two papillomavirus types most frequently found in cervical cancer.

The identification of three viral families with representative types clearly causing widespread human cancers gradually resulted in the acceptance of infectious agents as important human carcinogens. The subsequent identification of additional infections linked to other cancers further strengthened the role of infectious agents in human carcinogenesis. The hepatitis C virus (HCV) was identified in 1989 (Choo et al., 1989), and first reports on its relationship to a subset of HCC appeared in the same year (Bargiggia et al., 1989; Simonetti et al., 1989). There had been, however, some earlier reports, linking non-A, non-B hepatitis infections to liver cancer (Kiyosawa et al., 1982, Resnick et al., 1983 and others). Human herpesvirus type 8 (HHV-8) now called Kaposi sarcoma herpes virus (KSHV) was discovered in 1994 (Chang et al., 1994) as the most likely responsible agent for Kaposi's sarcoma. In the early 1990s *Helicobacter pylori*, as a bacterial infection, was added to the list of potential human carcinogens (Forman et al., 1991; Nomura et al., 1991; Parsonnet et al., 1991;

and Wotherspoon et al., 1993), and several additional human papillomavirus genotypes were added to the list of oncogenic viruses.

Merkel cell polyomavirus (MCPyV), a novel member of the polyomavirus family has been recently identified (Feng et al., 2008). The available evidence seems to support an important role for this infection in the development of Merkel-cell carcinomas (Shuda et al., 2008).

Today, more than one hundred years after early attempts to link infections to human cancer, infections are recognized as a major factor in human carcinogenesis.

2. Global contribution of infections to human cancers

In 2002, it was estimated that 17.8% of cancers (1.9 million cases) were caused by viral (12.1%), bacterial (5.6%), and helminth (0.1%) infection (Parkin, 2006). Of these, the majority occur in developing countries (1.5 million cases), reflecting the higher prevalence of the major oncogenic infections in these areas. If the relevant infections could be controlled, it is conservatively estimated that there would be about 26% fewer cancers in developing countries, and approximately 8% fewer in developed countries. Since then, several new links between infectious agents and specific cancers have been established (Bouvard et al., 2009; this volume), further increasing the burden of infection-related cancers.

A better understanding of the role of infectious agents in the etiology of cancer is an essential element in public health policy, because such cancers are theoretically preventable by vaccination or early treatment of infection. Furthermore, cancer-causing infections often cause substantial morbidity and mortality from non-malignant conditions (e.g. HBV). Therefore, an additional benefit of any public health plan to reduce the burden of cancers caused by infections would involve a reduction in the incidence of other diseases as well.

Temporal changes in the incidence of infection-associated cancers are difficult to predict. Although there is evidence that the prevalence of infection with, for example, *Helicobacter pylori* and HBV is declining as a result of efficient antibiotic treatments and vaccination respectively, other important oncogenic infections remain uncontrolled. For instance, it is unclear how changes in the prevalence of infection with HIV, or indeed how the roll-out of effective antiretroviral treatments for this virus, will impact on the associated cancer burden. Furthermore, vaccination against HPV is still too expensive for many developing countries.

3. Mechanistic considerations

3.1 Specific tropism of the infectious agents leads to very specific cancers

The major distinctive feature of the biological agents as compared to other carcinogenic agents evaluated in the IARC monographs is that they are biological entities that have evolved to preferentially target specific host species, specific organs or cell types within those species, and often – in the case of viruses – even cell types with a specific differentiation status. As a result, cancers associated with viral infections are often very specific cancers, e.g. "adult T-cell leukaemia/lymphoma" associated with HTLV-1 and "extranodal NK/T-cell lymphoma (nasal type)" and "nasopharyngeal carcinoma," both associated with EBV. Cell type-specific tropism also applies to bacteria such as *Helicobacter pylori*, associated with "non-cardia gastric carcinoma," whereas worms such as liver

flukes or *Schistosoma haematobium*, associated with cholangiocarcinoma and urinary bladder cancer, respectively, only show organ-specific tropism.

3.2 Mechanisms of carcinogenesis

From the overall data summarized in this volume, three major mechanisms of carcinogenesis have been recognized for biological agents that could be defined either as direct, indirect (acting via chronic inflammation), or indirect (acting via immune-suppression). To fully exploit their carcinogenic potential, these agents have developed different strategies to evade the immune system. Finally, the data emphasize the potential role of cofactors, which are, however, largely understudied.

