

CONTENTS

NOTE TO THE READER	1
LIST OF PARTICIPANTS	3
PREAMBLE	
Background	9
Objective and Scope	9
Selection of Topics for Monographs.....	10
Data for Monographs	11
The Working Group	11
Working Procedures.....	11
Exposure Data.....	12
Studies of Cancer in Humans.....	14
Studies of Cancer in Experimental Animals.....	17
Other Data Relevant to an Evaluation of Carcinogenicity and Its Mechanisms.....	20
Summary of Data Reported	21
Evaluation	23
References.....	27
GENERAL REMARKS	31
INTRODUCTION	33
1. Structure of herpesviruses	33
1.1 The virion	33
1.2 Genomic organization.....	34
2. Taxonomy of herpesviruses.....	36
2.1 Alphaherpesviruses.....	37
2.2 Betaherpesviruses	39
2.3 Gammaherpesviruses.....	40
2.4 Current classification.....	40
3. Herpesviruses and human disease	41
THE MONOGRAPHS	
Epstein-Barr virus	47
1. Virus–host interactions.....	47
1.1 Structure, taxonomy and viral gene products	47
1.1.1 Structure.....	47

1.1.2	Taxonomy	47
1.1.3	Host range	48
1.1.4	Target cells.....	48
1.1.5	Genome, episomal and integrated virus forms and gene products	49
1.1.5.1	EBV-encoded RNAs	54
1.1.5.2	Nuclear proteins	55
	(a) EBNA-LP.....	56
	(b) EBNA-2	56
	(c) EBNA-3A, -3B, -3C	58
	(d) EBNA-1	58
1.1.5.3	Latent membrane proteins.....	59
	(a) LMP-1	59
	(b) LMP-2A and -2B	62
1.1.5.4	Other latent viral genes	62
1.1.5.5	Genes of the productive viral cycle.....	62
	(a) Immediate early genes	63
	(b) Early genes.....	64
	(c) Late genes	64
1.2	Methods of detection	65
1.2.1	Assays to detect antibodies to EBV	65
1.2.1.1	Immunofluorescence	65
1.2.1.2	Enzyme-linked immunosorbent assay.....	66
1.2.1.3	Immunoblotting.....	66
1.2.1.4	Complement fixation.....	67
1.2.1.5	Functional assays.....	67
1.2.2	Detection of EBV in tissues.....	67
1.2.2.1	Southern blot hybridization and the polymerase chain reaction	68
1.2.2.2	In-situ hybridization and immunohistochemistry	69
1.3	Biology of EBV infection.....	70
1.3.1	Target tissues	70
1.3.1.1	Infection <i>in vitro</i>	70
1.3.1.2	Infection of non-neoplastic cells <i>in vivo</i>	72
1.3.1.3	Infection in neoplasms	74
1.3.2	Persistence and latency	74
1.3.3	Immune responses	77
1.3.3.1	Antibody responses	77
1.3.3.2	Cell-mediated responses.....	78
1.4	Epidemiology of EBV infection.....	82
1.5	Clinical conditions other than malignancy	84
1.5.1	Infectious mononucleosis	84
1.5.2	Oral hairy leukoplakia	87
1.5.3	The X-linked lymphoproliferative syndrome	88

1.6	Control and prevention	88
1.6.1	Drugs.....	88
1.6.2	Prospects for vaccines.....	90
1.6.2.1	Selection of an EBV vaccine antigen molecule	91
1.6.2.2	Animal models of EBV infection, disease and vaccination	92
1.6.2.3	Natural gp350 subunit vaccines	93
1.6.2.4	Recombinant gp350 subunit vaccines	94
1.6.2.5	T- and B-cell epitopes on the gp350 molecule.....	95
1.6.2.6	Choice of adjuvant	96
1.6.2.7	Live virus–vector recombinants	96
1.6.2.8	Cell-mediated immune responses to gp350	98
1.6.2.9	Vaccines against EBV latent antigens.....	99
1.6.2.10	Conclusions	99
1.6.3	Passive immunotherapy	100
2.	Studies of cancer in humans	101
2.1	Burkitt's lymphoma	101
2.1.1	Clinical features and pathology	101
2.1.1.1	Clinical features.....	101
2.1.1.2	Gross pathology.....	104
2.1.1.3	Histological characteristics	105
2.1.2	Descriptive epidemiology.....	106
2.1.2.1	Historical aspects.....	106
2.1.2.2	Incidence	107
2.1.2.3	Climatic determinants	108
2.1.2.4	Time–space clustering.....	110
2.1.2.5	Familial cases	111
2.1.3	Epidemiology of Burkitt's lymphoma in association with EBV	111
2.1.3.1	Case series	112
	(a) African patients.....	112
	(b) Non-African patients.....	116
2.1.3.2	Case–control studies.....	118
	(a) African patients.....	118
	(b) Non-African patients.....	119
2.1.3.3	Cohort study	120
2.1.4	Cofactors.....	121
2.1.4.1	Malaria	121
	(a) Ecological studies	122
	(b) Relationship between Burkitt's lymphoma and sickle-cell trait.....	124
	(c) Intervention study	125
2.1.4.2	<i>Euphorbia tirucalli</i> and other medicinal plants.....	125
2.1.5	Molecular epidemiology	126

