WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

# BIENNIAL REPORT

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# INTRODUCTION

During the two years covered by the present report, the activities of IARC have continued to focus on the collection and dissemination of data on cancer occurrence, on the search for causes of cancer, and on the possibilities for cancer prevention. That this approach is a valid one for an organization of the limited size and resources of IARC is demonstrated by the high reputation of the Agency's programmes and scientists worldwide, by the number of external collaborators and funding bodies that are keen to be associated with the Agency and by the continual interest of further states in becoming new members. Within the period under review, IARC has been delighted to welcome as new participating states Denmark and Switzerland. Both countries have long traditions of outstanding research activity in the cancer field, and a great interest in cancer prevention and they bring the Agency's membership up to 16 nations. Denmark is notable in being the first country to have established a national system for cancer registration (in 1942), and its registry was also among the pioneers of the use of its own data in epidemiological research. In this context, it is with great sadness that we record the death in September 1991 of Dr Ole Møller Jensen, a recently appointed member of the IARC Scientific Council who was a staff member of the Agency before his appointment as director of the Danish Cancer Registry (a short obituary appears on p. ix).

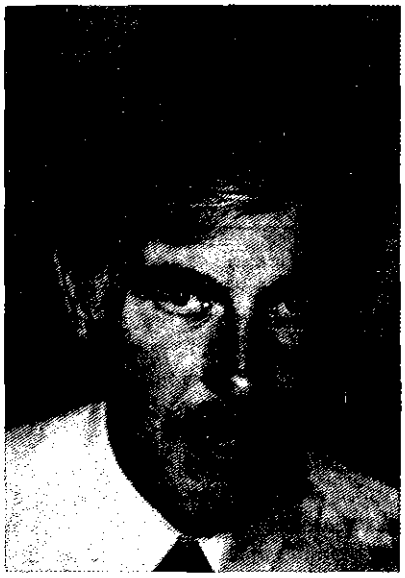
An event marking a recognition of the Agency's international reputation was the visit in March 1991 of Professor Dr HRH the Princess Chulabhorn Mahidol, of Thailand, for the signature of a research collaboration agreement between IARC and the Chulabhorn Institute, Bangkok. The agreement provides for information exchange, staff visits and collaborative research agreements.

Although the approach to cancer research adopted by IARC at the outset continues to be pursued, the emphases and detailed activities have evolved considerably, with major emphasis put on close collaboration between experimentalists and epidemiologists, and on prevention. The overall aims and strategy of the Agency are under review, and new criteria are being established to ensure that all research projects undertaken are fully consistent with the Agency's capabilities and in particular with its public health-oriented aims.

Due to the decline of the US dollar/French franc exchange rate, the late arrival of voluntary contributions to the Agency's budget and the disruption and unbudgeted costs of the operation to remove asbestos from the main building, the Agency underwent a difficult biennium.

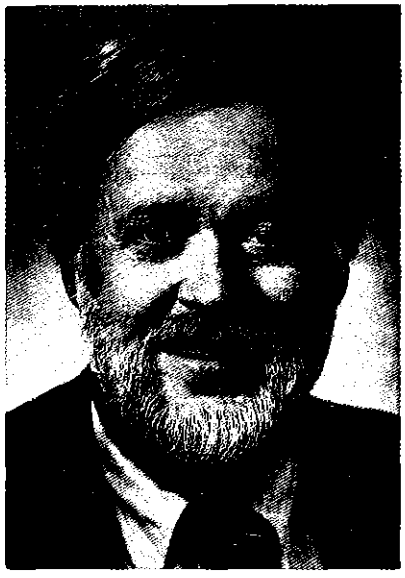
The asbestos layers installed between the floors of the tower to conform with fire-protection regulations in force in the late 1960s were found to be disintegrating, and the fibres risked dispersal throughout the building via the ventilation system. The removal of this asbestos had therefore to be undertaken before the concentration of fibres in the air reached a level where it would present a health hazard. The efficient management of the operation to remove these layers of asbestos and the cooperation of all personnel reduced to the minimum the disruptive effects of this first internal IARC cancer-prevention initiative, which involved two moves of the entire Agency within five months. A particular expression of thanks goes to the City of Lyon for its willingness to cover a large part of the cost of this operation. This and other problems of maintenance and space utilization have emphasized the limitations of the form of building currently occupied by the Agency.

As far as the budgetary problems are concerned, it is clear that the Agency will have great



Dr P. A. Cerutti
(1990–1993)

Dr K. P. Hanson
(1989–1992)



Dr C. C. Harris
(1989–1992)

Professor L. G. Israels
(1989–1992)

New members of the Scientific Council in 1989 and 1990

# IARC Biennial Report 1990 - 91

## CORRIGENDA

Pages viii and ix: The terms of office of the members of the IARC Scientific Council appointed in 1989 and 1990 should read as follows:

| | |
|---|---|
| Dr P.A. Cerutti | 1991–1994 |
| Dr K.P. Hanson | 1990–1993 |
| Dr C.C. Harris | 1991–1994 |
| Professor L.G. Israels | 1990–1993 |
| Professor G.R. Mohn | 1991–1994 |

Page 15: In Table 1, the SMR for soft-tissue sarcoma among the total exposed and probably exposed population should read 196 instead of 19; the 95% CI for soft-tissue sarcoma in the production cohort should read 3 – 541 instead of 3 – 5 and in the same cohort the observed mortality for non-Hodgkin lymphoma should read 8 instead of 418.

Dr O. M. Jensen

## OBITUARY

Ole Møller Jensen's first contact with the Agency was in 1973 when he applied successfully for a Research Training Fellowship tenable at the London School of Hygiene and Tropical Medicine. After spending six months there, he came to the Agency to complete his fellowship, and became involved in the on-going study on alcohol and cancer. He was appointed as a staff member and was able to develop and complete an extensive cohort study among Danish brewery workers which culminated in 1980 in an IARC publication *Cancer Morbidity and Causes of Death among Danish Brewery Workers.* The Danish translation was presented as his doctoral thesis to the University of Copenhagen.

In 1980, Dr Jensen left the Agency to become Director of the Danish Cancer Registry, where he continued the great tradition initiated by Dr Clemmensen and contributed to making the Registry one of the leading centres in cancer epidemiology research. He was elected a member of the Agency's Scientific Council in May 1990 at the time Denmark became a Participating State. His courage and determination to work in spite of his progressing illness won the admiration of all his colleagues in Lyon and Copenhagen.

*Ole Møller Jensen: born 9 November 1944, died 20 September 1991*

Professor G. R. Mohn
(1990–1993)

difficulty in making medium- and long-term plans if an adequate and stable level of financial support is not guaranteed.

In early 1991 several meetings had to be cancelled because of the problems of air travel associated with the international crisis. The main casualties were the 27th session of the Scientific Council, which instead succeeded, through the special effort made by its Chairman, Professor A. J. McMichael, in conducting the more important items of business by correspondence, and the IARC Monographs Working Group meeting on ultraviolet and solar radiation. The latter meeting has been re-scheduled to take place in February 1992.

The end of 1990 was marked by the retirement from IARC of one of its first staff members, Dr Calum Muir, who has now moved to Edinburgh as Director of Cancer Registration in Scotland. The importance of the contributions of Dr Muir, as an epidemiologist of world renown, to the Agency's work over nearly 25 years cannot be over-stressed, particularly his building up of the network of cancer registries and the resulting expansion of the Cancer Incidence in Five Continents data-base. His position as Deputy Director of IARC has been filled by Dr Bruce Armstrong, previously Professor of Epidemiology and Cancer Research at the University of Western Australia and, more recently, Commissioner of Health for Western Australia.

The principal scientific activities of the Agency during the last two years are highlighted below.

### *Descriptive epidemiology*

The data have been collected for Volume VI of *Cancer Incidence in Five Continents*, and cover 184 populations in 48 countries, including a significant number appearing for the first time. Many of these are from cancer registries set up with support from the Agency. The data are now being validated and documents being prepared for printing, with publication due at the end of 1992. For the first time a diskette version of the data will be supplied with the printed book.

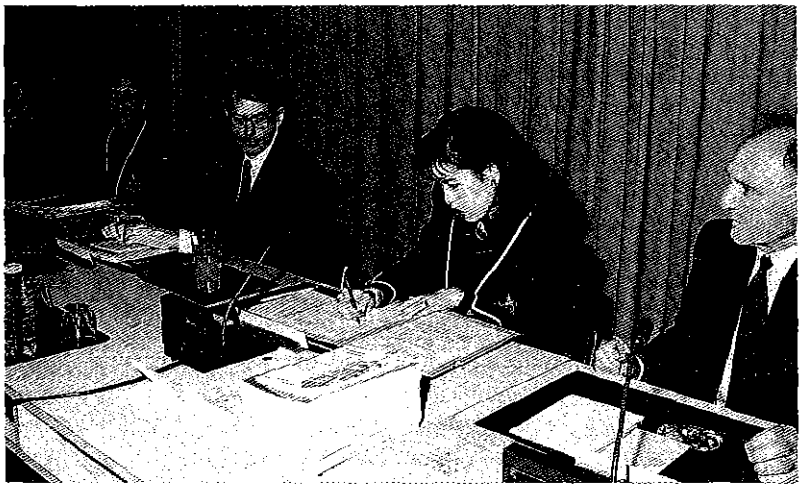
The series of volumes of *Cancer Incidence in Five Continents* and the mortality data-base of WHO have formed the basis for a major analysis of time trends in cancer. Among the results emerging from the analysis are the divergent patterns in the cumulative risks for lung cancer in various European countries. A monograph is in preparation which will present results by world region, sex and broad age group.

Studies of migrant populations, which the IARC, as an international organization, is particularly well placed to conduct and coordinate, are of considerable value for investigating possible interactions between genetic and environmental factors in cancer etiology. Data are being analysed on migrants from Italy and Poland and on immigrants to Australia and South America. The effects of age at migration and of duration of stay provide interesting opportunities for study. Of special interest is the study on cancer incidence in offspring of migrants to Israel, aimed at demonstrating possible changes in risk between first-generation migrants and the next generation, born in the host country.

An EEC-funded project, jointly coordinated by the IARC and the Danish Cancer Reigstry, has set up a network of European cancer registries, with the aim of improving data quality, comparability and availability. As part of this project, an electronic data-base of incidence and mortality figures has been prepared for publication, with a range of statistical and graphical software. Over 40 EEC cancer registries participated in the first meeting held in Lyon in February 1991 to define the programme of work for the next biennium.

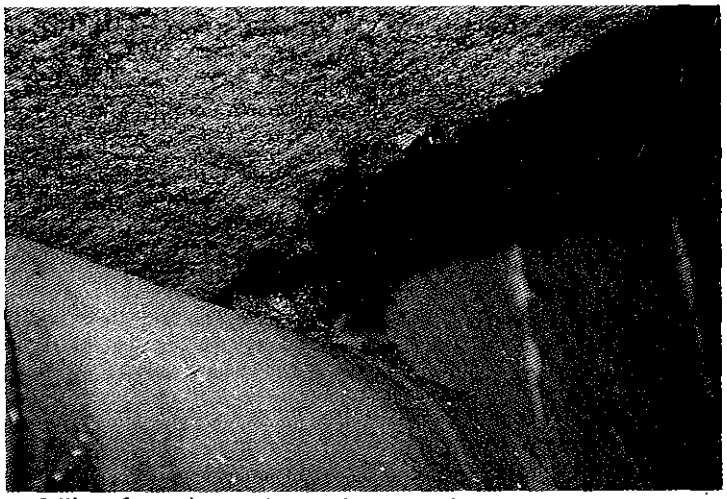
### *Childhood cancer*

The large international data-base on incidence of childhood cancer which has been built up in recent years has been used to provide detailed analyses of lymphoma and renal tumours.



HRH the Princess Chulabhorn of Thailand signing a Memorandum of Understanding (25 March 1991)

Childhood Hodgkin's disease incidence seems to be related to levels of socio-economic development but even more to ethnic and environmental factors; Burkitt's lymphoma is commoner in tropical Africa and in Papua New Guinea and rare elsewhere. Among renal tumours, the three-fold differences in incidence along mainly ethnic lines suggest that genetic predisposition may have an important role in its etiology. A separate study has suggested that the genetically determined fraction of all childhood cancer is at least 4.4% and may be much higher.



Asbestos fibres falling from beneath the beams of the 11th floor in the IARC tower (November 1989)

*Occupational cancer*

From its inception the Agency has maintained a keen interest in identifying exposures that may be carcinogenic to humans within the working environment.

The results of the extension of the historical prospective study of workers in the man-made mineral fibre industry in seven European countries, to cover the period 1982–1987, are expected by mid 1992. The investigation of workers employed in the vinyl chloride industry has confirmed an exposure–response relationship for all liver cancers and for angiosarcomas of the liver and has indicated a possible slight increase of mortality from lymphosarcomas and brain tumours. The study of persons exposed to phenoxy acid herbicides and contaminants, conducted in collaboration with the US National Institute of Environmental Health Sciences, has been further extended. The preliminary results point to an increase in mortality for soft tissue sarcomas and non-Hodgkin lymphomas. A new study on workers exposed to lead will produce its first results in 1992. The international project to assess cancer risks in biology research laboratory workers, initiated following a feasibility study conducted between 1988 and 1990, has been extended to include cohorts established in nine European countries. Financed largely by the Europe Against Cancer Programme of the EEC, the study should produce results by 1995.

The effects of occupational low-dose exposures to ionizing radiation are also being examined in order to clarify the dose–response relationships that are needed to extrapolate from previous studies at high doses and dose rates. Data from earlier studies of cancer in nuclear workers are being combined for re-analysis and a major new international study is being set up involving workers in 13 countries.

*Tobacco and cancer*

A multi-centre case-control study of the cancer risks of environmental tobacco smoke (passive smoking) is in progress, following a successful methodological study that checked the reliability of self-reported data on exposure to environmental tobacco smoke. The effectiveness of anti-smoking measures such as legislation and health education is being evaluated. In parallel, laboratory work is examining DNA adducts excreted by smokers, in part to provide more precise measures of biological doses of carcinogens in tobacco smoke and in part to clarify the nature and mechanisms of action of the carcinogens involved, and the possible differences between black and blond tobacco.

*Second malignancies following chemotherapy*

Following the quantification of risks for leukaemia after treatment for Hodgkin's disease or ovarian cancer, the risk for bladder cancer among patients treated for ovarian cancer has been measured. Cyclophosphamide treatment entailed a four-fold increased risk, whether or not radiotherapy was concurrently used. A relative risk of 5.2 was seen when radiotherapy and chemotherapy were combined.

A related aspect of this problem that is being studied is the DNA damage caused by cytotoxic drugs. Data on various measures of DNA damage in Hodgkin's disease patients from a pilot project are being analysed. A number of collaborative studies are further examining this and the effects of cis-platinum. It is expected that DNA adduct levels may provide an indicator of clinical outcome of therapy as well as being useful indicators of the significance of DNA lesions in predicting long-term adverse effects. Methylation adducts have also been measured in cancer patients treated with *N*-nitroso-*N*-methylurea.

*Nutrition and cancer*

Many epidemiological studies have found associations of cancer incidence with nutritional factors, but precise causal or protective relationships have been difficult to prove because of the multitude of components in most human diets and the unreliability of recalled data on past

consumption. The IARC programme of prospective studies is based on the use of validated questionnaires to record current consumption for all subjects, and blood and urine samples will be collected. Cancer follow-up is expected to last for 8–12 years. This large prospective study, coordinated by IARC and funded by the Europe Against Cancer programme of the EEC, involves teams in France, Germany, Greece, Italy, Netherlands, Spain and UK, and is cooperating with similar work in Denmark and Sweden.

Biochemical markers of diet, already tested in pilot studies, will be measured in cancer cases and in control samples, and will be used in conjunction with the questionnaire data to help elucidate the relationships with cancer incidence, to provide a sounder basis for the implementation of preventive measures.

Dietary factors are also being examined in case-control studies. For colorectal cancer, high meat consumption has again been found to be associated with increased risk and cruciferous vegetables to be protective. Within the SEARCH programme (see below), diet has been one of the factors of interests in relation to pancreas, brain, breast and colorectal cancers. A study in Singapore has shown a protective effect for breast cancer of soya products, which could be related to richness of these foods in phyto-estrogens, thought to inhibit hormone-dependent carcinogenesis.

### *N-Nitroso compounds*

The role of *N*-nitroso compounds in human carcinogenesis is being studied in various contexts. Their formation can occur within the body, depending on levels of nitrate, nitrite and ascorbic acid ingestion; others may be absorbed pre-formed in tobacco smoke and certain cooked foods. A bacterial enzyme catalysing nitrosation has been identified and is being characterized. DNA alkylating adducts formed by *N*-nitroso compounds are being analysed as markers of human exposure and to clarify the mechanisms by which these compounds exert their effects.

The significance of *N*-nitroso compounds, either ingested or endogenously formed, in diet-related carcinogenesis is being explored in laboratory and epidemiological studies, with special attention being paid to stomach cancer.

A striking result was the finding of levels of nitrosamines in Sudanese snuff that are orders of magnitude higher than previously reported in any smokeless tobacco. This could be related to the high incidence of oral cancer in Sudan.