3.2.1 Direct carcinogens

Infectious agents can be direct carcinogens, and the ones known today are all viruses that fulfill the following criteria:
The viral genome or part of it can usually be detected in each cancer cell.
The virus can immortalize after the growth of target cells *in vitro*.
It expresses several oncogenes that interact with cellular proteins and have multifunctional properties leading to disruption of the cell-cycle checkpoints, inhibition of apoptosis and cell immortalization.

Four viral agents have been described as direct carcinogens: several types of the human papillomavirus family, the human T-cell lymphotropic virus type 1 (HTLV-1) and the two herpesviruses: Epstein-Barr virus (EBV) and Kaposi sarcoma- associated herpes virus (KSHV).

3.2.2 Indirect carcinogens that act via chronic inflammation

Infectious agents can be indirect carcinogens by causing chronic inflammation. Chronic infection followed by chronic inflammation will lead to the production of chemokines, cytokines, prostaglandins secreted by infected cells and/or inflammatory cells. This also leads to the production of reactive oxygen species – which have direct mutagenic effects – to the deregulation of the immune system, and to the promotion of angiogenesis, which is essential for tumour neovascularization and tumour survival.

Six infectious agents have been shown to be carcinogenic primarily by inducing chronic inflammation. Those are the two hepatitis viruses, HBV and HCV, the bacterium *Helicobacter pylori* and, the three worms *Schistosoma haematobium*, *Opistorchis viverrini*, and *Clonorchis sinensis*.

3.2.3 Indirect carcinogens that act via immune-suppression

Infectious agents can act as indirect carcinogens by causing immune-suppression. This has been shown for HIV-1 infection which strongly increases the incidence of many different human cancers. Strikingly, the majority of cancers associated with HIV-1 infection have another known infectious etiology, and HIV-1 infection increases their incidence rate considerably. Among these cancers, those associated with the herpesviruses KSHV and EBV are the most strongly enhanced by immune suppression. The same cancers are also increased by iatrogenic immune-suppression as shown by their increased incidence in transplant recipients, which lends additional support to the notion that HIV-1 acts as a carcinogen mainly through immune-suppression. These considerations may suggest that

other cancers whose incidence is increased by immune suppression (e.g. non-melanoma skin cancer) may also have an infectious etiology.

3.2.4 Contribution of additional factors

It is estimated that about 5% of HTLV-1 carriers when infected before the age of 20 years will potentially develop adult-T-cell leukaemia/lymphoma (Cleghorn et al., 1995). Likewise, only a small proportion of carriers of the high-risk human papillomavirus type 16 in the *cervix uteri* will develop cervical cancer. The fact that infection with these carcinogenic viruses does not always lead to cancer is a common feature for all the infectious agents that were studied strongly suggests the involvement of cofactors in the carcinogenic process. Carcinogenesis would result from the interaction of multiple risk factors including those related to the infectious agent itself (e.g. variants or subtypes), host-related factors (e.g. gene polymorphisms and immune status) and environmental cofactors (e.g. chemicals, ionizing radiation, immunosuppressive drugs, or another infection that may lead to reactivation of latent oncogenic viruses such as EBV or KSHV). The contribution of several of these additional factors to the development of infection-associated cancers is likely to be substantial, but has not yet been elucidated in detail.

4. Other remarks

4.1 The absence of a Section 3 "Cancer in Experimental Animals" in the Monographs on viruses

The Working Group decided not to include in this Volume a separate section on "Cancer in experimental animals" in the *Monographs* on viruses, but rather to include description of such studies under Section 4 "Other Relevant Data" for the following reasons:

