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BIENNIAL REPORT

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International Agency for Research on Cancer

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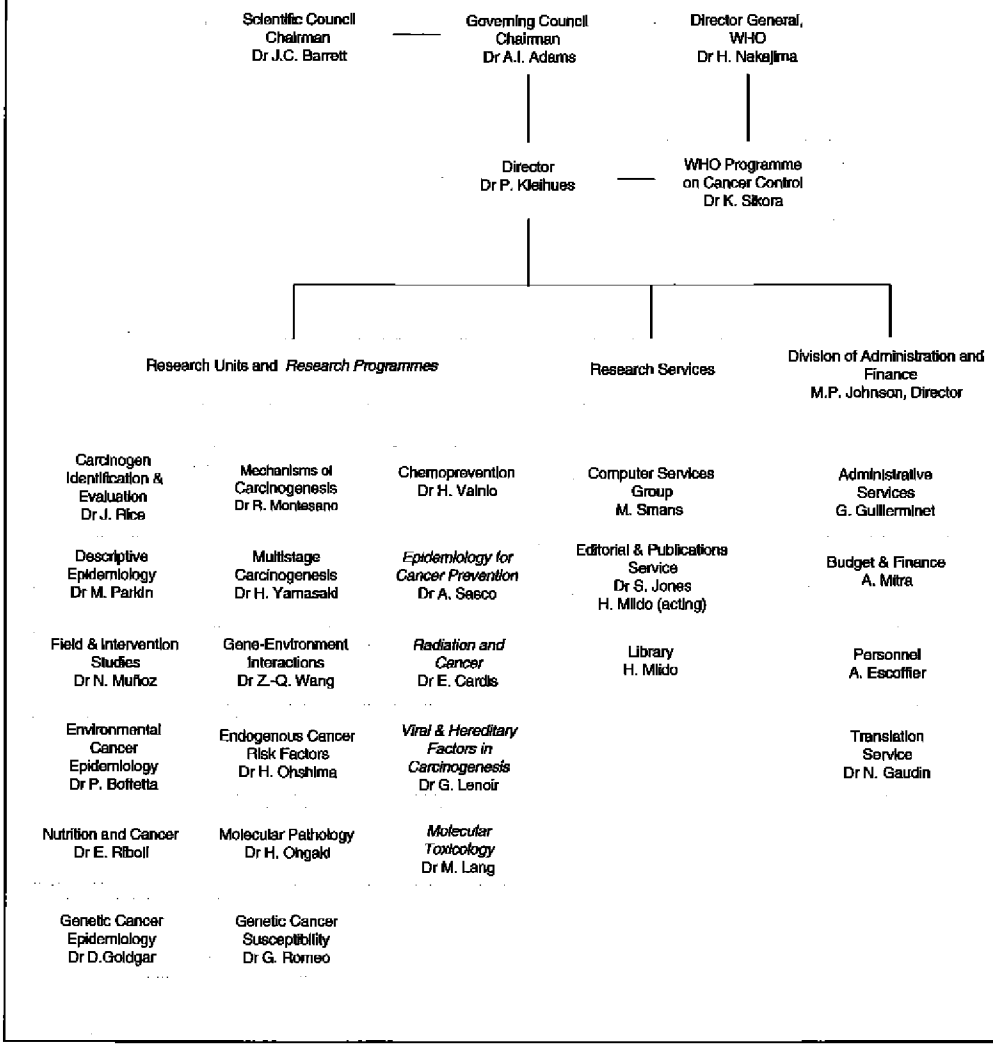
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)



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INTRODUCTION

This biennial report covers two calendar years, from 1 January 1996 to 31 December 1997. Its main objective is to report on IARC's scientific achievements during that period and, as far as this can be assessed, on the impact of the Agency's work on public health. Despite considerable progress in the treatment of some cancers, the overall cancer mortality worldwide has not shown any significant reduction. Epidemiologists, clinicians and public health authorities now acknowledge that we are unlikely ever to achieve this goal without a stronger emphasis on primary prevention, and this is indeed the area towards which the Agency's work has always been targeted. The present report provides further insight into avoidable cancer risks and many of our research results are suitable for public health application.

Geographic variations in cancer occurrence

We are witnessing, in many parts of the world, a dramatic shift of disease patterns, characterized by a reduction in mortality from infectious diseases and an increased burden of non-communicable diseases, in particular, cancer, cardiovascular diseases and diabetes. In several newly industrialized regions, cancer has become one of the leading causes of death. In the 1997 World Health Report, the Director-General of WHO stressed the necessity to devote more attention and resources to non-communicable diseases. This report also pointed out that during a transitional period, several regions of the world will face a double burden, i.e., a disease pattern resulting from traditional exposures and health risks and, at the same time, adverse health effects resulting from their new lifestyle, in particular smoking and a 'western' diet rich in calories and animal fat. These changes have been predicted by cancer epidemiologists for many years, but we have been surprised by the speed at which they are occurring. Examples are the emergence of cancer of the breast, colon and prostate in several countries in which these neoplasms were almost unknown only 30 years ago. These developments are documented in Volume VII (1997) of IARC's flagship epidemiological publication, *Cancer Incidence in Five Continents*, which covers the years 1988–92 and contains data from 182 populations in 50 countries. For the first time, we were able to include data from registries in Korea, Viet Nam, Argentina and Uruguay. This compilation of data is also available in an electronic form that allows rapid estimation and regional comparison of cancer incidence through visual display of charts, tables and maps.

The contribution of childhood tumours to the overall cancer burden is less than 1%, but these neoplasms constitute a challenge for treatment, which may be life-saving at the cost of long-lasting adverse health effects. Very little is known about their etiology. Volume 2 of *International Incidence of Childhood Cancer* contains data from 121 registries in 56 countries and provides a knowledge base for researchers and clinicians alike.

Survival of cancer patients

The first comprehensive, population-based study on *Survival of Cancer Patients in Europe (EUROCARE)* was released by the Agency in 1995 and evoked a strong reaction in the public health community, since it documented surprisingly large differences even between highly developed countries. This provided an incentive to look for possible weaknesses in national programmes for prevention, early detection and treatment.

A revised and extended publication is in preparation. In the meantime, the Agency has also compiled data on survival from cancer in developing countries. In comparison to western Europe and North America, large differences still exist for cancers that can be successfully treated by chemotherapy (malignant lymphomas, leukaemia, testicular tumours). Modest differences are observed for neoplasms that can be cured by early detection and surgical intervention, while no significant difference is seen in survival from tumours largely refractory to therapy, such as carcinomas of the pancreas, lung and liver. These data allow calculation of the prevalence of organ-specific neoplasms in a given country and provide a basis for national cancer control strategies, to be pursued in collaboration with the WHO Programme on Cancer Control.

Environmental carcinogens

Chemical carcinogens remain an important factor in the causation of human cancer and these include medicinal drugs. Volume 66 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains evaluations of a variety of benzodiazepines widely used as sedatives and in the treatment of anxiety, and of phenytoin, a drug that has been used for decades to treat epilepsy. Oxazepam and phenytoin were classified as possibly carcinogenic to humans (Group 2B), mainly on the basis of their hepatocarcinogenicity in rodents.

The international toxicology and public health community paid much attention to the Agency's evaluation of polychlorinated dibenzodioxins and dibenzofurans, which are inadvertently formed in the production and use of polychlorinated biphenyls (PCBs), and also in a variety of thermal processes. At very low levels, they constitute an unavoidable contaminant of the environment. The IARC working group classified the most notorious member of this class of chemical agents, 2,3,7,8-TCDD ('dioxin') as carcinogenic to humans (Group 1), mainly on the basis of epidemiological studies showing an increased overall risk of human cancer, most notably lung cancer.

Following a scientific meeting on mechanisms of fibre carcinogenesis in January 1996, another working group evaluated the available evidence regarding the carcinogenicity of silica and related dusts, and reached the consensus that crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans (Group 1).

The identification of carcinogens and their elimination from the workplace have led to a marked decline in occupational cancer worldwide, but for several exposures, a causative link to human cancer has not yet been established. IARC scientists have coordinated several analytical epidemiological studies on the adverse health effects of exposure to styrene, man-made vitreous fibres and inorganic mercury, and in workers employed in the paper, wood, leather and asphalt industries and in biological research laboratories.

International collaborative studies have been initiated to evaluate the carcinogenic effects in Chernobyl accident recovery workers and on the ethiopathogenesis of thyroid cancers in children and adolescents.

Tobacco remains the most widely disseminated carcinogen, with an annual death toll of about 3.5 million, that has been estimated as likely to increase to 10–12 million annually by the year 2020. Only few countries have, through a combination of health education and legislative measures, succeeded in reducing tobacco consumption, and have seen a corresponding incipient decline in tobacco-associated cancer and cardiovascular disease. In many regions of the world, however, tobacco consumption is on the increase and thus constitutes one of the major health threats for future generations. IARC activities during the past biennium have concentrated on a variety of

problems related to tobacco consumption, ranging from study of genetic polymorphisms predisposing to tobacco-related cancer of the bladder and pancreas, to dietary phenolics as anti-mutagens in tobacco-related urothelial tumours and epidemiological studies on tobacco use and mortality in India and Africa. Noting a worldwide increase in the prevalence of smoking among adolescents, IARC scientists have also carried out studies on health habits in young people and on the efficacy of various anti-smoking strategies. A major epidemiological study on environmental tobacco smoke has been completed and revealed a significant dose–response relationship between passive smoking (from a smoking spouse or at the workplace) and lung cancer, providing further evidence that passive smoking does indeed carry a significant health risk.

Cancers associated with chronic infections

There is firm evidence that chronic infections caused by oncogenic viruses, bacteria (*Helicobacter pylori*) and parasites (liver flukes, schistosoma) contribute significantly to the causation of cancer in humans. IARC epidemiologists have estimated that in developing countries, up to 20% of all human neoplasms develop in association with chronic infections. For this reason and because of the interaction of infectious agents with chemical carcinogens, biological agents have been included in the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* In the past biennium, working groups concluded that there is sufficient evidence to classify infection with human immunodeficiency virus (HIV-1), human T-cell lymphotrophic virus (HTLV-1), and Epstein–Barr virus (EBV) as carcinogenic to humans while the Kaposi's sarcoma-associated herpes virus 8 was classified as probably carcinogenic (Volumes 67 and 70).

The Agency's Unit of Field and Intervention Studies provided additional evidence for the causative relationship between chronic infection with human papillomavirus (HPV) and cervical cancer. It was shown that the risk of developing this neoplasm is closely related to sexual behaviour of both women and their male partners. Multi-centre case–control studies clearly show a cervical cancer risk associated with several human papillomavirus types in addition to types 16 and 18. There is circumstantial evidence that HPV 18 is closely associated with adenocarcinoma, while HPV 16 and its variants more frequently relate to squamous cell carcinoma of the cervix.

Nutrition and cancer

Epidemiological studies strongly suggest that in western countries, more than 30% of tumours are associated with dietary habits, but the nutritional components modulating malignant transformation, e.g. in the breast, colon and prostate, are still ill-defined and the biological basis of these effects is poorly understood. EPIC, the Agency's major epidemiological study on nutrition and cancer, addresses these questions. Seventeen centres from seven European countries participate in this prospective study, in which recording of dietary habits, nutritional and anthropomorphic status, lifestyle and environmental factors is combined with laboratory investigations. By the end of 1997, more than 440 000 individuals had been recrui ted and already more than 340 000 blood samples have been deposited at the Agency for long-term storage in liquid nitrogen. Biochemical analyses of serum samples have begun and it is anticipated that in 1998, data on the most frequent cancer sites will begin to be collected and evaluated.

Cancer genetics

A new Unit of Genetic Cancer Epidemiology was established in January 1996, headed by Dr David Goldgar, who

previously worked at the University of Utah. He was involved in the discovery of the first two breast cancer susceptibility genes (*BRCA1*, *BRCA2*) and provided crucial data on the familial clustering of breast tumours that pointed, through linkage analysis, to the precise chromosomal location and identification of the genes. Mutations in the *BRCA1* and *BRCA2* genes show regional and ethnic variation. Together with the Programme of Viral and Hereditary Host Factors, the genetic epidemiology unit is setting up an international study to examine the frequency and type of breast cancer gene mutations in various parts of the world, including countries for which adequate data are not yet available. Information on the occurrence of such mutations is important for the estimation of genetic cancer risks and for early breast cancer detection.

Considerable progress has been made towards identification of the gene underlying the X-linked lymphoproliferative disease (XLP), which is associated with a very high sensitivity to Epstein–Barr virus infection. The XLP gene has been mapped and the candidate XLP genomic region at Xq25 encompassing a 130 kB deletion sequenced. More than 50 potential exons have been identified but so far, disease-associated mutations have not been identified.

The Unit of Genetic Cancer Susceptibility is also investigating genetic predisposition to papillary thyroid carcinoma (PTC), the prevalence of which has increased enormously among children and adolescents in some regions of Belarus and Ukraine following the Chernobyl accident. Linkage studies in some pedigrees have confirmed the hypothesis that predisposition to PTC is polygenic and genetically heterogeneous.

Gene–environment interactions and genomic integrity

In February 1997, Dr Zhao-Qi Wang was appointed chief of the former Unit of Environmental Carcinogenesis, previously headed by Dr Christopher Wild, who early in 1996 left the Agency to become professor of molecular epidemiology at the University of Leeds, UK. Dr Wang conducted his graduate studies in cell biology at the Peking Union Medical College. In 1988, he worked at the European Molecular Biology Laboratories (EMBL) in Heidelberg and later joined the developmental biology group of Dr Erwin Wagner at the Research Institute of Molecular Pathology (IMP) in Vienna. Dr Wang has extensive expertise in the use of genetically modified animals for the identification of gene function. Currently, his group is elucidating the biological role of the genes responsible for DNA repair and recombination, including the gene encoding poly(ADP-ribose) polymerase (*PARP*). Immunodeficient SCID mice that lack PARP activity show a high frequency of T-cell lymphomas. This unit will focus increasingly on the role of environmental factors in the evolution of tumours in animals in which cancer-associated genes are overexpressed or disrupted. To reflect this broader approach to environmental carcinogenesis, the Unit has been renamed the Unit of Gene–Environment Interactions.

Several studies by other IARC units have shown that genetic polymorphisms can significantly influence the process of malignant transformation and that in patients with genetic predisposition, environmental and lifestyle factors still play an important role by either accelerating or delaying the clinical manifestation of neoplasms.

Organ-specific carcinogenesis

Over the past decade, it has been clearly established that the process of malignant transformation involves the sequential acquisition of genetic alterations which typically lead to overexpression of transforming genes (oncogenes) or inactivation of tumour-suppressor genes. However, the type and sequence of genes concerned varies considerably between organs and target cells. The

elucidation of this process is a major research focus at the Agency, since it would provide a molecular basis for possible intervention strategies, including gene therapy.

Oesophageal carcinomas have a regionally distinct etiology and molecular genetic analyses have revealed that this is associated with a distinct pattern of mutations of the *p53* gene. Squamous cell carcinomas associated with tobacco and alcohol abuse frequently contain transversions on guanine or adenine, while in adenocarcinomas that develop in connection with chronic oesophagitis and Barrett's oesophagus, GC →AT transitions prevail.

Bladder cancer also has a variety of etiologies, with tobacco smoking as the principal cause. Even in Egypt, where there is a high prevalence of schistosome infection, the majority of cases are tobacco-related carcinomas. Molecular analyses have not yet identified genetic alterations specifically associated with bladder cancer risk factors such as tobacco, phenacetin or schistosome infection.

Glioblastomas, the most common and malignant brain tumours, develop through different genetic pathways. Primary (*de novo*) glioblastomas typically show overexpression of the EGF receptor and, less frequently, PTEN mutations, *p16* deletions and *MDM2* overexpression. In contrast, secondary glioblastomas that develop from low-grade astrocytomas carry *p53* mutations as a genetic hallmark. GC →AT transition mutations at GpC sites prevail, indicating endogenous formation rather than causation by environmental mutagens.

In some regions, the incidence of *head and neck cancer* is dramatically elevated due to alcohol plus tobacco abuse (central and eastern Europe, Asia) or tobacco chewing (India). In addition, in several studies, infection with HPV has been detected in a significant fraction of cases of carcinoma of the oral cavity. The role of HPV infection in oral cancer etiology and its interaction with other risk factors are being investigated in a multinational molecular epidemiology study.

IARC studies on *skin cancer* have concentrated on the role of ultraviolet-induced *p53* gene mutations in preneoplastic keratinocytes. Using an ultrasensitive PCR-based assay, it was shown that CC→TT tandem mutations are predictors of basal cell carcinoma but do not reflect total UV exposure. Telomerase activation appears to be an early event in skin cancer, possibly preceding the acquisition of *p53* mutations.

Molecular toxicology

The Programme of Molecular Toxicology has made important contributions to the role of cytochrome P450 (CYP) and related carcinogen-metabolizing enzymes in the process of carcinogenesis. It has been shown that toxic or infectious liver injury induces CYP2A5, which could explain the induction of cholangiocarcinomas of the liver by parasites (liver flukes) and of hepatocellular carcinomas by the murine *Helicobacter hepaticus* and the synergistic effects of hepatitis B and aflatoxin B_1.

In April 1997, the head of this programme, Dr Matti Lang, left the Agency to become professor of biochemistry at the University of Uppsala, Sweden. He remains engaged in several on-going collaborative projects. The Scientific Council has recommended using the resources of this programme for the establishment of a young investigator's group. A decision on the scientific direction of this group will be taken in 1998.

Tumour biology

Several studies focus on the role of DNA repair enzymes in carcinogenesis and response to radiotherapy. Heterozygous carriers of a mutation in the ataxia telangiectasia (ATM) gene apparently have an increased risk for breast cancer. Such patients may also present with an acute or late overreaction to

radiotherapy and this can be predicted from the response of lymphoblastoid cell lines derived from these patients. A similar abnormal response to ionizing radiation was observed in cells from patients with the inherited Nijmegen breakage syndrome and appears to be due to an abnormal *p53*-mediated response to DNA damage. Functional loss of DNA mismatch repair manifests as genomic microsatellite instability and plays a role in some human neoplasms (e.g., inherited colon cancer) and *in vitro* studies showed that microsatellite instability may greatly enhance vulnerability to environmental carcinogens. This effect was enhanced in cells lacking gap-junctional intercellular communication (GJIC) but could be mitigated by transfection with the connexin 43 gene. Connexins are capable of tumour suppression and screening of human neoplasms has revealed several polymorphisms in connexin genes, but mutations appear to be rare and to date no inherited tumour syndrome caused by a germline connexin mutation has been identified.

The IARC database on *p53* mutations is extensively used by scientists worldwide and has been extended to include germline mutations. Biochemical studies have revealed that binding of the p53 protein to DNA is stabilized by zinc ions and that metal chelators modulate p53 conformation and activity. Studies with tumour necrosis factor (TNF-α) and nitric oxide suggest that free radicals can modulate the function of this important tumour-suppressor gene. There is further evidence that oxidative stress is associated with chronic infections, e.g. of the gastric mucosa. Eradication of *H. pylori* infection leads to a significant reduction in the expression of inducible nitric oxide synthase in the gastric mucosa.

Prevention and early detection

The most ambitious project of the Agency in the domain of primary cancer prevention is the Gambia Hepatitis Intervention Study, that was launched in 1986 with the goal of determining the extent to which the occurrence of primary hepatocellular carcinoma can be reduced in a high-prevalence country by preventing chronic viral hepatitis. A total of 122 577 children were vaccinated against hepatitis B virus (HBV) and at age 9 years, 83% were still free of infection and 94% free of the chronic carrier state. The children will be followed up for a further 25 years to reliably assess the net effect of vaccination in disease prevention in comparison to other causative factors such as aflatoxin B_1 exposure.

The Agency currently co-ordinates intervention studies on precancerous lesions of the stomach (β-carotene, vitamins C and E) and oral cancer (vitamin A). Due to adverse effects observed in some studies, smokers and recent ex-smokers were switched to placebo or excluded from these trials. Protocols have been designed for clinical trials to test the safety and efficacy of vaccination against HPV infection in high-prevalence regions, as soon as vaccines are available and approved for clinical studies. Successful HPV vaccination constitutes one of the most promising strategies for cancer prevention in women.

Cancer chemoprevention

In May 1996, a new Unit of Chemoprevention was established, headed by Dr Harri Vainio, previously Chief of the Unit of Carcinogen Identification and Evaluation. The motivation for creation of this unit was the increasing possibility to identify members of the population who are at increased cancer risk due to, for example, genetic predisposition, past exposure to carcinogens or the occurrence of a tumour at a site where multiple primary tumours are frequent. It was felt insufficient to advise such individuals to undergo regular tests for early cancer detection. Natural products, micronutrients and drugs have been screened for their capacity to either prevent formation of

tumours or to delay the clinical manifestation of a tumour by interference with the malignant progression of initiated cells. As a first stage, the unit is evaluating cancer-preventive agents with international working groups in a manner similar to that of the *IARC Monographs on Evaluation of Carcinogenic Risks to Humans*. Experts in the field are invited to the Agency to form a consensus evaluation focusing on (i) whether a given compound has been proven to be cancer-preventive and (ii) whether there are adverse side-effects, including carcinogenicity. The outcome of the first meeting on aspirin and related non-steroidal anti-inflammatory drugs was published in September 1997 as Volume 1 of the new book series *IARC Handbooks of Cancer Prevention.* Although more than 20 observational studies suggest that regular aspirin intake reduces the risk of colon cancer in humans, the working group judged the evidence to be limited, mainly because of a lack of reliable information on dose and length of treatment, and recommended that controlled trials be conducted to address these questions. A second meeting was held in December 1997 on cancer prevention by carotenoids. It is anticipated that in the long run, this unit will also become engaged in laboratory research on mechanisms of cancer chemoprevention.

Publications

During 1996–97, IARC staff authored a total of 527 publications. Of these, 328 (62%) were published in critically edited, peer-reviewed journals, including many with a very high international reputation and impact. Our staff further contributed 114 book chapters and edited 49 books. During the same period, the Agency published five volumes of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* eleven volumes of the series *IARC Scientific Publications* and the first volume of the new series *IARC Handbooks of Cancer Prevention.* Realizing the need to present complex epidemiological data in a graphics-oriented, electronic form, the first two volumes of a new series *IARC CancerBase* were produced in-house and released, one on Cancer in the European Union (EUCan90), the other as an electronic version of Volume VII of *Cancer Incidence in Five Continents* (CI5VII).

The Agency has a long tradition in the publication of books on tumour pathology in animals; the series on the histology and classification of tumours of the rat, mouse and hamster were concluded in 1997. At the same time, the first IARC book on human pathology was published under the title *Pathology and Genetics of Tumours of the Nervous System*. If successful, a series on the pathology and genetics of various types of human cancer may emerge.

In addition to WHO Headquarters and Oxford University Press, IARC publications are now also promoted and distributed by IARC*Press,* a small in-house office that excels in rapidly satisfying the needs of mail-order customers worldwide.

Fellowships and training courses

The IARC Cancer Research Fellowship Programme continues to award some 12 postdoctoral fellowships per year to bright young scientists who wish to obtain further training in an outstanding research institution abroad. In future, similar selection criteria will be used for all post-doctoral fellows who plan to work at the Agency on a fellowship paid from the IARC regular budget.

During the past biennium, the Agency conducted eight training courses, mainly on cancer epidemiology. A first course on cancer genetics was held 1996 in Sestri Levante (Italy) and repeated in 1997. The response from students and faculty was very positive and the course may become an annual event, similar to the IARC summer school on cancer registration and epidemiology in Lyon.

Investment in new instrumentation

With the generous support of the Governing Council, the Agency has been able to continue updating its scientific instrumentation. In 1996, we thus acquired an instrument for automatic screening and sorting of cancer cells *in vitro* by fluorescence-activated cell sorting (FACS). In 1997, we installed a microscope suitable for cytogenetic analyses by fluorescence *in situ* hybridization (FISH) and comparative genomic hybridization (CGH). Further, we have considerably strengthened our computer system, which was in need of more powerful central processors and extended storage space, particularly for epidemiological data.

Personnel policy

The pace of progress in biomedical research is continuously increasing, and this confronts research institutions worldwide with the need to establish a personnel policy that allows the continuous appointment of brilliant young scientists with expertise in new research areas. At times of zero nominal budget increases or even decreased funding, new scientists can be appointed only if a significant fraction of our staff leaves the Agency and moves on to other positions once their project has come to a conclusion. The Agency has, therefore, started to introduce five-year fixed-term appointments for professional staff. We also plan to create young investigator's groups, again on a five-year fixed-term basis. Such groups would work independently, with personnel and budgetary support. An increased need for flexibility and renewal exists at all levels of the institution; at its 1997 session, the Governing Council passed a resolution that the term of office of the IARC Director is five years, renewable once.

IARC Day

The annual IARC Day has become a tradition and is increasingly popular in the scientific, medical, political and diplomatic community of Lyon. This occasion is used to thank our many supporters holding public office in the Lyon region, to present our activities and to facilitate contacts between our guests, staff and members of the Governing Council. In 1996, the keynote Sohier lecture was given by Professor Dirk Bootsma, Erasmus University, Rotterdam, who gave a fascinating presentation under the title 'DNA repair: maintaining nature's perfection'. In 1997, a renowned specialist on population genetics, Professor Luca Cavalli-Sforza, Stanford University, California, gave an inspiring talk on 'Gènes, peuples, langues, cultures'. On each occasion, the programme was complemented by musical performances by students from the Conservatoire Régional de Lyon and concluded with a reception for our guests and the entire staff.

Extrabudgetary funds

Approximately 25% of our funding is provided by extrabudgetary sources. We particularly appreciate research grants awarded by the European Union, Directorates V (Europe Against Cancer) and XII (Biomed programmes 1 and 2) which have greatly contributed to our work, particularly towards large international trials that are increasingly difficult to finance if conducted over extended periods of time. Significant funds continue to be provided by the US National Cancer Institute, particularly for the production of the *IARC Monographs on Evaluation of Carcinogenic Risks to Humans*. Other US agencies have also contributed to our programmes, including the National Institute of Environmental Health Sciences (NIEHS), the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OHSA) and the Department of Defense, which supports our project on early detection of breast cancer in the Philippines. The Italian Government, the Swedish Medical Research Council and the Regione

Autonoma Valle d'Aosta (Italy) have generously provided the funds needed to continue the Gambia Hepatitis Intervention study. We are particularly grateful to the many French citizens and charities who have supported our work through donations, legacies and grants. These funds enable us to start new, exciting research projects not originally foreseen in the programme budget.

Scientific Council

The Scientific Council currently consists of 16 members with an international reputation in areas of cancer research pertinent to our work. The Council members meet once per year, usually in January, to evaluate past work and future projects. This critical evaluation is of great importance for the work of the Agency and I wish to thank those members who left the Council during the past biennium: Dr Valerie Beral (Oxford), Dr N.N. Blinov (St. Petersburg), Dr Adèle Green (Brisbane), Dr D.R. Krewski (Ottawa), Dr A.R. Sarasin (Villejuif/Paris), Dr B. Standaert (Brussels) and Dr M. Terada (Tokyo). My special thanks go to the chairmen of the Scientific Council, Dr Adèle Green (1995–96) and Dr Alain Sarasin (1996–97). Under their guidance, the Scientific Council has maintained its exceptional scientific rigour and independence. Both chairmen have given valuable advice to the Director during their term of office.

Governing Council

The IARC Governing Council, consisting of the delegates from the 16 Participating States and the Director-General, WHO, has continued to generously support the Agency and its scientific programmes. Many of these states are currently in a difficult phase of financial and economic restructuring and at its 38th session in May 1997, the Council felt unable to increase the budget of the Agency for the forthcoming biennium 1998–99. Instead, the budget was nominally reduced by 0.34%, which is difficult to absorb since some expenses beyond our control will increase at the same time. Despite budgetary restraints, the entire staff of the Agency is committed to maintain and enhance the status of the Agency as one of the leading cancer centres worldwide.

The chairman of the Governing Council, Professor Anthony Adams (Australia) has very actively pursued our objective of increasing the number of Participating States. On the occasion of the 1997 World Health Assembly, Argentina formally submitted to the Director-General, WHO, a letter of intent to become a member of IARC in 1998 and two other countries have expressed their intention to join in the near future. If approved by the Governing Council, this extension of our membership will not only provide a more global representation of the delegates, but also allow us to expand our scientific programme.

On behalf of the Agency and its staff, I should like to thank Dr Hiroshi Nakajima for his continuous support and encouragement during his term as Director-General of the World Health Organization. He was instrumental in giving IARC a greater visibility within our parent organization and thereby fostered our interactions with WHO Headquarters and the Regional Offices.

Dr Paul Kleihues
Director

PART 1. CANCER OCCURRENCE AND OUTCOME

1.1 Support to cancer registries

Cancer registries are the source of information on incidence of cancer in defined populations, as well as on outcome, in terms of survival. They also provide a framework for conducting epidemiological studies into the cause of different cancers. In many parts of the world, cancer registries provide the only available information on the nature and evolution of the local cancer problem. The comparative value of the statistics which cancer registries produce depends upon the use of common methods, and definitions, so that intentional collaboration in this area has a very important role.

1.1.1 International Association of Cancer Registries

D.M. Parkin and S.L. Whelan; in collaboration with J. Young, Sacramento, CA, USA; and H.H. Storm, Copenhagen, Denmark

The International Association of Cancer Registries (IACR), a non-governmental organization in official relations with WHO since 1979, has been supported by a secretariat within IARC since 1973, and provides a link between registries across the world. In 1997 the Association had 404 members in 100 countries, 75% of them cancer registries. Membership fees are used to support the participation of members from developing countries in the annual scientific meetings of the Association.

Members collaborate with the Agency in publications on cancer morbidity, such as the *Cancer Incidence in Five Continents* series (Section 1.2.1) and *International Incidence of Childhood Cancer* (Section 1.4.1), and in collaborative studies such as ECLIS (childhood leukaemia incidence in relation to the Chernobyl accident; Section 2.5.2). The secretariat maintains a specialized library containing some 1800 publications.

A fellowship has been created by the Association in memory of Dr Calum S. Muir, who was president of the IACR from 1992 until his death in 1995. The fellowship is intended to help personnel working in cancer registries to spend some time in host institutions which can offer learning opportunities not available locally. The first fellowship will be awarded in 1998.

A scientific meeting lasting two to three days is held each year. The 1996 meeting took place in Edinburgh, UK, hosted by the United Kingdom Association of Cancer Registries, and focused on survival and cancer, with sessions on comparison and comparability of survival data, variations in survival, time trends, survival by social class and ethnic group and survival in developing countries. Sir Kenneth Calman, Chief Medical Officer for England, presented the first Calum S. Muir Memorial Lecture, entitled *Cancer — Science and Society: the assessment of communication of risk* .

The 1997 meeting was held in November in Abidjan, Côte d'Ivoire, hosted by the Cancer Registry of Abidjan. The main theme was infection and cancer, and the programme covered AIDS and human immunodeficiency virus (HIV), herpes viruses, *Helicobacter pylori*, hepatitis viruses, human T-cell lymphotropic virus (HTLV), papillomavirus and parasites. There was also a session devoted to cancer registration with emphasis on the presentation of descriptive data from developing countries.

1.1.2 European Network of Cancer Registries

D.M. Parkin, R.J. Black, J. Ferlay, E. Démaret and J. Estève; in collaboration with F. Berrino, Milan, Italy; T. Davies, Cambridge, UK; C. Martínez-Garcia, Granada, Spain; F. Ménégoz, Meylan, France; R. Otter, Groningen, The Netherlands; H.H. Storm, Copenhagen, Denmark; and H. Tulinius, Reykjavik, Iceland

The European Network of Cancer Registries (ENCR) was established in 1989 with support from the 'Europe Against Cancer' programme of the European Commission. The aims of the ENCR are to improve the quality, comparability and availability of data from cancer registries, and to promote the use of these data in research and cancer control activities. There are 85 general, population-based cancer registries in European Union (EU) countries which are full ENCR members. Registries in non-EU countries in Europe are accorded associate member status, as are specialized registries which collect information on a limited range of cancers, for example childhood cancer. The Steering Committee of the ENCR comprises elected members and nominees of cancer registry associations; IARC provides the secretariat.

The main activities of the Network are:

(a) Surveillance of cancer registration methods. Two surveys have been conducted by the Danish Cancer Registry, the first of which has been published [445]. This activity has revealed some differences in the definitions and data collection practices used by European registries.

(b) Establishing standards and definitions. In response to the survey results, working groups have been established to review aspects of registration practice and to make recommendations for standards for the European registries. A special working group was set up to discuss computerized data collection in cancer registries and to prepare recommendations for the registries. A technical report is in preparation.

(c) Training in cancer registration and data analysis methods. A standard set of training modules for supervisors of cancer registrars has been established. This forms the basis for an annual course in cancer registration for European registries, which aims to promote the use of common definitions and data collection methods. Such courses were held in Toulouse, France in 1996 and Ventnor, UK in 1997. A series of training courses in data analysis methods has been introduced. These cover basic descriptive epidemiological methods using the EUROCIM software (see below), survival analysis methods, geographical studies and analysis of time trends.

(d) Fellowships. Registry personnel can obtain support to attend ENCR courses or to exchange skills through working visits to other cancer registries. Ten 'mini-fellowships' are available each year.

(e) Consultancy. Cancer registries, particularly those in development, can request a consultant visit by an experienced person to advise on cancer registration methodology or specific local problems.

(f) Provision of information on cancer in Europe. Information on the frequency of cancer in European populations is provided through traditional and, increasingly, electronic publications. These are:

(i) *EUROCIM*. The EUROCIM project provides a database of cancer incidence and mortality for European countries and regions covered by cancer registries, along with software for data analysis and presentation. The first version was distributed to contributing registries in 1995. The latest update was released in 1997, with data from 87 European registries.

(ii) *Estimates of cancer incidence in EU countries*. The aim of this activity is to provide estimates of cancer incidence in EU countries in which full population-based cancer registration has not been established. The most recent published estimates are for

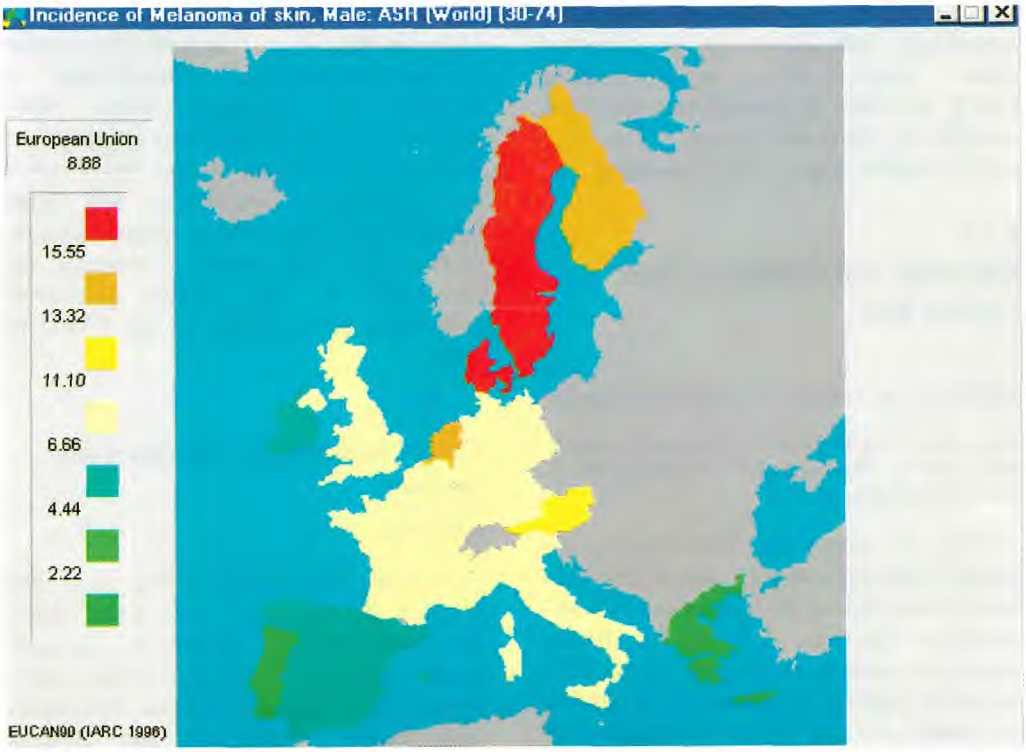

Figure 1. Example of a EUCAN90 screen display of cancer incidence in the European Union: skin melanoma in men

1990, using data from *Cancer Incidence in Five Continents* and EUROCIM.

(iii) *EUCan90.* This software package, using the 'Windows' operating system, provides access to the estimated national-level incidence, prevalence and mortality data for the 15 EU countries. EUCan90 is the first in the new IARC electronic publication series 'CancerBase' (see Section 7.1.7).

(iv) *CANCERMondial.* An Internet service is being developed to provide remote access to information about IARC activities in support of cancer registries, including the ENCR, and statistical data held by the Unit of Descriptive Epidemiology. The service at present provides data only from Europe, but the range will be expanded. Partial funding has been obtained from DGXIII of the European Commission.

(v) *Cancer in European countries and regions.* A programme of collaborative studies of trends in incidence and mortality in relation to risk factors in specific countries has been established. A report on trends in France appeared in 1997 [258], and a similar exercise for Spain is in progress.

(vi) *Monitoring of progress towards European cancer targets for the year 2000.* The aim of this project is to evaluate progress towards the target of a 15% reduction in cancer mortality in Europe. Intermediate results for the major cancers in 15 EU countries were presented to the European Cancer Experts Committee on Cancer Prevention. A technical report providing detailed results is in preparation.

(vii) *European Cancer Registries Newsflash.* The Newsflash is published twice a year to inform registries about ENCR activities. A commitment has been made by the *European Journal of Cancer* to publish regular digests of the Newsflash.

1.1.3 Reliability and validity of cancer registry data

1.1.3.1 Histological subtypes of common cancers

D.M. Parkin, J. Ferlay and S.L. Whelan; in collaboration with K. Shanmugaratnam, Singapore; and L. Sobin, Washington, DC, USA

Data on cancer incidence have traditionally been presented by the largely site-based categories of the International Classification of Diseases. However, the characteristics of certain cancers, particularly with respect to etiology, treatment and prognosis, are better defined by a combination of tumour site plus morphology, and registries are increasingly analysing certain cancers by histological type as well as by site alone. In the interests of comparability, histological subgroups have been established for the principal cancers, together with the appropriate ICD-O morphology codes. The distribution of codes is exhaustive (which is not the case for the International Histological Classification of Tumours, with which it is compatible). The diagnostic groups are published in an IARC Technical Report [334], including software that allows recoding of data to the proposed histological groups, to permit comparative studies.

1.1.3.2 International Classification of Diseases

D.M. Parkin and S.L. Whelan; in collaboration with C. Percy, Bethesda, MD, USA; D. Pheby, Bristol, UK; and R. Otter, Groningen, The Netherlands

IARC was involved in the preparation of the neoplasms chapter for the tenth revision of the *International Classification of Diseases* (WHO, 1992) and the first revision of the *International Classification of Diseases for Oncology* (WHO, 1990). Several national and international groups are working on a revision of the classification for lymphomas, leukaemias and brain tumours and these will be coordinated by IARC, which will prepare a proposal for discussion by the WHO committee responsible for revisions to the ICD-O in 1998.

1.1.3.3 Cancer Registration: Principles and Methods

D.M. Parkin

Cancer Registration: Principles and Methods (Jensen *et al.*, 1991, IARC Scientific Publications No. 95) provides guidance on the techniques required to collect, store, analyse and interpret data on individuals with cancer. Portuguese and Spanish editions were published in 1995, and French and Japanese editions in 1996, as a result of collaborations with cancer registries in the respective countries.

1.1.3.4 Comparability and quality control in cancer registration

D.M. Parkin, S.L. Whelan and J. Ferlay; in collaboration with V. Chen, New Orleans, LA, USA; J. Galceran, Tarragona, Spain; and H.H. Storm, Copenhagen, Denmark

Comparability and Quality Control in Cancer Registration (IARC Technical Reports No. 19; Parkin *et al.*, 1994) presented techniques to measure completeness of coverage of the population in the registration area, and to check the accuracy and detail of the information collected, with a diskette of the IARC-CHECK program. Spanish and French editions were published in 1995 and 1996 respectively.

1.1.4
Computer software for cancer registries

D.M. Parkin, J. Ferlay and A. Cooke

CanReg is a configurable computer program designed for cancer registration in population-based registries. The new version, CanReg3, has been completely rewritten to be more powerful and robust. New features include searching for duplicate records and multiple primaries using probability matching, full consistency checking for impossible or rare cases, and immediate language swapping. A graphical user interface allows it to run equally on all modern PCs.

The participants of this year's IARC summer school (see Section 1.1.6) were fully trained in use of CanReg3, which is now being used by cancer registries in:

Calcutta, India; six sites in the Republic of Korea; Oman (national registry); Manila and Rizal, Philippines; Khon Kaen, Sonkhla and Chiang Mai, Thailand; Hanoi and Ho Chi Minh City, Viet Nam; Setif and Tlemcen, Algeria; Blantyre, Malawi; Namibia (national registry); Ibadan and Benin City, Nigeria; Cape Town, South Africa; Kampala, Uganda; Harare, Zimbabwe; Izmir, Turkey; Trinidad & Tobago; Fiji and New Caledonia.

1.1.5
Support to specific cancer registries

D.M. Parkin, P. Pisani, R. Sankaranarayanan, S.L. Whelan, R. Black and A. Cooke

Advice is given both to organizations wishing to set up cancer registries, and to established registries, on the methodology of registration and the analysis of data. Staff of the Unit of Descriptive Epidemiology have made visits to several cancer registries in the

Figure 2. Sites of CanReg installations

course of the biennium, and many individuals working in cancer registries have visited the unit for training or discussion.

The basic training programme comprises three weeks at IARC (registry methods, including computing and epidemiological applications) and one week of practical experience in a cancer registry. In 1996 and 1997, training of cancer registry staff has been principally by means of a structured course in cancer registration and applications in epidemiology. The first course was held in August 1996 with 12 participants from 10 countries, and the second in May 1997 with 20 participants from 14 countries.

Several collaborating cancer registries have assisted with training, including the East Anglian Cancer Registry (Dr T. Davies and Mrs M. Page), the Yorkshire Cancer Registry (Dr D. Forman and Ms L. Rider) and the West of Scotland Cancer Registry (Dr C. Gillis) in UK, the cancer registries of Bas-Rhin (Dr P. Schaffer) and Isère (Dr F. Ménégoz) in France, the cancer registries of Maastricht (Dr L. Schouten) and Groningen (Dr R. Otter) in the Netherlands, the Danish Cancer Registry (Dr H. Storm), the cancer registry of Geneva (Dr C. Bouchardy) in Switzerland and the cancer registry of Granada (Dr C. Martinez) in Spain. Several commonly used computer programs are available to registries free of charge (see Section 1.1.4).

The Unit of Descriptive Epidemiology also provides more direct support and encouragement for cancer registration activities in Africa, Asia, Central and South America, and Oceania, often in the form of collaborative research agreements between the registry and IARC.

Figure 3. Training course in cancer registration at IARC, August 1996

1.1.5.1 Africa

Algeria, Setif (H. Cherif): Support to the registry continued through a collaborative research agreement. Cancer incidence data for the period 1990–93 and survival data for 1986–93 have been analysed.

Alger (D. Hammouda): The principal investigator spent a period at IARC during 1996.

Tlemcen (K. Meguenni): The principal investigator spent a four-week training period in Lyon and Strasbourg to develop plans for population-based cancer registration in Tlemcen.

Cameroon, Yaounde (A. Mbakop and G. Enow-Orok): Following training of the registry supervisor, support was provided for data collection, and the data for 1995–96 were evaluated.

Congo, Brazzaville (C. Gombe-Mbalawa and M. Dississa): Following a planning visit, the registry supervisor received training in Lyon, and registration for the city of Brazzaville began in 1996. The results for the first 18 months appear very satisfactory.

Gabon (F.E. Nze-Nguema and D. Minko-Mi-Etoua): The results from the pathology registry, which has existed in the national laboratory of anatomical pathology for many years, were published.

Gambia (A. Jack and E. Bah): The cancer registry was established as part of the Gambia Hepatitis Intervention Study (see Section 5.1.1). In mid-1997, responsibility for the registry was transferred to the Unit of Descriptive Epidemiology.

Guinea (M. Koulibaly and I. Kabba): The registry manager spent a four-week period at IARC to analyse the registry's data for 1992–95 [206].

Ivory Coast (A. Echimane and A. Ahnoux): The registry was able to employ two clerks, which permitted the extension of data collection activities. All hospital services in the city of Abidjan are now covered, and collaboration with pathology services secured.

Malawi (N.G. Liomba and L.T. Banda): Support for the registry continued, permitting active data collection from all hospitals in the Blantyre district. The registry supervisor attended the training course in Lyon in 1997 and prepared the report of the first registry results for 1985–96.

Mali (S. Bayo and S. Kané): Data are now available for about 10 years. An analysis of this material, including a review of possible temporal trends for certain cancers, is planned.

Namibia (S. Dichtl): The registry director attended the training course in Lyon in 1997. Until recently, the registry covered histopathologically diagnosed cases only, but population-based collection for the central district (Khomas) began in 1995.

Niger (H. Nouhou): Registration remains incomplete, and plans were made for further staff training.

South Africa (F. Sitas): Plans have been made to move from the current system of a national pathology-based register, to develop population-based registration in several locations in the country, including five rural areas and the urban populations of Durban and Greater Johannesburg. A request for support from the EU was rejected.

Swaziland (S. Okonda): A visit was made in 1996 to plan registration activities. A request for support from the EU was rejected.

Uganda (H. Wabinga and S. Nambooze): The cancer registry provides the framework for the studies of Kaposi's sarcoma in adults and children (Section 2.6.4) and surveillance of temporal trends in HIV-related cancers

Figure 4. IARC supports cancer registration in numerous African countries. Kampala, Uganda

(Section 1.2.3). Plans were made for studies of time trends in incidence since the 1960s.

Zimbabwe (L. Levy, E. Chokunonga, B. Mauchaza and M. Bassett): A report for 1995 was published. The registry supervisor attended the training course in Lyon in 1997. The staff have continued to provide training and support for the extension of registration activities to Bulawayo and plans have been made to support registration activities in Gweru (Midlands Province).

1.1.5.2

Asia

India, Ambilikkai (J. Cherian and R. Rajkumar): Dr Rajkumar visited Lyon, and registration began in this rural area, with a population of 400 000. The first results (for 1995–96) are now available.

Barshi (B. Nene and K. Jayant): Support to encourage registration activities and analysis of data in this new registry serving a rural population in Maharashtra state was continued and data were analysed in the study on survival (see Section 1.5.2).

Bombay (D.J. Jussawalla and B.B. Yeole): Technical support for the analysis of survival data was provided. The registry assists in the follow-up of the cohort study of tobacco-related cancer (Section 2.4.3) .

Calcutta (M. Siddiqi and U. Sen): Following a planning visit, a population-

based registry was established in the Cancer Institute serving the population of the greater Calcutta area. The principal investigator spent a period of training in Lyon in 1997.

Madras (V. Shanta and C.K. Gajalakshmi): Collaboration, particularly in the field of methods of follow-up and survival studies, has continued.

Trivandrum (K. Nair and C. Varghese): The registry continues to provide valuable information related to the various research projects in the Kerala population, particularly the oral cancer screening trial (Section 5.4.3).

Indonesia: (R. Mangunkusoma and Sarjadi): Technical support for the cancer registry in Semarang was continued.

Oman (J. Al Lawati): A consultant visit was made in December 1995. The cancer registrar attended IARC for training in 1997. A report of registry results for 1993–96 is available.

Pakistan, Karachi (Y. Bhurgri): A population-based registry covering the population of the southern part of Karachi has been established, with some technical support. The principal investigator visited Lyon for training and to prepare the Canreg system. First results (1995–96) are available.

Philippines (D. Esteban, A. Laudico and B. Talaver): The two registries in greater Manila play an active role in the follow-up of the breast cancer screening project, and in the Rizal population extra staff ensure careful staging and follow-up of all breast cancer cases (Section 5.4.1). The data of the Rizal registry were included in the study of survival (Section 1.5.2).

Saudi Arabia: (N. Al Hamdan and A. Al Zahrani): A consultant visit was made by a staff member in December 1995. The registry supervisor took part in the 1996 training course. The data for 1994 have been published as a report.

Thailand: (N. Martin, S. Srisukho, S. Sontipong, S. Sriamporn, H. Sriplung and V. Vatanasapt): Results from cancer registration in Lampang province (northern Thailand) were published. Data from Chiang Mai and Khon Kaen were analysed in the study on survival. Staff from Khon Kaen and Chiang Mai received training in Lyon in 1996 and 1997 respectively. Khon Kaen registry provides follow-up for the cholangiocarcinoma study (Section 3.3.2).

Turkey: (G. Aydemir, C. Fidaner, S. Eser and R. Burgut): Trainees from Izmir and Adana registries participated in the training course in Lyon in 1996. Registration for Izmir province is now complete, and incidence data for 1996 are in preparation. A training course in Canreg was held in 1996.

Viet Nam (Pham Hoang Anh, Nguyen Chan Hung, Nguyen Manh Quoc): Registry staff from Hanoi (1996) and Ho Chi Minh City (1997) participated in training courses. Population coverage for Ho Chi Minh City and province is now considered to be complete, and results for 1995–96 were analysed and submitted for publication.

1.1.5.3

Americas

Argentina, Bahia Blanca (E. Laura and C. DiMartini): Continuing support has been provided for the registry. A consultant visit was made in 1996. The first results have been published locally.

Concordia: (M.A. Prince and D. Loria): A consultant visit was made in 1996.

La Plata: (S. Bonicatto): The registry aims to cover several subdistricts of La Plata province. A visit was made in 1996.

Barbados (P. Prussia, B. Lashley and R. Knight): Cancer registration activities are supported by a joint initiative with the regional office of PAHO.

Bolivia: (J. Rios Dalenz): A consultant visit was made with a view to evaluating completeness of the registry data.

Costa Rica (A.C. Rodriguez): The registry participated in the study of survival in developing countries.

Cuba (L. Fernandez): The registry has received technical support for cancer survival analysis and to increase computing facilities. Two staff members spent one month in Lyon, to receive training in statistical methods of survival analysis and to attend the training course in cancer registration.

Peru (P.J. Albujar): Continuing support was provided for the registry in Trujillo.

Surinam: Plans have been made to expand cancer registration to cover the whole country. The Canreg system has been installed.

Trinidad (E. Quamina and V. Roach): A registry has been established covering the city of Port of Spain; data collection started in 1995. It is planned to extend coverage to the whole island. Technical support has been provided, and the Canreg system installed.

Uruguay (E. de Stefani): Continuing support for the registry (which covers the city of Montevideo) was provided. The results were prepared for publication by the principal investigator.

1.2 Geographic variation in cancer occurrence

Documenting the enormous range in incidence and mortality from disease in different populations has been a powerful stimulus to research into the causes responsible. These may represent to varying degrees the presence or absence of environmental exposures, or differing susceptibility of the populations concerned. Therefore the collation, processing, analysis and presentation of cancer data are important activities. At the same time, it is possible to estimate how much of the cancer burden in different parts of the world might reasonably be ascribed to environmental exposures susceptible to modification; this provides a quantitative indication of the priorities for public health intervention.

1.2.1 Cancer Incidence in Five Continents, Volume VII

D.M. Parkin, S.L. Whelan and J. Ferlay; in collaboration with L. Raymond, Geneva, Switzerland; and J. Young, Sacramento, CA, USA

Data on the incidence of cancer for the years 1988–92 were submitted for 220 populations in 64 countries for Volume VII of the *Cancer Incidence in Five Continents* series. As a first step, the data were verified using the computer software IARC-CHECK (see Section 1.1.3.4), to identify data errors and inconsistencies, and wrong or unlikely combinations of site or morphology codes. Tables of incidence and indicators of quality were produced following correction of the basic data. During four editorial meetings held in 1996 and 1997, each data-set was systematically reviewed for comparability, completeness and validity. The process was assisted by the development of automated flags to draw attention to rates or quality indicators which fell outside expected values.

Data for 182 populations in 50 countries were retained for the book, published in 1997. Of particular note is the reappearance of Uganda, Kyadondo County—a registry for which data were published in Volume I (Doll *et al.*, 1966) but which was not able to provide data again until the period covered by the present volume. There are contributions from five new registries in Asia (including, for the first time, data from Korea and Viet Nam), and four in South America (presenting data from Argentina and Uruguay for the first time).

Every contributing registry sent data in the form of a computerized case-listing, and the vast majority of these included coded histological diagnoses. Expert pathologists

met in 1996 to define groupings of morphological codes for presenting results, taking into account both appropriate combinations of codes and the relative frequency of histological diagnoses in international data-sets (see Section 1.1.3.1). The percentage distribution of microscopically verified cases is presented by histological subtype for 14 cancers in this volume, using the groupings so defined.

The rest of the book provides age-specific and standardized incidence rates for each population, at the three-digit level of the International Classification of Diseases, and world age-standardized rates for selected 4th digit sites. The traditional pattern of presentation has been followed, with a description of each individual registry accompanying the population pyramid and tables of incidence. The text chapters provide a guide to the contents of the book and to the interpretation of the data.

1.2.2

European cancer incidence and mortality database (EUROCIM)

D.M. Parkin, R.J. Black, J. Ferlay, T. Valdivieso and J. Estève; in collaboration with F. Berrino, Milan, Italy; F. Ménégoz, Meylan, France; C. Navarro, Murcia, Spain; R. Otter, Groningen, The Netherlands; D. Pheby, Bristol, UK; E. Schifflers and A. de Coninck, Namur, Belgium, H.H. Storm, Copenhagen, Denmark; and H. Tulinius, Reykjavik, Iceland

The EUROCIM database and software package permits access to incidence data at the level of 'epidemiological entities', which are histological types of tumours classified within anatomical site. It has provided the basis for training courses in statistical methods for cancer registries during 1996–97. The courses cover the theoretical basis for descriptive epidemiology, methods of calculation of rates, comparative methods and statistical modelling of rates. A course in English was held in Utrecht (The Netherlands) in October 1996. Courses in other languages (Spanish and Italian) are being planned.

A new European database, to contain the data provided for *Cancer Incidence in Five Continents* Volume VII, is in preparation, for distribution to 87 European cancer registries.

1.2.3

Analysis of data from collaborating cancer registries

Investigators working in cancer registries are assisted in analysing and presenting their data Priority is given to data-sets of special interest, representing hitherto unpublished material, and to combined analysis of data from several registries in the same country.

The final results from the cancer registry in Rwanda, which ceased to function in 1994, were published, comprising data collected over a 32-month period [304]. Although low rates suggested under-enumeration, the data indicate that stomach cancer is relatively common in men and cervix cancer in women. AIDS-related Kaposi's sarcoma comprises 9.5% of male cancers and 2.5% in women. The data of the cancer registry in Conakry, Guinea, for 1992–95 were analysed by the registry staff, and published [206]. The incidence of liver cancer in men is high (age-standardized rate 32.8 per 100 000), while rates of stomach cancer (6.1 per 100 000) and prostate cancer (8.1 per 100 000) are more modest. Incidence of cervix cancer in women is very high (46.0 per 100 000).

The data from the histopathology laboratory of Gabon, collected over a 10-year period, were analysed by a visiting staff member and published [306].

Elsewhere in Africa, registry staff were assisted in producing reports based on their registry data (Malawi, Zimbabwe, Namibia), and data-sets from five African registries were accepted for *Cancer Incidence in Five Continents*, Volume VII (see Section 1.2.1).

In Asia, the first results of the cancer registry of Ho Chi Minh City in Viet Nam were prepared for publication. They suggest high rates of liver, lung and stomach cancer in men, and (in contrast to the north of the country) cervix cancer in women.

A visiting fellow began the analysis of the results of the three cancer registries in the Philippines, in order to produce a third edition of *Cancer in the Philippines* . An editorial committee comprising representatives of the five population-based cancer registries in Thailand met in 1997, with a view to publishing a second edition of *Cancer in Thailand*. Staff from the cancer registries of Ambilikkai and Barshi (India) and Oman were assisted in the analysis of their results. A visiting fellow from Kazakstan analysed data on geographical variation in the incidence of oesophageal cancer in that country.

In Europe, incidence data from cancer registries have been analysed and published within the framework of the European Network of Cancer Registries (Sections 1.1.2 and 1.2.2).

The extensive database from cancer registries has been used for a study of the international incidence of squamous cell cancers of the conjunctiva [303]. A study of trends in incidence of non-Hodgkin lymphoma in childhood was carried out by a visiting fellow.

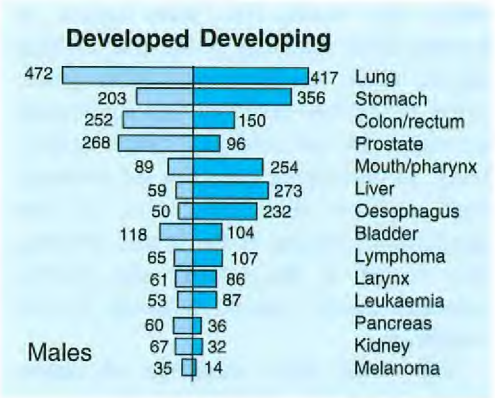

Figure 5. Estimated numbers of cancer cases (1000s) by site and sex, 1990

1.2.4
Worldwide burden of cancer

D.M. Parkin, P. Pisani and J. Ferlay

Provisional estimates of cancer incidence around 1990 and 1995 for 19 cancers and all sites were published in the World Health Reports 1995, 1996 and 1997. The complete set of final estimates of incidence, mortality and prevalence taking advantage of Volume VII of *Cancer Incidence in Five Continents* is being prepared. The list of cancer sites considered has been expanded: separate estimates will be available for cancers of the mouth, nasopharynx and pharynx and for non-Hodgkin lymphomas, Hodgkin's disease and multiple myeloma; additional sites included are brain and nervous system, thyroid and testicular cancer.

Figure 5 shows estimates of incidence around 1990, by sex, cancer site and level of development. Although the figures are only provisional, some remarkable changes in the ranking of the cancer sites compared with the 1985 estimates are evident: in the more affluent countries cancer of the prostate in men is now the second most common site (after cancer of the lung), with almost the same number of cases as colorectal cancer,

which was second five years earlier. In women, most alarming is the rise of lung cancer, which has taken over from gastric cancer in the third position; first and second are still breast and colorectal cancer respectively. In developing countries the formerly most common site, the cervix, is now paralleled by cancer of the breast. In men, lung cancer is the leading site, having overtaken gastric cancer, in steady decline worldwide.

The usual basic measures of cancer burden, mortality, prevalence and years of life lost, will be derived by combining existing data (e.g., the WHO mortality data-bank, population-based survival, Sections 1.5.1 and 1.5.2) with the estimated incidence.

1.2.5
Cause-attributable cancer

P. Pisani, P. Boffetta, D.M. Parkin, E. Riboli and J. Estève, in collaboration with: H-O. Adami, Stockholm, Sweden; D. Eston and N.E. Day, Cambridge, UK; M. Kogevinas, Barcelona, Spain; H. Sancho-Garnier, Montpellier, France; and R. Saracci, Pisa, Italy

Rational planning of preventive interventions requires quantification of the number of cases which can theoretically be prevented by avoiding exposure to the causative agents. The first comprehensive evaluation of cancer fractions attributable to known causes, by cause and cancer site, was that of Doll and Peto in 1981, which applied to cancer mortality in the USA in 1980. A new systematic evaluation of the amount of the cancer burden 'explained' and 'unexplained' by current knowledge is being made. The proportion of all cancers attributable to tobacco smoking has been estimated as 15% or 1.1 million new cases per year worldwide (25% in men and 4% in women). In developing countries, the etiological fraction is 10%, compared with the 16% estimated for 'western' countries (Parkin *et al.*, 1994, *Int. J. Cancer*, **59**, 494–504). In developing countries; at least 21% of all new cancer cases are due to infection with viruses (hepatitis B and C viruses, some human papillomaviruses, Epstein–Barr virus, HIV and HTLV-I), parasites (*Schistosoma* and liver flukes) or bacteria (*H. pylori*); the corresponding figure in developed areas is estimated at 9%. Figure 6 shows the details by cancer site.

Systematic evaluation is also being undertaken of the following factors: diet, alcohol consumption, reproductive habits of women, obesity, drugs and exogenous sex hormones, occupational and environmental pollution, radiation and genetic factors. For each exposure/cancer association, a complete review of the literature is being performed to evaluate the evidence that the association is causal; data on the strength of the association (relative risk) are abstracted and summarized by meta-analysis. The

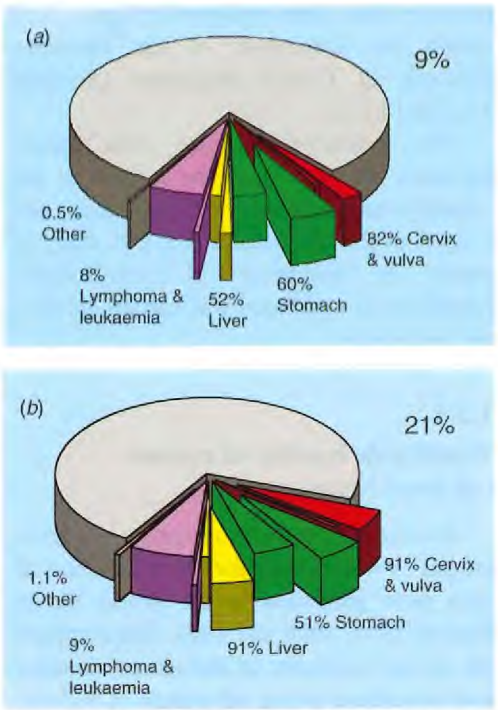

Figure 6. Etiological fractions of cancers caused by infectious agents, by cancer site, in (a) developed and (b) developing countries, 1990

prevalence of the factor in the population is estimated from analytical studies and other sources. Percentage etiological fractions are then computed and applied to the estimated annual numbers of new cases and deaths (Sections 1.1.2 and 1.2.4). The review of the causes of cancer and detailed numerical results for countries of the European Union will be published in a book, with the support of the Europe Against Cancer Programme.

1.2.6
Natural history of breast cancer

A.J. Sasco, I. Gendre and V. Bourdès; in collaboration with M. Abrahamowicz, Montreal, Canada; and J.Y. Bobin, A. Niveleau and S. Saez, Lyon, France

Breast cancer is the most common cancer among women in the world and the Rhône département in France is characterized by a high incidence of the disease, in particular among premenopausal women. Taking advantage of the data at IARC on a population-based cohort of 801 subjects corresponding to all breast cancer cases diagnosed in 1985 in the Rhône, several studies are being conducted to evaluate prognostic factors both for disease recurrence and for mortality. The goals are double: on one hand, to obtain results easily usable by clinicians to monitor their patients and on the other hand to develop methodology for evaluation of the etiological role both of tumour characteristics and of treatment on the outcome of cancer following its diagnosis. Results are already available on the prognostic significance of some modified urinary nucleosides [364, 409]. Studies are continuing on survival and recurrences.

A more didactic exercise has been conducted to prepare a book on breast cancer, from etiology to treatment, at the request of the Swiss Cancer League and Swiss Federal Office of Public Health [360, 361]. This publication is available in English, French and German and destined to an audience of physicians and educated lay persons.

1.2.7
Cancer genes: from families to epidemiology in world populations

D.E. Goldgar and G.M. Lenoir

Our present knowledge of genes conferring markedly increased susceptibility to cancer is largely restricted to the highly industrialized countries of Western Europe, North America and Australia. To examine the contributions of specific high-risk mutations to cancer in other populations, an IARC-coordinated effort is being established to investigate mutational patterns and associated risks of known genes predisposing to cancers that are already common in the industrialized world, but whose incidence is rising in developing nations. The focus is on recurrent mutations found in diverse populations, on mutations unique to specific populations, and on the transfer of country-specific mutation detection methods to areas where they are not yet available. Training and advice will be provided in the delivery and interpretation of mutation information to the family and patient at risk. The next stage is to conduct population-based studies to examine the interaction between genes and environmental factors in determining cancer risk in these populations. The project takes advantage of an existing network of collaborators in Europe and North America through the Breast Information Core database and the Breast Cancer Linkage Consortium. To date we have enlisted potential collaborators in 20 countries, of which about 10 are developing countries, including China, India, Iran and Turkey. Samples from familial breast cancer cases have been received from a number of these countries and are being screened for germline mutations in the *BRCA1/2* genes. A pilot project has been launched focusing on breast cancer susceptibility in a selected set of international centres in eastern Europe, Asia, Africa and Latin America.

1.3 Cancer incidence and mortality in migrant populations

Studies of migrant populations are of particular value in estimating the relative contributions of genetic and environmental factors in cancer etiology. In such studies, the risk of cancer in a migrant population is compared with that in persons of the same genetic background (living in the place of origin of the migrants), or with persons in the host country sharing a common external environment. The aim is to see how much the risk of cancer changes from that of the country of origin to that of the host country, and to determine how rapidly such changes occur. The emphasis in recent projects has been upon hitherto unstudied groups, and on exploiting data-sets which permit analysis of trends in risk by time since migration, or comparison between first-generation migrants and their offspring.

1.3.1 Cancer in migrants to France

D.M. Parkin; in collaboration with C. Bouchardy, Geneva, Switzerland; and M. Khlat, Paris, France

Analysis of cancer mortality in the various migrant populations in France during 1979–85 has been completed. The full results are published in an IARC Technical Report [41]. Certain subsets have been published separately, covering the risk of different cancers in migrants from China and south-east Asia (Bouchardy *et al.*, 1994, *Int. J. Cancer*, **58**, 638–643), sub-Saharan Africa (Bouchardy *et al.*, 1995, *Cancer Causes Control*, **6**, 539–544) and north Africa [42].

1.3.2 Cancer in migrants to Israel and their offspring

D.M. Parkin; in collaboration with J. Iscovich, Jerusalem, Israel

This study made use of data from the Israel Cancer Registry for a 30-year period (1960–89). This data-set contained information on the birthplace of individuals with cancer, and on the birthplace of their parents. It was possible, therefore, to compare incidence rates in migrants with those in their offspring born in Israel, and with those of individuals born in Israel with Israel-born parents. For technical and practical reasons, the analysis was confined to young individuals (aged under 30). The full results are published in an IARC Technical Report [168] and the results for leukaemias and lymphomas and for carcinomas and germ-cell tumours have been published separately [167, 329]. Non-Hodgkin lymphomas show quite marked differences in risk in migrants from different regions, which per sist in their offspring, and a similar pattern was observed

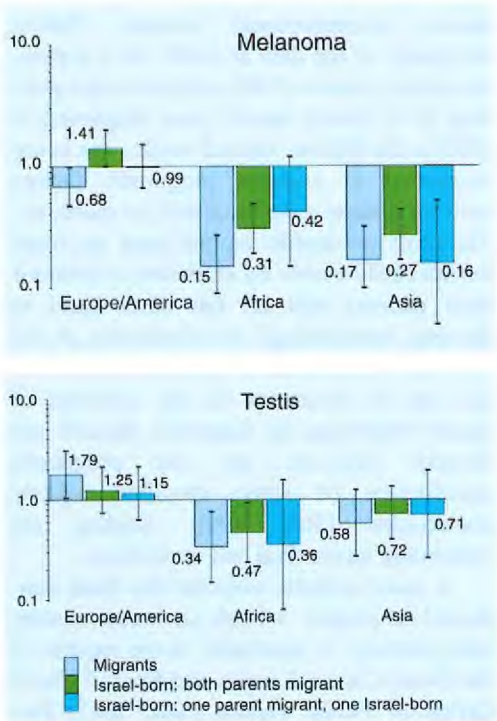

Figure 7. Risk of cancer (odds ratio) in migrants and their offspring, relative to the population born in Israel of Israel-born parents, according to continent of origin. (a) Melanoma, (b), testis

for cancers of the testis, naso pharynx, and melanoma; this suggests that inherited susceptibility may underlie some of the variation. For ovarian, colorectal, cervi cal and thyroid cancers, differences in risk between the migrant groups had largely disappeared in their offspring, suggesting that environmental exposures, which were modified by migration, are the major causative factors.

1.3.3
Cancer in migrants to Australia

D.M. Parkin, P. Pisani and H. Garcia-Giannoli

The mortality data-set from Australia has been updated, so that it contains information on deaths from cancer for a 30-year period (1964–93). Each record contains details of cause of death, place of residence, place of birth and date of migration to Australia. It is possible, therefore, to examine not only the variation in risk of death from cancer according to birthplace, but also how this is modified by age at migration or duration of residence in Australia. This information is of relevance to etiological mechanisms (period of life at which environmental factors modify risk) and preventive strategies (how soon lifestyle modifications can change risk). A previous analysis (Khlat *et al.*, 1992, *Am J. Epidemiol.*, **135**, 1103–1113) examined melanoma. The new study will concentrate upon cancers of the breast, stomach, colon-rectum and prostate.

1.4 Childhood cancer

Childhood cancer is rare (usually less than 1% of new cases in western populations) and, although survival has greatly improved in recent years, there are long-term health implications for the survivors. The spectrum of tumour types occurring is very different from adults, indicating different etiological factors. The surveillance of geographical patterns of cancer incidence and monitoring time trends in incidence are important in suggesting possible causative associations, as well as illustrating priorities for control of cancer in this age group. Sufficiently large data-sets for this purpose have been obtained through international collaboration.

1.4.1
International Incidence of Childhood Cancer, Volume 2

D.M. Parkin, E. Kramárová and E. Masuyer; in collaboration with G.J. Draper and C. Stiller, Oxford, UK; J. Michaelis, Mainz, Germany; J. Neglia, Minneapolis, MN, USA; and S. Qureshi, Islamabad, Pakistan

The second volume of *International Incidence of Childhood Cancer* contains data from 121 registries in 56 countries, 96% of them population-based. In 12 registries, data were available for two or more ethnic groups. The selection criteria included a sufficient number of cases for the study period (minimum 200), balanced number of registrations per year, typical age-distribution patterns, acceptable proportion of cases registered from a death certificate only and an acceptable proportion of microscopically confirmed cases. Any deviations from the generally observed incidence rates overall or within some diagnostic subgroups were communicated to the reporting centre and, if necessary, a comment was included in the introductory text, accompanying the incidence tables. All childhood cancer tumours are classified according to the International Classification of Childhood Cancer (ICCC). An automatic conversion program is available to convert the ICD-O codes into ICCC.

The main purpose of the study is worldwide dissemination of the data collected regionally or nationally. Due to careful verification of the quality of the

submitted data-sets, and fairly strict inclusion criteria, comparability of the published incidence rates is high. The results suggest a small increase in the overall incidence rates of childhood cancer in many countries, mainly as a result of a rise in the rates of leukaemias, brain tumours and lymphomas, compared with the figures published in the first volume. Also notable is a decrease in the proportion of tumours in the 'unspecified' categories.

1.4.2
Neonatal and childhood tumours

A.J. Sasco, I. Gendre and M. Marsot; in collaboration with J. Little, Aberdeen, UK; E. Robert, Lyon, France; and D. Satgé, Tulle, France

Potential sources of data on the occurrence of benign or malignant neonatal tumours are being explored, such as population-based registries of congenital malformations. A case–control study of neonatal angiomas is being conducted in public obstetric units in Lyon to evaluate the role of maternal exposures during pregnancy. Recent attention has been directed to a study of the association between Down's syndrome and early childhood tumours. We have observed an excess risk of testicular germ cell tumours [415] and in contrast a great scarcity of neuroblastoma among Down's syndrome subjects [413], suggesting the possibility of a tumour suppressor gene on chromosome 21 [416].

Another axis of research is the relationship of exposure *in utero* to drugs on neonatal occurrence of tumours. A comprehensive review has been published [417] and relevant cases published [414].

1.5 Survival from cancer

Population-based cancer survival refers to survival rates based on the experience of all incident cancer cases occurring in the population of a given region. Such data are important to evaluate the effectiveness of cancer care in that region. Intra- and inter-regional variations in cancer survival may be due to differences in organization and access to health care, allocation of resources, use of health services, attitudes and awareness of the population and socioeconomic status. Thus, comparisons of cancer survival across geographic regions, after taking into account random variation and confounding variables, provide valuable leads to implementing specific cancer control measures.