### *Surveillance of environmental aspects related to cancer (SEARCH) programme*

In the SEARCH programme, multi-centre case-control studies of particular forms of cancer are coordinated by IARC in order to increase the numbers and diversity of subjects covered and to ensure the use of sound and consistent methodology.

The first study, on pancreas, gallbladder and bile duct cancer, has been completed and the results have been analysed. The data from all five centres are considered consistent with a causal role for cigarette smoking with respect to pancreatic cancer, and among dietary factors there were positive associations with carbohydrate and cholesterol intake, and inverse associations with fibre and vitamin C intake. No association was found with lifetime intake of coffee and tea. The principal effect observed for gallbladder cancer was an association with a history of gallbladder disease (gallstones), and the same applied to bile duct cancer.

In the SEARCH studies of childhood and adult brain tumours, data collection has been completed in most centres and results are beginning to become available. The protocol for the childhood leukaemia study, in collaboration with the EORTC, is ready for implementation. Work on clustering of childhood leukaemia cases has led to an assessment of different statistical techniques for identifying clusters. This is just one of the methodological developments which

was made possible by the SEARCH programme. A possibly more important development has been the in-depth analysis of differential measurement errors in analysing results of case–control studies.

### *Cervical cancer etiology*

The importance of human papillomavirus (HPV) in the etiology of cervical cancer remains a subject of intensive research. The case-control study in Colombia and Spain has shown strong associations between the presence of HPV DNA and invasive cervical cancer in both countries, and a predominance of HPV type 16, but it also showed the important role played by the method used to detect the viral DNA in making the estimates of relative risk. Further studies are in progress in Brazil, Mali, Morocco, Thailand and The Philippines which are intended to clarify the respective roles of HPV and other sexually transmitted agents. In the International Biological Study on Cervical Cancer, coordinated in collaboration with Professor Julian Peto, over 700 samples of invasive cervical cancer tissue have already been collected from 15 countries, which will be examined in the same reference laboratory for specific HPV types by DNA hybridization methods.

### *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

A total of 53 volumes of the IARC Monographs have been published or are in press. The fiftieth working group meeting was held in October 1989 and evaluated evidence relating to 15 pharmaceutical drugs, among which the antineoplastic agent thiotepa was classified as carcinogenic to humans, as was the immunosuppressive drug ciclosporin (Group 1). Azacitidine and chlorozotocin were considered probably carcinogenic on the basis of animal studies and other relevant data, while the antimicrobial agent chloroamphenicol was given a similar evaluation on the basis of limited human evidence.

Volume 51 contains evaluations of carcinogenic risks of coffee, tea and mate drinking, and of the related methylxanthines and methylglyoxal. The Working Group found limited evidence for increased bladder cancer risk associated with coffee drinking in humans, while evidence in relation to other sites, and from animal experiments, was either negative or inadequate. For tea, both epidemiological and experimental evidence were inadequate for a classification with regard to carcinogenicity, but hot mate drinking was classified as probably carcinogenic. Data on caffeine, theophylline, theobromine and methylglyoxal were absent or inadequate.

It was not possible to classify chlorinated drinking water or most of the halogenated compounds considered in Volume 52 with the limited data available. Bromodichloromethane as well as cobalt and cobalt compounds were classified as being possibly carcinogenic to humans. In Volume 53, 17 pesticides and occupational exposures in spraying and application of nonarsenical insecticides were evaluated. The latter were classified as probably carcinogenic to humans. The fungicide captafol was considered probably carcinogenic to humans.

The working group meeting due for February 1991 was cancelled due to the international crisis. An ad-hoc group of experts that met in June advised the Agency that biological agents should be included in the Monographs programme, listing a number of viruses, bacteria and parasites as having high priority for evaluation.

The final meeting of the biennium within the Monographs programme was held in June 1991 and assessed the use of knowledge regarding mechanisms of action in making evaluations of carcinogenicity. The Working Group of experts considered that in certain circumstances, such knowledge might influence the evaluation, and suggested a number of situations in which relevant information on mechanisms could be used in evaluating carcinogenic risks to humans. Guidelines were added to the Monographs preamble accordingly. The background papers and consensus document will be published in the IARC Scientific Publications series.

*Genetics and cancer*

The Agency uses three approaches in the study of genetic susceptibility to cancer: (*a*) by identifying genetic predispositions to cancer within the general population; (*b*) by investigating variations in host susceptibility to carcinogenic agents; and (*c*) by developing statistical methods for use in genetic epidemiology. The genes involved in three forms of cancer are being sought by a genetic linkage approach. The rare X-linked lymphoproliferative syndrome occurs in boys carrying a mutated gene, that has now been mapped to the Xq25–q26 chromosomal region. Multiple endocrine neoplasia type 2A accounts for 30% of all medullary thyroid cancers. The responsible gene has previously been linked to a locus near the centromere of chromosome 10, and restriction fragment length polymorphism analysis is now used alongside conventional endocrine challenge methods to identify individuals at high risk who can then be monitored for early neoplastic change. Work aimed at more precisely localizing the gene is continuing. The third form of cancer being studied by this approach is breast cancer, a disease which has been observed to occur with abnormal frequency in certain families, often along with ovarian cancer. Linkage analysis applied among a number of such families has now allowed the assignment of a breast cancer susceptibility locus to chromosome 17q12–q23.

Another aspect of individual susceptibility to cancer is the differential metabolism of carcinogens by isozymes of the cytochrome P450 family. The genetic basis for the different levels of certain isozymes known to activate carcinogens is being examined in terms of differences in the DNA coding, in its expression and in the enzyme molecules. Particular attention has been paid to enzyme variations in lung cancer cases and controls. The level of expression or inducibility of certain enzymes appears to be correlated with lung cancer risk, implying that in some smokers, enhanced activity of these enzymes can generate higher levels of carcinogenic metabolites from tobacco smoke constituents.

*Mechanisms of carcinogenesis*

The programme of research on mechanistic aspects of carcinogenesis, initially developed as a contribution to the Agency's general aim of identifying causes of cancer, has evolved towards promotion of the integration of biochemical and molecular biology techniques within epidemiological studies. Elucidation of mechanisms of action can confirm the activity of agents identified by experimental or epidemiological work and can point to other agents that would be expected to operate similarly. Early points on the mechanistic pathway can then be monitored to provide either exposure markers or indicators of early carcinogenic lesions. In addition, basic principles emerging from these studies can yield new test systems for laboratory testing of suspected carcinogens so that preventive measures may be adopted before human exposure has occurred.

Mechanisms of viral carcinogenesis are being studied with a focus on lymphomas associated with Epstein-Barr virus and with human immunodeficiency virus. Similar tumours occurring in patients with either of these viruses are being examined at the molecular level in order to more clearly define their etiology. It has been demonstrated that EBV integration can be a consistent mechanism of EBV maintenance upon infection of certain B cells *in vitro*, and this may be involved in the genesis of Burkitt's lymphoma and nasopharyngeal carcinoma.

The study of aflatoxin adducts to biological molecules has led to the development of sensitive assays that are being used for exposure measurement in studies of hepatocellular carcinoma epidemiology. The level of serum aflatoxin-albumin adducts has been shown to be an informative marker of relatively recent exposure to aflatoxin $B_1$. 95% of individuals examined in the Gambia had detectable levels of the adduct. Methods for detection of low levels of DNA methylation adducts are also under development, and are being applied in studies of smoking, gastric cancer risk factors and chemotherapeutic agents. It has been found that effect of cigarette smoking on 3-methyladenine levels can be measured if subjects are given special liquid diets to ensure that the background adduct levels are low.

Intensive research is in progress to characterize the oncogene mutations induced by carcinogens that lead to tumorigenesis. Studies of mutations in the p53 oncogene have shown interesting differences between oesophageal squamous cell carcinomas and hepatocellular carcinomas, the latter frequently having a specific G to T base substitution in codon 249, while base transversions at A:T pairs constitute a major fraction of p53 mutations in oesophageal tumour samples.

A highly sensitive method has been developed to measure the frequency of a specific mutation induced by 7,12-dimethylbenz[*a*]anthracene in *ras* genes. This mutation is being examined for its involvement in transformation of BALB/c 3T3 cells and in transplacental carcinogenic effects of this agent in the mouse.

The significance of altered cell-to-cell communication in carcinogenesis is being studied both at the functional level and in terms of gene and protein expression. Proteins specific to gap junctions in different tissues have been examined to establish the mechanisms by which their expression is regulated. A progressive decrease in communication capacity occurs during carcinogenesis, and early lesions with the greatest disorders in communication may be those most likely to develop into carcinomas. The use of measurements of intercellular communication as an assay system for tumour-promoting agents is supported by the results of experiments with a series of compounds.

*Cancer prevention*

The slow progress in cancer control in most countries and the unsatisfactory use of the available knowledge of etiology of cancer justifies the growing involvement of the Agency in studies on prevention. The Agency has initiated intervention studies and is evaluating the efficacy of initiatives taken in the field of primary and secondary prevention.

The Gambia Hepatitis Intervention Study, conducted jointly with the Gambian Government and the UK Medical Research Council Unit in Fajara, and funded by the Italian Government, completed recruitment of subjects during 1990, and hepatitis B vaccine is now administered routinely to all infants within the Gambia's expanded programme of immunization.

Within this study, the vaccine was progressively introduced across the country between 1986 and 1990. The population is being monitored for liver cancer through a newly established cancer registry. In addition, subgroups of the study population have been examined at intervals to determine levels of infection with hepatitis B virus and of carrier status. The fact that 93% of a group of 1000 children remain uninfected three years after vaccination and that initial data suggest a 94% effectiveness of the vaccine in preventing positivity to the hepatitis B surface antigen, are among the satisfying results already obtained. Other encouraging results are that the viral infection profile of a family has little effect on a new-born child's antibody response to the vaccine, and that even children with poor antibody response are protected against carriage of the virus.

Among ancillary studies to the main intervention trial, a study of routes of transmission of hepatitis B virus has shown that arthropods do not have a major role.

Another intervention trial is now being set up, to assess the effect of treatment for *Helicobacter pylori* infection followed by treatment with anti-oxidants ($\beta$-carotene and vitamins C and E) in preventing the evolution of early precancerous lesions towards cancer. This is being conducted in Tachira state, Venezuela, using the infrastructure of an existing screening programme for early gastric cancer. Pilot studies have established the activity of different antibiotics against *H. pylori* and will in particular examine the frequency of recurrence of the infection, and have examined different vitamin C formulations. Questionnaires and protocols for endoscopic and histological examinations have been tested and refined, and the recruitment of 300 subjects has started.

Screening programmes for cervical, gastric and lung cancers are being evaluated in the Philippines, Venezuela and Czechoslovakia. In the analysis of lung cancer screening in Czechoslovakia, no difference in mortality was seen between the screened and unscreened groups.

*Statistical methodology*

The Unit of Biostatistics Research and Informatics provides substantial advice and assistance to other units in the Agency and to national institutes on suitable statistical procedures for cancer research studies, and carries out research on improving the statistical tools available in this area. Current projects are assessing models used in looking for interactive effects between carcinogenic exposures and in studying survival on the basis of cancer registry data. A major study is in progress to examine and develop methods for use in genetic epidemiology in conjunction with other Agency projects on this subject, and a monograph is in preparation, for publication in the IARC Statistical Methods in Cancer Research series.

Another responsibility of this Unit is the Agency's computing facilities, which have recently been substantially upgraded to meet the widening range of scientific and administrative activities dependent upon this system, and the growing needs for enhanced power in epidemiological studies.

*Fellowships, courses and publications*

During the biennium 1990–91, a total of 26 research training fellowships were awarded to young scientists, of which seven were to work in epidemiology or biostatistics, two in chemical carcinogenesis, four in viral carcinogenesis, six in cell biology or genetics and seven in biochemistry or molecular biology. The successful candidates come from 14 different countries.

Twelve training courses have been held, and were attended by a total of 645 participants. Among them were epidemiology courses in French and Spanish as well as courses on the safe handling of toxic agents, molecular biology for cancer epidemiologists, the scientific basis of carcinogenicity testing, held in Moscow, and an epidemiological methods course which was held in Manila. The Agency also participated in the European Educational Programme in Epidemiology in Florence.

Among the 13 new volumes in the IARC Scientific Publications series are No. 95 *Cancer Registration: Principles and Methods*, and No. 100 *Cancer: Causes, Occurrence and Control*. A project has been set up to develop a CD-ROM electronic publication of the monographs series and several other Agency information resources.

The regular budget of the Agency for the biennium 1990–91 was US $26 126 000. On 30 June 1991, the Agency's staff consisted of 50 scientists, 51 technicians and 73 administrative and secretarial staff.

Lorenzo Tomatis, M.D.
Director

# PART 1. STUDIES ON CANCER OCCURRENCE, ETIOLOGY AND MECHANISMS

## 1.1 *Studies on Geographical Incidence and Time Trends*

Knowledge of the size and nature of the cancer problem in the world is fundamental in planning and evaluating appropriate control measures, and the Agency's work on this subject represents an essential complement to the work of WHO Headquarters.

Studies of the variation in the risk of different cancers according to geographical location have a long history, and continue to provide important clues as to possible etiology. Changes in risk over time and between different population subgroups (defined in terms of ethnicity, socioeconomic status, birthplace etc.) provide additional dimensions which enhance the interpretation of the geographical patterns. These descriptive epidemiological studies constitute a major component of the work of the Agency.

Since the value of the descriptive studies depends upon their completeness and quality of the data-sets used, considerable effort is also put into improvement of cancer registration worldwide, as detailed in section 3.1.

### 1.1.1 *Cancer Incidence in Five Continents, Volume VI*

(D.M. Parkin, S. Whelan, J. Ferlay and C.S. Muir; in collaboration with J. Powell, Birmingham, UK; and Y.T. Gao, Shanghai, China)

The five published volumes of *Cancer Incidence in Five Continents* present data on the incidence of cancer worldwide from the late 1950s up to 1982. For Volume VI, 170 cancer registries in 50 countries were invited to provide data for the years 1983–87 and were sent a questionnaire designed to obtain comprehensive information on differences in local conditions, registration practices and definitions in the contributing cancer registries. The deadline for acceptance of material was June 1991. At that time data had been processed for 184 populations in 48 countries. These included contributions from a number of new registries which, with support from the Unit of Descriptive Epidemiology (see section 3.1.1) and the implementation of CANREG (see section 3.1.7) are producing data from countries in Africa, Asia and South America for which no information was available before.

Computer programs to treat incoming data for this volume were created during 1989 and 1990. A great degree of flexibility is required to read tapes and diskettes coming in a wide variety of formats from all parts of the world. A program to check unlikely combinations of site or histological diagnosis and age, and unlikely site–histology combinations, created for this volume, has proved very valuable and it is planned to make the program available for use in cancer registries.

By the end of June 1991 all registries had received preliminary tables of their data and lists of errors and queries. The majority of the data had been corrected at least once. Software to make

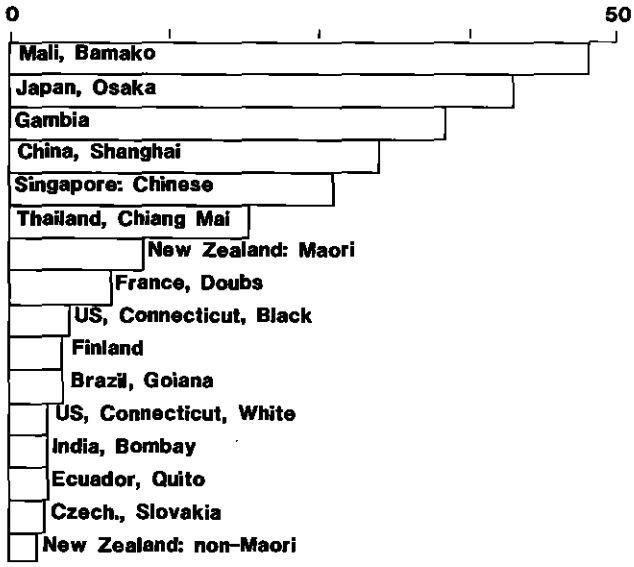



Fig. 1. Some of the data for primary cancer of the liver are shown in age-standardized incidence rates (per 100 000) for liver cancer, from registries in Africa, America, Asia and Europe (from data compiled for *Cancer Incidence in Five Continents,* Volume VI)

the Volume VI data available on a micro-computer diskette was created in 1991, and the diskette will be included with the published book. Figure 1 is a sample of the graphics that can be generated with this system.

The final editorial meeting, during which all data were assessed for reliability and completeness and decisions taken on which should be included in the publication, was held in June 1991.

### 1.1.2 *Patterns of Cancer in Five Continents*

(S. Whelan, D.M. Parkin and E. Masuyer)

*Patterns of Cancer in Five Continents*[1], published in 1990, presents the results published for the 137 populations in Volume V of *Cancer Incidence in Five Continents* in graphic form. Histograms illustrate incidence rates age-standardized to the 'world' population for 40 geographically representative populations in rank order by site and sex. The highest and lowest rates among all the populations included in Volume V are given as additional bars for each histogram.

The relative frequencies of the 10 top-ranking sites of cancer within each population are given in pie-diagrams, and graphs of the age-specific rates show the average annual incidence by sex, selected site and age-group per 100 000 population for 24 populations.