- The use of animals as surrogate hosts for the study of a human tumour virus is often problematic since species-specificity limits the feasibility of this approach for most of these viruses. HTLV-1 is one exception: this virus can infect several different animal species (rabbits, rats and monkeys) but does induce adult T-cell leukaemia/lymphoma in monkeys only. For some human tumour viruses (e.g. KSHV), the use of humanized SCID mice, in which the human target cell for the virus is placed into a mouse host context, can provide a platform for in-vivo infection. However, apart from EBV, which causes lymphoproliferative diseases in New World monkeys and humanized SCID mice, the use of surrogate hosts has not proven very useful for assessing the carcinogenicity of human viruses in humans.
- Cancer models for human tumour viruses that make use of animal viruses are very scarce. In fact, although many viruses that infect non-human primate species are related to the human tumour viruses, the incidence of cancer is low in these species – as it is in humans – which makes cancer studies costly and difficult. Moreover, animal tumour virus models in non-primate species often do not accurately reflect the mechanism of the disease caused by the cognate human tumour virus. For instance, woodchuck hepatitis virus induces HCC that is histopathologically very similar to that caused by HBV in humans, but it does so through a different mechanism.
- Transgenic mouse models provide powerful means for performing mechanistic studies to investigate the role of individual viral genes in cancer. Indeed, for many of the human tumour viruses described in this volume, transgenic mouse studies provide critical mechanistic

evidence. However, such transgenic mouse models do not represent models for understanding the cancer etiology in the context of natural viral infections, and are therefore more appropriately discussed in Section 4.

4.2 Difficulties in assessing causality for some cancers

The Working Group acknowledged the difficulties of assessing causality, on the basis of epidemiological data, for certain rare cancer types in which presence of a specific infection was already been incorporated into the diagnostic criteria (e.g. HTLV-1 in relation to ATLL; KSHV and primary effusion lymphoma). In these instances, there was generally, but not always, convincing evidence for a causal relationship. Further epidemiological research on these cancers, often hampered by the rarity of the tumour, would require that currently accepted diagnostic criteria be reassessed.

4.3 Classification of weakly carcinogenic human papillomavirus types

Previous IARC Monographs summarized the considerable evidence showing that virtually all cases of cervical cancer are caused by persistent infections with a restricted set of human papillomaviruses. However, the carcinogenic potential of HPV types is very heterogeneous. Most are not carcinogenic. Some HPV types, like HPV 16 and HPV 18, are clear and powerful carcinogens. It is the categorization of the most weakly carcinogenic HPV types that is most challenging. The distinctions are important for screening tests and vaccine development. Carcinogenic types are targeted in HPV-screening assays to maximize sensitivity while others are excluded to preserve specificity. The types that are most carcinogenic are included in multivalent HPV vaccines to prevent the largest feasible fraction of cervical and other cancers. Thus, the Working Group made great efforts to consider the carcinogenic potential of each individual HPV type, with a strong emphasis on evolutionary relationships and detection within cases of invasive cancers (Schiffman et al., 2009).

A summary of the findings of this volume appears in *The Lancet Oncology* (Bouvard et al., 2009).

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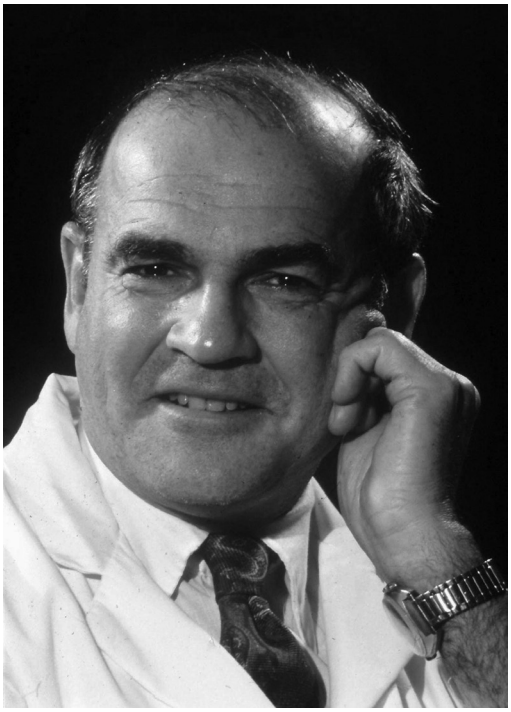

Baruch Blumberg (1925-2011)

Dr. Baruch Blumberg received the Nobel Prize in Physiology or Medicine in 1976 for his discovery of the hepatitis B virus, one of the agents discussed in this Volume.

Dr. Blumberg died on 5 April 2011.
We wish to commemorate his achievements in the development of an HBV vaccine and the promotion of blood testing, which allowed millions of lives to be saved worldwide.