1.5.1
Survival from cancer in Europe

J. Estève; in collaboration with F. Berrino and M. Sant, Milan, Italy; A. Verdecchia, Rome, Italy; J.W.W. Coebergh, Eindhoven, The Netherlands; M.P. Coleman, London, UK; J. Faivre, Dijon, France; T. Hakulinen, Helsinki, Finland; C. Martinez, Granada, Spain; and D. Forman, Leeds, UK

The EUROCARE concerted action funded by the European Union is pursuing its efforts to study in detail the survival of cancer patients in European countries. Besides follow-up of the previous cohort, detailed data on stage, diagnostic methods and treatment are required in order to understand the large between-country differences in survival observed in the initial study. A recent decrease in mortality from breast cancer in the United Kingdom may be a reflection of a change in the stage of the disease and in its death rate during the first months after diagnosis. A new publication is in preparation to update the successful volume published in 1995.

1.5.2
Survival from cancer in developing countries

R. Sankaranarayanan, R.J. Black, D.M. Parkin and J. Estève; in collaboration with M. Hamdi-Cherif, Setif-Wilaya, Algeria; Jian-Guo Chen, Qidong, China; Fan Jin, Shanghai, China; C. Bratti, San Jose, Costa Rica; M. Graupera and L. Fernandez, Havana, Cuba; A. Nandakumar, Bangalore, India; K. Jayant and B. Nene, Barshi, India; B.B. Yeole and D.J. Jussawalla, Bombay, India; C.K. Gajalakshmi, R. Swaminathan and V. Shanta, Madras, India; M. Krishnan Nair, Trivandrum, India; D. Esteban, Manila, The Philippines; N. Martin and S. Srisukho, Chiang Mai, Thailand; and S. Sriamporn and V. Vatanasapt, Khon Kaen, Thailand

Population-based cancer registries in Algeria, People's Republic of China, Costa Rica, Cuba, India, the Philippines and Thailand are collaborating with IARC to analyse survival rates from major cancers diagnosed around 1980 and to compare the results with those from developed countries. Data collected from Costa Rica and Cuba relate to the entire national populations; those from other countries involve selected regions. Both active and passive methods were used to determine the vital status of patients on the closing date of the study. Data are being analysed using standard statistical methods; training in such analysis has been provided to participating registry staff.

Results indicate wide variations in survival rates for cancer sites such as breast, uterine cervix, testis and Hodgkin's disease. Comparison of cancer survival rates with those seen in the USA and western Europe has revealed large differences in survival for cancers treated by intensive chemotherapeutic regimens (Hodgkin's disease, testicular cancer), modest differences for those in which early diagnosis and treatment lead to improved survival (large bowel, breast and cervix cancers) and practically no difference for tumours associated with a poor prognosis (liver, pancreas and lung cancers) (Table 1).

This multinational study has provided a framework to investigate the problems of cancer registration, patient follow-up and statistical methods for studying cancer survival in developing countries. The results imply that developing countries should consider balanced development of a range of cancer control measures such as primary prevention, early detection linked to treatment facilities and palliative care in their health services, in view of the limited resources available. Further in-depth studies are planned to identify population subgroups with poor survival.

Table 1. Age-standardized [a] five-year relative survival of patients with selected cancers (age, birth to 74 years)

Site or type of cancer	% of patients surviving				
	USA (1967–73)	USA (1974–86)[b]	USA (1986–91)	Europe (1978–85)	Developing countries (late 1980s)
Stomach	13	17	20	23	7–17
Large bowel	46	55	60	43	29–37
Pancreas	3[b]	4	6	6	6–7
Lung	10	15	15	10	3–10
Breast	65	76	82	69	43–63
Cervix	59	68	68	61	27–65
Testis	69	92[c]	93	85	42–61
Hodgkin's disease	62	77[c]	79	71	30–55

[a] Age standardization involved direct standardization of the site-specific age distributions of the estimated global incidence of major cancers in 1985 (Parkin et al., 1993, Int. J. Cancer, 54, 594–606)
[b] Includes whites patients only
[c] Represents three-year survival
[d] Represents data for 1981–86

PART 2. ENVIRONMENTAL CAUSES OF CANCER

2.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

J.M. Rice, M. Blettner, D. McGregor, C. Partensky and J.D. Wilbourn. The following members of other units have contributed to the programme: R.J. Black, P. Boffetta, J. Cheney, M. Friesen, P. Hainaut, E. Kramarova, V. Krutovskikh, M. Lang, S. Lea, G. Lenoir, C. Malaveille, N. Malats, E. Merler, H. Nakazawa, H. Ohshima, D.M. Parkin, P. Pisani, I. Rajower, G. Romeo, A. Sasco, B. Sylla, J. Vena, H. Yamasaki and J. Ziegler

The *IARC Monographs* are founded on an international consensus approach to qualitative identification of environmental causes of cancer in humans. Each volume is produced by a working group of some 20 independent scientific experts from 8–10 countries. For an agent or exposure circumstance to be evaluated in the programme, there must be evidence or suspicion of cancer causation in humans or animals, and evidence of human exposure. Seventy volumes of *Monographs* have been published, containing evaluations of 838 agents or exposure circumstances, based on critical reviews of the published scientific literature. As new data become available, re-evaluations may be made. Lists of evaluations and summaries of individual recent evaluations are now available in searchable format through the World Wide Web IARC home page (see Section 7.1.7).

In addition to the *Monographs* themselves, the programme organizes scientific meetings on mechanisms of carcinogenesis and other topics relevant to evaluations of carcinogenic hazard. Three such meetings were held during the period under review, as detailed below. The programme also maintains a *Directory of Agents being Tested for Carcinogenicity*, which constitutes a database of bioassays in progress worldwide (see Section 7.1.6).

2.1.1 Mechanisms of fibre carcinogenesis

(9–11 January 1996)

An ad-hoc group of 18 scientists from eight countries met in Lyon to discuss strengths, weaknesses and gaps in present knowledge on mechanisms of fibre carcinogenesis. Papers prepared before the meeting reviewed the use of physicochemical and cell-free assays to evaluate the potential carcinogenicity of fibres; the use of in-vitro genotoxicity and cell transformation assays for this purpose; the effects of fibres on cell proliferation, cell activation and gene expression; short-term animal studies to detect inflammation, fibrosis and pre-neoplastic changes induced by fibres; evaluation and use of animal models to assess mechanisms of fibre carcinogenicity; and mixed exposures to fibrous and non-fibrous dust and interactions between agents in fibre carcinogenesis. A general review paper on mechanisms of fibre carcinogenesis was also prepared in which the several different hypotheses that have been proposed to explain the carcinogenicity of natural and man-made fibres were discussed.

During the meeting, the group prepared a consensus document discussing strengths, weaknesses and gaps in (i) fibre characterization, (ii) genotoxicity studies, (iii) cell proliferation and cell activation studies and (iv) short- and long-term animal studies. The relevance of in-vitro and in-vivo assays was discussed critically with a view to formu-

lating a summary statement on the relevance of mechanistic data in the evaluation of fibre carcinogenicity to humans. The background papers and collective documents were published as IARC Scientific Publications No. 140.

2.1.2 Some pharmaceutical drugs

(Volume 66, 13–20 February 1996)

Evaluations of the evidence relevant to the carcinogenicity of 13 pharmaceutical drugs were made by a group of 17 experts from eight countries. Representatives from several important classes of drugs were considered: phenytoin, an anticonvulsant used in epilepsy and, more recently, in the treatment of certain cardiac arrhythmias; benzodiazepines (diazepam, doxefazepam, estazolam, oxazepam, prazepam, ripazepam and temazepam), which are widely used in the treatment of anxiety and as sedatives and anticonvulsants; triphenylethylene antiestrogenic drugs (droloxifene, tamoxifen and toremifene), used principally in adjuvant therapy of breast cancer; and so-called cholesterol-lowering drugs (clofibrate and gemfibrozil), used to lower plasma triglyceride concentrations in the treatment of patients who are at high risk of developing cardiovascular diseases.

Phenytoin was classified as *possibly carcinogenic to humans* (Group 2B) mainly because in mice it causes liver tumours following oral administration and lymphomas and leukaemias following intraperitoneal injection.

Of the benzodiazepines, oxazepam was classified as *possibly carcinogenic to humans* (Group 2B) on the basis of its hepatocarcinogenicity, mainly to mice, in a number of rodent studies. The other benzodiazepines evaluated were *not classifiable as to their carcinogenicity to humans* (Group 3).

Among the triphenylethylene antiestrogenic drugs, there was sufficient evidence for carcinogenicity to humans of tamoxifen (Group 1) on the basis of increased risk of developing endometrial cancer, but there was also conclusive evidence that the drug reduces the risk of contralateral breast cancer in women with a previous diagnosis and treatment of the disease, for which it has been used since the early 1970s. The other two drugs in this category, droloxifene and toremifene, are much more recent introductions to clinical practice and were *not classifiable as to their carcinogenicity to humans* (Group 3). Similarly, the two lipid-lowering drugs, clofibrate and gemfibrozil, were *not classifiable as to their carcinogenicity to humans* (Group 3). In both cases, it was considered that although hepatocellular carcinomas were induced in some rodent studies, other observations suggested that the mechanism of liver carcinogenesis (involving peroxisome proliferation) would not be operative in humans.

2.1.3 Infections with human immunodeficiency viruses and human T-cell lymphotropic viruses

(Volume 67, 11–18 June 1996)

A working group of 26 experts from 12 countries was convened to evaluate the carcinogenic risks to humans associated with infections by the human immunodeficiency viruses (HIV-1 and HIV-2) and human T-cell lymphotropic viruses (HTLV-I and HTLV-II).

HIV-1 and HIV-2 are etiological agents of the acquired immune deficiency syndrome (AIDS). The main routes of HIV-1 transmission are sexual intercourse, blood–blood contact and from mother to infant, including breast-feeding. The median incubation period (from infection to AIDS) for HIV-1 in developed countries is 10 years, and may be longer for persons infected with

HIV-2. Epidemiological evidence indicates that the incidence of Kaposi's sarcoma is greatly increased in certain categories of persons infected with HIV-1. The incidence increases markedly as HIV-1-related immunosuppression progresses. Within developed countries, the risk varies among HIV-1 transmission categories. These variations suggest the existence of other cofactor(s), for which human herpesvirus type 8 (HHV-8; see Section 2.1.6) is the leading candidate.

Non-Hodgkin lymphoma incidence is greatly increased in persons with HIV-1 infection. This increased risk has been found to be similar in all HIV-1 transmission groups. It appears that the association is mediated by HIV-1-related immune dysregulation. Co-infections with specific viruses are associated with primary lymphoma of the brain (Epstein–Barr virus; EBV) and body-cavity lymphomas and multicentric Castleman's disease (HHV-8). The Working Group concluded that infection with HIV-1 is *carcinogenic to humans (Group 1)* and that infection with HIV-2 is *possibly carcinogenic to humans (Group 2B).*

HTLV-I infection is endemic in some parts of Japan, central and west Africa, South America and the Caribbean basin. The main routes of transmission are mother-to-child during breast-feeding, sexual (mainly male to female) and intravenous by blood products. HTLV-II infection occurs in African pygmies and in New World Amerindian tribes and is endemic among intravenous drug users in America and Europe. HTLV-I infection is associated with several diseases other than cancer, e.g. tropical spastic paraparesis. Adult T-cell leukaemia/lymphoma (ATLL) occurs exclusively where HLTV-I is endemic and evidence of HTLV-I infection is a diagnostic criterion for ATLL. HTLV-I is *carcinogenic to humans (Group 1).* HTLV-II *could not be classified as to its carcinogenicity to humans (Group 3).*

2.1.4
Silica, some silicates, dusts and organic fibres

(Volume 68, 15–22 October 1996)

Re-evaluation of carcinogenic risks to humans from exposure to crystalline and amorphous silica, palygorskite, sepiolite and wollastonite and evaluations of carcinogenicity of some natural and synthetic zeolites (other than erionite), *para*-aramid fibrils and coal-mine dust were made by a working group of 19 experts from 11 countries, with 8 observers. Monographs on all but the last three of these substances were previously published in Volume 42 of the *IARC Monographs* (1987). Erionite, a fibrous component of some natural zeolite deposits in various areas of the world, was previously classified into Group 1, *carcinogenic to humans*, in Supplement 7 to the *IARC Monographs* (1987).

Crystalline silica inhaled in the form of quartz or cristobalite from occupational sources was classified as *carcinogenic to humans (Group 1)*, upgraded from its previous classification as *probably carcinogenic to humans (Group 2A)* on the basis of a relatively large number of epidemiological studies that together provided sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica under the conditions specified. In many (although not all) of these studies, lung cancer risks were elevated and could not be explained by confounding factors, such as cigarette smoking or arsenic or radon inhalation, or other exposures. Rodent carcinogenicity studies fully supported the human evidence. Mechanistic evidence suggests that development of lung tumours in rats in response to crystalline silica is a result of marked and persistent inflammation and epithelial proliferation; however, a role for surface-generated oxidants or even a direct genotoxic effect is not ruled out. In contrast, evidence that amorphous silica is a

carcinogenic risk factor was considered to be *inadequate* upon grounds of both epidemiological and experimental studies. Amorphous silica was, consequently, *not classifiable as to its carcinogenicity to humans (Group 3)*.

Palygorskite (attapulgite) is a fibrous, hydrated magnesium aluminium silicate, but fibre lengths in commercial samples are generally less than 5 μm. The epidemiological evidence for palygorskite carcinogenicity was *inadequate*; carcinogenicity studies with rats indicated that long fibres are carcinogenic—particularly with respect to mesothelioma induction—whereas short fibres are not carcinogenic. Consequently, long palygorskite fibres (> 5 μm) were classified as *possibly carcinogenic to humans (Group 2B)*, while short palygorskite fibres (< 5 μm) *cannot be classified as to their carcinogenicity to humans (Group 3)*.

All the other materials evaluated, i.e., sepiolite, wollastonite, some natural and synthetic zeolites (other than erionite), *para*-aramid fibrils and coal-mine dust were also classified in *Group 3*, because both the epidemiological and experimental studies provided *inadequate evidence* for carcinogenicity.

2.1.5 Polychlorinated dibenzodioxins and polychlorinated dibenzofurans

(Volume 69, 4–11 February, 1997)

A working group of 25 experts from 11 countries was convened to evaluate the evidence for carcinogenicity of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). This meeting was the third time at which these substances have been considered within this programme; previous evaluations were made in Volume 15 (1977) and Supplement 7 (1987) of the *IARC Monographs*.

PCDFs are formed as inadvertent by-products in the production and use of polychlorinated biphenyls (PCBs) and, in combination with PCDDs, in the production of chlorophenols and have been detected as contaminants in these products. PCDFs and PCDDs also may be produced in thermal processes such as incineration and metal processing and in the bleaching of paper pulp with free chlorine. PCDFs may be found in residual waste from the production of vinyl chloride and the chloralkali process for chlorine production. The relative amounts of PCDF and PCDD congeners produced depend on the production or incineration process and vary widely.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD, or 'dioxin', the PCDD that has caused most concern) was classified as *carcinogenic to humans (Group 1)*. The most important epidemiological studies for the evaluation of 2,3,7,8-TCDD were four cohort studies of herbicide producers (one each in the United States and the Netherlands, two in Germany). These studies involved the highest exposures to 2,3,7,8-TCDD. The strongest evidence for carcinogenicity of 2,3,7,8-TCDD was for all cancers combined, rather than for any specific site (average relative risk about 1.4). An increased risk of lung cancer, with about the same relative risk, was also present in these four studies. On the basis of these data, it was considered that there was *limited evidence* in humans for the carcinogenicity of TCDD. In several experiments with rats and mice in which 2,3,7,8-TCDD was administered, increases in incidence of liver tumours were consistently found in both males and females of both species; tumour incidence was also increased at several other sites in rats, mice and Syrian hamsters. These data led to the conclusion that there is *sufficient evidence* in experimental animals for the carcinogenicity of 2,3,7,8-TCDD. In reaching the final evaluation, the Working Group took into consideration the following supporting evidence:

(i) 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor;

(ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals;

(iii) tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.

Other polychlorinated dibenzo-*p*-dioxins, dibenzo-*p*-dioxin (the nonchlorinated parent compound of the PCDD family) and all of the polychlorinated dibenzofurans were *not classifiable as to their carcinogenicity to humans (Group 3).*

2.1.6 Lymphotropic herpesviruses: Epstein–Barr virus and Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8

(Volume 70, 17–24 June 1997)

A working group of 19 experts from eight countries met to evaluate the carcinogenic risk to humans of infection with lymphotropic herpesviruses: Epstein–Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8). This was the fifth and final Monographs working group in the series on infectious agents and human cancer that have been held each June since 1993.

Epstein–Barr virus (EBV) is a γ_1-herpesvirus found in all human populations, with a prevalence of over 90% in adults. Primary infection usually occurs in early childhood and is asymptomatic, whereas delayed primary infection may cause a usually self-limiting lymphoproliferative disease, infectious mononucleosis. Infection results in the establishment of a life-long carrier state characterized by the persistence of antibodies to several viral gene products and secretion of infectious virus in saliva, which is the usual vehicle of transmission. EBV can induce growth transformation of human and non-human primate B lymphocytes *in vitro*, and causes malignant lymphomas when experimentally transmitted to certain New World primates. Cellular immune responses in normal individuals contribute to the control of primary EBV infection and mediate the transition to asymptomatic persistence of the virus.

In persons whose immune system is compromised, EBV infection may not be controlled and the resulting lymphoproliferative disease may progress to non-Hodgkin lymphoma. Such persons include organ transplant recipients who receive immunosuppressant drugs, individuals infected with HIV and individuals with immunodeficiency due to genetic disorders. Molecular and epidemiological evidence strongly implicates EBV as a causative or co-causative factor also in Burkitt's lymphoma, Hodgkin's disease, certain other lymphomas, and undifferentiated nasopharyngeal carcinoma. The Working Group concluded that there is *sufficient evidence* for the carcinogenicity of EBV in the causation of Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppression-related non-Hodgkin lymphoma, Hodgkin's disease and nasopharyngeal carcinoma, and that EBV is *carcinogenic to humans* (Group 1).

KSHV/HHV8 is a γ_2-herpesvirus (a rhadinovirus), most closely related to herpesvirus saimiri, a tumorigenic rhadinovirus of New World primates. It establishes a persistent infection and is readily detected in endothelial Kaposi's sarcoma spindle cells and in primary effusion lymphoma cells, involving a disease-specific pattern of expression of viral genes. Infection with the virus is uncommon among the general population of northern Europe and the USA, but is more common in some Mediterranean countries and frequent in parts of Africa. There is

some evidence that this virus is sexually transmitted, but other routes of transmission are likely.

KSHV/HHV8 is consistently present in more than 90% of Kaposi's sarcoma lesions, but at a generally low rate in neoplastic and non-neoplastic tissues from control patients. Limited evidence suggests that infection with this virus precedes the development of Kaposi's sarcoma in the majority of cases.

Primary effusion lymphoma has been recognized as a new disease entity only since the identification of KSHV/HHV8. Tumour cells often contain clonal EBV as well as KSHV/HHV8. In multicentric Castelman's disease, a rare and usually polyclonal lymphoproliferative disorder that occurs in HIV-infected patients, KSHV/HHV8 has also been found in a substantial proportion of cases.

The Working Group concluded that there is strong but as yet limited evidence for a role of KSHV/HHV8 in the causation of Kaposi's sarcoma, and that KSHV/HHV8 is *probably carcinogenic to humans* (Group 2A).

2.1.7 Evaluation of data from short/medium term carcinogenicity tests and on genetic and related effects

(6–10 October 1997)

Data from new test systems and end points for ascertaining carcinogenicity to animals and on genetic toxicity *in vivo* and *in vitro* are increasingly used in the *Monographs* evaluations. This meeting addressed the use of assays in genetically engineered mice and in non-mammalian species, of initiation–promotion assays in rodents with tumours as endpoints, and of histologically defined preneoplastic lesions to determine carcinogenicity in animals. The use of DNA and protein adducts, mutation assays in mammalian cells and tissues and in non-mammalian eukaryotic and prokaryotic species, induction of chromosomal and genomic abnormalities, and patterns of mutations in tumour-related genes in human and animal tumour cells were also discussed.

Tumours in mice transgenic for v-Ha- *ras* (Tg.AC) or for human Ha- *ras* (CBF1-Tg H*ras*2) and knock-out mice (heterozygous *p53*-deficient) were considered relevant for consideration as evidence for carcinogenicity, but such mice cannot at present be recommended as equivalent or preferable to conventional animals for bioassays. Data from carcinogenicity assays in fish and invertebrates can be used in evaluations when available, in combination with those from assays in mammals.

Initiation–promotion assays may have either tumours or preneoplastic lesions as endpoints and are frequently completed in one year or less. Activity as an initiator in such assays provides strong evidence of carcinogenicity, especially when neoplasms are the endpoint. In well defined systems, such as rat liver, preneoplastic lesions in tests for initiating activity may also provide strong evidence for carcinogenicity. The evidence is less compelling when tests are positive only for promoting, and not for initiating, activity.

A minimal set of data to identify an agent as a mutagen or non-mutagen is widely accepted to consist of gene mutations in bacteria and in mammalian cells, combined with cytogenetic alterations in mammalian cells *in vitro* and *in vivo*, preferably generated in commonly used test systems. Experience has shown that data from certain assays of genetic effects are not suitable for classifying or predicting carcinogenic hazard. However, because of the very large number of assays and the many variations in them, a proscriptive process was not considered feasible. Consequently, expert judgement must be applied to the use of data from such assays during carcinogenic hazard identification.

The individually authored papers and a consensus report will be published as IARC Scientific Publications No. 146.

2.1.8 Species differences in thyroid, kidney and urinary bladder carcinogenesis

(3–7 November 1997)

In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans. However, the possibility that an agent causes cancer in animals through a mechanism that does not operate in humans is also taken into consideration. This meeting addressed the predictive value of neoplasms arising at three anatomic sites in rodents, under specific conditions, for identification of carcinogenic hazard to humans: thyroid follicular-cell neoplasms associated with imbalances in thyroid-stimulating hormone, renal cortical neoplasms arising in male rats in association with α-2 urinary (α_{2u}) globulin nephropathy, and urinary bladder carcinomas associated with calculi, microcrystalluria and precipitates.

The Working Group concluded that agents that cause thyroid neoplasia through an adaptive hormonal mechanism belong to a different category from those acting through genotoxic effects or mechanisms involving pathological responses to tissue injury. To define an agent as causing thyroid follicular-cell neoplasia in rodents solely through hormonal imbalance, the agent and its metabolites should lack genotoxic activity, based on an overall evaluation of *in vivo* and *in vitro* data, and persistent hormonal imbalance should have been demonstrated under the conditions of the carcinogenicity assay. Such agents usually also interfere with thyroid homeostasis in humans if given at a sufficient dose for a sufficient time, but can be expected not to be carcinogenic in humans at exposure levels that do not lead to alterations in thyroid homeostasis. When tumours are observed both in the thyroid and at other sites in bioassays for carcinogenicity, tumours at other sites should be evaluated separately from those arising in the thyroid, taking into account the various modes of action of the agent in different tissues.

Humans lack the α_{2u}-globulin that is abundantly secreted by male rats and that is associated with a specific form of nephropathy, persistent hyperplasia, and renal cell tumour formation in male rats in response to chronic exposure to certain chemicals. Criteria were developed to identify a carcinogen that acts solely through α_{2u}-globulin nephropathy. In the opinion of the Working Group, the induction of renal-cell tumours alone, and in male rats only, by agents that fulfil these criteria is not predictive of a carcinogenic hazard to humans. If an agent also causes tumours at other sites in experimental animals, evidence regarding these other responses should be evaluated independently of the kidney tumours.

There is evidence that urinary tract calculi are associated with an increased risk of urinary bladder cancer in humans as well as in rodents. For chemicals that induce urinary bladder neoplasms in rats and mice as a result of calculus formation in the bladder, the Working Group thus concluded that such a tumour response *is* relevant to evaluations of carcinogenicity to humans, although large quantitative sex and species differences in response exist. Microcrystalluria is often associated with calculus formation, but its relevance to species-specific mechanisms could not be assessed. Amorphous precipitates of various compositions that can form in the urine may also be associated with bladder cancer development in rats. Precipitates that contain

calcium phosphate, such as those resulting from administration of high doses of some organic sodium salts, including sodium saccharin and sodium ascorbate, can lead to production of urinary bladder tumours in that species. This sequence is not known to occur in humans, and therefore the Working Group concluded that production of bladder cancer in rats is not predictive of carcinogenic hazard to humans, providing the agent fulfils criteria that were defined for activity exclusively involving calcium phosphate-containing precipitates. In cases where an agent also induces tumours at other sites in rats, evidence for tumorigenicity at non-bladder sites should be evaluated independently of tumours in the urinary bladder.

The individually authored papers and the Consensus Report will be published as IARC Scientific Publications No. 147.

2.2 Occupational causes of cancer

Occupational cancers have long been a focus of attention in research on the etiology and mechanisms of cancer because individual exposures, and therefore risks, in the work environment tend to be higher than in the general environment. In addition, the exposed population can be relatively easily defined, and exposures can be estimated from measurements or known characteristics of the work environment.

Studies at IARC have adopted two main approaches: on the one hand, multicentric international studies are conducted, mainly in industrialized countries, to investigate the effects of either low-level exposure to known carcinogens or suspected carcinogens with relatively weak potency; on the other hand, collaborative studies are conducted in specific circumstances in developing countries, where high levels of exposure are often encountered but the conduct of studies focused on occupational risks may be problematic. These studies in developing countries are based on the case–control approach, and are listed by cancer site (see Section 3.7 for studies of lung cancer, Section 3.8 for studies of laryngeal cancer and Section 3.6 for studies of urinary bladder cancer).

In addition, IARC has been active in methodological developments in the field of occupational epidemiology, in particular with respect to retrospective assessment of exposures [389] and quantification of the burden of occupational cancer [249, 457]. Extensive reviews have also been prepared on selected occupational risk factors for cancer [31, 204, 432].

2.2.1 Workers exposed to phenoxyacid herbicides and contaminants

P. Boffetta, P. Brennan and D. Colin; in collaboration with H. Becher, Heidelberg, Germany; T. Benn, Bootle, UK; P.A. Bertazzi, Milan, Italy; H.B. Bueno de Mesquita, Bilthoven, The Netherlands; D. Coggon, Southampton, UK; M. Fingerhut and K. Steenland, Cincinnati, OH, USA; D. Flesch-Janys, Hamburg, Germany; L.M. Green, Toronto, Canada; T. Kauppinen, Helsinki, Finland; M. Kogevinas, Barcelona, Spain; M. Littorin, Lund, Sweden; E. Lynge, Copenhagen, Denmark; J.D. Mathews, Casuarina, Australia; M. Neuberger, Vienna, Austria; N. Pearce, Wellington, New Zealand; R. Saracci, Pisa, Italy; and J. Vena, Buffalo, NY, USA

Studies of cancer risk have revealed excesses of soft-tissue sarcoma and non-Hodgkin lymphoma in populations exposed to phenoxy herbicides, chlorinated phenols and dioxins during manufacture, spraying or accidents. Dioxins, present as contaminants in some types of phenoxy herbicides, have been suggested as a causal factor, although excess risks have also been associated with exposure to herbicides not believed to have been contaminated with dioxins. Chronic bioassays and mechanistic data have

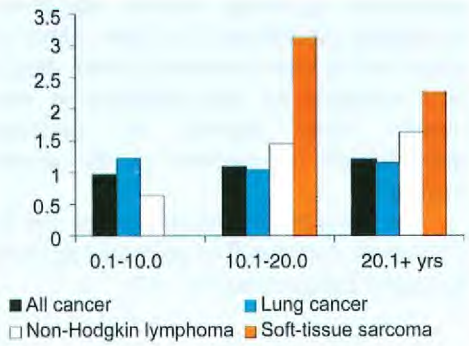

Figure 8. IARC study of herbicide workers. Mortality (SMR) by years since first exposure

indicated that contaminants of herbicides, particularly 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), are extremely potent carcinogens (see Section 2.1.5). Other chemicals in the same occupational environment (herbicides, chlorophenols, dioxin congeners other than TCDD, polychlorinated dibenzofurans, solvents) have also been associated in epidemiological studies and/or chronic bioassays with adverse health effects, including cancer.

IARC coordinates a cohort study of workers exposed to phenoxy herbicides, chlorophenols and dioxins in pesticide manufacture and spraying. In a cohort mortality analysis, excess risk was found among exposed subjects for soft-tissue sarcoma (SMR = 2.03, 6 deaths), while only slightly elevated risks were observed for lung cancer (SMR = 1.12, 225 deaths) and non-Hodgkin lymphoma (SMR = 1.39, 24 deaths). Risks for all neoplasms, sarcomas and lymphomas increased with time since first exposure (Figure 8). In an internal analysis, workers exposed to TCDD had an increased risk for all neoplasms (RR = 1.29, 95% CI 0.94–1.76) compared with workers exposed to phenoxy herbicides but with minimal or no TCDD exposure [200].

Additional analyses on non-neoplastic mortality showed increased risks of ischaemic heart disease (RR = 1.67) and diabetes (RR = 2.25) among TCDD-exposed workers compared with workers having minimal or no TCDD exposure.

TCDD serum levels are available for subgroups of workers included in this cohort in several countries. Analysis of 2310 workers from two factories in the Netherlands, based on estimated TCDD levels derived from extrapolations from a subset of 49 workers, showed increased risks of all cancers, lung cancer, non-Hodgkin lymphoma and ischaemic heart disease in workers with estimated high or medium TCDD level, compared with workers with predicted low TCDD level.

2.2.2 Workers exposed to styrene

P. Boffetta and G. Ferro; in collaboration with A. Andersen and J.E. Bjerk, Oslo, Norway; M. Biocca and C. Galassi, Bologna, Italy; D. Coggon and B. Pannett, Southampton, UK; V. Gennaro, Genoa, Italy; M. Kogevinas, Barcelona, Spain; H. Kolstad, Aarhus, Denmark; I. Lundberg and T. Bellander, Stockholm, Sweden; E. Lynge, A. Astrup-Jensen and N.O. Breum, Copenhagen, Denmark; T. Partanen and P. Pfaffli, Helsinki, Finland; R. Saracci, Pisa, Italy; and A. Spence, Bootle, UK

Increased risks for leukaemia and lymphoma have been suggested in studies of workers exposed to styrene in the rubber and plastics industry. An IARC-coordinated historical cohort study in Denmark, Finland, Italy, Norway, Sweden and the United Kingdom involved 40 688 workers employed in the reinforced plastics industry, where high exposure to styrene occurs. Exposure was estimated from job histories, environmental and biological monitoring data and production records of the plants. Analysis of cancer mortality suggested an association between styrene exposure and lymphohaematopoietic neoplasms.

Additional analyses have been conducted on non-neoplastic diseases in workers in this cohort. Mortality from diseases of the central nervous system increased with increasing exposure to styrene: the relationship with

cumulative exposure and duration of exposure followed a quadratic regression [492]. Mortality from diseases of the genitourinary system increased with increasing average intensity of exposure, but no relationship was present with cumulative exposure or duration of exposure [493]. Finally, there was no association between mortality from non-neoplastic respiratory diseases and styrene exposure [494].

2.2.3 Workers employed in the man-made vitreous fibre production industry

P. Boffetta, K. Kjaerheim, D. Sali and G. Ferro; in collaboration with A. Andersen, Oslo, Norway; P.A. Bertazzi, D. Consonni and I. Bernucci, Milan, Italy; J. Chang-Claude, Heidelberg, Germany; J. Cherrie, Edinburgh, UK; R. Frentzel-Beyme, Bremen, Germany; K. Guldner, Würzburg, Germany; J. Olsen and J. Hansen, Copenhagen, Denmark; N. Plato, Stockholm, Sweden; R. Saracci, Pisa, Italy; L. Teppo, Helsinki, Finland; P. Westerholm, Solna, Sweden; and P. Winter, Southampton, UK

A historical cohort study has been conducted since 1977 in 13 factories producing man-made vitreous fibres in seven European countries. A follow-up to 1991 showed an increased risk of lung cancer in the rock/slag wool component of the study, which was related to technological phase, time since first employment and duration of employment. No such increase was present in the other components of the study, glass wool and continuous filament production [34]. However, analyses based on a mathematical model of past fibre exposure in the rock/slag wool component did not show a dose–response relationship between lung cancer mortality and estimated cumulative fibre exposure when short-term workers were excluded and time since first exposure was accounted for (IARC Internal Report 96/002). A case–control study of lung cancer in the rock/slag wool component is in progress, to disentangle the contributions to the lung cancer excess of fibres, other occupational agents such as asbestos, and extra-occupational factors such as tobacco smoking. This study concerns 160 cases of lung cancer and over 600 controls, and follows a feasibility study conducted on 120 living workers, their next-of-kin and the next-of-kin of 149 deceased workers that indicated that interviewing next-of-kin of deceased workers yielded valid information on tobacco smoking and occupational exposures of the workers [142].

2.2.4 Workers employed in the pulp and paper industry

P. Boffetta, P. Brennan and D. Colin; in collaboration with A. Andersen, Oslo, Norway; P. Band, Ottawa, Canada; A. Bergeret, Lyon, France; W. Boal, Cincinnati, OH, USA; C. Bruno, Rome, Italy; D. Coggon; Southampton, UK; L. Facchini, Pelotas, Brazil; S. Finchen and C. Soskolne, Edmonton, Canada; M. Finkelstein, Toronto, Canada; P.K. Henneberger, Morgantown, WV, USA; P. Jäppinen, Imatra, Finland; T. Kauppinen, Helsinki, Finland; D. Kielkowski, Johannesberg, South Africa; A. Kraut, Winnipeg, Canada; E. Lynge, Copenhagen, Denmark; H. Miyake, Sapporo, Japan; N. Pearce, Wellington, New Zealand; B. Persson, Linköping, Sweden; J. Sunyer and M. Kogevinas, Barcelona, Spain; I. Szadkowska-Stanczyk, Lodz, Poland; and K. Teschke, Vancouver, Canada

In view of a possible increased risk of cancer at certain sites (lung, gastrointestinal tract, lymphatic tissues) among workers in the pulp and paper industry (which employs hundreds of thousands of workers worldwide), a multicentric international cohort study is being conducted. Personnel employed in plants producing pulp, paper and paper products and in mills involved in recycling are included. The cohort study has been completed in British Columbia (Canada), Brazil, Denmark, Finland, France, New Zealand, Norway, Poland, South Africa, Spain, Sweden, the United Kingdom and the USA; it is near to completion in Alberta, Manitoba, Ontario (Canada), Italy and Japan. The final cohort is planned to comprise over 100 000 workers. Reports from national components of the study have been published [78, 451]

and the combined results will be available in 1998. An industrial hygiene study is in progress [188], the final results of which will also be available in 1998.

2.2.5 Workers employed in the wood and leather industries

P. Boffetta, E. Merler and D. Colin; in collaboration with A. Blair and B.A. Miller, Bethesda, USA; S. Bonassi, Genoa, Italy; P. Demers, Vancouver, Canada; L. Hagmar, Lund, Sweden; M. Kogevinas, Barcelona, Spain; A. Seniori-Constantini, Florence, Italy; C.F. Robinson, R.J. Roscoe and F. Stern, Cincinnati, USA; S. Stellman, New York, USA; and P.D. Winter, Southampton, UK

Employment in the wood and leather industries entails exposures that are carcinogenic to humans. The main target sites in both cases are the nose and the nasal sinuses. Although information on specific exposures such as wood dust, leather dust, formaldehyde, solvents and preservatives was collected in many epidemiological studies, it could not be fully used, because of the relatively small size of each individual study. The raw data of the cohort studies on workers employed in these industries and case–control studies on nasal cancer, obtained from the original investigators, were transformed into a common format and analysed according to specific exposures [87].

A combined analysis of cohort studies of shoe-manufacturing workers showed an increased risk of haematopoietic neoplasms [113].

2.2.6 Workers employed in asphalt industry

P. Boffetta, M. Castegnaro and C. Genevois; in collaboration with P. Bonnet, M. Lafontaine and S. Binet, Vandoeuvre, France; H. Brandt, Amsterdam, The Netherlands; M. de Méo, Marseille, France, R. Frentzel-Beyme, Bremen, Germany; D. Heederik and H. Kromhout, Wageningen, The Netherlands; B. Jarvholm, Umeå, Sweden; T. Kauppinen, T. Partanen and P. Heikkilä, Helsinki, Finland; A.J. Kriech, Indianapolis, IN, USA; S. Langård, Oslo, Norway; A. Pfohl-Leszkowicz, Toulouse, France; J. Shaham, Raanana, Israel; I. Stücker, Paris, France and O. Svane, Copenhagen, Denmark (with support from a contract with the European Asphalt Pavement Association, Breuktlen, The Netherlands and a grant from the French Association pour la Recherche sur le Cancer)

The assessment of cancer risk from exposure to asphalt fumes is particularly difficult because of the complex and variable nature of asphalt, the occurrence of co-exposures (motor engine exhaust, tobacco smoking) and the characteristics of the workforce (seasonal employment, instability, low skill). Epidemiological studies have suggested an increased risk of cancer of the lung and other organs, but could not separate the contribution of asphalt fumes from those of other agents.

An historical cohort study was initiated in 1996 in seven European countries (Denmark, Finland, France, Germany, the Netherlands, Norway, Sweden) and in Israel. The aim is to enrol 54 000 asphalt workers with an average of 11 years of follow-up for cancer mortality, and a conventional cancer mortality study will be completed in 1998 for the major cancer sites. In parallel, exposure data are being collected from participating companies and from other sources, to classify workers according to estimated exposure to asphalt fumes and to other agents. Subsequently, a nested case–control study may be initiated, including some 150 workers who suffered from lung cancer and 450 matched controls.

In parallel with the epidemiological study, a study on DNA adduct formation following inhalation of bitumen or coal-tar vapour/particulates has been undertaken in collaboration with the French Institut National de Recherche et de la Sécurité (INRS) and the Heritage Research Group in the USA.

A new inhalation chamber developed at INRS (Vandoeuvre France) and a new fume generator developed by the Heritage

Research Group (Indianapolis, USA) and adapted at INRS were used. Under the conditions of use, the concentration of particles was homogeneous in the inhalation chamber and the particle size distribution was reproducible.

In the first series of experiments, specific pathogen-free BD6 rats from Charles Rivers (Germany) were exposed during six hours a day for five days to concentrations in the generation chamber of 5 ± 2 mg/m^3 of particulate matter from bitumen heated at 200 °C or coal-tar at 110 °C. No adducts were detected in lung or lymphocytes in either experiment (at a detection limit of ≈5 adducts per 10^9 normal nucleotides). This may be explained by the poor sensitivity of the rat to inhalation of particulates (Schlesinger, 1985, *J. Toxicol. Environ. Health*, **15**, 197–214). It has been demonstrated that extreme conditions are required to induce lung tumours in the rat by inhalation of coal-tar particulates (Heinrich *et al.*, 1994, *Toxicol. Lett.*, **72**, 155–161).

In a further inhalation study with about 10 times more particulate matter in the atmosphere of the cage (i.e., 50 mg/m^3) and proportionately much higher concentrations of polycyclic aromatic hydrocarbons, an adduct corresponding to the major adduct formed in the lung during a skin painting study with BD4 rats was detected at an RAL of 6 per 10^9 normal nucleotides. This adduct may therefore become a candidate biomarker of exposure to bitumen fumes to be used in epidemiological studies.

In order to identify cytochrome P450s implicated in the biotransformation of coal tar and bitumen fumes and the role of the aryl hydrocarbon receptor (AhR), incubations were performed in the presence of liver microsomes from untreated C57BL/6 mice (AhR-responsive) and from genetically modified C57BL/6 mice defective in the AhR or in CYP 1A2. In addition, liver microsomes of benzo[*a*]pyrene-treated mice (AhR-responsive and AhR-defective) were used, to assess the involvement of CYP 1A1 and other enzymes induced by benzo[*a*]-pyrene. Incubations were also carried out in the presence of yeast microsomes expressing specifically human CYP 1A1 or 1A2 and human CYP 1A1 with microsomal epoxide hydrolase (mEH).

The results obtained indicate that the AhR plays an important role in the biotransformation of both types of condensate. CYP 1A isoforms (1A1 and 1A2) are by no means exclusively responsible for the genotoxicity of the compounds contained in these condensates. These CYPs are both involved in the generation of the genotoxic compounds found in coal tar vapour condensates and the reactive metabolites formed by CYP 1A1 are substrates for epoxide hydrolase. The genotoxicity of the bitumen fume condensates, in contrast, is independent of CYP 1A2 and the reactive metabolites formed by CYP 1A1 in this case are not substrates for epoxide hydrolase; CYP 1A2 may have detoxifying activity or no activity at all. These results strongly suggest that the genotoxic substances in these two classes of condensates are different.

2.2.7 Workers exposed to inorganic mercury

P. Boffetta, E. Merler, P. Brennan and D. Colin; in collaboration with T. Bellander, Stockholm, Sweden; M. Garcia-Gomez, Madrid, Spain; V. Pompe-Kirn, Ljubljana, Slovenia; G. Sallsten, Gothenburg, Sweden; and D.G. Zaridze and M. Bulbulyan, Moscow, Russian Federation

An increase in lung cancer risks among workers exposed to mercury has been suggested in a number of epidemiological studies. Among the industries entailing, in the present or the past, high levels of exposure to mercury are the mining or milling of the metal, thermometer production and felt-hat manufacture.

A historical cohort study has been conducted under the coordination of IARC

in the four European countries with large mercury mines (Italy, Slovenia, Spain, Ukraine). Special care is being given to the reconstruction of industrial hygiene data (exposure levels to mercury and co-exposures such as silica) [10]. The results of the mortality analysis did not show increased risk of cancers of the kidney, liver or brain, that were sites of a-priori interest (Table 2). Liver cancer mortality was increased in Italy and Slovenia, but liver cancer incidence was not increased among Slovenian miners. Lung cancer mortality was increased, but the increase was restricted to miners and was not associated with duration of employment. Among female workers from Ukraine, five deaths from ovarian cancer occurred, representing a strong excess. Additional analyses are in progress to estimate the risk from cumulative exposure to inorganic mercury.

Table 2. Mortality from selected neoplasms among male mercury miners and millers

Cause of death	Obs. no.	SMR	95% CI
All malignant neoplasms	577	0.90	0.83–0.98
Stomach	87	0.92	0.74–1.13
Liver [a]	41	1.59	1.14–2.16
Lung	214	1.28	1.11–1.46
Prostate	36	0.88	0.61–1.21
Kidney [a]	6	0.58	0.21–1.27
Brain [a]	14	1.00	0.54–1.67

[a] Reference rates for Ukraine not available: results are shown for Italy, Spain and Slovenia.

2.2.8

Workers exposed to vinyl chloride

P. Boffetta, P. Brennan, V. Gaborieau, R. Montesano and D. Sali; in collaboration with A. Andersen and S. Langård, Oslo, Norway; S. Belli and R. Pirastu, Rome, Italy; G. Engholm and I. Lundberg, Stockholm, Sweden; L. Hagmar, Lund, Sweden; J. Hodgson, Bootle, UK; and M.C. Marion, Lyon, France

An international cohort study of cancer mortality and incidence among workers exposed to vinyl chloride in its production and polymerization was coordinated by IARC and conducted in Italy, Norway, Sweden and the United Kingdom during the 1980s (Simonato *et al.*, 1991, *Scand. J. Work Environ. Health*, **17**, 159–169). The study showed an increased risk of liver angiosarcoma; the statistical power to evaluate the risk of other neoplasms possibly linked to vinyl chloride, such as hepatocellular carcinoma and brain tumour, was limited. The cohort study is therefore currently being updated, yielding 10 additional years of follow-up. The data will be analysed in 1998. In addition, archival tumour samples are being collected from workers who suffered from hepatocellular carcinoma, brain tumour or lung cancer, to assess whether the mutation spectrum in the *p53* tumour-suppressor gene resembles that found in liver angiosarcomas of exposed workers and laboratory animals (Hollstein *et al.*, 1994, *Carcinogenesis*, **15**, 1–3).

2.2.9

International study of cancer risk in biology research laboratory workers

A.J. Sasco, B. Rachet and I. Gendre; in collaboration with A. Ahlbom, Stockholm, Sweden; S. Belli, Rome, Italy; S. Benhamou, Villejuif, France; F. Berrino, Milan, Italy; B. C. Chilvers, Nottingham, UK; F. Hatton, Le Vésinet, France; B. Herity, Dublin, Ireland; O.H. Iversen, Oslo, Norway; T. Kauppinen, Helsinki, Finland; J.J. Moulin, Vandœuvre-lès-Nancy, France; C. Teissier, Strasbourg, France; M. Tirmarche, Paris, France; F. van Leeuwen, Amsterdam, The Netherlands; and D. Vecchio and R. Puntoni, Genoa, Italy

Following the occurrence of several cancer clusters in research institutions, and confronted with the lack of any large-scale assessment of cancer risk linked to biological hazards, IARC proposed a retrospective cohort study of all staff having been employed for at least one year and one day in public research institutions. Following a feasibility phase, the study was implemented in eight European countries (Finland, France, Ireland, Italy, the Netherlands, Norway, Sweden and United King-

dom). So far, approximately 60 000 subjects have been enrolled in the cohort, which is now complete. Mortality assessment has been carried out at most collaborating institutions and results for several subcohorts (Italy [477], Ireland, the Netherlands [476] and United Kingdom [48]) have been published. Analysis of the whole pan-European cohort is now proceeding at IARC. Cancer risk will be assessed for specific scientific activities such as virology, molecular biology and biochemistry. In addition, smaller-scale projects are being conducted to study issues of exposure assessment. In particular, a specific study (Exposure to Viruses in the Laboratory (EVIL) Programme) is evaluating exposures to animal retroviruses as well as selected DNA viruses in various occupational research groups. All these projects benefit from funding from the Europe Against Cancer and BioMed programmes of the European Union, as well as various national funds.

2.2.10

Asbestos exposure and mesothelioma risk in Europe

P. Boffetta and E. Merler; in collaboration with A. Biggeri, Florence, Italy; A. Burdorf, Rotterdam, The Netherlands; M. Goldberg, Paris, France; and J. Siemiatycki, Montreal, Canada

Asbestos is the main cause of pleural and peritoneal mesothelioma. The aims of this project are to describe the pattern of use of asbestos in European countries and the occurrence and temporal trends of mesothelioma incidence and mortality, to explore the implications of changes in diagnostic practices on observed trends, to explore models for prediction of future trends, and to explore existing surveillance programmes to study detailed aspects of the asbestos–mesothelioma relationship, including the pattern of risk after cessation of exposure [250]. A meeting of European investigators took place in Paris in December 1997, at which areas for future collaboration were identified, including the estimation and prediction of mesothelioma trends, and pooled analyses of studies based on lung fibre burden and of nationwide surveillance programmes of asbestos-exposed workers.

2.2.11

Estimation of the burden of occupational cancer in Europe

P. Boffetta, E. Merler and P. Brennan; in collaboration with W. Ahrens and K.H. Jockel, Hessen, Germany; A. Andersen, Oslo, Norway; L. Barlow, Stockholm, Sweden; F. Berrino, Milan, Italy; R. Cartwright, Leeds, UK; J. Chang-Claude, Heidelberg, Germany; S. Cordier and D. Luce, Paris, France; C.A. González and J. Sunyer, Barcelona, Spain; T. Kauppinen, T. Partanen and E. Pukkala, Helsinki, Finland; M. Kogevinas, Barcelona, Spain; E. Lynge and J. Olsen, Copenhagen, Denmark; F. Merletti and P. Vineis, Turin, Italy; L. Simonato, Padua, Italy; and T. Tzonou, Athens, Greece

The prevalence and intensity of occupational carcinogenic exposures and the incidence of occupational cancer in European countries are being estimated in order to provide a basis for a comprehensive programme of prevention and control of occupational cancer in Europe. Extensive epidemiological and industrial hygiene data are used to estimate the number of workers exposed to occupational carcinogens at levels above background and to identify the occupations and industries facing the greatest risk. In addition, combined analyses are being carried out on available population-based case–control studies from Europe of sinonasal cancer (see Section 2.2.5), bladder cancer, laryngeal cancer and lung cancer (see Section 3.7.3), in order to estimate the proportion of cancers attributable to occupational exposures.

2.2.12

Occupational cancer in women

P. Boffetta, K. Kjaerheim and P. Brennan; in collaboration with L. Carpenter, Oxford, UK; E. Lynge, Copenhagen, Denmark; H. Gunnarsdottir, Reykjavik, Iceland; M. Kogevinas, Barcelona, Spain; A. Miranda, Lisbon, Portugal; T. Partanen, Helsinki, Finland; R.

Pirastu, Rome, Italy; E. Roman, Leeds, UK; and E. Weiderpass, Stockholm, Sweden

Relatively few epidemiological studies have specifically examined cancer risks among female workers and these studies have tended to be inconclusive, largely because insufficient numbers of events were studied. In some European countries, occupational information is routinely collected at cancer registration, whilst in others —most notably the Nordic countries —occupational information can be obtained by linking cancer registry files with occupational information collected at census surveys. These large population-based data-sets provide an opportunity to investigate cancer risks in women across a wide range of occupational groups. A project has been initiated to analyse the mortality of women by occupation and industry in Denmark, Finland, Italy, Norway, Portugal, Sweden and the United Kingdom.

2.2.13
Social inequalities and cancer

P. Boffetta; in collaboration with F. Faggiano, Turin, Italy; M. Kogevinas, Barcelona, Spain; T. Partanen, Helsinki, Finland; N. Pearce, Wellington, New Zealand; and M. Susser, New York, USA

It has been known for many decades that incidence and survival of cancer markedly vary according to social class. The pattern depends on the tumour site, with breast, prostate and colon cancers being more frequent in higher social classes and lung, stomach, oesophageal, laryngeal and oral cancers showing the opposite association. Most studies have been conducted in the USA, Canada, the United Kingdom and the Nordic countries. A systematic review of published and unpublished data on cancer incidence and mortality (Figure 9) and on survival from cancer by social class has been conducted and published in the IARC publication *Social Inequalities and Cancer* . This publication also contains a series of contributions addressing the contribution of

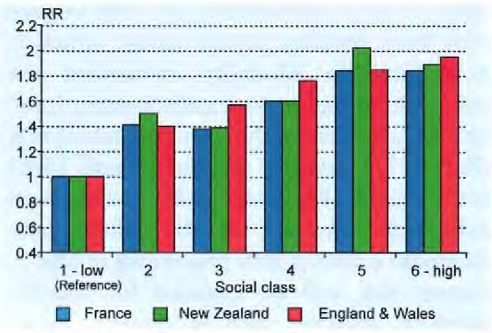

Figure 9. Mortality from all cancers among men in selected countries by social class. Note: social class was measured using different scales in the different countries

social differences in the exposure to risk factors, such as tobacco smoke and diet, and in access to health care, in explaining cancer patterns by social class [202].

2.2.14
Other collaborative studies of occupational cancer

P. Boffetta, G. Ferro and D. Colin; in collaboration with M. Bulbulyan, Moscow, Russian Federation; P.L. Cocco, Cagliari, Italy; N. Jourenkova, Paris, France; and E. Lynge, Copenhagen, Denmark

A collaborative study of Russian fertilizer workers, with the Institute of Carcinogenesis in Moscow, suggested an increased risk of stomach cancer, possibly related to exposure to nitrogen oxides, and of lung cancer, probably due to exposure to arsenic [51]. A collaborative study with the Insti tute of Occupational Medicine in Cagliari, Italy, focused on cancer risk among lead smelter workers: an increased risk of lung cancer was found, as in previous studies in the same group of workers [76]. An analysis based on results from linkage between census and cancer registry data in, Denmark, Finland, Norway and Sweden suggested an increased risk of sinonasal cancer among service-station attendants exposed to gaso line vapours: no increase in kidney cancer risk was seen [227].

2.3 *Diet, nutrition, hormones and cancer*

Epidemiological studies on nutrition and cancer have provided strong evidence that diet, as well as other related variables such as body measurements and physical activity, can influence the risk of developing various types of cancer. However, the relationship between diet and cancer is a complex one in which the relative balance between different types of food may be as important as the absolute intake of any single food. On the one hand, a dietary pattern characterized by high intake of vegetables and fruit is associated with a reduced risk of cancers of the digestive and respiratory tracts and possibly of other cancer sites (breast) and, on the other hand, a diet characterized by high intake of meat, particularly red meat and animal fat, is associated with an increased risk of cancer of the colon and rectum. In addition, some particular foods consumed in limited geographical areas have been found to increase the risk of specific cancers, e.g., salted and fermented fish and naso-pharyngeal cancer in some areas of south-east Asia. Epidemiological and laboratory research is now attempting to identify the specific food constituents which are biologically responsible for these complex effects of either reduction (vegetables and fruit) or increase (meat and meat products) in cancer risk.

In order to investigate these issues, which have worldwide public health implications, IARC has developed several epidemiological and laboratory research projects based on different populations around the world. The largest IARC project in this field is the network of prospective cohort studies, which incorporates over 400 000 study subjects in 10 countries (see Sections 2.3.1 and 2.3.2).

2.3.1 European Prospective Investigation into Cancer and Nutrition (EPIC)

E. Riboli, R. Kaaks, N. Slimani, C. Casagrande and B. Hémon; in collaboration with: *Denmark:* A. Tjønneland, Copenhagen; K. Overvad, Aarhus; *France:* F. Clavel, M. van Liere and C. Guibout, Villejuif; *Germany:* H. Boeing and A. Kroke, Potsdam; J. Wahrendorf and N. Becker, Heidelberg; *Greece:* A. Trichopoulou and K. Katsouyanni, Athens; *Italy:* F. Berrino and V. Krogh, Milan; P. Vineis and B. Terracini, Turin; D. Palli and E. Buiatti, Florence; R. Tumino and L. Gafà, Ragusa, S. Panico, Naples; *The Netherlands:* P. Peeters, Utrecht; H.B. Bueno de Mesquita, J. Seidell, Bilthoven; *Spain:* C.A. González and A. Agudo, Mataró; J.R. Quíros, Oviedo; C. Martinez, Granada; M. Dorronsoro, San Sebastian; C. Navarro, Murcia; A. Barricarte, Pamplona; *Sweden*: G. Berglund, Malmö; G. Hallmans, Umeå; *UK*: N.E. Day, S. Bingham, S. Oakes and A. Welch, Cambridge; T.J.A. Key and G. Davey, Oxford; and R. Saracci, Pisa, Italy (coordinator of the EPIC-HEART European Concerted Action)

The EPIC project is a multi-centre prospective cohort study designed to investigate the relation between diet, nutritional status, various lifestyle and environmental factors and the incidence of different forms of cancer and other chronic diseases (e.g., cardiovascular diseases, stroke and diabetes). The study includes over 400 000 subjects in nine European countries, for whom detailed data on diet and lifestyle as well as biological samples (plasma, serum, lymphocytes and erythrocytes) have been collected. The study is designed to address the major issues regarding the role of diet in relation to the occurrence of specific cancers, namely:

(1) Search for the specific food components which could explain why diets rich in fruit and vegetables can reduce the risk of cancer of the digestive, respiratory and upper aerodigestive tracts and of other anatomical sites.

(2) Identification of the factors responsible for the increase in risk of cancers of the colorectum observed in relation to high consumption of animal fats, meat and meat products.

(3) Search for the factors which could explain the large geographical variations in cancers of the organs of the reproductive system, particularly cancers of the prostate, testis, breast, ovary and endometrium, for which little is known about their relationship to environment and lifestyle.

(4) Investigation of the interaction of genetic predisposition and metabolic host factors with the environment and lifestyle in determining the risk of cancer.

A unique characteristic of the EPIC study is that biological samples have been collected from an unprecedentedly large number of study subjects and stored at very low temperature (–196°C in liquid nitrogen), which will allow biochemical, molecular biology and genetic studies to be conducted on samples from the subjects who subsequently develop cancer (or other diseases of interest) and control subjects who remain free of cancer.

Follow-up of the study subjects has been initiated through population-based cancer registries, health insurance schemes, medical records and death certificates. In addition, follow-up questionnaires are being sent to all study subjects every 3–5 years to collect information on self-reported health problems and lifestyle changes.

Baseline data: Data on usual current diet were collected by means of detailed dietary assessment methods developed and tested during methodological studies. In addition, full information was obtained, by means of a standardized questionnaire, on physical activity, tobacco smoking, alcohol consumption, occupation and socioeconomic status, reproductive history, contraception and hormone replacement therapy, previous illnesses and current drug use. These factors were selected because they may be related to diet and nutritional status or may interact with diet in multifactorial carcinogenic processes.

Anthropometric measurements (weight, height, waist and hip circumferences, sitting height) were taken using standard procedures.

Table 3. Subject recruitment in the EPIC study (September 1997)

	Subjects included in the study with		Additional subjects	End of subject
	Questionnaire	Blood collection	to be recruited	recruitment
Spain	41 529	40 040	–	Completed 1996
Italy[a]	43 351	43 667	4 000	Jan. 1998
UK	76 041	40 901	–	Dec. 1997
Netherlands	38 350	34 850	4 000	Dec. 1997
France	72 000	12 000	–	Completed 1993[b]
Germany	37 163	35 348	8 000	Nov. 1998
Greece	18 200	19 104	6 000	July 1998
Total 7 countries	326 534	225 910	22 000	
Associated projects:				
Sweden	57 932	62 122	–	Completed in 1996
Denmark	57 100	56 800	–	Completed in 1997
Total 9 countries	441 566	344 832	22 000	

[a] Italy includes the EPIC-associated project in Naples

[b] Collection of blood samples only will be extended until December 1998.

Figure 10. Collaborating centres in the European Prospective Investigation into Cancer and Nutrition

The full project was started in 1992 after completion of methodological and feasibility studies conducted between 1989 and 1992 in each of the collaborating centres. Results of the studies on the validity of the dietary questionnaires designed for EPIC and of the relationship between measured nutrient intakes and biomarkers were published in a supplement to the *International Journal of Epidemiology* devoted entirely to the EPIC study [235].

Participating centres: The study originally included 17 centres in seven countries (France, Germany, Greece, Italy, the Netherlands, Spain and the United Kingdom). In 1995 and 1996 the investigators in charge of four similar prospective studies decided to join EPIC as associated projects: in Sweden the Malmö Diet and Cancer Study (Malmö) and the Västerbotten County project (based in Umeå), in Denmark (one study in two centres, Copenhagen and Aarhus), and in Italy (the ATENA study in Naples). The extension of the study to these two Nordic countries and one additional Mediterranean region will further increase the scientific power of the project by increasing the diversity of the populations included and the total study size. Table 3 summarizes the situation of subject recruitment in September 1997 and the expected final size of the cohort. Figure 10 illustrates the geographical coverage of the study.

2.3.2

The New York University Women's Health Study: nutrition and cancers of the breast and colorectum

E. Riboli, R. Kaaks, G. Schulgen and M. Miginiac; in collaboration with: P. Toniolo, R.E. Shore and A. Zeleniuch-Jaquotte, New York, USA

The main goal of this study, which was initiated in 1985, was to investigate hormonal and nutritional factors in the etiology of cancers of the breast, endometrium, ovary and colorectum. During 1985–88, about 14 500 women living in the New York metropolitan area volunteered to participate. Data and blood samples were collected while the women were attending mammographic screening at the Guttman Institute. Data on diet were collected by means of a self-administered food frequency questionnaire originally designed by the US National Cancer Institute.

During the study, the reproducibility of the questionnaire was tested in field conditions by asking a subsample of the subjects to complete the questionnaire on three occasions. The results indicated fairly good reproducibility of dietary measurements, both short-term (3 months) and long-term (1–5 years) [372].

The risk of developing breast cancer in relation to dietary habits was first analysed in a preliminary case–control study nested in the cohort, and has now been investigated on the entire cohort data, based on 600 incident breast cancer cases diagnosed after subject recruitment between 1985 and 1995. The main results are that the risk of developing breast cancer is lower in women who consume more vegetables and fibre-rich foods. Consumption of fish was associated with reduced risk in post- but not pre-menopausal women.

A biochemical epidemiology study on prediagnostic blood levels of carotenoids and tocopherol has been carried out on 270 breast cancer cases and 270 matched controls (see Section 2.3.3).

2.3.3

Studies on breast cancer and prediagnostic levels of carotenoids, tocopherols and retinol

E. Riboli, A.L. van Kappel, B. Vozar and D. Achaintre; in collaboration with G. Hallmans, K. Hulten and A. Winkvist, Umeå, Sweden, J.P. Steghens and C. Collombel, Lyon, France; and P. Toniolo and R.E. Shore, New York, USA

In recent years, several case–control and prospective studies have found that women with very low intake of vegetables seem to be at higher risk of breast cancer. Blood concentrations of the different carotenoids have been shown to be related to consumption of different types of vegetables, to the way they are cooked, and to a number of nutritional and biological factors influencing carotenoid absorption and metabolism.

A new rapid and reliable method for measuring carotenoids, tocopherols and retinol by HPLC was set up at IARC [440], to be used mainly for analyses on blood samples from biological banks of prospective cohort studies such as EPIC. A first investigation on prediagnostic levels of carotenoids, tocopherols and retinol was conducted within the New York University Women's Health Study (see above) on stored samples from 270 subjects who developed breast cancer and from 270 matched control subjects who remained free of breast cancer during the follow-up period. We measured seven carotenoids (α-carotene, β-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, canthaxanthin) and two tocopherols (α- and γ-) and retinol. The main results are that incidence of breast cancer among women with low levels of α- and β-carotene is twice as high as among women with higher levels. Overall the carotenoid levels in these subjects were relatively low and related to dietary intake. The effects found cannot be ascribed to the use of β-carotene supplements.

2.3.4
Studies on breast cancer and fatty acid concentrations in plasma and cell membrane phospholipids

E. Riboli, V. Chajès, B. Vozar and D. Achaintre; in collaboration with F. Berrino, Milan, Italy; P. Bougnoux, Tours, France; and G. Hallmans, Umeå, Sweden

Experimental studies on laboratory animals on the role of different types of fats have shown that mammary carcinogenesis is generally promoted by saturated and *n*–6 polyunsaturated fatty acids, while *n*–3 fatty acids (particularly the long-chain eicosapentaenoic and docosahexanoic acids) generally have an anti-carcinogenic effect. The main source of long-chain *n*–3 fatty acids in the human diet is fatty fish, while *n*–6 fatty acids are very widely present in vegetable oils and meats.

A few epidemiological studies have investigated the relationship between consumption of fish and breast cancer risk. Some found a protective effect; others did not. Other studies have measured fatty acids in plasma from breast cancer patients and controls, with contradictory results.

In 1996 two studies were initiated on fatty acids and breast cancer risk nested within two prospective cohort studies, one in the north of Sweden (the Västerbotten study) and the other in Italy (ORDET), with the aim of investigating whether the fatty acid composition of biological samples collected years before diagnosis is related to the risk of developing breast cancer.

In the Swedish study, measurements of plasma phospholipids have been made on 196 cases and 390 controls. It has been possible to determine the levels of 24 different fatty acids including all the saturated as well as the *n*–9, *n*–6 and *n*–3 series of unsaturated fatty acids. In addition, the level of the *trans* fatty acid 18:1 (*n*–9) has been determined. Preliminary statistical analyses of the data indicate that there are no strong differences in overall fatty acid composition between breast cancer cases and controls but that, as expected, the levels of eicosapentaenoic acids are lower among cases. In addition, the level of stearic acid was lower in plasma phospholipid from breast cancer patients compared to controls.

In the Italian component of the study, fatty acids are being measured in erythrocyte membranes, and results will be available in early 1998.

2.3.5
Nutrition, hormones and cancers of the breast and colorectum

R. Kaaks and E. Riboli; in collaboration with G. Berglund, Malmö, Sweden; F. Berrino, Milan, Italy; H. Dechaud, Lyon, France; and G. Hallmans, Umeå, Sweden

Increasing evidence suggests that in western societies the high incidence rates of cancers of the colon and rectum, as well as of the breast (in women), may be explained by the high prevalence of a metabolic profile, often referred to as 'syndrome X', characterized by (fasting and non-fasting) hypertriglyceridaemia and hyperinsulinaemia. The development of this metabolic profile is intricately related to the development of mild to more severe forms of (intra-abdominal) obesity, to a sedentary type of lifestyle with low levels of physical activity, and to a diet rich in fat (especially saturated fats) and refined carbohydrates and poor in dietary fibre. Hypothetical mechanisms by which this metabolic profile may be related to increased risk of colorectal cancer are that:

(1a) high plasma levels of triglycerides may lead to increased excretion of bile acids into the gut lumen; the bile acids, in turn, may be transformed by the gut microflora into secondary bile acids with tumour-initiating or -promoting activity; and

(1b) insulin at higher plasma concentrations may act as a growth factor, stimulating the proliferation of normal or neoplastic cells, and inhibiting apoptosis.

Mechanisms by which the same metabolic profile may be related to an increase in breast cancer risk are that:

(2a) chronic hyperinsulinaemia causes an increase in plasma concentrations of ovarian sex steroids (estradiol, testosterone) by decreasing the hepatic production and plasma levels of sex hormone-binding globulin (SHBG) and, possibly, by enhancing ovarian sex steroid production; and

(2b) insulin may act directly as a growth factor [173].

The processes linking insulin to the development of colorectal and breast cancers may be enhanced by increased activity of insulin-like growth factors, especially insulin-like growth factor type I (IGF-I), which is also modulated by factors related to nutritional status and to insulin metabolism [173].

The relationships between diet, plasma levels of insulin, IGF-I, IGF-binding proteins and plasma steroid hormone levels, and the relationships of these hormonal factors with cancer risk are being investigated in collaboration with some established projects:

The 'DIANA' intervention study (National Cancer Institute, Milan, Italy; project leader: Dr F. Berrino) was designed in collaboration with IARC, to investigate the effects on plasma hormone levels of a number of simultaneous changes in diet (reduction of total fat intake, a change in fat composition towards higher intake of *n*–3 fatty acids, reduced consumption of foods with high glycaemic and insulinaemic responses, consumption of foods rich in phyto-estrogens). The main results of the dietary intervention (an increase in plasma levels of SHBG, and a decrease in intra-abdominal body fat stores, plasma levels of testosterone, free estradiol, and insulin) were all as expected. Additional analyses on the relation between diet-related changes in plasma levels of growth hormone, IGF-I and IGF-binding proteins, and changes in plasma levels of SHBG are in progress.

Network of ongoing prospective cohort studies, including the *New York University Women's Health Study* (see Section 2.3.2), the *'ORDET' study* (National Cancer Institute, Milan, Italy), the *Västerbotten County Cohort Study* (Umeå University; northern Sweden), and the *Malmö Diet and Cancer Study* (University of Malmö; southern Sweden). Within the New York University Women's Health Study, the relation between the risk of developing colon cancer and serum levels of insulin, IGF-I, and IGF-binding proteins is under investigation. The laboratory analyses of serum levels of the various peptide hormones started in autumn 1997 at the Hôpital de l'Antiquaille, Lyon (collaboration with Dr Dechaud), and first results are expected in early 1998. This study on colorectal cancer will be extended to the cohorts in Sweden (Västerbotten; Malmö) and in Italy (Milan).

Similar studies on plasma levels of insulin, IGF-I and IGF-binding proteins are being planned in relation to breast cancer risk (this study will include the cohorts in Västerbotten, Malmö, and Milan; first results expected during 1998) and in relation to cancer of the prostate (Västerbotten County Study).

2.3.6 Nutrition, hormones, genetic predisposition and cancer of the prostate

E. Riboli, R. Kaaks and B. Sommersberg; in collaboration with G. González and A. Agudo, Mataró, Spain; L. Fernandez, R. Jimenez, V. Osorio, T. Norat, and Y. Galan, Havana, Cuba; P. Toniolo, New York, USA; S. Shankar, Baltimore, MD, USA; and J. Iscovich, Jerusalem, Israel

The incidence of prostate cancer varies very widely between different populations, being highest in black Americans, intermediate in white Americans and western Europeans, and lowest in Asians. It is hypothesized that these differences (up to 20-fold between the highest and lowest rates) are

probably due to a combination of genetic susceptibility and lifestyle factors, including western diet and obesity.

A network of case–control studies in various populations of Caribbean islands, North America and Israel has been planned, to test specifically the interaction between genetic, hormonal and nutritional factors. Two genetic polymorphisms have already been identified which could play a role in prostate cancer incidence, one on the androgen receptor gene (chromosome X) and the other on the testosterone 5- α-reductase gene (SRD5A2, chromosome 2). Genetic polymorphisms of these genes, encoding for the most active forms of the receptor and the enzyme, have been found to be more frequent among American-African blacks than in Caucasians or Asians. A case–control study is being set up in Havana, Cuba, in which questionnaire data will be collected on current diet, lifestyle and reproductive and sexual history. Anthropometric measurements will be taken using standardized methods, and past height and weight will be sought. Blood samples from both cases and controls and tumour samples will be collected and stored. This first component of the project is planned to be completed in 1999. Studies in other populations will be started during 1998.

2.4 Tobacco and cancer

Tobacco is certainly the most widely disseminated carcinogen in the world. Whereas some countries have reacted to that evidence by effective efforts to control tobacco use and promotion, others clearly lag behind and for the developing world, predictions are extremely pessimistic. Currently the annual world burden of tobacco-related deaths is about 3.5 million, but by the year 2020 it will be around 10 to 12 million. Scientific questions remain to be solved, in particular in terms of genetic susceptibility to tobacco, both for smokers and non-smokers, as well as interaction with putative dietary anticarcinogens. For public health purposes, urgent action is needed with careful evaluation of its outcome.

A number of studies of lung, bladder and head and neck cancers addressing various aspects of the carcinogenic effect of tobacco smoke are reported in Sections 3.6, 3.7 and 3.8.

2.4.1 Health habits and knowledge of children and young people

A.J. Sasco, I. Gendre and C. Dussart; in collaboration with G. Dubois, Versailles, France; A. Hirsch, Paris, France; M. Jambon, Lyon, France; S. Linn, Haifa, Israel; T. Sahi, Helsinki, Finland; and E. Wynder, New York, USA

Detailed investigations are being carried out among children, adolescents and young adults to evaluate risk factors for smoking and other substance abuse behaviour. Studies of nearly 2000 children have been conducted in the Loire and Rhône départements of France [406], of 1000 adolescents in the Rhône, and of 5000 military recruits also in the Rhône region. The study on military recruits is now being conducted also in Israel and in Finland, using a common questionnaire. Specific aspects of cancer prevention in relation to health promotion have been studied [396, 397].

2.4.2 Evaluation of the efficacy of various anti-smoking strategies

A.J. Sasco, R. Ah-Song and I. Gendre

Evaluation of anti-smoking strategies is being carried out at the local, national and European levels. This comprises evaluation of activities for health promotion among children and adolescents, as well as

activities more specifically targeted at decreasing involuntary exposure to tobacco smoke [397], particularly in the workplace, and at inducing general practitioners to become more determined health advocates [115]. At the national level, legislation is an integral part of any comprehensive anti-smoking programme and may have a substantial impact [391]. The 1992 study comparing all European Community anti-smoking legislation is being updated, within the framework of the EuroLego programme funded by the Europe Against Cancer programme of the European Union. The report being prepared will now include all 15 member states as well as an update to 1997.

2.4.3

Cohort study of tobacco use and mortality in India

D.M. Parkin, A.J. Sasco and R. Sankaranarayanan; in collaboration with P.C. Gupta, Bombay, India; A. Lopez, Geneva, Switzerland; B. Mathew, K.T. Shenoy, Trivandrum, India; and R. Peto, Oxford, UK

A cohort of 150 000 individuals (90 000 males and 60 000 females) aged at least 35 years was recruited from among permanent residents of a specific area of Mumbai (Bombay), India, during 1991–97, in a house-to-house survey and interviewed about smoking and smokeless tobacco use.

Among 40 071 men and 59 527 women recruited during 1991–94, 55.6% of males and 57.3% of females were current smokeless tobacco users, while 23.6% of males and 0.4% of females were smokers. The study cohort is now being followed up. An active search for a sample of subjects is being undertaken in order to estimate migration out of the study area. All deaths occurring in Bombay municipality are being matched with the study cohort, and a link is also made with the file of the Bombay cancer registry. Preliminary analysis suggests a higher mortality rate in smokers than in non-smokers.

Figure 11. Measuring blood pressure in the cohort study of tobacco use and mortality in India

Recruitment of another cohort of subjects aged at least 35 years began in the Trivandrum district of Kerala, India, in December 1995, and 68 000 subjects had been recruited by the end of July 1997. Among a subset of 37 655 individuals, 52.4% of males and 1.9% of females are smokers; 31.6% of males and 23.1% of females are chewers. Data collection from municipal death registration systems is in progress.

Height, weight, blood pressure and peak expiratory flow measurements are recorded for all individuals in both cohorts. Follow-up will continue for many years to provide information on tobacco-related mortality.