This presentation allows the user to rapidly interpret the data describing cancer incidence internationally and has highlighted the striking differences in cancer occurrence which can give clues to the etiology of the disease.

[1] Whelan, S.L., Parkin, D.M. & Masuyer, E. (1990) *Patterns of Cancer in Five Continents* (IARC Scientific Publications No. 102), Lyon, International Agency for Research on Cancer

### 1.1.3 Cancer in developing countries

In 1990/91, several studies have been undertaken in collaboration with local investigators to analyse incidence or mortality data of special interest.

#### 1.1.3.1 *Mali*

(D.M. Parkin; in collaboration with S. Bayo, Bamako, Mali)

The results from the second and third years of this cancer registry (1987–88) have been published, and confirm the very high incidence of liver cancer and high rates for cancers of the stomach and cervix[2].

#### 1.1.3.2 *Bulawayo, Zimbabwe*

(D.M. Parkin and A. Vizcaino; in collaboration with M.E.G. Skinner, South Africa)

The Bulawayo cancer registry functioned between 1963 and 1977, and data on the 11 000 cases registered during this period have been computerized and subjected to extensive validation and correction. This material has been analysed for geographic and temporal patterns of cancer incidence over the 15-year period. The data also include a substantial amount of information collected from interviews of cancer cases, and case–control studies within the 11 000 registrations are being completed (using selected 'other cancers' as controls) to investigate the importance of tobacco, alcohol, occupation and reproductive factors in determining risk of the common cancers.

#### 1.1.3.3 *Sétif, Algeria*

(M.P. Coleman; in collaboration with M. Hamdi Cherif, Sétif, Algeria)

Data from this newly established population-based registry have been analysed for the first years of registration (1986–88, retrospective collection)[3]. They are the first reasonably accurate estimates of cancer incidence from a north African population. They show high incidence rates of respiratory cancers in males and of gallbladder cancers in females, and confirm the moderately high incidence of nasopharyngeal carcinoma in males. The registry has served as a model for creation of additional registries in Algiers and Oran.

#### 1.1.3.4 *Samoa*

(D.M. Parkin and C. Bouchardy; in collaboration with N. Paksoy, Antalya, Turkey)

The data from a retrospective survey of cancer cases diagnosed in Western Samoa during an eight-year period (1980–88)[4] are interesting in deriving from a large Polynesian population, with an as yet relatively unwesternized lifestyle. Tobacco-related cancers are rare; stomach cancer is the most frequent neoplasm of males, while breast and cervix cancer account for about 40% of female neoplasms.

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[2] Bayo, S., Parkin, D.M., Koumaré, A.K., Diallo, A.N., Ba, T., Soumaré, S. & Sangaré, S. (1990) *Int. J. Cancer*, **45**, 679–684

[3] Hamdi Cherif, M., Sekfali, N. & Coleman, M.P. (1991) *Bull. Cancer*, **78**, 155–167

[4] Paksoy, N., Bouchardy, C. & Parkin, D.M. (1991) *Int. J. Epidemiol.* (in press)

#### 1.1.3.5 *Argentina*

(D.M. Parkin; in collaboration with E. Matos, Buenos Aires, Argentina)

Death certificate and census data from 1980 were analysed to investigate geographic variations in cancer mortality rates between the 22 provinces. The results show marked regional variations for some cancer sites (e.g., stomach, colon, breast)[5]; for certain cancers—most notably cancer of the oesophagus—the geographic pattern was quite different in the two sexes.

#### 1.1.3.6 *Rio de Janeiro State, Brazil*

(M.P. Coleman; in collaboration with C.B. Pinto, Rio de Janeiro, Brazil)

Cancer mortality data for the state of Rio de Janeiro have been analysed[6] for the peri-censal period 1979–81, providing the first detailed picture of mortality patterns for the state. Age-standardized mortality rates for all cancers were 146.5 and 99.9 for males and females, respectively. Cancers of the stomach, lung and female breast were the most common; cervix cancer mortality was unexpectedly low. Regional variation in cancer mortality within the state has been analysed[7].

#### 1.1.3.7 *São Paulo, Brazil*

(D.M. Parkin and C. Bouchardy; in collaboration with A.P. Mirra, São Paulo, Brazil)

The cancer registry of São Paulo records ethnic group, educational attainment and occupation for the great majority of registered cancer cases. Incidence data for 1969–74 and mortality data for 1978–82 have been analysed to investigate the risk of different cancers by ethnic group and by socio-economic status[8]. Because of missing data, and non-comparability of definitions between registry and census data, the principal analyses have used case–control methodology.

The analyses by ethnicity (controlling for social status) show that black and mulatto populations were at higher risk than whites for cancers of the oesophagus, stomach, cervix and prostate and for myeloma. Conversely, whites had higher risks for cancers of the colon, lung bladder, breast, corpus uteri and testis, and for leukaemia and malignant melanoma.

The analyses by socio-economic status control for ethnic group and show many of the features familiar in developing countries: increasing risk of breast and colon cancer, and decreasing risk of stomach and cervix cancer with higher socio-economic status. However, lung cancer remained at that time a disease of the better-educated.

### 1.1.4 Time trends in cancer

(M.P. Coleman, P. Damiecki, H. Renard, A. Arslan and J. Estève; in collaboration with E. Schifflers, Namur, Belgium)

Trends in cancer incidence and mortality have been examined for 28 major cancers, using data from 30 cancer registries and many countries, and covering periods of up to 25 years. New statistical methods and computer software have been developed to apply age, period and cohort models to data with irregular population denominators.

The main analyses have been completed and will be presented in a monograph showing trends by calendar period of incidence and death and by period of birth. Results will be shown

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[5] Matos, E.L., Parkin, D.M., Loria, D.I. & Vilensky, M. (1990) *Int. J. Epidemiol.*, **19**, 860–870

[6] Pinto, C.B. & Coleman, M.P. (1990) *Int. J. Cancer*, **46**, 173–177

[7] Pinto, C.B., Coleman, M.P. & Castilho, E.A. (1991) *Rev. Saude Publica* (in press)

[8] Bouchardy, C., Mirra, A.P., Khlat, M., Parkin, D.M., Pacheco de Souza, J.M. & Davidson Gotlieb, S.L. (1991) *Cancer Epidemiol. Biomarkers Prev.* (in press)

by world region, by sex and by broad age group. The monograph will comprise the first comprehensive analysis of international trends in cancer applying a systematic approach to all available data sets of adequate quality.

As an example of the results, the cumulative risk of lung cancer (35–64 years) (Figure 2) shows dramatically divergent patterns by year of birth in Germany (rising) and the UK (falling rapidly). Figure 3 shows the mean percentage changes in lung cancer mortality per five-year period during 1970–85, by sex and broad age group, for various European countries. The trends vary from a 20% increase to a 10% decrease per five-year period in males, and from a 40% increase to an 8% decrease in females.

### 1.1.5 Studies of 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 objective 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

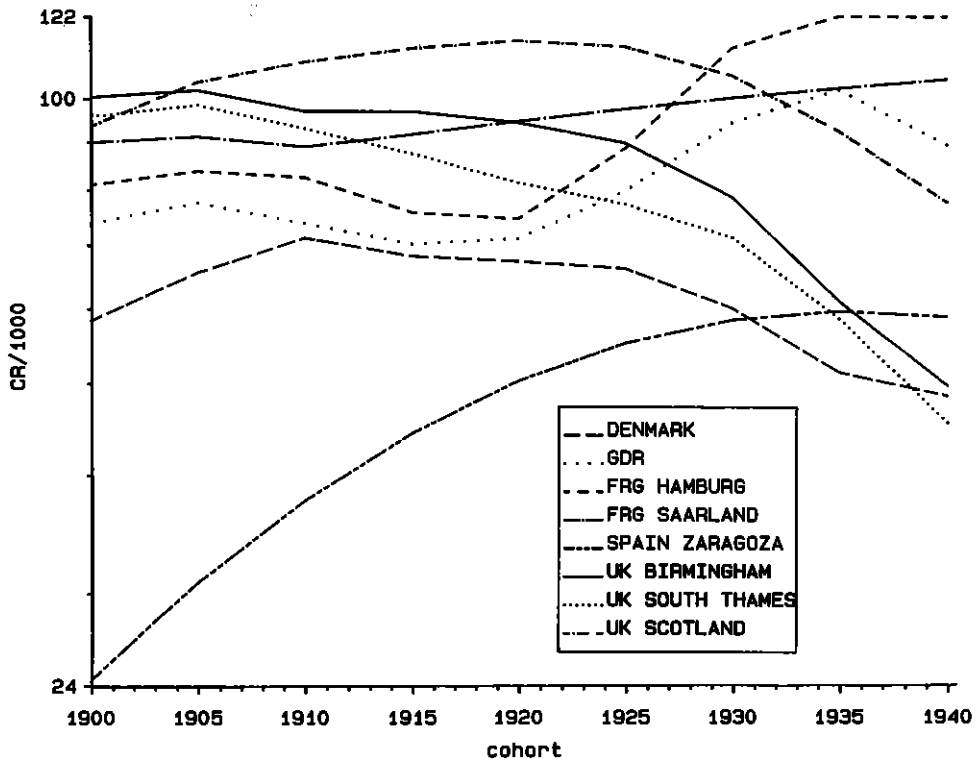


Fig. 2. Cumulative risk of lung cancer, per 1000 (ages 35–64) by year of birth, in eight European registries

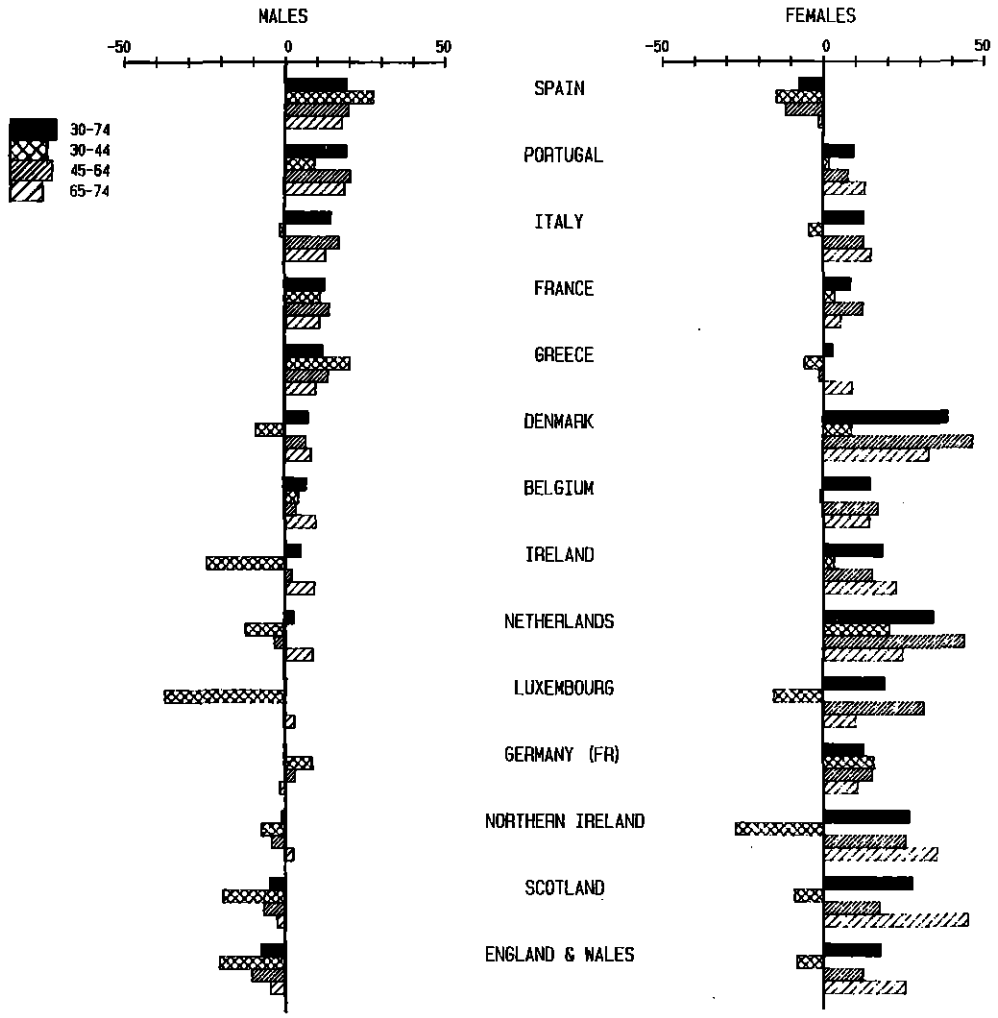


Fig. 3. Mean percentage change in lung cancer mortality during the period 1970–85, in four age groups (EEC countries)

occur. The results are useful in formulating hypotheses on the relative importance of environmental factors in etiology, and on the probable stage of carcinogenesis on which they act.

### 1.1.5.1 *Methodological aspects*

(J. Kaldor, M. Khlat and D.M. Parkin; in collaboration with D. Balzi, Florence, Italy)

The statistical analysis of cancer risk in migrant populations raises problems of identifying the contributions to risk of temporal trends and effects due to duration of stay or age at arrival in the host country. Other difficulties are the result of lack of appropriate denominator populations and the desirability of controlling for extraneous variables such as socio-economic status and place of

residence, which produce differences in risk between migrant populations and those of the host country. Log–linear modelling techniques have been used in several studies to overcome these problems[9] and the validity of the results obtained has been investigated with several data sets.

### 1.1.5.2 *Cancer incidence in offspring of migrants to Israel*

(D.M. Parkin and M. Khlat; in collaboration with L. Katz and J. Iscovich, Jerusalem, Israel)

The study of cancer in migrants to Israel[10] is being extended to examine how the incidence in the Israel-born population relates to the place of birth of their parents. This is equivalent to investigating change in risk between first-generation migrants (born in country of origin) and the next generation, born in the host country. All cancer registrations for the years 1961–86, in individuals born in Israel and aged 0–29, have been matched with the population register in order to record parental birthplace. The study is focusing upon those cancers for which incidence rates in young age groups are substantial, and for which there are clear differences in incidence by country of birth (e.g., nasopharynx cancer, Ewing's sarcoma, lymphoma, lymphatic leukaemia). Analysis of the results is in progress.

### 1.1.5.3 *Cancer in Italian migrant populations*

(D.M. Parkin, J. Kaldor, M. Khlat and C. Bouchardy; in collaboration with E. Buiatti, M. Geddes and D. Balzi, Florence, Italy; L. Bernstein, Los Angeles, CA, USA; R. Black, Edinburgh, UK; A. Brancker, Ottawa, Canada; M. Coates, North Ryde, Australia; E. de Stefani, Montevideo, Uruguay; J.T. Flannery, Hartford, CT, USA; M. Marmot, London, UK; E. Matos, Buenos Aires, Argentina; A.P. Mirra, São Paulo, Brazil; L. Raymond, Geneva, Switzerland; P. Reynolds, Emeryville, CA, USA; and A.J. Swerdlow, London, UK)

This study is examining cancer incidence and/or mortality rates in populations born in Italy but resident in other countries. The objective is to compare rates for the major cancer sites in these migrant populations (*a*) with each other, (*b*) with the population born in the host country, and (*c*) with the population of Italy, both national and resident in the south (from where most migrants originate). Incidence data have been included from the USA (Connecticut, San Francisco, Los Angeles), Australia (New South Wales), Brazil (São Paulo), England and Wales, and Switzerland (Geneva). Mortality data from Australia, Brazil (São Paulo), Canada, Uruguay, Argentina, France and Great Britain are also included. The incidence data from the USA permit a distinction to be made between childhood and adult migrants, while mortality data for Australia permit analysis by duration of stay or age at arrival.

A workshop in February 1990 reviewed results of the study, which will be published in full in 1992. Those for colon cancer are presented in Figure 4, which shows the risk of death from colon cancer in Italy (national and south), and in migrants from Italy in each of the eight countries, relative to the local-born population (=1.0). Except for Brazil, mortality rates for colon cancer are higher in the host countries than in Italy, but in all cases, migrants acquire a risk intermediate between the two.

A review of previous studies of Italian migrants has been published[11].