2.2	Non-Hodgkin's lymphomas other than Burkitt's lymphoma	127
2.2.1	Pathology	127
2.2.2	Epidemiology.....	127
2.2.2.1	Descriptive epidemiology	127
2.2.2.2	Case reports and case series	129
	(a) B-Cell non-Hodgkin's lymphoma	129
	(b) Angiocentric T-cell lymphoma	130
	(c) Other peripheral T-cell lymphomas	135
2.2.2.3	Cohort studies.....	138
2.2.3	Human immunodeficiency virus as a cofactor	138
2.2.3.1	Primary central nervous system lymphomas.....	139
2.2.3.2	Systemic non-Hodgkin's lymphomas	139
2.2.4	Congenital immunodeficiency syndromes	143
2.3	Hodgkin's disease.....	144
2.3.1	Pathology and clinical features	144
2.3.2	Epidemiology.....	145
2.3.2.1	Descriptive epidemiology	145
2.3.2.2	Association with EBV	148
	(a) Case reports and case series	148
	(b) Case-control studies	157
	(c) Cohort studies	162
2.4	Nasopharyngeal carcinoma.....	164
2.4.1	Clinical features and histopathology	164
2.4.1.1	Clinical features.....	164
2.4.1.2	Histopathology	165
2.4.2	Epidemiology.....	165
2.4.2.1	Descriptive epidemiology	166
	(a) International patterns	166
	(b) Migration	166
	(c) Sex and age	167
	(d) Race and ethnicity.....	168
	(e) Socioeconomic status.....	170
	(f) Urbanization.....	170
	(g) Time trends	170
	(h) Correlation with age-specific prevalence of EBV infection	171
2.4.2.2	Case series	172
	(a) Antibodies in sera and throat washings	172
	(b) Nucleic acid markers in carcinoma cells	173
	(c) Viral gene expression in tumour specimens	174
2.4.2.3	Case-control studies.....	175
	(a) Based on pre-diagnostic serological tests	175
	(b) Based on serological tests at time of diagnosis.....	175
2.4.2.4	Cohort studies.....	175

2.4.2.5	Mass serological surveys.....	177
2.4.3	Cofactors.....	179
2.4.3.1	Dietary factors.....	179
	(a) Cantonese-style salted fish.....	179
	(b) Other types of salted fish.....	183
	(c) Other preserved foods.....	183
	(d) Deficits of fresh vegetables and fruit.....	185
2.4.3.2	Other environmental factors.....	185
	(a) Fumes, smoke and dust.....	185
	(b) Formaldehyde.....	187
	(c) Tobacco.....	189
	(d) Alcohol.....	191
	(e) Herbal drugs.....	191
	(f) Incense and anti-mosquito coils.....	192
	(g) Chinese nasal oil.....	193
2.4.3.3	Host factors.....	193
2.4.3.4	Familial aggregation.....	194
2.5	Comparison of characteristics of Burkitt's lymphoma, Hodgkin's disease and nasopharyngeal carcinoma.....	194
2.6	Other malignancies.....	194
2.6.1	Lymphoepithelial carcinomas outside the nasopharynx.....	194
2.6.2	Other carcinomas.....	201
	2.6.2.1 Stomach.....	201
	2.6.2.2 Other sites.....	203
2.6.3	Smooth-muscle tumours.....	204
2.6.4	Other tumours.....	205
3.	Studies of cancer in animals.....	205
3.1	EBV in non-human species.....	205
3.1.1	Infection of non-human primates with EBV.....	205
	3.1.1.1 New World primates.....	205
	3.1.1.2 Old World primates.....	207
3.1.2	Transformation of monkey cells by EBV <i>in vitro</i>	207
3.1.3	Rodent models for EBV infection and pathogenesis.....	207
	3.1.3.1 Severe combined immunodeficiency (SCID) mouse model.....	207
	3.1.3.2 Nude mouse model.....	208
3.2	EBV-like viruses isolated from non-human primates.....	208
3.2.1	<i>Herpesvirus papio</i> (cercopithecine herpesvirus 12).....	209
	3.2.1.1 Cell lines, persistence and transformation.....	210
	3.2.1.2 Prevalence of infection with <i>Herpesvirus papio</i>	210
	3.2.1.3 Molecular biology.....	210
	3.2.1.4 Pathogenesis and immune response to <i>Herpesvirus papio</i>	211