2.4.4

Tobacco use in Africa

A.J. Sasco, I. Gendre and D.M. Parkin

Although estimates have been produced on lung cancer incidence attributable to tobacco use worldwide, little is known for some parts of the developing world, in particular for Africa. Tobacco use surveys using a standardized data collection form have been carried out in Egypt, Ghana, Kenya, Morocco, Nigeria, Senegal, Tanzania, Uganda, Zambia and Zimbabwe. Plans have been made for an international case–control study of lung cancer, implementation of which is dependent on funding.

2.4.5
Dietary phenolics as anti-mutagens and inhibitors of tobacco-related DNA adduction in the urothelium of smokers

C. Malaveille, A. Hautefeuille and B. Pignatelli; in collaboration with H. Bartsch, Heidelberg, Germany; G. Talaska, Cincinnati, USA; and P. Vineis, Turin, Italy

Human diet contains a wide variety of non-nutrient agents, mostly phenolics of plant origin, which inhibit carcinogenesis in animals (Wattenberg, 1992, *Cancer Res.*, **52**, 2085s–2091s). We have obtained a range of experimental evidence suggesting that bladder mucosal cells of smokers are partially protected by such dietary phenolics, probably flavonoids, against the harmful effects of tobacco-derived bladder carcinogens [231, 232]. To obtain more direct evidence on the role of such substances as anti-carcinogens in humans, we have planned a randomized trial of inhibition by dietary phenolics of DNA damage in exfoliated urothelial and white blood cells of smokers categorized according to relevant metabolic genotypes.

2.4.6
Genetic polymorphism of carcinogen-metabolizing enzymes in relation to risk of pancreatitis and pancreatic cancer

C. Malaveille and A. Hautefeuille; in collaboration with H. Bartsch, Heidelberg, Germany; A. Lowenfels, New York, USA; and P. Boyle and P. Maisonneuve, Milan, Italy

Carcinogens present in cigarette smoke and diet have been associated with pancreatic cancer. Heterocyclic and aromatic amines implicated in these exposures may be relevant causative agents and therefore genetic variation in enzymes metabolizing these carcinogens could modify the risk of developing pancreatic disease. Blood samples collected from patients (all of Caucasian origin) with pancreatic cancer (n = 81) or non-alcoholic (n = 41) or alcoholic pancreatitis (n = 73) and from asymptomatic control subjects (n = 78) were analysed to determine the genotype of genes encoding various carcinogen-metabolizing enzymes. The prevalence of glutathione *S*-transferase (GST) M1 null genotype and *N*-acetyltransferase (NAT)2 fast and slow acetylator genotypes, and the distribution of frequencies of NAT2 genotypes and NAD(P)H: quinone oxidoreductase (NQO1) genotypes were similar in subjects with pancreatic disease and in controls. NAT1 slow acetylators were 1.5 times more frequent among pancreatic cancer cases than in controls, but this finding did not reach statistical significance (p = 0.18). There was a significant overrepresentation of the GSTM1 AB or B genotype in all pancreatic disease cases combined (OR = 2.6, $p < 0.05$). These results suggest that polymorphism of GSTM1 and NAT1 is associated with susceptibility to pancreatic disease, presumably as a consequence of a compromised ability to detoxify aromatic heterocyclic amines in the case of NAT1 and of activation of unknown carcinogens by GSTM1 B or AB types. Since (*a*) glutathione *S*-transferase P1 (GSTP1) has been shown to detoxify DNA oxidation products and may also contribute to the detoxification of tobacco-related carcinogens and (*b*) our previous data [231] show that *O*-methylation of dietary flavonoids by catechol *O*-methyltransferase (COMT) increases their activity as inhibitors of cytochrome P450s that activate heterocyclic amines, methods involving PCR and RFLP have been developed to analyse the genetic polymorphism of genes encoding GSTP1 and COMT so as to allow examination of its role in pancreatic disease susceptibility.

2.4.7

Genetic polymorphism of carcinogen-metabolizing enzymes with putative relevance to tobacco-related bladder carcinogenesis: a case–control study

C. Malaveille, A Hautefeuille; in collaboration with M. Peluso, Genoa, Italy; L. Airoldi, Milan, Italy; and P. Vineis, Turin, Italy

Tobacco smoking causes a major fraction of male urinary tract cancers. Previous molecular dosimetry studies have implicated aromatic amines and possibly heterocyclic amines in tobacco smoke as bladder carcinogens (Bartsch *et al.*, 1993, *Eur. J. Cancer*, **29A**, 1199–1207). Allelic differences at loci encoding enzymes that metabolically detoxify carcinogenic aromatic amines, such as NAT2 and GST M1, may account for inter-individual variations in susceptibility to tobacco-related urinary bladder cancer (D'Errico *et al.*, 1996, *Biomarkers*, **1**, 149–173). In a case–control study involving 114 bladder cancer patients and 46 hospital controls (all male of Caucasian origin), we have shown that the level of carcinogen adducts (measured by ^{32}P-postlabelling assay) in DNA of white blood cells (as surrogate for urothelial cells) was strongly associated with NAT2 genotype ($p = 0.001$). In a logistic regression model, the logarithm of DNA adduct levels was related in a highly significant way to the risk of bladder cancer (regression coefficient = 0.44; $p = 0.0003$). After controlling for DNA adducts, no association was detected between the case–control status and NAT2 genotype, suggesting that the relationship between bladder cancer and this metabolic polymorphism may be mediated by the formation of DNA adducts [342]. To examine whether 4-aminobiphenyl–DNA adduction in urothelial cells and p53 mutation in tobacco-related urinary bladder cancer are associated with particular metabolic traits as revealed by genotypic analysis of NAT2 and GSTM1, we carried out a preliminary study involving biopsies from 45 patients with bladder cancer. No clear association between GSTM1 and NAT2 genotype, 4-aminobiphenyl adducts and the type of p53 mutation was found [236].

2.5 *Radiation and cancer*

The main objective of research in this area is to provide answers to some outstanding questions in radiation protection and radiation carcinogenesis. Activities include studies of the carcinogenic effects of radiation, in particular low doses of ionizing radiation, in relation to the type of radiation, patterns of exposure and host and environmental factors. The motivation for this work is twofold: to strengthen the scientific basis of radiation protection and to increase our understanding of biological mechanisms of carcinogenesis. The major focus hitherto has been on ionizing radition, but the scope of the programme is now being extended to other types of radiation.

2.5.1

International collaborative study of cancer risk among radiation workers

E. Cardis, M. Martuzzi, E. Amoros, I. Thierry-Chef, M. Kilkenny and H. Renard; in collaboration with: *Australia:* C. Hacker and R. Habib, Menai; J. Kaldor, Sydney; *Belgium:* P. Deboodt and H. Engels, Mol; *Canada:* P. Ashmore, Ottawa; L.M. Green and G. Howe, Toronto; G. Cowper, Chalk River; *Finland:* M. Hakama, Tampere; T. Rytomaa and A. Auvinen, Helsinki; *France:* F. Berman, Paris; A. Biau, Le Vésinet; C. Hill, Villejuif; *Germany:* M. Blettner, Heidelberg; G. Seitz, Cologne; *Hungary:* A. Kerekes and I. Turai, Budapest; *Japan:* Y. Hosoda, T. Iwasaki, M. Kuba and S. Ohsima, Tokyo; T. Yoshimura, Kitakyushu; *Slovak Republic:* G. Gulis and O. Fitz, Trnava; K. Holan, Bratislava; *Spain:* J. Bernard Solano and A. Diez Sacristán, Madrid; *Sweden:* M. Eklöf, Osthammar; H. Malker, Sundsvall; G. Engholm, Stockholm; *Switzerland:* E. Guberan,

Geneva; M. Moser, Bern; *UK:* L. Carpenter, Oxford; G. Kendall, C. Muirhead and M. Marshall, Chilton; *USA:* E. Gilbert, Rockville; J. Fix, Richland; B. Murray and R. Rinsky, Cincinnati; A. Mazzocchi, Washington

The International Collaborative Study of Cancer Risk among Radiation Workers is a retrospective cohort study of over 500 000 nuclear industry workers from fourteen countries (Table 4). The objective is to obtain precise direct estimates of the effect of low-dose protracted exposure to ionizing radiation in order to assess the adequacy of radiation protection standards for environmental and occupational exposures. Data collection is based upon a detailed procedures document (Cardis *et al.*, 1997, IARC Internal Report 97/002). As of the end of 1997, the data from several countries have been received at IARC, and data from the remainder should be received in 1998.

A detailed study of biases and random errors in the radiation dose estimates is being carried out within the study using questionnaires on dosimetry technology and monitoring and recording practices as well as expert opinion on exposure conditions and radiation protection practices. The primary objectives of this study are (*a*) to identify workers with substantial doses from neutrons or from internal contamination with radionuclides for which dose estimates may be inaccurate, and (*b*) to quantify the systematic and random errors in dose estimates for workers whose dose is predominantly from higher-energy γ-rays. The major sources of

Table 4. Countries, facilities and approximate numbers of workers included in the International Collaborative Study of cancer risk among radiation workers

Country	Facilities	No. of workers
Australia	All	4 500
Belgium	SCK, Belgo Process, Belgo Nucléaire	4 859
	Doel, Tihange	3 000
Canada	All	50 000
Finland	All	13 000
France	CEA-COGEMA, civil	30 000–35 000
	CEA-COGEMA, other	10 000–15 000
	Electricité de France	21 000
	Contracting companies	10 000
Germany	All	6 000–8 000
Hungary	All	3 500
Japan	All	115 000
Slovak Republic	All	2 804
Spain	All	3 846
Sweden	All	22 500
Switzerland	All	2 025
UK	All	125 000
USA	Savannah River	9 600
	Oak Ridge National Laboratory	8 318
	Hanford	36 235
	Portsmouth	10 000
	Idaho National Engineering Laboratory	Not yet known

CEA: Commissariat à l'Energie Nucléaire, COGEMA: Compagnie Générale des Matières Nucléaires.

systematic and random errors in the dose estimates have been identified by facility, time period, dose level and, where relevant, activity. These errors are being quantified using the information collected, complemented by results of dosimetric experiments and technical literature. Approaches for modelling the errors in doses and for taking them into account formally in the estimation of risk are being tested.

A socioeconomic status indicator is being constructed to adjust for the possible confounding effects of lifestyle factors on the relationship between low-dose radiation and cancer risk. A study of comparability of coding of cause of death across countries and over time will be carried out using anonymized death certificates in most countries. Cross-sectional surveys of smoking habits are planned or in progress in most of the participating countries.

Different approaches for the analyses of data and risk estimation are being evaluated and programmes for their use are being developed and implemented.

2.5.2
Health consequences of the Chernobyl accident

2.5.2.1

Chernobyl accident recovery workers

E. Cardis, A. Kesminiene, D. Guo, E. Amoros and H. Renard; in collaboration with V.K. Ivanov, A.P. Konogorov, E.P. Rastopchin and V.A. Pitkevitch, Obninsk, Russian Federation; V. Krjuchkov, M. Savkin and A. Tukov, Moscow, Russian Federation; I. Shantyr, St. Petersburg, Russian Federation; A.E. Okeanov, N.I. Bazoulko, S. Poliakov, E.P. Demidchik and E. Ivanov, Minsk, Belarus; V. Chumak, Kiev, Ukraine; S. Illychov, Chernobyl, Ukraine; P. Jacob and R. Meckbach, Munich, Germany; and A. Bouville, Bethesda, MD, USA

Among Chernobyl accident recovery workers (the so-called 'liquidators'), an official limit of 0.25 Gy was set for the dose each was allowed to receive. Some workers received this dose in a matter of minutes, while others received it over months or even years, and the predominant radiation type varied according to the time and activity of each worker. The liquidators therefore constitute a unique population for the study of the effects of exposure rate on the risk of cancer in the low to medium dose range.

Following pilot studies which indicated that it is feasible to carry out case–control studies of specific cancers among these liquidators, two case–control studies have been set up in Belarus and Russia —one of leukaemia and non-Hodgkin lymphoma, and the other of thyroid cancer risk. The aim is to estimate the risk of radiation-induced leukaemia and NHL and of thyroid cancer among liquidators of the Chernobyl accident residing in these countries, and, in particular, to study the effect of exposure rate.

The study population consists of the approximately 31 000 Belarusian and 51 000 Russian liquidators (residing in five regions of Russia) who worked in the 30 km zone in the period 26 April 1986 to 31 December 1987, and who have been included in the National Chernobyl Registries of Belarus and Russia. The study includes both retrospective and prospective cases diagnosed between 1 January 1993 and 30 December 1998. Four controls were selected from the same study population for each case, matched on age (±5 years), gender and region of residence at the time of the accident (same oblast).

Information on all study subjects is obtained mainly from the National Chernobyl Registries of Belarus and Russia and face-to-face interviews using a detailed standard questionnaire. It includes demographic data, information on variables related to radiation dose and information about exposure to potential confounding factors. Questions important for reconstructing probable radiation dose are included in the questionnaire. They were designed by a working group of experts knowledgeable

about dosimetry and dosimetric control practices in force in the 30 km zone around the Chernobyl reactor. The questionnaire was tested on a sample of 117 liquidators from the Ministry of Atomic Energy and the Military Registry in Russia during the spring and summer of 1996. In addition, a blood sample is obtained from each prospective case (before treatment) and relevant control for the purpose of biological dosimetry by techniques that may become available in the future.

The interviewers for this study were trained during a workshop in Kiev in April 1996. Identification of retrospective cases and selection of their controls is in progress and interviews started in November 1997.

2.5.2.2

Thyroid cancer in young people

E. Cardis, A. Kesminiene, D. Guo, E. Amoros and H. Renard; in collaboration with V.K. Ivanov, M. Maksyoutov, E.P. Parshkov, Parshin, Shakhtarin, V.A. Stepanenko and V.A. Pitkevitch, Obninsk, Russian Federation; Y. Gavrilyn, Moscow, Russian Federation; E.P. Demidchik, L.N. Astakhova, Cherstvoy, E. Korotkevich, A. Mrochek, A.E. Okeanov, N.I. Bazoulko, S. Poliakov and E. Ivanov, Minsk, Belarus; T. Motomura, Gomel, Belarus; G. Goulko, Munich, Germany; S. Yamashita, Y. Shibata and M. Ito, Nagasaki, Japan, M. Hoshi, Hiroshima, Japan; D. Williams and G. Thomas, Cambridge, UK; and A. Pinchera and F. Pacini, Pisa, Italy

A very early and large increase in the incidence of thyroid cancer in children and young adults in Belarus, and later in the Ukraine and Russia following the Chernobyl accident has been reported (Baverstock *et al.*, 1992, *Nature,* **359**, 21–22; Williams *et al.*, 1996, in: *One Decade after Chernobyl, Summing up the Consequences of the Accident,* Vienna, IAEA, pp. 207–238). There is strong circumstantial evidence that this increase is due to the radioactive fall-out from the accident. The observation of such a large and early increase in the incidence of a very rare cancer raises the possibility that host and environmental factors may play a role in the risk of radiation-induced cancer [64].

A case–control study aimed at assessing the role of genetic predisposition, iodine status and very short-lived isotopes of iodine in radiation-induced thyroid cancer is therefore being set up in Belarus and in contaminated areas of Russia. Because of the rarity of this disease, this situation provides a unique opportunity to identify factors which may modify radiation risk and to quantify their effect. This work, in addition to contributing to the understanding of the mechanisms of carcinogenesis, may have important public health implications for the protection of patients treated with radiotherapy, of radiation workers and of the general population in the event of further nuclear accidents.

The source population consists of all persons in Belarus and in the regions of Bryansk, Kaluga, Oriol and Tula in Russia who were children or adolescents at the time of the Chernobyl accident. The study period is from 1 January 1990 until the 30 June 1998. The cases are patients with a thyroid carcinoma occurring in the study population during this period and operated in Belarus or Russia. All cases will be independently verified by two pathologists. For each case, four controls matched closely on age are being selected.

Information on variables of interest is obtained using a questionnaire administered by a trained interviewer. This includes questions about familial history of cancer, thyroid disorders, congenital malformation and mental retardation, about the behaviour of the subject at the time of the accident, in the following days and the first two months and about stable iodine prophylaxis and thyroid hormone administration. This information is complemented with information from medical and school records, results of current and past geographical surveys of iodine deficiency, surveys of counter-

measures and analysis of biological samples and ultrasound evaluation of thyroid volume.

Estimates of thyroid radiation dose from ^{131}I and short-lived isotopes will be reconstructed on the basis of the questionnaire and information on environmental contamination and thyroid measurements by a team of dosimetrists from Russia, Belarus, Germany and Japan.

Information on possible genetic predisposition is obtained by the questionnaire. If a subject reports a history of the diseases of interest among first- or second-degree relatives, an investigation is carried out and the pedigree drawn. In a second phase, once candidate genes have been identified under a parallel project (see Section 4.3.7), blood samples obtained from study subjects will be analysed to screen for mutations of these genes and thus evaluate the risk of radiation-induced thyroid cancer associated with the genetic predisposition.

Data collection for this study is being carried out jointly (using a common questionnaire) with investigators of a collaborative Belarus/Russian/Japanese study with complementary objectives and overlapping study populations.

2.5.2.3

European Childhood Leukaemia and Lymphoma Incidence Study

D.M. Parkin, R.J. Black and E.Masuyer; in collaboration with: *Austria:* B.G. Bennett and J. Langgaßner, Vienna; *Belarus:* E. Ivanov, Minsk; *Belgium:* J. Sinnaeve, Brussels; *Bulgaria:* C.G. Tzvetansky, Sofia; *Czech Republic:* H. Hrstková, Prague; *Denmark:* H.H. Storm, Copenhagen; *Estonia:* M. Rahu, Tallinn; *Finland:* E. Pukkala, Helsinki; *France:* J.-L. Bernard, Marseille; P.-M. Carli, Dijon; B. Lacour, Nancy; F. Ménégoz, Grenoble; P. Schaffer, Strasbourg; S. Schraub, Besançon; *Germany,* J. Michaelis, Mainz; *Hungary:* E. Apjok, Budapest; *Italy,* P. Crosignani, Milan; C. Magnani and B. Terracini, Turin; *Latvia,* A. Stengrevics, Riga; *Lithuania:* R. Kriauciunas, Vilnius; *The Netherlands:* J.-W.W. Coebergh, Eindhoven; *Norway:* F. Langmark, Oslo; *Poland:* W. Zatonski, Warsaw; *Romania:* R. Tulbure, Bucharest; *Russian Federation:* A. Boukhny, Moscow; V.M. Merabishvili, St Petersburg; *Slovakia,* I. Plesko, Bratislava; *Slovenia:* V. Pompe-Kirn, Ljubljana; *Sweden:* L. Barlow, Stockholm; *Switzerland,* T. Fisch, St Gallen; F.G. Levi, Lausanne; L. Raymond, Geneva; G. Schüler, Zurich; J. Torhorst, Basel; *Ukraine:* G. Moroz, Kiev; *UK:* D. Brewster, Edinburgh; D. Clayton, Cambridge; C.A. Stiller, Oxford

The main aims of the European Childhood Leukaemia and Lymphoma Incidence Study (ECLIS) are to evaluate the incidence of childhood leukaemia in Europe since 1980, and to determine whether observed trends are related to exposure to radiation from the accident at the nuclear power plant at Chernobyl in April 1986. The study follows the recommendations of an expert committee established by the European Commission to review possible health effects of the accident in European populations.

The study began in 1988. Cancer registries throughout Europe provide annual listings of data on incident cases of childhood leukaemia (and, where possible, lymphomas) and denominators for the populations at risk, according to a standard protocol. Currently, 39 registries in 24 countries are participating. Agreements have been established with participants in eastern and central Europe to ensure high standards of registration and data-processing, and the regions represented in ECLIS now include Ukraine. Estimates of the excess radiation doses received as a result of the accident are provided by UNSCEAR. During the first five years of follow-up (1987–91), there was no evidence of an association between radiation doses received due to the accident and risk of childhood leukaemia in the populations studied. A preliminary analysis of leukaemia risk among cohorts of European children with the highest exposures to radiation from Chernobyl *in utero* has also revealed no evidence of a

Figure 12. Map of Europe with regions included in the ECLIS study (shaded area). The numbers indicate different levels of average radioactive exposure within a country.

substantially greater risk of leukaemia, compared with children with zero or low doses *in utero*.

The collaborative framework of ECLIS has been used to undertake a study of possible effects of the Chernobyl accident on childhood and young adult thyroid cancer in European populations outside the former USSR. Participating registries were asked to provide data on thyroid cancers in the age group 0–19 years. Preliminary analysis suggests that incidence trends are not related to potential exposures to radioactive iodine resulting from the accident.

2.5.3
Health and environmental effects of static and time-varying electric and magnetic fields

E. Cardis; in collaboration with A. Ahlbom and T. Hardell, Stockholm, Sweden; R.A. Cartwright, Leeds, UK; P. Comba and M. Grandolfo, Rome, Italy; C. Johnsen, Copenhagen, Denmark; M. Linet, Bethesda, MD, USA; B. Modan, Tel Aviv, Israel M. Repacholi, Geneva, Switzerland; D. Savitz, Los Angeles, CA, USA; and A. Swerdlow, London, UK

The aim of this project is to assess health and environmental effects of exposure to static and time-varying electric and magnetic fields (EMF) in the frequency range 0–300

GHz. This range is divided into: static (0 Hz), extremely low frequency (ELF, > 0–300 Hz) and radiofrequency (RF, 300 Hz–300 GHz) fields.

Resources are being pooled through the establishment of the International EMF project, with an international advisory group. The project is run by WHO in collaboration with IARC, the International Commission on Non-Ionizing Radiation Protection, the United Nations Environment Programme, national governments, and other key institutions.

The specific involvement of IARC is to evaluate the carcinogenic risk associated with exposure to EMF, to identify gaps in scientific knowledge and to recommend research protocols. The literature on ELF and RF radiation has been critically reviewed. The feasibility of carrying out a multicentric case–control study of brain cancer and acoustic neurinoma in relation to mobile phone use is being investigated.

2.6 Viruses and cancer

The expected epidemic of HIV-related cancers in sub-Saharan Africa is being monitored in the two populations which have been continuously served by a cancer registry since the infection began to spread. Monitoring is performed by classical methods of descriptive and analytical epidemiology. The first aims at formulating hypotheses on interactions between the infection and other characteristics of the population and the second tests these hypotheses at the individual level.

2.6.1 Monitoring of trends in incidence of cancers related to infection with HIV

D.M. Parkin and J. Ziegler; in collaboration with V. Beral and R. Newton, Oxford, UK; H. Wabinga, Kampala, Uganda; and L. Levy and E. Chokunonga, Harare, Zimbabwe

Two of the African cancer registries (Kampala, Uganda and Harare, Zimbabwe) provide long enough time series to evaluate trends. Kaposi's sarcoma has increased enormously in incidence and in these countries is now predominantly of the 'epidemic' HIV-related clinical types, at ages closely paralleling prevalence of HIV infection. There also appears to have been an increase in the incidence of HIV-negative Kaposi's sarcoma in children [525]. In contrast, there is little evidence of an increase in the incidence of non-Hodgkin lymphomas, and there has been no change in the distribution of cervix cancer cases by age group.

2.6.2 Case–control studies of cancers related to HIV infection in Africa

D.M. Parkin and J. Ziegler; in collaboration with V. Beral, R. Newton, R. Weiss, Oxford, UK; H. Jaffe, Atlanta, USA; K. deCock, London, UK; M. Raphaël, Paris, France; E. Katangole Mbidde and H. Wabinga, Kampala, Uganda; and J. Whitworth and L. Carpenter, Entebbe, Uganda

The study in Uganda initially concentrated upon Kaposi's sarcoma, with specific interest in the HIV-related 'epidemic' and HIV-negative 'endemic' types and Kaposi's sarcoma in childhood. HIV-positive adults and HIV-negative men with Kaposi's sarcoma show similar demographic factors related to relative affluence and mobility, and both reported more sexually transmitted diseases than the general population, suggesting that the relevant etiological agent may also be sexually transmitted. Subjects with endemic Kaposi's sarcoma were also more likely to have had contact with water or walked barefoot. Mothers of children with Kaposi's sarcoma are more likely to be from crowded households than control mothers, suggesting that close interpersonal contact

may also be important in the spread of the agent. Human herpesvirus 8 is now generally recognized as the cause of Kaposi's sarcoma (see Section 2.1.6), and the study results suggest how this virus may be transmitted in the African context.

The study is now concentrating upon other cancers, particularly those related to viral infections (cervical cancer, penile cancer, liver cancer) and the lymphomas. The primary concern is whether HIV infection increases the risk of these cancers. Since Burkitt's lymphoma was very common in Uganda before the onset of the AIDS epidemic, and in practically all cases the genome of the Epstein–Barr virus was demonstrable, this cancer is of particular interest. All lymphomas are immunophenotyped and examined for presence of the Epstein–Barr viral genome and chromosomal changes characteristic of Burkitt's lymphoma. In HIV-positive cases and controls, the degree of immunosuppression, as assessed by CD4 cell counts, is evaluated. Recruitment into the study is expected to continue until 1998, with analysis of data for a further 1–2 years.

2.7 *Second malignancies following cancer treatment*

Although cancer is still often a fatal disease, for which the use of aggressive therapies is justified, better and earlier diagnoses combined with more effective forms of treatment have led to the complete cure or at least much prolonged survival of many cancer cases. In these circumstances, it is essential to clearly understand the possible carcinogenic effects, as well as other toxicity, of the treatments available.

2.7.1 Prospective study on markers of DNA damage and risk of second malignancy in Hodgkin lymphoma patients

P. Boffetta, S. Lea and J. Hall; in collaboration with A. Daudt, Porto Alegre, Brazil; M. Henry-Amar, Caen, France; S.A. Kyrtopoulos, Athens, Greece; L. Simonato, Padua, Italy; V. Shanta, Madras, India; C.P. Wild, Leeds, UK; and D.G. Zaridze, Moscow, Russian Federation

Hodgkin lymphoma patients treated with alkylating agents are at increased risk of second neoplasms, in particular leukaemia, non-Hodgkin lymphoma and lung cancer. Hodgkin lymphoma patients treated at hospitals in India, Italy and the Russian Federation are being prospectively followed up for the occurrence of second malignancies. As each second malignancy arises, the therapy record for that case and several matched controls will be examined, to try to identify carcinogenic therapeutic modalities as rapidly as possible. In parallel, blood samples taken at recruitment will be analysed for markers of DNA damage and repair, and comparisons made between the second malignancy cases and controls. In particular, the promutagenic adducts, O^6- and N7-methylguanine have been investigated in a pilot study of 45 Hodgkin lymphoma patients [14] and will be measured in the full study. A total of 400 patients have been enrolled up to 1997; additional patients may be enrolled in a Brazilian centre. Follow-up will continue for a further five years.

2.7.2 DNA damage following chemotherapy for testicular cancer

P. Boffetta; in collaboration with D. Bron, Brussels, Belgium; A.M.J. Fichtinger-Schepman, Rijswijk, The Netherlands; J. Kaldor, Sydney, Australia; and R. Somers, Amsterdam, The Netherlands

The reaction between alkylating chemotherapeutic agents and cellular DNA is probably the main pathway to both their cytotoxic and their carcinogenic effects. A

collaborative study has been set up to measure cisplatin–DNA adducts in testicular cancer patients, and to assess to what extent adduct levels can be used to predict the clinical outcome of chemotherapy.

The study is being performed in conjunction with a clinical trial of cisplatin in testicular cancer conducted by the genito-urinary groups of the European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Council of the United Kingdom. DNA adducts and haemoglobin have been measured in testicular cancer patients and will be analysed in relation to the response to chemotherapy. The results suggest strong correlations between cisplatin–DNA adducts and total platinum protein content, as well as a correlation between DNA adduct levels before and after treatment. No association was detected between DNA adduct levels and response to therapy.

2.7.3

Case–control study of selected second primary cancers following breast cancer and tamoxifen use

A.J. Sasco, I. Gendre and R. Ah-Song; in collaboration with C. Bouchardy, Geneva; T. Fisch, St Gallen, Switzerland; E. Buiatti, Bologna, Italy; L. Hardell, Orebro, Sweden; J. Iscovich, Jerusalem, Israel; and P. Schaffer, Strasbourg, France

Tamoxifen is a synthetic non-steroidal anti-estrogen of the triphenylenethylene family which has been widely used for the treatment of breast cancer, and more recently has also been proposed for the prevention of the disease among high-risk women. However, the carcinogenicity of this product warrants further investigation before widespread preventive use [403]. In order to evaluate the risk of occurrence of selected second primary cancers following breast cancer, a series of international case–control studies has been set up. The initial study was restricted to endometrial cancer following breast cancer and was conducted in the Rhône and Côte d'Or départements of France. Women who have been treated for breast cancer with tamoxifen have an increased risk of developing endometrial cancer and the risk increases with duration of treatment [402]. Elevated risk may persist after cessation of tamoxifen administration [400, 407]. Risk seems higher for women exposed premenopausally rather than postmenopausally [393]. An international study is now in progress. Cases of selected second cancers, namely endometrial, liver and ovarian cancers occurring among women who had previously developed breast cancer are being selected from population-based cancer registries in Denmark, France, Israel, Italy, Sweden and Switzerland. They are matched to controls who had breast cancer at the same time and age as each case and who are still at risk of disease. The role of tamoxifen and other treatment modalities in the occurrence of second cancers will be evaluated. It is envisaged that about 150 endometrial, 150 ovarian and a few liver cancer cases will be recruited. In parallel, reviews have been also conducted on other potential side-effects of tamoxifen [2, 399].

This study benefits from the support of the BioMed programme of the European Union, as well as support from various national sources such as INSERM, the Fondation de France and the Federal Office of Public Health from Switzerland.

PART 3. CARCINOGENESIS BY ORGAN SITE

3.1 Cancer of the oesophagus

Cancer of the oesophagus is the fifth most frequent cause of cancer death worldwide, with a particularly high incidence in developing countries. This cancer exists in two major forms with distinct etiopathological features, squamous cell carcinoma (SCC) and adenocarcinoma (ADC). SCC is the most common form and occurs at a particularly high frequency in some areas of Asia, South America and western Europe. Epidemiologically identified exogenous risk factors include tobacco and alcohol in western countries, and a number of dietary factors, vitamin deficiencies and cultural habits in other parts of the world. ADC often occurs in the context of a pre-cancerous lesion, Barrett's mucosa, in which normal squamous epithelium is replaced by a metaplastic, intestinal-type epithelium. ADC is one of the most rapidly increasing cancers in Europe and the United States, but no exogenous risk factors have been clearly defined.

Little is known of the molecular events that occur in the natural history of oesophageal cancers and of their relation to exogenous risk factors. Therefore, we are attempting (1) to analyse molecular alterations which may reveal clues to the etiology of these cancers, including mutations in the *p53* gene, (2) to determine the temporal sequence of genetic events that occur during cancer progression, and (3) to identify molecular differences between SCC and ADC.

3.1.1 Cellular and molecular alterations in oesophageal cancer

P. Hainaut, C. Barnas, G. Martel-Planche, P. Tanière and R. Montesano, in collaboration with A. Casson, Birmingham, UK; A. Chanvitan, Songkhla, Thailand O.A. Hass and T. Henn, Vienna, Austria; C. Lombard-Bohas, Lyon, France; S.H. Lu, Beijing, China; F. Pinto and C. Gallo, Porto Allegre, Brazil; and Lian Shi Yong, Linzhou City, China

Missense mutation of the *p53* gene is the most frequent genetic event observed to date in cancers of the oesophagus (48% in SCC and 71% in adenocarcinoma) [273]. The p53 protein plays an essential role in controlling the proliferation and survival of cells exposed to DNA-damaging agents, and loss of p53 function by mutation is thought to facilitate the propagation of cells containing potentially oncogenic DNA lesions.

To determine whether the type and site of p53 mutation can yield information on the nature of the carcinogens involved in oesophageal carcinogenesis, we are collecting samples of oesophageal lesions from cases with a well defined history of exposure to different risk factors in various areas of western Europe, China, Thailand and Brazil. Mutations within the central portion of the *p53* gene (exons 4 and 9) are determined by denaturing gradient gel electrophoresis and direct analysis by automated DNA-sequencing. In parallel, immunohistochemical analysis of p53 protein is performed on paired tissue samples, to allow correlation of genetic alterations with protein expression.

In SCC from southern Thailand, we found a high frequency of mutations (60%), with a higher proportion of G to T transitions compared with tumours from western Europe. These results suggest that there are geographical differences in the mutation spectrum of SCC, correlated with specific exogenous risk factors. Initial data on SCC from southern Brazil indicate that the frequency of *p53* mutations is high. Analysis

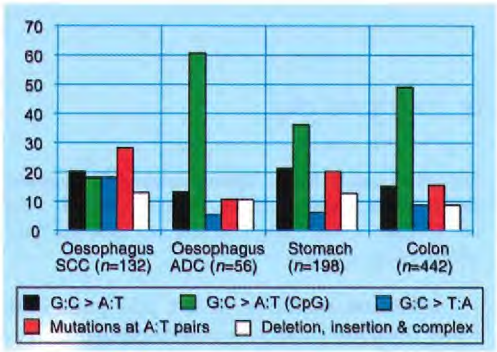

Figure 13. Mutation spectrum of p53 in various tumours of the digestive tract. SCC, squamous cell carcinoma; ADC, adenocarcinoma n=number of samples

of cancers from other countries, including France, Italy and China, is in progress.

We have also analysed adenocarcinomas of the cardia region of the gastric mucosa (distinguished from oesophageal adenocarcinoma by lacking any microscopic or macroscopic evidence of pre-existing Barrett's metaplasia). These tumours had a relatively low frequency of *p53* mutations (25–30%), but often showed overexpression of the *MDM-2* gene product. Some also showed amplification of *MDM-2*. At the molecular level, ADC of the cardia are thus distinct from ADC of the oesophagus and from ADC of other regions of the gastric mucosa (antrum, fundus), suggesting that they represent a new, distinct pathological entity.

Cancers of the oesophagus have a very poor cure rate (the survival rate at five years is less than 10%). To assess the significance of mutations in p53 for the prognosis of cancer and for response to treatment, we are following up a group of patients under treatment at the Hôpital Edouard Herriot, Lyon. This project is based on the observation that mutations, particular in SCC, do not occur at classical mutational 'hotspots' in the *p53* gene and may therefore have particular functional properties.

To further elucidate the molecular pathology of oesophageal cancer, we are also investigating a number of other genetic endpoints. We are currently analysing the expression of the *p16/MTS-1* gene (a negative regulator of cell-cycle progression at the G1/S border) (by comparative reverse transcriptase PCR analysis of MTS-1 transcripts a and b) and of the repair enzyme thymidine glycosylase. In collaboration with O. Haas (Vienna), we have initiated a systematic comparison between SCC and ADC using comparative genomic hybridization. Multiple chromosomal modifications have been detected in most cancers and the number of alterations appears inversely correlated with tumour stage and patient survival. In addition to already known loci on chromosomes 3, 5, 8, 9, 11, 13, 17 and 18, several other chromosomes were frequently altered, including 1p and 1q, 4q and 20q. Interestingly, deletion of 4q was detected in 80% of the ADC and in 25% of the SCC tested. Further studies using comparative genomic hybridization and fluorescent *in situ* hybridization are in progress to characterize these alterations.

In addition to analysing primary tumour samples, we are also studying alterations in cell-cycle regulatory genes, their expression and the activity of their protein products in a panel of nine oesophageal cancer cell lines (Nishihira *et al.* 1993, *J. Cancer Res. Clin. Oncol.*, 119, 441–449). All of these cell lines were deficient for p53 function, due to either mutation of the *p53* gene or impaired p53 expression. One of the mutant p53 proteins (with a methionine instead of a valine at codon 272) is temperature-sensitive for both protein conformation and function. Thus, upon culture of the cells at 32 °C, this p53 mutant induces a reversible and transient cell-cycle arrest in G1. This cell line lacks expression of the Retinoblastoma gene product (Rb), suggesting that the p53-dependent cell-cycle arrest in G1 does not require intact Rb function. We are using this cell model to analyse the involvement of other genes in the regulation of G1/S cell cycle arrest, including cyclin D1.

3.1.2
Cytochrome P450 expression in human oesophageal mucosa

C.P. Wild, M. Lechevrel, A. Schouft and R. Montesano; in collaboration with A.G. Casson, Warwick, UK; and C.R. Wolf, Dundee, UK

A possible mechanism of interaction between alcohol and tobacco in the etiology of oesophageal cancer is that alcohol modulates the metabolism of tobacco carcinogens either in the liver or in the oesophagus itself. As a first approach to addressing this hypothesis, oesophageal mucosa was obtained from 25 oesophageal cancer patients (19 adenocarcinomas and 6 squamous cell carcinomas) undergoing surgery. Microsomes from histologically normal mucosa were used for immunoblotting using cytochrome P450-specific antibodies, while mRNA was analysed with P450-specific probes. This dual approach revealed the presence of CYP 1A, 2E1 and 3A proteins in human oesophageal mucosa. In addition, mRNA of CYP 1A1, 2E1 and 3A3/4 was detected in almost all samples tested. There were significant interindividual variations in the amount of CYP proteins detected, but the amounts did not correlate with individual data on tobacco and alcohol consumption, hot drink consumption or gastro-oesophageal reflux, although the small number of subjects limited the possibility of finding such correlations. These data demonstrate that a range of CYP enzymes are expressed in human oesophageal mucosa and indicate that this tissue has the capacity to activate chemical carcinogens to reactive DNA-binding metabolites.

3.1.3
Co-carcinogenicity of fumonisins and *N*-nitrosamines in oesophageal cancer

C.P. Wild, M. Castegnaro and L.Garren

Fumonisins and *N*-nitrosamines have been suggested to be risk factors in the development of human oesophageal cancer; exposure to both occurs in high-risk populations in Africa and the People's Republic of China. The hypothesis that the two interact in oesophageal carcinogenesis was tested by treating male rats with the known oesophageal carcinogen *N*-methylbenzylnitrosamine (NMBA) and fumonisin B_1 separately or together. Similar numbers of animals had oesophageal papillomas or dysplasia in groups treated with NMBA or with both agents together. There thus appears to be no synergistic interaction between NMBA and fumonisin B_1 in the rat oesophagus when the two compounds are administered together. Sphingolipid biosynthesis was affected in the kidney and possibly the liver after fumonisin treatment but not in the oesophagus or lung, as determined by sphinganine : sphingosine ratios in urine and tissues using a newly developed method (see Section 6.1.4.2) [500]. This lack of alteration in the sphinganine : sphingosine ratio in the oesophagus could provide an explanation for the lack of interaction with NMBA if such alteration is involved in the carcinogenic action of fumonisin B_1. It appears that fumonisin B_1 does exert an effect on cell proliferation in the rat oesophagus (Lim *et al.*, 1996, *Nat. Toxins*, 4, 34–41), but probably not through the mechanism of altered sphingolipid biosynthesis.

3.2 Cancer of the stomach

Cancer of the stomach remains the second most common cancer in the world, despite a steady decrease in incidence. Among the possible causes of stomach cancer, dietary factors and *Helicobacter pylori* infection are being investigated in case–control studies in high-risk populations of Venezuela and Costa Rica. Prevalence surveys of *H. pylori* strains and laboratory studies are also being carried out to

determine why only a very small fraction of *H. pylori*-infected individuals develop stomach cancer.

A chemoprevention trial on precancerous lesions of the stomach is under way in Venezuela (Section 5.1.3).

3.2.1

Case–control study of stomach cancer in Tachira, Venezuela

N. Muñoz, M. Plummer, C. Lavé and D. Magnin; in collaboration with J.L. Fauchère, Poitiers, France; G. Lopez, W. Oliver, S. Peraza and J. Vivas, San Cristobal, Venezuela; and A. Ponzetto, Turin, Italy

Gastric cancer is the leading cause of death from cancer in Venezuela. The mortality rate from gastric cancer is particularly high in the Andean region of Venezuela which includes the state of Tachira. In the early 1980s, a gastric cancer screening programme was set up in Tachira. A case–control study is now in progress to evaluate the protective efficacy of this programme and study the causes of gastric cancer in this high-risk population. Special attention is being paid to the role of *Helicobacter pylori*.

The fieldwork was completed in August 1997 after 303 cases and 606 controls were recruited. All new, histologically confirmed cases of stomach cancer diagnosed at the central hospital in San Cristobal, the capital of Tachira, since January 1991 were included, and two neighbourhood controls per case matched by age and sex. Information on diet was collected by personal interview using a questionnaire focusing on habitual diet one year before the disease. Information on screening has been retrieved from the records of the cancer control centre in San Cristobal. Serum samples to measure selected micronutrients and antibodies to *H. pylori* have been collected from all subjects; biopsies from tumoural and non-tumoural gastric mucosa have been taken from cases to look at genetic alterations.

In a preliminary analysis of the first 119 cases and their controls, no association was found with *H. pylori*. However, the serological assay used to detect antibodies to *H. pylori* was shown to be inaccurate. New serological assays using antigens derived from Venezuelan *H. pylori* strains have been developed in collaboration with Professor Fauchère. These antigens show higher reactivity in the controls, which is more consistent with the high prevalence of *H. pylori* infection in this population (see Section 5.1.2). However, there was still no association between *H. pylori* infection and case–control status in this preliminary analysis.

The cagA strain (cytotoxin-associated gene A) of *H. pylori* was investigated after reports that this strain is associated with increased risk of gastric cancer. An ELISA test for antibodies to cagA revealed no significant difference in the prevalence of *H. pylori* antibodies between cases and controls. The prevalence of cagA antibodies was 40% in cases and 47% in controls.

3.2.2

Case–control study of stomach cancer in Costa Rica

N. Muñoz and R. Herrero; in collaboration with F. Mégraud, Bordeaux, France; and R. Sierra, San José, Costa Rica

Enrolment has been completed for a pilot case–control study to determine if *H. pylori* strains isolated from non-tumorous gastric mucosa of patients with gastric cancer are genetically or antigenically different from those found in patients with chronic gastritis. *H. pylori* strains are being cultured in collaboration with F. Mégraud. Preliminary results indicate that *H. pylori* cultures were successful in 52% of cases and 25% of controls.

The strains cultured are being typed with the random polymerase chain reaction (PCR) method. In addition, the presence of the cag pathogenicity island (a genetic region that putatively encodes for virulence factors) is being investigated in biopsies from cases and controls.

3.2.3

Surveys of *H. pylori* prevalence and pepsinogen levels in high- and low-risk areas for stomach cancer

N. Muñoz, R. Herrero, B. Pignatelli and H. Ohshima; in collaboration with B.J. Appelmelk, Amsterdam, The Netherlands; S. Bayo, Bamako, Mali; E. Buiatti, Bologna, Italy; F. Carneiro, Porto, Portugal; I.S. Chung, Seoul, Korea; A. Covacci, Siena, Italy; M. Crespi, Rome, Italy; V. Gloria, Manila, The Philippines; H. Sridhar, Bangalore, India; P. Mairaing, Khon Kaen, Thailand; M.C. Matamoros, Tres Rios, Costa Rica; F. Mégraud, Bordeaux, France; K. Miki, Tokyo, Japan; W. Oliver, San Cristobal, Venezuela; J.L. Rios-Dalenz, La Paz, Bolivia; P.A. Rolón, Asunción, Paraguay; D. Saito, Tokyo, Japan; C. Saul, Porto Alegre, Brazil; J. Torrado, San Sebastian, Spain; and H.R. Wabinga, Kampala, Uganda

H. pylori is one of the most common bacterial infections of humans. Although this bacterium is considered to be carcinogenic, only a small fraction of infected subjects develop stomach cancer, a disease characterized by a striking geographical variation in incidence [291]. The bacterial, host or environmental factors associated with progression to cancer among infected persons need to be clarified.

A study has been initiated of geographical variation in the strains of *H. pylori* associated with chronic non-atrophic gastritis, chronic atrophic gastritis (CAG), intestinal metaplasia, gastric dysplasia and stomach cancer. A consecutive series of patients in each diagnostic category attending gastroscopy clinics for a variety of symptoms will be enrolled in 17 areas of the world with high, intermediate and low incidence of stomach cancer. These areas include three countries in America where age-standardized incidence is over 34 per 100 000 (Costa Rica, Venezuela and Brazil) and two countries where incidence is below 15 per 100 000 (Bolivia and Paraguay). Among five participating centres in Europe, incidence is high in Portugal, Spain and parts of Italy (Romagna), intermediate in another (Rome) and low in Lyon, France. In Africa, the study centres in Mali and Uganda have reported intermediate and low incidence of stomach cancer, respectively. Finally, in Asia, Japan and Korea, with the highest reported incidences (80 and 66/100 000), will be compared with low-incidence countries such as India, Thailand and the Philippines. Collaborators in all countries have been identified and have agreed to participate. A study protocol is being finalized in consultation with the key scientists responsible for the laboratory work (Drs Covacci, Appelmelk and Mégraud).

Patients will be interviewed on risk factors for stomach cancer, and multiple biopsies from the stomach will be taken to define the histological diagnosis, prepare cultures of *H. pylori* and perform genetic studies of the strains detected, in an effort to identify characteristics associated with increased virulence of specific strains associated with atrophic gastritis or cancer.

In addition, a variety of markers of activation of inflammatory cells, oxidative stress, enzymatic antioxidant defence and cytokine induction in human gastric mucosa will be investigated in relation to *H. pylori* strains and individual susceptibility (see Section 4.4.1). A blood sample will also be collected to investigate antibody responses against *H. pylori*, *H. pylori*-associated autoimmunity and pepsinogen levels. The data will be analysed as a comparative preva lence survey and as a multi-centre case–control study of stomach cancer and CAG.

3.2.4

Tobacco smoking and stomach cancer

P. Boffetta; in collaboration with J. Trédaniel, Paris, France

A meta-analysis of tobacco smoking and stomach cancer risk has shown an overall 50% increase in risk among smokers as compared to non-smokers [460]. Because of the high incidence of stomach cancer, its public health importance may be larger than that of other cancers more strongly associated with tobacco smoking, despite the small magnitude of the effect.

3.3 *Cancer of the liver*

The studies on liver cancer address issues of mechanisms of hepatocarcinogenesis, genetic susceptibility to aflatoxins and the use of biomarkers in pilot intervention studies to assess how effective primary prevention measures may be in reducing exposure to these carcinogens.

3.3.1

Cohort study of HBsAg carriers in Thailand

M. Plummer, N. Muñoz, H.R. Shin, C. Lavé and D. Magnin; in collaboration with P. Srivatanakul and S. Puribahat, Bangkok, Thailand; and C.P. Wild, Leeds, UK

Chronic carriers of hepatitis B virus (HBV) are at high risk of developing hepatocellular carcinoma (HCC). The purpose of this study is to identify cofactors for development of HCC in a cohort of 1800 males over 30 years of age, all of whom have been identified as carriers of hepatitis B surface antigen (HBsAg). Follow-up of the cohort was completed in June 1995 and accumulated 5800 person-years of observation. During active follow-up, blood and urine samples were collected at regular intervals and stored. Environmental and behavioural risk factors were assessed through a questionnaire at recruitment.

A nested case–control study of HCC is being conducted. Forty-one cases have been diagnosed and two age-matched controls have been selected for each case. The risk factors for HCC being investigated are diet, alcohol and smoking, as well as aflatoxin exposure, measured by aflatoxin–albumin adducts in plasma, and genetic polymorphisms of aflatoxin-metabolizing enzymes (glutathione *S*-transferase (GST) M1, T1, P1 and epoxide hydrolase). In addition, markers of HBV and hepatitis C virus (HCV) are being investigated. Preliminary analysis of diet, alcohol, smoking and socioeconomic status shows no association with HCC. Likewise, analysis of the genetic polymorphisms and of aflatoxin exposure shows no association.

A further nested case–control study of chronic liver disease (chronic active hepatitis or cirrhosis) is planned, using subjects with normal liver function as controls.

3.3.2

Epidemiology of cholangiocarcinoma in Thailand

P. Pisani and D.M. Parkin; in collaboration with V. Vatanasapt and S. Sriamporn, Khon Kaen, Thailand

A cohort study was set up in 1992 to investigate the causes of liver cancer in a province of north-east Thailand, where this disease is the most common malignancy in both sexes. The annual age-standardized incidence rates (ASRs) of liver cancer in the years 1988–91 reported by the Khon Kaen Cancer Registry were 94.8 in men and 39.4 in women (a risk comparable to those of lung cancer in men and colorectal cancer in women in the USA). Cholangiocarcinoma represents 90% of all liver cancers occurring in this population, while hepatocellular carcinoma is the predominant type everywhere else in the world.

Over 10 000 individuals have been enrolled. Interview data are complemented with samples of blood and faeces; the first is separated and stored at –20 °C for future analysis and the second provides evidence of current infection with *Opisthorchis viverrini*, a parasite of the biliary ducts endemic in the area. Procedures to link the cohort with the database of the provincial population-based cancer registry have been developed. Excluding prevalent cases diagnosed within three months of recruitment, 50 incident cases occurred within an average of two and a half years of follow-up. Each case was matched

to three controls from within the cohort. Analysis of the first nested case–control study is in progress.

This cohort is one of very few examples of multi-purpose prospective studies in a developing country, so far limited only by its size, which is too small to allow study of other disease endpoints. A second phase of recruitment to double the size of the cohort in three years started in October 1997. The increased size of cohort will permit examination of: (*a*) all-cause and cardiovascular mortality and life-expectancy in relation to a variety of lifestyle factors, with particular emphasis on tobacco and alcohol consumption; (*b*) cervix cancer and infection with various types of human papillomavirus (see Section 3.4.7) and (*c*) lung, colorectal and breast cancer in relation to genetic factors and environmental exposures. Metabolic phenotypes such as GSTM1 and CYP1A1, which may predispose to cancer at various sites, have shown race-specific polymorphisms, but previous studies on Caucasians and Asians have given inconsistent results.

3.3.3
Expression of carcinogen-metabolizing enzymes in relation to liver injury

3.3.3.1
Helicobacter hepaticus mice

C.P.Wild, P. Chomarat and J.M. Rice; in collaboration with L. Anderson, Frederick, MD, USA

A bacterium, *Helicobacter hepaticus*, infects the intrahepatic bile canaliculi of mice, causing a severe chronic hepatitis culminating in liver cancer. This is a useful model for studying mechanisms of bacteria-associated carcinogenesis. In this model, specific cytochrome P450s (CYP2A5 and CYP1A2) are increased in livers of infected mice in relation to the degree of liver pathology, as demonstrated by immunohistochemical staining, enzyme activities and mRNA levels. Perfusion of the liver with nitroblue tetrazolium, an indicator for superoxide formation, demonstrated that in livers of infected mice, hepatocytes often showed co-staining of CYP2A5 and reactive oxygen species. In parallel to these alterations in CYP levels there was an age-specific increase in GST pi and alpha class enzymes, whereas catalase and glutathione-peroxidase activities, as well as glutathione content, were decreased in the early stages of disease. These alterations in CYP, GST and antioxidant systems were also associated with increased levels of 8-hydroxydeoxyguanosine in infected livers. Overall, these results suggest that CYP2A5 and CYP1A2 contribute to superoxide generation and 8-hydroxydeoxyguanosine formation and this may be one mechanism involved in carcinogenesis in this model, which is of relevance to human tumours associated with chronic bacterial infection [75, 434].

3.3.3.2
HBV transgenic mice

C.P. Wild, P. Chomarat, I. Chemin and J.M. Rice; in collaboration with B. Slagle, Houston, TX, USA

We have previously shown that the specific cytochrome P450s 2A5 and 1A are increased in HBV transgenic mice. This was both in a model of chronic liver injury, as a result of accumulation of HBsAg in hepatocytes, and in a model of fulminant hepatitis, due to the action of cytotoxic T cells specific to HBV antigens (Kirby *et al.*, 1994, *Molec. Carcinog.*, 11, 74–80; [74]). Subsequently, we wished to examine whether the increase in P450 was associated with expression of the transactivating hepatis B virus X gene (HBx) or whether liver injury associated with HBV gene expression was a prerequisite for the increase. We therefore studied a number of HBV transgenic lineages accumulating different levels of HBsAg and consequently different associated degrees of liver injury. The strongest induction of CYP2A5 and CYP1A was in those lineages where liver injury was most marked. These studies were extended to a lineage (designated

ATX) where the HBx gene is expressed under the control of human α-1-antitrypsin regulatory elements and where only minor histopathological changes in the liver are observed. In this model there was no evidence either of CYP1A and 2A5 induction or of alterations in GST levels in transgenic mice aged 12 days or 3 months old compared with age-matched control mice. In addition, neither catalase and glutathione peroxidase activities nor reduced glutathione content were altered in ATX mice compared with control mice. These results support the conclusion that expression of HBx alone is insufficient to induce transactivation of CYP and GST genes or to alter the antioxidant system and that the induction in other HBV models is a result of inflammatory injury in the liver, a feature absent in the HBx transgenic mice.

3.3.4
Alterations in minisatellite sequences in relation to hepatitis and aflatoxin exposures

C.P. Wild, C. Kaplanski and A. Schouft

Minisatellites represent hypervariable regions of DNA showing multiallelic variation due to differences in the number of repeats of a specific DNA sequence. Probes corresponding to minisatellite core sequences (consensus sequences common to a family of minisatellites) allow simultaneous study of many hypervariable loci throughout the genome by producing a multilocus DNA fingerprint. Somatic rearrangements in minisatellite sequences are observed in a variety of human tumours and in animal tumours induced by chemical carcinogens. Minisatellite sequences therefore represent an attractive target for screening alterations occurring throughout the genome. We examined minisatellites in human and mouse liver tumours in relation to exposure to aflatoxin and HBV to test whether such exposure could induce genetic instability and thus contribute to the process of carcinogenesis. In addition, genetically engineered yeast capable of metabolizing aflatoxin was used to examine the induction of alterations in minisatellite sequences more directly in an *in vitro* model.

3.3.4.1
HBV transgenic mice

In collaboration with F. Chisari, La Jolla, CA, USA; and V.S. Turusov, Moscow, Russian Federation

Liver tumours from HBV transgenic mice either untreated or treated transplacentally with aflatoxin B_1 were examined. In a total of 28 liver tumours from HBV transgenic mice receiving no aflatoxin B_1, no minisatellite rearrangements were detected with any of the three multilocus probes employed (frequency of rearrangements < 0.2%). In 11 tumours from mice exposed transplacentally, six contained at least one rearrangement, with rearrangement frequencies between 1.1 and 2% depending on the probe. These data show that genetic alterations can be induced by transplacental exposure to aflatoxin B_1 and suggest that genetic instability may be important in hepatocarcinogenesis with combined exposures to aflatoxin B_1 and HBV [183].

3.3.4.2
Hepatocellular carcinomas from Thai patients

In collaboration with P. Srivatanakul, Bangkok, Thailand; and J.D. Groopman, Baltimore, MD, USA

Hepatocellular carcinoma (HCC) is one of the most common cancers in Thailand, where chronic HBV infection is endemic and aflatoxin exposure occurs. Twenty-six HCC from Thai patients were examined for the presence of somatic rearrangements using three multilocus minisatellite probes. Probes 33.15 and 33.6 detected rearrangements in 11 and 12 HCC respectively, all of them carrying integrated HBV DNA (frequency of rearranged bands was 3.7% with probe 33.15

and 4.2% with probe 33.6). In order to look for clustering of these rearrangements at specific loci, we used minisatellite locus-specific probes previously cloned from 33.15 and 33.6. Minisatellites located at 1p33-35, 7q36-ter and 12q24.3-ter were frequently affected by rearrangement events in HBV-positive HCC. Frequent rearrangements at minisatellite locus D7S22 (7q36-ter) have not been reported previously. Analysis of aflatoxin exposure in the same individuals was attempted by measuring hepatic DNA for the presence of aflatoxin–DNA adducts. A sensitive method was developed by a combination of immunoaffinity columns containing antibodies recognizing aflatoxin–DNA adducts and HPLC with diode array detection. However, in all cases the adduct level was below the detection limit of the assay (1 adduct per 10^6 guanine molecules). These studies show that genetic alterations in minisatellite sequences are frequent in HBV-associated HCC, but no conclusion can be drawn about the specific role of HBV in these alterations in the absence of HBV-negative tumours [184].

3.3.4.3

Minisatellite sequences in yeast treated with aflatoxin B_1

In collaboration with C. Sengstag, Zürich, Switzerland

The role of aflatoxin B_1 in the induction of rearrangements affecting minisatellite sequences was studied in an *in vitro* yeast model. The yeast strain used is a metabolically competent diploid strain of *Saccharomyces cerevisiae* expressing human cytochrome P450 (CYP) 1A2 and NADPH-cytochrome P450 oxidoreductase (hOR). DNA multilocus fingerprinting was performed using probe M13 core hybridizing to a set of hypervariable minisatellite sequences in *S. cerevisiae*. Frequent spontaneous minisatellite rearrangements leading to the formation of new length sequences were observed in this yeast strain. In the aflatoxin B_1-treated (80 μg/ml) group, 47.8% of the yeast cultures showed rearrangements affecting minisatellite sequences, while in the control group only 23.8% of cultures showed rearrangements. A total of approximately 29 DNA bands for each colony were detected using the M13 probe. Given the number of colonies examined (46 aflatoxin-treated and 42 controls), the frequency of rearrangement events was calculated as 1.27% in the aflatoxin-treated group; this value was twice that in the control group. These data suggest that aflatoxin B_1 can promote the genetic events responsible for minisatellite rearrangements in the yeast genome. Such aflatoxin-induced genetic alterations may be important events during the natural history of liver carcinogenesis in people chronically exposed to dietary aflatoxins.

3.3.5

Genetic and environmental determinants of aflatoxin–albumin adducts in exposed populations

C.P. Wild, B. Chapot, Yin Fen and I. Chemin; in collaboration with A.J. Hall, London, UK; M. Mendy, Fajara, The Gambia; and H. Whittle, The Gambia

Previously HBV infection in children (Wild *et al.*, 1993, *Cancer Epidemiol. Biomarkers Prev.*, 2, 555–561) and genetic polymorphisms in carcinogen-metabolizing enzymes, e.g., microsomal epoxide hydrolase (McGlynn *et al.*, 1995, *Proc. Natl Acad. Sci.*, 92, 2384–2387), have been associated with higher levels of aflatoxin–albumin adducts. In the current cross-sectional study, we sought to identify the major environmental and genetic determinants of aflatoxin–albumin adducts in a group of approximately 350 Gambian subjects, half of whom were known to be long-term chronic HBV carriers. The adduct level was not related to sex, age or HBV status. There was also no association with GST M1 genotype or with cytochrome P450 3A4 phenotype as determined by urinary cortisol : 6β-hydroxy-

cortisol ratio. Epoxide hydrolase genotype was studied but the prevalence of low-activity alleles was much lower than in other populations studied. The major determi nants of adduct level were season and place of residence of the subject; subjects had higher adduct levels in the dry season after extended storage of crops and in rural compared to urban areas. This indicates that in adults, at least, HBV does not appear to influence aflatoxin–albumin adduct levels and that in this high-exposure population the genetic polymorphisms examined have a minor impact on aflatoxin levels compared with levels of environmental exposure.

3.3.6
Pilot intervention studies to reduce aflatoxin exposure in Guinea, west Africa

C.P. Wild, M. Castegnaro, B. Chapot, L.Garren and B. Sylla; in collaboration with M. Diallo and A. Sylla, Conakry, Guinea; A.J. Hall, London, UK; and J.D. Groopman, Baltimore, MD, USA

In a first survey in Kindia, over 90% of subjects were positive for serum aflatoxin–albumin adducts, while 15% of subjects were positive for hepatits B surface antigen (HBsAg) and 7% for antibodies to hepatitis C virus. A second survey was conducted in the four natural geographical zones of the country, namely Lower, Middle and Upper Guinea as well as Guinea Forestiere.

Adult subjects (male and female) from one to three villages per region were included. In all four zones, the high percentage of HBV chronic carriers was confirmed (11% to 19% positive), with an overall prevalence in the country of just over 14%. Aflatoxin–albumin adduct measurements revealed similar prevalence and levels of exposure between villages within a zone. However, the level of exposure was lower in Guinea Forestiere than in the other three zones. Questionnaire data on food consumption suggest that groundnuts are the primary source of aflatoxin exposure. These results provide the basis for sample size calculations for the intervention.

A preliminary study to determine the source of contaminated food and the most critical stage for contamination (pre- or post-harvest) is being carried out in four villages representative of Lower Guinea. In each village, 15 families have been selected for food collection. In each family, blood samples will be taken from two adults for analysis of aflatoxin–albumin adducts.

Food sampling is being carried out at three seasons: just after the crop, after about four months and after about eight months. The samples are stored at –20°C until analysis. Two methods have been set up at IARC for analysis of aflatoxins, using either high performance liquid chromatography or thin-layer chromatography. The thin-layer chromatography method will be used in the Conakry laboratory because it involves no sophisticated equipment.

3.3.7
Experimental studies on fumonisin B_1

C.P. Wild, M. Castegnaro, W.C.A. Gelderblom, D. Galendo and M.-P. Cros

3.3.7.1
Effect of regenerative cell proliferation on cancer-initiating potential of fumonisin B_1

Fumonisin B_1 inhibits cell proliferation in various biological systems *in vitro* and *in vivo*. This property appears to be a prerequisite for cancer promotion in rat liver [119], but could also explain the low cancer-initiating potential of this mycotoxin. Regenerative cell proliferation is required for cancer initiation, and studies have shown that carbon tetrachloride, but not the mitogenic lead nitrate, enhance the cancer-initiating activity of fumonisin B_1. These results suggest that the cancer-initiating potential of fumonisin B_1 could be synergistically enhanced by factors that induce regenerative cell proliferation in rat liver. To examine this hypothesis, an experiment is

being conducted to investigate a possible synergistic interaction between HBV and fumonisin B_1 in transgenic mice.

3.3.7.2

The effect of fumonisin B_1 on fatty acid metabolism

In vivo studies in rat liver have indicated that fumonisin B_1 interrupts phospholipid and fatty acid metabolism [117]. Subse quent studies with rat liver microsomes showed that the levels and fatty acid profiles of the major membrane phospholipids were significantly altered, implying that the membrane structure is altered as a result of the treatment. The activity of the rate-limiting enzyme in the fatty metabolic pathway, the delta-6 desaturases, decreased in a dose-dependent manner as a result of fumonisin B_1 treatment, presumably due to the structural changes in the membranal environment of the enzyme.

3.3.8 Molecular analyses of liver tumours in c-*myc* transgenic mice and c-*myc* & TGF-α double transgenic mice

H. Ohgaki; in collaboration with S.S. Thorgeirsson, Bethesda, MD, USA

Co-expression of c-*myc* and transforming growth factor α (TGF-α) as transgenes in mouse liver results in a great acceleration of neoplastic development in this organ compared with expression of either transgene alone. High expression of the TGF-α transgene was found in 9 of 14 (64%) liver tumours in c-*myc* & TGF-α double transgenic mice, suggesting that TGF-α overexpression confers a growth advantage in hepatocarcinogenesis. In contrast, in c-*myc* or c-*myc* & TGF-α double transgenic mice, most liver tumours showed lower expression of the c-*myc* transgene than non-tumorous parts of their livers. These results suggest that c-*myc* transgene expression cooperates with TGF-α in the early stages of hepatocarcinogenesis but may lead to a growth disadvantage in later stages. Only one of 14 (7%) liver tumours in double transgenic mice but none of 13 liver tumours in c-*myc* transgenic mice showed overexpression of IGF-II, which was frequently observed in liver tumours that developed in TGF-α transgenic mice (Takagi *et al.*, 1992, *Cancer Res.*, 52, 5171). This suggests that the presence of c-*myc* transgenes together with TGF-α from an early stage of hepatocarcinogenesis may lead to carcinogenic pathways that are independent of IGF-II overexpression [311].

3.4 Cancer of the cervix

Cancer of the cervix is the second most common cancer in women. Epidemiological studies carried out by the IARC during the last 10 years have shown that the association of human papillomavirus (HPV) with cervical cancer is very strong, independent of other risk factors and consistent in several countries. This strong association is not only with the most common HPV types (HPV 16 and 18) but also with the less prevalent types (HPV 31, 33, 45, 52, 58, 59). Case–control studies in 10 countries are also investigating co-factors that influence progression from persistent HPV infection to invasive cervical cancer. International prevalence surveys of HPV types in women with cervical cancer and in normal women are being conducted in 20 countries, as well as cohort studies in high-risk populations in Costa Rica and Colombia. These studies will provide essential background information on the natural history of HPV infection and cervical neoplasia for planning preventive strategies using the HPV vaccines that are under

development (Section 5.1.4). In all these studies, the latest tools of molecular biology are being used to assess exposure to HPV and other infectious agents, coupled with appropriate epidemiological methods.

3.4.1 Case–control studies of cervical cancer in Spain and Colombia

N. Muñoz, R. Herrero, A. Arslan and D. Magnin; in collaboration with N. Ascunce, Pamplona, Spain; F.X. Bosch, X. Castellsagué, S. de Sanjosé and P. Viladiu, Barcelona, Spain; M. Gili, Seville, Spain; L.C. Gonzalez, Salamanca, Spain; I.P. Icenogle and J. Icenogle, Atlanta, GA, USA; I. Izarzugaza, Vitoria-Gasteiz, Spain; C. Martos and P. Moreo, Zaragoza, Spain; C. Navarro and M.J. Tormo, Murcia, Spain; J. Schlehofer, Heidelberg, Germany; P. Stern, Manchester, UK; K.V. Shah, R. Daniel and K. Cho, Baltimore, MD, USA; L. Tafur, Cali, Colombia; and V. Vonka, Prague, Czech Republic

Data from the four concurrent case–control studies conducted in Colombia, a country with high risk for cervical cancer, and Spain, a country of low risk, have been analysed in terms of the role of the male factor in the etiology of the disease [69]. In Spain, the presence of human papilloma virus (HPV) in the husband's penis conveyed a five-fold risk of cervical cancer to their wives. Risk was strongly related to HPV type 16, to the number of extramarital partners of the husband and to the number of prostitutes as extramarital partners [38]. In Colombia, however, no risk was associated with these variables, probably as a consequence of high frequency of exposure among males [288].

The number of sexual partners, antibodies to *Chlamydia trachomatis* and socioeconomic level were identified as the most important determinants of HPV DNA detection in middle-aged women, using the control series from these four case–control studies, as well as data from Brazil [292].

Further analysis of sociodemographic data suggested that the higher incidence of cervical cancer in the lower socioeconomic groups could be explained, at least in part, by higher prevalence of HPV DNA and lower frequency of Pap smears [83].

Antibodies to various serological markers of HPV have been measured in the sera of cases and controls. Antibodies to early antigens of HPV 16 (E2 and E7) were associated with cervical cancer risk, but these associations were less strong than those with HPV DNA [83].

Data from the two population-based studies on invasive cervical cancer were analysed to investigate the use of HPV DNA and serological markers of HPV 16 as predictors of survival of these patients. Clinical stage was the only independent prognostic factor for recurrence or survival. Although seropositivity to HPV 16 E7/3 peptide predicted a two-fold excess risk of mortality, the association was restricted to stage I; different estimates of the HPV viral load and the HPV type identified were not predictors of tumour recurrence or survival [482].

A separate small study suggested that antibodies to virus-like particles of HPV are partially type-specific [140].

The prevalence of sequence variations in the E6 and E7 genes isolated from the cancers is being investigated in collaboration with I.P. Icenogle, as are the immortalizing activity of some of these variants and their ability to degrade p53 protein.

The roles of HLA genes and adeno-associated virus as biological modifiers of HPV-associated cervical cancer are being investigated in collaboration with Drs P. Stern and J. Schlehofer.

The laboratory of Dr K. Cho has found that alterations in FHIT expression (Fragile Histidine Triad), a candidate tumour-suppressor gene, are frequent in cervical cancer but not in normal tissue, suggesting that these genetic alterations may play an important role in cervical carcinogenesis.

Women who were identified as HPV-positive in the Colombia/Spain case–control studies were contacted again to assess

(*a*) their exposure to risk factors for cervical cancer in the interval; and (*b*) whether or not cervical cancer or its precursors had been diagnosed in the interval. One control per case was selected as follows. Cases were defined as women without cervical cancer who were HPV DNA-positive in the 1992 HPV test. Controls were women without cervical cancer who were also HPV DNA-negative in 1992. Controls were matched by age and place of residence among participants in the original study, randomly identified and invited to participate. Men who were found HPV-positive or women whose husbands were HPV-positive were also invited to participate.

Each participant was asked to reply to a brief questionnaire and to provide a blood specimen and a specimen of exfoliated cells from the cervix or penis. All specimens were pre-processed in the field as usual, frozen and sent to the central research laboratory for testing.

Table 5 shows the number of subjects targeted for investigation, the number traced and interviewed and the number who provided a biological specimen.

Preliminary results from the questionnaires evaluated show that no cases of cervical intraepithelial neoplasia (CIN) III or invasive cervical cancer have been identified in the interval. The cell pellets are now in Baltimore (Dr K.V. Shah, Johns Hopkins University) and protocols are being prepared to test for HPV DNA, viral load and viral integration. The goal of the study is to identify factors (behavioural and viral) related to viral DNA persistence.

3.4.2
Multi-centre case–control study of cervical cancer

N. Muñoz, R. Herrero, J. Smith, D. Magnin and A. Arslan; in collaboration with S. Bayo, Bamako, Mali; F.X. Bosch, Barcelona, Spain; E. Caceres, Lima, Peru; N. Chaouki, Rabat, Morocco; S. Chichareon, Hat Yai, Thailand; P. Coursaget, Tours, France; J. Eluf-Neto, São Paulo, Brazil; D. Hammouda, Alger, Algeria; C. Ngelangel, Manila, The Philippines; T. Rajkumar, Madras, India; P.A. Rolón, Asunción, Paraguay; K.V. Shah, Baltimore, USA; J. Walboomers and C. Meijer, Amsterdam, The Netherlands; and C. Wheeler, Albuquerque, NM, USA

This study was designed to investigate the role of different types of HPV in the etiology of cervical cancer in high-risk areas of the world and where few studies have been conducted. In particular, we wish to evaluate the role of less prevalent HPV types and of certain types of male and female behaviour. In addition, the roles of hormonal agents, parity, other sexually transmitted agents and tobacco smoking as potential co-factors with HPV infection are being investigated. A PCR-based assay capable of detecting over 30 HPV types is being employed to assess their association with the two main histological types of cervical cancer: squamous cell carcinoma and adenocarcinoma.

Case–control studies have been completed in Brazil, Mali, Morocco, the Philippines and Thailand; new studies are in progress in Peru and Algeria and similar ones in India and Mauritius are under consideration (Figure 14).

The results of the studies in the Philippines and Thailand, which included in total more than 600 cases of invasive cervical cancer and 600 hospital controls, indicated that HPV was present in more than

Table 5. Numbers of subjects interviewed and of samples collected in Colombia and Spain

	Target		Interviewed		Specimens	
	Women	Men	Women	Men	Women	Men
Spain	89	43	22	33	19	9
Colombia	159	77	103	16	87	13
Total	248	120	125	49	106	22

Figure 14. Locations of collaborating centres in multi-centre case–control study of cervical cancer

90% of the cases of both squamous cancers and adenocarcinomas. It also demonstrated very strong associations with risk of squamous carcinoma for HPV types 16, 18, 31, 33, 45, 52 and unknown types (Figure 15).

In adenocarcinoma, HPV 18 was the most common type detected, and elevated risks of disease were observed for HPV 16, 18, 45 and unknown types.

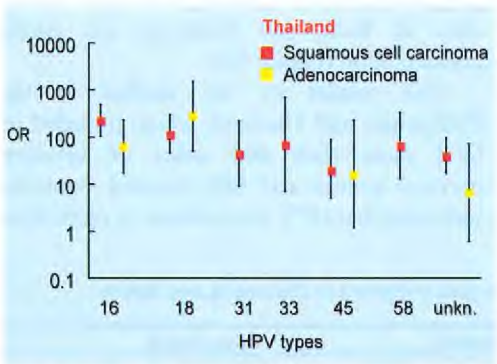

Figure 15. Odds ratios for squamous cancers and adenocarcinomas, for HPV types 16, 18, 31, 33, 45, 52 and unknown types, in Thailand

These results demonstrate for the first time the association of types other than 16 and 18 with risk of cervical cancer and warrant the addition of these other types to the list of human carcinogens.