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[9] Kaldor, J., Khlat, M., Parkin, D.M., Shiboski, S. & Steinitz, R. (1990) *Int. J. Epidemiol.*, **19**, 233–239

[10] Parkin, D.M., Steinitz, R., Khlat, M., Kaldor, J., Katz, L. & Young, J. (1990) *Int. J. Cancer*, **45**, 614–621

[11] Geddes, M., Balzi, D., Buialti, E., Khlat, M. & Parkin, D. (1991) *Cancer Causes Control*, **2**, 133–140

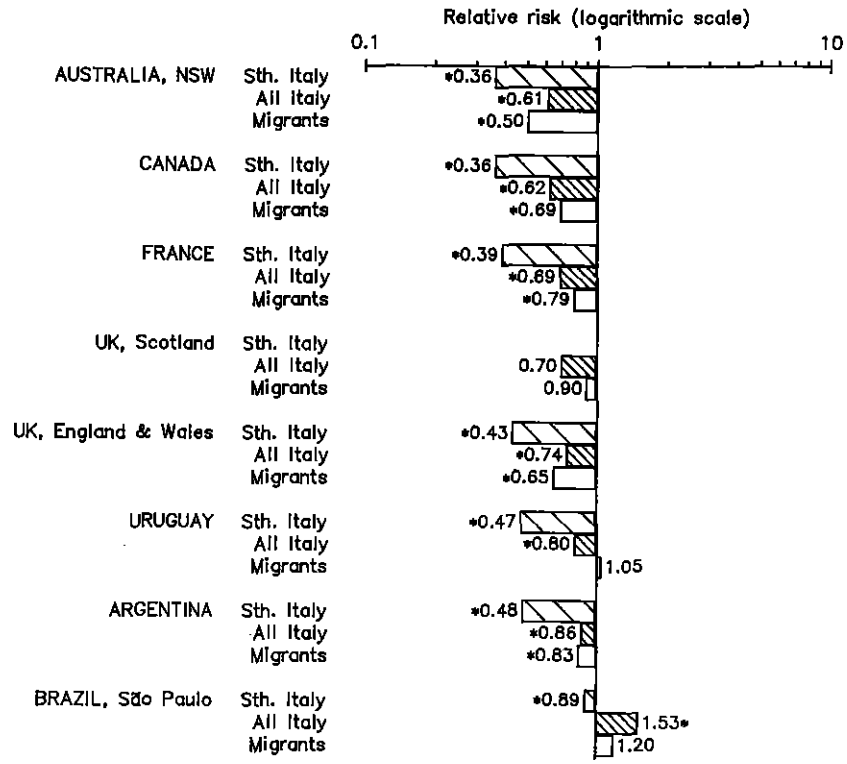


**Fig. 4. Risk of colon cancer mortality in Italy (national and south) and in Italian migrants, relative to the local-born population (1.0) of eight countries. Males**

### 1.1.5.4 *Cancer in Polish migrant populations*

(D.M. Parkin and E. Masuyer; in collaboration with W. Zatonski and J. Tyczynski, Warsaw, Poland)

Previous studies of Polish migrant populations to North America and Australia suffer from defects of inadequate data (particularly on mortality rates in Poland) and methodology. A new series of analyses is being undertaken, to study cancer risk in Polish migrants to Canada, the USA, England and Wales, France, Australia, Israel and Argentina. The quality of incidence and mortality data from Poland is now much higher than in earlier years, and the effect of including confounding variables such as socio-economic group and place of residence will be investigated. the influence of age at arrival and duration of stay on risk will be studied for migrants to Australia, Israel and the USA.

### 1.1.5.5 *Mortality from cancer in migrants to Australia*

(D.M. Parkin, J. Kaldor and M. Khlat)

Australian death certificates record not only country of birth, but also date of immigration to Australia. Limited data are available from population censuses in 1961, 1971 and 1981 on the size of the immigrant populations by period of residence. The importance of age at arrival in Australia, and of the duration of residence there in determing risk of different cancers is being

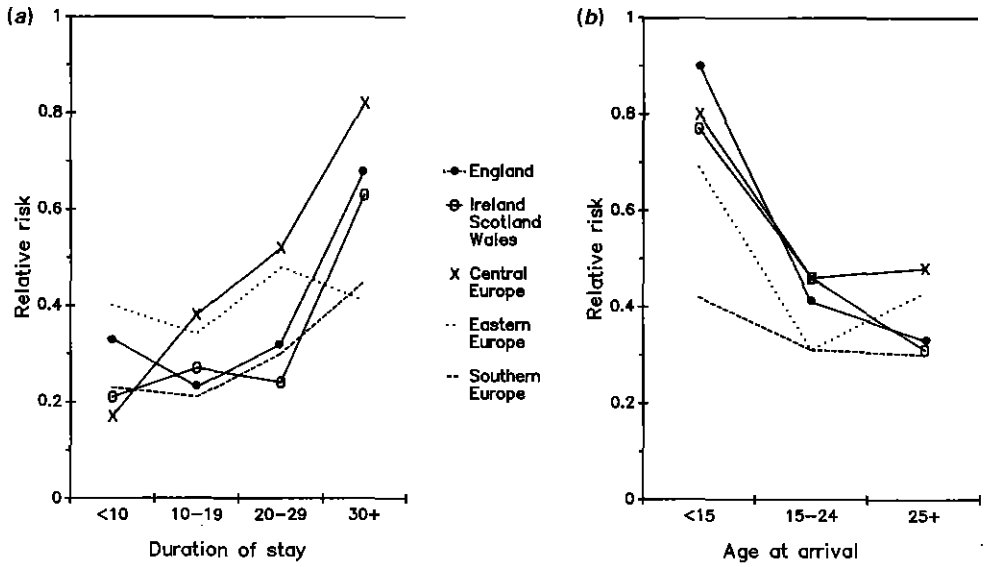


Fig. 5. Risk of mortality from melanoma in migrants to Australia, relative to the local-born (1.0) according to (a) duration of stay and (b) age at arrival. Males

investigated. Analysis for melanoma is complete and suggests a high risk for Europeans arriving in Australia as children (Figure 5)[12].

1.1.5.6 *Cancer in European migrants to South America*

(D.M. Parkin, J. Kaldor and M. Khlat; in collaboration with E. Matos, Buenos Aires, Argentina; A.P. Mirra, São Paulo, Brazil; H. Pracilio, La Plata, Argentina; and E. de Stefani, Montevideo, Uruguay)

Country of birth is recorded on death certificates in several South American countries, and in some mortality rates for cancer are sufficiently reliable to allow calculation by place of birth. Data from Argentina[13], Uruguay[14] and Brazil (São Paulo) have been analysed. Some interesting exceptions to the generally expected pattern (migrant rates between those of country of origin and host country) are seen, and suggest opportunities for further study.

### 1.1.6 The burden of cancer

(D.M. Parkin, C.S. Muir and M. Khlat)

Updating of the estimates of incident cancers, by world area, for 1985 awaits the availability of data from Volume VI of *Cancer Incidence in Five Continents* (see section 1.1.1). In 1990/91, preliminary work on the methodology of estimating incidence from mortality data was undertaken.

[12] Khlat, M., Vail, A., Parkin, M. & Green, A. (1991) (submitted for publication)
[13] Matos, E.L., Khlat, M., Loria, D.I., Vilensky, M. & Parkin, D.M. (1991) *Int. J. Cancer* (in press)
[14] De Stefani, E., Parkin, D.M., Khlat, M., Vassallo, A. & Abella, M. (1990) *Int. J. Cancer*, **46**, 233–237

The analysis of person-years of life lost due to cancer[15] will be extended when data become available for 1989–91, allowing publication of the results for four time periods (1960, 1970, 1980, 1990).

### 1.1.7 European network of cancer registries

(J. Estève, M.P. Coleman and C.S. Muir; in collaboration with O.M. Jensen and H.H. Storm, Copenhagen, Denmark; F. Berrino, Milan, Italy; E. Grundmann, Münster, Germany; T. Hakulinen, Stockholm, Sweden; F. Ménégoz, Meylan, France; R. Otter, Groningen, Netherlands; E. Schifflers, Namur, Belgium; A.J. Swerdlow, London, UK; H. Tulinius, Reykjavik, Iceland; and B. Noble, Bristol, UK)

An EEC-funded project to create a network of European cancer registries began in 1989, with the aims of improving the quality and comparability of their data and of making these data available more widely and more promptly. An electronic publication of incidence and mortality data (EUROCIM) has been prepared (see section 5.3.1). The data will be provided on two diskettes for IBM-compatible microcomputer, together with a wide range of statistical and graphical software, permitting access to the data by age, sex, site, year and registry (for incidence) or country (for mortality). The cancer 'site' to be tabulated can be defined by the user from among almost 700 site-histology combinations ('entities') into which the data have been classified, although ICD-9 groupings of site are provided by default. The diskette publication is undergoing field testing (June 1991) and will be released in late 1991.

The first meeting of participating cancer registries was held in Lyon in February 1991. Over 40 EEC cancer registries were represented, with observers from Switzerland and the Nordic countries. A programme of work for the next two years was planned, including regular estimations of cancer incidence in the EEC, monitoring of trends and further development of EUROCIM. An extensive survey of cancer registration practice in EEC registries, to be carried out by the Danish Cancer Registry, is in preparation.

### 1.1.8 Cancer incidence and mortality mapping

(M. Smans and J. Estève; in collaboration with J. Augustin, Brno, Czechoslovakia; M. Bancovic, Belgrade, Yugoslavia; N. Becker, Heidelberg, Germany; H. Friedl, Vienna, Austria; M. Möhner, Berlin, Germany; Z. Peter, Budapest, Hungary; I. Plesko, Bratislava, Czechoslovakia; V. Roman, Bucharest, Romania; J. Tyczynski and W. Zatonski, Warsaw, Poland; and C. Tzvetansky, Sofia, Bulgaria)

An atlas of cancer mortality in central Europe is being prepared which will include eight countries (Austria, Bulgaria, Czechoslovakia, Germany, Hungary, Poland, Romania and Yugoslavia). The technical work is well advanced, and a series of maps and supporting figures will be ready by the middle of 1992.

To follow up the forthcoming atlas of cancer mortality in EEC[16], plans are in preparation for an update which will include the twelve current member countries as well as Sweden and Switzerland.

This programme has also provided advice to teams in several countries for the preparation of their own work in geographic epidemiology and has helped lay the foundations for the analysis of cancer mortality for the "Europe against Cancer" programme.

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[15] *IARC Biennial Report 1988/89*, pp. 3–4

[16] Smans, M., Muir, C.S. & Boyle, P., eds (1991) *Atlas of Cancer Mortality in the European Economic Community* (IARC Scientific Publications No. 107), Lyon, International Agency for Research on Cancer (in press)

## 1.2 *Determination of Environmental and Occupational Hazards*

The objective of this programme is to identify possible carcinogenic risks to humans resulting from exposures to chemical, physical and biological agents which occur in the environment. The projects include epidemiological studies in which exposure is assessed both by questionnaire and by laboratory methods, analysis of occupational mortality statistics, case–control studies in various geographical areas and the dissemination of evaluated data in the form of IARC Monographs. The results of these studies and the evaluations of data made by international groups of experts in carcinogenesis are used for generation and testing of etiological hypotheses, to aid governments and regulatory agencies and to help scientists to select priorities for preventive measures in cancer control.

Multi-centre case–control studies for several cancer sites are being used to examine etiological hypotheses, particularly in relation to the roles of nutritional and occupational factors.

Other epidemiological studies are investigating the carcinogenicity to humans of substances to which exposure occurs mainly in occupational settings. This usually involves identifying suitable cohorts of workers exposed in the past and followed up to the present for possible long-term health effects, notably cancers.

In the series of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, all published studies relevant to the carcinogenicity of a chemical, group of chemicals, complex mixture or occupational exposure are summarized and evaluated by an international group including experts in epidemiology and experimental carcinogenesis.

Most quantitative information on the relation between carcinogenic exposure and risk of cancer comes from animal experiments. Only in a few situations are humans exposed to known levels of carcinogens. A number of studies are being conducted to assemble and analyse relevant human data in order to improve our knowledge of quantitative relationships between exposure and carcinogenic risk.

### 1.2.1 Carcinogenic risk of inhalable particles

#### 1.2.1.1 *Mesothelioma in central Turkey*

(R. Saracci and R. Winkelmann; in collaboration with L. Simonato, Padua, Italy; Y.I. Baris, Ankara, Turkey; and P. Sébastien, Montreal, Canada)

Monitoring is continuing of mortality and morbidity in the villages of the Cappadocian region of Turkey where mesothelioma is endemic. Because of the small size of the populations, it is likely to take the next two to three years to accumulate enough new cases for an analysis that will provide information on the evolution of the disease. The results to date, as well as the methodological approaches followed in the investigation of this unique example of environmental cancer, will be summarized in a book resulting from a meeting in Rome in October 1990 on small-area statistics and detection of clusters[17].

[17] Baris, I., Simonato, L., Saracci, R. & Winkelmann, R. (1992) In: Elliott, P., Cuzick, J. & English, D., eds, *Geographical and Environmental Epidemiology: Methods for Small-Area Studies*, Oxford, Oxford University Press (in press)

#### 1.2.1.2 *Cancer mortality among gold miners*

(L. Simonato, R. Saracci, R. Winkelmann, G. Ferro; in collaboration with B. Javelaud, Salsigne, France; and J. J. Moulin, Vandoeuvre-lès-Nancy, France)

A cohort of 1990 workers ever employed after 1955 for at least three months in the gold mine and in the factory of the Société des Mines et Produits Chimiques de Salsigne, France, was set up during 1988. Excluded from the analysis for various reasons (e.g., employment less than one year) were 627 workers. Completeness of follow-up for workers in the analysis was 97.6%, but cause of death was not obtained for 47 out of 211 recorded deaths. There was an excess risk for lung cancer (36 deaths, SMR = 213, 95% CI 149–295), irrespective of employment in the mine or the factory. This excess was concentrated among workers first employed before 1955, when measures leading to decreased exposure to arsenic, dusts in general and radon were taken. Increased mortality from rectal cancer (7 deaths, SMR = 272, 95% CI 110–561), especially among factory workers, requires further confirmation. No excess mortality of non-malignant disease was reported.

#### 1.2.1.3 *Historical prospective study of workers employed in the man-made mineral fibre industry*

(R. Saracci, P. Boffetta, M. Kogevinas and G. Ferro; in collaboration with A. Andersen, Oslo, Norway; P.A. Bertazzi, Milan, Italy; J. Cherrie, Edinburgh, UK; R. Frentzel-Beyme, Heidelberg, Germany; M. Gardner, Southampton, UK; J. Olsen, Copenhagen, Denmark; L. Simonato, Padua, Italy; L. Teppo, Helsinki, Finland; and P. Westerholm, Stockholm, Sweden)

An historical cohort study was conducted during the 1980s in 13 factories producing man-made mineral fibres in seven European countries, which identified an excess of lung cancer in workers employed in the early phases of the production of rockwool–slagwool fibres. Results from an extension of the follow-up of this cohort from the end of 1982 to the end of 1987 are expected by mid-1992. A case–control study on lung cancer within the cohort will be conducted if initial testing demonstrates that valid information on exposures at work and outside (e.g., smoking habits) can be obtained from proxy informants of deceased cancer cases. A Poisson regression re-analysis of the data of the 1982 follow-up has been conducted and confirmed the results of the previous analysis. Time since first exposure was the variable most strongly associated with lung cancer risk (see Figure 6).

### 1.2.2 Carcinogenic risk of occupational exposures

#### 1.2.2.1 *Exposure to vinyl chloride monomer*

(R. Saracci, K. A. L'Abbé, R. Winkelmann and G. Ferro; in collaboration with A. Andersen, Oslo, Norway; S. Belli, P. Comba and P. Pirastu, Rome, Italy; G. Engholm, Danderyd, Sweden; L. Hagmar, Lund, Sweden; S. Langård, Porsgrunn, Norway; I. Lundberg, Stockholm, Sweden; L. Simonato, Padua, Italy; and P. Thomas, Bootle, UK)

Investigators from Italy, Norway, Sweden and the United Kingdom participated in the cohort study of workers employed for at least one year in the vinyl chloride (VC) industry. Among 12 706 subjects retained for the analysis, increased liver cancer mortality was observed (24 deaths, SMR = 286, 95% CI 183–425). An exposure–response relationship was evident for all

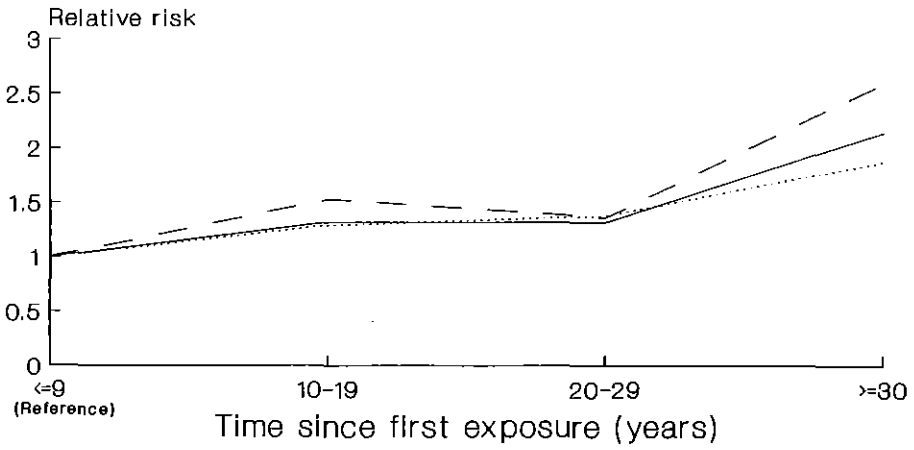


**Fig. 6. Relative risk of lung cancer in man-made mineral fibre production workers by time since first exposure. Results of Poisson regression analysis, adjusted for country, age, calendar period, duration of employment and technical phase. —— all workers; ... rockwood/slagwool; —— glasswool**

liver cancers and for angiosarcomas of the liver, both for ranked and for estimated cumulative exposure to VC monomer (Figure 7). Slight increases in mortality from lymphosarcomas (7 deaths, SMR = 170, 95% CI 69–351) and brain tumours (14 deaths, SMR = 107, 95% CI 59–180) do not appear consistently associated with exposure, while no excess mortality was seen for lung cancer (144 deaths, SMR = 97, 95% CI 82–114) or other main causes of death.