3.2.2	Gamma-1 herpesvirus from cynomolgus monkey (<i>Macaca fascicularis</i>)	212
3.2.3	Rabbit model of malignant lymphoma induced by EBV-like virus from <i>Macaca arctoides</i>	212
3.3	Other models of relevance to EBV	212
3.3.1	Murid herpesvirus 4	212
3.3.2	Marek's disease	212
4.	Other data relevant to an evaluation of carcinogenicity and its mechanisms	214
4.1	Growth transformation	214
4.1.1	Role of EBV	214
4.1.2	Minimal set of transforming genes	214
4.1.3	Growth transformation <i>in vitro</i> and induction of lymphoproliferation <i>in vivo</i>	215
4.1.4	Viral transcription pattern after infection of human primary B lymphocytes by EBV	215
4.1.5	Viral proteins involved in growth transformation	216
4.1.5.1	EBNA-1	216
4.1.5.2	EBNA-LP	217
4.1.5.3	EBNA-2	217
4.1.5.4	EBNA-3A, -3B and -3C	219
4.1.5.5	LMP-1	219
4.1.5.6	LMP-2A and -2B	220
4.1.6	Cellular genes induced during growth transformation by EBV	220
4.2	Burkitt's lymphoma	221
4.2.1	Molecular abnormalities in relation to the tumour-cell precursor	221
4.2.1.1	Translocation of the <i>c-myc</i> oncogene	221
4.2.1.2	The Burkitt's lymphoma-cell phenotype resembles that of a germinal-centre cell	223
4.2.1.3	Mutations in <i>p53</i> in Burkitt's lymphoma	224
4.2.2	EBV infection in Burkitt's lymphoma	224
4.2.2.1	EBV is monoclonal in Burkitt's lymphoma	224
4.2.2.2	Integration of viral DNA in Burkitt's lymphoma cells	225
4.2.2.3	Expression of EBV genes in EBV-associated Burkitt's lymphoma	225
4.2.2.4	Expression only of EBNA-1 is associated with reduced immunogenicity	225
4.2.2.5	The proliferation programme driven by <i>c-myc</i> -immunoglobulin is incompatible with expression of EBNA-2 and LMP-1 in the type-III latency programme	226
4.2.2.6	Contribution of the viral strategy for latent persistence to lymphomagenesis	227
4.2.2.7	EBNA-1 subtypes	227
4.2.3	Effects of malaria on B-cell activation and EBV infection	227
4.2.4	Plant products	228