Sera from case and control women in the Philippines and Thailand will be tested for the presence of antibodies against *C. trachomatis* (using micro-immunofluorescence) and herpes simplex virus-2 (using Gull-ELISA with Western blot confirmation), possible co-factors of HPV infection in the development of cervical cancer. We have already conducted preliminary analysis of the sera of women participating in the study in the Philippines for serum IgG antibodies against recombinant HPV 16 virus-like particles (VLPs) by an ELISA method. Overall positivity for HPV 16 VLP antibodies was 47% among squamous-cell cancers, 28% among adenocarcinoma and 25% among controls. The age-adjusted odds ratio for HPV 16 seropositivity in squamous cell cancers was 2.7 (95% CI 1.9–3.7). When

considering only HPV 16 DNA-positive squamous cell cancers, the age-adjusted OR was 5.1 (95% CI 3.2–7.9). These prelimi nary results indicate that the prevalence of antibodies to HPV 16 is higher in cases of squamous cancer than in controls, but the sensitivity and specificity of the serological assay is lower than that of HPV DNA.

The risk associated with the different variants of HPV 16 identified in our case–control studies is being investigated in collaboration with C. Wheeler.

3.4.3

International prevalence survey of human papillomavirus markers in cervical cancer tissue and sera

N. Muñoz, R. Herrero, A. Arslan and D. Magnin; in collaboration with E. Alihonou, Cotonou, Benin; S. Bayo, Bamako, Mali; F.X. Bosch V. Moreno, Barcelona, Spain; H. Cherif Mokhtar, Sétif, Algeria; S. Chichareon, Hat-Yai, Thailand; A. Daudt, Porto Alegre, Brazil; E. de los Rios, Panama City, Panama; P. Ghadirian, Montreal, Canada; M. Jacobs and J. Walboomers, Amsterdam, The Netherlands; J.N. Kitinya, Dar es Salaam, Tanzania; M. Koulibaly, Conakry, Guinea; M. Manos, Oakland, CA, USA; C. Ngelangel, Manila, The Philippines; J. Peto, London, UK; Ll. M. Puig Tintoré, Barcelona, Spain; J.L. Rios-Dalenz, La Paz, Bolivia; P.A. Rolón, Asunción, Paraguay; Sarjadi, Semarang, Indonesia; M. Schiffman, Bethesda, MD, USA; A. Schneider, Jena, Germany; K.V. Shah and R. Daniel, Baltimore, MD, USA; L. Tafur, Cali, Colombia; A.R. Teyssie, Buenos Aires, Argentina; M. Torroella, Havana, Cuba; A. Vila Tapia, Concepción, Chile; H.R. Wabinga, Kampala, Uganda; C. Wheeler, Albuquerque, NM, USA; and W. Zatonski, Warsaw, Poland

An international prevalence survey of HPV markers in over 1000 tissue specimens of invasive cervical cancer from 22 countries has been completed. Initial PCR-based analysis revealed an overall HPV DNA-positivity of 93% using primers which target the HPV L1 sequences (MY09/11 PCR). Further PCR-based assays using more sensitive primers targeting the L1, E1 and E7 regions were carried out in Dr Walboomers's laboratory. These assays increased HPV DNA-positivity to 99%, suggesting that the occurrence of HPV-negative cervical cancer is extremely rare or perhaps non-existent.

The intratypical sequence variation of 13 HPV types (16, 18, 33, 35, 39, 45, 51, 52, 58, 59, 68, 73 and a novel type) has been investigated in collaboration with C. Wheeler. Diversity in the L1 open reading frame varied between 0 and 2.9% and the majority of the changes were synonymous (amino-acid-conserving). 92% of HPV 16 variants belonged to previously reported HPV 16 variant lineages and 8% harboured variants with novel hybridization patterns, novel nucleotide changes or both. Nucleotide sequences were determined for the E6, L1 and the long control region (LCR) of each new variant [441, 506]. The epidemiological correlates of these variants will be investigated.

3.4.4

Comparison of two methods for sampling from the normal cervix in assessing HPV DNA prevalence

N. Muñoz; in collaboration with F.X. Bosch, S. de Sanjosé, Ll. Balaguero, Ll. Gine, M.J. Pla, B. Lloveras and E. Condom, Barcelona, Spain; S. Chichareon, Hat-Yai, Thailand; C. Ngelangel, Manila, The Philippines; and J.M.M. Walboomers, Amsterdam, The Netherlands

To assess the importance of the type of specimen in determinations of HPV prevalence, a validation study is being performed. Cervical scrapes and biopsies have been collected in the Philippines, Spain and Thailand from 300 women with normal cytology in whom hysterectomy was performed for reasons other than cervical cancer. The three participating centres have contributed subjects and specimens as indicated in Table 6.

The study aims at estimating the validity of using exfoliated cells as a source of DNA for HPV identification among women with

Table 6. Numbers of interviews and samples in study of cervical sampling methods

Location	Interviews	Biopsies	Cells
Thailand	117	468	351
Philippines	115	460	345
Barcelona	110	392	343

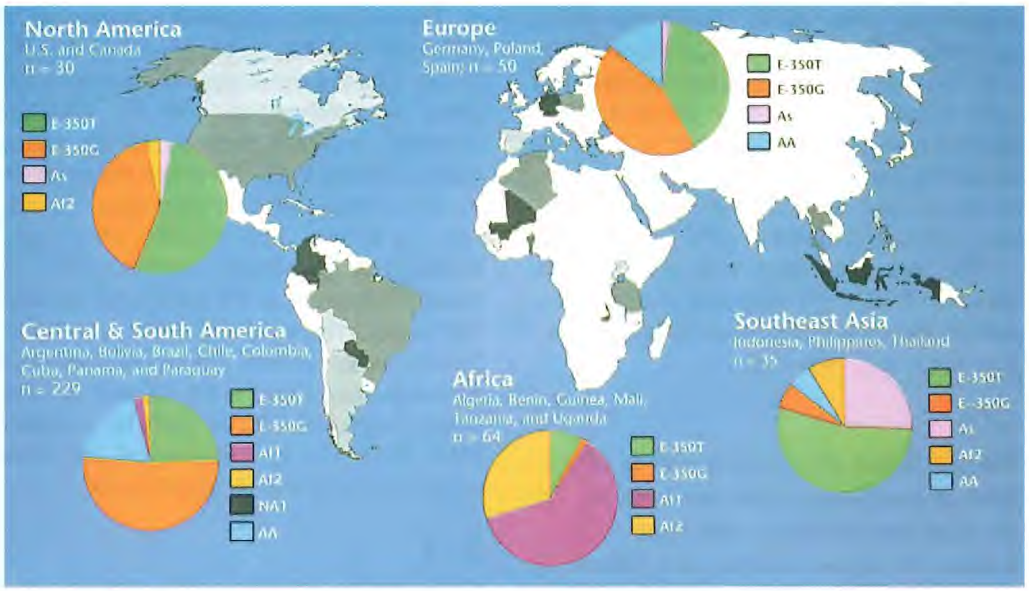

Figure 16. Distribution of HPV 16 variants in cervical carcinomas, by continent

non-neoplastic cervix. The standard will be corresponding tests in systematic biopsies of the cervix. Women undergoing hysterectomy for reasons other than cervical cancer have been invited to participate. A brief questionnaire on risk factors for cervical cancer was administered and specimens were taken at the time of surgery as follows: three exfoliated cell specimens, two with the Ayre spatula in the exocervix and one in the endocervical canal with a cervical brush. Four biopsies were then taken in the four quadrants of the cervix. All material was frozen and stored until processing in Amsterdam.

Testing of the specimens is in progress. All cytological specimens have been initially screened for HPV DNA and HPV typing of the positives has been performed using the GP5+/6+ system. Twenty-nine women were found to harbour HPV DNA as follows: HPV 16, $n = 6$; HPV 18, $n = 5$; HPV 45, $n = 5$; HPV X, $n = 14$. Further, one of the four cervical biopsies of the 29 HPV-positive women is being tested as well as a sample of the biopsies from HPV-negative women. In a preliminary analysis, exfoliated cells had detectable HPV DNA in 96% of the women whose biopsies were HPV-positive. The cells were negative in 90% of the women whose biopsies were negative. These results support the notion that exfoliated cells constitute adequate specimens for ascertainment of cervical HPV infection.

3.4.5

Cohort study on HPV, hormonal contraception and cervical neoplasia

N. Muñoz, R. Herrero and A. Arslan; in collaboration with O. Meirik, Geneva, Switzerland; H. Posso, O. Orozco and M. Molano, Bogotá, Colombia; K. Shah, Baltimore, MD, USA; and J. Walboomers, Amsterdam, The Netherlands

This cohort study was initiated in November 1993 in Bogotá, Colombia, to

Figure 17. Processing samples for HPV DNA detection in Bogotá

investigate the natural history of HPV infection and in particular to identify the determinants of progression to persistent HPV infection and cervical neoplasia. Special attention is being paid to the role of hormonal contraception as a predictor of progression in women with HPV infection.

2140 women attending several health centres in Bogotá have been enrolled. Personal interviews on risk factors and gynaecological examinations are performed at study entry and during follow-up examinations every 6–9 months. Cervical cells are collected for a Pap smear and HPV DNA detection by PCR-based assays at entry and at each follow-up examination. Compliance with the follow-up visits ranges from 61% at the third to 94% at the sixth follow-up visit. A total of 6251 cervical cell pellets had been collected up to June 1997 and 16% of the women have completed six follow-up examinations. Follow-up will continue until most women have completed six follow-up examinations.

The prevalence of squamous intraepithelial lesions (SIL) at the baseline examination of 2011 women was 4.2%. Of these, 3.7% were low-grade SIL and 0.5% high-grade SIL. Invasive cervical cancer was diagnosed in five women (0.2%) at study entry.

The prevalence of HPV DNA in a random sample of 405 women was 14.1% and was higher among women under 24 years of age (16.1%) than in women over 24 years (7.5%). It tended to increase again in women over 60 years of age (12.6%). Half of the HPV types identified fall into the so-called high-risk group, with HPV 52 and 58 the most common types, followed by HPV 16.

HPV DNA-positivity was twice as high among current users of oral contraceptives (28%) as as among non-current users (13%). HPV DNA detection in all specimens from this study will be carried out in the laboratory of Dr J. Walboomers.

3.4.7

Population-based natural history studies of cervical neoplasia in a high-incidence area of Latin America: the Guanacaste Project

R. Herrero and A. Arslan; in collaboration with C. Bratti and A.C. Rodriguez, Guanacaste, Costa Rica; R. Burk, New York, NY, USA; A. Lörincz, Silver Spring, MD, USA; and M.H. Schiffman, A. Hildesheim and M.E. Sherman, Bethesda, MD, USA

A prospective cohort study of 10 000 randomly selected women in a rural province of Costa Rica is being conducted under the aegis of the US National Cancer Institute and the Costa Rican Bureau of Social Security. The purpose of the study is to investigate determinants of the occurrence of high-grade cervical intraepithelial neoplasia (CIN) in this high-risk population, including the role of HPV [148, 149].

The enrolment screening will allow a prevalent case–control study of the different degrees of cervical neoplasia, as well as evaluation of several new screening techniques (cervicography, hybrid capture HPV DNA testing, monolayer cytology, semi-automated cytology). A random sample of 16% of the census areas (population 240 000) was selected, and enumeration of all adult resident women in those areas was conducted. Women were sent personal letters of invitation to local clinics where

study staff performed the study procedures after obtaining written informed consent. Of 11 742 women in the sample, 10 738 were considered eligible, and 10 049 were interviewed (94%). After exclusion of virgins, 9466 were considered eligible for pelvic examination and 9175 (97%) were examined. Exfoliated cells from all women were tested for HPV by a non-amplifying method (hybrid capture). In addition, all women with cervical neoplasia and a sample of those with equivocal or normal diagnoses were tested with a PCR method for the presence of more than 30 individual HPV types. Overall prevalence of HPV infection was 8.6% with hybrid capture and 15.2% with PCR, and was highest in the younger age groups, decreasing rapidly to a minimum around age 40 years and increasing again after age 60. Preliminary analysis of the performance of the different screening techniques [151] revealed that conventional cytology in this setting detected 90% of the cancers, 75% of the high-grade CIN and 64% of the low-grade CIN. Cervicography detected 100% of the cancers but only a limited number of precursor lesions. HPV DNA testing with hybrid capture detected 64% of the cancers and similar percentages of precursor lesions to conventional cytology. Combinations of different methods improved sensitivity but would require referral of higher numbers of women for colposcopic evaluation [152].

Regarding previous history of participation in screening programmes, a surprisingly high 87% of the women reported having been screened [151], and 80% of women aged 25–49 years reported having had a Pap smear test in the previous three years. However, incidence of cervical cancer in Costa Rica has not changed in the last 12 years in any age group. These results suggest that the current screening programme is highly ineffective, probably because of inadequate quality control in the laboratories and inappropriate follow-up of lesions detected. In a sample of women participating in this study [427], it was demonstrated that exfoliated cells collected in liquid medium can be used for both cytology and HPV testing and that this would increase the sensitivity and specificity of the screening process. Several subcohorts are being followed at different intervals to investigate determinants of the occurrence of high-grade CIN.

3.4.8 Prevalence surveys of HPV infection in high- and low-incidence areas for cervical cancer

R. Herrero, N. Muñoz, D.M. Parkin, P. Pisani, A. Arslan and D. Magnin; in collaboration with P.T.H. Anh, Hanoi, Viet Nam; F.X. Bosch, Barcelona, Spain; N.T. Hieu, Ho Chi Minh City, Viet Nam; E. Lazcano Ponce, Cuernavaca, Mexico; E. Matos and G. Amestoy, Buenos Aires, Argentina; T. Rajkumar, Madras, India; J. Sellors, Hamilton, Ontario, Canada; H.R. Shin, Pusan, Korea; S. Sukvirach, Bangkok, Thailand; J.M.M. Walboomers, Amsterdam, The Netherlands; and C.-Y. Zang, Chang Chun City, China

There are marked regional differences in the incidence of cervical cancer and, since HPV infection is the strongest risk factor identified (with risk estimates in the range of several tens to hundreds), it has been postulated that the HPV prevalence in certain segments of the population may be the most important correlate of the incidence of cervical cancer in a specific country or region. For example, the reported incidence of cervical cancer in Hanoi, in northern Viet Nam, is 7–8 per 100 000 women, while in the south, in Ho Chi Minh City (Saigon), it is at least 22 per 100 000. We are setting up several population-based prevalence surveys, including interviews, pelvic examinations and collection of cervical cells for HPV DNA detection. These surveys are designed to provide essential background information for the planning of HPV vaccine trials in these populations.

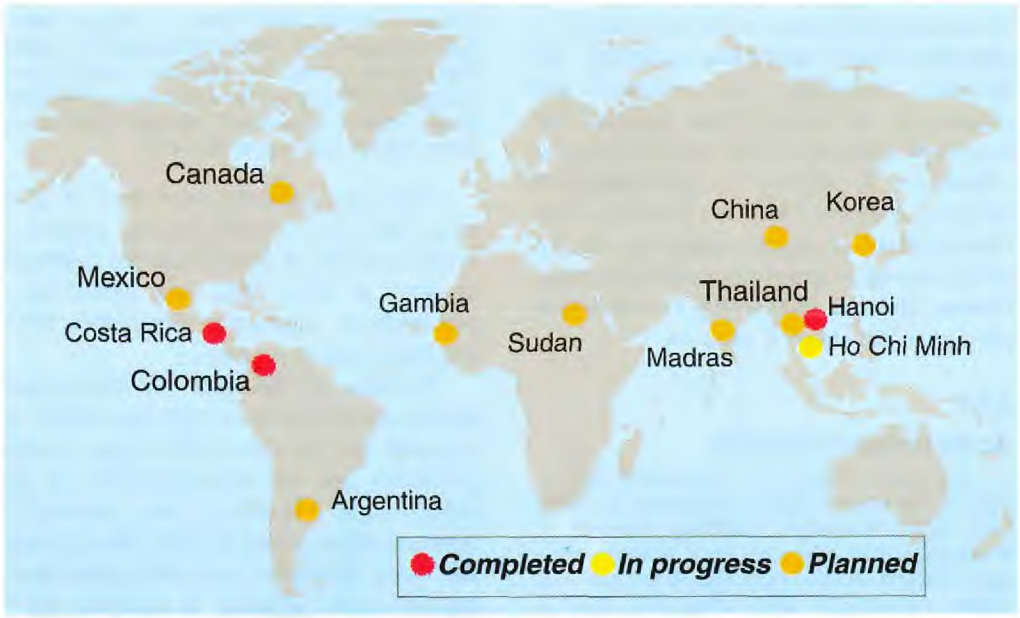

Figure 18. Collaborating centres in prevalence surveys of HPV infection

The study has been completed in Hanoi, with participation rates over 90% for both the interview and biological specimen collection. A total of 1245 women were enrolled after being randomly selected in an age-stratified sample of the population in several districts of Hanoi. In Ho Chi Minh City, 749 women have been enrolled, also with high participation. Similar studies comparing areas of high and low incidence are being set up in China, where mortality data indicate wide regional variation in cervical cancer, and in Argentina, Canada, The Gambia, Mexico (Morelos State), Spain (Barcelona) and Thailand, where a sample of males will be included.

A comparative study of the use of urine samples as samples to determine the presence of HPV DNA in the urogenital tract of males will be performed. 150 male solders in Cuernavaca, Mexico, have been invited to donate 50 ml of urine and exfoliated cells from the distal urethra and colonal sulcus are being collected at the same time. All specimens will be centrifuged and frozen at –70°C until tested by PCR. The comparison of urine samples with exfoliated cells from those areas of the penis will indicate if the former is an adequate specimen for this kind of study. If such is the case, future studies of male subjects will be much easier to implement. HPV testing with a PCR method will be carried out at Dr Walboomers's laboratory in Amsterdam over the next year.

3.5 Brain tumours

Brain tumours are relatively rare tumours, but pose a significant clinical challenge due their frequent occurrence in children and their generally poor prognosis. Despite major epidemiological efforts, therapeutic X-irradiation has remained the only exposure unequivocally associated with the evolution of human brain tumours. Nervous

system neoplasms also occur in a variety of inherited cancer syndromes, including *p53* germline mutations. The evolution and progression of human brain tumours are associated with sequentially acquired genetic alterations. In addition to epidemiological projects, studies at IARC are focused on the identification of genetic pathways in the evolution and progression of astrocytic brain tumours and their relationship to histological phenotype and patients' survival.

3.5.1
Brain tumours in adults

J. Little and R. Saracci; in collaboration with A. Ahlbom, Stockholm, Sweden; M. Blettner, B. Schlehofer and J. Wahrendorf, Heidelberg, Germany; P. Boyle, Milan, Italy; N.W. Choi and E. Kliewer, Winnipeg, Canada; S. Cordier, Paris, France; R. Gurevicius, Vilnius, Lithuania; G. Howe, New York, USA; J. McNeil, Melbourne, Australia; F. Ménégoz, Meylan, France; B. Modan, Tel Hashomer, Israel; S. Preston-Martin, Los Angeles, CA, USA; and P. Ryan, Adelaide, Australia

Data have been collected on all cases of brain tumours newly diagnosed in nine centres in seven countries during the period 1984–92 and on population-based controls. Data were obtained on a total of 1238 cases of glioma, 412 cases of meningioma and more than 2500 controls. A programme for combined analysis of these data was agreed at a collaborators' meeting in September 1995, and this is now in progress.

Interim combined analyses suggest inverse associations with participation in various sports and with allergic diseases and fever. An excess risk related to a previous head injury was observed only for meningiomas in men. No clear elevation in risk of glioma or meningioma associated with any occupational group or specific occupational exposure has been observed.

3.5.2
Brain tumours in children

J. Little and R. Saracci; in collaboration with P. Boyle, Milan, Italy; N.W. Choi and E. Kliewer, Winnipeg, Canada; S. Cordier, Paris, France; G. Filippini, Milan, Italy; R. Gurevicius, Vilnius, Lithuania; E.A. Holly, San Francisco, USA; M. McCredie, King's Cross, Australia; B. Modan, Tel Hashomer, Israel; B. Mueller, Seattle, USA; R. Peris-Bonet, Valencia, Spain; and S. Preston-Martin, Los Angeles, CA, USA

Data were collected on a total of 1218 cases and 2223 controls in nine centres in seven countries. A programme for combined analysis of these data was agreed at a collaborators' meeting in September 1995, and this is now in progress.

Analysis of the data on medications shows marked variation between centres in maternal use of nitrosatable drugs during pregnancy and use of such drugs by the index child. However, no association between maternal use of these drugs during the index pregnancy and subsequent brain tumours in the offspring is apparent, nor is an association evident for use by the index child. An elevated risk associated with the index child's use of anticonvulsant drugs may be secondary to the use of these drugs for the treatment of seizures before diagnosis of the tumour. Maternal use of vitamin supplements for at least two trimesters during the index pregnancy is inversely associated with childhood brain tumours. However, this finding is largely based on data from the centres where maternal use of supplements is common.

An analysis of data from the three areas in the United States (Los Angeles, San Francisco and Seattle) which participated in the study did not show any association between the risk for childhood brain tumours and maternal or paternal smoking before pregnancy, and there was no association between childhood brain tumours and maternal smoking during pregnancy (Norman *et al.*, 1996, *Cancer Epidemiol. Biomarkers Prev.*, 5, 127–133). There was a slight increase in the relative risk for brain tumours associated with maternal exposure to environmental tobacco smoke. These findings are consistent with those from previous centre-specific analyses of this study.

In an analysis of data from the three European centres (Ile de France, Milan–Varese–Como and Valencia), there was an association with paternal occupation in agriculture or maternal occupation as a nurse (Cordier *et al.*, 1997, *Cancer Causes Control*, 8, 688–697). In addition, application of a job–exposure matrix suggested an increased risk in the highest category of maternal exposure to solvents.

3.5.3
Genetics of glioma progression and the definition of primary and secondary glioblastoma

K. Watanabe, W. Biernat, A. Peraud, O. Tachibana, K. Sato, P. Kleihues and H. Ohgaki; in collaboration with E.R. Fearon, Ann Arbor, MI, USA; K. Plate, Freiburg i. Br., Germany; M. Reyes-Mugica and M.A. Reale, New Haven, CT, USA; and Y. Yonekawa, Zürich, Switzerland

Glioblastoma multiforme, the most malignant human brain tumour, may develop *de novo* (primary glioblastoma) or through progression from low-grade or anaplastic astrocytoma (secondary glioblastoma). We have found evidence that these subtypes of glioblastoma constitute distinct disease entities which evolve through different genetic pathways, affect patients at different ages and are likely to differ in prognosis and response to therapy [17, 191, 195, 197, 363, 415, 490]. Primary glioblastomas develop in older patients (mean, 55 years) and typically show *EGFR* overexpression, whilst secondary glioblastomas occur in younger patients (mean, 40 years) and frequently contain *p53* mutations [489, 490]. Only one out of 49 glioblastomas analysed showed *EGFR* overexpression together with a *p53* mutation, suggesting that amplification and overexpression of the *EGFR* gene and mutations in the *p53* tumour-suppressor gene are mutually exclusive events defining two different genetic pathways in the evolution of glioblastomas as the common phenotypic endpoint [490]. Further, we found that overexpression of the *MDM2* gene was frequent in primary glioblastomas (52%) but rare in secondary glioblastomas (11%), suggesting that *MDM2* overexpression with or without gene amplification constitutes a molecular mechanism of escape from *p53*-regulated growth control, operative in the evolution of primary glioblastomas that typically lack *p53* mutations [17]. In addition, we found that *p16* deletions are common in primary glioblastomas [19], whereas the *DCC* (deleted in colorectal cancer) gene expression is more frequent in secondary glioblastomas (Figure 19) [363].

The giant cell glioblastoma, a rare glioblastoma variant, is characterized by a predominance of bizarre, monstrous multinucleated giant cells. We have shown that, like the primary glioblastoma, it rapidly develops *de novo* but manifests in younger patients (including children) but has genetic alterations typical of secondary glioblastomas, i.e. frequent *p53* mutations and a lack of *EGFR* overexpression (Figure 19) [343].

3.5.4
Genetic alterations in paediatric glioblastomas

O. Tachibana, H. Ohgaki and P. Kleihues; in collaboration with U. Sure, M.E. Hegi and Y. Yonekawa, Zürich, Switzerland

Glioblastoma is a rare neoplasm in children and is often located infratentorially, particularly in the brainstem. We investigated 20 paediatric glioblastomas for mutational inactivation of the *p53* gene, loss of p16 protein expression and overexpression of the *EGFR* gene. *p53* mutations were found in 5 of 20 (25%) glioblastomas, 4 of which occurred in primary glioblastomas in patients with a clinical history of less than four months and neither clinical nor histological evidence of a less malignant precursor lesion. Loss of p16 expression was seen in 11/18 (61%) glioblastomas. Overex-

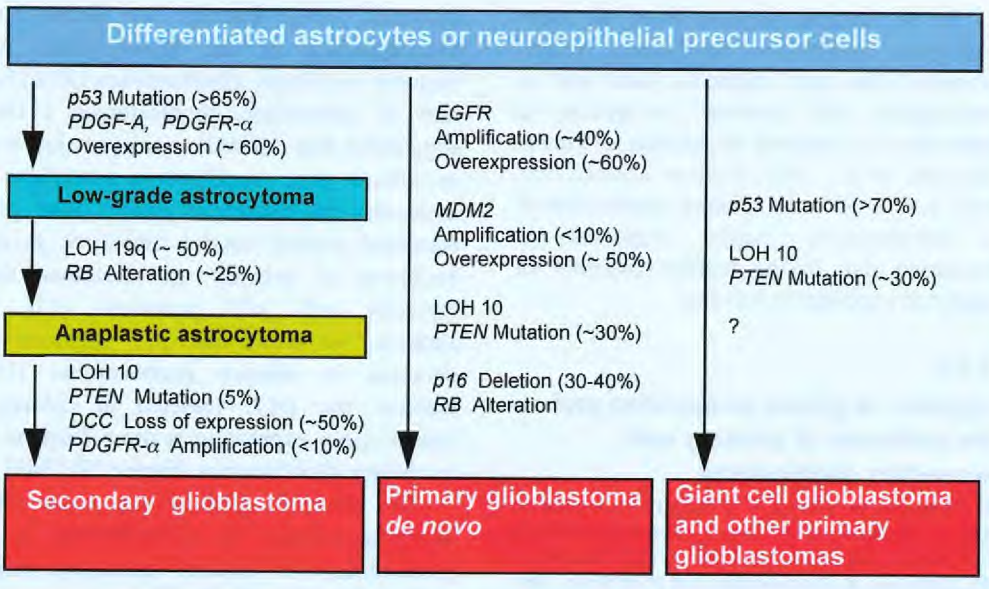

Figure 19. Genetic pathways operative in the evolution of primary (de novo) and secondary glioblastomas

pression of the *EGFR* gene was rare (2/19, 11%). Of four secondary glioblastomas that progressed from histologically diagnosed lower-grade tumours, one contained a *p53* mutation. These results are at variance with studies in adult patients, in whom primary and secondary glioblastomas are characterized by *EGFR* overexpression and *p53* mutations, respectively, suggesting that the development of paediatric glioblastomas follows different genetic pathways [449].

3.5.5
Incidence and timing of *p53* mutations during astrocytoma progression

K. Watanabe, K. Sato, W. Biernat, O. Tachibana, P. Kleihues and H. Ohgaki; in collaboration with M. Nagai, Mibu, Japan; and N. Ogata, K. von Ammon and Y. Yonekawa, Zürich, Switzerland

Mutations of the *p53* tumour-suppressor gene are a genetic hallmark of human astrocytic neoplasms, but their predictive role in glioma progression remains poorly understood. We analysed 144 biopsies from 67 patients with recurrent astrocytoma by single-strand conformational polymorphism (SSCP) and direct DNA sequencing. We found that 46 out of 67 patients (69%) had a *p53* mutation in at least one biopsy. In 41 of these (89%), the mutation was already present in the first biopsy, indicating that *p53* mutations are early events in the evolution of diffuse astrocytomas. Of 28 low-grade astrocytomas with a *p53* mutation, 7 (25%) showed loss of the normal allele in the first biopsy. The allele status remained the same in 95% of cases, irrespective of whether the recurrent lesion had the same or a higher grade of malignancy. Progression of low-grade astrocytomas to anaplastic astrocytoma or glioblastoma occurred at similar frequencies in lesions with (79%) or without (63%) *p53* mutations (p=0.32), indicating that this genetic alteration is associated with tumour recurrence but not predictive of progression to a more malignant phenotype. However, the time interval to progression was shorter in patients with low-grade astro-

cytomas carrying a *p53* mutation (p=0.055) [489].

Although *p53* mutations appear to be present from an early stage of astrocytoma progression, there is a clear trend of significant increases in the fraction of p53-positive cases, i.e. biopsies containing p53-immunoreactive cells, and in the p53 labelling index during progression [488, 489].

3.5.6
Role of gemistocytes in astrocytoma progression

K. Watanabe, O. Tachibana, P. Kleihues and H. Ohgaki; in collaboration with Y. Yonekawa, Zürich, Switzerland

The presence of gemistocytes in low-grade astrocytomas is considered a sign of poor prognosis, since the majority of gemistocytic astrocytomas rapidly progress to anaplastic astrocytoma or glioblastoma. We have shown that the time interval to progression was significantly shorter in patients with a low-grade astrocytoma containing more than 5% gemistocytes (35 months) than in patients with lesions containing less than 5% gemistocytes (64 months). All of the 11 astrocytomas with >5% gemistocytes contained a *p53* mutation, whilst the incidence of *p53* mutations in astrocytomas with <5% gemistocytes was 61% (p=0.017). Our data show that low-grade astrocytomas with a significant fraction of gemistocytes progress more rapidly and typically carry a *p53* mutation. However, the vast majority of gemistocytes are in a G_0 phase of the cell cycle, suggestive of terminal differentiation. Their accumulation within astrocytomas may be due to *bcl*-2-mediated escape from apoptosis [491].

3.5.7
Apoptosis and necrosis in glioblastomas

Y. Tohma, C. Gratas, O. Tachibana, P. Kleihues and H. Ohgaki; in collaboration with J. Lampe and M. Klein, Zürich, Switzerland; and E.G. Van Meir, Lausanne, Switzerland

Fas/APO-1 (CD95)-mediated apoptosis is one of the major mechanisms of programmed cell death. Immunoreactivity to Fas protein was detected in one out of 9 (11%) low-grade astrocytomas (WHO Grade II), 2 of 11 (18%) anaplastic astrocytomas (WHO Grade III) and in 13 of 15 (87%) glioblastomas (WHO Grade IV). In glioblastomas, Fas expression was observed almost exclusively in glioma cells surrounding foci of necrosis, a histological hallmark of glioblastomas [452].

Although primary and secondary glioblastomas have been considered histologically indistinguishable, we found that the pattern and pathogenesis of necrosis are different, large areas of ischaemic necrosis surrounded by Fas-expressing tumour cells being a hallmark of primary glioblastomas.

We also assessed the expression of Fas ligand (FasL) in 10 glioblastoma cell lines and in 14 astrocytic brain tumours. Reverse transcriptase (RT)-PCR revealed that all 10 glioblastoma cell lines and 14 primary astrocytic brain tumours (3 low-grade astrocytomas and 11 glioblastomas) expressed FasL. FasL was seen by immunohistochemistry to be predominantly expressed on the plasma membrane of glioma cells. These results suggest that FasL expression is common in human astrocytic brain tumours and may cause apoptosis of glioma cells if Fas expression is induced [130].

3.5.8
Cell cycle-related genes involved in the development of non-astrocytic human brain tumours

K. Sato, P. Kleihues and H. Ohgaki; in collaboration with B. Schäuble, Zürich, Switzerland

We analysed the *p15*, *p16*, *CDK4* and *cyclin D1* genes in 69 non-astrocytic human brain tumours, including 17 oligodendrogliomas, 16 medulloblastomas/primitive

neuroectodermal tumours, 14 ependymomas and 22 meningiomas. Southern blot analysis of DNA from frozen samples showed no homozygous deletions in *p15* or *p16* genes in any of these tumours. No mobility shift was found by PCR-SSCP analysis in exons 1 and 2 of the *p15* gene or in exons 1 and 2 of the *p16* gene, except for one oligodendroglioma. Sequencing of DNA from this tumour showed a G→A transition at nucleotide 436 (codon 140) in exon 2 of the *p16* gene, which is a common polymorphism. Southern blot analyses revealed no amplification of the *CDK4* and *cyclin D1* genes in any of the neoplasms analysed. In contrast to astrocytic brain tumours, which show frequent loss of the *p16* gene and amplification of the *CDK4* gene, alteration of these genes appears to be rare in non-astrocytic human tumours [419].

3.5.9

Reduced expression of connexin 43 in meningiomas

K. Sato, C. Gratas, W. Biernat, H. Yamasaki, P. Kleihues and H. Ohgaki; in collaboration with J. Lampe, Zürich, Switzerland

We assessed mutations and expression of the connexin 43 (Cx43) gene in 49 intracranial meningiomas. SSCP analyses followed by direct DNA sequencing showed a GCG→GTG (Ala→Val) transition mutation in codon 253 of the cytoplasmic carboxyl terminal of the Cx43 gene in 1 of 31 (3%) benign meningiomas and 1 of 14 (7%) anaplastic meningiomas. The same base change was present in normal tissue from these patients and also in 4 of 80 (5%) DNA samples extracted from lymphocytes of healthy Europeans, suggesting that this constitutes a newly identified Cx43 polymorphism. Western blot analyses showed expression of phosphorylated P_1 (45 kD) and P_2 (47 kD) Cx43 as well as the unphosphorylated form (42 kD) in 11 of 14 (79%) benign meningiomas. In contrast, the P_2 form was not detectable in the majority (7 of 9; 78%) of atypical and anaplastic meningiomas. Since the presence of the P_2 form is often associated with optimal function of Cx43, these results suggest that loss or impairment of gap junctional cell–cell communication may be associated with more rapid growth of meningiomas and a less favourable prognosis [418].

3.6 Cancer of the urinary tract

Tobacco smoking and diet are the major known risk factors for cancers of urinary tract, which comprise mainly neoplasms of the kidney and the bladder. The studies in progress at IARC on these cancers address two broad questions: the etiological role and the mechanism of less investigated risk factors that are of particular importance in non-Western countries, such as *Schistosoma* infection in bladder cancer and ochratoxin A in kidney cancer, and the modification of risk due to polymorphism of metabolic enzymes.

3.6.1

Case–control study of bladder cancer in Egypt

P. Boffetta; in collaboration with R. Bedwani and E. Rangatanam, Alexandria, Egypt; and C. La Vecchia, Milan, Italy

Bladder cancer incidence is very high in Egypt, and infection with *Schistosoma haematobium* has been suggested to be a major cause, but the role of other risk factors, such as tobacco smoke, diet and industrial exposures, has not been adequately investigated. A hospital-based case–control

study was conducted in Alexandria between 1994 and 1996. The results show that tobacco smoking is the main risk factor in this population, explaining about 75% of bladder cancer among men. The relative risk of schistosome infection was 1.7 (95% CI 1.0–2.9): this factor could explain only 17% of bladder cancer cases [8, 9].

3.6.2
Environmental risk factors and genetic susceptibility to bladder cancer in northern Italy

P. Boffetta and C. Malaveille; in collaboration with S. Porru and F. Donato, Brescia, Italy

A collaborative case–control study of bladder cancer was conducted with the University of Brescia, Italy, which suggested an association with exposures in the metal and the transport industries [356]. Additional analyses confirmed the role of tobacco smoking in bladder cancer etiology and suggested a role of coffee and alcohol drinking [88, 89]. The project is now being extended to investigate the interaction between tobacco smoking, occupational exposures and *N*-acetyltransferase-2 genetic polymorphism. Results are expected in 1998.

3.6.3
Mechanism of action of ochratoxin A

M.Castegnaro; in collaboration with U. Mohr, J. Steinman and T. Tillmann, Hannover, Germany; H. Bartsch, Heidelberg, Germany, and A. Leszkowicz, Toulouse, France

Ochratoxin A (OTA), a nephrotoxic and carcinogenic mycotoxin produced by *Aspergillus* and *Penicillium* species, has been implicated in outbreaks of porcine nephropathy, and is suspected of being the etiological agent of Balkan endemic nephropathy (BEN), a chronic disease affecting populations in Bulgaria, Romania and former Yugoslavia. Patients suffering from BEN, urinary tract tumours or both diseases are reported to more frequently be extensive debrisoquine metabolizers than unaffected individuals. Cytochrome P450 2D6 (CYP2D6), involved in the 4-hydroxylation of debrisoquine, displays genetic polymorphism in man. Earlier studies, using female DA rats phenotyped as poor debrisoquine metabolizers and Lewis female rats phenotyped as extensive metabolizers, have demonstrated a parallelism between debrisoquine and OTA hydroxylation. In a long-term study in DA and Lewis rats of both sexes, OTA induced malignant basophilic cell adenocarcinoma of the kidneys and karyomegalies, male DA being most affected and female DA resistant. Male and female Lewis rats showed intermediate incidence of tumours and karyomegalies. In addition, OTA may contribute to malignant transitional cell carcinoma of the bladder in DA rats. Sodium 2-mercaptoethane sulfonate (MESNA) protected male DA rats and Lewis (both sexes) against karyomegalies, but not against renal tumours. OTA-related DNA adducts in the kidney, as judged by modification level, spot multiplicity and prevalence, paralleled the carcinogenic effect of OTA, being highest in male DA and lowest in female DA rats. The results implicate OTA as a genotoxic carcinogen, and suggest that CYP2D is not involved in the formation of proximate metabolites.

In order to try to elucidate the biotransformation enzymes responsible for the carcinogenicity of OTA, we have determined by western blot analysis the expression of CYP 1A, 2A, 2B, 2C, 2D and 3A in the liver and kidney of these rats, and correlated them with carcinogenicity and DNA adduct formation. The role of glutathione-*S*-transferases was also investigated. The results confirm that CYP 2D is not implicated in the carcinogenic potency of OTA in the rat and show (1) that sex- and strain-dependent CYPs (2C but also 1A1/2and 2A) are implicated in the mechanism of OTA carcinogenicity, (2) the implication of GST in the carcinogenic potency of OTA, and (3) that OTA modifies expression of CYPs.

3.7 *Cancer of the lung*

Lung cancer is the most frequent malignant neoplasm worldwide: tobacco smoking is responsible for most cases, and the control of smoking represents the most important approach to prevent lung cancer (see Section 2.4). Among the important research questions still to be answered are the contributions of other risk factors (occupation, diet, environmental pollution) in both smokers and non-smokers and the role of genetic predisposition: these questions are being addressed in a series of studies conducted in areas of high and low risk for lung cancer.

3.7.1

Case–control study of lung cancer in northern Thailand

D.M. Parkin and P. Pisani; in collaboration with P. Srivatanakul, Bangkok, Thailand; N. Martin, Chiang Mai, Thailand; V. Saensingkaew, Bangkok, Thailand; and T. Bishop, Leeds, UK

This study is investigating the reasons for the relatively high incidence of lung cancer, particularly in women, in northern Thailand. Age-standardized incidence rates in Lampang province are 41.8 per 10 000 in men and 20.1 per 10 000 in women. A case–control study comparing 196 cases of lung cancer with two groups of controls (217 hospital controls and 156 community controls drawn at random from the population of this province) was carried out from 1993 to 1995 and data analysis began in 1996.

Because one hypothesis under investigation is the role of air pollution from numerous coal-fired electricity generating plants, place of residence is an important variable of interest, linked to corresponding environmental measurements of arsenic and cadmium. Other factors investigated include tobacco habits, exposure to domestic smoke, and cooking practices. Blood samples from all subjects have been stored for analysis of heavy metals and of metabolites and adducts of components of tobacco smoke. DNA is being extracted from white blood cells of cases and controls to study metabolic polymorphism at the GSTM1 and CYP1A1 loci.

3.7.2

Lung cancer and exposure to environmental tobacco smoke

P. Boffetta, P. Brennan, S. Lea and G. Ferro; in collaboration with W. Ahrens, Bremen, Germany; E. Benhamou and S. Benhamou, Villejuif, France; S.C. Darby, Oxford, UK; F. Forastiere and C. Fortes, Rome, Italy; C.A. González and A. Agudo, Barcelona, Spain; J. Trédaniel, Paris, France; S.K. Jindal, Chandigarh, India; K. H. Jöckel, Essen, Germany; A. Mendes, Lisbon, Portugal; F. Merletti, Turin, Italy; G. Pershagen and F. Nyberg, Stockholm, Sweden; R. Saracci, Pisa, Italy; L. Simonato, Padua, Italy; H. Wichmann, Munich, Germany; C. Winck, Porto, Portugal; and D. Zaridze, Moscow, Russian Federation

Environmental tobacco smoke (ETS) is a likely cause of lung cancer [27, 37], while evidence of an association with other neoplasms is inconclusive. However, the quantitative aspects of the association between ETS exposure and lung cancer risk are not yet well established, nor is the interaction between exposure to ETS and exposure to other carcinogens.

An IARC-coordinated international collaborative case–control study was aimed at investigating the relationship between exposure to ETS and to other environmental and occupational risk factors and the risk of lung cancer in subjects who have never smoked tobacco. A total of 650 cases and 1542 controls have been enrolled in 12 centres in seven European countries. Information on exposure to occupational carcinogens, urban air pollution, background radiation and dietary habits, as well as lifelong exposure to ETS, has been collected by personal interview of cases and controls. Self-reported (non-)smoking status was

confirmed by interviews of relatives. The relative risk (RR) of lung cancer risk was 1.16 (95% CI 0.93–1.44) for exposure to ETS from the spouse, 1.17 (0.94–1.45) for workplace ETS exposure and 1.14 (0.88–1.47) for combined spousal and workplace exposure. Several quantitative indicators of ETS exposure showed a dose–response relationship with lung cancer risk; RRs were higher for squamous cell carcinoma and small cell carcinoma than for adencarcinoma (Figure 20). There was no association between lung cancer risk and ETS exposure during childhood. Additional analyses are continuing on risk factors other than ETS.

A parallel study was conducted in Chandigarh, India, where ETS exposure comes mainly from bidi smoking. The statistical analysis will be completed in 1998. A further study of non-smoking women in Moscow, Russian Federation, confirmed the results on ETS of the larger international investigation and suggested a role of environmental air pollution independent of the effect of ETS [517]. In a separate exercise, the number of lung cancers occurring in the countries of the European Union that can be attributed to spousal ETS exposure was estimated to be about 800 among women and 300 among men [461].

3.7.3 Combined analysis of case–control studies of lung cancer in western Europe

P. Boffetta, P. Brennan and V. Gaborieau; in collaboration with W. Ahrens and H. Pohlabeln, Bremen, Germany; E. Benhamou and S. Benhamou, Villejuif, France; S.C. Darby, Oxford, UK; F. Forastiere and C. Fortes, Rome, Italy; C.A. González and A. Agudo, Barcelona, Spain; K. H. Jöckel, Essen, Germany; F. Merletti, Turin, Italy; G. Pershagen and F. Nyberg, Stockholm, Sweden; R. Saracci, Pisa, Italy; J. Siemiatycki, Montreal, Canada; L. Simonato, Padua, Italy; and H. Wichmann, Munich, Germany

In parallel to the study on non-smokers described in Section 3.7.2, cases of lung cancer and controls have been enrolled in a series of studies in 10 centres in western Europe, irrespective of their smoking habits. Comparable information on tobacco smoking, exposure to occupational carcinogens and urban air pollution has been collected from about 9000 cases and 10 000 controls. The analysis focuses on detailed aspects of tobacco carcinogenesis that cannot be addressed in smaller studies, such as the effect of very light smoking, long-term quitting and smoking of products other than cigarettes (Figure 21). These analyses will be completed in 1998. In parallel, information on exposure to occupational carcinogens

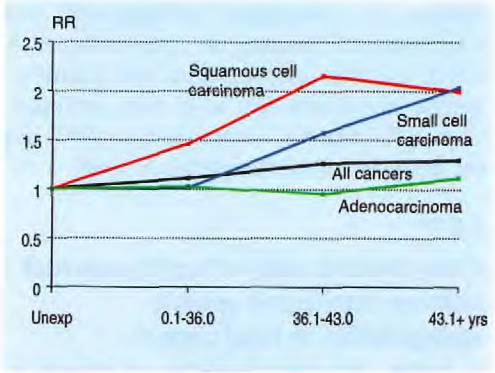

Figure 20. Relative risk of lung cancer by years of exposure to environmental tobacco smoke from spouse or workplace and by histological

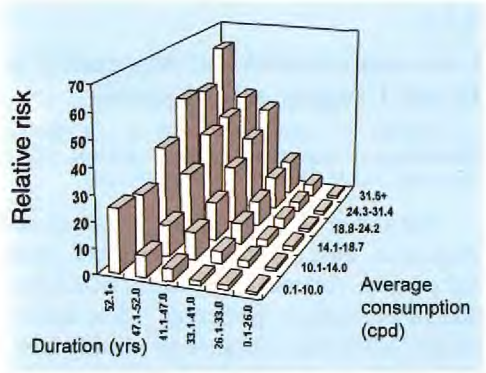

Figure 21. Relative risk of lung cancer by fine categories of cigarette consumption and duration of smoking. Reference category: never smokers.

and urban air pollution will be integrated into the common database.

3.7.4

Multicentric case–control study of lung cancer in central and eastern Europe

P. Brennan and P. Boffetta; in collaboration with E. Fabianova, Banska Bystrica, Slovakia; J. Fevotte, Lyon, France; A. Fletcher, London, UK; D. Mates, Bucharest, Romania; P. Rudnai, Budapest, Hungary; J. Siemiatycki, Montreal, Canada; N. Szeszenia-Dabrowska, Lodz, Poland; D.G. Zaridze, Moscow, Russian Federation; and W. Zatonski, Warsaw, Poland

Countries of central and eastern Europe have the highest incidence and mortality of lung cancer ever recorded. Air pollution is often blamed as the main contributor to this excess, but evidence for its role is limited. A study has been initiated in six areas of Hungary, Poland, Romania, the Russian Federation and Slovakia, to assess the relative contributions of tobacco smoking, occupational exposures and outdoor air pollution in lung carcinogenesis. Enrolment of a total of 3000 cases and a comparable number of controls has started. Special efforts are being made to assess past occupational exposures using detailed employment histories evaluated by panels of local experts. Blood samples will also be collected, to investigate polymorphisms of metabolic enzymes.

3.7.5

Case–control studies of lung cancer in Brazil, Uruguay and Argentina

P. Boffetta; in collaboration with E. de Stefani, Montevideo, Uruguay; E. Matos, Buenos Aires, Argentina; and V. Wunsch, São Paulo, Brazil

The urban areas of Brazil, Uruguay and Argentina have among the highest death rates in the Americas for cancer of all sites and of the lung in particular. Three similar studies have been designed to identify associations between environmental and occupational exposures and risk of lung cancer in São Paulo, Brazil, in Uruguay and in Buenos Aires, Argentina, and to examine the synergistic effect of selected occupational exposures and tobacco smoking. The study in Uruguay confirmed the important role of known carcinogens, such as tobacco smoking and asbestos, and suggested an increased risk among workers of the meat industry and workers exposed to pesticides [86]; it is also addressing the risks for other cancer sites. The study in São Paulo suggested a smaller role than expected for occupational exposures, with increased risks in only a few categories, such as machinery and pottery workers. Data collection for the study in Argentina was completed in 1997 and analysis will be carried out in 1998.

3.7.6

Multicentric case–control study of lung cancer in India

P. Boffetta and R. Sankaranarayanan; in collaboration with M. K. Nair, Trivandrum, India; D.N. Rao, Bombay, India; and V. Shanta, Madras, India

Although the industrial population in India is very large and many hazardous industries are present, virtually no information exists on occupational risk factors for cancer. The presence of a network of well organized cancer registries is a favourable condition for conducting multicentric case–control studies, and therefore such a study has been started in Bombay, Trivandrum and Madras, to investigate occupational and environmental factors for lung cancer. A series of cases of lymphatic and haematopoietic neoplasms has also been included. Data collection was completed in 1997 and the analysis will be completed in 1998.

3.7.7

Case–control study of environmental tobacco smoke and genetic susceptibility to lung cancer

P. Boffetta, M. Lang, N. Malats, M. Friesen, S. Atawodi, S. Lea and J. Hall; in collaboration with W. Ahrens, Bremen, Germany; S. Benhamou, Villejuif, France; I. Brüske-Hohlfeld and H. Wichmann, Munich,

Germany; V. Constantinescu, Bucharest, Romania; F. Forastiere and C. Fortes, Rome, Italy; B. Gabriel, Poznan, Poland; K. Husgafvel-Pursiainen, Helsinki, Finland; A. Menezes, Pelotas, Brazil; F. Merletti, Turin, Italy; G. Pershagen and F. Nyberg, Stockholm, Sweden; L. Simonato, Padua, Italy; and D.G. Zaridze, Moscow, Russian Federation

Among lung cancer cases, non-smokers have been exposed on average to lower levels of carcinogens than smokers; genetic susceptibility may play a greater role in risk of lung cancer in the former group of cases.

In ten centres from Brazil, France, Germany, Italy, Poland, Romania, the Russian Federation and Sweden, blood samples have being collected from about 150 non-smoking lung cancer cases, 150 smoking lung cancer cases and 200 non-smoking control subjects, in order to determine (i) genetic polymorphism of glutathione *S*-transferase M1 and T1, (ii) the levels of the DNA repair enzyme O^6-methylguanine-DNA methyltransferase, (iii) the formation of haemoglobin adducts with 4-hydroxy-1-(3-pyridyl)-1-butanone (a metabolite of tobacco-specific nitrosamines), and (iv) genetic alterations in the *p53* gene and K-*ras* mutations in lung neoplastic tissue of cases. Cases and controls have been interviewed about their smoking habits and exposure to environmental tobacco smoke. Enrolment of patients and laboratory analyses have been completed and statistical analysis will take place in 1998.

3.8 Head and neck cancer

Cancers of the head and neck comprise an important group of neoplasms that are showing increasing incidence in many parts of the world. Although alcohol drinking and tobacco smoking are established causes of these cancers, infection with the human papillomavirus may represent an additional important risk factor, as do some occupational exposures. In addition, patients with head and neck cancer are at increased risk of developing a second tobacco-related neoplasm, making them an important population in which to explore genetic susceptibility.

3.8.1 Multicentric case–control study of laryngeal cancer in Brazil, Argentina and Uruguay

P. Boffetta, P. Brennan and R. Herrero; in collaboration with E. de Stefani, Montevideo, Uruguay; M. Kogevinas, Barcelona, Spain; S. Koifman, Rio de Janeiro, Brazil; E. Matos, Buenos Aires, Argentina; A. Menezes, Pelotas, Brazil; J. Siemiatycki, Montreal, Canada; and V. Wunsch, São Paulo, Brazil

Argentina, Uruguay and southern Brazil have high incidence rates of laryngeal cancer, that do not seem to be explained only by exposure to known carcinogens such as tobacco smoking and alcohol drinking. Following a series of studies of lung cancer (see Section 3.7.6), a multicentric study of laryngeal cancer has been initiated in three areas of Brazil (Rio de Janeiro, São Paulo and Pelotas and Porto Alegre), in Buenos Aires and in Montevideo. The study aims to identify occupational risk factors of this disease; additional aims are the assessment of the role of HPV infection, quantification of the contribution of tobacco smoking and alcohol drinking, and clarification of the role of other possible lifestyle risk factors, such as diet and mate drinking. Collection of interview data and biological samples started in 1997 and will be completed in 1999. In some of the centres, the study is being conducted in parallel with an investigation of the role of human papillomavirus infection in oral cancer (see Section 3.8.4).

3.8.2 Combined analysis of case–control studies of sinonasal cancer

P. Boffetta, E. Merler and D. Colin; in collaboration with R.B. Hayes, and L.A. Brinton, Bethesda, MD,

USA, U. Bolm-Audorf, Wiesbaden, Germany; P. Comba, Rome, Italy; P. Demers, Vancouver, Canada; L. Hardell, Örebro, Sweden; M. Kogevinas, Barcelona, Spain; A. Leclerc and D. Luce, Paris, France; C. Magnani, Turin, Italy; S. Preston-Martin, Los Angeles, CA, USA; S. Rodella, Verona, Italy; T.L. Vaughan, Seattle, WA, USA; and W. Zheng, Minneapolis, MN, USA

As part of the project on cancer risk among workers in the wood and leather industries (Section 2.2.5), a combined analysis of 12 case–control studies of sinonasal cancer led to the report of results according to wood dust exposure (Demers *et al.*, 1995, *Am. J. Ind. Med.*, 28, 151–166). An analysis by occupational title has shown an increased risk among workers of the food industry and among transport workers [221]. Additional analyses are being conducted according to exposure to formaldehyde and leather dust.

3.8.3

Survival and occurrence of second primaries among laryngeal and hypopharyngeal cancer patients

P. Boffetta, J. Estève and A. Tuyns; in collaboration with C. Bouchardy and L. Raymond, Geneva, Switzerland; P. Crosignani and F. Berrino, Milan, Italy; and F. Merletti and B. Terracini, Turin, Italy

During the 1980s, IARC conducted a multicentric case–control study of cancer of the larynx and the hypopharynx in relation to tobacco smoking, alcohol drinking, occupational exposures and diet. The study included over 1100 cases and 3000 controls from areas of Italy, Spain, Switzerland and France covered by cancer registration. The series of cases is now being investigated with respect to the association between risk factors and survival and occurrence of second primary tumours. Analysis of survival of cases from Varese, Italy, suggested a protective role in survival of dietary factors that were also associated with reduced risk of laryngeal cancer, such as high intake of citrus fruits and vegetables (Crosignani *et al.*, 1996, *Int. J. Cancer*, 65, 308–313), but this finding was not replicated in a parallel analysis of cases from Turin, Italy [33].

The occurrence of second primaries in the series of cases is being investigated and will be analysed with respect to exposure to risk factors. In parallel, occurrence of cancer will be studied in the series of population controls. The project is expected to be completed in 1998.

3.8.4

Molecular epidemiology of cancer of the oral cavity and oropharynx

R. Herrero, N. Muñoz, P. Hainaut, R. Sankaranaraynan, P. Boffetta, A. Arslan and D. Magnin; in collaboration with P. Balaram, Trivandrum, India; F. Barbone, Udine, Italy; X. Castellsagué, Barcelona, Spain; A. Daudt, Porto Alegre, Brazil; E. de Stefani, Montevideo, Uruguay; L. Fernandez, Havana, Cuba; S. Franceschi, Aviano, Italy; E.L. Franco, Montreal, Canada; A.M. Idris, Khartoum, Sudan; F. Kee, Belfast, UK; S. Koifman, Rio de Janeiro, Brazil; G. Launoy, Caen, France; C. La Vecchia, Milan, Italy; F. Levi, Lausanne, Switzerland; J. Lissowska, Warsaw, Poland; C. Martinez, Granada, Spain, E. Matos, Buenos Aires, Argentina; U. Nair, Heidelberg, Germany; A. Nieto, Seville, Spain; B. Rose, Sydney, Australia; T. Rajkumar, Madras, India; H. Sridhar, Bangalore, India; and J.M.M. Walboomers, Amsterdam, The Netherlands

Although smoking, tobacco chewing and alcohol drinking are clearly established as the main risk factors for cancer of the oral cavity and oropharynx, only a small proportion of smokers and drinkers develop significant disease, suggesting the presence of genetic or environmental co-factors.

The strong association of human papillomavirus (HPV) with cervical cancer and other anogenital malignancies suggests that some HPV types might also be involved in the etiology of other epithelial tumours. In several case series, the average prevalence of HPV in cancers of the oral cavity (measured by PCR-based assays) was 44% [108]. In addition, some investigators have noted integration of the viral genome in the tumour cells. On the other hand, several enzyme systems have been identified that are involved in the metabolism of carcinogens,

Figure 22. Collaborating centres in multi-centre case–control study of cancer of the oral cavity and oropharynx

and genetic polymorphisms of these enzyme systems could be potential markers of susceptibility. The prevalence and type of p53 mutations in different tumours have been correlated with exposure to specific risk factors and their analysis in oral cancers can provide valuable etiological clues. We are conducting a multi-centre case–control study in Australia, Brazil, Canada, Cuba, India, Italy, Poland, Spain, Sudan, Switzerland and United Kingdom (Northern Ireland) to determine the role of HPV in the etiology of these cancers. Table 7 shows the numbers of cases and controls enrolled to date in the study. It is planned to include additional centres in Argentina, Brazil, France and Uruguay.

Table 7. Current status of recruitment of subjects for multi-centre case–control study of cancer of the oral cavity and oropharynx

Status	Centre	Cases enrolled	Controls
Completed	Madras	200	200
In progress	Trivandrum	110	92
	Bangalore	190	190
	Cuba	85	66
	Aviano	29	29
	Udine	18	21
	Barcelona	76	53
	Granada	31	28
	Seville	30	17
	Northern Ireland	38	16
	Poland	13	13
	Sudan	47	10
	Montreal	6	0
Total		873	735

Incident cases are enrolled before treatment and hospital controls selected according to specific criteria. All participants are interviewed on socio-demographic, medical, reproductive and sexual history, smoking, chewing and alcohol drinking habits and family history of cancer. Exfoliated cells from the oral cavity are collected for detection of different types of HPV with PCR techniques. In addition, blood specimens are collected and buffy coats prepared for DNA extraction for determination of

genetic polymorphisms of carcinogen-metabolizing cytochromes P450 and glutathione *S*-transferases. Frozen biopsies from cases are being stored for study of further details of HPV infection as well as determination of p53 mutations and local expression of carcinogen-metabolizing enzymes.

3.9 Skin cancer

Skin cancer incidence is the highest among all cancers and solar radiation, especially ultraviolet radiation, is considered to be the major risk factor for both melanocytic and non-melanocytic cancers. The descriptive epidemiology (3.9.1), molecular epidemiology (3.9.2) and molecular mechanisms (3.9.3) of skin cancers are studied at IARC.

3.9.1 Case–control study on plantar melanoma in Paraguay

D.M. Parkin and E. Kramárová; in collaboration with M. Khlat, Paris, France; and P. Rolón, Asuncion, Paraguay

Most malignant melanomas observed in the population of Paraguay occur on the plantar surface of the foot. The cases come predominantly from rural areas, where walking barefoot during long periods of life is common. Several risk factors, notably trauma and pigmented marks on the feet, have been suspected as possible causes of plantar melanoma, which is also the most frequent type of melanoma in populations of African origin. A case–control study was established to identify possible risk factors in Paraguay, and 60 newly diagnosed cases and 256 controls were recruited during 1988–93. The specific exposures of interest were wearing of shoes in different settings and life-periods, a history of trauma to the feet, colour of the skin, eye and hair, and type and number of pigmentation marks on the feet and legs.

Few factors were significantly associated with the occurrence of plantar melanoma [373]. Adjusted for confounders, the strongest associations were with the occurrence of injuries to the feet (OR = 41, 95% CI 15–113) and occurrence of naevi on the sole (OR = 5.9, 95% CI 2.5–14.3). Outdoor occupation increased the risk about two-fold (OR = 2.3, 95% CI 1.1–4.8), although this factor did not contribute significantly to the fit of a multiple logistic regression model to the data, in the presence of the first two. The patterns of barefoot walking throughout life were examined in detail, but no association was found (OR = 1.7, 95% CI 0.6–5.3) compared to those wearing shoes).

3.9.2 Early detection of ultraviolet-specific *p53* gene mutations in normal human skin

A. Ouhtit, H. Nakazawa, N. Martel and H. Yamasaki; in collaboration with M. Ueda and M. Ichihashi, Kobe, Japan; A. Sarasin, Villejuif, France; B.K. Armstrong and A. Kricker, Kings Cross, NSW, Australia and D.R. English, Perth, Australia

Ultraviolet (UV) radiation is the major etiological factor in human skin carcinogenesis. The tumour-suppressor *p53* gene is considered to be one of its target genes for non-melanocytic skin cancer and is mutated at a high prevalence, in both basal cell carcinoma (BCC) and squamous cell carcinoma. We have previously developed sensitive methods to detect and quantify UV-specific (CC to TT) mutations at codons 247–248 of the *p53* gene in normal skin, that detect this mutation at frequencies as low as 10^{-6}. This allows detection of the mutation in normal skin from sun-exposed sites of volunteers. We have applied this method in two case–control studies of non-melanocytic skin cancers.

Among a small number of samples from Japan, this mutation was more frequent in skin from chronically sun-exposed body sites than in skin from non-exposed sites. In samples from exposed sites, the mutation frequency was higher for older subjects, suggesting that *p53* gene mutations accumulate at exposed sites. The prevalence of the mutations in normal skin was higher among subjects who had (pre-)cancerous lesions (Figure 23) [324].

In order to examine further whether the UV-specific p53 mutation frequency in normal skin is associated with the risk of BCC and with sun exposure, we conducted a case–control study using biopsies from normal skin of Australian subjects [323]. Subjects with evidence of p53 mutation were at increased risk of BCC (OR = 3.1, 95% CI 1.3–7.1, likelihood ratio test p = 0.007); cases tended to have more p53 mutations than controls (Wilcoxon's rank sum test, p = 0.01). Furthermore, the odds of BC C increased monotonically with increasing frequency of p53 mutation. Age was positively associated with p53 mutation, and mutations were more common in males than females (OR = 1.7, 95% CI 0.78–3.9). Neither total lifetime sun exposure nor total exposure to the anatomic site of biopsy was related to p53 mutation, and mutations were more common on occasionally-exposed parts of the body than on usually-exposed parts. Only weak and inconsistent associations were seen with indicators of sun damage to the skin (solar elastosis, solar keratoses and telangiectasia). However, there was some evidence that subjects whose sun exposure all occurred on non-working days had increased odds of mutation (OR = 2.3, 95% CI 0.80–7.1; p trend = 0.16). Subjects with the lightest skin colour on an unexposed part of the body were most likely to have mutations (OR = 2.6, 95% CI 0.80–8.5, p trend = 0.06). These results suggest that CC to TT p53 mutations at codons 247/248 in normal skin can be used to predict risk of BCC, but are not an accurate measure of total UV exposure. A tandem mutation which does not provide mutant cells with a growth advantage (i.e., a silent mutation) might be a better measure of UV exposure and this possibility is now being explored [323].

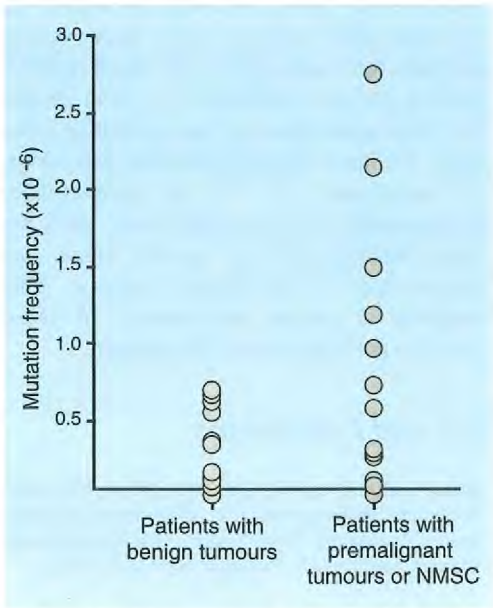

Figure 23. Measurement of the CC → TT mutation at codons 247/248 of the p53 gene in normal skin samples from Japanese patients; relationship to the type of lesions of subjects

3.9.3
Regulation of telomerase and other critical genes during skin carcinogenesis

H. Nakazawa, M. Kallassy, J. Lübbe and N. Martel; in collaboration with R. Toftgård, Huddinge, Sweden; and M. Ueda, Kobe, Japan

We have found telomerase activity not only in malignant tumours (91%) but also in most benign (60%) and premalignant (89%) skin tumours [465]. This suggests the involvement of telomerase activation in a crucial biological step of human skin carcinogenesis. We examined telomerase activity in normal skin samples adjacent to benign, premalignant and malignant skin

lesions and in samples unassociated with lesions. Data for chronically sun-exposed body sites were compared with those for covered sites. Among normal skin samples, 39% (26 of 67) had telomerase activity, and this activity was unrelated to neighbouring lesions but strongly associated with the level of sun-exposure. Among normal skin samples from chronically sun-exposed sites, 21 of 39 (54%) were telomerase-positive, compared with only 3 of 26 (12%) samples from covered sites. In the normal skin samples, only 43% (7 of 16) of telomerase-positive samples at sun-exposed sites contained the UV-specific CC to TT mutation at codons 247/248 of the *p53* gene, while all seven of the samples with the UV-specific *p53* mutation showed telomerase activity ($p = 0.019$). These data suggest that telomerase activation is involved in an early stage of human skin carcinogenesis, possibly preceding the acquisition of UV-associated *p53* mutations. Telomerase activity was also found in plucked hair follicles and enzymatically separated epidermis, which may be associated with the presence of stem cells in the skin.

As most non-melanocytic human skin cancers have *p53* mutation(s), it remains unclear whether the aberrant growth of these cancers is simply a result of the loss of a *p53*-downstream mediator, the universal cyclin-dependent kinase inhibitor $p21^{WAF1}$. To investigate the role of $p21^{WAF1}$ in human skin carcinogenesis, we studied its regulation in normal and *p53*-mutated immortalized human keratinocytes [179]. No $p21^{WAF1}$ expression was detected in human immortalized keratinocytes (HaCaT) or in two *ras*-transformed variants which have two p53 mutations. Retrovirus-mediated expression of $p21^{WAF1}$ stopped the growth of all these cell types, but expression of wild-type p53 did not affect cell growth. $p21^{WAF1}$ also downregulated expression of mRNA of human telomerase RNA component in HaCaT cells. This novel function of $p21^{WAF1}$ partly explains the suppression of telomerase activity by $p21^{WAF1}$ expression in HaCaT cells. Taken together, these results are consistent with the idea that $p21^{WAF1}$ inhibits the growth of non-melanocytic skin cancers, even those with alterations in p53, $p21^{ras}$ and/or pRB (retinoblastoma protein) and telomerase activity.

It has been postulated that a tumour-suppressor gene and gatekeeper gene, *ptch* (patched), acts in the genesis of human BCC. However, we have found that not only *ptch* but also a downstream gene of *ptch*, smoothened (*smoh*), is overexpressed in all of nine BCC tested. *ptch* may instead activate the transcription of *smoh* mRNA, leading to overexpression of *smoh* protein and thus stimulation of the signalling pathway. We have demonstrated that expression of exogenous $p21^{WAF1}$ in immortalized keratinocytes downregulates both *ptch* and *smoh* accompanied by growth arrest and suppression of telomerase activity. This suggests a critical involvement of these genes in the regulation of telomerase.

3.10 Soft-tissue tumours and lymphomas

3.10.1 Case–control study of soft-tissue sarcoma and non-Hodgkin lymphoma in relation to exposure to herbicides in Viet Nam

D.M. Parkin; in collaboration with Nguyen Chan Hung and Cung Thuyet Anh, Ho Chi Minh City, Viet Nam; Hoang Dinh Cau and Vu Ngoc Phan, Hanoi, Viet Nam; S. Cordier, Villejuif, France; M. Kogevinas, Barcelona, Spain; M. Raphaël, Paris, France; J.M. Rivera-Pomar, Vizcaya, Spain; and S. Stellman, New York, USA

During the second Indochina war, large quantities of herbicides contaminated with dioxins were sprayed onto the territory of what was, at the time, South Viet Nam, in

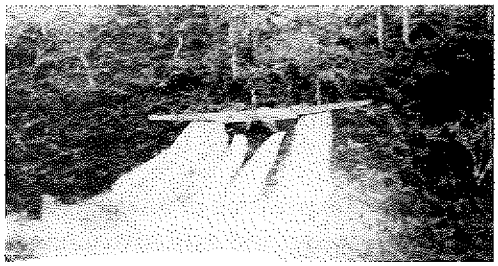

Figure 24. Herbicide spraying of forest in Viet Nam during the second Indochina war

order to defoliate the forests and to destroy crops. Most of this spraying took place in 1965–71, but because of the relatively long biological half-life of dioxins, human exposure will have been more prolonged. The objective of the study is to investigate whether any excess risk for two cancers —soft-tissue sarcoma and non-Hodgkin lymphoma—exists. The target is to interview 150 cases of each disease and two hospital controls per case, and samples of blood and adipose tissue are being stored. Estimation of exposures is initially based on detailed residential history in relation to the known location, type and quantity of herbicide sprayed by US forces. Direct measurement of dioxins in body tissues is expensive, but adipose tissue from each subject is available, should this become feasible. The study began in mid-1993, with support from the French Ministry of the Environment and the Ligue Contre le Cancer of France, and by May 1997 some 700 subjects had been enrolled. Recruitment in scheduled to be completed in 1998, when analysis of the full results will begin. Preliminary analysis suggests that exposure, as reflected by residential history, is not a powerful determinant of risk.

3.11 Gall bladder cancer

3.11.1 Study of gall bladder cancer in northern India

R. Sankaranarayanan and D.M. Parkin; in collaboration with V.K. Shukla and M. Pandey, Varanasi, India

A high incidence of gall bladder cancer is observed in females in northern India. A case–control study has been initiated in Varanasi, India, to test the hypothesis that increased lipid peroxidation of dietary fatty acids by the hepatocyte cytochrome system results in increased excretion of peroxide products such as 4-hydroxynonenal, which have genotoxic and neoplastic potential; the prolonged retention of these secondary bile acids in a non-functioning gall bladder may induce carcinogenesis. Tissue, blood and bile samples have been collected from 87 patients with cholelithiasis and 38 patients with cancer of the gall bladder, but collecting bile from apparently healthy subjects has proved difficult.

PART 4. MECHANISMS OF CARCINOGENESIS

4.1 DNA damage, cell cycle control and carcinogenesis

Mammalian cells respond to DNA damage with a transient inhibition of DNA synthesis, induction of expression of several genes and a delay in cell cycle progression. At least two stages of the cell cycle can be modulated in response to DNA damage, namely the G1/S and G2/M transitions. Such delays could be considered as a surveillance mechanism allowing time for detection and repair of DNA damage. The *p53* gene product has been linked to activation of the G1/S inducible checkpoint in response to DNA damage. The level of the wild-type protein is greatly increased in response to various forms of DNA damage and acts as a transcriptional activator of many genes that directly control cell cycle progression. This response is compromised in cells lacking functional p53 protein and cells in which the damage-recognition factors are absent. The objectives of the studies presented here are two-fold: (1) to assess the role in cancer induction and development of the repair of some forms of DNA damage induced by alkylating agents and reactive oxygen species and (2) to investigate the role of various gene products in signal-transduction pathways resulting in cell-cycle arrest, with particular emphasis on those involved in the detection of DNA damage produced by ionizing radiation. Cell lines established from patients with the rare autosomal cancer-prone diseases ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS), which both show considerable radiation sensitivity and abnormal cellular responses to DNA damage, are being used as model systems and the potential contribution of the *AT* and *NBS* gene products to other forms of cancer in which radiation sensitivity is observed is being assessed.

4.1.1

Control of expression of enzymes for DNA alkylation and oxidative damage repair during single and chronic exposures to carcinogens

J. Hall, H. Brésil, P. Pelkonen, G. Rodrigo, P. Boffetta and R. Montesano; in collaboration with F. Bianchini and J. Cadet, Grenoble, France; F. Donato, Brescia, Italy; P. Karran, South Mimms, UK ; L. Simonato, Padua, Italy; and A.A. van Zeeland and L. Mullenders, Leiden, The Netherlands (with support from EU grant number: EV5V-CT94-0401)

The levels of enzymes involved in the repair of DNA alkylation and oxidative damage, together with DNA adduct formation and urinary excretion, are being examined in populations exposed to tobacco smoke. In the samples analysed to date, the O^6-methylguanine-DNA methyltransferase (AGT) activity measured was of a similar order to that previously found in leukocytes, with no apparent difference in activity between smokers and non-smokers, confirming previous results (Hall *et al.*, 1993, *Int. J. Cancer*, **54**, 728–733). In contrast, AGT activity in lymphocytes isolated from 34 Hodgkin's disease patients before treatment was considerably lower (0.0337 ± 0.0270 pmol/mg protein) than that observed in healthy individuals (0.146 ± 0.088 pmol/mg protein). The polymorphism recently described in this gene in a Japanese population (10.7% in the control population studied) does not appear to be present at the same frequency in the European population —no homozygous mutations were detected in 51 samples analysed. The gene for the methylpurine-DNA glycosylase repair enzyme has been cloned by several groups and simultaneous expression of alternatively spliced

transcripts has been reported. In order to investigate whether the expression of these alternative transcripts might account for the bimodal distribution of enzyme activity observed in a population study, reverse transcriptase–PCR techniques have been established to detect the two transcripts. The simultaneous expression of two RNA transcripts has been confirmed, but there is no apparent correlation between their levels and enzyme activity in lymphoblastoid cell lines. Urinary excretion of the oxidized DNA base 5-hydroxymethyluracil has been validated as a potential indicator of oxidative damage in human studies and would appear to be a promising biomarker for the assessment of such DNA damage and its repair [13].