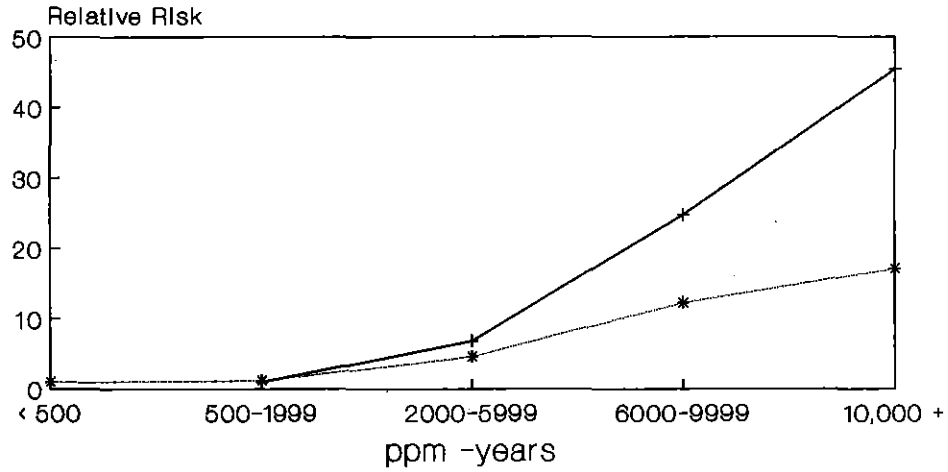


**Fig. 7. Risk of liver cancer and angiosarcoma by cumulative exposure to vinyl chloride (in ppm-years). ... Liver cancer; —— angiosarcoma. Reference for liver cancer <500 ppm-years; reference for angiosarcoma <2000 ppm-years**

Increased risks of bladder cancer and malignant melanoma were confined to one country only and do not appear to be related to exposure to VC.

#### 1.2.2.2 *Cohort study on workers exposed to styrene*

(M. Kogevinas, R. Saracci, R. Winkelmann and P. Boffetta; in collaboration with A. Astrup-Jensen, Taastrup, Denmark; A. Andersen and J. Bjerk, Oslo, Norway; R.T. Benn, Bootle, UK; T. Bellander and I. Lundberg, Stockholm, Sweden; M. Biocca, Bologna, Italy; D. Coggon and B. Pannett, Southampton, UK; K. Kurppa and P. Pfaffli, Helsinki, Finland; E. Lynge, Copenhagen, Denmark; and S. Tolomei, Parma, Italy)

Epidemiological studies in the styrene–butadiene rubber industry have indicated increased risk of leukaemia and lymphoma. A collaborative working group of researchers from six European countries has been formed in order to collect and evaluate data on exposure to styrene in the reinforced plastics industry. The total population suitable for the epidemiological study is approximately 20 000 workers. All cohorts will be followed for mortality, and cancer incidence information will be available for five countries. A group of industrial hygienists has evaluated levels of present and past exposures to styrene in the industry and a matrix is being constructed for exposure to styrene taking into account time period, job title, type of product and process ventilation. Extensive biological monitoring data (urinary mandelic and phenylglyoxylic acid) are available in Italy, and will be analysed separately. Epidemiological data from some centres have already been transferred to IARC and results of the study are expected to be available in late 1992.

#### 1.2.2.3 *International Register of Persons Exposed to Phenoxy Acid Herbicides and Contaminants*

(R. Saracci, M. Kogevinas, R. Winkelmann, P. Boffetta and G. Ferro; in collaboration with H. Becher, Heidelberg, Germany; P.A. Bertazzi, Milan, Italy; H.B. Bueno de Mesquita, Bilthoven, Netherlands; D. Coggon, Southampton, UK; L.M. Green, Toronto, Canada; E. Johnson, Research Triangle Park, NC, USA; T. Kauppinen, Helsinki, Finland; M. Littorin, Lund, Sweden; E. Lynge, Copenhagen, Denmark; J.D. Mathews, Casuarina, Australia; M. Neuberger, Vienna, Austria; J. Osman, Bootle, UK; and N. Pearce, Wellington, New Zealand)

The objective of this project, conducted through a collaboration between IARC and the US National Institute of Environmental Health Sciences (NIEHS), is to maintain an international register of workers exposed to chlorophenoxy herbicides, chlorophenols and contaminants (principally chlorinated dibenzodioxins), which can serve as a basis for follow-up of possible long-term health effects. Previous epidemiological studies have reported an increased risk of cancer, particularly soft-tissue sarcoma (STS) and non-Hodgkin lymphoma, in subjects occupationally exposed to these chemicals. The register currently includes information on 18 910 production workers or sprayers forming 20 cohorts from 10 countries. Exposure of workers was reconstructed through questionnaires and other documents at the level of factory or spraying cohort, combined with job histories. The first mortality and cancer incidence follow-up has been completed. No increase was observed in all-causes mortality, nor for all neoplasms, the most common epithelial cancers or lymphomas. Table 1 gives standardized mortality ratios for exposed and probably exposed workers of both sexes for all neoplasms, STS and non-Hodgkin lymphoma. A statistically non-significant two-fold excess risk, based on four observed deaths,

Table 1. Mortality for all malignant neoplasms, soft-tissue sarcoma and non-Hodgkin lymphoma (both sexes) in relation to exposure to phenoxyacid herbicides

| | All malignant neoplasms | | | Soft-tissue sarcoma | | | Non-Hodgkin lymphoma | | |
|---|---|---|---|---|---|---|---|---|---|
| | Observed | SMR | 95% CI | Observed | SMR | 95% CI | Observed | SMR | 95% CI |
| Total exposed and probably exposed | 515 | 101 | 93–110 | 4 | 19 | 53–502 | 11 | 95 | 47–169 |
| Non-exposed | 100 | 99 | 81–120 | 0 | 0 | 0–878 | 4 | 178 | 48–455 |
| *Type of cohort*[a] | | | | | | | | | |
| Production | 253 | 98 | 86–111 | 1 | 97 | 3–5 | 418 | 149 | 64–294 |
| Sprayers | 262 | 105 | 93–118 | 3 | 297 | 61–868 | 3 | 49 | 10–140 |
| *TCDD exposure*[a] | | | | | | | | | |
| Probable TCDD exposure | 236 | 110 | 96–125 | 2 | 200 | 24–723 | 5 | 87 | 28–203 |
| Exposure to TCDD unlikely | 279 | 95 | 84–107 | 2 | 193 | 23–695 | 6 | 102 | 37–222 |
| *Years since first exposure*[a] | | | | | | | | | |
| 30+ | 74 | 84 | 66–105 | 0 | 0 | 0–1537 | 2 | 119 | 14–430 |
| 20–29 | 171 | 107 | 92–125 | 0 | 0 | 0–709 | 3 | 89 | 18–259 |
| 10–19 | 170 | 102 | 87–119 | 4 | 606 | 165–1552 | 5 | 127 | 41–296 |
| 0–9 | 100 | 106 | 86–129 | 0 | 0 | 0–738 | 1 | 38 | 1–209 |
| *Duration of exposure (years)*[a] | | | | | | | | | |
| 20+ | 36 | 85 | 60–118 | 0 | 0 | 0–2459 | 1 | 98 | 3–546 |
| 10–19 | 74 | 97 | 76–122 | 2 | 690 | 84–2491 | 1 | 55 | 1–308 |
| 1–9 | 234 | 102 | 89–115 | 0 | 0 | 0–415 | 3 | 56 | 12–164 |
| <1 | 168 | 108 | 92–126 | 2 | 339 | 41–1125 | 6 | 179 | 66–390 |

SMR, standardized mortality ratio; 95% CI, 95% confidence interval

[a] Exposed and probably exposed workers

was observed overall for STS; this was concentrated as an about six-fold statistically significant excess, occurring 10 to 19 years from first exposure in the cohort as a whole, and as an about nine-fold excess among sprayers. Risks appeared elevated for cancers of the testis, thyroid, other endocrine glands, nose and nasal cavity, based on small numbers of deaths. The observed excess of STS among sprayers is compatible with a causal role of chlorophenoxy herbicides. In the present set of data, the excess does not appear specifically associated with those herbicides probably contaminated by tetrachlorodibenzo-*p*-dioxin (TCDD). The register is being enlarged with incorporation of cohorts from Germany, and nested case–control studies on STS and non-Hodgkin lymphoma are planned. A further follow-up for mortality and cancer incidence is being conducted.

### 1.2.2.4 *Mortality study of a cohort of slate quarry workers in the German Democratic Republic*

(L. Simonato and R. Winkelmann; in collaboration with W. Ahlendorf and W. Müller, Gera, Germany; and B. Beck, G. Konetzke, W. H. Mehnert, M. Möhner and W. Staneczek, Berlin, Germany)

Following reports from other countries indicating an excess risk of lung cancer among silicotics, a cohort of 2483 workers employed for at least one year in slate extraction and processing during the period 1953–1985 in the German Democratic Republic was constructed and followed up for mortality from 1970 to 1985. The results of the study show a mortality excess for infectious (7 deaths, SMR = 258, 95% CI 104–531) and respiratory diseases (74 deaths,

SMR = 226, 95% CI 177–284). The overall lung cancer mortality is not in excess but shows a tendency to increase with time since first exposure. A mortality excess from lung cancer is concentrated among workers receiving compensation for silicosis, suggesting a possible carcinogenic risk for individuals suffering from this pathological condition.

### 1.2.2.5 *International cohort study on cancer risk among workers in the pulp and paper industry*

(M. Kogevinas, P. Boffetta, R. Saracci, H. Vainio, R. Winkelmann and G. Ferro; in collaboration with A. Andersen, Oslo, Norway; W. Boal, Cincinnati, OH, USA; D. Coggon, Southampton, UK; L. Facchini, Pelotas, Brazil; D. Heederik, Wageningen, Netherlands; P.K. Henneberger, Syracuse, NY, USA; M. Hours, Lyon, France; P. Jäppinen, Imatra, Finland; V. Katsouyiannopoulos, Thessaloniki, Greece; J.-M. Lutz, Meylan, France; E. Lynge, Copenhagen, Denmark; F. Merletti, Turin, Italy; H. Miyake, Sapporo, Japan; N. Pearce, Wellington, New Zealand; B. Persson, Linköping, Sweden; L. Raymond, Geneva, Switzerland; V. Rodrigues, Coimbra, Portugal; C. Soskolne, Edmonton, Canada; J. Sunyer, Barcelona, Spain; I. Szadkowska-Stanczyk, Lodz, Poland; and P. Wild, Vandoeuvre-lès-Nancy, France)

The paper and pulp industry employs hundreds of thousands of workers worldwide. The few prospective epidemiological studies in this industry indicate that cancer risk, particularly for lung cancer, gastrointestinal cancer and neoplasms of the lymphatic tissue, may be elevated, but evidence is still not convincing. The objective of the study is to evaluate cancer risk in relation to specific processes and specific exposures in this industry. Personnel employed in plants producing pulp, paper and paper products and in mills involved in recycling will be included. Cohorts are currently being assembled, and it is expected that the international study will include data for more than 100 000 workers. In the light of the results of an initial historic cohort study, case–control studies within the cohort on specific neoplasms will be considered. A parallel industrial hygiene study is being conducted. The first results of the study are expected in 1996.

### 1.2.2.6 *International collaborative study on workers exposed to lead*

(P. Boffetta, R. Saracci and M. Kogevinas; in collaboration with C. Boreiko, Research Triangle Park, NC, USA; J. Davies and G. Kazantzis, London, UK; D. Easton and J. Peto, Belmont, Surrey, UK; D. Fanning, Manchester, UK; G. Nordberg, Umeå, Sweden; K. Steenland, Cincinnati, OH, USA; and O. Wong, Alameda, CA, USA)

Cohort studies of workers exposed to lead have suggested increased incidences of lung and stomach cancers. This project aims to examine in detail the pattern of cancer risk with respect to exposure to lead. The first phase is a combination of existing cohorts, to be consistently re-analysed with respect to duration of exposure and time since first exposure. On the basis of the results of the first phase, further steps of the project may include a combined update of existing and new cohorts, a comprehensive industrial hygiene survey and nested case–control studies. Results of the first phase will be available in 1992.

### 1.2.2.7 *Cancer risk among steel workers in Vale do Aco, Minas Gerais, Brazil*

(S. Barreto, P. Boffetta, M. Kogevinas and R. Saracci; in collaboration with A. Swerdlow, London, UK)

This project is being carried out in a recently industrialized area with few large steelworks and many medium-sized and small foundries; over 30% of the adult male population is engaged in this industry. A descriptive analysis of cancer mortality in Vale do Aco has already been initiated. Next, cancer mortality among workers in the largest steelworks will be compared with those of the entire valley and of the capital of the State (Belo Horizonte), and related to levels of exposure of the steelworkers to polycyclic aromatic hydrocarbons. Finally, a population-based case–control study of lung cancer is planned.

### 1.2.2.8 *International study of cancer risk in biology research laboratory workers*

(A.J. Sasco and R. Saracci; in collaboration with A. Ahlbom, Stockholm, Sweden; N. Becker, Heidelberg, Germany; S. Belli, Rome, Italy; S. Benhamou, Villejuif, France; G.J. Bourke, Dublin, Ireland; C. Chilvers, Nottingham, UK; F. Hatton, Le Vésinet, France; O.H. Iversen, Oslo, Norway; T. Kauppinen, Helsinki, Finland; J. Laporte and R. Maximilien, Paris, France; J.J. Moulin, Vandoeuvre-lès-Nancy, France; C. Tessier, Strasbourg, France; and F. van Leeuwen, Amsterdam, Netherlands)

The need to assess cancer risk in research laboratory personnel is based on several considerations[18]: (*a*) the existence of documented health risks in research laboratories, such as accidents, infections, occurrence of unwanted reproductive outcomes (spontaneous abortions, perinatal mortality, congenital malformations), increased frequency of chromosomal abnormalities; (*b*) evidence of documented excess cancer risk among chemists (cancer of the lymphohaematopoietic system, brain, pancreas); (*c*) the preliminary evidence of excess cancer risk for biomedical research personnel, based on two small pilot studies in France and Italy[19,20]; (*d*) the lack of any large, convincing study in this field; (*e*) the recommendations of various bodies that cancer risks be assessed for people handling carcinogens in laboratories or occupationally exposed to potentially oncogenic viruses; and (*f*) the interest and concern among the general public about potential risks linked to genetic engineering.

Following funding from the Europe Against Cancer programme of the European Commission, an in-depth feasibility study was conducted from 1988 to 1990 at IARC and in eight collaborating countries (Canada, Finland, France, Ireland, Italy, the Netherlands, Switzerland and USA) which clearly demonstrated that a study of cancer risk in biology research laboratory workers could and should be carried out. The populations are of sufficient size and can be divided into fields of activity. Exposures can be determined and the best approach is at the group or unit level. Mortality can be assessed at all places, provided adequate permission is sought and granted, although valid assessment of cancer incidence is not possible in all countries.

An international retrospective cohort study of mortality has now started. Cohorts are being established in parallel in biomedical and agronomic laboratories belonging to public European research institutions in nine countries (Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Sweden and United Kingdom). The study covers a population of at least 70 000

[18] Sasco, A.J. (1989) *Médecine/sciences*, **5**, 489–498
[19] Cordier, S. (1990) *Lancet*, **i**, 1097
[20] Belli, S., Comba, P., De Santis, M., Grignoli, M. & Sasco, A.J. (1990) *Lancet*, **i**, 1597–1598

persons currently employed in these institutions. As the cohort will be composed of any person having been employed for at least one year and one day in these institutions during the period 1970 to 1989, it is estimated that more than 1 million person-years will be available. Cancer risk in the whole study population will be compared to that of the general population and will also be evaluated in exposed and non-exposed subjects within the cohort. For the first time the cancer experience of groups defined by job title and type of scientific activity will be compared. Results should be available by 1995.

### 1.2.3 Tobacco and cancer

Tobacco use in various forms causes by far the most cases of cancer among all identified carcinogens. Research at IARC is little concerned with establishing the risk to smokers of their habit, which is taken as proven, but is examining the effect on non-smokers (passive smoking) and the risks of tobacco chewing and snuff-taking. Biochemical studies are being conducted on the carcinogenic compounds responsible for tobacco's effects and on the DNA adducts formed.

In the SEARCH programme, cigarette smoking has emerged as the strongest identifiable risk factor for pancreatic cancer (see section 1.3.1.1).

Individual susceptibility to the effects of tobacco smoke is being studied in terms of the levels of enzymes that metabolize the substances absorbed by the body into active carcinogens. This susceptibility appears to have genetic basis (see section 1.6.3).