4.2.5	Genetic disposition	229
4.2.6	Burkitt's lymphoma in AIDS patients	229
4.3	Other non-Hodgkin's lymphomas and lymphoproliferative conditions	230
4.3.1	Immunosuppressed patients	230
4.3.1.1	Primary immune defects due to genetic abnormalities with EBV-positive lymphoproliferation as one consequence	230
4.3.1.2	Post-transplant lymphoproliferative disorders	231
4.3.1.3	AIDS	234
	(a) Viral factors	234
	(b) Disturbances of immunity as cofactors	235
	(c) Oncogenes and genetic abnormalities as possible cofactors	236
	(d) Pathogenesis of EBV-associated, AIDS-related non-Hodgkin's lymphoma: A scenario	237
4.3.2	T-Cell lymphomas	237
4.4	Hodgkin's disease	238
4.5	Nasopharyngeal carcinoma	240
4.5.1	EBV infection	240
4.5.1.1	Molecular and biochemical studies	240
4.5.1.2	EBV expression	241
4.5.1.3	Phenotype and cellular gene expression	242
4.5.1.4	EBV infection and transformation of epithelial cells <i>in vitro</i>	243
4.5.1.5	Detection of EBV infection in normal, premalignant and malignant nasopharyngeal tissues	244
4.5.1.6	Strain variation	246
4.5.2	Contribution of environmental and genetic factors	248
4.5.2.1	Dietary cofactors	248
	(a) Experiments in rodents	248
	(b) High-risk populations	249
4.5.2.2	Genetic factors	250
4.6	Other malignancies, including lymphoepithelial carcinomas	251
4.7	Immune responses and EBV-associated malignancies	253
4.7.1	B-Cell lymphoma and other tumours associated with severe immunosuppression	253
4.7.2	Burkitt's lymphoma	253
4.7.3	Hodgkin's disease	254
4.7.4	Nasopharyngeal carcinoma	254
5.	Summary of data reported and evaluation	255
5.1	Virus-host interactions	255
5.2	Human carcinogenicity	256
5.2.1	Burkitt's lymphoma	257
5.2.2	Non-Hodgkin's lymphomas	257

5.2.3	Hodgkin's disease.....	258
5.2.4	Nasopharyngeal carcinoma.....	258
5.2.5	Other tumours	258
5.3	Studies of cancer in animals	259
5.4	Other relevant data.....	259
5.4.1	Burkitt's lymphoma.....	260
5.4.2	Non-Hodgkin's lymphomas and lymphoproliferation.....	260
5.4.3	Hodgkin's disease.....	261
5.4.4	Nasopharyngeal carcinoma.....	261
5.4.5	Other malignancies, including lymphoepithelial carcinomas.....	262
5.5	Evaluation.....	262
6.	References	262
Kaposi's sarcoma herpesvirus/human herpesvirus 8		375
1.	Virus-host interactions.....	375
1.1	Taxonomy, structure and biology.....	375
1.1.1	Taxonomy.....	375
1.1.2	Structure.....	375
1.1.2.1	Morphology.....	375
1.1.2.2	Genomic structure and properties of gene products.....	376
	(a) Terminal-repeat region	378
	(b) Long unique region.....	378
1.1.3	Strain variation.....	379
1.1.4	Host range.....	384
1.1.5	Related non-human viruses.....	384
1.1.6	Tropism and persistence of infected cells <i>in vivo</i>	384
	1.1.6.1 Persistence and gene expression in infected endothelial cells.....	386
	1.1.6.2 Persistence in haematopoietic cells	387
	1.1.6.3 Presence in other tissues.....	387
1.2	Methods of detection	388
1.2.1	Nucleic acids	388
1.2.2	Serology.....	389
1.2.3	Culture <i>in vitro</i>	391
1.3	Epidemiology of infection	392
1.3.1	Prevalence in peripheral blood mononuclear cells	392
1.3.2	Prevalence in semen	392
1.3.3	Seroprevalence and geographical distribution.....	393
1.3.4	Routes of transmission.....	394
1.4	Control and prevention	395
2.	Studies of cancer in humans.....	395
2.1	Kaposi's sarcoma.....	395
2.1.1	Pathology and clinical disease	396
	2.1.1.1 Epidemiological and clinical presentation	396