Single and chronic exposures to alkylating agents and ionizing radiation have been shown to cause species- and tissue-specific induction of certain repair enzymes including AGT. It has been found that the induction of AGT in response to ionizing radiation in mice is *p53* gene dose-dependent (Rafferty *et al.*, 1996, *Oncogene*, **12**, 693–697). In order to investigate whether the inducibility of the human AGT is also p53-dependent, changes in AGT mRNA and enzymatic activity have been assessed in human lymphoblastoid cell lines from ataxia telangiectasia patients, which show a suboptimal p53 response after exposure to ionizing radiation, and from normal individuals and in the Raji Burkitt's lymphoma cell line, which has both gene copies of *p53* mutated. No increase in either AGT mRNA or activity was found in any of the cell lines over a 48 hour period after exposure to 5 Gy ionizing radiation, while the expected changes in p53 protein levels were observed. These results suggest that the control of AGT expression shows distinct species differences, so that extrapolation of results obtained from one model system to another must be made with care.

4.1.2
Regulation of the mammalian cellular response to DNA damage

W. Jongmans, M. Vuillaume, H. Brésil and J. Hall

4.1.2.1

Role of DNA-protein kinase and the Nijmegen breakage syndrome gene product in DNA damage recognition

In collaboration with K. Chrzanowska, Warsaw, Poland; S.P. Jackson, Cambridge, UK; W.J. Kleijer, Rotterdam, The Netherlands; Y. Shiloh, Tel Aviv, Israel; D. Smeets, Nijmegen, The Netherlands; and K. Sperling, Berlin, Germany (with support from EU grant CT 94051)

The structural similarities between the catalytic subunit of the DNA-protein kinase (DNA-PK) and the ataxia telangiectasia gene (*ATM*) product and their involvement in the repair and/or recognition of DNA damage caused by ionizing radiation suggest that both enzymes may be involved in signal transduction pathways specific for responses to ionizing radiation. The levels of expression of the subunits of the DNA-PK complex and the overall DNA-PK activity in normal and AT cell lines after treatment with ionizing radiation have been examined. The results were related to the transcriptional induction of the *WAF1/Cip1(p21)* gene (which is transcriptionally regulated by p53) to determine whether DNA-PK, like ATM, is upstream of p53 and whether DNA-PK and ATM can substitute for each other in a p53-dependent signal-transduction pathway that controls cell-cycle progression in response to radiation-induced DNA damage. Normal protein and transcription levels of the ku70 and ku86 DNA-binding components of the DNA-PK protein, as well as DNA-PK activity, were found in six different AT cell lines 1–4 hours after exposure to ionizing radiation, a time when transcriptional induction of WAF1/Cip1(p21) was reduced and delayed. In normal cell

lines *WAF1/Cip1(p21)* was found to be transcriptionally induced by p53 over the same period after exposure to ionizing radiation. These results suggest that although DNA-PK can phosphorylate p53 *in vitro*, it does not appear to play a central role in the activation of p53 as a transcription factor *in vivo*, nor can it substitute for the *ATM* gene product in the cellular response following exposure to ionizing radiation [170].

The functionality of the p53-mediated pathway, activated in response to DNA damage, has also been assessed in primary fibroblast cell cultures and Epstein–Barr virus-transformed lymphoblastoid cell lines derived from Nijmegen breakage syndrome (NBS) patients. This autosomal recessive disease is characterized by microcephaly, growth and mental retardation, chromosomal instability, radiosensitivity and high cancer incidence. Changes in p53 protein levels were significantly reduced and delayed in all the NBS fibroblast cell cultures and lymphoblastoid cell lines examined compared to normal cultures over a 4 h period after irradiation (5 Gy). The transcriptional activation of WAF1/CIP1(p21) mRNA was also lower in the NBS fibroblast cultures after such treatment. In contrast, the increase in p53 protein and WAF1/CIP1(p21) mRNA expression following exposure to the alkylating agent methylmethane sulfonate (100 μg/ml) was similar in both NBS and normal cell cultures. In agreement with a loss of p53 function, NBS cells exposed to ionizing radiation show an abnormal cell cycle arrest at G1/S and a prolonged accumulation of cells in G2 phase. These responses are remarkably similar to those seen in cell lines derived from ataxia telangiectasia (a clinically and genetically distinct disease) and suggest that both gene products are involved in the activation of the p53-mediated damage response following exposure to ionizing radiation [171]

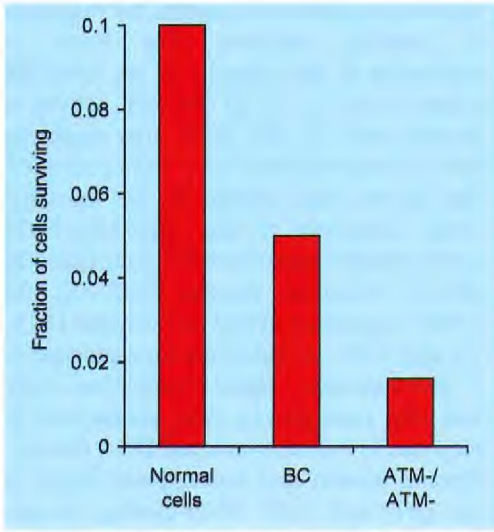

Figure 25. Cellular sensitivity to X-irradiation. Mutation of the ATM gene is associated with increased sensitivity to radiation. Cells mutant in both copies of the gene (ATM–/ATM–) are more readily killed by X-rays than are normal cells. Cell lines from breast cancer patients (BC) have an intermediate sensitivity

4.1.2.2

Role of the ATM gene in breast cancer

In collaboration with J.O. Bay, Clermont Ferrand, France; and A. Brémond, J.P. Gérard and P. Romestaing, Lyon, France (with support from the Ligue nationale contre le cancer and the Association pour la recherche sur le cancer)

Carriers of a homozygote *ATM* mutation have been shown to have extreme radiosensitivity and increased cancer risk. *ATM* heterozygotes, while having none of the neurological symptoms of the disease, do appear to have an increased cancer risk. The *ATM* gene has been implicated as a predisposing gene in breast cancer and it has been suggested that *ATM* heterozygotes may be responsible for up to 5% of all cases. A significant proportion of breast cancer patients show an exaggerated acute or late reaction to radiotherapy. To assess the relevance of this gene to breast cancer in such cases, collaborative studies have been set up to establish lymphoblastoid cell lines from

breast cancer patients showing hypersensitivity to radiotherapy and to examine their cellular response to ionizing radiation in relation to their *ATM* gene status. So far 12 lymphoblastoid cell lines have been established and fully characterized. The adverse skin reaction observed in the breast cancer patients correlates well with the enhanced radiosensitivity in most of the cell lines, which was intermediate between those observed in normal and AT cell lines; only two lines showed *in vitro* radiosensitivity that fell within the range observed in normal cell lines (Figure 25). The mean increase in p53 levels after exposure to ionizing radiation was significantly reduced in the breast cancer lines compared with normal cell lines (3.5 ± 0.5-fold compared with 7.2 ± 1.1-fold four hours after exposure to 5 Gy ionizing radiation), suggesting that there is indeed a defect in the *ATM* signalling pathway. However the induction of *WAF1/Cip1(p21)* mRNA, which is transcriptionally regulated by p53, is of the same order in the breast cancer and normal cell lines. This is in direct contrast with the results obtained with AT cell lines, where the increases in both p53 protein levels and *WAF1/Cip1(p21)* mRNA are reduced following exposure to ionizing radiation. These results suggest that the normal WAF1/Cip1(p21) expression is due to other additional components of the DNA damage response pathways.

4.2 Genetic determinants of specific cancers

The aim of the programme on genetic susceptibility to cancer is to evaluate the role and importance of inherited conditions predisposing to cancer through molecular, familial and population-genetic approaches. Another goal is to establish how molecular genetics can be used to better define the genetic make-up of individuals in epidemiological surveys.

Probably less than 5% of cancers occur in individuals who are strongly predisposed to a particular cancer type. If a genetic marker of risk is identified, these individuals (and their relatives) may benefit from screening and early diagnosis. Molecular investigations may allow the identification of the predisposing genes and elucidation of how they operate. Such information would be of wider importance, since the more common non-familial forms of such a cancer may result from somatic mutation of the same gene.

The approach being used to study inherited predisposition to cancer is mainly through linkage analysis in high-risk families. In linkage analysis, co-segregation of cancer susceptibility is sought with a specific allele of a polymorphic system which has been mapped to a known chromosomal location.

During the last 10 years, IARC has contributed to the identification of the genes predisposing to familial medullary thyroid cancer (in the framework of multiple endocrine neoplasia type 2 (MEN 2)), to neurofibromatosis type 2 and to familial breast cancer. A major effort remains the identification of the X-linked lymphoproliferative syndrome (XLP) gene, now well localized, and the mapping of papillary thyroid carcinoma susceptibility gene(s). Activity in this area has been broadened by the creation of the Unit of Genetic Epidemiology.

4.2.1
X-linked lymphoproliferative syndrome

L. Yin, B.S. Sylla, J. Lamartine, F. Heitzmann, M. Creaven, S. Gaudi, L. Bjørkhaug, M.F. Lavoué, S. Pauly, G. Lenoir and G. Romeo; in collaboration with the International XLP Consortium

X-linked lymphoproliferative disease (XLP) is a rare form of genetic immune

deficiency characterized by a selective susceptibility to Epstein–Barr virus (EBV). Primary EBV infection of affected boys invariably results in severe or fatal infectious mononucleosis, acquired agammaglobulinaemia or B-cell lymphoma. Since XLP patients respond abnormally to EBV infection, the XLP gene appears to play an important role in the control of EBV infection by the immune system. XLP disease is a good model for examining the interaction between an environmental factor (EBV) and a genetic component (XLP gene) in the genesis of malignant lymphoma.

The XLP gene has been mapped to the X chromosome at the Xq25–q26 region. In order to isolate this gene, physical mapping of the region was undertaken. Screening of yeast artificial chromosome (YAC) libraries with probes closely linked to the XLP locus enabled us to estimate the physical distance from some markers in the region. During the last few years, genetic and physical mapping has defined the candidate XLP genomic region to approximately 3–4 Mb in Xq25. More recently, a novel constitutional deletion of approximately 130 kb in an XLP patient was reported ([213]; Lanyi *et al.*, 1997, *Genomics*, **39**, 55–65). A cosmid contig encompassing this deletion was constructed in our laboratory. Sequencing of the whole region was performed and breakpoints of the deletion were established. The analysis of the 197 620 base pairs encompassing the deletion and surrounding its breakpoints revealed a high frequency of repeated sequences, a low G/C content and the absence of CpG islands, indicating that this region is very poor in genes. A total of 52 potential exons made of unique sequences were identified by combination of GRAIL and Gene-Finder programs and by exon trapping. Among these, the four best candidates were screened by the single-strand conformational polymorphism (SSCP) method in 40 patients and studied with reverse transcriptase PCR for expression in various human tissues and cell lines. Although no mutations were detected in any of the 40 patients studied, the experimental evidence collected so far indicates that the region encompassing this deletion is still the most likely location of the XLP gene.

4.2.2

Genetic susceptibility to breast and ovarian cancers

G. Lenoir, O. Serova-Sinilnikova, S. Mazoyer, N. Puget and C. Bonnardel; in collaboration with H. Lynch, Omaha, NE, USA; J. Feunteun, Villejuif, France; S. Narod, Toronto, Canada; and the Breast Cancer Consortium

Following the discovery of the second breast cancer susceptibility gene (*BRCA2*) at the end of 1995, we have tried to estimate the proportion of families in which susceptibility to breast cancer is due to either *BRCA1* or *BRCA2* genes.The approach has been to detect germline deleterious mutations in either of these two very large genes using various molecular strategies. The studies have been performed on the collection of nearly 100 breast cancer families identified through the cancer genetic clinic of Dr H.T. Lynch (Creighton University, Omaha, NE, USA). The analysis of families with associated breast and ovarian cancers has led to the identification of *BRCA1* mutations in 80% of them [422]. A small proportion (around 10%) do carry a *BRCA2* mutation. Some germline *BRCA1* mutations are extremely difficult to detect by classical mutation detection techniques since they correspond to large (one to several kilobase) deletions, some of them probably resulting from alu-mediated recombinations (Figure 26) [358]. An effort is being made to better define the laboratory strategies required to detect this type of germline mutation, that probably corresponds to 5–10% of the deleterious *BRCA1* mutations.

To estimate the proportion of breast cancer families due to *BRCA1* or *BRCA2* mutations, we performed mutation screening

of the entire coding regions of both genes, supplemented with linkage analysis of 31 families, eight containing male breast cancers and 23 site-specific female breast cancer families. A combination of protein truncation test and SSCP or heteroduplex analyses was used for mutation screening complemented, where possible, by analysis of the expression level of *BRCA1* and *BRCA2* alleles. In six of the eight families with male breast cancer, frameshift mutations were detected, two in *BRCA1* and four in *BRCA2*. Although in most families, female site-specific breast cancers were thought to be due to mutations in either *BRCA1* or *BRCA2*, we identified only eight mutations in our series of 23 female breast site-specific cancer families (34%), four in *BRCA1* and four in *BRCA2* [423]. According to the posterior probabilities calculated for mutation-negative families, based on linkage data and mutation screening results, we would expect eight to ten site-specific female breast cancer families of our series to be due to neither *BRCA1* nor *BRCA2*. Thus, our results suggest the existence of at least one more major breast cancer susceptibility gene.

Within the framework of this search for breast cancer gene mutations, a *BRCA2* polymorphism stop codon resulting in loss of the putative granin domain of the protein has been identified [239]. This major gene alteration (removal of the last 93 amino-acids of *BRCA2*) was shown not to modify breast or ovarian cancer risk, suggesting that this region of the protein does not contribute to the putative tumour-suppressor function of *BRCA2*. In assigning risks to carriers, it is clearly essential to be as cautious with truncating mutations as with missense mutations: this ter3326 variant has been reported once as a mutation, which could have serious consequences for the family in which it was detected if used for genetic counselling.

The set of our breast cancer families in which neither *BRCA1* nor *BRCA2* mutations have been so far identified is being used for the mapping of non-*BRCA1*/*BRCA2* breast cancer susceptibility loci (see Section 4.3.5).

4.2.3 Genetic susceptibility to breast and ovarian cancer: clinico-pathological issues

G. Lenoir and O. Serova-Sinilnikova; in collaboration with C. Lerman, Washington, DC, USA; H. Lynch, Omaha, NE, USA; and S. Narod, Toronto, Canada

An evaluation of the outcomes of participation in the *BRCA1* testing programme in the families for which we performed genetic tests [223] has indicated that only a proportion of members of breast/ovarian cancer families are likely to request *BRCA1* testing when available. Rates of testing tend to be higher in persons of a higher socioeconomic status and among those with more relatives affected with breast cancer. For some high-risk individuals who receive test results in a research setting that includes counselling, there may be psychological benefits. More research is needed to assess the generalizability of these results and to evaluate the long-term consequences of *BRCA1* testing.

A study aimed at assessing pathobiological differences between *BRCA1*- and *BRCA2*-related hereditary breast cancers [44, 233] has led to the conclusion that *BRCA1*-related cancers are more frequently aneuploid and have higher tumour cell proliferation rates compared with other hereditary breast cancers. Despite these adverse prognostic features, *BRCA1*-related hereditary breast cancer patients have paradoxically lower recurrence rates than others. The excess of tubular lobular group cancers among 'other' hereditary breast cancer patients may be associated with *BRCA2* linkage [234].

There is no consensus yet on whether or not in-situ carcinoma of the breast is part of the *BRCA1* spectrum. To help address this question, we reviewed the pedigrees of the

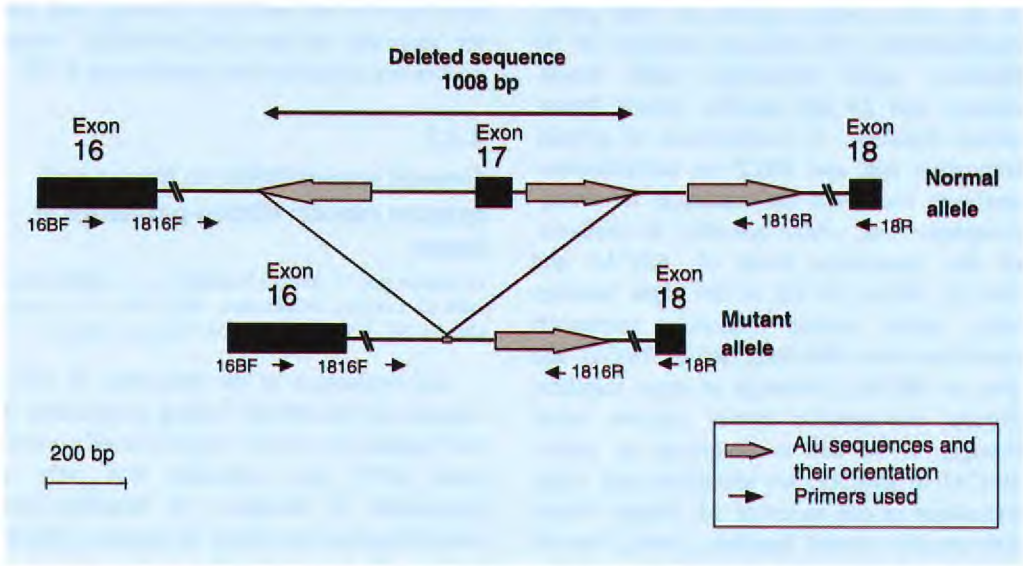

Figure 26. Schema of the normal and mutant alleles of BRCA1, showing the location of the 1008-bp deletion removing exon 17 in one family

Analysis by SSCP of a carrier's cDNA revealed the presence of a transcript, at a reduced level, lacking exon 17. Long-range PCR was used to amplify the BRCA1 gene from exon 16 to exon 18. With the DNA of carriers only, the PCR produced a smaller extra band of equal intensity. The fragment containing the breakpoint of the deletion was cloned and its sequence compared with that of the wild type.

36 families in the Creighton University database for which *BRCA1* mutations have been identified [446]. There were 202 cases of invasive breast cancer, but only four of carcinoma in-situ documented in these families. If in-situ cancer were a characteristic preinvasive lesion in *BRCA1* carriers, we would have expected a greater number, given that most young women in these families undergo regular mammography. Furthermore, genetic testing revealed that only two of the cases of in-situ cancer were in gene carriers, and two were sporadic —this is the expected distribution if the four cases were due to chance. Currently, for the purpose of family assessment, we do not believe that in-situ breast cancer is clinical evidence of the breast–ovarian cancer syndrome, nor do we use this diagnosis to predict the carrier status of individuals within these families.

4.2.4

The international *BRCA1* and *2* gene carrier cohort study

D.E. Goldgar, H. Renard and A. Sasco; in collaboration with the IBCCS Consortium (with support from the European Union DG-V Europe against Cancer programme)

Now that large numbers of mutations in the *BRCA1* and *BRCA2* breast cancer predisposition genes have been identified, there is a need to determine more precisely cancer risks due to mutations in these genes, to examine the role of other known risk factors in modifying these risks, and to gauge the efficacy of various prevention strategies. These questions are best answered by a multi-centric observational prospective study of identified carriers of *BRCA1* and *BRCA2*. The specific goals of the project are to (*a*) develop a computer database/registry of

mutation carriers worldwide; and (*b*) collect clinical and risk factor follow -up data on at least 3000 carriers followed for a median observation period of 7.5 years. Agreements to participate have been obtained from cancer genetics centres in 12 European and North American countries. Following a preliminary organizational meeting held in Lyon in March 1997, we have developed a consensus questionnaire to be used in the study and are setting up the database using the ORACLE relational database system. A second organizational meeting was held in September 1997 in Pisa, Italy. Enrolment of subjects will begin on 1 January 1998 .

4.2.5

Mapping of non-*BRCA1* and *2* breast cancer susceptibility loci

D.E. Goldgar, C. Bonnardel, H. Renard and Y. Shugart; in collaboration with D.F. Easton, Cambridge, UK; and M.R. Stratton, Sutton, UK (with support from the Association for Intern ational Cancer Research)

Although *BRCA1* and *BRCA2* are believed to account for the vast majority of families with high incidence of early onset breast cancer, these genes explain only about half of the excess familial aggregat ion observed for premenopausal breast cancer. Data from the Breast Cancer Linkage Consortium show that these genes account for only about 40% of families with 4 or 5 cases of breast cancer and without any cases of ovarian cancer. The goal of this project is to identify the chromosomal location of one or more additional breast sus ceptibility loci and to estimate the frequ ency and risks due to these genes. Currently 135 DNA samples from 17 breast cancer kindreds are being studied for a set of candidate genes on chromosomes 10 (Cowdens), 8p (reported linkage), and 6q (ESR+linkage). A similar set of samples are being studied by our collaborators in the UK, and the results will be pooled for analysis, giving a combined set with sufficient power to detect a susceptibility locus accounting for at least 50% of the non-*BRCA1/BRCA2* families [423]. The candidate search will be followed by a total genomic screen of approximately 250 highly polymorphic short tandem repeat markers spread throughout the genome at 10 cM intervals. We have analysed the first 80 markers from the genome search with largely negative results, although a few interesting areas have been selected for more detailed analysis. Contacts have been made with other investigators to obtain more family material. A family with six cases of breast cancer under age 60 has been contributed by Dr K. Offit at the M emorial Sloan Kettering Cancer Center, while several DNA samples from smaller families have been contributed by Dr F. Olopade at the University of Chicago . We have also set up a collaboration with Dr E . Ostrander, of the Fred Hutchinson Cancer Center in Seattle, who will contribute six families to be used for following any leads developed from the primary family material.

4.2.6

Mapping of gene(s) affecting papillary thyroid carcinoma susceptibility

F. Canzian, M. Stark, S. Pauly, T. Tocco, R. Corvi, G. Romeo, E. Cardis and H. Yamasaki; in collaboration with M. Schlumberger, Villejuif, France; M. Stratton, Sutton, UK; and the International Consortium for the Genetic Study of PTC

The aim of this project is the identification of gene(s) which influence the chain of events leading to the most common type of thyroid cancer, papillary thyroid carcinoma (PTC). Familial PTC is a clinical entity apparently distinct from sporadic PTC. It is more often multifocal and relapses more frequently than the sporadic form. All reports suggest autosomal dominant inheritance with incomplete penetrance. This phenotype could be explained by the influence of environmental factors (particularly ionizing radiation) and/or polygenic inheritance. A systematic study (Goldgar *et al.*, 1994, *J. Natl Cancer Inst.*, **86**, 1600–

1608) showed that, among 28 cancer types, the familial relative risk (FRR = 8.60) was highest among first-degree relatives of thyroid tumour (mainly PTC) probands.

In order to locate genes of susceptibility to PTC by linkage analysis, an international consortium of clinicians has been established and 103 families with two or more cases have been identified so far, giving a total of 175 patients (to our knowledge, the largest existing collection of samples from PTC families). In some of these families, multinodular goitre is present and segregates together with PTC. A random search for linkage in two such families has led to the identification of a gene (*MNG1*) predisposing to multinodular goitre on chromosome 14q31 [20]. However in 37 of our families with recurrence of PTC only, *MNG1* seems not to be a major gene predisposing to this type of cancer. This conclusion is supported by results obtained with a large French pedigree with recurrence of multinodular goitre and PTC, which does not show any linkage with the 14q31 region (Bonneau *et al.*, personal communication). These results indicate the presence of genetic heterogeneity among families with multinodular goitre and PTC. Finally, in a large Bedouin pedigree from Israel in which PTC and multinodular goitre segregate, two regions of interest have been mapped using the shared DNA segment approach by typing more than 300 microsatellite markers.

Once one or more genes predisposing to PTC are identified, their role in apparently sporadic PTC can be further investigated through association studies in genetically isolated populations (such as the Finnish population, for which samples are already available through a collaboration with the Finnish Cancer Registry) and/or populations exposed to the radioactive fall-out from the Chernobyl accident. About two thirds of the PTC tumours from Chernobyl accident-related patients, as well as lower proportions of sporadic PTC tumours from all over the world, show rearrangement of the *RET* protooncogene leading to activation of its oncogenic capacity. Since the mechanism by which the *RET* pathway becomes activated is still unclear, we are studying the expression of genes involved in intercellular communication which might be regulated by an activated form of *RET*, as already reported for the cytoskeletal protein paxillin in cells transfected with *RET* carrying the M918T mutation [26]. For this purpose, 14 sporadic PTC tumours (two of which showed the PTC1 rearranged form of *RET*) were analysed for expression of connexins 32 and 43, components of intercellular gap junctions. Since a surprisingly high expression of both connexins in the proximity of the cellular membrane was observed in all tumours, an *in vitro* expression system has been set up in order to study the possible correlation of this phenomenon with activation of *RET*.

4.2.7

Genetic and family studies of cancers of the head and neck

D.E. Goldgar; in collaboration with R. Eeles and S. Jefferies, Sutton, UK; and W. Foulkes, Montreal, Canada

The goal of this project is to characterize the familial risks of squamous cell carcinomas of the head and neck (SCCHN) and to identify potential tumour-suppressor loci that may be involved in the development of these tumours. A further aim is to examine the interaction between genetic/familial factors and the known environmental risk factors (tobacco and alcohol consumption) in producing disease. The protocol has been finalized for a case–control study that will focus on cases of multiple primary tumours, one of which is SCCHN and the other is either also SCCHN or another smoking-associated tumour. Controls are (*a*) age-matched cases of single primary SCCHN, and (*b*) age-matched healthy volunteers. Enrolment started in July 1997. All subjects

provide data on personal alcohol and tobacco usage and other relevant demographic and risk factor data, as well as smoking and alcohol data on all first-degree relatives and information on any cancers among their relatives. Data on epidemiological risk factors in families with two or more cases of related cancers will be compared with those for families with no history of cancer in order to assess potential gene–environment interactions. The two tumo urs from the cases of multiple primary cancer and a corresponding sample of lymphocyte DNA will be examined for a series of 100 highly polymorphic microsatellite markers through - out the genome. Over 100 cases of multiple primary tumours have been identified in the databases of three London hospitals; 14 of these patients have already been enrolled into the study. The collaborating groups met in London in July 1997 and in Baltimore in October 1997 to discuss progress.

4.3 Role of oxidative stress in carcinogenesis

The involvement of free radicals (e.g., superoxide, nitric oxide) and other reactive species (hydrogen peroxide, peroxynitrite) in the carcinogenic process is now widely recognized. Reactive oxygen and nitrogen species are produced not only by normal physiological processes, but also in excess amounts during certain pathophysiological conditions such as chronic inflammation. Various cellular components including DNA, proteins and lipids are damaged by these reactive species, resulting in mutations as well as altered functions. Identification and quantification of the products of oxidative modification of cellular components will permit us to define more precisely the role of oxidative stress in carcinogenesis. Understanding the nature of the processes involved and the mechanisms for defence against oxidative damage is a necessary basis for cancer prevention.

4.3.1

Helicobacter pylori infection, oxidative stress and stomach cancer

B. Pignatelli, C. Malaveille, S. Calmels, J. Estève, M. Laval, N. Lyandrat, H. Ohshima; in collaboration with B. Bancel, L.-M. Patricot, R. Lambert, B. Moulinier, Lyon, France; and P. Correa, New Orleans, USA

Chronic inflammation induced by *Helicobacter pylori* infection has been associated with an increased risk of stomach cancer. Excessive formation of reactive oxygen and nitrogen species leading to tissue injuries may contribute to gastric pathologies. We have analysed immunohistochemically 172 stomach biopsies from 99 patients for catalase, Mn-superoxide dismutase (MnSOD) and inducible nitric oxide synthase (iNOS) as markers of oxidative stress (Pignatelli *et al.*, 1994, *Eur. J. Cancer Prevention*, **3**, 108–109; [347]). Biopsies were graded as follows: normal, superficial gastritis, atrophic gastritis of variable severity (mild, moderate or marked) with or without intestinal metaplasia and dysplasia. There was a high prevalence of iNOS in inflammatory cells in all types of gastritis (76–90% of positive biopsies), independently of its severity, and in dysplasia (87%). In foveolar cells, iNOS was less prevalent in all types of gastritis (17 to 32%) but markedly increased in dysplasia (67%). The percentage of biopsies positive for catalase and Mn-SOD in inflammatory cells increased from superficial to atrophic gastritis, reaching 65% in marked atrophic gastritis. In foveolar cells, Mn-SOD was absent, whereas catalase was 6% in normal biopsies and increased from 3% to 35% with increasing severity of gastritis. The prevalence of positive biopsies for catalase and Mn-SOD in inflammatory cells and that of catalase in epithelial cells decreased marked-

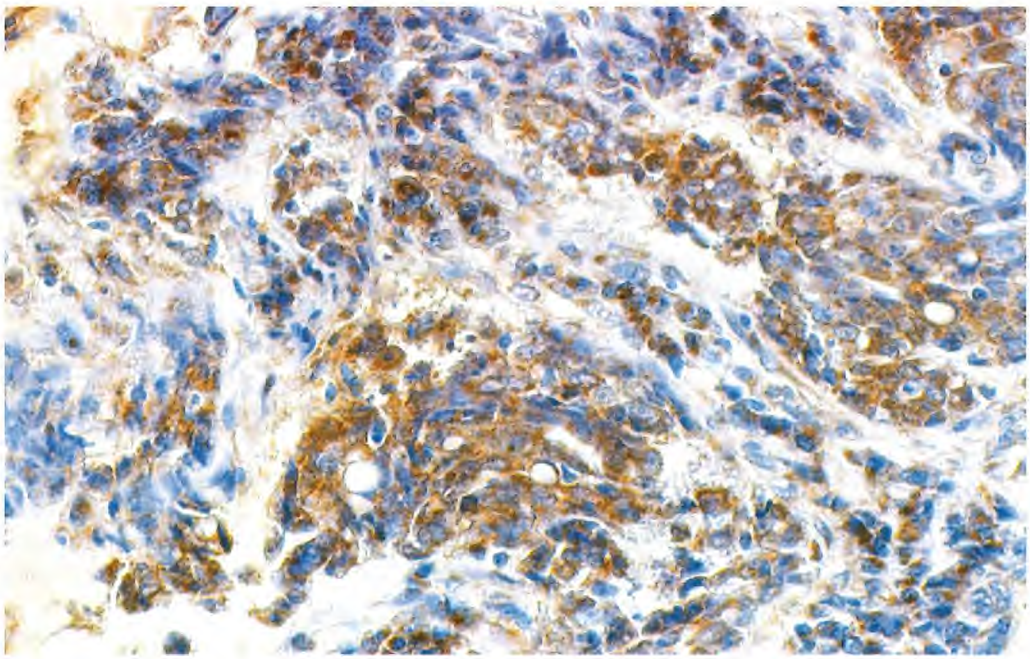

Figure 27. Human gastric tubular adenocarcinoma, moderately differentiated: carcinomatous cells immunoreactive for iNOS

ly in dysplasia compared with marked atrophic gastritis. The three above enzymes were differentially associated with severity of lesions. These results suggest that increased levels of both NO and superoxide could be generated in advanced gastritis. These radicals react rapidly to form a strong oxidant and nitrating agent, peroxynitrite, which may be responsible for tissue or DNA damage, thus playing a role in *H. pylori*-associated gastritis and cancer.

The production of NO by iNOS in some tumour cell lines and the expression of iNOS in human solid tumours have been reported. However, the role of NO in tumour biology remains unclear and the presence of iNOS in gastric adenocarcinoma has never been explored. We have investigated the possible relationship between expression of iNOS and anti-oxidant enzymes and the tumour grade and histological subtype of adenocarcinoma. iNOS was expressed in tumour-infiltrating inflammatory cells in half of biopsies with the various types of adenocarcinoma. The frequency of positive staining for iNOS in carcinomatous cells was higher in biopsies from tubular adenocarcinomas (48%) than in those from from atypical or polymorphic tumour subtypes (15%). Anti-oxidant enzymes were sometimes expressed in tumour-infiltrating inflammatory cells from tubular adenocarcinoma samples, but much less often in other subtypes. Anti-oxidant enzymes were largely absent from tumorous cells of any type.

Since NO can induce accumulation of p53 protein in cultured tumour cells, we studied the relationship between iNOS expression and p53 accumulation in these tumour samples. The p53 protein was present with similar frequency in the various subtypes of adenocarcinoma (29% and 33% in tubular and atypical or polymorphic subtypes respectively). Simultaneous posi-

tive immunostaining for iNOS and p53 was observed in 5 out of 28 tubular adenocarcinomas and in 1 out of 12 of the atypical or polymorphic subtypes. iNOS expression in tumours is now being studied in relation to prognosis, because NO has been proposed to play a role in regulation of tumour growth, invasion and metastasis.

4.3.2 Effects of *Helicobacter pylori* eradication on oxidative stress

B. Pignatelli, M. Laval, N. Lyandrat and H. Ohshima; in collaboration with B. Bancel, L.-M. Patricot, Lyon, France; A.L. Blum and E. Felley-Bosco, Lausanne, Switzerland; and C. Felley, Geneva, Switzerland

The effects of *H. pylori* eradication on oxidative stress in the stomach are being investigated using as markers the expression of iNOS and anti-oxidant enzymes (catalase, Mn-SOD), and the levels of nitrotyrosine (a marker for formation of peroxynitrite and other nitrating agents *in vivo*) and carbonyl-containing proteins (a marker of oxidative damage).

In collaboration with a group in Lausanne, the effects of *H. pylori* eradication by amoxicillin, clarithromycin and omeprazole in 21 volunteers have been studied. Among these subjects, 10 were found to be infected with *H. pylori* and eradication was successful in 8 of them. All biopsies from infected subjects showed positive staining for iNOS, catalase and Mn-SOD in inflammatory cells before eradication. Non-infected subjects exhibited normal gastric histology and no staining for these enzymes. After eradication, the expression of these three enzymes was considerably

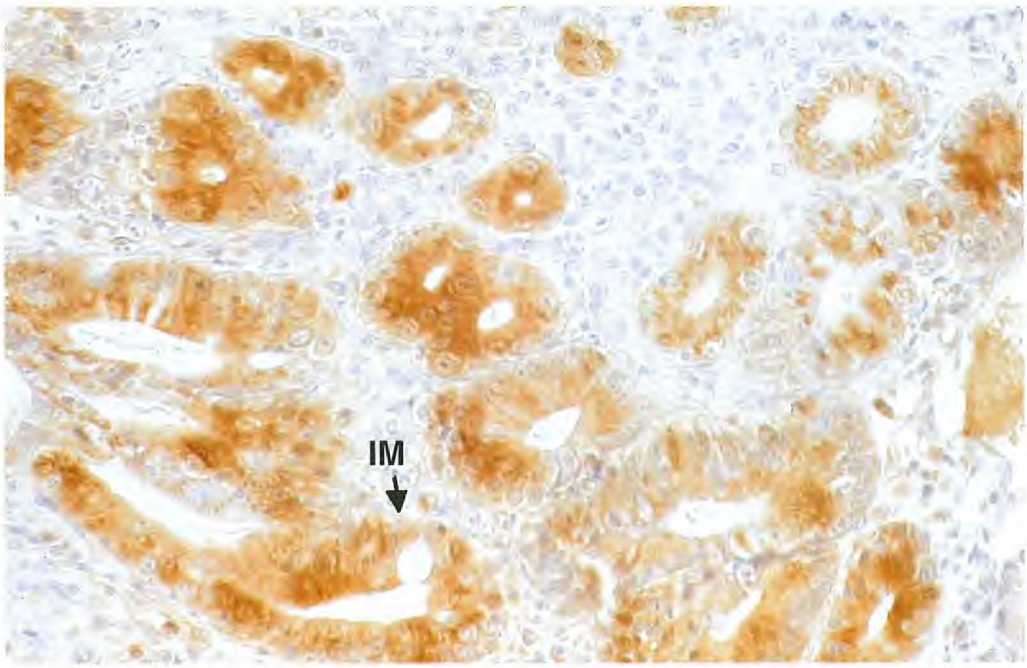

Figure 28. Nitrotyrosine immunostaining in human gastric mucosa localized to foveolar cells in active moderate atrophic gastritis (antrum) with severe H. pylori infection.

Note: The staining is cytoplasmic (in some foveolae only supranuclear).

Reactive foveolae with intestinal metaplasia (IM). The inflammatory cells are unstained.

reduced or disappeared in the infected subjects. In contrast, the biopsies from two subjects for whom eradication failed showed positive staining for these three enzymes even after antibiotic treatment. Preliminary results of immunohistochemical analyses for nitrotyrosine showed that nitrating species are often formed in patients infected with *H. pylori* and suffering from various forms of gastritis. Other factors, such as the level of IL-8, are now being studied in relation to *H. pylori* infection and its eradication. These preliminary results clearly show that *H. pylori* eradication reduces oxidative stress in gastritis patients.

4.3.3

Effect of gastric acid secretion inhibitors on bacterial overgrowth and *N*-nitroso compound concentrations in gastric juice

B. Pignatelli; in collaboration with M.Fried, Zürich, Switzerland; and J. Thorens and A.L. Blum, Lausanne, Switzerland

Gastric and duodenal bacterial overgrowth frequently occurs in conditions where acid secretion is diminished. Omeprazole inhibits acid secretion more effectively than cimetidine and might therefore more frequently cause bacterial overgrowth. Some bacteria can reduce nitrate to nitrite and catalyse *N*-nitrosation.

In a prospective study, we compared the incidence of gastric and duodenal bacterial overgrowth with levels of nitrate, nitrite and *N*-nitroso compounds in patients treated with omeprazole or cimetidine [456]. Bacterial overgrowth ($\geq 10^5$ colony-forming units/ml) was present in 53% of the patients receiving omeprazole and in 17% of those receiving cimetidine ($p < 0.05$). Basal gastric pH was higher in patients treated with omeprazole than in those treated with cimetidine (4.2 versus 2.0) and in patients with bacterial overgrowth compared with those without bacterial overgrowth (5.1 versus 2.0). The results show that the incidence of gastric and duodenal bacterial overgrowth is considerably higher in patients treated with omeprazole compared with cimetidine. No patient developed signs of malabsorption. The nitrate, nitrite and *N*-nitroso compound values in gastric juice did not increase after treatment with either cimetidine or omeprazole.

4.3.4

Helicobacter pylori infection, anti-oxidant status, precursors of mutagens in gastric juice, oxidative stress in gastric mucosa and risk of malignancy in the human stomach

C. Malaveille, B. Pignatelli, A. Hautefeuille and H. Ohshima; in collaboration with C.J. Schorah, M.F. Dixon and A.T.R. Axon, Leeds, UK

Gastric cancer develops on a background of *H. pylori*-induced chronic gastritis. This condition can cause increased tissue concentrations of reactive oxygen and nitrogen species. This has led to an interest in eradicating *H. pylori* and the use of anti-oxidants as potential therapeutic or prophylactic agents.

The objectives of this study are (*a*) to evaluate anti-oxidant status, to measure oxidative damage in mucosa and plasma and precursors of genotoxic compounds in gastric juice of patients with various gastric pathologies which represent a range of risk for stomach cancer; and (*b*) to determine how anti-oxidant treatment and/or *H. pylori* eradication modify the above parameters and affect the pathology in terms of the presence of pre-malignant and malignant changes (metaplasia, dysplasia and cancer).

So far, 144 gastric juice samples collected before and after treatment for *H. pylori* eradication and/or with vitamins C and E have been analysed for bacterial mutagenicity after nitrosation. Other parameters such as level of vitamins C and E and free iron were also analysed in the same

samples. The study data will be evaluated after the analysis of another 100 gastric juice samples.

4.3.5
Characterization of bacterial cytochrome cd$_1$-nitrite reductase as one enzyme responsible for catalysis of nitrosation of secondary amines

S. Calmels and H. Ohshima; in collaboration with H. Bartsch, Heidelberg, Germany; and Y. Henry, Orsay, France

Chronic bacterial infections are recognized or suspected risk factors associated with several malignancies, including cancer of the stomach, urinary bladder and uterine cervix. Bacterial formation of carcinogenic *N*-nitroso compounds *in situ* is a possible etiological mechanism. A number of studies have now unequivocally shown that bacterially mediated formation of nitrosamines can occur *in vitro* and *in vivo*, both in animal models and in human cancer cases. We have characterized a nitrosating enzyme purified from denitrifying bacteria (*Pseudomonas aeruginosa*) as a cytochrome cd$_1$-nitrite reductase. This enzyme catalyses nitrosation of secondary amines to form carcinogenic nitrosamines through the production of nitric oxide or NO^+-like species. Electron paramagnetic resonance studies have shown that large quantities of nitric oxide or NO^+-like species are also produced by non-denitrifying enterobacteria (*Escherichia coli, Proteus morganii*) [55].

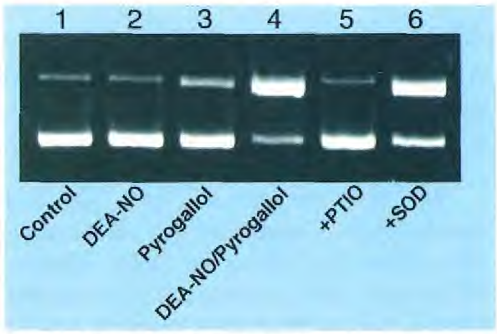

Figure 29. Synergistic induction of DNA strand breakage by NO and pyrogallol, and its inhibition by carboxy-PTIO (an NO-trapping agent) and superoxide dismutase. Upper bands: open circular form; lower bands, supercoiled form

4.3.6
DNA damage induced by endogenous free radicals

H. Ohshima, Y. Yoshie, I. Brouet and S. Auriol

Reactive oxygen and nitrogen species play an important role in many human diseases including cancer. In studies of DNA damage induced by nitric oxide (NO), we have found that incubation of pBR322 plasmid DNA with an NO-donor (diethylamine NONOate, spermine NONOate etc.) and a polyhydroxyaromatic compound (e.g. catechol or 1,4-hydroquinone) caused synergistic induction of single-strand breaks, whereas either compound alone induced much less breakage (Figure 29) [514]. Generation of potent reactive species by reaction between NO and polyhydroxyaromatic compounds may be important in the etiology of various human diseases including cancer and neurodegenerative disease.

Cigarette smoking. The mechanisms underlying carcinogenesis associated with cigarette smoking remain unestablished. We have observed synergistic induction of DNA strand-breakage by NO and cigarette tar (rich in catechol and hydroquinones) [513]. NO is present at high concentrations in the gas phase of smoke, and can also be formed endogenously by a constitutive or inducible NO synthase in the lung. It could therefore react directly with polyhydroxyaromatic compounds in cigarette tar such as catechol and 1,4-hydroquinone to form reactive species that might play an important role in smoking-related diseases.

Neurodegenerative disease. Similarly NO reacts with various catecholamines (e.g., L-dopa and dopamines) to form oxidants which can cause DNA strand breakage

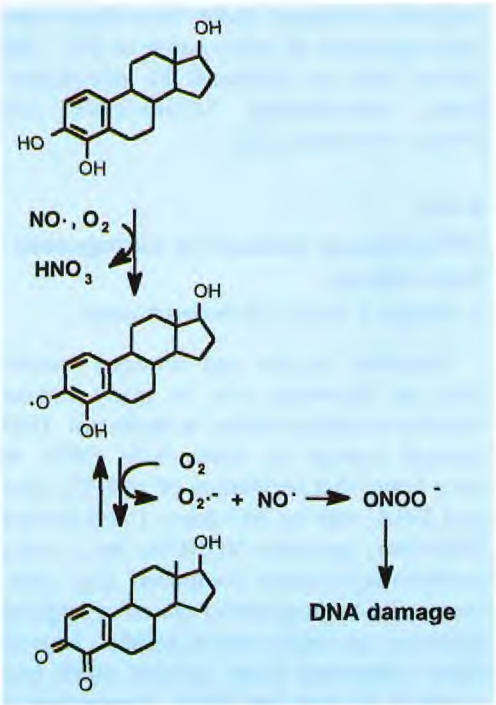

Figure 30. Proposed mechanisms for synergistic effects of catechol-estrogen and NO on DNA strand-breakage

[516]. These results implicate a reaction between catecholamines formed in dopaminergic neurons with NO formed by microglia or astrocytes, or between the two compounds produced within the same neuronal cells, to produce a potent oxidant(s) which could be responsible for pathogenesis of various neurodegenerative diseases.

NO and estrogens. Estrogen is a known risk factor for human breast cancer, although the mechanism of action remains uncertain. Several recent studies have established the importance of catechol-estrogen metabolites in DNA damage. The 2- and 4-hydroxylated metabolites of both β-estradiol and estrone can directly or indirectly damage DNA, protein and lipids through the redox cycling of semiquinone/quinone derivatives. We have recently presented evidence that NO can potentiate DNA-damaging effect of catechol-estrogens even in the absence of metal ions [515]. A possible mechanism for the induction of this synergistic effect on DNA strand-breakage is a reaction between NO and $O_2^{\cdot-}$ generated by NO-mediated autooxidation of catechol-estrogens, to form peroxynitrite ($ONOO^-$), a strong oxidant and nitrating agent (Figure 30). These results suggest that catechol-estrogens and NO formed in the breast or uterus may react with each other to produce a potent oxidant(s), playing an important role in hormonal carcinogenesis.

There is now substantial evidence that peroxynitrite plays an important role in various pathophysiological conditions such as various types of acute and chronic inflammation, and the reperfusion of ischaemic organs [450]. It has been demonstrated that simultaneous generation of NO and superoxide causes DNA strand-breakage, which activates poly-(ADP-ribose) polymerase. Extensive activation of this enzyme may result in depletion of NAD^+ and ATP, leading to cell injury and death due to energy depletion (Figure 31). The role of poly-(ADP-ribose) polymerase in cell/tissue injury induced by NO and superoxide is being studied in collaboration with Z.Q. Wang.

4.3.7
Anti-oxidant and pro-oxidant properties of NO and flavonoids

H. Ohshima, Y. Yoshie, I. Brouet and S. Auriol

We have demonstrated that NO and catechol-type compounds in combination exert deleterious effects on DNA, whereas NO protects DNA from metal-ion-mediated damage due to the Fenton reaction or 1,4-hydroquinone plus Cu^{2+} [514]. Such inhibition could be due to formation of a complex between NO and a metallic ion, inhibiting generation of reactive species

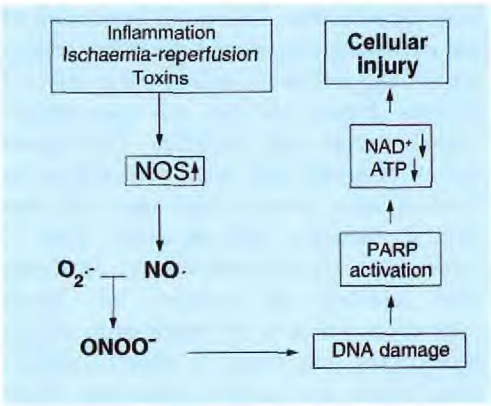

Figure 31. Proposed scheme for cytotoxic pathway involving nitric oxide, superoxide and peroxynitrite via activation of poly (ADP-ribose) polymerase (PARP)

from H_2O_2. Our results imply that NO can play both detrimental and beneficial roles in disease pathology, depending on the type and amounts of reactive oxygen species and metallic ions concurrently generated or present. These data may explain in part the contrasting activities of NO that have been reported in relation to tissue injury.

Similarly, both anti-oxidant and pro-oxidant properties of plant flavonoids have been reported. We have found that some flavonoids, especially those having a pyrogallol structure on either the A or B ring (e.g., epigallocatechin, myricetin etc.; Figure 32), can induce DNA strand-breakage in the presence of NO. These flavonoids could generate superoxide, which reacts with NO to form strong oxidant(s) including peroxynitrite. The physiological relevance of such pro-oxidant effects of certain flavonoids is not known. On the other hand, most flavonoids exhibited inhibitory effects against DNA damage (strand breaks, 8-nitroguanine formation) mediated by preformed peroxynitrite.

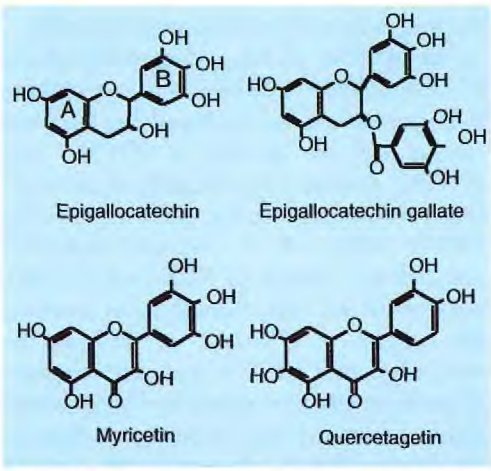

Figure 32. Flavonoids which show pro-oxidant activity in the presence of NO

4.3.8
Modulation of p53 conformation and function by nitric oxide and apoptosis

S. Calmels, L. Chazotte, I. Brouet, H. Ohshima and P. Hainaut

NO reacts with various enzymes and other proteins to either activate or inhibit their function. We have hypothesized that, in inflamed tissues, excess endogenously formed NO may alter the function of the p53 tumour-suppressor protein, a zinc-dependent transcription factor, that is regulated by oxidation–reduction. Incubation *in vitro* of recombinant wild-type murine p53 protein with *S*-nitroso-*N*-acetyl-DL-penicillamine (an NO-releasing compound) resulted in a change of p53 conformation and also a significant decrease of its specific DNA-binding activity. Similarly, upon treatment with *S*-nitroso-*N*-acetyl-DL-penicillamine (2–5 mM) or *S*-nitrosoglutathione (1–2 mM), human breast cancer cells (MCF-7), which express wild-type p53, rapidly accumulated p53 protein in the nuclei. This p53 protein, however, possessed significantly decreased activity of specific DNA-binding. In contrast, lower concentrations of NO donors (0.25–0.5 mM) stimulated p53 accumulation and enhanced DNA-binding activity. These results suggest that excess NO produced in inflamed tissues could play a role in carcinogenesis by impairing the

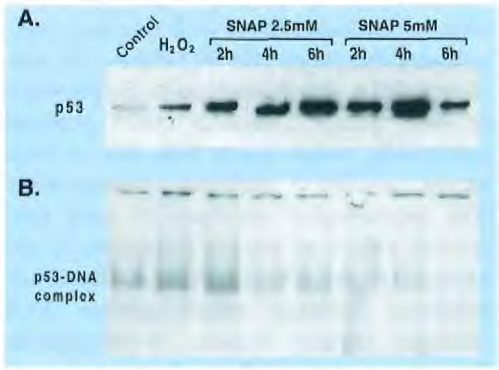

Figure 33. Effects of S-nitroso-N-acetyl-DL-penicillamine on p53 accumulation (A) and its DNA-binding activity (B) in human breast cancer MCF-7 cells

tumour-suppressor function of p53. Over half of all human cancers are linked with loss of function of p53 due to mutation or deletion of the gene. However, in many other cancers, the p53 gene remains intact; in such cases, a new mechanism may operate in which excess NO produced in inflamed tissues causes loss of the tumour-suppressor function of the protein [53].

It has been reported that NO can either induce or inhibit apoptosis, depending on cell types. We are studying the molecular mechanisms of apoptosis/cell death induced by NO, superoxide and peroxynitrite. Factors involved in cell death (e.g., sphingomyelin metabolism, caspase, bcl-2, bax, cytochrome c release, etc.) are being characterized.

4.3.9

Role of schistosome infection in carcinogenesis

Q. Shao, I. Brouet, H. Ohshima, H. Ohgaki, Y. Tohma, M. Lang, A.-M. Camus and A. Ellul; in collaboration with W. Anwar, Cairo, Egypt

Infection with schistosomes has been associated with an increased risk of cancer in the liver, colon and urinary bladder. We have analysed cell apoptosis and the expression of Fas protein (CD95/APO-1) and Fas ligand in the liver of mice with or without infection with schistosomes. Decreased expression of Fas in hepatocytes around the inflammatory area of egg granuloma was found in infected animals (Figure 34); this was most prominent 21 weeks after infection. The highest rate of apoptotic cell death occurred in the liver of mice seven weeks after infection with *S. mansoni*, and decreased from 12 weeks to reach the control level 21 weeks after infection. In contrast, Fas ligand expression, which is not observed in normal hepatocytes, was found in infected hepatocytes inside and outside granuloma where there was dense infiltration of inflammatory cells. This Fas ligand expression mainly appeared in animals seven weeks after infection with either *S. japonicum* or *S. mansoni*. Inflammatory cells positive for Fas ligand were also occasionally seen in egg granuloma during the acute stage of infection. Fas ligand was also expressed in the membrane of epithelial cells of bile ducts in both uninfected and infected mice. Abnormal proliferation of capillary bile ducts was observed inside egg granuloma in the liver of infected animals, especially from 21 weeks after infection. The epithelial cells of the proliferating bile ducts were positive for Fas ligand. Our data indicate that expression of Fas and Fas ligand may be altered in association with inflammation or lesions in the liver induced by schistosome infection.

In addition, we have studied the effects of schistosome infection on cytochrome P450 in mouse liver. We found that the P450 content and the activity of CYP2A5 and CYP2E1 decreased significantly at the acute stage of infection. On the other hand, at the chronic stage of *S. mansoni* infection, although the content of P450 and CYP2E1 activity did not differ from those of controls, the activity of CYP2A5 as well as the expression of CYP2A5 analysed immunohistochemically were dramatically enhanced. Immunoreactivity was strongest in hepatocytes immediately adjacent to the area of egg granuloma of both *S. japonicum* and *S.*

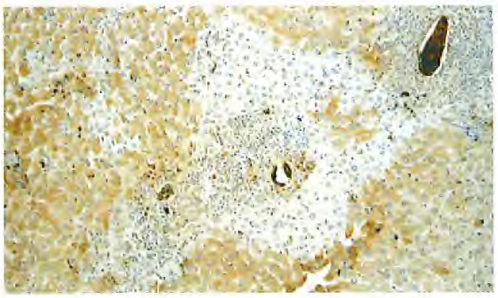

Figure 34. Decreased Fas expression in the hepatocytes around egg granuloma in the liver of the mouse 12 weeks after infection with S. mansoni (× 80).

mansoni. These results were similar to those found in hamster liver infected with *Opisthorchis viverrini* (Kirby *et al.*, 1994, *Molec. Carcinog.*, **11**, 81–89) and suggest that CYP2A5, which catalyses the activity of carcinogens such as *N*-nitrosodimethylamine, could play a role in liver carcinogenesis associated with parasite infection.

In collaboration with Dr W. Anwar, Cairo, Egypt, we have initiated studies on *S. haematobium* infection and bladder cancer. Human bladder tissues from bladder cancer patients in Egypt are being analysed for expression of inducible nitric oxide synthase in relation to *S. haematobium* infection.

4.4 Role of cell–cell communication in carcinogenesis

Intercellular communication plays an important role in the maintenance of growth control at the tissue level. Most, if not all, cancers show aberrant intercellular communication ability. Among various forms of intercellular communication, gap junctional intercellular communication and its role in carcinogenesis are being studied most intensively (Sections 4.4.1–5). A new project to explore the molecular control mechanisms of the cell adhesion molecule, E-cadherin, has also been initiated (Section 4.4.6).

4.4.1
Tumour suppression by connexin genes

M. Mesnil, V. Krutovskikh, C. Piccoli and H. Yamasaki; in collaboration with M. Asamoto and H. Tsuda, Tokyo, Japan

Our previous results have suggested that connexins (Cx) are tumour-suppressors and that they show cell-type specificity; only the smallest connexin, Cx26, but not Cx32, Cx40 nor Cx43, reduces the growth of HeLa cells *in vivo* and *in vitro* (Mesnil *et al.*, 1995, *Cancer Res.*, **55**, 629–639) To elucidate the mechanisms involved in the HeLa tumour-suppression induced by Cx26 expression, we investigated the possible role of the cell–cell recognition process. HeLa cells express all the molecules necessary for making adherens junctions (catenins and N-cadherin), but these molecules are not correctly localized at the plasma membranes. The cell–cell recognition molecules were localized in the membrane at the cell–cell contact areas only in the Cx26 transfectants. We previously reported that gap junctional intercellular communication (GJIC) mediated by Cx43 can be induced by the establishment of cell–cell adhesion (Jongen *et al.*, 1991, *J. Cell Biol.*, **114**, 545–555). We have now shown the reverse situation: a particular connexin (Cx26) seems to be important for the induction of cell–cell adhesion of HeLa cells, suggesting reciprocal requirements of these two types of cell–cell interaction apparatus.

In the rat bladder carcinoma cell line BC31, there was a substantial level of Cx43 expression and GJIC was readily detectable. However, when the *Cx43* gene was transfected into these tumorigenic cells, their tumorigenicity was eliminated. These results confirm the tumour-suppressive effect of connexin genes and that the level of connexin expression plays an important role in growth control.

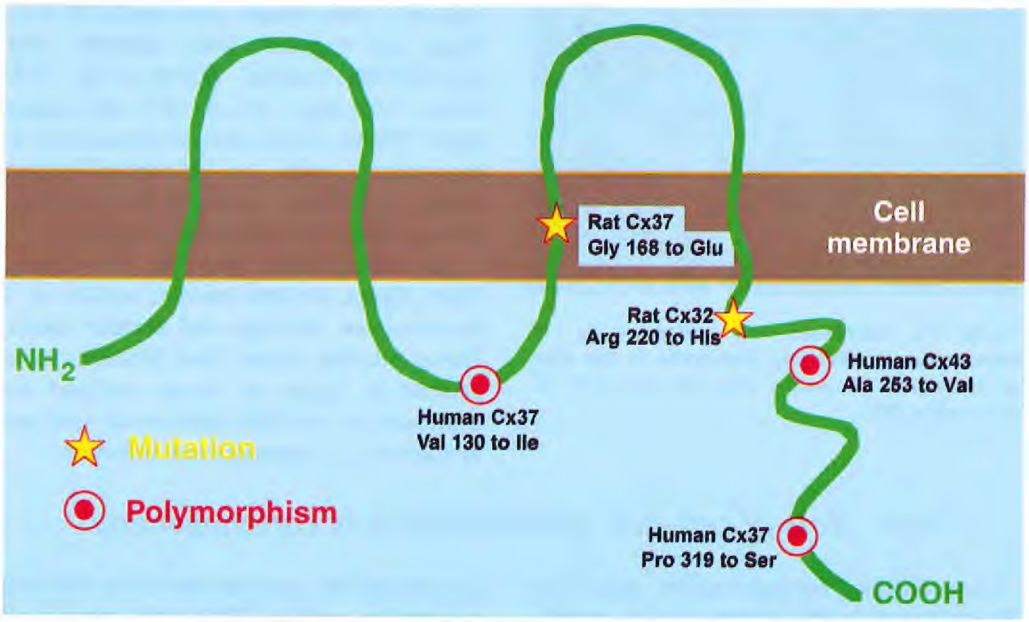

Figure 35. Mutations and polymorphisms in connexin genes discovered at IARC

4.4.2
Connexin gene mutations and polymorphisms

T. Saito, Y. Omori, V. Krutovskikh, A. Barbin, K. Sato, H. Ohgaki, P. Kleihues and H. Yamasaki; in collaboration with W. Bennett, Bethesda, MD, USA; M.-J. Marion, Lyon, France; and H. Tsuda, Tokyo, Japan

In order to examine the role of connexin gene mutations in carcinogenesis, we analysed a panel of rodent and human tumours. The data indicate that mutations in *Cx32*, *Cx37* and *Cx43* genes are quite rare in animal and human cancers. We found only one *Cx32* gene mutation in rat liver tumours [321] and two missense *Cx37* gene mutations in rat haemangiosarcomas [378]. In previous studies, we detected no mutation of *Cx32* either in 20 human liver tumours or in 22 human stomach tumours. Similarly, no mutation was found in *Cx43* of 49 human meningiomas [418]. In 18 human breast carcinomas and eight human lung adenocarcinomas, no mutation of *Cx37* was found [211].

On the other hand, we found genetic polymorphism in the human *Cx43* gene and in rodent and human *Cx37* genes [378]. To date, our data suggest that these polymorphisms do not contribute to the occurrence of cancers we have examined. The connexin gene mutations and polymorphisms found at IARC are summarized in Figure 35.

4.4.3
Dominant-negative effect of mutant connexin genes on cell growth regulation

Y. Omori, A. Duflot-Dancer, V. Krutovskikh, M. Mesnil and H. Yamasaki; in collaboration with C. Naus, London, Ontario, Canada; and H. Tsuda and M. Asamoto, Tokyo, Japan

4.4.3.1
Cx26 in HeLa cells

In order to see whether mutated Cx26 protein can prevent the tumour-suppressive effect of wild-type Cx26 in HeLa cells in a dominant-negative fashion, we transfected mutated Cx26 cDNA into HeLa cells

expressing wild-type Cx26. Three mutations of Cx26 were chosen. One changed arginine at codon 143 to tryptophan (R143W) in the third transmembrane domain, which is involved in the pore function of gap junctions. The second affected cysteine 60, which is highly conserved. Changing this cysteine to phenylalanine (C60F) was previously shown to prevent the communication function of Cx32 in HeLa cells in a dominant-negative manner [322]. The third mutation changed proline 87 to a leucine residue (P87L), which is located in the second transmembrane domain and is highly conserved between different connexins. This residue has been shown to be involved in voltage gating of gap junctions (Suchyna *et al.*, 1993, *Nature*, **365**, 847–849). The mutated *Cx26* genes were transfected into HeLa cells expressing the wild-type *Cx26* gene, which are communication-competent and non-tumorigenic. Transfection of P87L and R143W mutants enhanced the tumorigenicity of the cells without affecting their communication capacity [91]. Transfection of the C60F mutant reduced the communication capacity without inducing tumorigenicity of the HeLa Cx26 cells [91]. Immunostaining demonstrated that the mutated Cx26 did not prevent correct localization of the wild-type Cx26 protein at the cell–cell contact areas. These results suggest that certain mutant Cx26 proteins exert a dominant-negative effect on Cx26-regulated growth of HeLa cells and that such effects may be independent of the effect on communication ability.

4.4.3.2

Cx43 in rat bladder cells

The rat bladder carcinoma cells, BC31, communicate through gap junctions despite their malignancy. In order to explore this paradoxical phenomenon, we have studied the effect on tumorigenicity of loss of GJIC in this cell line, using a dominant negative strategy.

In cells transfected with a mutant Cx43 with seven residues deleted from the internal loop at positions 130–136, oligomerization of the mutant protein with endogenously expressed wild-type Cx43 and transport of the resulting connexons to the plasma membrane occurred normally, but the GJIC of the cells was effectively abolished at the level of permeability of established gap junctions (Figure 36(1)). This, in turn, drastically accelerated the growth of mutated Cx43 transfectants in nude mice (Figure 36(3)). In addition, decreased phosphorylation of the mutated Cx43 (Figure 36(2)) suggested that an interaction of the internal loop with the C-terminal tail of the connexin molecule is involved in gap junction permeability. In contrast, when GJIC in BC31 cells was artificially enhanced by additional transfection of wild-type Cx43 (Figure 36(1)), the cells lost the capacity to grow *in vivo* (Figure 36(3). We conclude that intrinsic GJIC observed in cancer cells should be considered as a tumour-suppressor factor and its level may influence malignant growth capacity.

4.4.3.3

Cx43 in rat glioma cells

Transfection of *Cx43* gene into rat C6 glioma cells has revealed that Cx43 functions as a growth- and tumour-suppressor. We have examined the dominant-negative effect of mutant Cx43 on growth control exerted by the wild type in C6 cells. Three mutant Cx43s (Leu 160 to Met (L160M), Ala 253 to Val (A253V) and Ser 364 to Pro (S364P)) were transfected into Cx43-transfected C6 cells (clone C6-13). All restored anchorage-independent growth capacity that is suppressed in C6-13 (in particular, A253V enhanced the tumorigenicity of C6-13), implying that these three mutants can inhibit the growth-suppressive function of wild-type Cx43 in a dominant-negative manner. Intriguingly, the mutants A253V and S364P did not suppress GJIC capacity, implying a

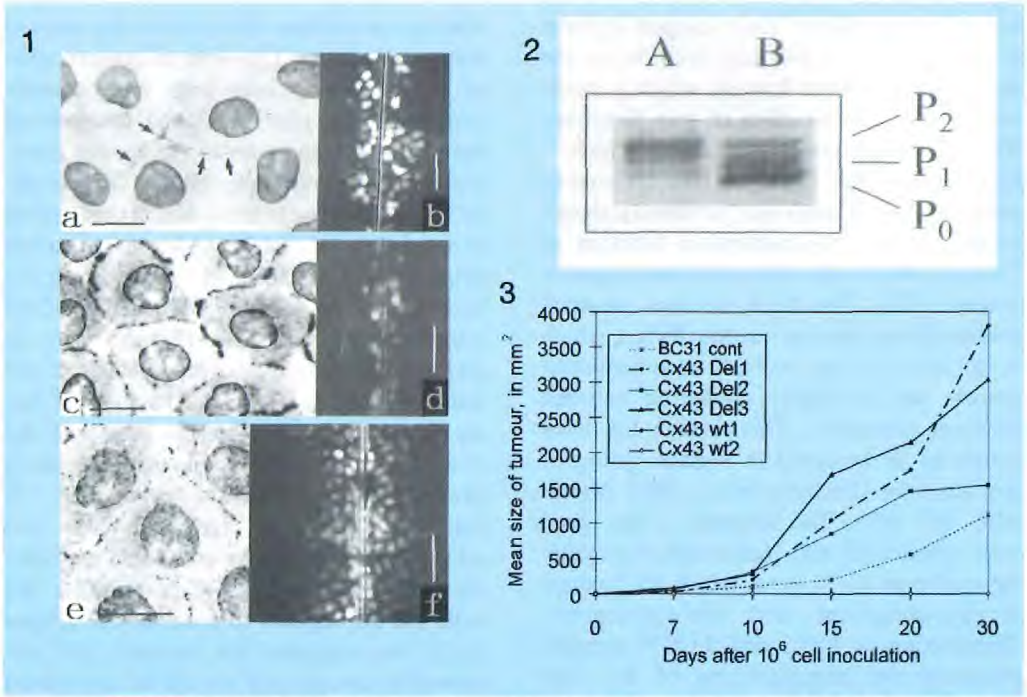

Figure 36. Effect of Cx43 transfection into the rat bladder cancer cell line BC31. (1) Gap junctional intercellular communication and Cx43 subcellular localization in BC31 cells and its transfectants with either Cx43 carrying a deletion at positions 130–136 or wild-type. (a) Immunohistochemical detection of Cx43 expression in BC31 cells. (b) Intercellular communication of BC31 cells as revealed by scrape loading dye transfer assay. (c) Subcellular localization of Cx43 carrying a deletion at positions 130–136 in BC31 transfectants. (d) Lack of Lucifer Yellow spreading in deletion-bearing Cx43 transfectants. (e) Wild-type Cx43 in BC31 transfectants revealed by indirect immunostaining as discrete spots both in the lateral plasma membranes and in the nuclei. (f) Extensive Lucifer Yellow spreading in transfectants detected by the scrape loading method. (2) Western blot of Cx43 from BC31 cells (A) and its Cx43 deleted transfectant (B). Three isoforms of Cx43, corresponding to non-phosphorylated (P_0), phosphorylated with one (P_1) and two (P_2) phosphate groups were recognized. (3) Tumour promotion by BC31 cells and their transfectants either with deletion-bearing Cx43 (three individual clones), or wild-type Cx43, in nude mice.

growth-suppressive pathway mediated by Cx43 but not by GJIC.

4.4.4

Creation of liver-specific Cx32 knock-out mice employing a dominant-negative mutant transgene

Y. Omori, V. Krutovskikh, M. Mesnil and H. Yamasaki

To generate tissue-specific connexin knock-out mice, we introduced into mice a dominant-negative connexin mutant transgene driven by a tissue-specific gene promoter. We introduced a Val139Met mutant of the *Cx32* gene driven by an albumin gene promoter, since this mutant exerts a strong dominant-negative effect on wild-type Cx32 protein [322] and since *Cx32* is a major connexin gene expressed in hepatocytes. We now have founder mice which express the transgene specifically in the liver. GJIC in the liver of these mice is significantly lower than that of the parental mice (Figure 37). These transgenic mice are being propagated

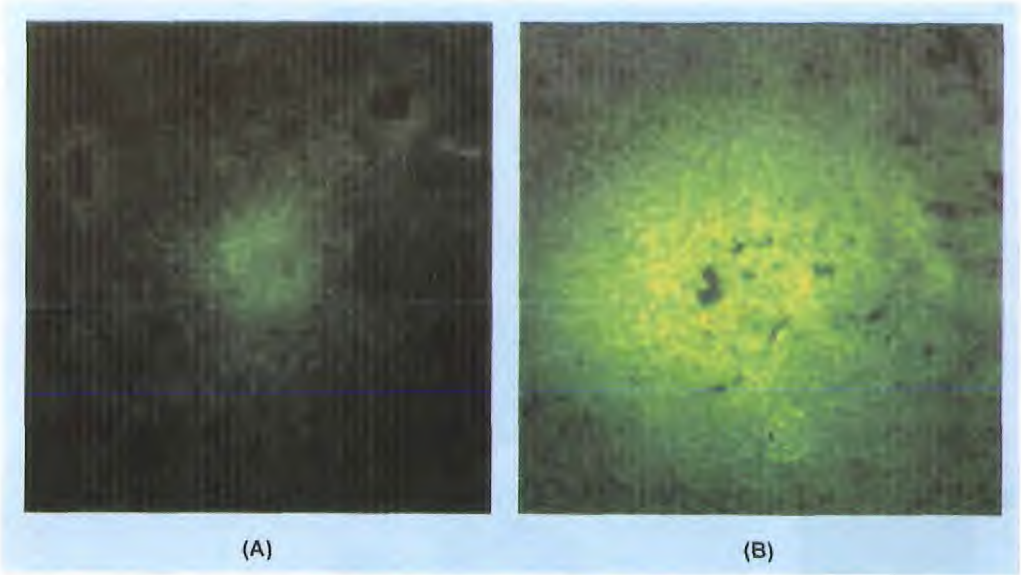

Figure 37. Gap-junctional intercellular communication in liver-specific Cx32 knock-out mice carrying a dominant-negative mutant Cx32 gene

A V139M mutant Cx32 gene was linked to a liver-specific albumin gene promoter and injected into mouse oocytes to generate transgenic mouse lines. The founder mice expressed the transgene only in liver, as revealed by semi-quantitative RT-PCR. The mutant Cx32 proteins are expected to form non-functional chimeric hexamers with wild-type Cx32, and also with wild-type Cx26, resulting in down-regulation of gap junctions exclusively in the liver. GJIC was significantly decreased in liver of the transgenic mouse(A) compared with wild-type mice (B).

for further experiments, including chemical hepatocarcinogenesis.

4.4.5

Role of gap junctional intercellular communication in the bystander killing of cancer cells by anticancer gene therapy

M. Mesnil, A. Duflot-Dancer, C. Piccoli and H. Yamasaki; in collaboration with P. Leroy, Strasbourg, France; J.-P Reynès and G. Tiraby, Toulouse, France; M.-G. Sacco, Milan, Italy; and K. Willecke, Bonn, Germany

In anticancer gene therapy, it has been observed that cytotoxicity is not limited to the cells into which a suicide gene has been transfected, but also affects neighbouring cancer cells. This 'bystander effect' is a prominent feature of a therapeutic strategy combining the thymidine kinase gene from the herpes simplex virus (HSV-tk) and ganciclovir treatment, and is reminiscent of a previous observation that the effect of certain anticancer agents can be enhanced by diffusion through gap junctions (Yamasaki & Katoh, 1988, *Cancer Res.*, 48, 3490–3495).