#### 1.2.3.1 *Lung cancer in non-smokers and environmental tobacco smoke*

(E. Riboli, P. Boffetta and R. Saracci; in collaboration with W. Ahrens, Bremen, Germany; S. Benhamou, Villejuif, France; M. Blettner, Liverpool, UK; S.C. Darby, Oxford, UK; Y.T. Gao, Shanghai, China; C. A. Gonzales, Mataro (Barcelona), Spain; G.R. Howe, Toronto, Canada; A. Hirsch, Paris, France; S.K. Jindal, Chandigarh, India; L. LeMarchand, Honolulu, HI, USA; F. Levi, Lausanne, Switzerland; R. Mak, Ghent, Belgium; F. Merletti and N. Segnan, Turin, Italy; S. Panico, Naples, Italy; G. Pershagen, Stockholm, Sweden; L. Simonato, Padua, Italy; D. Trichopoulos, Athens, Greece and Boston, MA, USA; F.E. van Leeuwen, Amsterdam, Netherlands; G. Vutuc, Vienna, Austria; UK; and W. Zatonski, Warsaw, Poland)

A methodological study of the relationship between self-reported exposure to environmental tobacco smoke (ETS) and biochemical indicators measured in urine showed that subjects are capable of describing quite precisely their exposure to ETS, and that the frequency of smokers falsely declaring themselves as non-smokers is very low[21]. Exposure to ETS from the spouse was found to be by far the major determinant of cotinine levels in non-smokers' urine. Exposure at work for women employed outside the home was the second strongest source of ETS. Duration of exposure was shown to be the best overall indicator of the biochemically measured dose.

An international collaborative case–control study initiated in 1988 is examining the relationship between exposure to ETS and to other environmental risk factors and the risk of lung cancer in subjects who have never smoked tobacco. A common questionnaire on exposure to ETS was adopted as well as a common basic protocol. About 1000 cases and 2000 controls will

[21] Riboli, E., Preston-Martin, S., Saracci, R., Haley, N.J., Trichopoulos, D., Becher, H., Burch, J.D., Fontham, E.T.H., Gao, Y.T., Jindal, S.K., Koo, L.C., Lemarchand, L., Segnan, N., Shimizu, H., Stanta, G., Wu-Williams, A.H. & Zatonski, W. (1990) *Cancer Causes Control*, **1**, 243–252

be investigated in 11 centres in Europe, North America and Asia. Information on exposure to occupational carcinogens, urban air pollution, background radiation and dietary habits, as well as lifelong exposure to ETS, is being collected by personal interview of cases and controls. Self-reported (non-)smoking status will be cross-checked by interview of spouses in a subsample of subjects. Data collection started in eight centres during 1989–90, and will be extended to three more during 1991. It will last until 1992–1993. In some centres, ancillary studies of biochemical epidemiology will also be carried out, using urine samples and blood samples.

### 1.2.3.2 *Smoking, drinking and drug use among French adolescents*

(A.J. Sasco; in collaboration with M. Danzon, Vanves, France; and M. Jambon, Lyon, France)

The studies are conducted at two levels: local and national. Since 1985, several large-scale surveys have been carried out in a representative sample of students (aged 11 to 20 years) from high schools and colleges in Lyon and the surrounding area, using anonymous self-administered questionnaires. Analysis of the data showed a high prevalence of smokers which increases consistently with age. However, a decrease in smoking prevalence from 1985 to 1988 has been observed for the first time among French adolescents on both local and national scales[22]. Some of these schools have also been divided into two similar groups, one receiving a health education campaign according to a specified schedule and the other not. Comparison of results between the two groups demonstrated the inefficacy of the health education programme as originally designed[23] (a simple afternoon intervention). A more comprehensive programme based on eight interventions covering various aspects of health education (smoking, nutrition, physical exercise, etc.) will be evaluated during the coming year.

In 1990, collaboration was established with the French Committee for Health Education to study in depth the smoking habits of the French population, both adolescents and adults, on a national scale. In particular, trends over time will be evaluated for men and women, as well as association of smoking with social class.

### 1.2.3.3 *Evaluation of the efficacy of various anti-smoking strategies*

(A.J. Sasco; in collaboration with J.C. Cêtre, C. Ducos-Mieral, J. Fabry, C. Gindre and B. Laumon, Lyon, France)

At the request of the Conseil Général du Rhône and in collaboration with INSERM (U 265), IARC is evaluating three large anti-smoking programmes at present being conducted in the Rhône department. Their target populations are respectively: children (aged 9–10), medical doctors and workers in specific factories and work-places in both the public and private sectors (railways, marketing, public administration, asbestos workers, etc.). Smoking surveys were conducted in 1991 and evaluation will be carried out in 1992.

### 1.2.3.4 *Anti-smoking legislation in the EEC countries*

(A.J. Sasco; in collaboration with P. Dalla-Vorgia, Athens, Greece)

Legislation is an integral part of any national programme against smoking. In this context, and at the request of the EEC, a comprehensive survey of existing anti-smoking legislation in the

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[22] Sasco, A.J., Pobel, D., Grizeau, D. & Danzon, M. (1991) *Pédiatrie* (in press)

[23] Sasco, A.J. & Pobel, D. (1991) *Epidémiologie du cancer dans les pays de langue latine*, XVème réunion, Fort de France, May 1990 (IARC Technical Report No. 9), Lyon, International Agency for Research on Cancer, pp. 201–210

EEC countries was completed[24]. In addition, the evaluation of these anti-smoking laws was carried out[25], confirming the impact of such measures on tobacco consumption.

### 1.2.3.5 *Tobacco use in India*

(A.J. Sasco and D.M. Parkin; in collaboration with P.C. Gupta, Bombay, India; and R. Peto, Oxford, UK)

The role of cigarette smoking in the etiology of cancer, cardiovascular and chronic respiratory diseases has been studied extensively in developed countries. In contrast, few precise estimates of tobacco-attributable mortality and morbidity in developing countries are available, and the use of tobacco other than in cigarette form has been little studied.

A feasibility study has therefore been initiated to explore the possibility of conducting a prospective cohort study of 100 000 men aged 35 years and over, chosen from the lists of voters in Bombay. Provided the results are satisfactory, a five- to ten-year follow-up study will be started to assess the cause-specific mortality of the cohort, with particular attention being given to cancer and other causes of death in relation to the various forms of tobacco use (smoking, chewing, snuff etc.).

### 1.2.3.6 *Placental DNA adducts in relation to smoking*

(M. Castegnaro and H. Bartsch; in collaboration with C.C. Harris and G. Trivers, Bethesda, MD, USA; M. Pasanen, P. Sivonen, O. Pelkonen and K. Vähäkangas, Oulu, Finland)

Carcinogen–DNA adducts and microsomal AHH activity in 12 human placenta samples were measured[26]. Recent cigarette smoking status of the subjects was confirmed by plasma cotinine measurements. Adducts (none of which corresponded to a benzo[*a*]pyrene diol epoxide–DNA (BPDE–DNA) adduct) were detected by $^{32}$P-postlabelling in all placentas, but no correlation with either serum cotinine or AHH activity was found. Adduct levels in all samples were low as measured by ultrasensitive enzymatic radioimmunoassay and undetectable by synchronous fluorescence spectrophotometry. Microsomes with high AHH activity were able to catalyse formation of BPDE–DNA adducts *in vitro*.

### 1.2.3.7 *Analysis of DNA adducts and urinary mutagens from smokers of black tobacco*

#### *Implication of 2-amino-1-methyl-6-phenylimidazo*[4,5-b]*pyridine (PhIP) as a major DNA-damaging agent in urine of smokers of black tobacco*

(M. Castegnaro, M. Peluso, C. Malaveille, M. Friesen and H. Bartsch; in collaboration with F. Kadlubar, Jefferson, AR, USA; G. Talaska, Cincinnati, OH, USA; P. Vineis, Turin, Italy

A previous study[27] characterized the tobacco-derived mutagens excreted by black tobacco smokers as aromatic amines. DNA adducts formed by reacting urinary mutagens with calf

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[24] Sasco, A.J., van der Elst, P. & Dalla-Vorgia, P. (1991) *Comparative Study of Anti-smoking Legislation in the Member States of the EEC* (IARC–EEC Technical Report) (in press)

[25] Dalla-Vorgia, P., Sasco, A.J., Skalkidis, Y., Katsouyanni, K. & Trichopoulos, D. (1990) *Scand. J. Soc. Med.*, **18**, 81–89

[26] Vähäkangas, K., Trivers, G., Castegnaro, M., Bartsch, H., Pasanen, M., Sivonen, P., Harris, C.C. & Pelkonen, O. (1991) (submitted for publication)

[27] Peluso, M., Castegnaro, M., Malaveille, C., Talaska, G., Vineis, P., Kadlubar, F. & Bartsch, H. (1990) *Carcinogenesis*, **11**, 1307–1311

thymus DNA in the presence of a metabolic activation system were compared by $^{32}$P-postlabelling with those of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), 2-amino-6-methyldipyrido[1,2-*a*:3′,2-*d*]imidazole (Glu-P-1) and PhIP. The urinary mutagen–DNA adducts did not match those derived from either MeIQx or Glu-P-1, but several did correspond well to DNA adducts formed from *N*-hydroxy-PhIP *in vitro*[28]. It therefore appears that PhIP is a major DNA-damaging agent present in the urine of smokers of black tobacco.

*Substances in human urine strongly inhibiting PhIP mutagenicity in* Salmonella

(C. Malaveille, A. Hautefeuille, G. Brun and H. Bartsch; in collaboration with P. Vineis, Turin, Italy)

The mutagenicity of PhIP in TA98 in the presence of rat liver S9 showed a linear dose–response relationship (up to 25 ng per assay), with a specific activity of 70 000 revertants per μg. Mutagenicity was strongly inhibited by addition of urine extracts that did not affect bacterial survival[29], being reduced 50-fold by 10 μl urine extract from either smokers or non-smokers. We are currently characterizing these non-tobacco-derived urinary inhibitors and their mode of action.

*Measurement of exposure to PhIP*

(M. Friesen, L. Garren, J.-C. Bérézíat and H. Bartsch; in collaboration with F. Kadlubar and D. Lin, Jefferson, AR, USA)

Among a number of heterocyclic amine mutagens isolated from food, PhIP has been identified in grilled beef and fish at microgram per gram levels. A preliminary study in rats has shown that only about 0.6% of a 50 μg oral dose of PhIP is excreted unchanged in the urine. To assess human exposure to this compound, a sensitive GC–MS method has been developed. Use of this method is being extended to complex mixtures such as cigarette smoke condensate and to the determination of PhIP–DNA adducts.

### 1.2.3.8 *Levels of carcinogenic tobacco-specific nitrosamines (TSNA) in Sudanese snuff and in saliva of snuff-dippers*

(H. Ohshima, M. Friesen, I. Brouet and H. Bartsch; in collaboration with A.M. Idris, Khartoum, Sudan; and J. Nair, Bombay, India)

This study has investigated the role of TSNA in the etiology of oral cancer, which is relatively common in Sudan[30]. Saliva samples from snuff dippers (males aged 18–70 years) were collected before, during and after snuff-dipping. Snuff and saliva samples were analysed for TSNA and nicotine. Sudanese snuff contained high TSNA concentrations (up to milligrams per gram) with unusually high levels of 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), the most potent known carcinogenic TSNA (smokeless tobacco from other regions of the world has been reported to have maximum levels of *N*-nitrosonornicotine and NNK in the parts per million range). Levels of these nitrosamines in the saliva of Sudanese snuff-dippers were in the microgram per millilitre range, 10–100 times higher than those of subjects using other smokeless tobacco. Further, two NNK-derived alcohols (NNAL and iso-NNAL) were detected in the saliva of smokeless tobacco users for the first time.

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[28] Peluso, M., Castegnaro, M., Malaveille, C., Friesen, M., Garren, L., Hautefeuille, A., Vineis, P., Kadlubar, F. & Bartsch, H. (1991) *Carcinogenesis*, **12**, 713–717

[29] Malaveille, C., Hautefeuille, A., Brun, G., Vineis, P. & Bartsch, H. (submitted for publication)

[30] Idris, A.M., Nair, J., Ohshima, H., Friesen, M., Brouet, I., Faustman, E.M. & Bartsch, H. (1991) *Carcinogenesis*, **12**, 1115–1118

### 1.2.3.9 *DNA damage as a marker of exposure to betel quid and tobacco*

(M. Friesen, C. Malaveille, M. Castegnaro, I. Richard, L. Garren and H. Bartsch; in collaboration with S.V. Bhide, G.B. Maru and J. Nair, Bombay, India; R.C. Grafström and K. Sundquist, Stockholm, Sweden; R. MacLennan and S. Thomas, Brisbane, Australia; and G. Obe, Essen, Germany; supported in part by NIH Grant No. CA 43176)

The aim of this three-year study was to develop, validate and apply methods for measuring DNA damage as a marker of carcinogen exposure in chewers of betel quid with and without tobacco.

Despite the complex chemical composition of betel quid, only a few genotoxic agents were found to be present in tobacco-containing betel quid or are formed during chewing, mainly some alkaloids and a few derived tobacco-specific and areca nut-specific nitrosamines. These cause DNA damage in several experimental systems[31,32] including human buccal epithelial cells, and thus seem likely to have a role in oral cancer causation. Monitoring for specific DNA or protein adducts should be useful for future epidemiological studies.

In addition to tobacco- and areca nut-derived carcinogens, reactive oxygen species, generated from polyphenols present in areca nut at alkaline pH in the presence of lime, have been characterized. *In vitro,* they modified DNA and thus may well cause chromosomal aberrations in betel quid chewers. We have recently found that chewers of betel quid containing tobacco and lime had the highest frequency of micronucleated buccal epithelial cells[33].

The calcium hydroxide content of the lime (samples from Papua New Guinea and India were analysed) was found to be the major determinant of pH and thus the generation of reactive oxygen species from areca nut-derived polyphenols[34]. The formation of reactive oxygen species *in vitro* was strongly inhibited by $Mg^{2+}$ supplementation to the quid. Therefore, the use of $Mg^{2+}$-enriched lime containing low calcium hydroxide levels should lead to a lower level of DNA and chromosomal damage in buccal epithelial cells of betel quid chewers; this hypothesis will be explored.

## 1.2.4 Second malignancies following chemotherapy

### 1.2.4.1 *Epidemiological studies*

(J. Kaldor, D. English, P. Roy, A. Arslan and J. Estève; in collaboration with D. Assouline, Lyon, France; P. Band, Vancouver, Canada; J. Bell, Sutton, UK; V. Blair, Manchester, UK; W. Choi, Winnipeg, Canada; E.A. Clarke, Toronto, Canada; N.E. Day, Cambridge, UK; P. Fraser, London, UK; C. Garton, Leicester, UK; H. Hakama and S. Karjalainen, Helsinki, Finland; M. Henry-Amar, Villejuif, France; H. Host and F. Langmark, Oslo, Norway; B. Kittelmann and W. Staneczek, Berlin, Germany; M. Koch, Edmonton, Canada; F. Neal, Sheffield, UK; D. Pedersen, Aarhus, Denmark; D. Peters, Leeds, UK; F. Pettersson and B. Zarén, Stockholm, Sweden;

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[31] Sundqvist, K., Liu, Y., Erhardt, P., Nair, J., Bartsch, H. & Grafström, R.C. (1991) In: O'Neill, I.K., Chen, J. & Bartsch, H., eds, *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105), Lyon, International Agency for Research on Cancer, pp. 281–285

[32] Maru, G.B., Castegnaro, M. & Bartsch, H. (1990) In: Bhide, S.V. & Rao, K.V.K. eds, *Biology and Chemistry of* N-*Nitroso Compounds,* New Delta, Omega Scientific Publications, pp. 207–214

[33] Nair, U., Obe, G., Nair, J., Maru, G.B., Bhide, S.V., Pieper, R. & Bartsch, H. (1991) *Mutat. Res.* (in press)

[34] Nair, U.J., Friesen, M., Richard, I., MacLennan, R., Thomas, S. & Bartsch, H. (1990) *Carcinogenesis,* **11,** 2145–2148

V. Pompe-Kirn, Ljubljana, Yugoslavia; P. Prior, Birmingham, UK; H.H. Storm, Copenhagen, Denmark; M. Stovall, Houston, TX, USA; S.B. Sutcliffe, Toronto, Canada)

After the completion of the study on leukaemia following treatment for Hodgkin's disease and ovarian cancer[35], two further case–control studies have been conducted.

In a study of patients treated for ovarian cancer[36], the risk of bladder tumours was increased among those treated by radiotherapy alone (RR 1.9, 95% CI 0.77–4.9), chemotherapy alone (RR 3.2, 95% CI 0.97–10) and by both radiotherapy and chemotherapy (RR 5.2; 95% CI 1.6–16) compared with patients treated only by surgery. Among patients treated with cyclophosphamide, there was a roughly four-fold increase in risk, independent of whether radiotherapy had also been used. There were also substantial increases in risk among patients treated with other drugs, with or without radiotherapy.

Results of a study of lung cancer following Hodgkin's disease are being analysed.