2.1.1.2	Histology	397
2.1.2	Epidemiology.....	397
2.1.2.1	Incidence and geographical distribution	397
2.1.2.2	Demographic variations	400
2.1.2.3	Behavioural factors	400
2.1.2.4	Second primary malignancies after Kaposi's sarcoma	402
2.1.3	Case series and case-control studies	402
2.1.3.1	Detection of KSHV/HHV8 DNA in tumour tissue	402
2.1.3.2	Detection of KSHV/HHV8 DNA in peripheral blood mononuclear cells.....	410
2.1.3.3	Detection of KSHV/HHV8 DNA in other tissues.....	413
2.1.3.4	Serology	413
2.1.4	Temporal associations	420
2.2	Lymphoproliferative disorders	421
2.2.1	Primary effusion lymphomas.....	421
2.2.1.1	Pathology and clinical presentation.....	421
2.2.1.2	Descriptive epidemiology	424
2.2.1.3	Case reports and case series	425
2.2.2	Castleman's disease	425
2.2.2.1	Pathology and clinical presentation.....	425
2.2.2.2	Descriptive epidemiology	430
2.2.2.3	Case reports and case series	430
2.2.3	Multiple myeloma.....	432
2.2.4	Other lymphoproliferative disorders.....	432
2.3	Other tumours	433
3.	Studies of cancer in animal models	433
3.1	<i>Herpesvirus saimiri</i> (saimiriine herpesvirus 2)	433
3.1.1	Description.....	433
3.1.2	Host range, virus isolation and virus multiplication.....	434
3.1.3	Host response: antibody detection	435
3.1.4	Human exposure	435
3.1.5	Molecular aspects	435
3.1.6	Oncogenicity in non-human primates, rabbits and transgenic mice	436
3.1.7	Transformation of mammalian cells <i>in vitro</i>	437
3.2	<i>Herpesvirus ateles</i> (ateline herpesvirus 2).....	438
3.2.1	Description.....	438
3.2.2	Host range, cytopathogenicity and viral multiplication.....	438
3.2.3	Molecular analysis	438
3.2.4	Oncogenicity in non-human primates.....	438
3.3	Bovine herpesvirus 4 (Movar herpesvirus)	439
3.3.1	Classification	440
3.3.2	Description.....	440
3.3.3	Host range.....	441

3.3.4	Natural transmission	443
3.3.5	Evidence that bovine herpesvirus 4 causes disease	443
3.3.6	Isolates	444
3.4	Murid herpesvirus 4	445
3.5	Retroperitoneal fibromatosis herpesviruses.....	445
4.	Other data relevant to an evaluation of carcinogenesis and its mechanisms.....	446
4.1	Kaposi's sarcoma.....	446
4.1.1	Cell biology	446
4.1.1.1	Origin of spindle cells	446
4.1.1.2	Vascular lesions induced by Kaposi's sarcoma cell cultures in nude mice.....	447
4.1.1.3	Growth factors involved in proliferation of spindle cells ..	448
	(a) Fibroblast growth factors	448
	(b) Platelet-derived growth factor	448
	(c) Interleukin-1.....	449
	(d) Interleukin-6.....	449
	(e) Tumour necrosis factor α	449
	(f) Miscellaneous growth factors	449
4.1.1.4	Role of HIV-1 Tat in promoting Kaposi's sarcoma lesions.....	449
4.1.1.5	Clonality of Kaposi's sarcoma lesions	450
4.1.2	Role of KSHV/HHV8 in development of Kaposi's sarcoma	451
4.2	Primary effusion lymphomas.....	452
4.3	Multicentric Castleman's disease	452
4.4	Viral genes with cellular growth promoting or oncogenic potential	453
4.4.1	<i>Open reading frame K1</i>	453
4.4.2	Growth factor homologues	454
4.4.3	<i>bcl-2</i> homologue	454
4.4.4	Viral interferon regulatory factor.....	455
4.4.5	Viral proteins that inhibit fas-associated death domain protein interleukin-1 β converting enzyme (FLICE)	455
4.4.6	Viral cyclin	456
4.4.7	Latency-associated nuclear antigen	456
4.4.8	G Protein-coupled receptor homologue.....	457
4.5	Summary of potential roles of KSHV/HHV8 in tumorigenesis	457
4.5.1	Kaposi's sarcoma.....	457
4.5.2	Primary effusion lymphoma	458
4.5.3	Multicentric Castleman's disease	459
4.6	Antiviral agents.....	459
5.	Summary of data reported and evaluation.....	460
5.1	Virus-host interactions	460
5.2	Human carcinogenicity.....	461
5.3	Animal models	462
5.4	Molecular mechanisms of carcinogenesis	462

CONTENTS

xiii

5.5 Evaluation.....	463
6. References	463
ABBREVIATIONS.....	493
SUPPLEMENTARY CORRIGENDA TO VOLUMES 1–69.....	495
CUMULATIVE INDEX TO THE <i>MONOGRAPHS</i> SERIES.....	497

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean the probability that exposure to an agent will lead to cancer in humans.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.