We have demonstrated that gap junctions may be responsible for such a bystander effect (Figure 14) [255]. For this purpose, we transfected the *HSV-tk* gene into HeLa cells, which exhibit a very low capacity for communication through gap junctions. When these cells were cocultured with nontransfected cells, only the *HSV-tk*-transfected cells (tk^+) were killed by ganciclovir (Figure 14B). However, when HeLa cells transfected with a gene encoding for the gap junction

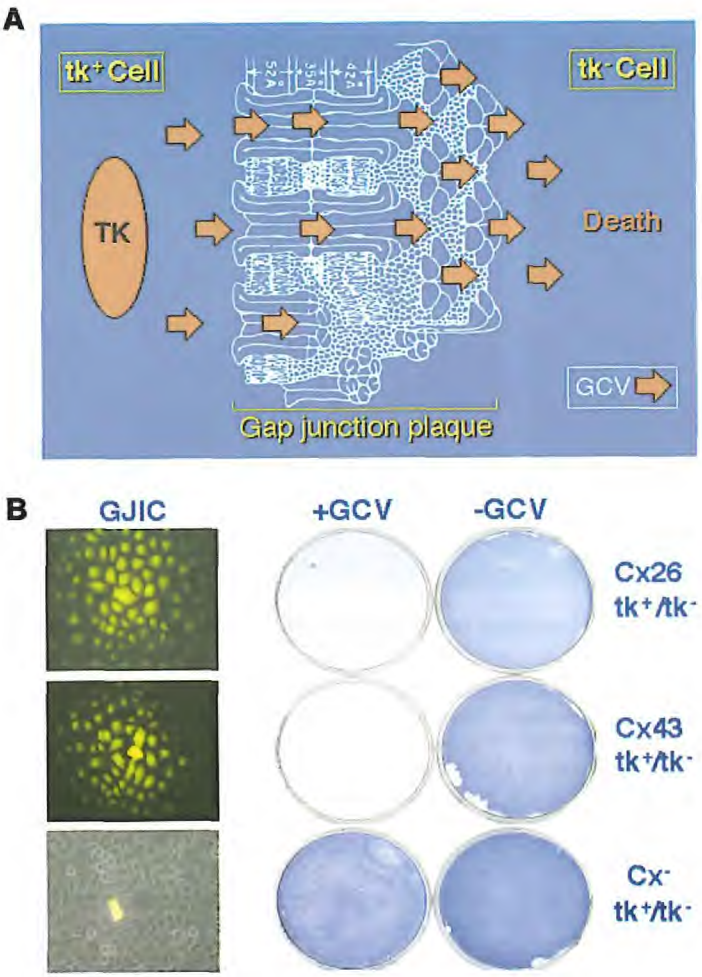

Figure 38. Bystander effect in cancer gene therapy due to gap junctional intercellular communication; toxic phosphorylated ganciclovir (GCV) molecules can pass from a cell transfected with the thymidine kinase (TK) gene of Herpes simplex virus to neighbouring tumour cells. (A) The toxic phosphorylated GCV (red arrows) passes from tk^+ to tk^- cells through the gap junctions. (B) In HeLa cells, the bystander killing effect is observed only when the cells expressing Cx43 or Cx26 communicate (as shown by the dye transfer assay) through gap junctions. Cells expressing HSV-tk (tk^+) were mixed with their counterparts (tk^-) at a 1:1 ratio.

protein connexin 43 (Cx43) were used, not only tk^+ cells were killed by ganciclovir, but also those lacking the *HSV-tk* gene, presumably because of transfer via Cx43 gap junctions of toxic ganciclovir molecules phosphorylated by HSV-tk into the tk^- cells (Figure 14A). Total killing of the coculture was observed even when only 10% of the cells were tk^+. No bystander effect was observed when tk^+ and tk^- cells were cocultured without direct cell–cell contact or when the coculture was treated with a potent and long-term inhibitor of GJIC (18- α-glycyrrhetinic acid, AGA) [256].

We have also shown that other types of gap junction protein can mediate the bystander effect *in vitro*. In particular, the smallest one, Cx26, may have therapeutic potential since it acts as both a down-regulator of growth and a mediator of the bystander effect in HeLa cells (Figure 14C) [256].

We have confirmed that gap junctions can also mediate the bystander effect *in vivo* by subcutaneously injecting different ratios of tk^+ and tk^- cells into nude mice that were subsequently treated intraperitoneally with ganciclovir. Tumours were eliminated only if the HeLa cells expressed Cx43, even when only 10% of them were tk^+. Similarly, incomplete eradication of mammary tumours by retrovirally mediated *HSV-tk* gene transfer into *neu*-transgenic mice seemed to be due to a lack of GJIC in the tumour cells (Sacco *et al.*, 1996, *Gene Therapy*, **3**, 1151–1156).

These results demonstrate that induction of GJIC in tumours, by either chemical treatment or connexin gene transfer, can drastically enhance the bystander effect, thus overcoming the low efficiency of suicide-gene transfer *in situ* [257].

More recently, we have observed that connexins can induce a bystander effect for another type of suicide gene, cytosine deaminase, even when only 5% of the cells express the gene.

4.4.6 Identification of transcription factors controlling E-cadherin expression

L. Giroldi and H. Yamasaki; in collaboration with J.A. Schalken , Nijmegen, The Netherlands

The intercellular adhesion molecule E-cadherin limits the invasive capacity of cancer cells in *in vitro* and *in vivo* models. Decreased E-cadherin expression is correlated with tumour aggressivity in a variety of carcinomas, and clinical follow-up studies have revealed the potential of E-cadherin immunohistochemistry as a prognostic marker. Because accumulated data point to E-cadherin as a key molecule in the maintenance of epithelial differentiation and integrity, disturbance or loss of E-cadherin is regarded as a likely causal event in tumour progression.

In most cases, decreased E-cadherin expression results from decreased transcription of the E-cadherin gene. Our initial results suggest the existence of a transcriptional repressor acting in cancer cells through binding to a DNA sequence known as 'E-box'. We are setting up a library of transcription factors interacting with the promoter of E-cadherin. We have constructed yeast strains carrying in their genome the selection marker *his* under control of the E-cadherin promoter. Factors binding specific motifs of the promoter, including E-box, will be identified by screening the library with appropriate mutated versions of the promoter.

4.5 Mutator phenotypes and cancer

It is generally considered that typically 5–10 genetic changes need to accumulate in a cell for it to become malignant. Assuming that the mutation frequency of a gene is around 10^{-6} per cell division, it is reasonable to assume that a mutator phenotype is induced in a cell at an early stage of carcinogenesis. A class of mutator phenotype is known to be caused by the functional loss of the mismatch DNA repair system. This is manifested by genomic (microsatellite) instability and IARC laboratories are interested in the molecular mechanisms of such genomic instability and its possible interplay with environmental carcinogens.

4.5.1
Role of genomic (microsatellite) instability in carcinogenesis

W.-B. Zhu, A.-M. Aguelon, H. Yamasaki and N. Mironov

Microsatellite instability is seen in various types of human cancer. We hypothesize that the genomic instability represented by microsatellite instability destabilizes preferentially those genes containing simple base repeats.

We have examined microsatellite changes in three genes (TGF-β receptor II and tumour-suppressor genes *DPC4* and *CTCF*) in colon cancer cell lines and HeLa cells. These genes are all believed to be involved in carcinogenesis and contain short repeat sequences in their coding regions. Repeated sequences in *DPC4* and *CTCF* appeared to be unchanged, but three of seven colon cancer cell lines had mutations in the sequence $(A)_{10} \rightarrow (A)_9$ in both alleles of the TGF-β receptor II gene and one cell line in one allele. This suggests that TGF-β receptor II, but not DPC4 or CTCF, may play a role in colon carcinogenesis. When used as a polymerase chain reaction (PCR) template, the TGF-β receptor II gene produced several bands in polyacrylamide gel, creating difficulty in identifying samples containing only one mutated allele. In order to overcome this problem, we developed a method where a special PCR primer is introduced in the restriction site if the $(A)_{10} \rightarrow (A)_9$ mutation is present in at least one allele. Applying this approach to 22 human samples, we found that two of them contained a mutated allele of the TGF-β receptor II gene.

In order to see whether microsatellite instability is also responsible for induction of mutations in other genes, we examined the frequency of sponaneous and chemically-induced mutations in the *HPRT* gene in cell lines with (RER^+, replication error-positive) or without (RER^-) microsatellite instability (Figure 39). Three RER^+ and two RER^- human cancer cell lines were used, and 6-thioguanine resistance was used as a marker of mutant selection. *N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) induced a level of mutations in the *HPRT* gene some 100–1000-fold higher in RER^+ cells than in cells with the RER^- phenotype. It therefore seems that the RER^+ phenotype predisposes cells to MNNG-induced hypermutability.

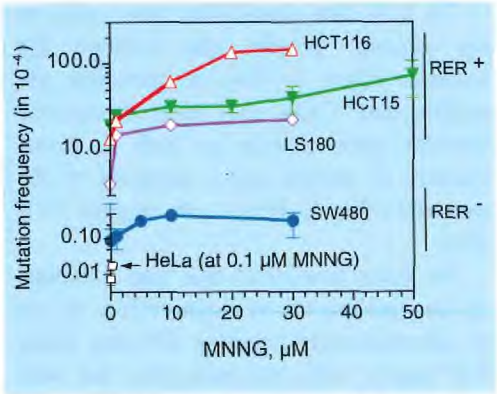

Figure 39. Mutation frequency of genes in cells with microsatellite instability. MNNG induced more HPRT gene mutations in cells with genomic instability (RER^+)

Most spontaneous mutations in HCT116 cells are deletions or insertions; MNNG produced a shift in the mutation spectra, so that approximately half were GC →AT transitions, which could be produced by O^6-meG pairing with thymine during replication. Thus, in cell lines with microsatellite instability, mutagenesis by MNNG added many additional transitions to the existing frameshift mutations.

4.5.2
Role of cell–cell communication in genetic stability

N. Mironov, W.-B. Zhu, A.-M. Aguelon and H. Yamasaki

In order to test the hypothesis that intact gap-junctional intercellular communication (GJIC) is necessary for genomic stability, we compared the frequencies of spontaneous

and chemically-induced mutations in GJIC-proficient and -deficient HeLa cells. For this purpose, we measured microsatellite instability and mutation frequency in the *HPRT* gene in parental HeLa cells, which have no GJIC ability, and in HeLa cells in which GJIC was restored by transfection with the connexin 43 gene. When HeLa cells with ($Cx43^+$) or without Cx43 gene ($Cx43^-$) were treated with MNNG or *N*-methyl-*N*-nitrosourea (MNU), the $Cx43^+$ cells survived better than $Cx43^-$ cells.

Microsatellite instability was measured with shuttle vector; in the vector, the coding region of the β-galactosidase gene was rendered out of frame by insertion of CA-repeats and the frame could be restored by inserting or deleting mutations of the CA-repeats. The mutation frequency of CA-repeats in $Cx43^+$ cells was only half of that in $Cx43^-$, both before and after exposure to MNNG or MNU ($p < 0.05$). The frequency of spontaneous *HPRT* gene mutations, selected by resistance to 6-thioguanine, was three-fold lower in $Cx43^+$ than in $Cx43^-$ cells. Similarly, the frequency of MNNG-induced *HPRT* mutations was significantly higher in $Cx43^-$ cells ($p<0.001$). Similar results were obtained even when the mutant selection process was carried out in the presence of α-glycyrrhetinic acid, a long-term inhibitor of GJIC, suggesting that the effect is not due to unwanted killing of cells by GJIC-mediated metabolic cooperation.

Thus, our data demonstrate that HeLa cells transfected with the Cx43 gene become more resistant to spontaneous as well as chemically-induced genetic changes [519].

4.6 Genomic integrity and cancer

Tumour development involves several genetic and epigenetic changes, including oncogene activation, repression of tumour suppressors and chromosomal translocation and deletion. Numerous studies have pointed out the importance of genomic integrity in human disease and tumour development and much effort has therefore been made to elucidate the involvement of molecules which play a role in chromatin functions, such as DNA repair and recombination, in pathological conditions. The aim of our studies is to investigate the function of certain such molecules in genomic integrity and their relation to cancer and disease susceptibility. To address these questions we are taking a genetic approach by generating and using gain-of-function and loss-of-function mutations in cells and animals.

4.6.1
The function of poly(ADP-ribose) polymerase (PARP)

Z.-Q. Wang; in collaboration with C. Morrison, L. Stingl and . F. Wagner, M. Jantsch, Vienna, Austria; H. Kolb. Düsseldorf, Germany; T. Dawson, Baltimore, MD, USA; and M. Moskowitz, Boston, MA, USA

PARP is a very abundant (10^6 molecules/cell), chromatin-associated protein and catalyses poly-ADP-ribosylation of nuclear proteins following DNA damage, which modulates chromatin functions. This enzyme is thought to play a role in numerous cellular processes, such as cell death, proliferation, DNA repair and recombination, as well as genomic stability. After cells are exposed to ionizing radiation, alkylating agents or free radicals, PARP binds to DNA strand breaks and undergoes rapid automodification , leading to the formation of long, branched poly -(ADP-ribose) structure s. Negatively charged PARP subsequently dissociates from DNA ends, facilitating the DNA repair process. To elucidate the function of PARP in these processes, mice lacking the corresponding gene were generated. While young PARP –/– mice display no phenotypic abnormalities, older mice originating from a mixed genetic background (129/Sv × C57BL/6) are suscep -

tible to epidermal hyperplasia and obesity. However, mutant mice are resistant to skin papilloma induction by 7,12-dimethylbenzanthracene with *O*-tetradecanoylphorbol 13-acetate (TPA).

In an attempt to better define the consequences of lacking PARP in mice, we studied various chromatin functions using mutant cells and mice. PARP–/– fibroblasts grow more slowly *in vitro*, an effect which is more pronounced at 39°C than at 37°C, implying that a lack of PARP either affects cell proliferation or sensitizes the cells to experimental stress. This effect on cell proliferation was also observed *in vivo* in chimeric fetuses generated by aggregating wild-type and mutant embryos. The role of PARP in free radical-induced pancreatic cell toxicity was studied in collaboration with H. Kolb's laboratory using PARP–/– mice. Mutant pancreatic islet cells are resistant to free radical-induced cell lysis and mice lacking PARP are protected from streptozotocin (SZ)-induced diabetes, indicating that pancreatic cell death and streptozotocin-induced diabetes are mediated by activation of PARP. In collaboration with groups of T. Dawson and M. Moskowitz, we have further demonstrated that *N*-methyl-D-aspartate/glutamate-mediated neurotoxicity is also mediated by PARP activation.

Since PARP is thought to play a role in DNA repair, recombination and chromosomal stability, we examined immunoglobulin (Ig) class switch and V(D)J recombination of T-cell receptors as well as chromosomal recombination by examining sister chromatid exchange (SCE). While PARP–/– mice carry out normal Ig class switching and V(D)J recombination, they exhibit high levels of spontaneous SCE, an indication of an increased rate of chromosomal recombination. These results suggest that PARP functions as an anti-recombinogenic molecule. In addition, mutant cells contain more micronuclei following treatment with γ-radiation and mitomycin C, demonstrating a role for PARP in maintaining genomic integrity (Figure 40).

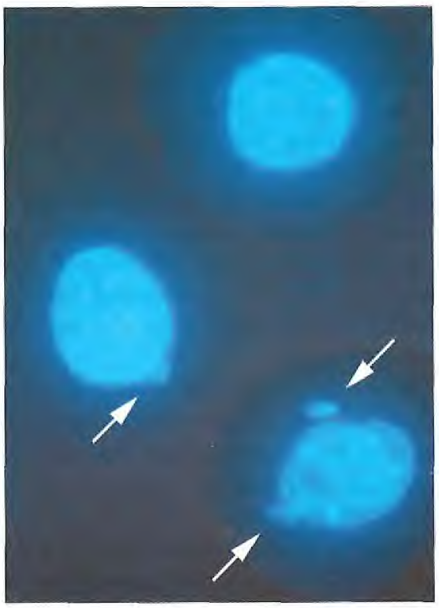

Figure 40. Mice lacking PARP exhibit high levels of formation of micronuclei (arrows) following γ-irradiation, indicating an unstable genome

4.6.2
Role of PARP in apoptosis

Z. Herceg and Z.-Q. Wang; in collaboration with K. Schultz-Osthoff, Tübingen, Germany

Apoptosis, or programmed cell death, is an essential process in development and tissue homeostasis of multicellular organisms. Although the apoptotic process can be initiated by different physiological and pathological stimuli, all apoptotic cells undergo similar morphological and biochemical changes. It has been shown that the ICE/CED-3 family of cysteine proteases (termed caspases) are key players in apoptosis, presumably through their proteolytic action on specific targets. A common target of several caspases is the nuclear enzyme PARP. Upon treatment with tumour necrosis factor α (TNF-α) or anti-Fas antibody, cas-

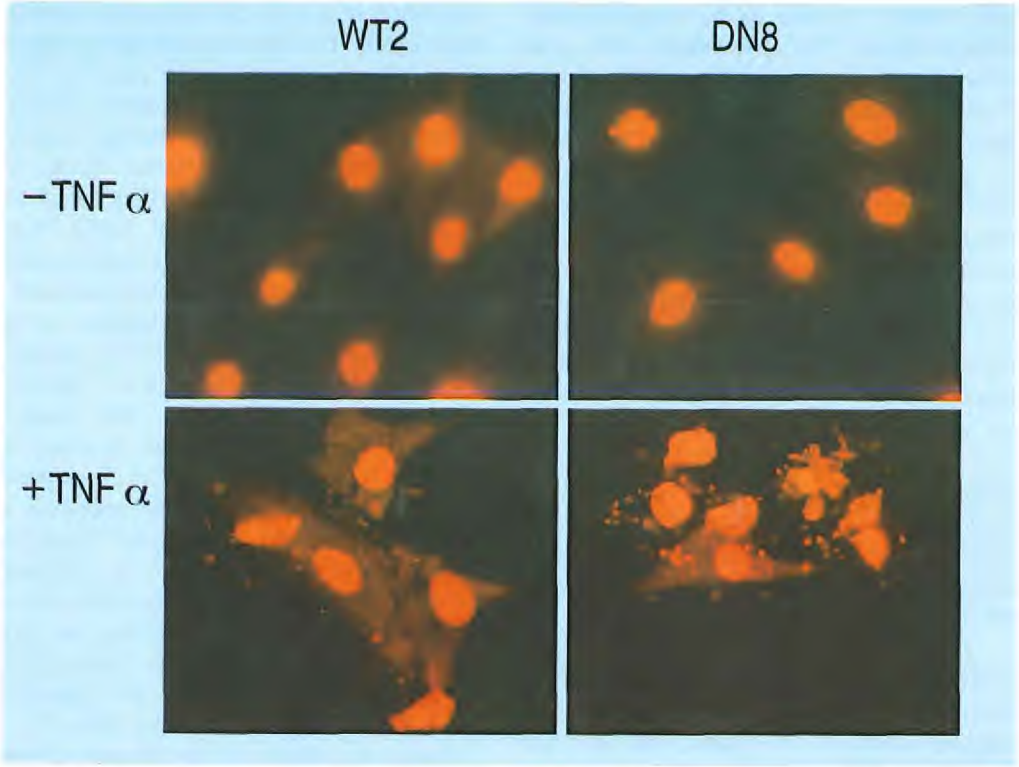

Figure 41. Apoptotic response of cells expressing wild-type (WT2) or caspase-resistant PARP (DN8). Cells were either treated or untreated with TNF-α in the presence of actinomycin D and analysed for nuclear fragmentation by staining with propidium iodide.

pase-3 specifically cleaves PARP between Asp214 and Gly215, resulting in the separation of the two zinc finger DNA-binding motifs from its C-terminal catalytic domain and functional inactivation of the enzyme. The proteolytic cleavage of PARP occurs during an active phase of apoptosis, suggesting that PARP may play a role in this process.

To study the role of PARP in apoptosis, we treated cells isolated from PARP–/– mice with various apoptotic agents. PARP–/– fibroblasts had the same sensitivity to TNF-α and anti-Fas antibody as wild-type controls. While lymphoid cells treated with γ-radiation and dexamethasone exhibited normal apoptotic response, PARP–/– mice were hypersensitive to high doses (8 Gy) of whole-body radiation. These results indicate that PARP is dispensable in the apoptotic cascade mediated by TNF-α and anti-Fas antibody, but suggest that it is important for recovery from γ-irradiation in certain cell types.

However, why PARP has to be cleaved during apoptosis is not known and cannot be addressed using PARP–/– cells. To answer this question, we have generated a vector expressing a mutant PARP which is resistant to caspase-3 proteolysis, and transfected it into PARP–/– cells. The apoptotic response to various stimuli in cells expressing exogenous PARP (wild-type or mutant) was examined by flow cytometry, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling (TUNEL) analysis and

MTT assay, as well as by morphological change (Figure 41). The results show that cells expressing cleavage-resistant mutant PARP exhibit an enhanced apoptotic response to TNF-α treatment. Since PARP can be activated by DNA breaks, which use NAD+ to form (ADP-ribose) polymers resulting in depletion of the ATP pool in cells, we hypothesized that this enhanced apoptosis might be due to NAD+ depletion. Cells expressing wild-type and caspase-resistant PARP were treated with TNF-α together with 3-aminobenzamide, an inhibitor of PARP, and exhibited no difference in their apoptotic profile, indicating that the enhanced apoptosis is indeed due to NAD+ depletion. This was confirmed by measurement of intracellular NAD+ levels in these cells, showing that cell death correlated with the drop of NAD+ content.

These results suggest that PARP cleavage plays an inhibitory role in execution of the apoptotic programme and that caspase cleavage of PARP, and perhaps other substrates, is a step in a programmed and concerted process in multicellular organisms, in which different molecules have to be inactivated in order to complete the process. Therefore, an *in vivo* model in which cleavage-resistant PARP is expressed in different tissues would be useful to elucidate the function of this cleavage.

4.6.3
Interaction of PARP and DNA-dependent protein kinase in T cell development and tumorigenesis

Z.-Q. Wang; in collaboration with S. Jackson, Cambridge, UK; and C. Morrison, L. Stingl and E.F. Wagner, Vienna, Austria

PARP and DNA-dependent protein kinase (DNA-PK) are DNA break-activated molecules. Although mice lacking PARP display no gross phenotypic abnormality and normal DNA excision repair, they exhibit high levels of sister chromatid exchange, indicative of a high chromosomal recombination rate. The DNA end-binding activity of PARP suggests that its role in DNA rearrangement may be mediated through interplay with other end-binding proteins such as DNA-PK. A mutation in the C-terminal end of the kinase domain of the catalytic subunit of DNA-PK (DNA-PKcs) leads to defective processing and rejoining of V(D)J recombination intermediates and a block in B and T cell development in the murine SCID mutant. SCID V(D)J recombination can be partially rescued in T lymphocytes by either γ-irradiation or null mutation of the *p53* gene putatively due to either the elevated recombination activity in response to radiation or to the delayed apoptosis of p53-deficient SCID thymocytes. Since the absence of PARP results in increased chromosomal rejoining, we speculate that its absence might lead to processing and ligation of V(D)J recombination intermediates that accumulate in SCID. We generated mice lacking both PARP and DNA-PK to examine the effects of the absence of both activities. These animals, though fertile, showed a marked perinatal mortality and size reduction compared to littermates. We analysed lymphoid development of PARP–/– SCID mice. While double mutant B cells failed to develop further than in SCID animals, up to 50% of total thymocytes were positive for both CD4 and CD8 coreceptor molecules (Figure 42), indicating a bypass of the SCID block in T cells. This was only a partial rescue, as these thymocytes failed to express the mature CD3 marker and surface T cell receptor (TCR), while TCRγ sequences showed SCID-like joins. In lymph nodes of six-week-old double mutant mice, we found CD4 and CD8 single positive cells expressing the mature CD3 marker and TCRβ, indicating increased levels of recombination, leading to productive TCRβ joins, and that PARP acts as an anti-recombinogenic factor. In addition, a high frequency of T-cell lymphoma developed in double mutant mice, suggesting that DNA-PK has a

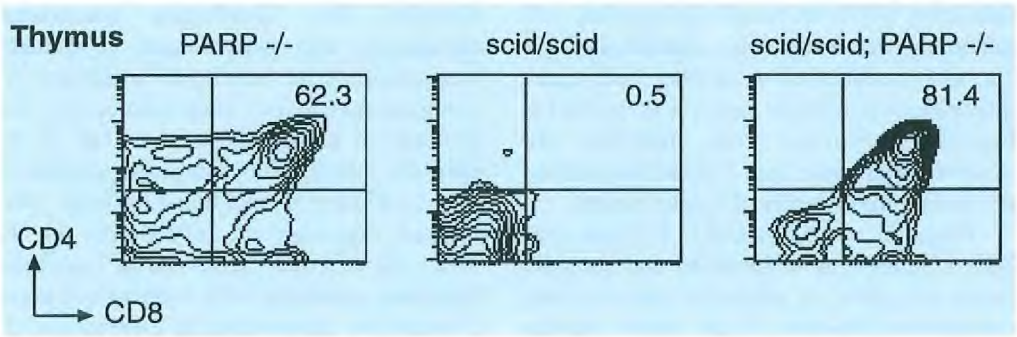

Figure 42. Mice lacking both PARP and DNA-PK activity (PARP-/- SCID) have partially rescued T cell development, as demonstrated by FACS analysis showing the appearance of thymocytes expressing both CD4 and CD8 coreceptors

tumour-suppressor function which is potentiated by the absence of PARP.

In summary, these results demonstrate genetic and biochemical interactions between PARP and DNA-PK in T-cell and lymphoma development and suggest that PARP and DNA-PK act in a coordinated manner to minimize genomic damage caused by DNA strand breaks.

4.6.4
Cooperation between c-fos and junB in tumour development

W. Hulla and Z.-Q. Wang; in collaboration with H.-C. Theussl and E.F. Wagner, Vienna, Austria

Overexpresssion of c-*fos* in transgenic mice results in a high frequency of osteosarcoma formation, whereas overexpression of other members of the transcription factor complex AP-1, such as c-*jun*, *jun*B or *fos*B, does not produce a distinct phenotype. Previous studies demonstrated specific cooperation between c-*fos* and c-*jun* in tumorigenesis, resulting in enhanced osteosarcoma development compared to c-*fos* single transgenic mice and in transformation of osteoblasts and/or cells interactive with osteoblasts. To study the cooperative effect of c-*fos* with another *jun*-related gene, namely *jun*B, in oncogenesis *in vivo*, we generated mice overexpressing both proto-oncogenes. These animals develop osteosarcomas at a similar frequency to c-*fos* single transgenic mice but additionally display nodal tumours in the tail and other soft tissues from 3–4 weeks of age. Palpatory and radiological examination as well as morphological and histological analysis revealed that the tumours were fibrous with an additional osseous component, implying that the overexpression of *jun*B together with c-*fos* transforms not only osteoblasts but also, perhaps, a cell type from a different cellular compartment. Cell lines have been established from these tumours to be used in studying the molecular basis of cooperation between c-*fos* and *jun*B in tumorigenesis.

4.7 Role of p53 in carcinogenesis

The *p53* tumour-suppressor gene encodes a nuclear phosphoprotein with cancer-inhibiting properties. The development of human cancer often involves inactivation of this suppressor function through a mechanism such as loss of alleles at the *p53* locus (on 17p13), deletions, insertions, point mutations or silencing of the p53 protein by complex

formation with viral or cellular proteins. *p53* mutations frequently arise somatically, but may also be inherited in families with a predisposition to multiple cancers, as in the Li-Fraumeni syndrome. Point mutations are scattered over more than 250 codons and are common in most forms of human cancer.

Research on *p53* at IARC includes analysis of mutations in inherited and sporadic forms of cancer, in particular cancer of the oesophagus (Section 3.1.1), brain, bladder (Section 2.4.7), skin (Section 3.9.2) and oral cavity (Section 3.8.4) and vinyl-chloride-induced tumours (Section 2.2.8), as well as studies on p53 protein structure, function and regulation, in particular in relation to cellular response to DNA damage (Section 4.1) and to the action of nitric oxide (Section 4.3.8). A database of *p53* mutations in human cancers is maintained.

4.7.1

Tumours associated with *p53* germline mutations

P. Kleihues, J. Estève, P. Hainaut, T. Hernandez and H. Ohgaki; in collaboration with B. Schäuble and A. zur Hausen, Zürich, Switzerland

Analysis of 551 tumours in 108 families with *p53* germline mutations reported in 1990–96 shows that breast carcinomas are most frequent (24.0%), followed by bone sarcomas (12.6%), brain tumours (12.0%), and soft-tissue sarcomas (11.6%). The sporadic counterparts of these tumours also carry a high incidence of *p53* mutations, suggesting that in these tissues *p53* mutations are capable of initiating the process of malignant transformation. Of the 67 brain tumours recorded, 40 (59.7%) were histologically classified and of these, 31 (77.5%) were of astrocytic origin, including low-grade astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, oligo-astrocytoma and gliosarcoma. Paediatric brain tumours, i.e., medulloblastomas and related primitive neuroectodermal tumours (PNET), were less frequent. This distribution corresponds remarkably well to that seen in sporadic brain tumours, in which *p53* mutations are common in astrocytic brain tumours and less frequent in medulloblastomas. Half of the families fulfilled the diagnostic criteria of the Li–Fraumeni syndrome. There were marked organ-specific differences in the mean age at which carriers of *p53* germline mutations presented with neoplastic disease: 5 years for adrenocortical carcinomas, 16 years for sarcomas, 25 years for brain tumours, 37 years for breast cancer and almost 50 years for lung cancer. Analysis of the mutational spectrum showed a predominance of G:C→A:T transitions at CpG sites, suggesting that the mutations were of endogenous origin (e.g., due to deamination of 5-meC), rather than induced by reactions with environmental mutagenic carcinogens. The location of mutations within the *p53* gene is similar to that of somatic mutations in sporadic tumours. There is no evidence of organ- or target cell-specificity of *p53* germline mutations; the occasional familial clustering of certain tumour types is more likely to reflect the genetic background of the respective kindred or the additional influence of environmental and non-genetic host factors [196, 310].

4.7.2

Regulation of conformation and activity of the p53 protein by redox factors, metal compounds and cytokines

P. Hainaut, Y. Furukawa, C. Méplan, G. Luciani, F. El-Ghissassi and G. Martel-Planche; in collaboration with M.J. Richard, Grenoble, France; and K. Vähäkangas, Oulu, Finland

The p53 protein is a transcription factor which regulates the expression of target genes by specifically binding to DNA through a highly flexible protein domain which is stabilized by the binding of zinc on conserved cysteine residues. *In vitro*, remo-

val of zinc by chelation led to loss of DNA-binding capacity and induced p53 to adopt a conformation similar to that of many p53 mutants. Using cell-permeant metal chelators, we have shown that modulation of the intracellular availability of zinc can also regulate p53 conformation and activity in intact cells. Moreover, dithiocarbamates down-regulated the activity of p53 by increasing the level of intracellular copper ions, an observation that suggests that p53 is controlled by complex metallo-regulatory interactions in intact cells [480].

To further analyse the role of metals and reactive oxygen species in p53 regulation, we have studied the effects of cytokines, such as TNF-α, that induce intracellular production of free radicals. At physiological concentrations, TNF-α induced low levels of DNA-damage, leading to p53 activation; this process could be blocked by several anti-oxidants. In another study (in collaboration with S. Calmels and H. Ohshima), p53 was found to be activated by low concentrations of nitric oxide, but inhibited at higher concentrations, probably as a result of p53 oxidation. These results indicate that free radicals are involved at different levels in the control of p53 functions [53].

We are currently analysing the effects of toxic metals on the functions of wild-type p53. Toxic metals such as cadmium can compete with physiological copper and zinc and alter a number of redox-regulated and metallo-regulated intracellular processes. Exposure to low concentrations of cadmium significantly altered p53 protein conformation and activity, and prevented p53 activation by DNA-damaging agents. We are now studying whether down-regulation of p53 protein activity plays a role in mechanisms of cadmium-induced carcinogenesis.

In the long-term, metal and redox regulation of p53 may be useful for pharmacological control of p53 activity, in particular in early cancer lesions that may express non-mutated *p53* genes. As a first step towards

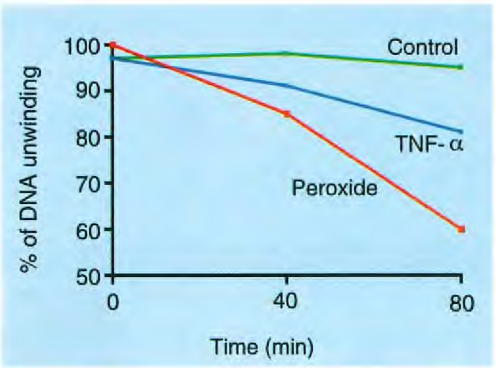

Figure 43. Induction of DNA-damage by TNF-α. The proportion of single and double DNA strand breaks was estimated by alkaline unwinding assay in MCF-7 cells exposed to TNF-α hydrogen peroxide or untreated

investigating this possibility, we have demonstrated that the redox-active compound amifostine can functionally activate wild-type p53. This molecule is known for its radio-protective and anti-mutagenic properties. Our results suggest that these properties may be mediated, at least in part, by p53.

4.7.3
IARC database of somatic p53 mutations in human cancers

P. Hainaut, T. Hernandez, D. Goldgar and R. Montesano; in collaboration with C.C. Harris, Bethesda, MD, USA; M. Hollstein, Heidelberg, Germany; and T. Flores, A. Robinson and P. Rodriguez-Tomé, Hinxton, UK

Since the first identification of tumour-specific mutations in human cancers in 1989, more than 7000 p53 mutations in various human cancers have been reported. A database maintained provides links between specific mutations, cancer pathologies and, depending of the amount of information available, exposure to specific risk factors. Over the past two years, we have undertaken a major effort to re-construct the database, to improve its quality, to develop its links with other genetic databases and to add reliable pathological and epidemiological informa-

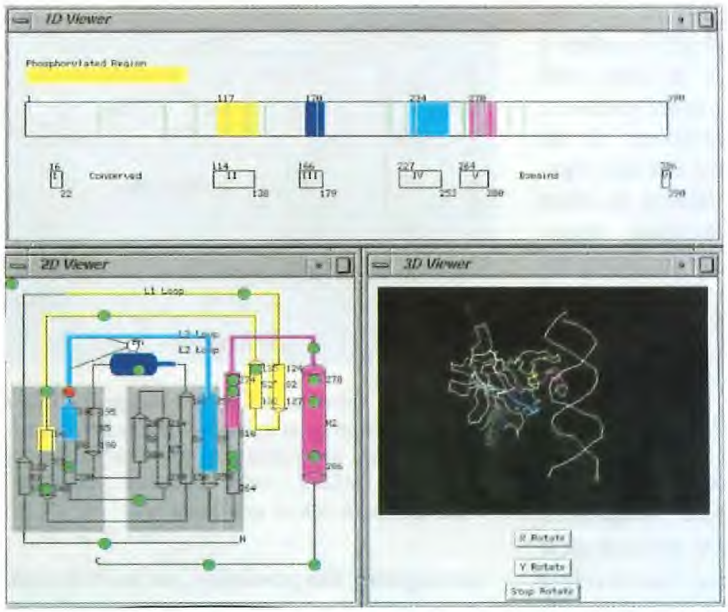

Figure 44. Mutation viewer for visualization on Internet of data from the p53 mutation database
The viewer allows sorting and retrieval of mutations from the database, and shows their location in the primary, secondary and tertiary structure of the p53 protein. This example shows the distribution of mutations in tumours from ex-tobacco smokers

tion. The p53 mutation database is now available in several electronic formats at URL http://www.iarc.fr/p53/homepage.htm [136] (Figure 44). The July 1997 release of the database contains 6800 somatic mutations. In parallel, a database of germline p53 mutations, developed by P. Kleihues and H. Ohgaki, is also maintained. Using protein visualization programmes, we are now developing strategies to analyse the impact of mutations on the structure and functions of the p53 protein.

4.8 Telomerase

The ribonucleoprotein telomerase is an RNA-dependent DNA polymerase that catalyses addition of telomeric repeats $(TTAGGG)_n$ to telomeric DNA termini using a segment of its endogenous RNA component as a template (Greider *et al.*, 1996, *Sci. Amer.*, **274**, 92–97). Approximately 90% of a series of over 1000 human tumour biopsies were found to be telomerase-positive (Kim *et al.*, 1994, *Science,* **266**, 2011–2015). Telomerase activation plays a crucial role in genome stability from yeast to humans, but regulatory aspects of this activation *in vivo* are poorly understood. We are therefore investigating various aspects of this problem. Studies on telomerase activity in skin cancer are reported in Section 3.9.3.

4.8.1
Role of telomerase in carcinogenesis

H. Nakazawa, M. Kallassy and N. Martel; in collaboration with A. Schneider, Jena, Germany; and T. Saito, Sapporo, Japan

We have investigated telomerase activity in the endometrium [380]. Telomerase

activity was detected in normal endometrium, in association with proliferation, and regulated the menstrual cycle in a hormone-dependent manner. The activity was maximal at the late-proliferative phase to mid-secreting phase, and was absent or extremely low at the early-proliferative and late-secreting phases. Activity was also detected in all endometrial simple hyperplasias tested (16 of 16) and in most cancers (17 of 18 G1, 6 of 7 G2, 4 of 4 G3 adenocarcinomas and 1 of 1 adenosquamous carcinoma), but none was detected in endometrium of either pregnant or postmenopausal women in the absence of hyperplasia (Figure 45). Our data provide evidence that telomerase activity in postmenopausal endometrium reflects a hyperproliferative condition, and we conclude that telomerase may provide a marker for early endometrial cancer diagnosis.

Human telomerase RNA component (hTR) is a major regulator of telomerase function. We have cloned the 5′-flanking region of hTR by the genomic RACE (rapid amplification of cDNA ends) method. Examination of the genomic DNA sequence revealed the presence of putative promoter sequences. The region required for the basal level of hTR promoter activity is located between bases –225 and –1. Among many interesting putative regulatory elements found in the 5′-flanking sequence, we identified a functional progesterone receptor binding motif. Overexpression of the exogenous progesterone receptor gene (*PR*) strongly suppressed telomerase activity and growth of the telomerase-positive breast cancer cell line MCF7 and the endometrial cancer cell line, Ishikawa. These data suggest that *PR* can directly regulate the expression of hTR and subsequently control telomerase activity and tumour cell growth. These results also indicate the existence of cis-acting element(s), such as *PR*, responsible for selective regulation of the hTR promoter only in cells that express hTR mRNA; they suggest a molecular basis for regulation of hTR gene expression that could control telomerase function.

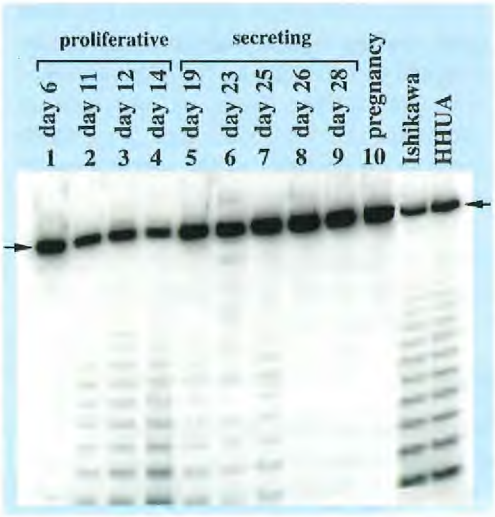

Figure 45. Telomerase activity in normal endometrium of regular menstrual cycle (lanes 1-9) and in the 14th week of pregnancy (lane 10). The series of bands below the internal control (arrow) indicate telomerase activity. Thus, we defined lanes 2, 3 and 4 as positive for telomerase activity, lanes 5, 6 and 7 as weakly positive and the others as negative.

4.9 *The cytochrome P450 (CYP) enzyme system*

CYP genes coding for cytochrome P450s are a superfamily of genes regulating the expression of enzymes that oxidize xenobiotics, including those that convert procarcinogens to their ultimate carcinogenic forms. The expression of *CYP* genes is regulated by environmental and genetic factors and most, if not all, have individual patterns of regulation. For each enzyme, either genetic polymorphism or wide inter-

individual variation in expression has been found, leading to great individual differences in capacity to generate carcinogenic metabolites. Our studies focus on enzymes of subfamilies 1A, 2A, 2E, and 3A, which appear to be essential in the metabolism of several important carcinogens.

Studies on the relation of cytochrome P450s to pareticular exposures or cancer sites are described in Sections 2.2.6, 3.1.2, 3.3.3, 3.6.3 and 4.4.9.

4.9.1

Structure–activity relationships

M. Lang; in collaboration with R.O. Juvonen, Kuopio, Finland; and M. Negishi, Research Triangle Park, NC, USA

A series of engineered proteins related to CYP2A enzymes, with highly similar structures, were produced by recombinant gene technology, in order to analyse in detail how homologous enzymes activate carcinogens such as aflatoxin B_1. It was shown that minor structural differences may lead to major differences in the catalytic properties. Thus, although highly similar CYP enzymes are expressed in different species, great differences may exist in their capacity to activate carcinogens. This may apply even to human populations with, for example, different ethnic backround and variability in the profile of CYP expression.

4.9.2

Expression of cytochromes P450 in liver injury and inflammation

M. Lang, A. Camus, A. Ellul and F. Raffalli; in collaboration with S. Sataruq, Khon Kaen, Thailand

4.9.2.1

Studies with experimental animals

In continuation of our previous experiments, we have shown that liver injury caused by toxic chemicals of various types or by viral or parasitic infestation induces CYP2A5 and to a lesser extent CYP1A2. As a result, the role of these enzymes in carcinogen metabolism may increase in certain pathological conditions. These findings could explain in part the synergistic effect of aflatoxin B_1 in hepatitis virus-induced hepatocarcinogenesis and the suggested role of nitrosamines in parasite-induced cholangiocarcinoma, as these carcinogens are good substrates of the two enzymes. They may also provide a mechanistic explanation for the cocarcinogenic effects of several hepatotoxins [56, 74, 205].

4.9.2.2

Studies on humans

The results obtained with experimental animals have been confirmed in humans. In a Thai population of 106 individuals, the level of induction of the CYP2A6 (orthologous to CYP2A5 in mice) was directly proportional to the degree of infestation by the liver fluke *Opisthorchis viverrini* and was stronger in males than in females [412]. These results are consistent with the hypothesis proposed above and the fact that *O. viverrini* infection in combination with nitrosamines may contribute to the high incidence of cholangiocarcinoma in parts of Thailand (Srivatanakul *et al.*, 1991, *Int. J. Cancer*, **48**, 821–825). In relation to this study, a genetic polymorphism of the CYP2A6 gene was discovered that results in inactivation of the enzyme in about 5–7% of the population. This observation provides a basis for further studies on how the modified genotype of CYP2A6 affects the enzyme activity *in vivo* and how this gene may contribute to hepatocarcinogenesis.

In our latest experiments, we have found a clear interdependence of glutathione *S*-transferase (GST) polymorphism and expression of CYP2A6 in inflamed liver, so that among subjects lacking GST, the induction of CYP2A6 is stronger. This suggests that GST somehow contributes to

the regulation of CYP2A6 by eliminating regulatory factors. This appears to be the first example of such interdependence of GST and CYP enzymes.

4.9.3
Mechanism of regulation

M. Lang, A. Ellul and F. Raffalli

We have shown that post-transcriptional events such as mRNA stabilization are important in the regulation of CYP2A5, in addition to its transcriptional control. We have also demonstrated that the 3′-untranslated region of the CYP2A5 mRNA forms a typical hairpin loop structure which is a specific binding site of a previously unknown 44 kDa protein. The mRNA binding of this protein is upregulated by at least some hepatotoxins and it appears that the increased binding is associated with increased stability and processing of the CYP2A5 mRNA. It is possible therefore that this 44 kDa protein plays an important role in the post-transcriptional control of the CYP2A5 gene [120]. Using a high-resolu tion gel, we have now identified several proteins possibly contributing to the stability and processing of the mRNA. Some of these also seem to interact with c-*jun* mRNA, an oncogene also responding to various forms of stress. With primary hepatocytes in culture, we have demonstrated that there is an interdependence between the transcriptional and post-transcriptional control of the CYP2A5 gene. If transcription is stopped, expression is maintained through increased mRNA stabilization.

In further experiments, we have obtained evidence that, as for CYP2A5, the 3′-untranslated region of CYP1A2 may also be important for its regulation. Two proteins, one of which seems to be related to hnRNPc, have been identified binding to the 3′-untranslated region of the CYP1A2 mRNA. The proteins compete for the binding and their binding profile is changed by 3-methylcholanthrene, an inducer of the CYP1A2 gene.

PART 5. PREVENTION AND EARLY DETECTION OF CANCER

5.1 Studies of primary prevention of cancer

Primary prevention of cancer covers all interventions aimed at preventing initiation of carcinogenesis, by either removing exposure to a carcinogenic agent or inducing mechanisms to counteract the effect of such exposure, for example by vaccination or by administration of a protective chemical substance (chemoprevention). In general, prevention of exposure to a carcinogen will always be beneficial, but it is still important to evaluate the extent of the benefit. In contrast, administration of a foreign substance, or of a natural substance in unnatural quantities, may well lead to undesirable side-effects that can negate any cancer-preventive benefit. It is therefore particularly important that such interventions are subjected to very careful scrutiny at all stages of their planning and implementation.

The first intervention study aimed at assessing the use of vaccines in cancer prevention was initiated 10 years ago in The Gambia, to evaluate the effectiveness of hepatitis B vaccination in the prevention of liver cancer. Similar intervention studies to assess the effectiveness of HPV vaccines, now under development, in the prevention and treatment of cervical neoplasia, are being planned.

Chemoprevention trials to evaluate the effect of antioxidant vitamins in prevention or regression of precancerous lesions of the stomach and of the oral cavity are in progress in Venezuela and India.

5.1.1
The Gambia Hepatitis Intervention Study

A.D. Jack, N. Maine, E. Bah, M. Mendy, J. Estève, G. Kirk and R. Montesano; in collaboration with H.C. Whittle, Fajara, Gambia; C.P. Wild, Leeds, UK; and A.J. Hall, London, UK

This longitudinal intervention study was launched in July 1986, with the aim of evaluating the effectiveness of hepatitis B vaccination in preventing the persistence of hepatitis B viral infection and the occurrence of chronic liver disease and hepatocellular carcinoma in a population at high risk. Over a four-year period, 124 577 children were recruited in two cohorts of vaccinated and unvaccinated groups. The incidence of the disease sequelae of HBV infection is being monitored in these children over a 35-year period in order to provide proof of the net effect of vaccination in disease prevention.

The study is being conducted in collaboration with the Government of The Gambia and the Medical Research Council of the United Kingdom. It is funded by the Direzione Generale per la Cooperatione allo Sviluppo of the Ministry of Foreign Affairs, Italy, the Swedish Medical Research Council and the Regione Autonoma Valle d'Aosta, Italy.

5.1.1.1
Monitoring the effect of HBV vaccination

A group of 1041 children (Group 1) who received hepatitis B vaccine in infancy have been followed up periodically over the past ten years in order to monitor the levels of antibody and the duration of protection against persistent infection. These children were selected from the first four centres to add hepatitis B vaccine to the existing schedule of the extended programme of immunization (EPI).

The ninth-year follow-up of these children was concluded in July 1996, when 65%

Table 8. Hepatitis B viral infection status of the unvaccinated sub-set in the first nine years of follow-up.

	HBsAb+ [a] HBcAb−	HBsAb− HBcAb−	HBsAb+ HBcAb+	HBsAb− [b] HBcAb+	Total
1st year	716 (94)*	11 (1)	33 (4)	4 (0.5)**	764
2nd year	664 (95)	27 (4)	8 (1)*	4 (0.6)**	703
3rd year	655 (93)	30 (4)	13 (2)*	6 (0.9)****	704
4th year	659 (91)	27 (4)	29 (4)**	4 (0.6)**	721
5th year	622 (84)	80 (11)	27 (4)	11 (1.5)****	740
7th year	479 (68)	178 (25)	28 (4)*	19 (2.7)***	704
9th year	425 (63)	194 (29)	37 (5.5)*	19 (2.8)*****	675

* The number of asterisks indicates the number of children positive for HBsAg
[a] HBsAb+: titres < 10mIU/ml; [b] HBsAb−: titres < 10 mIU/ml.

of all recruited children were traced and bled. While the majority of the children still showed protective levels of antibody, there is continued evidence of progressive antibody decay, a trend which is expected as the children grow older (Table 8). The frequency of exposure to HBV infection (core conversion) continues to increase with age. Fifty-six of the 675 children (8.3%) core-converted at year nine, with 37 of these children still showing apparently protective levels of antibody. Among children who were bled in both years 7 and 9, there were 22 new infections (3.3%), 17 of which occurred in the face of HBsAb titres in excess of 10 mIU/ml. Despite this evidence of continued exposure to infection, 92% of the children are still free of infection with HBV. Six of the 675 children (0.9%) tested HBsAg-positive. Four of these children tested positive for the first time sometime between the 7th and 9th year bleeds. The other two children have been confirmed chronic carriers since the age of three years. All children who tested HBsAg-positive or only core-converted at the time of the ninth year bleed were followed up one year later, firstly to confirm persistence of the infection, and secondly to investigate the possible occurrence of HBV variants as apart of the mutant study Two of the four children who were newly HBsAg-positive showed no evidence of surface antigenaemia a year later. Transient antigenaemia is not an unusual occurrence, although laboratory error cannot be excluded.

A second group of children (Group 2), consisting of randomly selected children aged between 8 and 9 years who had not received hepatitis B vaccine in infancy, were screened for evidence of infection. The aim was to describe the natural occurrence of hepatitis B infection among the unvaccinated members of the GHIS cohort and thereby estimate vaccine efficacy in the short term. 823 children were recruited, of whom 50% showed evidence of past exposure to

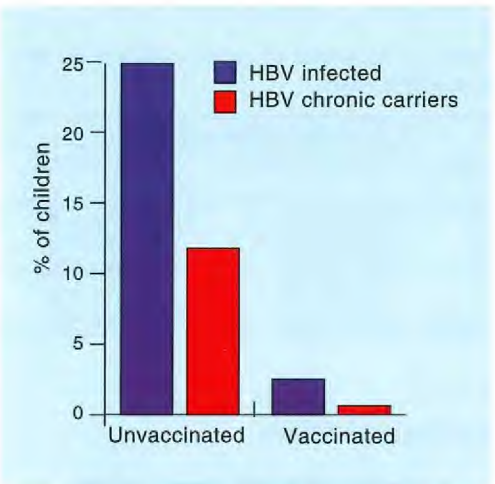

Figure 46. HBV status of Gambian children nine years after vaccination began

Table 9. Hepatitis B viral infection and chronic carriage in 8–9 year-old children not vaccinated against HBV

Zone	Number	Uninfected (%)	Infected (%)	Chronic carriers (%)[a]
1	205	97 (47)	108 (53)	17 (8)
2	207	117 (56)	90 (43)	19 (9)
3	209	101 (48)	108 (52)	22 (11)
4	202	99 (49)	103 (51)	27 (13)
Total	823	414 (50)	409 (50)	85 (10)

[a] 4 children lost to follow-up, one in area 1 and three in area 4, were not included in this group.

hepatitis B infection and 12% tested HBsAg-positive (Table 9). The 99 children who tested HBsAg-positive were followed up one year later. Serum samples were obtained from 95 of these children, of whom 90% showed persistence of surface antigenaemia.

Comparison of the rates of infection and of chronic carriage in the two sub-sets of the GHIS cohort shows that by age 10 years, the levels of vaccine efficacy in prevention of HBV infection and the carrier state were 83% and 94%, respectively (Figure 46 and Table 10).

Neither of these two indices has changed since the first estimates of efficacy were made when these children were four years old. This serves to confirm that it is earlier infections which are more likely to lead to persistence of the virus, and hence present greater risk of disease in later life.

Table 10. Estimates of vaccine efficacy by zone at age nine years.

Zone	% vaccine efficacy (95% CI)	
	Against infection	Against chronic carriage
1	93 (84–97)	100 (68–100)
2	77 (64–86)	87 (47–97)
3	83 (72–90)	100 (80–100)
4	79 (68–87)	92 (66–98)
Total	83 (78–87)	94 (84–98)

5.1.1.2

Cancer registration

A population-based cancer registry was launched at the beginning of the GHIS, with the primary aim of monitoring the occurrence of primary liver cancer in The Gambia, so as to provide the basis for future evaluation of the effect of vaccination on the incidence of this tumour in the Gambian population. Since then its role has been expanded to include all other types of cancer. Ten years of data on the incidence of different forms of malignancy are now available through the cancer registry. Liver cancer continues to be the most commonly reported malignancy in males and is a close second to cervical cancer in females. Attempts continue to be made to strengthen the reporting system through regular visits to all units. One registry clerk is now based at each of the two government hospitals which are the main sources of cancer reports. This redeployment of staff has served to improve contact with reporting medical officers, as well as to improve the interview rates of patients in hospital. Support for histopathology and ultrasonography continues to be maintained through regular replenishment of consumables.

5.1.1.3

Ancillary studies

There is continued interest in investigation of occurrence of mutant hepatitis B viruses since the discovery of a novel virus in two children in the village of Manduar. The possibility that genomic changes may enable the virus to escape neutralization by the current vaccine type is of serious public health concern and warrants continuous

monitoring. GHIS continues to collaborate with the MRC and School of Veterinary Medicine, London, UK, in this investigation. The surveillance for jaundice in the Gambian population was discontinued after two years, on the recommendation of the Steering Committee which met in Lyon in February 1996. Although surveillance was well established in the Bakau area through the participation of a well known herbalist, it could not be extended to the rest of the country due to unreliable reporting. The second case–control study to evaluate the etiology of primary liver cancer was launched in January 1997, with funding from the US National Cancer Institute. The study will investigate the effect of exposure to aflatoxin and possible interactions between hepatitis B, C and G viruses in liver carcinogenesis.

5.1.2 Chemoprevention trial on precancerous lesions of the stomach in Venezuela

N. Muñoz, M. Plummer, C. Lavé and D. Magnin; in collaboration with O. Andrade, E. Cano, D. Castro, G. Lopez, W. Oliver, V. Sanchez and J. Vivas, San Cristobal, Venezuela; C. de Minh and R. Salkeld, Basel, Switzerland; J. Torrado, San Sebastian, Spain; I. Filipe, London, UK; and E. Buiatti, Bologna, Italy

Gastric carcinogenesis is believed to be a multi-stage disease in which the occurrence of stomach cancer is preceded by a sequence of pre-cancerous stages: chronic gastritis, atrophy, intestinal metaplasia and dysplasia. The aims of this double blind, placebo-controlled intervention trial are to determine whether progression through the precancerous stages of the disease can be blocked by anti-oxidant vitamins (β-carotene, vitamins C and E) and to identify risk factors for progression. The trial is taking place in Tachira state, Venezuela, in a population at high risk of stomach cancer. It takes advantage of the infrastructure set up by the gastric cancer control programme of Tachira state, in particular the presence of highly skilled endoscopists.

The original design of the trial included treatment for *Helicobacter pylori* infection (94% of subjects are *H. pylori*-positive), but two pilot studies showed low *H. pylori* eradication rates compared with the same treatment regimen in Europe and North America. In view of the disappointing results, which may be due to either differences in *H. pylori* strains or frequent reinfection, the anti-*H. pylori* treatment phase was deleted from the protocol.

Subjects in the trial are randomized to treatment with anti-oxidant vitamins (vitamin C (750 mg/day), vitamin E (600 mg/day) and β-carotene (18 mg/day)) or to placebo. Treatment is distributed every 1–2 months for three years. At recruitment, a dietary questionnaire is completed, a gastroscopy is performed taking five biopsies and blood and urine specimens are collected from each patient.

These procedures are repeated at the end of the treatment phase. Physical examination and collection of biological specimens are carried out annually on all participants and gastroscopy on a subsample. In addition, all subjects with a histological diagnosis of intestinal metaplasia type III or dysplasia are followed up with gastroscopy every six months [294].

The main trial commenced in May 1992. The target for recruitment of 2200 subjects was achieved in February 1995. By July 1997, 853 subjects had completed the three years of treatment; 747 subjects are still being treated and 600 subjects have withdrawn from the trial.

The data collected at baseline, before randomization, have been analysed for prevalence of precancerous lesions [293], determinants of plasma pepsinogen levels (Kato *et al.*, 1995, *Int. J. Cancer*, **62**, 512–518), determinants of antioxidant vitamin levels [50] and risk factors for gastric precancerous lesions.

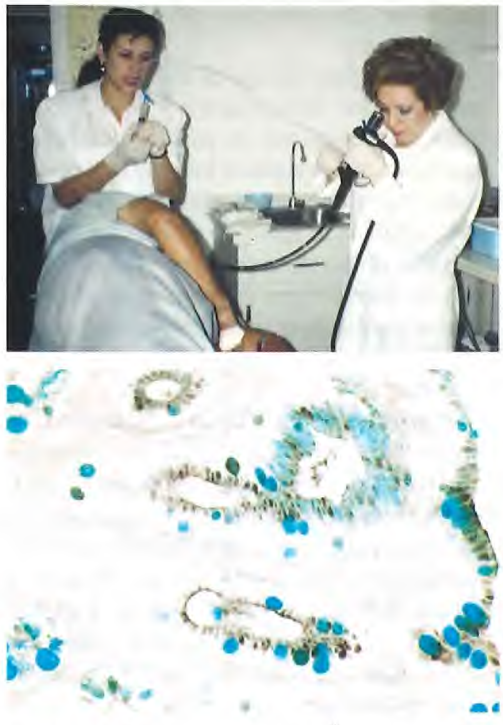

Figure 47. (a) Endoscopic examination for precancerous lesions of the stomach in Venezuela (b) Gastric biopsy showing intestinal metaplasia, type III (stained with HID/AB).

A reliability study was conducted for the histological diagnosis, based on two subgroups [352]. The first subgroup consisted of 45 subjects from the pilot phase of the study who received two endoscopies separated by a period of one month. The results show quite low agreement between the two diagnoses, mainly attributable to biopsy sampling error. The two biopsies were reviewed by a single pathologist. A second sample of 50 subjects had a single biopsy, reviewed by two pathologists. The agreement between pathologists was quite high for advanced lesions (intestinal metaplasia or dysplasia), but lower for less advanced ones.

The results of other chemoprevention trials using β-carotene have had important consequences for this trial. In 1994 the α-Tocopherol, β-Carotene (ATBC) cancer prevention study showed an adverse effect of β-carotene treatment with on lung cancer and cardiovascular disease in a cohort of heavy smokers and asbestos-exposed workers. In January 1996 the Carotene and Retinol Efficacy Trial (CARET), which had a similar protocol to the ATBC study, was stopped early because interim results indicated that supplements containing β-carotene and vitamin A provided no benefit and might be causing harm. In contrast, the Physicians' Health Study, which ended on schedule at the end of 1995 after more than 12 years of follow-up, showed no evidence of any effect of β-carotene on cancer or cardiovascular disease. In view of these results, an interim analysis was conducted in September 1996 based on the 220 subjects who had completed treatment and received the final endoscopy. No effect of treatment on progression of precancerous lesions was found. The numbers of deaths and the numbers of subjects withdrawing were similar in the treatment group and the control group. Out of the 19 deaths in the study, 4 were from cerebrovascular accident and 3 from myocardial infarction. These numbers are consistent with the expected cause-specific mortality rates in the general population of Tachira.

Since the results of the ATBC and CARET studies suggest that treatment with β-carotene may be harmful in subjects at high risk of lung cancer, all smokers and recent ex-smokers (less than ten years since cessation) who were receiving anti-oxidant vitamins were switched to placebo.

5.1.3
HPV vaccines for cervical neoplasia

N. Muñoz, R. Herrero and M. Plummer; in collaboration with C. Bratti and A.C. Rodriguez, San José, Costa Rica; P. Coursaget, Tours, France; L. Gissman, Heidelberg, Germany; and J. Schiller, M. Schiffman and A. Hildesheim, Bethesda, MD, USA

Several groups are currently involved in the development of prophylactic vaccines

against HPV infection. The immunogens of choice appear to be the virus-like particles (VLPs), which have been produced for HPV 16, 6, 11, 18, 31, 33, 35, 39 and 45 by different groups. Most of these VLPs are strongly immunogenic in animal models, but have not been tested in humans.

Since a small number of HPV types (16, 18, 31, 45, 59) are responsible for more than 80% of invasive cancer cases, the ideal vaccine is likely to include a combination of VLPs of those types. Alternatively, initial studies may reveal that VLPs from one type protect against infection with other types [278]. We are collaborating with Dr P. Coursaget, of Tours University in France, who has developed a baculovirus system to produce VLPs of HPV 16 (Figure 48). These particles are strongly immunogenic in mice and sheep and will be used in clinical trials once they are produced according to good manufacturing practices. We have prepared a protocol for phase I, II and III clinical trials, that was discussed at a meeting in Lyon in September 1996, with representatives from the Vaccine Research and Development Global Programme of WHO and from the IARC Scientific Council. It is envisaged that the phase I trials will be conducted in the country where the vaccine is produced and approved by the corresponding regulatory agencies.

Phase I trials to evaluate the safety and immunogenicity of the vaccine product will be conducted in small numbers of healthy volunteer medical or nursing female students (age 18–25). Subsequently, the phase II trials will determine the optimal dose and schedule for the HPV vaccine in three different groups, which constitute potential targets for the phase III trials and vaccination programmes: virginal women, sexually active women and young males.

The most appropriate populations for the conduct of phase III trials are in high-incidence areas where the epidemiology of HPV and cervical neoplasia has been investigated; candidate areas for these trials have been identified in Colombia and India.

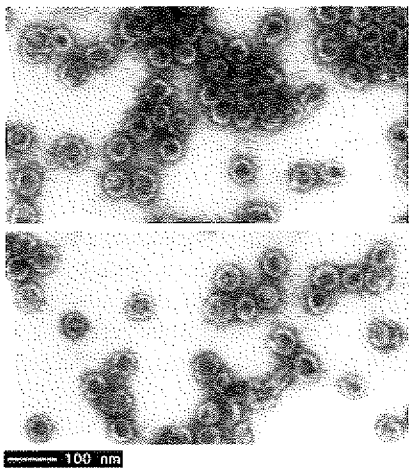

Figure 48. Virus-like particles of HPV 16 produced by Dr P. Coursaget for potential use in a vaccine

Another collaboration is being planned with the National Cancer Institute of the USA to jointly conduct a phase III trial of a prophylactic vaccine under development at that institute. The study would be conducted in Guanacaste, Costa Rica, where the natural history of cervical neoplasia is being studied (Section 3.4.7).

It is planned to begin the phase I–II trials in 1998, to be completed by 2000, when the phase III trials would start.

5.1.4 Chemoprevention of oral cancer

R. Sankaranarayanan; in collaboration with R. Maher and S.H. Zaidi, Karachi, Pakistan; B. Mathew, K. Ramadas, T. Somanathan and P.R. Sudhakaran, Trivandrum, India; and P.P. Nair, Washington, DC, USA

Although short-term administration of vitamin A has been shown to reverse oral precancerous lesions, it is not known whether long-term chemopreventive treatment can prevent malignant transformation to oral cancer. A randomized intervention trial to evaluate the cancer preventive potential of vitamin A in subjects with non-

homogeneous oral precancerous lesions in Kerala, India, has been initiated. Because some recent intervention studies have suggested an increased risk of cancer in smokers who are taking β-carotene supplements (see Section 5.1.3), recruitment into the trial is restricted to non-smokers.

A study involving supplementation of multiple micronutrients for a period of 1–4 years to 169 subjects with oral submucous fibrosis in Karachi, Pakistan, resulted in significant relief of symptoms, improvement in inter-incisor distance and regression of concomitant leukoplakias.

The effectiveness of vitamin A in preventing second primaries in 91 treated head and neck cancer patients was evaluated in a randomized controlled trial. Though no second primaries were observed in the vitamin A group, a higher frequency of loco-regional recurrences compared with the control arm was observed in this group. A larger study is being planned to address the role of chemoprevention in preventing second primaries.

5.2 Evaluation of cancer preventive agents

The Unit of Chemoprevention was established in May 1996, with the principal aim of critically evaluating the available evidence on cancer-preventive activity of classes of agents, and publishing the results as the *IARC Handbooks of Cancer Prevention*. In preparation for this, many leading international experts in the field gathered in Lyon on 6–10 November 1995 for a conference on Principles of Chemoprevention. During the conference, the experts gave enthusiastic support to the new IARC initiative, which aims to provide a scientific basis for national and international decisions on the implementation of cancer-preventive strategies, and for assessing the benefits and risks associated with them. Guidelines for the evaluation of putative cancer-preventive strategies were prepared and published in *Principles of Chemoprevention* (IARC Scientific Publications No. 139).

5.2.1 Aspirin and aspirin-like drugs

H. Vainio and G. Morgan. The following members of other units contributed: P. Boffetta, M. Friesen, V. Krutovskikh, C. Malaveille, D. McGregor, H. Ohshima, E. Riboli. J.M. Rice, J. Siemiatycki and J. Wilbourn

The first meeting for evaluation of potential cancer-preventive agents was held in Lyon on 2–8 April 1997. A working group of 25 scientists from 11 countries met to review the evidence on cancer-preventive effects of aspirin and aspirin-like drugs (sulindac, piroxicam, indomethacin). These are members of the family of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs have established value in the alleviation of pain, inflammation and fever and are commonly prescribed for treatment of rheumatoid disorders such as arthritis. The results of the meeting have been published in Volume 1 of the *IARC Handbooks of Cancer Prevention.*

Aspirin has been implicated in reducing the risk of colorectal cancer. The results of 21 out of 23 published epidemiological studies were consistent in showing that regular use of aspirin lowers the risk of cancer of the colon and rectum. Overall, these studies covered more than 18 000 cases of colorectal cancer and they differed in design, location, population and motivating hypothesis. While information on the duration of treatment and dose of aspirin was limited, the cancer-preventive effect was seen to increase with increasing years of use. An average risk reduction of approximately 50% was reported. However, the one randomized trial did not show protection by aspirin. The working group thus considered that more

research was needed before it could be concluded that a definite cause–effect relationship had been established. Among important questions is how long and how often must aspirin be taken to prevent colorectal cancer. Published studies suggest that regular, consistent use over many years may be required.

NSAIDs have important side-effects. The most frequent adverse reactions are gastrointestinal disturbances including, occasionally, diarrhoea and peptic ulcer. Given the uncertainties in dose, duration and frequency of use for preventive effect, and the risk of adverse side-effects, detailed consideration of the total benefits and of toxicity will be required before widespread use of aspirin can be recommended for the reduction of colorectal cancer.

Even more reservations apply to the other drugs considered. Sulindac shows promise for reduction of adenomatous polyps in patients with familial adenomatous polyposis, but further research is required to determine whether the risk of cancer is reduced in such patients.

5.2.2 Carotenoids

H. Vainio and M. Rautalahti. The following members of other units contributed: P. Boffetta, R. Kaaks, V. Krutovskikh, C. Malaveille, A.B. Miller, H. Ohshima, B. Pignatelli, M. Plummer, E. Riboli, R. Sankaranarayanan, J. Wilbourn and M.-L. Zaidan-Dagli

For the last twenty years, scores of epidemiological studies have noted a lower risk of cancer in people whose diets include a relatively large amount of vegetables and fruit. A popular explanation is that antioxidant vitamins, particularly carotenoids and especially β-carotene, found in vegetables and fruit prevent carcinogenesis by interfering with oxidative damage. However, the observational epidemiological studies notwithstanding, the results of large clinical trials on β-carotene have been disappointing, showing no protective effect, but suggesting rather that it increased the risk of lung cancer among cigarette smokers and among asbestos-exposed individuals.

A working group of 23 scientists from 10 countries met in Lyon on 10–16 December 1997 to review the evidence on the cancer-preventive efficacy of carotenoids. The group came to the conclusion that there is evidence suggesting lack of cancer-preventive activity for β-carotene when used as a supplement at high doses. There is inadequate evidence with regard to the cancer-preventive activity of β-carotene at the usual dietary levels. There is inadequate evidence with respect to the possible cancer-preventive activity of other individual carotenoids. The group considered that the use of carotenoid supplements as cancer-preventive agents among the general population could not be recommended. The outcome of the evaluation meeting will be published as Volume 2 of the *IARC Handbooks of Cancer Prevention* .

5.3 Safe handling of carcinogens and destruction of carcinogenic wastes

Several cytostatic drugs have been classified by IARC as human carcinogens or probable/possible human carcinogens. Hospital staff or family members handling excreta from patients treated with antineoplastic drugs or equipment contaminated by such excreta, such as urinals and chamber pots, may be more heavily exposed than trained hospital nurses or pharmacists. In addition, handling of these drugs, in pure

form or in solution, generates residual amounts of cytotoxic solutions, which should not be discarded into the domestic sewage system without prior inactivation. This section presents two approaches to protect personnel and the environment from risks due to these drugs.

5.3.1

Destruction of antineoplastic agents as hospital formulations

M. Castegnaro, J. Michelon and L. Garren; in collaboration with J. Barek, Prague, Czech Republic; M. de Méo and M. Laget, Marseille, France; E.B. Sansone and G. Lunn, Frederick, MD, USA; and M.H. Sportouch, S. Hansel and J.C. Milhavet, Montpellier, France (with support from the French Ministry of the Environment and National Institutes of Health, USA)

This work, co-ordinated by IARC, was carried out in four collaborating laboratories (Frederick Cancer Research Facility, Frederick, MD, USA; Charles University, Prague, Czech Republic; Hôpital St Charles, Montpellier and IARC, Lyon). Thirty-two drugs have been tested using three degradation agents (sodium hypochlorite, hydrogen peroxide and Fenton reagent) on drug formulations as used in the treatment of patients in the Hôpital Saint-Charles, Montpellier, France and the National Cancer Institute, Bethesda, USA.

Oxidation by 5% sodium hypochlorite degraded 28 of the 32 drugs within one hour into non-mutagenic residues and 30 of the 32 within four hours. In the presence of 0.9% NaCl, teniposide formulations were completely degraded in one hour into non-mutagenic residues, but in the presence of 5% glucose, mutagenic residues were obtained. The residues of degradation of vinblastine sulfate were mutagenic. Using degradation by the Fenton reagent, only 22 drug formulations were completely degraded into non-mutagenic residues. Degradation by 30% hydrogen peroxide was even less successful, with only 13 drug formulations completely degraded into non-mutagenic residues.

A solution of 5% sodium hypochlorite therefore seems to be the most suitable reagent for treatment of waste solutions from treatment with these 32 drugs. It may also be used for the treatment of contaminated urines from treated patients.

5.3.2

Safe handling of genotoxic su bstances, training courses and dissemination of information

M. Castegnaro and A.J. Sasco

A series of presentations in industries and courses at universities have been given. A document dealing with good practices for handling genotoxic substances and methods of decontamination of chemical carcinogens has been prepared in collaboration with the Société Française de Toxicologie Génétique and is being published by the International Programme on Chemical Safety (WHO, Geneva).

5.4 Studies of screening for cancer

Screening is a means of achieving early detection of certain cancers and precancerous lesions in asymptomatic people, so as to allow treatment before the disease becomes incurable. The efficacy of screening for a particular cancer is established if it results in a significant reduction in mortality from the disease without incurring enormous costs.

A screening procedure should be considered for implementation as a public health policy for entire populations or high-risk groups only after it has been thoroughly

evaluated for effectiveness and costs in experimental settings.

5.4.1
Screening for cancer of the breast in the Philippines

D.M. Parkin, P. Pisani and L.J. Gibson; in collaboration with D.B. Esteban, C.A. Ngelangel and A.V. Laudico, Manila, The Philippines

A randomized controlled trial of screening for breast cancer by physical examination performed by trained paramedical personnel is being conducted in the Manila area of the Philippines, with support from the US Army Medical Research Development Command.

During 1995, a coordinating centre was set up in Manila, and 202 health centres serving the area were randomized to the intervention and control arms. Hospital clinics for referral of positive women and mechanisms for documentation of results including questionnaires and forms have been established. Nurses have been recruited and trained, and the intervention has been fully operational since March 1996. Follow-up of the intervention and control populations is the responsibility of the two population-based cancer registries serving the greater Manila area, and case-finding procedures have been enhanced to permit more rapid identification of incident breast cancers. By the end of 1997, the first round of examinations will be complete, with 170 000 women being offered screening. Compliance with examination is high (91%), and some 2.6% of women are identified as having a referable abnormality by the examiner. Unfortunately, compliance with follow-up of the women screened positive (clinic attendance and diagnostic procedures) is poor, with only 30% receiving a definitive diagnosis after assessment. By August 1997, 26 malignant breast cancers had been identified by screening.

The characteristics of those accepting or refusing the screening examination were compared. In contrast to the experience in western countries, refusal is more frequent in women of higher social class. A survey of women who failed to attend the follow-up clinic was undertaken, and the most common reason given for non-attendance related to inconvenience and cost. However, the provision of mobile diagnostic teams (who examine the women in local health clinics), free transport and reimbursement of expenses has not greatly changed the compliance rate, and it seems likely that less evident cultural factors and/or health beliefs underlie the poor results.

A second round of screening is planned on a subset of the population, after which there will be no further intervention. The cohorts will be followed up for 5–10 years to study the onset of breast cancer and resulting mortality in relation to screening, and the incidence of breast and other cancers will be studied in relation to the data collected at interview during the initial examination.