### 1.2.4.2 *Studies of DNA damage following chemotherapy*

(J. Kaldor, D. English, P. Roy, J. Hall, C. P. Wild, H. Yamasaki, R. Montesano and J. Estève; in collaboration with D. Bron and M. de Pauw, Brussels, Belgium; A.M.J. Fichtinger-Schepman, Rijswijk, Netherlands; A. Hagenbeek, C. Rodenburg, G. Stoter and M.B. van't Veer, Rotterdam, Netherlands; M. Hayat and M. Henry-Amar, Villejuif, France; W.G. Jones, Leeds, UK; S.B. Kaye, Glasgow, UK; S. Kyrtopoulos and G.A. Pangalis, Athens, Greece; A. Natarajan, Leiden, Netherlands; D. Richel, R. Somers, G. ten Bokkel Huinink and F. Van Leeuwen, Amsterdam, Netherlands; D. Th. Steiffer, Groningen, Netherlands; A.T. Van Oosterom, Antwerp, Belgium)

The reaction between alkylating chemotherapeutic agents and cellular DNA is probably the main pathway to both their cytotoxic and their carcinogenic effects. Collaborative studies have been set up to study respectively methyl DNA adducts in Hodgkin's disease patients and cis-platinum DNA adducts in testicular cancer patients, and to what extent adduct levels can be used to predict the clinical outcome of chemotherapy.

A pilot study in Hodgkin's disease patients is still in progress, and the results related to the quantification and correlation of methylation adducts, micronuclei, DNA repair measurements and cellular gene mutations of about 30 patients are being analysed. The study of testicular cancer is being performed in conjunction with a clinical trial of cis-platinum in testicular cancer conducted by the genitourinary group of the European Organization for Research and Treatment of Cancer (EORTC). DNA adducts and haemoglobin adducts are being measured in the testicular cancer patients and will be analysed in relation to the response to chemotherapy.

Methylation adducts in chemotherapy patients given *N*-nitroso-*N*-methylurea are being investigated, as reported in section 3.3.4.4.

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[35] Kaldor, J.M., Day, N.E. *et al.* (1990) *New Engl. J. Med.*, **322**,7–13
Kaldor, J.M., Day, N.E., Pettersson, F. *et al.* (1990) *New Engl. J. Med.*, **322**, 1–6

[36] Kaldor, J.M., Day, N.E. *et al.* (submitted for publication)

## 1.2.5 Radiation

### 1.2.5.1 *Extremely low-frequency (ELF) electromagnetic fields*

(M.P. Coleman and P. Roy; in collaboration with P.-M. Carli, J. Faivre and P. Hillon, Dijon, France)

Results of a case–control study of leukaemia and residential proximity to electricity transmission equipment in London have been published[37,38]. Relative risks were non-significantly increased for residence within 100 m of an overhead powerline and within 50 m of a transformer substation. IARC staff participated in an international meeting to develop a protocol for ELF field exposure assessment in case–control studies of childhood leukaemia[39]. A survey of domestic environmental ELF field exposure in Côte-d'Or, France, is planned in collaboration with INSERM units in Dijon. A meeting was held with Electricité de France in May 1990 to prepare the protocol for these studies. IARC participated in the International Non-Ionizing Radiation Committee meeting in Rome in May 1991, and ELF field exposures will be evaluated in the IARC Monographs programme in 1993.

The SEARCH study of childhood leukaemias (see section 1.3.1.5) will include assessment of ELF field exposures.

### 1.2.5.2 *European Childhood Leukaemia/Lymphoma Incidence Study*

(D.M. Parkin, J. Kaldor, E. Cardis and E. Masuyer; in collaboration with J. Augustin, Brno, Czechoslovakia; L. Barlow, Stockholm, Sweden; D. Bobev, Sofia, Bulgaria; J.W. Coebergh, The Hague, Netherlands; G.J. Draper, Oxford, UK; G. Gerber and J. Sinnaeve, Brussels, Belgium; H. Hansluwka, Vienna, Austria; E. Ivanov, Minsk, USSR; S. Karjalainen, Helsinki, Finland; R. Kriauciunas, Vilnius, USSR; F. Langmark, Oslo, Norway; J.-M. Lutz, Meylan, France; V. Merabishvili, Leningrad, USSR; J. Michaelis, Mainz, Germany; M. Möhner, Berlin, Germany; I. Plesko, Bratislava, Czechoslovakia; V. Pompe-Kirn, Ljubljana, Yugoslavia; M. Rahu, Tallinn, USSR; L. Raymond, Geneva, Switzerland; D. Schuler, Budapest, Hungary; H.H. Storm, Copenhagen, Denmark; B. Terracini, Turin, Italy; J. Tyczynski, Warsaw, Poland)

This collaborative project was started in 1988 in collaboration with the Radiation Protection Programme of the European Commission, and involves the participation of representatives from cancer registries in 16 European countries. The objective is to follow geographic and temporal trends in the incidence of childhood leukaemia in Europe from 1980 until the mid-1990s, and to evaluate whether any changes can be related to exposure to radioactive material from the accident at Chernobyl in April 1986.

In 1990, it was decided to try to extend the study, using the agreed protocol (IARC Internal Report No. 89/002 Rev. 1), to encompass almost all of the western part of the USSR.

Cancer registries are supplying data on cases of childhood leukaemia and lymphoma and on populations at risk, so that incidence rates by cell type may be calculated for sub-national areas. Collaboration has been established with the United Nations Scientific Committee on the Effects

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[37] Coleman, M.P., Bell, C.M.J., Taylor, H.-L. & Primic-Zakelj, M. (1989) *Br. J. Cancer*, **60**, 793–798

[38] Bell, J. & Coleman, M.P. (1990) *Br. J. Cancer*, **62**, 331–332

[39] EPRI (1990) Proceedings: Discussion of an EMF Protocol (EN-6829 Project 2964-6), Palo Alto, CA, Electric Power Research Institute

of Atomic Radiation (UNSCEAR) to obtain estimates of the total body radiation dose attributable to the Chernobyl accident in children under age 15. Estimates are already available for large geographic regions; where appropriate, particularly for more highly exposed regions, the estimates will be recalculated for smaller regions.

A preliminary analysis of the data for 1980–87 showed little international variation in incidence before 1986, and no systematic changes for 1987[40]. In 1991, the incidence results for 1987–88 will be compared with the baseline period (1980–85) for the large geographic areas for which UNSCEAR dosimetry estimates are available.

### 1.2.5.3 *Chronic low-dose exposure to ionizing radiation*

(E. Cardis, B.K. Armstrong, K. Zaid and J. Estève; in collaboration with P. Ashmore, Ottawa, Canada; V. Beral, Oxford, UK; J. Bernar Solano, Madrid, Spain; M. Blettner, Heidelberg, Germany; L. Carpenter, A. Douglas and P.G. Smith, London, UK; G. Cowper, Deep River, Canada; J. Fix and E.S. Gilbert, Richland, WA, USA; S. Fry, Oak Ridge, TN, USA; R. Gun, Adelaide, Australia; M. Hakama, Tampere, Finland; C. Hill, Villejuif, France; Y. Hosoda, Tokyo, Japan; G.R. Howe, Toronto, Canada; J. Kaldor, Darlinghurst, Australia; L. Kheifets, Palo Alto, CA, USA; G. Laleman, Mol, Belgium; B.H. MacGibbon, Didcot, UK; H. Malker, Solna, Sweden; M. Moser, Bern, Switzerland; P. Pellerin, Le Vésinet, France; T. Rytömaa, Helsinki, Finland; L. Salmon, Harwell, UK; G. Schüler, Zürich, Switzerland; G. Seitz, Cologne, Germany; R. Shore, New York, USA; G.L. Voelz and L. Wiggs, Los Alamos, USA; and T. Yoshimura, Kitakyushu, Japan)

Because of controversies on the adequacy of existing radiation protection standards[41], two large studies of radiation-induced risks in nuclear workers have been initiated. The aim of these studies is to assess directly the effect of occupational low-dose, low-dose-rate exposure to low-LET (X- and $\gamma$-ray) ionizing radiation.

#### *Combined analyses of existing data*

Data collected for previous studies of cancer in nuclear workers in Canada, the UK and the USA are being combined, in order to increase the precision of risk estimates from chronic low-dose-rate exposures[42]. Preliminary data sets were sent to IARC in October 1989 and in July 1990, and have been used in testing and refining the methodological approach. The final data sets containing additional dosimetric data will be analysed in 1992.

#### *International collaborative study of nuclear industry workers*

A protocol and extensive questionnaire[43] were prepared to evaluate the feasibility of an international collaborative study on workers whose health has not been studied until now (in Australia, Belgium, Canada, Finland, France, Germany, Italy, Japan, Spain, Sweden, Switzer-

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[40] Parkin, D.M. (on behalf of the ECLIS Study Group) (1990) *Radiat. Res.*, **124**, 370–371

[41] Committee on the Biological Effects of Ionizing Radiation (BEIR) (1990) *Health Effects of Exposure to Low Levels of Ionizing Radiation*. Washington, DC, National Academy of Sciences

[42] Cardis, E. & Kaldor, J.M. (1989) Combined Analyses of Cancer Mortality among Nuclear Industry Workers, IARC Internal Report No. 89/005

[43] Cardis, E. & Estève, J. (1990) International Collaborative Study of Cancer Risk among Nuclear Industry Workers: Protocol of the Feasibility Study (IARC Internal Report 90/001A); Questionnaire of the Feasibility Study (IARC Internal Report 90/001B)

land, the UK and the USA). The questionnaire requested information on availability of data on an individual basis, on dosimetry, cancer mortality and morbidity, as well as on a number of potential confounders. The information in completed questionnaries received up to June 1991, together with that obtained as a result of site visits, suggests that such a study would add substantially to the information which can be obtained from the combined analyses of existing data from Canada, the UK and the USA (Table 2). A protocol for the collaborative study has been prepared with a view to starting the study in 1992 after a meeting of the international study group.

Table 2. Preliminary assessment of study populations

| | Combined analyses (Canada + UK + USA) | New study (at least 11 countries) |
|---|---|---|
| Number of monitored workers | 120 000 | 900 000 |
| Number with yearly doses above 10 mSv | 4000 | 80 000 |
| Number with yearly doses above 50 mSv | 600 | 1000 |
| Collective dose | — | 8800 person sievert |
| Average annual dose | — | 3 mSv |

*Biases and uncertainties in dose estimates*

A descriptive study of dosimetric and recording practices in Canadian, UK and US facilities was started in April 1989 to review the sources of biases and uncertainties in individual yearly dose estimates. For photons of 100 kV or more, the following sources of dose errors have been identified: recording practices and high threshold of dosimeters in the early years of the industry, calibration method, geometry of exposure and angular response of dosimeter, as well as laboratory practices in film processing and reading[44,45]. The magnitude of biases and uncertainties from each of these sources is being estimated on a facility and time period basis. Statistical methods for taking uncertainties into account are being compared.

### 1.2.6 *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

(H. Vainio, M. Marselos, E. Matos, D. McGregor, G. Nordberg, C. Partensky, I. Peterschmitt, L. Shuker and J. Wilbourn. The following members of other units have contributed to the programme: H. Bartsch, P. Boffetta, P. Boyle, J.R.P. Cabral, E. Cardis, M. Coleman, D. English, M. Friesen, M. Kogevinas, V. Krutovskikh, R. Montesano, N. Muñoz, I.K. O'Neill, S. San José Llongueras, R. Saracci, D. Shuker and H. Yamasaki)

The IARC Monographs Programme aims to identify factors which may increase the risk of cancer in exposed humans. The group of invited experts follow well defined guidelines, developed during several consultative meetings, in formulating their evaluations.

During the period July 1989–June 1991, volumes 45–53 and Supplement 8 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* were published or in preparation. Descriptions of the meetings concerning Volumes 45–49 were provided in the 1988/89 IARC Biennial Report (pp. 42–46).

[44] Cardis, E. & Estève, J. (1991) *J. Radiat. Prot. Dosim.* (in press)
[45] Cardis, E. (1990) *Radiat. Res.*, **124**, 339–340

### 1.2.6.1 *Volume 50*

In October 1989, an IARC Working Group was convened to prepare evaluations for an historic volume in the Monographs series, namely the fiftieth. The subject was pharmaceutical drugs; 15 drugs were considered by the Working Group, including five that had been evaluated previously but which were re-evaluated due to the availability of new data. The conclusions of the meeting are summarized in Table 3. Of the five antineoplastic drugs considered, thiotepa was evaluated as being *carcinogenic to humans (Group 1),* as was the immunosuppressive drug ciclosporin.

### 1.2.6.2 *Volume 51*

In February/March 1990, an IARC Working Group considered data relevant to the evaluation of carcinogenic risks to humans of coffee, tea, mate, methylxanthines and methylglyoxal. The evaluations made by the Working Group are summarized in Table 4. Particular problems were encountered when evaluating the possible carcinogenicity of coffee. The Working Group concluded that while there was *limited evidence* in humans for an increased risk of urinary bladder cancer associated with coffee drinking, there was also *evidence suggesting a lack of carcinogenicity* for the female breast and for the large bowel; the evidence for carcinogenicity was inadequate for pancreas, ovary and other sites. There was *inadequate evidence* for the carcinogenicity of coffee in experimental animals. The Working Group was unable to classify tea

Table 3. Carcinogenicity of some pharmaceutical drugs

| Agent | Degree of evidence for carcinogenicity | | Overall evaluation[a] |
|---|---|---|---|
| | Humans | Animals | Group |
| *Antineoplastic and immunosuppressive drugs* | | | |
| Azacitidine | No data | Sufficient | 2A |
| Chlorozotocin | No data | Sufficient | 2A |
| Ciclosporin | Sufficient | Limited | 1 |
| Prednimustine | No data | Inadequate | 3 |
| Thiotepa | Sufficient | Sufficient | 1 |
| Trichlormethine (Trimustine hydrochloride) | No data | Sufficient | 2B |
| *Antimicrobial agents* | | | |
| Ampicillin | Inadequate | Limited | 3 |
| Chloramphenicol | Limited | Inadequate | 2A |
| Nitrofural (Nitrofurazone) | Inadequate | Limited | 3 |
| Nitrofurantoin | Inadequate | Limited | 3 |
| *Other* | | | |
| Cimetidine | Inadequate | Inadequate | 3 |
| Dantron (Chrysazin; 1,8-dihydroxy-anthraquinone) | No data | Sufficient | 2B |
| Furosemide (Frusemide) | Inadequate | Inadequate | 3 |
| Hydrochlorothiazide | Inadequate | Inadequate | 3 |
| Paracetamol (Acetaminophen) | Inadequate | Limited | 3 |

[a]Group 1: Carcinogenic to humans, Group 2A: Probably carcinogenic to humans, Group 2B: Possibly carcinogenic to humans, Group 3: Not classifiable as to carcinogenicity to humans

Table 4. Carcinogenicity of coffee, tea, mate, methylxanthines and methylglyoxal

| Agent | Degree of evidence for carcinogencity | | Overall evaluation[a] |
|---|---|---|---|
| | Humans | Animals | Group |
| Coffee | Limited: urinary bladder<br>Evidence suggesting lack of carcinogenicity: female breast, large bowel<br>Inadequate: pancreas, ovary, other sites | Inadequate | 2B[b] (urinary bladder) |
| Tea | Inadequate | Inadequate | 3 |
| Mate | | No data | 3 |
| Hot mate drinking | Limited | | 2A |
| Caffeine | Inadequate | Inadequate | 3 |
| Theophylline | Inadequate | Inadequate | 3 |
| Theobromine | Inadequate | No data | 3 |
| Methylglyoxal | No data | Inadequate | 3 |

[a] See footnote to Table 3

[b] There is some evidence of an inverse relationship between coffee drinking and cancer of the large bowel; coffee drinking could not be classified as to its carcinogenicity to other organs.

with regard to its carcinogenicity to humans. However, there is some indication that the risk for cancer of the oesophagus may be increased in populations who drink their tea very hot. There was also *limited evidence* for the carcinogenicity in humans of hot mate drinking.

### 1.2.6.3 *Volume 52*

In June 1990, an IARC Working Group considered data relevant to the evaluation of carcinogenic risks to humans of chlorinated drinking-water, chlorination by-products and certain other halogenated compounds, as well as cobalt and cobalt compounds. The Working Group's evaluations are summarized in Table 5. It was not possible to classify chlorinated drinking-water or most of the halogenated compounds considered with respect to their carcinogenicity to humans, but the evidence for bromodichloromethane suggested that is is *possibly carcinogenic to humans (Group 2B).* Cobalt and cobalt compounds also were classified as *possibly carcinogenic to humans (Group 2B).*

### 1.2.6.4 *Volume 53*

In October 1990, an IARC Working Group was convened to evaluate the evidence for the carcinogenicity of 17 pesticides and occupational exposures in spraying and application of insecticides. The Working Group concluded that spraying and application of nonarsenical insecticides entail exposures that are *probably carcinogenic to humans (Group 2A).* Of the eight insecticides evaluated, there was considered to be *sufficient evidence* for carcinogenicity in experimental animals for chlordane, DDT, dichlorvos and heptachlor; in the absence of

Table 5. Carcinogenicity of chlorinated drinking-water, halogenated compounds and cobalt and its compounds

| Agent | Degree of evidence for carcinogenicity | | Overall evaluation[a] |
|---|---|---|---|
| | Humans | Animals | Group |
| Chlorinated drinking-water | Inadequate | Inadequate | 3 |
| Chemicals used in chlorination | | | |
| Sodium chlorite | No data | Inadequate | 3 |
| Hypochlorite salts | No data | Inadequate | 3 |
| By-products | | | |
| Bromodichloromethane | Inadequate | Sufficient | 2B |
| Bromoform | Inadequate | Limited | 3 |
| Chlorodibromomethane | Inadequate | Limited | 3 |
| Halogenated acetonitriles | | | |
| Chloroacetonitrile | No data | Inadequate | 3 |
| Dichloroacetonitrile | No data | Inadequate | 3 |
| Trichloroacetonitrile | No data | Inadequate | 3 |
| Bromochloroacetonitrile | No data | Inadequate | 3 |
| Dibromoacetonitrile | No data | Inadequate | 3 |
| Others | | | |
| Bromoethane | No data | Limited | 3 |
| Chloroethane | No data | Limited | 3 |
| 1,1,2-Trichloroethane | No data | Limited | 3 |
| Cobalt and cobalt compounds | Inadequate | | 2B |
| Cobalt metal powder | | Sufficient | |
| Cobalt[II] oxide | | Sufficient | |
| Cobalt[II] sulfide | | Limited | |
| Cobalt[II] chloride | | Limited | |
| Cobalt/chromium/molybdenum alloy | | Limited | |
| Cobalt[II] naphthenate | | Inadequate | |
| Cobalt[III] acetate | | Inadequate | |
| Cobalt[II,III] oxide | | Inadequate | |
| Cobalt/aluminium/chromium spinel | | Inadequate | |

[a]See footnote to Table 3

adequate data in humans, these were all classified as *possibly carcinogenic to humans* (*Group 2B*). For two of the four fungicides, the evidence for carcinogenicity in experimental animals was also considered to be *sufficient* and, in the absence of adequate data in humans, pentachlorophenol was also classified as *possibly carcinogenic to humans (Group 2B).* Captafol, however, was evaluated as *probably carcinogenic to humans (Group 2A)* on the basis of supporting evidence from other relevant data. The conclusions of the Working Group are summarized in Table 6.