5.4.2
Screening for cancer of the cervix in developing countries

D.M. Parkin, R. Sankaranarayanan and N. Muñoz; in collaboration with C.K. Gajalakshmi, Madras, India; K. Jayant, B.M. Nene and A.M. Budukh, Barshi, India; E. Lynge, Copenhagen, Denmark; R. Rajkumar and J. Cherian, Ambilikkai, India; B. Shyamalakumary, Ernakulam, India; N. Sreedevi Amma, M. Krishnan Nair and R. Wesley, Trivandrum, India; and P. Srivatanakul, Bangkok, Thailand

Since organized cervical cytology screening is not feasible in developing countries due to technical and financial constraints, several low-technology approaches such as health education to facilitate early detection, unaided and aided visual inspection of uterine cervix and low-intensity cytology have been suggested as alternative control measures. We have undertaken studies to evaluate the feasibility,

performance and effectiveness of these approaches to early detection of cervical cancer.

Two studies (community-based study, and in a high-risk population) have evaluated the performance of unaided visual inspection in the detection of early invasive cervical cancer and precursor lesions. Depending on the criteria used to define visual abnormality, the sensitivity to detect invasive cancer varied from 50 to 90% and the specificity from 43 to 90%; the test had even lower sensitivity and specificity to detect precursor lesions. Any attempt to increase the sensitivity resulted in unacceptable lowering of specificity and *vice versa*. Therefore, unaided visual inspection is not a satisfactory screening test for cervical cancer.

The relative performance of non-magnified aided visual inspection with 3% acetic acid impregnation of the cervix (cervicoscopy) in detecting cervical cancer and precursors compared with cervical cytology is being evaluated. Preliminary results based on 4500 subjects indicate that cervicoscopy has a similar sensitivity to that of Pap smear, although its specificity is significantly lower than that of cervical cytology. A large-scale randomized intervention trial with cervicoscopy as the screening test is being planned.

The feasibility of systematic evaluation of an organized low-intensity cervical cytology programme in Thailand is being explored.

5.4.3

Evaluation of oral cancer screening in developing countries

R. Sankaranarayanan and D.M. Parkin; in collaboration with L. Fernandez Garrotte, Havana, Cuba; P.C. Gupta, Bombay, India; B. Mathew, K. Ramadas, I. Ahmed, M. Pandey, N. Sreedevi Amma and Thara Somanathan, Trivandrum, India; and R. Rajkumar and J. Cherian, Ambilikkai, India

A randomized intervention trial to evaluate oral visual inspection in the early detection and prevention of oral cancer is in progress in Trivandrum district in Kerala, India. Twenty-six trained health workers identify, recruit, examine and refer subjects with suspect lesions for confirmation and management. Recruitment of participants into the study commenced in December 1995 and, as of July 1997, 66 173 subjects aged 35–64 years out of a target of 90 000 had been included. Three screening examinations will be carried out at three-year intervals.

Figure 49. Examination of a subject in the oral cancer screening trial in India

Performance evaluation of the screening test indicates that the health workers can identify oral lesions accurately [238]. Subjects with confirmed oral precancers are advised to stop tobacco habits, and encouraged to undergo removal of excisable non-homogeneous oral leukoplakias, if present. Subjects with overt invasive lesions are given appropriate treatment.

Oral cancers occurring in the control population, and non-screen-detected cancers in the intervention group are identified through the Trivandrum Population-based Cancer Registry. The ultimate aim of the study is reduction of mortality from oral cancer.

The role of health education in prevention and early detection of oral cancer is being evaluated in a randomized intervention trial in the predominantly rural Palani Taluk, in Tamil Nadu, India.

A case–control study to evaluate the Cuban Oral Cancer Screening Programme has been completed. This study addressed the risk of advanced oral cancer in relation to history of oral visual inspection offered by the Cuban programme. A further descriptive evaluation of the Cuban programme is being planned.

5.4.4 Screening for cancer of the liver in China

D.M. Parkin and P. Pisani; in collaboration with J.G. Chen, Qidong, China

Liver cancer is a disease with a five-year survival of only around 6% in western countries and even lower in developing countries. It is a major problem of many countries in south-eastern Asia and Japan as well as central and western Africa. In China, 70% of liver cancers are due to chronic infection with HBV and an additional 26% can be attributed to HCV (see Section 1.2.5). Since there is no effective treatment for cases diagnosed following symptoms, early diagnosis has been considered as an option to reduce mortality from the disease.

Non-experimental trials of screening for raised serum α-fetoprotein levels and/or by ultrasonography are being conducted in high-risk populations of South Africa, Thailand and Taiwan. A randomized trial of screening for liver cancer is being conducted in Qidong City, China, where the annual age-standardized rates of liver cancer are 72.1 and 19.1 per 100 000 population in men and women, respectively. A high-risk group of male chronic carriers of HBV was identified by an initial serological mass survey. HBsAg-positive subjects were then randomized to screening and control groups by township of residence. Testing for serological levels of α-fetoprotein was performed every six months in the screened group; if abnormal levels were detected, the subject was referred for ultrasound examination. No examination was offered to the control group after the initial test.

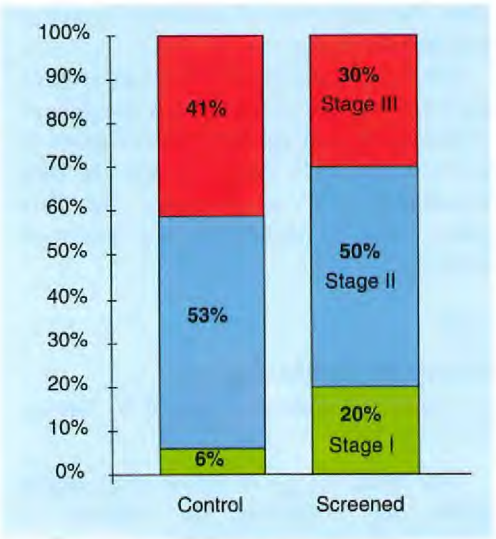

Figure 50 Frequency distribution of stage at diagnosis of primary liver cancer cases detected in screened and control groups.

The impact of screening on mortality has been evaluated after an average of 5.2 years of follow-up. The screening procedure was effective in advancing diagnosis, as shown by the higher incidence rate in the screened arm (1342/100 000) compared with the control group (1196) and by the more favourable distribution of stage at diagnosis in the first group (Figure 50). However, the risk of dying from the disease did not differ between the two groups: mortality rates were 1138 and 1114 in the screened and control arms, respectively, for a crude relative risk of 1.02. After exclusion of prevalent cases diagnosed within three months of entry, the adjusted RR was 0.86 (95% CI 0.69–1.07). The small advantage in the screened group, still not significant, suggested by the 14% lower mortality is explained by longer survival in the screened group due to lead time. The apparent advantage in the screened group disappears after the first two years,

when the proportion of survivors is around 10% in both arms.

Mass screening is an expensive activity, and implementation of any such programme should therefore depend on clear evidence of effectiveness. This study, to date the only randomized trial of screening for liver cancer, failed to demonstrate any impact on mortality.

5.4.5

Screening methodology

A.J. Sasco; in collaboration with W.D. Flanders, Atlanta, GA, USA

The methodology of use of case–control studies for evaluating the efficacy of screening for cancer is being assessed. Bias resulting from misclassification of exposure has been investigated [157].

A review has been carried out to examine whether screening for nasopharyngeal cancer should be performed using serological testing for Epstein–Barr virus [390]. The recommendation was for randomized studies to be carried out.

5.4.6

Evaluation of screening for neuroblastoma

J. Estève; in collaboration with F. Berthold, Cologne, Germany; A.W. Craft, L. Parker and D. Worthington, Newcastle, UK; R. Errtmann, Hamburg, Germany; A. Jenkner, Rome, Italy; R. Kerbl and I. Starz, Graz, Austria; C. Lasset, P. Mathieu and T. Philip, Lyon, France; J. Mann, Birmingham, UK; R. Pettersen and I. Storm-Mathison, Oslo, Norway; and F. Schilling, Stuttgart, Germany

Following the consensus reached among the participants in the Study Group for the Evaluation of Neuroblastoma Screening in Europe (Estève *et al.*, 1994), it was decided to study the feasibility of screening at 12 months in Lyon. Systematic screening at 12 months was started in Germany, where it was considered that an acceptable level of compliance had been demonstrated. In the meantime, a detailed comparative study of the incidence of neuroblastoma and of survival of children with the disease in Austria, France, Germany and the United Kingdom has been undertaken. The information obtained will be fundamental to decisions on the undertaking of further screening trials.

PART 6. METHODS FOR CANCER RESEARCH

6.1 Methods for measuring and monitoring exposure to particular carcinogens

Epidemiological studies have in the past often relied on very imprecise information about exposure to potentially carcinogenic agents, leading to misclassification and a consequent weakening of the resolving power of the study. An understanding of the molecular and cellular aspects of carcinogenesis now permits the development of biomarkers of exposure which improve the precision of exposure measurement. This improved precision is particularly critical where the relative risk associated with an exposure is small. Modern analytical techniques are being applied to this problem, for use both in IARC projects and more generally by cancer researchers worldwide.

6.1.1

Formation and metabolism of 8-nitro - guanine

H. Ohshima,V. Yermilov, I. Brouet and S. Auriol; in collaboration with H. Nukaya, Shizuoka, Japan; and T. Suzuki and K. Makino, Kyoto, Japan

We have found that peroxynitrite, a product of reaction between nitric oxide and superoxide, can form a specific DNA adduct , 8-nitroguanine. Carbon dioxide (CO_2) reacts with peroxynitrite to generate a highly reactive intermediate. In calf-thymus DNA incubated with 0.1 mM peroxynitrite at pH 7.5, CO_2 derived from bicarbonate (0 – 10 mM) dose-dependently caused an increase of up to six-fold in formation of 8-nitroguanine, while bicarbonate had no apparent effect on 8-oxoguanine formation. Since CO_2 is abundant ($\geq$ 25 mM) in physiological fluids, 8-nitroguanine could be easily formed *in vivo* in the presence of CO_2 and thus it can be measured as a marker for endogenous DNA damage induced by peroxynitrite (512). Antibodies against 8-nitroguanine are being prepared for use in immunoassays. On the other hand, 8-nitroguanine in DNA is unstable ($t_{1/2}$ = 4 h) and is rapidly eliminated by depurination; it may be possible to analyse the urinary metabolite(s) as a marker of endogenous DNA damage induced by peroxynitrite. In order to study the metabolism of 8-nitroguanine, we have synthesized ^{14}C-labelled 8-nitroguanine and administered it to rats. Samples of 24-h urine and f aeces were collected and fractionated by HPLC. Half of the radioactivity was excreted in urine as unchanged 8-nitroguanine and the remainder as an unknown metabolite , which is now being purified and characterized.

In addition to guanine modifications, we have found that peroxynitrite also reacts with adenine to form two major yellow products. These compounds have been isolated and their structures are being identified, in collaboration with Drs K. Makino and T. Suzuki, University of Kyoto, Japan.

6.1.2

Measuring human exposure to the food-borne carcinogen PhIP

6.1.2.1

Biomarkers of internal dose and biologically effective dose

M. Friesen and J. Michelon; in collaboration with F.F. Kadlubar, Jefferson, AR, USA; H.A.J. Schut, Toledo, OH, USA; and P.T. Strickland, Baltimore, MD, USA

DNA adducts of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), a colon carcinogen produced when meat is cooked at high temperature, can be detected

in rat and human colon tissue (112). Adduct levels were measured using alkaline hydrolysis–gas chromatography (GC/MS) and ^{32}P-postlabelling in 11 tissues of rats treated over three weeks with PhIP. Results from the two methods correlated well, but PhIP–DNA adducts could be detected only down to a dose of 0.1 mg PhIP/kg/day. However, using similar GC/MS methodology, a linear dose–response was obtained for urinary excretion of unmetabolized PhIP in these animals down to 0.1 µg PhIP/kg/day, a dose comparable with reported human exposure levels. Urinary PhIP as a quantitative biomarker of exposure to PhIP in the diet is now being validated in human volunteers eating char-broiled beef. The method has also been applied to study the effect in animals of indole-3-carbinol (421) and phenethyl isothiocyanate (199), two potential cancer chemopreventive agents, on the metabolism and genotoxicity of PhIP.

6.1.2.2

A new biomarker of long-term exposure to PhIP

M. Friesen and P. Jackson; in collaboration with M. Nagao, Tokyo, Japan

A biomarker to measure the extent of frameshift mutations in DNA of normal cells is being developed to measure long-term human exposure to carcinogens such as PhIP. The method relies on quantitative PCR and liquid chromatography/mass spectrometry for quantitation of specific, mutated oligonucleotides in the presence of appropriate internal standard oligonucleotides .

6.1.3 Postlabelling methodology study

M. Castegnaro; in collaboration with F. Kadlubar, Jefferson, AR, USA; J.E. Lewtas, Research Triangle Park, NC, USA; and D. Phillips, Sutton, UK (with the support of EU grant No. EU5V-CT94 0448 and a grant from the US Environmental Protection Agency)

This is a collaborative project aimed at improving and standardizing methodologies on postlabelling of bulky and small DNA adducts.

Agreed methodology for analysis of bulky adducts and for the analysis of O^6-methylguanine was tested in a collaborative study in late 1995. Participating laboratories received various standardized samples of modified DNA to analyse for bulky adducts with both centrally supplied polynucleotide kinase (PNK) and the PNK currently used in their laboratory. Certain laboratories also analysed standardized samples of methylated DNA for O^6-methylguanine using reagents and equipment provided by IARC, where not commercially available. The results were collated at IARC for qualitative and quantitative analysis and sent back to each participant for checking, before a meeting of participants convened to review and evaluate the data and assess how the methods could be improved.

Some variability in the results was explained by deviations from the prescribed protocols. All laboratories had generally achieved very comparable thin-layer chromatography mapping of adducts, except for adducts of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP). As compared to the 1992 trial, the quantitative results for bulky adducts demonstrated a distinct reduction in variability. For adducts with benzo[*a*]pyrene, all laboratories obtained results that were close to the actual value. With aminobiphenyl–DNA and PhIP–DNA samples, all values obtained were significantly lower than those calculated from tritium incorporation.

For analysis of O^6-methylguanine, there was some variability in results, due in part to lack of experience in many laboratories in analysing for this adduct.

Following clarification and investigation of several steps in the methods by a subgroup, a second collaborative study was initiated early in 1997. In this study, each participating laboratory was requested to analyse (*a*) for bulky adducts prepared with

DNA modified *in vivo* or *in vitro* with benzo[*a*]pyrene or aminobiphenyl and (*b*) for the small adducts group, a sample of DNA containing O^6-methylguanine. Analytical results on the samples and standards as analysed and on the samples corrected for recovery of the corresponding standard were collated and examined during a meeting held in Lyon in May 1997. It was established that correction is a key element in the inter-laboratory comparability of the results.

6.1.4

Analysis of fumonisins and of their potential biomarkers: sphingolipids

M. Castegnaro, L. Garren; in collaboration with A. Daudt, Ramiro Barcelos, Brazil; and C.P. Wild, Leeds, UK

6.1.4.1

Analysis of fumonisins in foods

In an area of Brazil with high oesophageal cancer incidence, food from families of oesophageal cancer cases and from control families has been collected for analysis of fumonisins. Urine and oesophageal cells have also been sampled from control families and patients, for analysis of sphingolipids (sphinganine: sphingosine ratio) as a possible biomarker of fumonisin exposure (see below). Analysis of the samples is in progress.

6.1.4.2

Analysis of sphingolipids

Fumonisins inhibit the acetylation of sphinganine, resulting in accumulation of sphinganine and an altered sphinganine (Sa)/sphingosine (So) ratio. This alteration in sphingolipid biosynthesis can alter signal transduction, cell growth, differentiation and possibly neoplastic transformation. A new method has been developed for the analysis of Sa and So in human and rat urine and in various animal tissues (kidney, liver, oesophagus, lung) (68). The method has also been modified for the analysis of sphingolipids in human and animal lymphocytes.

These methods are being applied to the analysis human urine samples in an area of South Africa with high exposure to fumonisins, to investigate the relevance of the Sa/So ratio as a biomarker of exposure to fumonisins. In addition, after validation, they will be used to determine the potential role of fumonisins in relation to oesophageal cancer in South Africa, stomach cancer in Venezuela and liver cancer in Thailand.

6.1.5

Biological monitoring of exposure to carcinogens that yield DNA etheno adducts

A. Barbin, G. Brun, A. Giles and Y. Grosse; in collaboration with H. Bartsch, Heidelberg, Germany; W.C.A. Gelderblom, Tygerberg, South Africa; J.A. Miller, Madison, USA; C.Y. Shi, Singapore; and C.P. Wild, Leeds, UK

Etheno adducts are promutagenic lesions formed with DNA bases by some environmental carcinogens such as vinyl chloride and urethane, and by the lipid peroxidation product 2,3-epoxy-4-hydroxynonanal (Chung *et al.*, 1996, *Carcinogenesis*, 17, 2105–2111). Therefore, they could be useful as biomarkers of exposure to specific carcinogens or of DNA damage induced by oxidative stress and lipid peroxidation. A sensitive method, previously developed at IARC and based on immunoaffinity purification and ^{32}P-postlabelling of the 3′-mononucleotides, was used to analyse 1,N^6-ethenoadenine (εA) and 3,N^4-ethenocytosine (εC) in human and rodent tissues.

6.1.5.1

Formation of etheno adducts in mice treated with urethane or its metabolites

The bioactivation of urethane (ethyl carbamate) involves metabolism to vinyl

carbamate followed by epoxidation to the ultimate carcinogenic species, vinyl carbamate epoxide. The capacity of these three compounds to form ethenobases was studied in liver and lung DNA of mice of various strains. Both εA and εC were detected in untreated control DNA samples from liver and lung. After five daily i.p. injections of 250 or 280 nmol/g b.w. vinyl carbamate to adult mice, increased levels of εA and εC were detected in liver and lung DNA of CD-1, C3H/HeJ and C57BL/6J mice. Under similar dose regimens, lower levels of etheno adducts were detected in B6C3F1 mice. DNA etheno adducts were also formed in liver and lung after treatment with ethyl carbamate in adult mice, but at three-fold lower levels as compared with vinyl carbamate. In 12-day old C3H/HeJ and C57BL/6J mice, 2- to 3-fold higher etheno adduct levels were detected in liver DNA, compared with adult animals, after a single treatment with 250 nmol/g b.w. vinyl carbamate, suggesting that young animals are more susceptible to adduct formation. These results demonstrate that ethyl carbamate and its activated intermediates bind to liver and lung DNA to form εA and εC, and the differences in DNA binding support the hypothesis that metabolic activation of ethyl carbamate to vinyl carbamate to its epoxide is involved (104).

6.1.5.2

Variations of endogenous levels of DNA ethenobases with diet in mice

εA and εC were analysed in liver and lung DNA from adult B6C3F1 mice fed either a high-fat diet (Wayne's Breeder Blocks), a purified diet (AIN-76) or a non-purified natural ingredient diet (NIH-07). Pronounced differences were observed between the three diets, background levels of ethenobases being higher in mice fed the AIN-76 diet than in mice fed the NIH-07 or the Wayne's Breeder Blocks diet. These diet-related effects were also observed in B6C3F1 mice treated with ethyl carbamate or vinyl carbamate (104).

6.1.5.3

Analysis of DNA etheno adducts in rats exposed to mycotoxins

Two pilot studies have been initiated to examine whether exposure to mycotoxins can lead to increased levels of ethenobases in DNA, following stimulation of lipid peroxidation.

Firstly, liver tissue samples were obtained from Fischer 344 rats given a single intraperitoneal dose of aflatoxin B_1 and killed at time intervals from 1 to 14 days after the treatment. Aflatoxin B_1 has been shown to induce the formation of lipid peroxidation products (Shen *et al.*, 1994, *Toxicol. Appl. Pharmacol.*, 127, 145–150) and oxidative damage to DNA (measured as 8-hydroxyguanine; Shen *et al.*, 1995, *Carcinogenesis*, 16, 419–422) in rat liver in a dose-dependent manner. εA and εC in DNA from these liver samples are being analysed.

In a second series of experiments, the hypothesis that fumonisin B_1 generates DNA damage through stimulation of lipid peroxidation is being tested. This hypothesis is based on the observations that, in rats treated with fumonisin B_1, polyunsaturated fatty acids accumulate in hepatocytes in culture (116) and that levels of malondialdehyde increase in the liver (W.C.A. Gelderblom, unpublished). Male Fischer rats were treated by gavage with fumonisin B_1 once a day for 14 days. Hepatic DNA has been prepared and analysis of ethenobases is in progress.

6.1.5.4

DNA etheno adducts in human tissues

A pilot study is being conducted to investigate DNA etheno adduct levels in circulating lymphocytes in relation to dietary intake patterns (see Section 2.3). Blood

samples have been obtained from two groups of non-smoking women (40 women in each group), aged 45–50 years, living in two regions of Europe (Sweden and southern Spain) with different dietary intake patterns. Preliminary results show that εA and εC are formed in human circulating lymphocytes.

εA and εC have been analysed in a series of oesophageal tissue samples (non-involved mucosa from tumour resection specimens) from oesophagus cancer patients. The molar ratios of εA/adenine range from 0.07 to 3.9 $\times$ 10^{-8} (mean $\pm$ SD = 0.83 $\pm$ 0.85; n = 23) and molar ratios of εC/cytosine from <0.01 to 2.1 $\times$ 10^{-8} (mean $\pm$ SD = 0.48 $\pm$ 0.47; n = 20). Levels of εA/adenine measured in currently smoking heavy drinkers (1.36 $\pm$ 1.46 $\times$ 10^{-8}, n = 5) seem to be higher than those in non-smoking non-drinkers (0.40 $\pm$ 0.30, n = 8) (two-sample t-test, p = 0.027). Despite the limited number of samples analysed, these results suggest that elevated levels of εA may be associated with tobacco and alcohol consumption, two risk factors for cancer of the oesophagus.

6.2 Epidemiological methods

6.2.1 Development and evaluation of analytical methods for genetic epidemiology

D.E. Goldgar, Y. Shugart and A Sibert (with support from the US National Institutes of Health)

The goals of this project are (*a*) to investigate the optimal strategies for mapping and identifying low-penetrance genes for common cancers in the presence of known rarer high-risk genes; (*b*) to examine the relative efficiency of different study designs for detecting gene–environmental interactions within both standard epidemio - logical and family-study frameworks; and (*c*) extension of our previous work on a powerful method for mapping quantitative trait loci. This first two compone nts depend largely on computer-simulation of data under appropriate genetic models in order to evaluate different sampling and gene detection strategies. Results of the first component of the project have shown that trios of affected siblings are an optimal design under a variety of different genetic models, and that mutation testing for known high-risk genes can be a cost-effective strategy for identifying lower -risk genes through a random genomic search (126). We have recently published methods for estimating penetrance from family data (93) and made substantial progress on our quantitative trait-mapping efforts. The relationship between family history, family size and penetrance is under examination, in order to better interpret family history data from population-based cases screened for mutations in particular genes. These studies will also help family cancer clinics set guidelines based on family history of cancer for deciding who should be eligible for genetic testing.

PART 7. PUBLICATIONS, EDUCATION AND TRAINING

7.1 Publications

J. Cheney, S. Cotterell, S. Jones, M. Mainaud, H. Miido and J. Thévenoux

The aim of the IARC publications programme is to ensure rapid and comprehensive dissemination of information from Agency projects to other cancer researchers and public health decision-makers worldwide. New ventures include the IARC Handbooks of Cancer Prevention (see Section 7.1.4) and the electronic IARC CancerBase series (see Section 7.1.7). A volume was published on *Pathology and Genetics of Tumours of the Nervous System* .

Improvements in computer technology have permitted simplification and acceleration of the processes of document transfer from authors to the Publications Service, editing and page layout, and transfer to printers.

The IARCPress complements the promotion and distribution activities of Oxford University Press and the World Health Organization Distribution and Sales Service, with the aim of improving the visibility and availability of the Agency's publications. Since its launch in early 1996, it has attracted large numbers of customers, especially on account of its rapid service.

7.1.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

This programme is described in detail in Section 2.1.1. New volumes published during the period under review are the following:

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 65, *Printing Processes and Printing Inks, Carbon Black and some Nitro Compounds*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 66, *Some Pharmaceutical Drugs*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 67, *Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 68, *Silica, some Silicates, Coal Dusts and Para-Aramid Fibrils*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 69, *Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 70, *Lymphotropic Herpesviruses: Epstein–Barr Virus and Kaposi's Sarcoma-Associated Herpesvirus/-Human Herpesvirus 8*

7.1.2 IARC Scientific Publications

The Advisory Committee, under the chairmanship of Dr P. Boffetta, continues to review all proposals for new publications, with particular emphasis on the relevance of the work to the Agency's programme and on the procedures in place for each volume to ensure high scientific quality. Publication of Part 1 of the important new series on nomenclature and description of tumours in laboratory animals, the International Classification of Rodent Tumours, has been completed, in collaboration with the Fraunhofer Institut für Aerosolforschung in Hannover, Germany, and with support from the International Life Sciences Institute, Washington, DC.

New publications during the period under review are the following:

International Classification of Rodent Tumours. Part I. *The Rat* (IARC Scientific Publications No. 122) (fascicles 8–10)

Pathology of Tumours in Laboratory Animals. Vol. 3, *Tumours of the Hamster* (IARC Scientific Publications No. 126)

Atlas of Cancer Mortality in Central Europe (IARC Scientific Publications No. 134)

Methods for Investigating Localized Clustering of Disease (IARC Scientific Publications No. 135)

Chemoprevention in Cancer Control (IARC Scientific Publications No. 136)

Directory of On-going Research in Cancer Epidemiology 1996 (IARC Scientific Publications No. 137)

Social Inequalities and Cancer (IARC Scientific Publications No. 138)

Principles of Chemoprevention (IARC Scientific Publications No. 139)

Mechanisms of Fibre Carcinogenesis (IARC Scientific Publications No. 140)

Applications of Biomarkers in Cancer Epidemiology (IARC Scientific Publications No. 142)

Cancer Incidence in Five Continents, Vol. VII (IARC Scientific Publications No. 143)

7.1.3

IARC Technical and Internal Reports

The IARC Technical Reports are specialized publications with a limited market. IARC Internal Reports are documents prepared within the framework of specific projects for use in-house and by collaborators in the project. The following reports were published during the period under review:

Survey of Cancer Registries in the European Union (IARC Technical Reports No. 28)

International Classification of Childhood Cancer, 1996 (IARC Technical Reports No. 29)

IARC Historical Cohort Study of Workers Employed in the Man-made Vitreous Fibre Industry in Seven European Countries. Lung Cancer Mortality in the Rock Wool/Slag Wool Subcohort. Analysis based on Mathematical Model of MMVF Exposure (IARC Internal Reports No. 96/002)

International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry. II. Procedures Document, 1997 Revision (IARC Internal Reports No. 97/002)

7.1.4

IARC Handbooks of Cancer Prevention

The aim of the IARC Handbooks of Cancer Prevention is to evaluate scientific information on agents and interventions that may reduce the incidence of or mortality from cancer. The programme is fully described in Section 5.2. The first volume, published in September 1997, is:

IARC Handbooks of Cancer Prevention, Volume 1, *Non-steroidal Anti-inflammatory Drugs*

7.1.5

Directory of On-Going Research in Cancer Epidemiology

E. Démaret and R. Sankaranarayanan; in collaboration with N. Becker and J. Wahrendorf, Heidelberg, Germany

This compilation of descriptions of current research in cancer epidemiology, published in collaboration with the German Cancer Research Centre in Heidelberg, was published annually until 1992, when the cycle became biennial. Data for the 1996 volume were collected and prepared in 1995 and the Directory published in April 1996. It contains details of 1101 projects carried out by 773 investigators in 80 countries. Eight indexes (investigator, key-word, cancer site, study type, chemical, occupation, country and cancer registry) facilitate access to the information. Each entry gives the address, telephone and fax number of the principal investigator. An address list of population-based cancer registries is also included.

The interest in genetic and molecular epidemiology, as well as in intervention studies has continued to increase. The inclusion of population-based survival studies is new and reflects the increasing interest in this topic. Other major areas of interest are diet, occu-

pational exposures and the health effects of radiation, in particular electromagnetic fields. The interest in lung cancer in non-smokers is also worth mentioning. A slight increase in the number of studies looking at cancer of the prostate and ovary is observed, for example in relation to diet, in particular dietary fat.

A special effort was made on this occasion to identify studies collecting or using biological materials and to obtain details of the material stored. In 20% of the projects, specimens of various types are being collected for later analysis. A special section on biological materials banks in included in the Directory, as well as an address list of the holders of the collections.

For twenty years this Directory has contributed to disseminating information to research workers all over the world and to facilitating contacts between them. However, due to budgetary constraints, the 1996 edition is the last in the series.

A new series entitled 'Directory of On-Going Research in Cancer Prevention' is being planned, as an electronic publication, to serve as a source of information on current work in the areas of primary prevention, chemoprevention, screening/early detection and biological materials banks.

7.1.6

Directory of Agents Being Tested for Carcinogenicity

J. Wilbourn

The Directory is an essential guide to the worldwide testing of agents for carcinogenicity in experimental animals.

Data are gathered by two-yearly comprehensive surveys of research institutes. The data received are collated, adding synonyms, chemical abstracts service registry numbers, chemical abstracts names and use categories. The Directory lists: participating institutions; principal investigator(s); agents under investigation; use categories; animal species, strain and number of animals used; stage of experiments; and references to published reports of completed studies. A cross-index of chemical names and synonyms lists all agents covered in editions since Volume 9. Cross-references to the IARC *Directory of On-Going Research in Cancer Epidemiology* are also provided.

The latest survey questionnaire was distributed in September 1995 to contributors who had reported for the preceding volume, and to newly identified laboratories undertaking long-term carcinogenicity testing. Participants were asked to update entries for studies planned, in progress or completed. In May 1996, Directory No. 17 was published, reporting tests on 533 chemicals or agents from 65 institutes in 21 countries. A total of 186 final reports on 153 chemicals were included. The current Directory No. 17 is now accessible on the World Wide Web through the IARC home page (see Section 7.1.7), and will be regularly updated in the future as an exclusively electronic publication.

7.1.7

Electronic publications

The dissemination of international cancer statistics has hitherto been through the IARC Scientific Publications series, IARC Technical Reports and articles in peer-reviewed journals. However, it has become increasingly evident that such data are required not only by epidemiologists, but also by a wider public, and that electronic media, which can be easily updated, can be used. As a result, the Agency has created a new electronic publication series *CancerBase*, to provide statistical data on cancer incidence, mortality and prevalence together with easily used software to manipulate the data. The two first releases, EUCan90 (Cancer in the European Union) and CI5VII (*Cancer Incidence in Five Continents* Vol. VII), are now available. EUCan90 is the first attempt to publish estimates of cancer incidence and

prevalence together with the official mortality statistics for the EU countries, while CI5VII includes the data included in the printed volume, at a much greater level of detail, together with several statistical tools. Another *CancerBase* publication is in preparation, named GloboCan, similar to EUCan90 but with estimates for all countries of the world and for a more recent period.

A second way to disseminate information to a large audience is through the World Wide Web. One project is to extract from IARC databases a set of data containing all the information on cancer incidence and mortality at the national and regional level, and make these accessible through an interactive web server. The project was started in 1997 and several databases were available by the end of the year (www-dep.iarc.fr). The IARC database of mutations in the p53 tumour-suppressor protein is also accessible via the IARC home page (see Section 4.7.3).

The summary and evaluation sections from the recent volumes of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (see Section 2.1), as well as lists of all evaluations in the series, are also accessible through the IARC home page, as is the latest *Directory of Agents being Tested for Carcinogenicity*, No. 17 (see Section 7.1.6).

7.2 *Cancer research fellowships programme*

7.2.1 IARC research training fellowships

R. Montesano and E. El Akroud

The aim of this programme is to provide young postdoctoral scientists from any country with training in aspects of cancer research ranging from biostatistics and epidemiology to mechanisms of chemical and viral carcinogenesis, so that they can return to their own country to implement and develop programmes in cancer research or cancer control. The majority (64%) of the 461 fellowships since 1966 have been awarded to candidates from western Europe, Japan, North America, Israel, Australia and New Zealand; 18% came from eastern Europe and 18% from other countries of Africa, Asia and South America (see Figure 51). Host laboratories have been located mainly in western Europe (51%) and North America (47%). The programme is one of the few to provide training in epidemiology, and the 100 fellowships awarded so far in this discipline have contributed substantially to the development of cancer epidemiology in a number of countries.

The Fellowships Selection Committee met twice in Lyon during 1996/97 to review applications; the members of the Committee were:

Dr D. Bootsma (1996, 1997) (*Chairman*)
Department of Cell Biology and Genetics
Erasmus Universiteit Rotterdam
Rotterdam, The Netherlands

Dr A.-L. Børresen-Dale (1996, 1997)
Department of Genetics
Institute for Cancer Research
Norwegian Radium Hospital
Oslo, Norway

Dr N. Breslow (1996, 1997)
Department of Biostatistics
University of Washington
Seattle, WA, USA

Dr E. Buiatti (1996)
Epidemiology Unit
Tuscany Cancer Registry
Florence, Italy

Dr J. Cairns (1996,1997) (*Vice-Chairman*)
Clinical Trial Service Unit
Radcliffe Infirmary
Oxford, UK

Dr S. Hirohashi (1996)
Research Institute, Pathology Division
National Cancer Center Research Institute
Tokyo, Japan

Dr M. Hollstein (1996)
German Cancer Research Centre
Heidelberg, Germany

Dr B. Mansourian (1996, 1997) (*WHO representative*)
Office of Research Policy and Strategy Coordination
World Health Organization
Geneva, Switzerland

Dr N. Odartchenko (1996, 1997) (*UICC representative*)
Swiss Institute for Experimental Cancer Research
Epalinges s/ Lausanne, Switzerland

Dr M.A. Pierotti (1997)
Divisione di Oncologia Sperimentale A
Istituto Nazionale per lo Studio e la Cura dei Tumori
Milan, Italy

Dr J. Pouysségur (1997)
Centre de Biochimie – CNRS UMR 6543
Faculté des Sciences
Nice, France

Dr H.M. Rabes (1997)
Institute of Pathology
Ludwig Maximilians University München
Munich, Germany

Dr J. Samarut (1996)
Ecole Normale Supérieure de Lyon
Laboratoire de Biologie Moléculaire et Cellulaire
Lyon, France

Dr H. Tsuda (1997)
Chemotherapy Division
National Cancer Center Research Institute
Tokyo, Japan

The Agency representatives were Dr R. Montesano and Dr P. Boffetta (1996–97).

In 1996, among a total of 106 candidates, 53 were declared eligible and 12 fellowships finally awarded; in 1997, among a total of 107 candidates, 63 were declared eligible and 15 finally awarded. In 1997 three fellowships were tenable at the IARC. The distribution of fellowships awarded by discipline is given in Table 11, the list of fellows in Table 12.

The Italian Association for Cancer Research has continued its generous support of the Fellowships Programme, providing a total of US$100 000 over the two-year period.

7.2.2
Visiting Scientist awards

In 1996, this Award was given to Dr J. Siemiatycki (Director, Priority research team in environmental epidemiology, Institut Armand-Frappier, Laval, Quebec, Canada), who spent one year in the Unit of Environmental Cancer Epidemiology and in 1997 to Professor P. Toniolo, (Director, Epidemio-

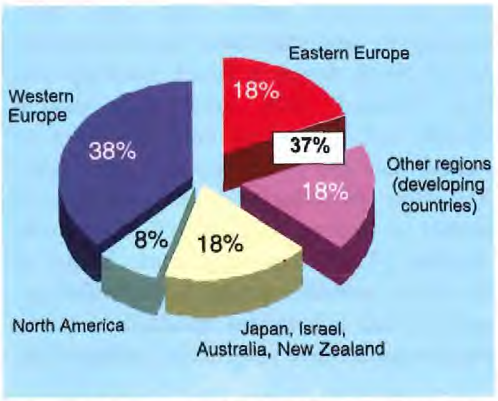

Figure 51. Origin of IARC fellows by region 1966–97 (total: 461)

logy and Prevention Program, Kaplan Cancer Center, Department of Environmental Medicine, New York University Medical Center, New York, NY, USA), who is spending one year in the Unit of Nutrition and Cancer.

Table 11. Distribution of research training fellowships awarded by discipline

Scientific discipline	No. of fellowships		
	1996	1997	1966–97
Epidemiology / biostatistics	2	–	100
Cell Biology, cell differentiation and cell genetics	3	6	104
Chemical carcinogenesis	1	1	64
Viral carcinogenesis	2	3	58
Biochemistry and molecular biology	3	5	83
Others	1	–	52
Total	12	15	461

Table 12. Fellowships awarded in 1996 and 1997

Name	Institute of origin	Host institute
1996		
AUVINEN, A.P.	Finnish Cancer Registry Helsinki, Finland	Radiation Epidemiology Branch National Cancer Institute, NIH Bethesda, MD, USA
CLIVIO, P.	Institut de Chimie des Substances Naturelles/CNRS Gif-sur-Yvette, France	Department of Chemistry Washington University St. Louis, MO, USA
FELICIELLO, A.	Department of Biology & Cellular & Molecular Pathology "L. Califano" University of Naples Faculty of Medicine & Surgery Federico II Naples, Italy	Institute of Cancer Research College of Physicians & Surgeons of Columbia University New York, NY, USA
FRANCESCHINI, I.A.	CRC Department of Medical Oncology/Neurology Glasgow, Scotland, UK	Glycobiology/Chemistry Program La Jolla Cancer Research Foundation La Jolla, CA, USA
GARCIA-QUINTANA, D.	Department of Biochemistry & Molecular Biology Universidad Autonoma de Barcelona Bellaterra, Spain	Department of Pathology Brigham & Women's Hospital Boston, MA, USA
JUILLARD, V.E.R.	Institut Cochin de Génétique Moléculaire INSERM U 152, Hôpital Cochin Paris, France	Scripps Research Institute La Jolla, CA, USA

MIRANDA, C.	Division of Experimental Oncology A Istituto Nazionale Tumori Milan, Italy	INSERM U. 145 – Hormones Polypeptidiques et Physiopathologie Endocrinienne Faculté de Médecine Nice, France
NIKIEMA, P.A.	O.C.C.G.E. Centre Muraz Bobo-Dioulasso, Burkina Faso	Molecular Epidemiology Unit Research School of Medicine University of Leeds Leeds, UK
OLSEN, S.L.	St Vincent's Institute of Medical Research Fitzroy Victoria, Australia	Cancer Research Laboratories Queen's University Kingston, Canada
POUPONNOT, C.	UMR 146. Laboratoire d'Oncologie Virale & Moléculaire Institut Curie, Section de Recherche, Centre Universitaire Orsay, France	Cell Biology & Genetics Program Memorial Sloan-Kettering Cancer Center Howard Hughes Medical Institute Research Laboratories New York, NY, USA
SALA, F.	Cancer Registry Hospital Center of Tirana Tirana, Albania	Department of Community Medicine University of Cambridge Institute of Public Health Cambridge, UK
ZEHBE, I.	Department of Pathology University Hospital Uppsala, Sweden	Abt. Virus-Wirtszell-Wechselwirkungen German Cancer Research Centre Heidelberg, Germany

1997

ALUNNI-FABBRONI, M.	Department of Biochemistry, Biophysics & Macromolecular Chemistry University of Trieste Trieste, Italy	Abt. Virus-Wirtszell-Wechselwirkungen Forschungsschwerpunkt Angewantde Tumorvirologie German Cancer Research Centre Heidelberg, Germany
BERKE, Z.	Division of Clinical Virology IMPI Karolinska Institute Huddinge University Hospital Huddinge, Sweden	Department of Tumour Cell Biology Danish Cancer Society Copenhagen, Denmark
CASTREN, K.	Department of Pharmacology & Toxicology University of Oulu Oulu, Finland	Unit of Mechanisms of Carcinogenesis IARC Lyon, France

EPINAT, J.-C.	Unité de Biologie Moléculaire de l'Expression Génique Institut Pasteur Paris, France	Department of Biology Boston University Boston, MA, USA
KARAGIANNI, N.E.	Institute of Biological Research & Biotechnology National Hellenic Research Foundation Athens, Greece	Department of Biochemistry Université Paris 7 Paris, France
JANSEN, L.A.M.	Agrotechnological Research Institute Wageningen, The Netherlands	Unit of Multistage Carcinogenesis IARC Lyon, France
LI, C.-Q.	Department of Gastroenterology Air Force General Hospital Beijing, PR China	Unit of Endogenous Cancer Risk Factors IARC Lyon, France
LUO, J.-L.	Research Laboratory of Otolaryngology Xiangya Hospital Hunan Medical University Changsha, Hunan, PR China	Toxicology and Cancer Risk Factors German Cancer Research Centre Heidelberg, Germany
NEVALAINEN, M.T.	Department of Anatomy Institute of Biomedicine University of Turku Turku, Finland	Department of Pathology Uniformed Services University of the Health Sciences Bethesda, MD, USA
RITCO VONSOVICI, M.L.	Department of Biochemistry Universitatea de Medicina si Farmacie "Carol Davila" Bucharest, Romania	Institute of Cancer Research Royal Cancer Hospital Chester Beatty Laboratories London, UK
SAGET, O.	Centre de Génétique Moléculaire, CNRS Gif-sur-Yvette, France	Developmental Biology Center University of California, Irvine Irvine, CA, USA
SKERRETT, I.M.	School of Biological Sciences Flinders University Adelaide, Australia	Center for Advanced Molecular Biology & Immunology State University of New York at Buffalo Buffalo, NY, USA
THOMAS, M.A.	Zoology Department University of the West Indies Trinidad, West Indies	Unit of Molecular Morphogenesis Laboratory of Molecular Embryology NIH Bethesda, MD, USA
TRAN QUANG, C.	UMR 146 CNRS, Oncogenèse Rétrovirale et Moléculaire Institut Curie, Centre Universitaire Orsay, France	Transcription Laboratory Imperial Cancer Research Fund London, UK
YIN, D.	Shanghai Institute of Cell Biology Chinese Academy of Sciences Shanghai, PR China	Holland Laboratory American Red Cross Rockville, MD, USA

7.3 Training courses

N. Muñoz and M. Davis

During the period under review, in addition to continuing its well established components such as cancer epidemiology, molecular biomarkers in environmental cancer epidemiology, the courses programme has innovated in three directions.

First, a three-week residential summer course in cancer registration has been initiated, designed in particular for IARC collaborators. This course combines theoretical and practical aspects and aims at providing comprehensive knowledge to ensure better management of cancer registry data.

A second innovation is a series of cancer genetics courses, in collaboration with the Gaslini Institute in Genoa, Italy.

Finally, the production of an IARC textbook on cancer epidemiology is well advanced. This volume, designed for use in basic courses on cancer epidemiology, is being published in three languages

Eight courses were organized during the period under review.

7.3.1

IARC summer school on cancer registration and applications in epidemiology, 5–26 August 1996, Lyon, France

This course was organized for IARC collaborators with the Unit of Descriptive Epidemiology (scientific director: Dr R. Sankaranarayanan) to provide training in cancer registration, cancer registry data management using CANREG software and cancer epidemiology. The participants came from Algeria, Bahrain, Cuba, India, Korea (Republic of), Romania, Saudi Arabia, Thailand, Turkey, Ukraine, and Viet Nam. This course was followed by practical training of a week in one of the European cancer registries.

7.3.2

Gaslini–IARC course in cancer genetics, 22–28 September 1996, Sestri Levante, Italy

More than 70 students from 22 countries attended this course, in which morning lectures were followed by afternoon workshops, part of which were devoted to discussions of genetic counselling for families with recurrence of cancer syndromes. Dr P. Kleihues and Dr G. Romeo co-chaired the scientific programme of the course.

7.3.3

International course on molecular biomarkers in environmental cancer epidemiology, 4–13 November 1996, Shanghai, China

Extending a series of similar courses, this one was intended for public health specialists, epidemiologists and laboratory scientists involved in activities aimed at identifying and reducing cancer risks in Asian and Australasian populations. The programme was directed towards the integration of molecular biomarkers into epidemiological studies to provide new information on cancer etiology. The course scientific directors were Dr H. Vainio (IARC) and Professor C.P. Wild from the Research School of Medicine, University of Leeds. A total of 39 participants, came from China, India, Japan, Korea (Republic of), Malaysia, Sri Lanka, Thailand and Vietnam. This course received financial support from the United States Environmental Protection Agency, that contributed to the funding of nine participants.

7.3.4

European Network of Cancer Registries (ENCR) course on survival analysis methods for cancer registries, 2–6 December 1996, Lyon, France

The ENCR, in collaboration with IARC, organized this course aimed at cancer registry staff and researchers involved in data analysis. Some 30 participants from Europe attended. The course director was Mr R. Black (IARC).

7.3.5

IARC summer school on cancer registration and applications in epidemiology, 12–30 May 1997, Lyon, France

The 1997 course in this successful series was was attended by twenty-one participants from China, India, Kazakstan, Republic of Korea, Malawi, Namibia, Nigeria, Oman, South Africa, Thailand, USA, Viet Nam, Yugoslavia and Zimbabwe. Dr R. Sankaranarayanan was the course director.

7.3.6

Advanced course on statistical methods - recent developments in biostatistics with potential applications in cancer research, 25–31 May 1997, Veyrier-du-Lac, France

This course was intended for confirmed biostatisticians and epidemiologists and attempted to provide an overview of the two main streams of theoretical development, i.e. the extension of the maximum likelihood modelling approach and the use of ideas such as 'quasi-likelihood' and 'estimating equations' to fit models which are specified in less detail and which make fewer assumptions. Forty candidates, coming from Australia, Brazil, Canada, China, Denmark, Finland, France, Germany, Hong Kong, Ireland, Israel, Japan, Spain Sweden, Thailand, United Kingdom and USA, were selected from 120 applications. The scientific direction was the co-responsibility of Dr J. Estève (IARC) and Professor D. Clayton from the MRC Biostatistics Unit, Cambridge, UK. The teaching responsibilities were shared with Professor N. Breslow (University of Washington, Seattle, USA), Dr Andrea Rotnitzky (Harvard School of Public Health, Boston (USA), Professor S. Zeger (Johns Hopkins School of Hygiene, Baltimore, USA) and Mr M. Plummer (IARC).

7.3.7

Gaslini–IARC course in cancer genetics, 25–30 September 1997, Sestri Levante, Italy

The number of students attending the second Gaslini–IARC course in cancer genetics was 57, from most of the countries of western Europe and the USA. Approximately one third of the students were supported by EC fellowships, within the framework of the EC Euroconference programme. Topics ranged from mapping and cloning of genes predisposing to cancer to social issues of genetic testing for cancer predisposition and genetic counselling for familial cancer.

7.3.8

Cancer epidemiology course, 20–31 October 1997, Abidjan, Côte d'Ivoire

This introductory course on epidemiology in French was open to medical doctors, as well as to other health-related professionals with an interest in initiating or pursuing work in cancer epidemiology. The emphasis was on methods of cancer epidemiology and the epidemiological

characteristics of cancer in Africa. The course was organized in collaboration with the World Health Organization, Office for Africa, and attended by 23 participants; the programme coordinator was Professor Michel Coleman from the London School of Hygiene and Tropical Medicine.

7.3.9
IARC Technical Transfer Awards

The recipients of these awards for the period concerned were Dr Yasmin Asif Bhurgri from the Karachi Cancer Registry, Pakistan and Dr Hai Rim Shin from Dong-A University, Korea. Two more awards were offered to participants from the cancer epidemiology course for French-speaking African countries, Dr N.Famoussa Diane, Conakry, Guinea, and Dr Sangwa Lugoma, Kinshasa, Democratic Republic of Congo.

Figure 52. Participants at the cancer epidemiology course in Abidjan, Côte d'Ivoire

7.3.10
IARC textbook on cancer epidemiology

The English, French and Spanish versions will be published early in 1998. This publication will be the reference book for all IARC introductory cancer epidemiology courses.

PART 8. SCIENTIFIC SUPPORT ACTIVITIES

8.1 Computing support service

M. Smans, P. Damiecki and B. Kajo

The rapid growth of the local area network (LAN) observed in previous years continued in the first part of the present biennium, so that more than 200 work stations are now connected (mostly PCs, but also Macintoshes and Unix workstations). More recently, acquisitions have generally been for replacement of older equipment rather than for entirely new connections.

This growth has led to overloading of the LAN and the main servers, which were originally planned to be used mainly for scientific computing. A new strategy for the use of computing resources at the agency has therefore been developed with the help of the Computing Services Committee and the scientific units. This will allow the increased demand for computing power to be absorbed and will also better respond to the evolution in the software packages used by scientists.

The new strategy, involving replacement of the computer cluster initially set up in 1989, was approved by both the Scientific Council and the Governing Council, and funding for the new equipment was made available. In the second half of 1997, the LAN was improved with the installation of an FDDI backbone; an Ethernet switch, a 400-gigabyte storage server, as well as applications servers, were installed, and applications are being moved to the new configuration.

File and print services for the 'office automation' users, previously provided by the main scientific server, are now running on a specialized NT server. In order to keep up with the ever-evolving standards in the area of office tools, the work stations used by secretaries have been updated, both in terms of hardware and software.

New services have been established in the administration area, for purchasing, budget and finance, inventory and registry, and possible further improvements are being assessed.

The use of Internet communications has been increasing, and use of electronic mail is now very extensive. The Agency's Web server has enjoyed a steadily growing number of visitors since its launch in 1995, and several units have now started their own dedicated servers, aimed at external or internal communications (see Section 7.1.7).

8.2 Library and information services

H. Miido, M. Coudert and L. Ossetian

The IARC Library works closely with the Computing Services Group to identify and implement technological advances which improve user access to scientific information. The library home pages, accessible on all office PCs through intranet, allow selection of library services from a single menu. Each service has a standard, easily used format, thus eliminating the need for library users to learn complicated database formats and languages. Services available through the library home pages include the ability to browse the latest Library Bulletin and order staff reprints or

borrow books; browse the journal holdings; search Medline through the US National Library of Medicine web browser; search other information sources through the Excite web browser; order reprints of articles not in the IARC library; and e-mail any requests or comments to the library. Future enhancements will include the ability to search the catalogue of library books, World Health Organization documents and annual reports held by the library.

The library home pages, accessed through a web browser installed on the Windows NT server are also available in modified form through the IARC Home Pages.

The basic library tasks of ordering and processing books and journals and maintaining the collections, managing in-house databases, and arranging interlibrary loans, previously performed on the VAX computer, have been transferred to the library Windows NT server. Medline records previously accessed through CD-ROMs are now searchable as a complete data-set from 1966 onwards. Current Contents has likewise been moved to the library server, where 36 weekly issues are retained for searching.

A Windows NT version of Reference Manager is expected to become operational by the end of 1997. FileMakerPro 3.0 has been installed, to allow relational capabilities in database implementation, and WinISIS provides access to the IARCPUB database containing details of IARC staff publications since 1993.

Educating library users and active dissemination of information continue to play an important role in library activities. Library staff present papers at meetings, take part in discussion groups concerning the future of libraries in the next century, and publish information about the unique systems and procedures developed at IARC (262).

8.3 Common laboratory services

8.3.1 Animal house

Z.-Q. Wang, H. Ohgaki, C.Witt, D.Galendo and M.-P. Cros

The animal house provides technical support for the various tumorigenesis studies of IARC. This animal facility is free of specific pathogens and now maintains 31 strains of rats and mice. Breeding stock and experimental animals are maintained and many strains of animals are also bought from commercial suppliers for specific experiments.

The technical staff of the animal house perform a variety of procedures for research projects, such as chemical carcinogenesis, tumour implantation, hepatectomy, vasectomy and administration of chemical substances by various routes, e.g. intravenous, intraperitoneal and subcutaneous, as well as painting and gavage. All manipulations are carried out under appropriate anaesthetic regimes following the specific IARC guidelines for the manipulation of animals.

While the rat has been the main animal model for many carcinogenicity studies in the past, transgenic and knock-out mice have become a powerful tool for the study of tumour biology, since genetically modified animals provide a unique system to study interactions of specific environmental insults and genetic information in mammals. The animal house has already hosted 25 strains of transgenic and knock-out mice, and a new laboratory has been set up for the production of such animals. This room is equipped with instruments necessary for manipulating mouse embryos and for generating new strains of transgenic and knock-out mice.

In order to facilitate the use of transgenic and knock-out mouse strains which have a lower health status than the animals already maintained, an embryo transfer procedure has been established, using an external holding room as well as a quarantine room in the main animal house. So far, 12 strains of mutant mice have been safely transferred into the animal house by embryo transfer.

The animals are used by all of the laboratory-based research units and programmes of IARC.

8.3.2
Histology laboratory

H. Ohgaki, M. Laval and N. Lyandrat

The histology laboratory processes all histological material from experimental animals in the Agency as well as human biopsy material sent by collaborators or Agency researchers carrying out fieldwork abroad. This includes routine histological stainings as well as immunohistochemical identification of marker proteins.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE THIRTY-SEVENTH SESSION OF THE IARC GOVERNING COUNCIL

16–17 May 1996

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United States of America
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Associate Director for International Affairs
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Mr E.E. Uhde
Comptroller and Director, Division of Budget and Finance

Dr C.-H. Vignes
Legal Counsel

Observers
Mr G. Miller
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Dr Adèle Green
Outgoing Chairman, Scientific Council

Professeur A. Sarasin
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Mr A.J. Turnbull
International Union Against Cancer, Geneva

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PARTICIPATING STATES AND REPRESENTATIVES AT THE THIRTY-EIGHTH SESSION OF THE IARC GOVERNING COUNCIL

1–2 May 1997

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Dr J.C. Barrett
Incoming Chairman, Scientific Council

Mr A.J. Turnbull
International Union Against Cancer, Geneva

External Audit
Mr F.A. Fakie
Representative of the Office of the Auditor General, Republic of South Africa

Annex 2

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS THIRTY-SECOND SESSION

29–31 January 1996

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---

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MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS THIRTY-THIRD SESSION

27–29 January 1997

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Annex 3

PERSONNEL AT IARC
1 January 1996 - 31 December 1997

Office of the Director

Director, IARC	Dr P. KLEIHUES
Special Adviser on Biostatistics	Dr J. ESTEVE (until 30.6.97) Dr A.B. MILLER (from 24 11.97)
Scientist	Dr I. RAJOWER (until 7.7.97)
Senior Editor	Dr J. CHENEY (half-time)
Administrative Assistant	Mrs E. RIVIERE
Assistant (Documents)	Mrs M.-H. CHARRIER

Unit of Environmental Cancer Epidemiology

Chief	Dr P. BOFFETTA
Scientists	Dr P. BRENNAN (from 1.3.1997) DR K. KJÆRHEIM (from 5.5.97) Dr E. MERLER (until 30.6.96 and 1.10.96–30.6.97)
Visiting Scientists	Dr V. BOURDES, Special Training Award (from 15.2.96) Dr N. JOURENKOVA, Special Training Award (until 30.6.96) Mr M. KRAUSS, Special Training Award (until 30.6.96) Dr S. LEA, Special Trai ning Award (1.9.96–31.8.97) Dr N. MALATS, Special Training Award (from 11.11.96) Dr E. RAPITI, Special Training Award (from 1.11.97) Dr L. RICHARDSON, Sabbatical (1.12.96–30.6.97, part-time) Mr F. ROESCH, Special Training Award (7.1.97–30.6.97) Dr D. SALI, Special Training Award (from 5.11.96, half-time) Dr J. SIEMIATYCKI, Visiting Scientist Award (11.12.96–5.12.97) Dr J. VENA, NIH Fogarty Senior International Fellowship (1.1.97–30.6.97) Dr V. WÜNSCH-FILHO, Brazilian National Council for Scientific and Technical Development Fellowship (until 29.3.96)
Assistants (statistics)	Mr D. COLIN Mr G. FERRO
Clerk	Miss V. GABORIEAU (from 29.4.96)
Students	Mr O. BOGILLOT, Special Training Award (from 1.10.97, half-time) Mr I. BURSTYN, Special Training Award (from 1.7.97) Miss E. COUTO, Special Training Award (9.4.96–24.4.97)

	Mrs M. GARRONI, Special Training Award (from 1.6.96, part-time)
	Miss G. RACINE, Special Training Award (until 15.5.96)
	Mr J.-M. REBOUILLAT, Special Training Award (from 7.4.97)
Secretary	Ms M. GEESINK

Unit of Nutrition and Cancer

Chief	Dr E. RIBOLI
Medical Officer	Dr R. SARACCI (from 1.5.97)
Scientists	Mr R. KAAKS
	Dr G. SCHULGEN (1.6.96–30.9.97)
Visiting Scientist	Dr P. TONIOLO, IARC Visiting Scientist Award (from 1.9 1997)
Technical Officers	Mrs N. SLIMANI
	Mrs R. CHARRONDIÈRE
	Mrs G. DEHARVENG (from 19.8.96)
	Mrs A.L. VAN KAPPEL–DUFOUR (until 30.9.97)
Laboratory Technicians	Miss B. VOZAR
	Mr D. ACHAINTRE (6.1.97–5.12.97)
Assistants (Statistics)	Mr B. HEMON
	Miss C. CASAGRANDE
	Mr M. MIGINIAC
Students	Ms B. BAUMEISTER, Special Training Award (from 14.10.96–15.4.97)
	Dr V. CHAJÈS, Special Training Award (from 15.4.96)
	Ms A. DE BREE (until 31.5.96)
	Ms F. DEMMA (13.2.96–30.6.96)
	Dr A. LUKANOVA (from 15.9.97)
	Ms T. NORAT (from 1.10.97)
	Ms B. SOMMERSBERG (15.2.97–14.8.97)
Secretary	Mrs S. SOMERVILLE

Unit of Field and Intervention Studies

Chief	Dr N. MUÑOZ
Scientist	Dr R. HERRERO (from 1.1.96)
Visiting Scientists	Dr Y.A. BHURGRI, IARC Technical Transfer Award (until 15.2.96)
	Dr H.R. SHIN, IARC Technical Transfer Award, (15.4.97–20.7.97)
	Dr A.P. VIZCAINO, grant from the Fundación para el fomento en Asturias de la investigación cientifica aplicada y la tecnologia (FICYT), Spain (until 30.6.97)

Statistician	Mr M. PLUMMER
Assistant (Courses)	Mrs M. DAVIS
Assistants (Statistics)	Mrs A. ARSLAN Mrs C. LAVE (8.1.96–25.10.96 and from 6.1.97)
Technical Assistant	Miss D. MAGNIN (until 31.12.97)
Student	Miss J.S. SMITH, grant from 3M Pharmaceuticals (from 1.9.97)
Secretary	Mrs H. LORENZEN

Unit of Descriptive Epidemiology

Chief	Dr D.M. PARKIN
Scientists	Mr R.J. BLACK (until 26.8.97) Miss L. GIBSON (Manila) (until 31.12.97) Dr E. KRAMAROVA Dr P. PISANI Dr R. SANKARANARAYANAN Miss R. WINKELMANN (from 4.4.97) Dr J. ZIEGLER (Uganda) (until 31.10.96)
Visiting Scientists	Dr S. BASHIR, Special Training Award (from 5.6.96) Dr V. BONADONA, Interne Santé Publique (28.5.96–27.11.96) Dr H. GARCIA-GIANNOLI, Special Training Award (half-time from 1.10.97) Dr P. PILLON, Interne de Pédia trie en DEA (2.11.96–31.10.97) Dr R. SWAMINATHAN, Special Training Award (15.7.96–15.10.96)
Technical Officers	Mr J. FERLAY Miss S. WHELAN
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Students	Ms A. HAEVE, Special Training Award (18.9.97–7.12.97) Ms K. PITAKSARINGKARN, Special Training Award (from 1.6.96) Mrs B. SINDIKUBWABO, Special Training Award (until 6.7.96) Mr B. TOHOUNDJONA, Special Training Award (from 1.6 .97)
Secretaries	Mrs E. BAYLE Miss O. BOUVY
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Unit of Genetic Epidemiology

Chief	Dr D. GOLDGAR (from 3.1.96)
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Laboratory Technician	Miss C. COUR (from 8.1.96)
Assistant (Statistics)	Miss H. RENARD
Technical Assistant	Miss C. BONNARDEL
Student	Mr A. SIBERT (from 7.10.96)
Secretary	Miss Y. GRANJARD (half-time)

Unit of Endogenous Cancer Risk Factors

Chief	Dr H. OHSHIMA
Scientists	Dr F. BIANCHINI-KAAKS (from 1.12.97) Dr S. CALMELS-ROUFFET (until 30.6.97) Dr C. MALAVEILLE Dr B. PIGNATELLI
Visiting Scientists	Dr B. AHN, Korea Science and Engineering Foundation Fellowship (from 20 October 1997) Dr C.-Q. LI, IARC Research Training Fellowship (from 9.12.97) Dr Q. SHAO, Fellowship from the Chinese Government and Special Training Award (until 30.9.97) Dr V. YERMILOV, Special Training Award (until 14.10.96) Dr Y. YOSHIE, Fel lowship from the Japan Society for the Promotion of Science (8.1.96–18.6.97)
Laboratory Research Assistant	Mrs I. GILIBERT
Laboratory Technician	Mrs A. HAUTEFEUILLE
Students	Mr S. AURIOL, Special Training Award (27.1.97–28.2.97 and from 11.6.97) Miss L. CHAZOTTE, Special Training Award (from 1.9.96)
Secretary	Mrs P. COLLARD

Unit of Gene–Environment Interactions

Chief	Dr Z.-Q. WANG (from 1.2.97) Dr C. WILD (until 19.3.96)
Scientists	Dr A. BARBIN Dr M. CASTEGNARO Dr M. FRIESEN (on sabbatical leave f rom 10.9.97)

Visiting Scientists	Dr S. ATAWODI, European Commission, Special Training Award (until 10.8.96) Dr P. CHOMARAT, Ligue Nationale contre le Cancer *and* the Johns Hopkins University, Special Training Award (until 9.4.97) Mrs D. GELDERBLOM, Natural Resources Institute (UK), Special Training Award (11.3.96–30.6.96 and 16.9.96–16.11.96; half-time) Dr W.C.A. GELDERBLOM, IARC Visiting Scientist Award (29.1.96–29.1.97) Dr A. GILES, European Commission, Special Training Award (18.3.96–20.6.97) Dr Y. GROSSE, European Commission, Special Training Award (5.2.96–31.3.97) Dr Z. HERCEG, Special Training Award (from 1.2.97) Dr W. HULLA, Special Training Award (from 1.2.97) Dr P. JACKSON, Association for International Cancer Research, Special Training Award (until 30.9.97) Mr A. SYLLA, Special Training Award (until 8.1.96) Dr W.-M. TONG, Special Training Award (from 20.9.97)
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Laboratory Technicians	Miss B. CHAPOT Mrs J. MICHELON Mr A. SCHOUFT (until 31.1.97)
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Secretaries	Mrs A.-M. MAILLOL Mrs Z. SCHNEIDER (half-time)

Animal House

Veterinary Adviser	Dr C. WITT
Laboratory Research Assistant	Mrs D. GALENDO
Laboratory Technicians	Mrs M.-P. CROS Mr J. GARCIA
Laboratory Aides	Mr J. CARDIA-LIMA Mr R. DRAY

Unit of Mechanisms of Carcinogenesis

Chief	Dr R. MONTESANO
Scientists	Dr J. HALL Dr P. HAINAUT Dr H. NAKAZAWA
Visiting Scientists	Dr C. BARNAS, Special Training Award and Fellowship from the Association pour la Recherche sur le Cancer Dr S. BOIVIN-ANGELE, Special Training Award (from 3.11.97) Dr K. CASTREN, IARC Research Training Fellowship (from 3.11.97) Dr F. EL-GHISSASSI (5.3.97–6.6.97) Dr Y. FURUKAWA, IARC Research Trainin g Fellowship and Special Training Award (20.1.96–31.7.97) Dr W. JONGMANS, Special Training Award (until 29.9.97) Dr S. NORTH, Special Training Award (from 20.10.97) Dr P. PELKONEN, Special Training Award (until 31.3.96) Dr P. TANIÈRE, Detachment from Hôpital Edouard-Herriot, Lyon (part-time) Dr G. VERHAEGH, Special Training Award (until 5.9.96)
Laboratory Research Assistants	Miss H. BRESIL (until 31.5.96) Mrs G. MARTEL-PLANCHE Mrs M. VUILLAUME
Students	Miss T. HERNANDEZ, Special Training Award (fro m 30.9.96) Ms M.G. LUCIANI (from 1.7.96) Miss S. LAEJABOK, Special Training Award (until 31.3.96) Mrs C. MEPLAN (from 14.10.96) Mr O. PLUQUET (from 4.8.97) Mr G. RODRIGO, Special Training Award (2.9.96–3.10.97) Ms S. ROTH, ICRETT Fellowship and Fellowship from European Science Foundation (2.1.96–21.1.96, 2.3.96–3.4.96 and 10.5–30.8.96) Mr A. SOUABNI (until 30.4.96)
Assistant (Fellowships)	Mrs E. EL-AKROUD
Secretary	Mrs M.WRISEZ

Programme of Molecular Toxicology

Head	Dr M. LANG (until 27.3.97)
Visiting Scientist	Dr C. SAPPEY, Special Training Award (until 31.12.96)
Laboratory Research Assistant	Mrs A.-M. RANDON
Students	Mrs A. TILLOY-ELLUL, Special Training Award

Mrs F. RAFFALLI-MATHIEU, fellowship from Association pour la Recherche sur le Cancer, Special Training Award (until 30.6.97)

Gambia Hepatitis Intervention Study

Project Leader/Epidemiologist	Dr A. JACK (until 31.12.97)
Project Co-ordinator	Dr R. MONTESANO
Research Assistants	E. BAH M. MENDY
Medical Officer	Dr S. VIVIANI (until 31.8.97)
Visiting Scientist	Dr G. KIRK (from 9.1.97)
Statistician/Programmer	Mr N. MAINE (until 31.7.96)

Unit of Genetic Cancer Susceptibility

Chief	Dr G. ROMEO
Scientists	Dr B. SYLLA (on sabbatical leave from 1.9.97) Dr F. CANZIAN (from 2.9.96) Dr L. YIN
Visiting Scientists	Dr A. BOLINO, Fellowship from the Association pour la Recherche sur le Cancer (4.4.96–1.10.96) Dr R. CORVI, Special Training Award (from 3.2.97) Dr M.R. DE MIGLIO, fellowship from Associazione Italiana per la Ricerca sur Cancro (from 17.7.97) Dr S. GAUDI, Special Training Award (until 15.12.96) Dr M. STARK, Special Training Award (from 1.2.96)
Laboratory Research Assistant	Mrs M. F. LAVOUE
Laboratory Technician	Mrs S. PAULY
Students	Ms L. BJØRKHAUG, Special Training Award (until 28.12.96) Ms M. CREAVEN, EC Fellowship (until 5.11.96) Ms H. DELAGE, Special Training Award (1.4.97–5.5.97 and 1.7.97–30.9.97) Mr F. HEITZMANN, Fellowship from Ligue Nationale contre le Cancer, Special Training Award and fellowship from the Association pour la Recherche sur le Cancer (until 1.11.97) Mr J. LAMARTINE, Université Claude Bernard, Lyon 1 (1.1.96–7.11.96) Ms T. TOCCO, Special Training Award (3.10.96–2.10.97)
Secretary	Mrs A. TROCHARD

Programme of Viral and Hereditary Factors in Carcinogenesis

Head	Dr G. LENOIR (joint appointment with the Université de Lyon)
Visiting Scientists	Dr V. DUBOIS (until 1.9.96) Dr G. LESCA (from 11.12.96) Dr S. MAZOYER, Special Training Award and INSERM Scientist Dr O. SEROVA-SINILNIKOVA, Post-Doctoral Fellow and Scientist from Hospices Civils de Lyon Dr R. WILMOTTE, Post-doctoral Fellow, Special Training Award (from 1.1.97)
Laboratory Technician	Miss F. COTTIN (10.1.96–12.7.96)
Students	Miss C. BIDAUD, Special Training Award (10.2.97–30.9.97) Ms L. BOUTRAND, Special Training Award Mrs V. DUBOIS, DEA student (until 1.9.96) M. G. LESCA, medical internship (11.12.96–31.5.97) Ms N. PUGET, Comité Départemental de Haute Savoie, Ligue Nationale contre le Cancer
Laboratory technician	Miss F. COTTIN (10.1.96–12.7.96)

Unit of Molecular Pathology

Chief	Dr H. OHGAKI
Visiting Scientists	Dr W. BIERNAT, Special Training Award (until 15.11.96 and 3.4.97–8.6.97) Mr P.-P. BRINGUIER, Special Training Award (1.7.96–31.7.97) Dr C. GRATAS, Special Training Award (5.2.96–30.9.97) Dr H. HUANG (from 1.10.97) Professor O.D. LAERUM (2.5.96–31.10.96) Dr A. PERAUD, Grant from Gertrud-Reemtsma-Stiftung (from 3.3.97) Dr K. SATO, Fellowship from the Japanese Ministry of Education (until 31.3.96) Professor G. STOICA (6.5.97 –5.11.97) Dr O. TACHIBANA Fellowship from the Japanese Ministry of Education (until 20.3.96) Mr Y. TOHMA, Special Training Award (3.6.96–31.12.97) Dr K. WATANABE Special Training Award (until 5.1.96 and 1.12.96–31.1.97)
Laboratory Research Assistant	Mr J.-C. BEREZIAT
Secretary	Mrs E. PEREZ (half-time)

Histopathology Laboratory

Laboratory Research Assistant	Miss M. LAVAL
Laboratory Technician	Mrs N. LYANDRAT

Unit of Multistage Carcinogenesis

Chief	Dr H. YAMASAKI
Scientists	Dr V. KRUTOVSKIKH Dr M. MESNIL Dr N. MIRONOV Dr Y. OMORI (8.1.97–5.12.97)
Visiting Scientists	Dr P.-P. BRINGUIER, Université Claude-Bernard (from 1.9.97) Dr A. DANCER, Special Training Award (until 31.10.97) Dr L. GIROLDI, Special Training Award (since 1.1.97) Dr G. GOLDBERG, ICRETT Fellowship (15.9.97–31.11.97) Dr L. JANSEN, IARC Research Training Fellow (since 1.7.97) Dr T. KASAMATSU, Special Training Award (14.8.96–31.12.97) Dr J. LÜBBE, Swiss Cancer League Fellowship (until 31.12.96) Dr C. NAUS, IARC Visiting Scientist Award (until 21.2.96) Dr A. OUHTIT, Special Training Award (until 27.6.97) Dr T. SAITO, Sapporo Medical College Fellowship (until 28.3.97) Dr T. SUZUKI, Fellowship from Japanese Ministry of Technology (from 1.8.97) Dr T. TANAKA, Japanese Fellowship (from 1.9.97) Dr K. YAMAKAGE, Special Training Award (from 1.4.96) Dr M.-L. ZAIDAN-DAGLI, FAPESP Fellowship (from 1.9.97) Dr W.-B. ZHU, Special Training Award (from 1.12.96)
Laboratory Research Assistants	Mrs A.-M. AGUELON-PEGOURIES Miss N. MARTEL Mrs C. PICCOLI
Students	Miss M. KALLASSY, Fellowship from the Université Claude-Bernard, Lyon Miss M. LALOO (3.3.97–31.7.97) Miss G. REGUER (21.4.97–31.8.97) Mr A. SOUABNI, Special Training Award (15.5.96–3.9.96)
Secretary	Mrs C. DECHAUX
Laboratory Aides	Mrs M. ESSERTEL Mrs N. FARINA Miss M. MARANHAO Mrs S. VEYRE

Unit of Carcinogen Identification and Evaluation

Chief	Dr J. RICE (from 6.6.96)
Scientists	Dr D. McGREGOR Mr J. WILBOURN Dr M. BLETTNER (from 1.9.97) Mr Y. GROSSE (7.4.97–6.6.97 and 25.8.97–5.12.97) Mrs F. MATHIEU-RAFFALI (28.7.97–30.9.97)
Technical Officer	Mrs C. PARTENSKY

Technical Assistants	Mrs D. MIETTON Mrs J. MITCHELL
Secretary	Miss S. REYNAUD
Clerks	Mrs M. LEZERE Mr J. CEREDA (8.1.96–6.12.96 and 2.1.97–28.11.97) Miss S. RUIZ

Unit of Chemoprevention

Chief	Dr H. VAINIO
Technical Officer	Mr G. MORGAN (3.3.97–1.8.97)
Technical Assistant	Mrs A. MENEGHEL
Secretary	Mrs J. THEVENOUX

Programme of Radiation and Cancer

Head	Dr E. CARDIS
Scientist	Dr M. MARTUZZI (from 1.4.96)
Visiting Scientists	Dr D. GUO, Special Training Award (until 30.9.96) Dr A. KESMINIENE, Special Training Award (from 9.6.97) Dr D. SALI, Special Training Award (until 16 2.96 and 22.4.96–24.5.96)
Clerk	Miss E. AMOROS (from 2.5.96)
Students	Dr M. HOURS (until 31.1.97) Miss M. KILKENNY (8.7.97–31.12.97) Miss I. THIERRY-CHEF, Special Training Award (3.4.96 – 31.12.97))
Secretaries	Mrs B. ANDRIEUX (half-time) Mrs O. DRUTEL (half-time)

Programme of Epidemiology for Cancer Prevention

Head	Dr A.J. SASCO (from INSERM, on special assignment to IARC)
Visiting Scientist	Professor M. ABRAHAMOWICZ (9.9.96–8.9.97)
Students	Dr R. AH-SONG, Special Training Award Miss C. CHESNEAU (until 30.9.96) Mr C. DUSSART (from 1.7.96) Miss I. GENDRE, Special Training Award Ms N. MARDIGUIAN (from 1.4.96) Mrs M. MARSOT Miss C. MUTATAYI (5.5.97–30.9.97) Dr M. PONCET (1.1.96–30.9.96) Mr B. RACHET, Special Training Award

	Mr E. SAAD, Interne en santé publique (until 30.4.96) Mrs M.-P. VERGNON (1.4.96–31.7.96 and 3.2.97–30.9.97)
Secretaries	Ms S. HAVER (until 15.11.96) Mrs M. RENAUD (from 9.4.96)
Clerk	Mrs V. BENHAIM-LUZON (2.1.96–1.11.96, 11.11.96–11.7.97 and from 3.11.97)

Editorial and Publications Service

Head	Dr S. JONES (on sabbatical leave from 1.9.97)
Technical Officer	Mrs C. GOLDGAR (from 29.9.97)
Assistant (IARC Press)	Miss S. COTTERELL
Secretary	Mrs M. MAINAUD (half-time)
Laboratory Research Assistant (Photography)	Mr G. MOLLON

Library

Librarian	Miss H. MIIDO
Technical Assistant (Search Analyst)	Mrs M. COUDERT
Assistant (Library)	Mrs L. OSSETIAN

Division of Administration and Finance

Director	Mr M.P. JOHNSON
Administrative Assistant	Mrs D. MARCOU
Translation	
Translator	Dr N. GAUDIN
Secretary	Mrs A.-C. MORET
Personnel	
Personnel Officer	Mrs A. ESCOFFIER
Clerk	Mrs C. MOGENET
Social Adviser	Mrs M.A. VIOT-COSTER (until 1.8.96, 5.9.96–31.7.97 and from 4.9.97)
Budget and Finance	
Finance Officer	Mr A. MITRA (from 1.3.96)
Administrative Assistants	Mr C. AUGROS Mrs W. FEVRE- HLAHOLUK

Assistant (Accounting)	Mrs M. HERIN
Assistant (Payments)	Mrs F. ROMAGNAN
Secretary	Mrs A. RIVOIRE
Clerk (Cashier)	Mr D. HORNEZ
Clerk (Accounts)	Mrs D. LOMBARDO
Clerks (Finance)	Mrs F. FLORENTIN (half-time) Mrs A. SEGURET (half-time)
Computing Service Group	
Head/Computer Systems Manager	Mr M. SMANS
Computer Analyst/System Manager	Mr P. DAMIECKI
Computer Operator	Mrs B. KAJO (half-time)
Administrative Services	
Administrative Services Officer	Mr G. GUILLERMINET
Administrative Assistant	Mrs R. ALLOIN
Clerk	Mrs M. LEPETIT
Switchboard Operator	Mrs R. KIBRISLIYAN
Driver	Mr J.-F. DURAND-GRATIAN
Usher (Messenger)	Mr M. JAVIN
Maintenance Technicians	Mr M. BARBIEUX Mr M. BAZIN Mr J.-P. BONNEFOND Mr G. THOLLY
Assistant (Registry)	Mrs M. GREENLAND
Clerk (Registry)	Mrs L. VIGIER
Assistant (Supplies)	Mrs J. POPOFF
Clerks (Supplies)	Mrs M. FILIPPI Mr M. PRAT (until 30.5.97)
Student	Mr L. RIPERT (from 2.6.97)
Equipment Operator (Reproduction)	Mr D. GRAIZELY

Annex 4

SHORT-TERM VISITING SCIENTISTS AND TRAINEES

Visitors

Dr R. Ariffin, Unit of Descriptive Epidemiology (29 September–26 October 1997)

Dr S. Bashir, Unit of Descriptive Epidemiology (9–25 March 1996 and 13 May–4 June 1996)

Dr I. Bernucci, Unit of Environmental Cancer Epidemiology (28 October–13 December 1996)

Dr R. Biggar, Unit of Carcinogen Identification and Evaluation (25–29 March 1996)

Ms L. Branston, Unit of Descriptive Epidemiology (16 June–15 July 1997)

Mr F. Bray, Unit of Descriptive Epidemiology (27 July–9 August 1997)

Mr A.M. Budukh, Unit of Descriptive Epidemiology (3 April–10 May 1996)

Dr E. Buiatti, Unit of Field and Intervention Studies (2–24 January 1997)

Dr M. Bulbulyan, Unit of Environmental Cancer Epidemiology (3–14 August 1997)

Dr K. Chindavijak, Unit of Descriptive Epidemiology (25–29 May 1997)

Dr K. Chrzanowska, Unit of Mechanisms of Carcinogenesis, ICRETT Fellowship (18–28 November 1997)

Dr E. De Stefani, Unit of Environmental Cancer Epidemiology (23 June–4 July 1997)

Dr O.T. Djatchenko, Unit of Descriptive Epidemiology (23 June–29 June 1996)

Dr W.C. Eastin, Unit of Carcinogen Identification and Evaluation (12–16 May 1997)

Dr I. Filipe, Unit of Field and Intervention Studies (2–11 February 1997)

Dr C. Fortes, Unit of Environmental Cancer Epidemiology (5–11 June 1997)

Dr S. Franceschi, Unit of Carcinogen Identification and Evaluation (25–29 March 1996) and Unit of Field and Intervention Studies (23 June–4 July 1997)

Dr C. Gallo, Unit of Mechanisms of Carcinogenesis, ICRETT Fellowship (10 February–27 March 1997 and 20 October–21 November 1997)

Dr M. Goldberg, Unit of Environmental Cancer Epidemiology (9–14 May 1996)

Dr C.Z. Guaman Unit of Descriptive Epidemiology (8–11 June 1996)

Dr I. Hertz-Piciotto, Unit of Environmental Cancer Epidemiology (several short-term visits)

Dr E. Hietanen, Unit of Chemoprevention and Unit of Nutrition and Cancer (16–27 June 1997 and 15 July–1 August 1997)

Dr J. Iscovich, Unit of Environmental Cancer Epidemiology and Unit of Nutrition and Cancer (several short-term visits, one of which with an ICRETT fellowship)

Dr Jian-Guo Chen, Unit of Descriptive Epidemiology (5 September–3 November 1996)

Mr I.S. Kabba, Unit of Descriptive Epidemiology (21 April–18 May 1996)

Dr S. Koifman, Unit of Environmental Cancer Epidemiology (23–27 June 1997)

Dr M. Konstandi, Programme on Molecular Toxicology, Unit of Mechanisms of Carcinogenesis (24 August–25 September 1996)

Dr E. Lazcano Ponce, Unit of Field and Intervention Studies (27 June–5 July 1997)

Dr G. Lovas, Unit of Molecular Pathology, Special Training Award (15 April–8 June 1997)

Mr J. Madhoo, Unit of Descriptive Epidemiology (2–19 March 1996)

Dr M. Marshall, Programme of Radiation and Cancer (19–25 October 1997)

Dr E. Matos, Unit of Environmental Cancer Epidemiology (22 May – 4 June 1997)

Dr K. Meguenni, Unit of Descriptive Epidemiology (27 November–20 December 1996)

Professor V.M. Merabishvili, Unit of Descriptive Epidemiology (23–29 June 1996)

Dr M. Miwa, Unit of Endogenous Cancer Risk Factors (27–31 October 1997)

Dr S. Moolgavkar, Programme of Radiation and Cancer (1–5 July 1996)

Ms S. Nambooze, Unit of Descriptive Epidemiology (13 May–5 June 1996)

Mrs G. Nicholson, Unit of Carcinogen Identification and Evaluation (15–23 September 1997)

Dr S. Nimmannit, Unit of Descriptive Epidemiology (25–29 May 1997)

Dr F. Nyberg, Unit of Environmental Cancer Epidemiology (3–14 February 1997)

Dr M.-E. Parent, Unit of Environmental Cancer Epidemiology (20–24 January 1997 and 1–12 September 1997)

Dr T. Partanen, Unit of Environmental Cancer Epidemiology, temporary staff member (23 October–31 December 1996)

Dr N. Pearce, Unit of Environmental Cancer Epidemiology (24–28 June 1996)

Dr P. Pelkonen, Unit of Mechanisms of Carcinogenesis (23 September–10 October 1996)

Dr Pham Hoang Anh, Unit of Descriptive Epidemiology (22 June–13 July 1996)

Dr F. Pinto, Unit of Mechanisms of Carcinogenesis, ICRETT fellowship (9–13 September 1996)

Dr R. Rajkumar, Unit of Descriptive Epidemiology (2–28 March 1996)

Mr M. Râmet, Unit of Mechanisms of Carcinogenesis (5–26 January 1996 and 2–13 July 1997)

Dr M. Rautalahti, Unit of Chemoprevention (22 September–17 October 1997 and 8–19 December 1997)

Dr L. Reyes, Unit of Descriptive Epidemiology (30 June 1997–19 July 1997)

Dr S. Roth, Unit of Environmental Cancer Epidemiology and Unit of Mechanisms of Carcinogenesis (27 March–3 April 1996)

Dr O. Rotimi, Unit of Descriptive Epidemiology (9–26 February 1996)

Mr M. Rowley, Unit of Carcinogen Identification and Evaluation (12–16 May 1997)

Dr R. Saracci, Unit of Environmental Cancer Epidemiology (several short-term visits in 1996)

Dr L. Simonato, Unit of Environmental Cancer Epidemiology (several short-term visits)

Miss Siriporn La-Ormatana, Unit of Mechanisms of Carcinogenesis, ICRETT fellowship (7 January–2 March 1997)

Ms T. Sørlie, Unit of Mechanisms of Carcinogenesis (23 April–11 May 1996)

Ms S. Sriamporn, Unit of Descriptive Epidemiology (29 April–4 May 1996 and 20–28 August 1996)

Dr P. Srivatanakul, Unit of Descriptive Epidemiology (7–17 May 1996 and 25–29 May 1997)

Mr A. Sylla, Unit of Gene–Environment Interactions, ICRETT fellowship and University of Leeds (UK) funding (19 September–30 November 1997)

Dr G. Taylor, Unit of Carcinogen Identification and Evaluation (25–29 March 1996)

Ms M. Terblanche, Unit of Descriptive Epidemiology, ICRETT Fellowship (2–19 March 1996)

Dr J. Torrado, Unit of Field and Intervention Studies (2–8 February 1997)

Dr K. Vähäkangas, Unit of Mechanisms of Carcinogenesis (24 July–2 August 1996 and 28 October–29 November 1996)

Dr Y. Wallis, Unit of Mechanisms of Carcinogenesis (4 August–30 September 1997)

Dr Q. Yang, Unit of Gene–Environment Interactions (30 June–27 July and 10 November–9 December 1997)

Dr Z.M. Zain, Unit of Descriptive Epidemiology (11–15 September 1996)

Dr L. Zeise, Programme of Radiation and Cancer (1–5 July 1996)

Trainees

Mr F. Aberkane, Unit of Genetic Cancer Susceptibility (3–7 February 1997)

Dr N. Bazoulko, Programme of Radiation and Cancer (25 February–19 March 1996 and 19–30 March 1997)

Mr J. Beaufort, Unit of Genetic Cancer Susceptibility (1 April–5 May 1996)

Mr T. Blanc, Unit of Nutrition and Cancer (28 July–25 August 1997)

Miss A.-C. Bocquet, Unit of Environmental Carcinogenesis (10 June–14 August 1996)

Miss M. Boutard, Unit of Multistage Carcinogenesis (21 April–27 June 1997)

Dr R. Brohet, Unit of Genetic Epidemiology (8 July–14 September 1996)

Mr J. Butler, Unit of Environmental Cancer Epidemiology, Special Training Award (3 November–31 December 1997)

Miss A.E. Carteau, Programme of Viral and Hereditary Factors in Carcinogenesis (6–10 January 1997)

Dr O. Changuina, Unit of Environmental Cancer Epidemiology, ICRETT fellowship (23 April–22 May 1997)

Dr T. Chervonobab, Unit of Environmental Cancer Epidemiology, CECHE fellowship (24 June–2 August 1996)

Ms D. Clerc, Unit of Descriptive Epidemiology (12 July–11 August 1996)

Ms C. Coiffier, Unit of Endogenous Cancer Risk Factors (29 January–1 March 1996 and 19 August–4 October 1996)

Mr U. Cortes, Unit of Mechanisms of Carcinogenesis (1 April–6 May 1996)

Ms C. Curial, Unit of Endogenous Cancer Risk Factors (13 May–15 June 1996)

Miss A. Damiron, Unit of Multistage Carcinogenesis (21 April–27 June 1997)

Miss L. Derain, Programme of Epidemiology for Cancer Prevention (3–8 February 1997)

Miss S. Dorel, Programme of Epidemiology for Cancer Prevention (9–27 June 1997)

Mr B. Duroux, Unit of Endogenous Cancer Risk Factors (3 June–19 July 1996)

Miss M. Fioretta, Programme of Epidemiology for Cancer Prevention (4–29 November 1996)

Mr T. Georg, Unit of Nutrition and Cancer (4–22 March 1996)

Miss S. Gidrol, Unit of Gene–Environment Interactions (1 April–5 May 1997)

Ms S. Grandidier, Unit of Endogenous Cancer Risk Factors (23 October–2 December 1997)

Miss P. Guicherd, Unit of Mechanisms of Carcinogenesis (17–28 February 1997)

Miss H. Hannah, Unit of Gene–Environment Interactions (21 April–27 June 1997)

Mr I. Kathiriya, Unit of Genetic Cancer Susceptibility (20 May–10 August 1996)

Dr D. Kielkowski, Unit of Environmental Cancer Epidemiology, ICRETT fellowship (9 May–8 June 1996)

Dr A. Konogorov, Programme of Radiation and Cancer (25 February–19 March 1996 and 19–30 March 1997)

Miss A. Kouchkar, Programme of Viral and Hereditary Factors in Carcinogenesis (10 September–10 October 1997)

Miss S. Laejabok, Unit of Environmental Carcinogenesis and Unit of Mechanisms of Carcinogenesis, Special Training Award (until 5 January 1996)

Miss F. Largardette, Unit of Mechanisms of Carcinogenesis (2 June–18 July 1997)

Mr A. Lebas, Unit of Multistage Carcinogenesis (21 April–27 June 1997)

Mr R. Léty, Unit of Multistage Carcinogenesis (21 April–27 June 1997)

Mr J. Lukanu, Unit of Mechanisms of Carcinogenesis (14 May–2 July 1997)

Miss M. Martin, Unit of Mechanisms of Carcinogenesis (10–14 June 1996)

Mr D. Maximovitch, Unit of Environmental Cancer Epidemiology, ICRETT fellowship (11 November–6 December 1996)

Dr R.M. Miñarro, Unit of Descriptive Epidemiology (13 January–28 February 1996)

Ms M. Nielsen, Unit of Multistage Carcinogenesis (9–11 May 1996)

Miss H. Ozdag, Programme of Viral and Hereditary Factors in Carcinogenesis (18 August–7 September 1997)

Miss G. Parnaud, Unit of Endogenous Cancer Risk Factors (6–31 October 1997)

Miss C. Patuzzo, Programme of Viral and Hereditary Factors in Carcinogenesis (24 June–21 July 1996)

Miss N. Perotto, Unit of Environmental Carcinogenesis (22 April–30 June 1996)

Miss L. Perrin-Vidoz, Programme of Viral and Hereditary Factors in Carcinogenesis (15 June–1 August 1997)

Mr N. Pirodon, Unit of Molecular Pathology (6 January–7 February 1997 and 5 May–6 June 1997)

Mr O. Pluquet, Unit of Mechanisms of Carcinogenesis (4 August–27 September 1997)

Miss S. Pons, Unit of Molecular Pathology, Special Training Award (12–30 August 1996)

Dr E. Rastopchin, Programme of Radiation and Cancer (25 February–19 March 1996)

Miss S. Rioufreyt-Laurençon, Unit of Gene–Environment Interactions (1 May–31 July 1997)

Miss N. Rivier, Programme of Epidemiology for Cancer Prevention (11 March–5 April 1996)

Mr A. Rolland, Unit of Multistage Carcinogenesis (21 April–27 June 1997)

Dr D. Sali, Programme of Radiation and Cancer (14 January–16 February 1996 and 22 April–24 May 1996)

Miss S. Seemann, Unit of Mechanisms of Carcinogenesis (1 April–2 May 1997)

Miss V. Serrano, Programme of Epidemiology for Cancer Prevention (8 January–2 February 1996)

Mr J. Sicard, Unit of Mechanisms of Carcinogenesis (29 February–6 March 1996)

Dr R. Swaminathan, Unit of Descriptive Epidemiology (8 August–17 October 1997)

Miss M.-L. Tramoni, Programme of Epidemiology for Cancer Prevention (24 February–14 March 1997)

Mrs S. Vacher, Programme of Epidemiology for Cancer Prevention (17 March–11 April 1997)

Dr S. Vanagel, Programme of Radiation and Cancer (25 February–19 March 1996)

Annex 5

RESEARCH AGREEMENTS BETWEEN IARC AND VARIOUS INSTITUTIONS
1 January 1996–31 December 1997

Cancer registries

DEB/73/16	International Association of Cancer Registries (Provision of a secretariat and other supporting services)
DEP/87/01	Hanoi Cancer Institute, Hanoi, Viet Nam (Cancer Registry of Hanoi)
DEP/87/02	National Institute of Public Health, Bamako, Mali (Cancer Registry of Mali)
DEP/89/10	Department of Pathology, National University of Trujillo, Trujillo, Peru (Cancer Registry of Trujillo)
DEP/89/11	Department of Epidemiology and Preventive Medicine, University Hospital, Sétif, Algeria (Cancer Registry of Sétif)
DEP/91/04	National Centre of Anatomo-Pathology, Faculty of Medicine, University of Conakry, Conakry, Guinea (Cancer Registry of Conakry)
DEP/92/02	Argentinian Association on Education and Prevention of Cancer, Bahia Blanca, Argentina (Cancer registry of Southern Buenos Aires Province)
DEP/92/10	Faculty of Medical Sciences, University of Niamey, Niamey, Niger (Cancer Registry of Niger)
DEP/92/16	Barshi Rural Cancer Registry, Ashwini Rural Cancer Research and Relief Society, Barshi, India (Barshi Rural Cancer Registry)
DEP/93/03	Zimbabwe Cancer Registry, Harare, Zimbabwe (Cancer Registry of Zimbabwe)
DEP/93/05	Queen Elizabeth Hospital, Blantyre, Malawi (Cancer Registry of Blantyre)
DEP/93/08	Comprehensive Cancer Centre North, Groningen, Netherlands (European Network of Cancer Registries: Mini-fellowships programme)
DEP/93/12	Regional Cancer Centre, Trivandrum, India (Establishment of a surveillance system to monitor cancer incidence and mortality in Trivandrum, Kazhakuttam and Chirayinkil development blocks in Kerala, India)
DEP/94/11	National Committee for the Fight Against Cancer in Cameroon, Yaoundé, Cameroon (Establishment of a population-based cancer registry in Yaoundé)
DEP/94/12	Makerere University Medical School, Kampala, Uganda (Kampala Cancer Registry)
DEP/95/01	Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire (Etablissement d'un registre du cancer du sein de la population d'Abidjan)
DEP/95/06	Christian Fellowship Community Health Centre, Ambilikkai, Tamil Nadu, India (Computerization of the population-based cancer registry in Ambilikkai for monitoring of cancer control)
DEP/95/07	Gujarat Cancer and Research Institute, Gujarat, India (Computerization of the population-based cancer registry for Ahmedabad, for improvement of registry operations)

DEP/95/08	Sindh Government Services Hospital, Karachi, Pakistan (Cancer Registry of Karachi)
DEP/95/17	Centre Claude Regaud, Toulouse, France (European Network of Cancer Registries Course in Cancer Registration, 1996)
DEP/95/18	Centre Hospitalier et Universitaire de Brazzaville, Congo (Cancer Registry of Brazzaville)
DEP/95/20	The Anti-Cancer and Non-Smoking Promotion Committee, Ministry of Health, Vientiane, Lao P.D.R. (Establishment of a cancer registry in Vientiane)
DEP/95/21	Registro de Cancer de La Paz, La Paz, Bolivia (Evaluation of cancer registration)
DEP/96/20	National Cancer Committee, Queen Elisabeth Central Hospital, Blantyre, Malawi (Cancer registration for the city and district of Blantyre)
DEP/96/21	UK Association of Cancer Registries, Sheffield, UK (European Network of Cancer Registries Course in Cancer Registration, 1997)
DEP/96/22	Ho Chi Minh City Cancer Center, Viet Nam (Population-based cancer registry for the City of Ho Chi Minh)
DEP/97/01	The Chittaranjan National Cancer Institute, Calcutta, India (Establishment of a population-based cancer registry in Metropolitan Calcutta)
DEP/97/03	Faculté des Sciences de la Santé, Université de Niamey, Niger (Registre du Cancer du Niger)

Incidence studies

DEP/96/04	Institute of Hematology, Minsk, Belarus (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/96/05	Department of Epidemiology and Cancer Control, National Oncological Centre, Sofia, Bulgaria (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/06	Czech National Cancer Registry, Brno, Czech Republic (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/07	Department of Pediatrics, National Institute of Child Health, Semmelweis Medical University, Budapest, Hungary (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/08	Latvian Cancer Registry, Riga, Latvia (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/09	Lithuanian Oncological Centre, Vilnius, Lithuania (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/96/10	Polish Cancer Registry, The Maria-Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/11	Institute of Hygiene and Publ ic Health, Bucharest, Romania (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/12	Research Institute of Pediatric Hematology, Moscow, Russian Federation (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/96/13	Cancer Research Institute, Bratislava, Slovak Republic (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/96/16	Cancer Registry of Slovenia, Institute of Oncology, Ljubljana, Slovenia (European Childhood Leukaemia/Lymphoma Incidence study (EC LIS))
DEP/96/17	Geneva Cancer Registry, Geneva, Switzerland (Cancer mortality in migrants to France, 1979–1985)
DEP/96/18	Estonian Cancer Registry, Institute of Experimental & Clinical Medicine, Tallinn, Estonia (European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/19 Petrov Research Institute of Oncology, St Petersburg, Russian Federation
(European childhood leukaemia/lymphoma incidence study (ECLIS))

DEP/96/24 Kyyiv Institute of Haematology and Blood Transfusion, Kiev, Ukraine
(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

DEP/97/05 Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden
(Cancer attributable to reproductive factors, obesity and physical exercise in the European Union)

Studies of cancer survival

DEP/96/14 Indian Cancer Society, Bombay, India
(Estimation of population-based survival rates for head and neck, colo-rectal and prostate cancers in Bombay)

DEP/97/02 Indian Cancer Society, Bombay, India
(Estimation of population-based sur vival rates for aerodigestive cancers and lymphoreticular neoplasms in Bombay)

Second cancers and DNA damage following chemotherapy

ECE/96/01 Institute of Carcinogenesis, Moscow, Russian Federation
(Second cancer following chemotherapy for Hodgkin's disease)

ECE/96/02 Cancer Institute (WIA), Madras, India
(Second cancer following chemotherapy for Hodgkin's disease)

ECE/96/03 Institute of Carcinogenesis, Moscow, Russian Federation
(Markers of DNA damage and lung cancer risk in non-smokers)

Studies on breast cancer

DEP/95/03 Rizal Cancer Registry, Rizal Medical Center, Manila, Philippines
(Enhanced surveillance of breast cancer incidence and mortality in the population of 12 municipalities of the greater Manila area)

DEP/96/01 Rizal Cancer Registry, Rizal Medical Center, Manila, Philippines
(Enhanced activity of the cancer registry)

DEP/96/03 Department of Health, Manila, Philippines
(Randomized controlled trial of breast cancer screening by physical examination in Manila)

ECP/95/01 Geneva Cancer Regis try, Geneva, Switzerland
(Etude du risque de deuxièmes cancers spécifiques après cancer du sein)

ECP/95/02 Association pour le développement et l'épidémiologie de santé publique, Strasbourg, France
(Etude du risque de deuxièmes cancers spécifiques après cancer du sein)

Studies on cervical cancer

FIS/95/01 Division de Epidemiologia, Instituto Nacional de Cancerologia, Bogotá, Colombia
(Cohort study on human papillomavirus and cervical cancer)

FIS/95/02 Department of Immunology and Infectious Diseases, Sch ool of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA
(Follow-up study to evaluate the role of human papilloma virus in the causation of cervical neoplasia)

FIS/95/05 Department of Social Medicine, Faculty of Medicine, Universidad del Valle, Cali, Colombia
(Follow-up study to evaluate the role of human papilloma virus in the causation of cervical neoplasia)

DEP/95/05	Regional Cancer Centre, Trivandrum, Kerala, India (Evaluation of unaided visual inspection, cervicoscopy and Pap s mear in screening for cervical cancer)
DEP/95/19	Cancer Institute (WIA), Madras, India (Feasibility of cervical cancer screening in Madras)
DEP/95/22	Hanoi Cancer Registry, Hanoi Cancer Hospital, Viet Nam (Prevalence of HPV infection)
FIS/96/01	Cancer Research Centre "Maes-Heller", Lima, Peru (Multicentric case–control study of HPV and cervical cancer)
FIS/96/02	Department of Preventive Medicine, Faculty of Preventive Medicine, São Paulo, Brazil (Follow-up study to evaluate the role of human papilloma v irus in the causation of cervical neoplasia)
FIS/96/04	Department of Neonatology, Hung Vuong Hospital, Ho Chi Minh City, Viet Nam (Prevalence of HPV infection in S.E. Asia)
FIS/97/01	Registre des Tumeurs d'Alger, Institut National de Santé Publique, Alger, Algeria (Etude cas-témoins multicentres sur le virus du papillome humain et le cancer du col utérin)
FIS/97/08	Cancer Institute (WIA), Agyar, Madras, India (Multicentric case–control study of HPV and cervical cancer)
FIS/97/09	National Institute of Pub lic Health, Cuernavaca, Mexico (HPV prevalence survey)
FIS/97/10	National Cancer Institute, Bangkok, Thailand (HPV prevalence survey)

Studies on liver cancer

FIS/87/01	National Cancer Institute, Bangkok, Thailand (Cohort study of HBsAg carriers in Bangkok)
DEP/92/09	Cancer Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (Prospective study on the etiology of liver cancer in northeastern Thailand)
MCA/93/05	Institut de Recherches et de Biologie Appliquée de Guinée (IRBAG), Kindia, République de Guinée (Enquête sur l'exposition aux facteurs de risque de carcinome hépatocellulaire en Guinée (Afrique occidentale))
MCA/95/01	Laboratoire de Biologie Moléculaire, INSERM U370, Paris, France (Etude des échantillons pour la détection du virus de l'hépatite C par des tests sérologiques (ELISA et RIBA) et moléculaires (PCR)
MCA/95/02	Khon Kaen University, Cancer Unit, Faculty of Medicine, Khon Kaen, Thailand (Determination of expression of P450 enzyme in human liver infested with *Opisthorchis viverrini*)
GHIS/97/01	MRC Laboratories, Fajara, The Gambia (Gambia Hepatitis Intervention Study)
GHIS/97/02	MRC Laboratories, Fajara, The Gambia (Epidemiology of viral, environmental and genetic factors in hepatocellular carcinoma – a case–control study in The Gambia)
GHIS/97/03	University of Leeds, Molecular Epidemiology Unit, Leeds, UK (Hepatocellular carcinoma – a case–control study in The Gambia, West Africa)

Studies on nutrition and on cancer of the gastrointestinal tract

FIS/90/12	Cancer Control Cen ter, San Cristobal, Venezuela (Etiology and prevention of stomach cancer in Venezuela)
AEP/93/02	Institute of Epidemiological and Clinical Research, Mataró, Spain (European prospective investigation into cancer and nutrition (EPIC))

AEP/93/03	Department of Health, Planning and Order, Government of Navarra, Pamplona, Spain (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/04	Health Administration of Guipuzcoa San Sebastian, Spain (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/05	Andalusian School of Public Health, Granada, Spain (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/06	Department of Epidemiology, Health Council, Murcia, Spain (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/07	Department of Health Planning, Regional Administration of Public Health, Oviedo, Spain (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/09	Imperial Cancer Research Fund, Cancer Epi demiology Unit, Radcliffe Infirmary, Oxford, United Kingdom (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/10	German Research Cancer Centre, Division of Epidemiology, Heidelberg, Germany (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/11	Department of Nutrition and Biochemistry, Athens School of Public Health, Athens, Greece (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/12	Department of Epidemiology, University of U trecht, The Netherlands (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/13	Department of Epidemiology, National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, The Netherlands (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/14	Cancer Epidemiology Research Unit (U.351), National Institute for Health and Medical Research (INSERM), Institut Gustave Roussy, Villejuif, France (European prospective investigation into cancer an d nutrition (EPIC))
AEP/93/15	Department of Epidemiology, National Institute for Research and Treatment of Cancer, Milan, Italy (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/16	Ragusa Cancer Registry, Italian League Against Cancer, Ragusa, Sicily, Italy (European prospective investigation into cancer and nutrition (EPIC))
AEP/93/17	Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy (European prospective investigation into cancer and nutr ition (EPIC))
AEP/93/20	Unit of Epidemiology, Centre for Preventive Oncology (CSPO), Florence, Italy (European prospective investigation into cancer and nutrition (EPIC))
FIS/93/02	Institute of Health Investigations, San José, Costa Rica (Aetiology and prevention of stomach cancer in Costa Rica)
FIS/93/04	The First Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan (Serum pepsinogen levels and precancerous lesions of the stomach)
ECR/95/01	Centre Hospitalier Universitaire Va udois, Lausanne, Switzerland (*Helicobacter pylori* infection, oxidative stress and gastric cancer)
NTR/95/01	Malmö Diet and Cancer Study, Malmö, Sweden (European Prospective Investigation into Nutrition and Cancer (EPIC))
DEP/95/23	Hanoi Cancer Registry, Hanoi Cancer Hospital, Hanoi, Viet Nam (Accuracy of *Helicobacter pylori* antibody tests)
NTR/96/01	Unit of Medical Epidemiology, German Institute of Human Nutrition, Potsdam-Rehbrücke, Germany (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/96/02	Department of Community Medicine, University of Cambridge, Cambridge, UK (European Prospective Investigation into Nutrition and Cancer (EPIC))

NTR/96/03	Cancer Epidemiology Research Institute (U.351), Institut Gustave Roussy, Villejuif, France (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/96/04	Division for Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/97/01	Service de Biochimie, Hôpital Edouard Herriot, Hospices Civils de Lyon, France (Analyses biochimiques de vitamines et autres marqueurs biologiques de l'équilibre antioxidatif cellulaire et plasmatique)
NTR/97/02	Service de Biochimie, Hôpital de l'Antiquaille, Hospices Civils de Lyon, France (Analyses biochimiques des taux sériques de facteurs hormonaux peptidiques)
NTR/97/03	Department of Nutritional Research, University of Umeå, Sweden (European Prospective Investigation into Nutrition and Cancer (EPIC))
NTR/97/04	Department of Clinical and Experimental Medicine, University of Naples, Italy (European Prospective Investigation into Nutrition and Cancer (EPIC))
FIS/96/03	Department of Gastroenterology, Azienda Ospedaliera, S. Giovanni Battista di Torino, Turin, Italy (Serological assays on the association of Cag A-positive *H. pylori* with gastric cancer)

Studies of brain tumours

MPA/95/01	University of Zurich, Zurich, Switzerland (The establishment of transgenic mice as models for human astrocytic brain tumours)

Studies of oral cancer

DEP/95/04	Jinnah Postgraduate Medical Centre, Karachi, Pakistan (Case–control study to evaluate the role of chewing areca nut/betel quid without tobacco and human papilloma virus (HPV) in the causation of oral cancer in Karachi, Pakistan
DEP/95/09	Regional Cancer Centre, Trivandrum, India (Evaluation of chemoprevention of oral cancer)
DEP/95/10	Regional Cancer Centre, Trivandrum, India (Oral cancer screening by mouth examination in Kerala)
FIS/95/03	Regional Cancer Centre, Trivandru m, India (Multicentric case–control study on oral cancer and HPV)
FIS/95/04	Department of Microbiology, Kidwai Memorial Institute of Oncology, Bangalore, India (Multicentric case–control study on oral cancer and HPV)
FIS/95/06	National Institute of Oncology and Radiobiology, Havana, Cuba (Multicentric case–control study on oral cancer and HPV)
FIS/95/07	Cancer Institute (WIA), Agyar, Madras, India (Multicentric case–control study on oral cancer and HPV)
FIS/97/02	Department of Cancer Epidemiology & Prev ention, Cancer Center & M. Slodowska Curie Institute of Oncology, Warsaw, Poland (Multicentric case–control study on oral cancer and HPV)
FIS/97/03	Istituto di Ricerca Farmacologica "Mario Negri", Milan, Italy (Multicentric case–control study on oral cancer and HPV)
FIS/97/04	Department of Pathology, Free University Hospital, Amsterdam, The Netherlands (Multicentric case–control study on oral cancer and HPV)
FIS/97/05	Department of Socio-sanitary Sciences, Faculty of Medicine, Seville, Spain (Multicentric case–control study on oral cancer and HPV)
FIS/97/06	Toombak Research Centre, Faculty of Dentistry, University of Khartoum, Sudan (Multicentric case–control study on oral cancer and HPV)
FIS/97/07	Gruppo Oncologico Clinico Cooperativo del Nord-Est, Aviano, Italy (Multicentric case–control study on oral cancer and HPV)

Studies of soft-tissue sarcomas and non-Hodgkin lymphomas

DEP/93/02	Oncology Center of Ho Chi Minh, Viet Nam (Case–control studies of soft tissue sarcoma and non-Hodgkin's lymphoma in th e south of Viet Nam)
DEP/93/06	The 10–80 Committee, Hanoi, Viet Nam (Case–control studies on soft tissue sarcoma and non-Hodgkin's lymphoma in Viet Nam: estimation of exposure index)

Other sites

DEP/95/16	Institute of Medical Sciences, Banaras Hindu University, Varanasi, India (Computing and analytical support to the case–control study on gall bladder cancer in Varanasi)
DEP/96/02	Uganda Cancer Institute, Mulago Hospital, Kampala, Uganda (Epidemiology, morphology and virology of HIV-associated lymphomas in Uganda)
DEP/96/15	Laboratoire d'Immunologie Cellulaire et Tissulaire, URA-CNRS 625, Bobigny, France (Aspects morphologiques, immunologiques, virologiques et moléculaires génétiques des lymphomes associés avec le VIH en Ouganda)
MCA/96/01	Institute of Esophageal Cancer, Zin Zhou City, People's Republic of China (Genetic alterations in esophageal cancer)

Studies on occupational cancer

AEP/90/16	National Institute of Health and Medical Research (INSERM), Villejuif, France (International study of cancer r isk in biology research laboratory workers in Europe)
AEP/93/19	Department of Occupational Medicine, Sahlgren Hospital, University of Gothenburg, Sweden (Multicentric study on European mercury workers)
AEP/93/24	Institute of Oncology 'Angel H. Roffo', Buenos Aires, Argentina (Case–control study to evaluate the importance of exposures in the occupational environment for the occurrence of lung cancer in Argentina)
AEP/93/31	Hospital Cancer Registry, Regional Cancer Centre, Trivandrum, India (Case–control s tudy on the associations between occupational exposure and neoplasms of the lung and the lymphatic and haematopoietic system)
AEP/93/33	Hospital Cancer Registry, Tata Memorial Hospital, Bombay, India (Case–control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and haematopoietic system)
AEP/94/09	Cancer Institute, Adyar, Madras, India (Case–control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and haematopoietic system)
AEP/94/10	Postgraduate Institute of Medical Education and Research, Department of Pulmonary Medicine, Chandigarh, India (International collaborative study on lung cancer)
AEP/94/11	Occupational Hygiene Programme, University of British Columbia, Vancouver, Canada (Re-analysis of cohort and case–control studies on cancer risk among workers in the wood and leather industries)
ECE/95/02	Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany (Environmental exposure s and lung cancer in non smokers)
ECE/95/07	Department of Epidemiology and Public Health, Institut Municipal d'Investigacio Medica, Barcelona, Spain (Estimation of the burden of occupational cancer in Europe)

ECE/95/09	Equipe de Santé Publique, Hôpital Maisonneuve-Rosemont, Montreal, Canada (Feasibility study of cancer risk among textile workers)
ECE/95/10	Cancer Registry of Norway, Oslo, Norway (Estimation of the burden of occupational cancer in Europe)
ECP/95/03	Department of Epidemiology, Institute of Environmental Medicine, Stockholm, Sweden (International study of cancer risk in biology research laboratory workers in Europe)
ECP/95/04	TEAGASC, Agriculture and Food Development Authority, Dublin, Ireland (International study of cancer risk in biology research laboratory workers in Europe)
ECP/95/05	Netherlands Cancer Institute, Amsterdam, Netherlands (International study of cancer risk in biology research laboratory workers in Europe)
ECP/95/06	Istituto Superiore di Sanita, Rome, Italy (International study of cancer risk in biology research laboratory workers in Europe)
ECP/95/07	Institute of Occupational Health, Helsinki, Finland (International study of cancer risk in biology research laboratory workers in Europe)
ECP/95/08	National Centre for Scientific Research (CNRS), Paris, France (International study of cancer risk in biology research laboratory workers in Europe)
ECE/96/05	Dow Medical College, Karachi, Pakistan (Case–control study of environmental risk factors of lung cancer in Karachi)
ECE/96/06	Institute of Occupational Health, Solna, Sweden (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/07	German Cancer Research Centre, Heidelberg, Germany (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/08	Danish Cancer Society, Copenhagen, Denmark (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/09	Cancer Registry of Norway, Oslo, Norway (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/10	Institute of Occupational Medicine, Edinburgh, UK (Case–control study of lung cancer within the rock/slag wool subcohort of the IARC MMVF study)
ECE/96/11	Slovenian Cancer Registry, Institute of Oncology, Ljubljana, Slovenia (Completion of follow-up of the cohort study of mercury miners from Idrija)
ECE/97/01	University of Leeds, Leeds, UK (Collection and analysis of data on occupational cancer among women in the UK)
ECE/97/02	Institut Municipal d'Investigació Mèdica, Barcelona, Spain (Analysis of data on occupational cancer among European women)
ECP/97/01	Laboratoire de Microbiologie, Faculté de Pharmacie, Marseille, France (Evaluations des expositions dans les laboratoires de recherche biologique)
RCA/97/01	Department of Histopathology, Addenbrooke's Hospital, Cambridge, UK (Study of factors influencing the risk of radiation-induced cancer following the Chernobyl accident)
RCA/97/02	Institute of Endocri nology, University of Pisa, Italy (Study of factors influencing the risk of radiation-induced cancer following the Chernobyl accident)

Studies on the effects of active and passive smoking

DEP/89/12	Tata Institute of Fundamental Research, Bombay, India (Prospective study on tobacco-related cancers and other diseases in the city of Bombay)
ECE/95/01	Epidemiology Institute, GSF Forschungszentrum für Umwelt und Gesundheit, Oberschleissheim, Germany (Environmental exposures and lung cancer in non-smokers)
ECE/95/03	Cancer Epidemiology Unit, University of Turin, Italy (Environmental exposures and lung cancer in non-smokers)
ECE/95/04	Venetian Tumour Registry, Padua, Italy (Environmental exposures and lung cancer in non smokers)
ECE/95/05	Associazione Ricerca Epidemiologica, Rome, Italy (Environmental exposures and lung cancer in non-smokers)
ECE/95/08	Institute of Occupational Health, Helsinki, Finland (Environmental exposures and lung cancer in non-smokers)
ECE/95/11	Karolinska Institute, Stockholm, Sweden (Environmental exposures and lung cancer in non-smokers)
ECE/96/04	Department of Medical Statistics, INSERM, U. 351, Villejuif, France (Environmental exposures and lung cancer in non-smokers)
ECE/97/03	Institute of Occupational Health, Helsinki, Finland (Environmental exposures and lung cancer in non-smokers)
DEP/97/04	Tata Institute of Fundamental Research, Bombay, India (Prospective study on tobacco-related cancers and other diseases in the city of Bombay)

Studies on chemical carcinogenesis

ECH/87/06	Laboratory of Microbiology, Faculty of Pharmacy, Marseille, France (Studies of methods for degradation of chemical carcinogens)
EVC/94/02	Institute of Cancer Research, Haddow Laboratories, Belmont, Sutton, UK (Interlaboratory standardization and validation of DNA adduct postlabelling methods for human biomarker studies)
EVC/95/01	Plant Research Centre, Agriculture & Agri-Food Canada, Ottawa, Canada (Carcinogenic action of fumonisins)
EVC/95/02	Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil (Carcinogenic action of *Fusarium moniliforme* toxins)
EVC/95/03	Medical Research Council, Tygerberg, South Africa (Second Pan-African Environmental Mutagen Meeting, Cape Town, South Africa, 23–25 January 1996)
CIE/96/01	National Institute of Public Health, Budapest, Hungary (Carcinogenicity testing of simazine in mice)
CIE/96/02	Institute of Preventive and Clinical Medicine, Bratislava, Federal Republic of Slovakia (Carcinogenicity testing of simazine in mice)
EVC/96/01	Centre National de la Recherche Scie ntifique (CNRS), Vernaison, France (Fréquence des mutations génétiques comme marqueur biologique de l'exposition longue durée au PhIP)
MCA/94/03	Sylvius Laboratory, Leiden University, Leiden, The Netherlands (Apurinic sites and oxidative adducts in DNA)
MCA/94/04	Laboratory of Nucleic Acid Lesions, Centre of Nuclear Studies, Grenoble, France (Urinary DNA adducts)
MCA/94/05	Faculty of Medicine, Brescia University, Brescia, Italy (The statistical descriptive analysis of host factors and biomonitoring endp oints)

Studies on mechanisms of carcinogenesis

MSC/94/01	Human Cancer Genetics Unit, Brunel University, Uxbridge, UK (Key genetic and epigenetic events generating the rate-limiting cell immortalization event in human and rodent cell transformation)
MSC/94/02	Division of Differentiation and Carcinogenesis, German Cancer Research Centre, Heidelberg, Germany (The role of epithelial mesenchymal interaction on genetic stability, and on transformation markers of keratinocytes in different stages of transformation)
MSC/94/03	Department of Radiation Genetics and Chemical Mutagenesis, University of Leiden, The Netherlands (The development of an assay system for transformation of epithelial cells, on the comparison of immortalization of human and rodent skin keratinocytes and on the induction of genetic instability by carcinogens)
MSC/94/04	Department of Toxicology, National Institute of Occupational Health, Oslo, Norway (The role of p53 gene in immortalization and transformation process of human epithelial cells)
MPA/96/01	Institute of Clinical Pathology and Medical Research, Westmead, Australia (The molecular basis of phenacetin-associated urothelial tumours)
MSC/96/01	University of Geneva, Geneva, Switzerland (Role of connexins in cell growth control)
MCA/96/02	Swiss Institute of Experimental Cancer Research, Epalinges, Switzerland (Markers of the response to oxidative stress in human cells)

Genetics and cancer

GCS/96/01	Giannina Gaslini Institute, Genoa, Italy (Gaslini–IARC course in cancer genetics, 29 Septe mber–5 October 1996)
GCS/96/02	Giannina Gaslini Institute, Genoa, Italy (Gaslini–IARC course in cancer genetics, 25–30 September 1996)

Annex 6

MEETINGS AND WORKSHOPS ORGANIZED BY IARC

Ad-hoc meeting on mechanisms of fibre carcinogenesis	Lyon, 9–11 January 1996
ENCR Survival Course planning meeting	Lyon, 9–10 January 1996
Cancer Incidence in Five Continents Editorial Board Meeting	Lyon, 10–12 January 1996
Meeting to prepare grant proposals for epidemiological studies of the Chernobyl accident	Lyon, 17–19 January 1996
Expert group on priorities for IARC studies on occupational cancer	Lyon, 25–26 January 1996
ENCR Cancer Registration Course	Toulouse, France, 29 January – 2 February 1996
Meeting of the EPIC Endpoint Committee	Lyon, 7–8 February 1996
Monographs working group on some pharmaceutical drugs	Lyon, 13–20 February 1996
International workshop on methodological issues in the application of biomarkers to cancer epidemiology	Lyon, 20–23 February 1996
Liaison meeting on study of styrene-exposed workers	Lyon, 1 March 1996
ENCR meeting on automated cancer registration	Venice, Italy, 12 March 1996
Meeting of liaison committee of the study of cancer risk among asphalt workers	Lyon, 19 March 1996
Meeting of the EPIC Steering Committee	Lyon, 20–22 March 1996
International Incidence of Childhood Cancer , Vol. 2. Editorial Board Meeting	Lyon, 26–28 March 1996
ENCR 11th Steering Committee Meeting	Lyon, 28–29 March 1996
Symposium Rhône-Alpin: cancers thyroïdiens différenciés	Lyon, 30 March 1996
Second training session of the interviewers in the MMVF lung cancer case–control study	Copenhagen, Denmark, 1–2 April 1996
Meeting of the liaison committee of the MMVF lung cancer case–control study	Copenhagen, Denmark, 2 April 1996
First meeting of the steering committee of the MMVF lung cancer case–control study	Copenhagen, Denmark, 2–3 April 1996
IARC Fellowships Selection Committee	Lyon, 11–12 April 1996
Editorial meeting *Application of Biomarkers to Cancer Epidemiology*	Lyon, 29–30 April 1996
Meeting of the audit panel of the MMVF lung cancer case– control study	Copenhagen, Denmark, 6 May 1996
Meeting of ENCR working group on data definitions	Paris, France, 9–10 May 1996
Genetic epidemiology studies of squamous cell carcinomas of the head and neck cancer	Lyon, 9–10 May 1996
Meeting of the working group of the study of cancer risk among asphalt workers	Helsinki, Finland, 20–21 May 1996
Meeting of liaison committee of the study of cancer risk among asphalt workers	Helsinki, Finland, 22 May 1996

Advanced course on statistical methods – recent developments in biostatistics with potential applications in cancer research	Veyrier-du-Lac, France, 25–31 May 1997
Editorial meeting *Metabolic Polymorphisms and Cancer*	Lyon, 11 June 1996
Monographs working group on infections with human immunodeficiency viruses and human T-cell lymphotropic viruses	Lyon, 11–18 June 1996
ENCR meeting on automated cancer registration	Lyon, 17–18 June 1996
Meeting of Dosimetry and Epidemiology Subcommittees of International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry	Lyon, 24–26 June 1996
Cancer genes: from families to epidemiology in world populations	Veyrier-du-Lac, France 24–25 June 1996
Working group on histological classification	Lyon, 8–10 July 1996
Meeting of editors to finalize publication on quantitative estimation and prediction of risk	Lyon, 2–5 July 1996
Meeting of ENCR working group on data definitions	Paris, France, 12 July 1996
International Incidence of Childhood Cancer , Vol. 2. Editorial Board Meeting	Lyon, 15–17 July 1996
IARC summer school on cancer registration and applications in epidemiology	Lyon, 5–26 August 1996
Three meetings to prepare the 1988 International Conference on Environmental and Occupational Cancer in Developing Countries, Brazil	São Paulo, Brazil, 21 August, and Rio de Janeiro, 22 & 24 August 1996
Meeting on collaborative studies on biomarkers of nutritional and hormonal status in relation to breast cancer	Lyon, 29–30 August 1996
Meeting on surveillance programmes on asbestos workers	Stockholm, Sweden, 18 September 1996
Meeting of the working group of the study of cancer risk among asphalt workers	Stockholm, Sweden, 19 September 1996
Meeting of the EPIC Endpoint Committee	Lyon, 19–20 September 1996
Meeting on attributable fractions of cancer in Europe	Lyon, 25–26 September 1996
Meeting on cancer survival in developing countries	Edinburgh, UK, 1 September 1996
30th Anniversary IACR Meeting	Edinburgh, UK, 3–5 September 1996
ECLIS collaborators meeting	Edinburgh, UK, 5 September 1996
ENCR General Meeting	Edinburgh, UK, 6 September 1996
ENCR 12th Steering Committee Meeting	Edinburgh, UK, 6 September 1996
Gaslini–IARC course in cancer genetics	Sestri Levante, Italy, 22–28 September 1996
Meeting on HPV vaccine trials	Lyon, 25 September 1996

Meeting of the liaison committee of the study of cancer risk among asphalt workers	Lyon, 3 October 1996
Meeting of proposed European lymphoma case–control study	Lyon, 4 October 1996
First meeting of the study group on occupation, environment and lung cancer in central and eastern Europe	Budapest, Hungary, 6–7 October 1996
Workshop to review results of test of dosimetry questionnaire: Chernobyl liquidator studies	Lyon, 7–9 October 1996
Workshop to compare protocols of leukaemia studies among liquidators in Belarus and Russia, Ukraine and Baltic countries	Lyon, 10–11 October 1996
European Breast Cancer Linkage Consortium meeting	Lyon, 10–11 October 1996
Monographs working group on silica, some silicates, dusts and organic fibres	Lyon, 15–22 October 1996
Dosimetry Working Group meeting for the International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry	Lyon, 28–29 October 1996
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 28 October 1996
ENCR meeting on automated cancer registration	Lyon, 29–31 October 1996
Meeting on proposed bladder cancer case–control study	Lyon, 31 October 1996
International course on molecular biomarkers in environmental cancer epidemiology	Shanghai, People's Republic of China, 4–13 November 1996
Collaboration meeting on X-linked lymphoproliferative syndrome	Lyon, 9–10 November 1996
Third training session of the interviewers in the MMVF lung cancer case–control study	Lyon, 1–2 December 1996
First meeting to prepare interviewer training workshop, study of leukaemia and non-Hodgkin lymphoma among liquidators	Moscow, Russian Federation, 2 December 1996
ENCR course on survival	Lyon, 2–6 December 1996
Meeting on studies of lung cancer in non-smokers	Venice, Italy, 16–18 December 1996
Meeting of investigators in multicentric study of laryngeal cancer in southern Europe	Lyon, 16 January 1997
Meeting of ENCR working group on data definitions	Leiden, The Netherlands, 20–21 January 1997
Workshop on coordination of epidemiological studies of thyroid cancer among young people in Belarus and Russia	Lyon, 22–23 January 1997
Cancer Incidence in Five Continents Editorial Board Meeting	Lyon, 22–24 January 1997
Meeting of the exposure assessment group of the study of lung cancer among rock/slag wool workers	Stockholm, Sweden, 3–4 February 1997
Meeting to finalize preparation of interviewer training workshop, study of leukaemia and non-Hodgkin lymphoma among liquidators	Obninsk, Russian Federation, 3–4 February 1997
Monographs working group on polychlorinated dibenzodioxins and polychlorinated dibenzofurans	Lyon, 4–11 February 1997
Meeting of the subgroup on smoking in lung cancer studies	Lyon, 7 February 1997

Meeting of the EPIC Steering Committee	Lyon, 11–13 February 1997
EPIC–HEART Coordination Meeting	Lyon, 13–14 February 1997
Meeting of the exposure assessment group of the study of cancer risk among pulp and paper workers	Helsinki, Finland, 17–18 February 1997
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 19 February 1997
ENCR course on cancer registration	Isle of Wight, UK, 25 February–1 March 1997
Meeting of the liaison committee of the study of cancer risk among asphalt workers	Lyon, 6 March 1997
Meeting of the subgroup on occupation in lung cancer studies	Essen, Germany, 6 March 1997
ENCR 13th Steering Committee Meeting	Lyon, 6–7 March 1997
Meeting of investigators in the study of occupational cancer in European women	Barcelona, Spain, 7–8 March 1997
International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Meeting of the Dosimetry Sub-Committee	Lyon, 11 March 1997
International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: Full Study Group Meeting	Lyon, 12–13 March 1997
Survival from Cancer in Developing Countries Editorial Meeting	Lyon, 12 November 1997
International Incidence of Childhood Cancer , Vol. 2, Editorial Board Meeting	Lyon, 12–14 March 1997
Meeting on attributable fractions of cancer in Europe	Lyon, 17–18 March 1997
Meeting of ENCR working group on data definitions	Leiden, The Netherlands, 17–18 March 1997
International BRCA1/2 carrier cohort study	Lyon, 18 March 1997
Meeting of the Working Group on the evaluation of the chemopreventive activity of non-steroidal anti-inflammatory drugs (NSAIDs)	Lyon, 2–8 April 1997
Interviewer training workshop: study of leukaemia and non-Hodgkin lymphoma among liquidators	Kiev, Ukraine, 14–18 April 1997
IARC Fellowships Selection Committee	Lyon, 24–25 April 1997
IARC summer school on cancer registration and applications in epidemiology	Lyon, 12 May – 30 May 1997
International meeting on methods of determination of DNA adducts by ^{32}P-postlabelling	Lyon, 30–31 May 1997
Meeting of the EPIC Endpoint Committee	Lyon, 3–4 June 1997
Meeting of investigators in case–control studies of lung cancer in non-smokers and smokers	Lyon, 5–6 June 1997
Meeting on the IARC p53 mutation database	Lyon, 9 June 1997
Meeting of investigators in multicentric cohort study of cancer risk among mercury workers in Europe	Lyon, 12–13 June 1997
Monographs working group on lymphotropic herpesviruses: Epstein–Barr virus and Kaposi's sarcoma-associated human herpesvirus 8	Lyon, 17–24 June 1997

Meeting for coordination of IARC and Sasakawa Memorial Health Foundation thyroid case–control studies in Belarus	Minsk, Belarus, 23 June 1997
Central Histology Review Meeting	Lyon, 23 June–4 July 1997
Meeting of the collaborators of the multi-centre study of cancer of the oral cavity and oropharynx	Lyon, 26–27 June 1997
Meeting on proposed project on genetic alterations in lung cancer	Lyon, 8–9 August 1997
Editorial board meeting *Metabolic Polymorphisms and Cancer*	Lyon, 1 September 1997
Meeting of EPIC Working Group on Biomarkers of Diet	Lyon, 10–11 September 1997
International BRCA1/2 carrier cohort study	Pisa, Italy, 22 September 1997
Gaslini–IARC course in cancer genetics	Sestri Levante, Italy, 25–30 September 1997
Meeting of the liaison committee of the MMVF lung cancer case–control study	Lyon, 30 September 1997
Meeting on proposed follow-up study of cancer incidence and mortality among vinyl chloride workers	Lyon, 1 October 1997
Meeting on occupational exposures and bladder cancer in Europe: pooled analysis of case–control studies	Lyon, 6 October 1997
Ad-hoc meeting on evaluation of data from short/medium term carcinogenicity tests and on genetic and related effects	Lyon, 6–10 October 1997
Meeting on multicentric study of bladder cancer in Europe	Lyon, 7 October 1997
Meeting of potential participants in multi-centric case–control study of brain tumours and mobile phones	London, 8–9 October 1997
ENCR 14th Steering Committee Meeting	Lyon, 9–10 October 1997
Cancer epidemiology course	Abidjan, Côte d'Ivoire, 20–31 October 1997
Meeting of the working group of the study of cancer risk among asphalt workers	Paris, 23–24 October 1997
Annual Meeting of the International Association of Cancer Registries	Abidjan, Côte d'Ivoire, 3–5 November 1997
Meeting on mechanisms of carcinogenesis which may be species-specific	Lyon, 3–8 November 1997
Joint meeting of collaborators in EPIC and in PACE (Pacific Area Cancer Epidemiology Study)	Los Angeles, CA, USA, 6–8 November 1997
Meeting of investigators in the MMVF lung cancer case–control study	Edinburgh, UK, 10–11 November 1997
Meeting of the liaison committee of the study of cancer risk among asphalt workers	Lyon, 14 November 1997
Workshop to prepare protocol of feasibility study for case–control study of head and neck tumours and RF radiation	Lyon, 24–25 November 1997
Meeting on on-going and future projects of asbestos-related diseases	Paris, 4–5 December 1997
Meeting on results of 24-hour diet recall interview in the EPIC study	Lyon, 8–9 December 1997
Meeting of the Working Group on the evaluation of the chemopreventive activity of carotenoids	Lyon, 10–16 December 1997
International mini-symposium on genomic instability; mechanisms and interplay with environmental carcinogens	Lyon, 18 December 1997

Annex 7

SEMINARS PRESENTED AT IARC

The following visitors to IARC presented seminars:

Professor M. Abrahamowicz, Hôpital général de Montréal, Canada
Flexible models for analysing survival data: motivation and applications

Dr A. Aguzzi, Institute of Neuropathology, University Hospital, Zurich, Switzerland
Creutzfeldt–Jakob and related prion diseases: neurotoxicity and neurotropism

Dr H. Ahsan, Columbia University, New York, USA
Epidemiology of brain tumours in adults

Dr F. Alexander, University of Edinburgh, UK
Evidence for an infectious etiology of childhood leukaemia

Dr V. Amberger, Brain Research Laboratory, London, Ontario, Canada
Invasion of central nervous system myelin by human gliomas

Dr V. Anisimov, Institute of Oncology, St Petersburg, Russian Federation
Effect of light–dark regimen and low-frequency electromagnetic fields on carcinogenesis in rodents

Dr A. Anttila, Finnish Institute of Occupational Health, Helsinki, Finland
Cancer risks following from occupational lead exposure

Dr W. Anwar, Faculty of Medicine, Cairo, Egypt
Schistosomiasis and susceptibility to bladder cancer

Dr P. Badrinath, University of Cambridge, UK
Acute leukaemia in the East Anglian region of the United Kingdom: registry and individual-based studies

Dr M. Badzioch, University of Texas, Houston, TX, USA
Genetic predisposition to prostate cancer

Dr M. Blettner, German Cancer Research Centre, Heidelberg, Germany
Meta-analysis: a tool to identify small risk factors?

Dr R. Bottelli, Royal Free Hospital, London, UK
HCV and hepatocellular carcinoma

Dr V. Bouvard, International Center for Genetic Engineering and Biotechnology, Trieste, Italy
Regulation of the papillomavirus type 16 transcription

Professeur E. Brambilla, Institut Albert Bonniot, Grenoble, France
Molecular biology of lung cancer

Dr P. Brennan, University of Manchester, UK
Genetic and reproductive associations with rheumatoid arthritis

Professor T.C. Campbell, Cornell University, Ithaca, NY, USA
Multicentric study on diet and cancer in China

Dr A.G. Casson, Mount Sinai Hospital, Toronto, Canada
Molecular biology of oesophageal cancer: potential clinical applications

Dr K. Chrzanowska, Children's Memorial Health Institute, Warsaw, Poland
Polish patients with Nijmegen Breakage Syndrome. clinical and genetic studies

Dr P. Cocco, Università di Cagliari, Italy
Exposure to silica and lung cancer risk in Chinese dusty trades. Effect of silicosis and concurrent exposure to other lung carcinogens

Dr M.P. Coleman, London School of Hygiene and Tropical Medicine, UK
Public health strategies for cancer control

Dr R. Corvi, German Cancer Research Centre, Heidelberg, Germany
Cytogenetics and molecular genetics of human neuroblastoma

Dr M. de Andrade, University of Texas, Houston, TX, USA
Statistical approaches to analyse cytogenetic biomarkers in epidemiological studies

Dr V. Diehl, University of Cologne, Germany
The biology of and clinical advances in Hodgkin's disease

Dr A.V. Diez-Roux, John's Hopkins University, Baltimore, MD, USA
Multilevel analysis: combining group-level and individual-level measures in epidemiologic studies

Dr N. Dracopoli, Sequana Therapeutics, La Jolla, CA, USA
Analysis of p16 and CDK4 mutations in familial melanoma

Dr C. Eng, Dana-Farber Cancer Institute, Boston, MA, USA
Molecular genetics of Cowden syndrome and related sporadic tumours

Professor J. Fagin, University of Cincinnati, OH, USA
Pathogenesis of thyroid cancer: insights from Chernobyl

Professor F. Feo, University of Sassari, Italy
Multistage models of hepatocarcinogenesis: from the epigenetic to the genetic option

Dr P. Flandre, CHU Pitié Salpêtrière, Paris, France
L'utilisation d'évènements auxiliaires dans les études de survie

Dr J.-F. Flejou, INSERM, Paris, France
Tumeurs de l'oesophage: dysplasie et cancer

Dr P. Gann, Northwestern University Medical School, Chicago, IL, USA
A prospective analysis of plasma anti-oxidant levels and prostate cancer risk

Dr S. Garte, University of Milan, Italy
Metabolic genes as biomarkers of exposure and susceptibility to carcinogens

Dr G. Goldberg, State University of New York, Buffalo, NY, USA
Capture and characterization of factors involved in growth control mediated by cell-to-cell communication

Dr M. Goldberg, McGill University, Montreal, Canada
Post-menopausal breast cancer and occupational and environmental exposures

Dr D.F. Goldsmith, California Public Health Foundation, Berkeley, CA, USA
Possible mechanisms of silicocarcinogenesis: harmonizing epidemiology and experimental findings

Dr E.W. Gunter, NHANES Laboratory, Atlanta, GA, USA
Specimen banking at the Centers for Disease Control and Prevention

Dr G.L. Hammond, London Regional Cancer Centre, London, Ontario, Canada
Sex hormone-binding globulin: a trap for xenobiotics

Dr C. Harris, National Cancer Institute, Bethesda, MD, USA
Tumour-suppressor genes: at the crossroads of molecular carcinogenesis and molecular epidemiology

Dr J. Haukka, National Cancer Institute, Helsinki, Finland
Some new methods for statistical analysis of observational screening study – example from lung cancer screening in the ATBC study

Dr H. Hayatsu, Okayama University, Japan
Detection of environmental polycyclic mutagens: are carcinogenic heterocyclic amines ubiquitously present?

Dr R. Hayes, National Cancer Institute, Bethesda, MD, USA
Epidemiological studies of benzene-exposed workers in China

Dr J.W. Henson, Massachusetts General Hospital, Charlestown, MA, USA
Regulation of apoptosis in astrocytomas

Professor P. Herrlich, University of Karlsruhe, Germany
Metastatic cancer: adaptation of embryonic genetic programmes

Dr I. Hertz-Picciotto, University of North Carolina, Chapel Hill, NC, USA
Does quantitative risk assessment overestimate the hazards from environmental chemicals? Using epidemiologic data to validate predicted risks from carcinogens in cigarette smoke

Dr U. Hibner, Institut de génétique moléculaire, Montpellier, France
Anti-apoptotic activity of p53

Dr S.V. Hodgson, South Thames Regional Genetics Center (East), London, UK
How can our understanding of genetic cancer susceptibility syndromes be used to reduce morbidity and mortality from cancer?

Professor A. Horii, Tohoku University, Japan
Genetic alterations in human pancreatic cancer

Dr M. Hours, Université Claude Bernard, Lyon, France
Les résultats de l'étude de surveillance des cancers professionnels dans le département du Rhône

Dr J.W. Ironside, Neuropathology Laboratory, University of Edinburgh, UK
Clinical and pathological findings in the new variant of CJD in the UK

Dr E. Jacobson, University of Kentucky, Lexington, KY, USA
Effects of niacin availability and intracellular NAD on carcinogenesis: at least three DNA strand break activated pathways dependent on NAD

Dr I. Jariel-Encontre, Institut de génétique moléculaire, Montpellier, France
Complex mechanisms for the degradation of proto-oncogenes c-jun and c-fos

Dr B. Jordan, Centre d'Immunologie, Marseille-Lumigny, France
Multiplex messenger assay and its applications

Dr H. Kasai, University of Occupational and Environmental Health, Kitakyushu, Japan
Mutagenesis and carcinogenesis induced by oxygen radicals; role of 8-hydroxyguanine, 2-hydroxyadenine and glyoxal formation

Dr W. Kaufmann, University of North Carolina at Chapel Hill, NC, USA
Checkpoints, DNA repair, and carcinogenesis in humans

Dr R. Kavlock, Environmental Protection Agency, Research Triangle Park, NC, USA
Research issues and needs related to the endocrine disruptor hypothesis

Dr G. King, University of Connecticut Health Center, Farmington, CT, USA
Smoking behaviour among French and American women

Dr G. Klopman, Case Western Reserve University, Cleveland, OH, USA
Expert system approach to assessing the environmental risk of chemicals

Professor T. Kuroki, Showa University, Tokyo, Japan
Signal transduction pathway mediating squamous differentiation and its implication in carcinogenesis and skin diseases

Skin carcinogenesis; a complex regulation by protein kinases C and A

Dr L. Le Marchand, University of Hawaii at Manoa, Honolulu, HI, USA
Gene–diet interaction and the high colorectal cancer risk of Japanese Americans

Professor E. Lund, University of Tromsø, Norway
Fish and cancer of the breast and colon: a prospective study in Norway

Professor H. Maeda, Kumamoto University, Japan
Nitric oxide and superoxide in infectious diseases and cancer

Professor N. Maitland, University of York, UK
The molecular biology of prostate cancer

Dr N. Malats, Institut municipal d'investicacio medica, Barcelona, Spain
K-ras mutations in pancreatic and biliary cancers: new clues for clinical and etiological studies

Dr F. Manca, University of Genoa Medical School, Italy
The molecular context of HIV epitopes dictates recognition by human T helper cells

Professor M. Mareel, University Hospital, Gent, Belgium
Cadherin/catenin complexes in cancer invasion

Dr M.L. Martelli, Università degli Studi di Reggio Calabria, Catanzaro, Italy
Isolation and characterization of a novel tyrosine-phosphatase

Dr M. Martuzzi, Imperial College of Science, Technology and Medicine, London, UK
Asbestos and lung cancer in Piedmont, Italy

Dr F. Mitelman, University Hospital, Lund, Sweden
Cytogenetic evidence of polyclonality in epithelial tumours

Professor M. Miwa, University of Tsukuba, Japan
Functional analysis of poly(ADP-ribose)polymerase of *Drosophila melanogaster*

Dr M. Molinari, University of York, UK
Regulation of p53 protein degradation: effect of p53:DNA interactions

Dr U. Moll, State University of New York, Stony Brook, NY, USA
Cytoplasmic sequestration of p53 in human tumours

Dr B. Müller-Myhsok, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
Genetic epidemiology of human *Schistosoma mansoni* infection

Dr B. Nagarajan, Cancer Institute, Madras, India
Biological dosimetry of cancer risk factors with reference to stomach cancer in India

Dr T. Nasu-Nakajima, Shinshu University School of Medicine, Matsumoto, Japan
Sarin poisoning in Matsumoto, Japan

Dr C. Naus, University of Western Ontario, London, Canada
Connexin-43 null mutation in astrocytes: effects on growth and transformation

Dr M. Obinata, Tohoku University, Sendai, Japan
Regulation of differentiation of haematopoietic stem cells by bone marrow stromal cells

Professor K. Ogawa, Asahikawa Medical College, Japan
Hepatic carcinogenesis using cultured hepatocytes

Dr O.A. Olivero, National Cancer Institute, Bethesda, MD, USA
Telomere shortening by long-term and transplacental 3′-azido-2′,3′-dideoxythymidine (AZT) treatment

Dr L.A. Poirier, National Center for Toxicological Research, Jefferson, AR, USA
Methyl insufficiency in cancer

Dr B.S. Polla, Université Paris V, France
Role of mitochondria in the induction and protective effects of heat-shock proteins

Dr E. Pukkala, Finnish Cancer Registry, Jarvenpaa, Finland
Register-based information in occupational cancer studies, with special reference to socioeconomic aspects

Dr F. Real, Institut municipal d'investigacio médica, Barcelona, Spain
Exocrine pancreatic cancer: are more dreadful genes involved in more dreadful tumours?

Dr A. Robinson, European Bioinformatics Institute, Cambridge, UK
Novel techniques for visualizing biological information

Dr J. Ryan, Bureau of Chemical Safety, Ottawa, Canada
Russian phenoxy herbicide workers: exposure to dioxins and sex ratio of offspring

Dr A. Salvador Peña, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Cytokines, genetics and control of inflammation in the gastrointestinal tract

Dr G. Schulgen, University of Freiburg, Germany
Multistate models for event-history data: an application in the analysis of occurrence and impact of nosocomial infections

Professor S. Shall, University of Sussex, Brighton, UK
Recent developments regarding the structure of poly (ADP-ribose) polymerase and its function in DNA repair and recombination

Dr M.K. Shigenaga, University of California, Berkeley, CA, USA
In vivo evidence for the biomarker 3-nitrotyrosine in inflammation

Dr K. Sikora, Hammersmith Hospital, London, UK
Public health strategies for cancer control

Mr M.S. Smuts, National Research Programme for Nutritional Intervention, Tygerberg, South Africa
The effect of dietary manipulation on the interaction between *n*–6 and *n*–3 fatty acids in plasma and erythrocyte membrane lipids

Dr H.H. Storm, Danish Cancer Society, Copenhagen, Denmark
Public health strategies for cancer control

Professor T. Sugimura, National Cancer Center Research Institute, Tokyo, Japan
My personal view on cancer prevention

Dr M. Takahashi, Nagoya University, Japan
Molecular mechanisms of development of MEN 2A, MEN 2B and Hirschsprung disease

Professor N. Taniguchi, Osaka University Medical School, Japan
Implication for nitric oxide and superoxide in cancer, diabetes, ageing and familial amyotrophic lateral sclerosis

Dr L. Teixeira da Costa, Johns Hopkins Oncology Center, Baltimore, MD, USA
Tumour suppressor genes: from identification to targeting

Dr J.L. Telford, Chiron Biocine Immunobiological Research Institute, Siena, Italy
The *Helicobacter pylori* cytotoxin: structure, function, virulence and vaccine potential

Dr H. te Riele, The Netherlands Cancer Institute, Amsterdam, The Netherlands
Genetic instability by loss of DNA mismatch repair: implications for the etiology and treatment of cancer

Dr B. Terracini, Unit of Cancer Epidemiology, University of Turin, Italy
Toxic oil syndrome in Spain: lessons for environmental epidemiology

Dr M.J. Thun, American Cancer Society, Atlanta, GA, USA
Aspirin and NSAIDs in the prevention of colorectal cancer

Dr E.G. Van Meir, Neurosurgery Department, University Hospital, Lausanne, Switzerland
p53 and the genetic progression of astrocytoma

Dr P. Vineis, University of Turin, Italy
Lymphomas and leukaemias in Italy – preliminary results of a multicentric case–control study

Professor S.E. Vollset, University of Bergen, Norway
Helicobacter pylori and gastric adenocarcinoma: a nested case–control study from Norway

Dr Z.-Q. Wang, Research Institute of Molecular Pathology, Vienna, Austria
The function of ADPRT/PARP in genomic stability: lessons from a genetic approach

Dr Q. Yang, National Center for Environmental Health, Atlanta, GA, USA
Gene–environment interaction: traditional and non-traditional epidemiologic approaches

Dr J. Ziegler, London, UK
Public health strategies for cancer control

Dr M. Zureik, INSERM U 408, Paris
Serum cholesterol concentration and risk of death from cancer and suicide

Annex 8

PUBLICATIONS BY IARC STAFF

1. Agarwal, M.L., Agarwal, A., Taylor, W.R., Wang, Z.Q., Wagner, E.F. & Stark, G.R. (1997) Defective induction but normal activation and function of p53 in mouse cells lacking poly-ADP-ribose polymerase. *Oncogene,* **15,** 1035–1041
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4. Barbieri, P.G., Merler, E. & Olmastroni, L. (1996) Studio di mortalità in addetti alla produzione di refrattari per l'industria siderurgica esposti ad IPA. In: Apostoli, P., Minoia, C. & Alessio, L., eds, *Atti del Convegno Nazionale Idrocarburi Policiclici Aromatici negli ambienti di Vita e di Lavoro (Gargnano, 27–29 March 1996),* Brescia, Cattedra di Medicina del Lavoro,Universita di Brescia, pp. 339–346
5. Barbin, A., Froment, O., Boivin, S., Marion, M.J., Belpoggi, F., Maltoni, C. & Montesano, R. (1997) p53 gene mutation pattern in rat liver tumours induced by vinyl chloride. *Cancer Res.*, **57,** 1695–1698
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