### 1.2.6.5 *Advisory Group on the Evaluation of Carcinogenic Risks of Viruses and Parasites*

Following an IARC meeting on Viral–Chemical Interactions in Human Cancers held in Lyon in June 1991 (see section 1.7.1.5), a small number of participants were asked to advise the Agency on the need to make evaluations of carcinogenic risks of biological agents, such as

Table 6. Carcinogenicity of occupational exposures in insecticide application and some pesticides

| Agent | Degree of evidence for carcinogencity | | Overall evaluation[a] |
|---|---|---|---|
| | Humans | Animals | Group |
| *Insecticides* | | | |
| Occupational exposures in spraying and application of nonarsenical[b] insectides | Limited | — | 2A |
| Aldicarb | No data | Inadequate | 3 |
| Chlordane | Inadequate | Sufficient | 2B |
| DDT | Inadequate | Sufficient | 2B |
| Deltamethrin | No data | Inadequate | 3 |
| Dichlorvos | Inadequate | Sufficient | 2B |
| Fenvalerate | No data | Inadequate | 3 |
| Heptachlor | Inadequate | Sufficient | 2B |
| Permethrin | No data | Inadequate | 3 |
| *Fungicides* | | | |
| Captafol | No data | Sufficient | 2A[c] |
| Pentachlorophenol | Inadequate | Sufficient | 2B |
| Thiram | Inadequate | Inadequate | 3 |
| Ziram | No data | Limited | 3 |
| *Herbicides* | | | |
| Atrazine | Inadequate | Limited | 2B[c] |
| Monuron | No data | Limited | 3 |
| Picloram | No data | Limited (tech. grade) | 3 |
| Simazine | Inadequate | Inadequate | 3 |
| Trifluralin | Inadequate | Limited (tech. grade) | 3 |

[a]See footnote to Table 3

[b]Arsenic and arsenic compounds are carcinogenic to humans (IARC Monographs Supplement 7, 1987)

[c]Supporting data from other relevant data influenced the making of the overall evaluation

viruses, bacteria and parasites. This ad-hoc Advisory Group was unanimous in agreeing that the IARC should evaluate the carcinogenic risks of biological agents and a list of priority agents was developed, based on considerations of both the public health importance and the state of epidemiological and biological studies concerning each agent. Priorities were classified as high, medium or low. Among the agents considered to be of high priority were the following viruses: hepatitis B, C and D viruses, human T-cell leukaemia/lymphoma virus type 1, Epstein–Barr virus, human papillomavirus and human immunodeficiency virus type 1. Among bacteria, *Helicobacter pylori* was assigned high priority for evaluation, as were the parasitic trematodes *Schistosoma haematobium, japonica* and *mansoni, Clonorchis sinensis* and *Opisthorchis viverrini.*

### 1.2.6.6 *Meeting on use of mechanistic information in making evaluations of carcinogenicity* (11–18 June 1991)

Recent developments in understanding the process of carcinogenesis may have important implications for the evaluation of agents within the IARC Monographs programme. Accordingly, a special Working Group was convened in Lyon on 11–18 June 1991 to advise the IARC

on whether and to what extent information on mechanisms of action of agents could be used to evaluate their carcinogenic risk to humans.

Twenty-eight background discussion papers on various aspects of mechanisms of carcinogenesis, prepared by members of the ad-hoc group, were circulated to all participants before the meeting. During the meeting, the group discussed these papers in depth and prepared a consensus report; these documents will be published as No. 116 of the IARC Scientific Publications series.

Mechanisms may be understood at many different levels. The Group proposed four descriptive dimensions for considering such data: (1) evidence of genotoxicity (i.e., structural change at the level of the gene); (2) evidence of effects on the expression of relevant genes (i.e., functional changes at the intracellular level); (3) evidence of relevant effects on cell behaviour (i.e., morphological or behavioural changes at the cellular or tissue level); and (4) evidence of time and dose relationships of carcinogenic effects and interactions between agents. These dimensions are not mutually exclusive and an agent may have effects on several or all dimensions. Because different agents act by different mechanisms, the relevance and importance of each of these levels depend on the agent and tumour site that are being considered.

The relevance of the mechanistic data to the evaluation of the carcinogenic risk of an agent to humans should be assessed. This requires consideration of (1) the evidence that the effect lies in the chain of events linking the agent with cancer; (2) the relevance of the test system to human responses; (3) the similarity of the endpoint of the test system to the human target cells (although the validity of the endpoint can override this consideration); (4) the similarity of toxicokinetic variables in the test system and in humans; and (5) the specificity of the measured endpoint for the mechanism.

The evidence may show that similar mechanisms are acting in humans and experimental animals, but situations in which species-specific activity seems possible are of particular concern. The possibility that humans are the more affected or susceptible species, in the absence of epidemiological data, could be assessed on the basis of knowledge of the mechanisms in humans and in animals. The converse possibility—that humans are the unaffected species—can be assessed only after consideration of certain principles: (1) that the mechanism in question is the primary one in inducing the tumour in the species in which it is observed; (2) that the same or a similar mechanism does not operate in humans; and (3) that the agent does not induce other types of tumour in the species under consideration.

The Group suggested a number of situations in which relevant information on mechanisms could be used in evaluating carcinogenic risk to humans. Firstly, such information may confirm the level of classification indicated by data from epidemiological and/or experimental carcinogenicity studies. Secondly, strong evidence for a mechanism of action that is relevant to carcinogenicity in humans could justify 'upgrading' of the overall evaluation for a particular agent. Thirdly, an overall evaluation of human cancer hazard based on the results of experimental carcinogenicity tests could be 'downgraded' by strong evidence that the mechanism responsible for tumour growth in experimental animals does not operate in humans.

### 1.2.6.7 *Supplement 8, Cross Index of Synonyms and Trade Names in Volumes 1 to 46* (M.J. Ghess and J. Wilbourn)

The Cross Index of Synonyms and Trade Names of the IARC Monographs was initiated in 1980 in collaboration with the WHO–ILO–UNEP International Programme on Chemical Safety (IPCS), Division of Environmental Health, WHO, Geneva and a computerized data-base was created.

To date three Cross Indexes have been published as supplements to the IARC Monographs. Supplement 8, published in December 1989, covers synonyms and trade names of the 660 individual chemicals in the first 46 volumes of the *Monographs*. It is envisaged to publish an updated edition of the Cross Index in the near future.

### 1.2.7 Role of mycotoxins in nephropathy and associated urinary tract tumours

(M. Castegnaro, C. Malaveille, M. Lang, J. Michelon, G. Brun and H. Bartsch; in collaboration with W. Bursch, W. Huber and R. Schulte-Hermann, Vienna, Austria; I.N. Chernozemsky, G. Manolov, I. Nikolov and T. Petkova-Bocharova, Sofia, Bulgaria; E.E. Creppy, Bordeaux, France; G. Dirheimer, Strasbourg, France; M. Goldberg, Guelph, Canada; E. Hietanen, Turku, Finland; U. Mohr, Hannover, Germany; and C.R. Wolf, Edinburgh, UK)

The role of mycotoxins as risk factors for Balkan endemic nephropathy and associated urothelial cancers[46] was reviewed in a meeting held in Lyon, from 6 to 8 June 1991. Although the evidence is suggestive, a causal role of mycotoxins in the diseases remains to be proven. However, human exposure to ochratoxin A (OA) was reported to be more widespread than previously believed. The proceedings of this meeting will contain over 40 papers dealing with disease etiology, new analytical and dosimetry methods for mycotoxins, mechanisms of OA-induced toxicity and carcinogenesis, the role of cytochrome P450 polymorphism in disease susceptibility, risk assessment and regulatory aspects of mycotoxin exposure[47].

#### 1.2.7.1 *Field studies*

Following recommendations by a peer review committee of the Scientific Council for analysis of mycotoxins other than OA, food samples have been collected from Balkan areas. OA, citrinin, aflatoxin $B_1$ and $G_1$ were detected more often and at higher levels in endemic areas than in control areas in 1989 and 1990, but these differences were significant only for OA and citrinin. In human blood samples collected in 1989 and 1990, OA was detected more frequently and at higher levels in samples from patients with endemic nephropathy and urinary tract tumours than in controls. These results are consistent with those from previous years.

A study has been initiated in France to investigate human ochratoxicosis linked to possible OA contamination of the food chain. Preliminary results from the regions of Aquitaine, Rhône/Ain and Alsace demonstrate that OA is a blood contaminant in France, but to a lower extent than in the Balkans. The range of contamination is similar to that in Germany, but only about 20% of samples are positive as compared to more than 50% in Germany.

The screening of urinary exfoliated cells from endemic nephropathy patients and controls from Bulgaria for the frequency of micronucleated cells is continuing, in order to obtain sufficient numbers for data analysis.

#### 1.2.7.2 *Genetic polymorphism and studies on ochratoxin A metabolism*

Blood has been collected from Bulgarian endemic nephropathy patients, from associated tumour cases and from healthy controls for CYP2D6 genotyping. The analysis of restriction

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[46] Castegnaro, M., Chernozemsky, I.N., Hietanen, E. & Bartsch, H. (1990) *Arch. Geschwulstforsch.*, **60**, 295–303

[47] Castegnaro, M., Plešťina, R., Dirheimer, G., Chernozemsky, I.N. & Bartsch, H., eds (1991) *Mycotoxins, Endemic Nephropathy and Urinary Tract Tumours* (IARC Scientific Publications No. 115), Lyon, International Agency for Research on Cancer (in press)

fragment length polymorphism is being performed using a CYP2D6 probe by a published procedure[48] and by a method more recently developed.

To examine the mechanisms of OA carcinogenicity and toxicity as related to metabolic phenotype, a two-year experiment has been started using DA and Lewis rats, strains which have been phenotyped, respectively, as slow and extensive metabolizers of debrisoquine (DB) and OA. As well as OA, 2-mercaptoethane sulfonate (Mesna), which is used clinically to protect against cytostatic drug-induced kidney and bladder damage, has been administered to see whether it also counteracts OA-induced kidney damage. The urinary ratios of OA/4-hydroxy-OA and of DB/hydroxy-DB are being measured, and other OA metabolites are also being sought that may be linked to OA toxicity or carcinogenicity.

OA 4-hydroxylase activity has been compared with activities of other P450-dependent drug-metabolizing enzymes in B6 and D2 mice. The data suggest that the isozyme catalysing OA hydroxylation is not identical to cytochrome P450IID and may share some common epitopes with cytochrome P450IA. Similarities to cytochrome P450IA are (i) inducibility by enzyme inducers (although rather weak), (ii) correlation with P450IA-catalysed oxidation reactions, (iii) partial inhibition by monoclonal antibody 1-7-1, and (iv) *in vitro* inhibition by benzoflavone. On the other hand, common properties with P450IID include (i) genetic cosegregation in rats and (ii) inhibition in human livers by an antibody against P450IID. However, the isozyme catalysing OA oxidation differs from P450IA in terms of lack of genetic cosegregation in D2 and B6 mice and from P450IID, which is not inducible[49].

### 1.2.7.3 *Mechanism of genotoxicity of ochratoxin A and structurally related compounds in* E. coli *strains*

OA and its major metabolite in rodents ochratoxin $\alpha$ (O$\alpha$), as well as seven structurally related substances, were assayed for SOS DNA repair-inducing activity in *E. coli* PQ37 strain. OA, chloroxine, 5-chloro-8-quinolinol, 4-chloro-*m*-cresol and chloroxylenol induced SOS DNA repair in the absence of an exogenous metabolic activation system. Ochratoxins B and $\alpha$ were cytotoxic. A carboxyl group *ortho* to a hydroxyl group (O$\alpha$, 5-chlorosalicylic acid, citrinin) is negatively associated with activity, and a chlorine atom in the *para* position (OA, chloroxine, 4-chloro-*m*-cresol, chloroxylenol and 5-chloro-8-quinolinol) positively associated. The presence of a chlorine atom at C-5 in OA appears to be a critical determinant of its genotoxic action. Using an inhibitor of cysteine conjugate $\beta$-lyase, aminooxyacetic acid, we have shown that OA can form a cytotoxic thiol-containing derivative, but that this is not responsible for bacterial genotoxicity[50].

As OA can form a strong complex with ferric ion leading to stimulation of lipid peroxidation *in vitro*, we have investigated whether bacterial genotoxicity is due to reactive oxygen species. The genotoxic activity of OA, 4-chloro-*m*-cresol and chloroxine in *E. coli* PQ37 strain was completely quenched in the presence of Trolox C, a hydrosoluble form of vitamin E. The mechanism of the SOS DNA repair-inducing activity of OA was further investigated by

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[48] Gough, A.C., Miles, J.S., Spurr, N.K., Moss, J.E., Gaedigk, A., Eichelbaum, M. & Wolf, C.R. (1990) *Nature*, **347**, 773–776

[49] Hietanen, E., Béréziat, J.-C. & Bartsch, H. (1991) In: Castegnaro, M., Pleština, R., Dirheimer, G., Chernozemsky, I.N. & Bartsch, H., eds (1991) *Mycotoxins, Endemic Nephropathy and Urinary Tract Tumours* (IARC Scientific Publications No. 115) (in press)

[50] Malaveille, C., Brun, G. & Bartsch, H. (1991) In: Castegnaro, M., Pleština, R., Dirheimer, G., Chernozemsky, I.N. & Bartsch, H., eds (1991) *Mycotoxins, Endemic Nephropathy and Urinary Tract Tumours* (IARC Scientific Publications No. 115) (in press)

comparing the response of PQ37 with those of PQ 300, OG 100 and OG 400 strains (the latter have a partially deleted oxy R gène, rendering them more sensitive to oxidative DNA damage). The four strains displayed very similar sensitive to oxidative DNA damage). The four strains displayed very similar sensitivity to the genotoxic effect of OA, while differential sensitivity was found with cumene hydroperoxide used as a positive control. These results suggest that an OA-derived free radical, rather than reactive oxygen species, is the genotoxic intermediate in bacteria[50].

### 1.2.8 HIV-related cancers in Africa

(D.M. Parkin; in collaboration with V. Beral, Oxford, UK; and G.T. O'Conor, Maywood, IL, USA)

The protocol for this project includes the investigation of the descriptive epidemiology, pathology and immunology of Kaposi's sarcoma and non-Hodgkin lymphoma in six centres in Africa (see section 3.1.1), and case–control studies of Kaposi's sarcoma and non-Hodgkin lymphoma in two centres: Harare, Zimbabwe (Professor A. Latif) and Butare, Rwanda (Dr. P.-J. Ngilimana). The study will begin during 1991. Lymphomas occurring in AIDS patients are also being studied at the molecular level (see section 1.7.1.2).

## 1.3 *Site-Oriented Studies*

Although all the research at IARC considers cancer in terms of the various body sites, certain studies are specifically concerned with identifying causal factors for particular sites and these are described in this section.

### 1.3.1 Case–control studies network (the SEARCH programme)

(P. Boyle)

SEARCH (Surveillance of Environmental Aspects Related to Cancer in Humans) is a programme whose principal objective is to generate, formulate and test by epidemiological methods, and on an international basis, hypotheses relating to risk factors for cancer occurrence. As a collaborative, international programme, it offers a number of advantages to participating centres in providing: professional contact and stimulation to personnel in participating centres; technical assistance and technology transfer in the study design, conduct, data analysis and interpretation of results; opportunity for investigators to examine data from other centres in assessing their own results; international support for the development of epidemiology which may assist local cooperation and funding; the opportunity for researchers to initiate and pursue studies which they may not ordinarily be able to undertake in isolation.

The SEARCH programme includes studies of forms of cancer which, because of their relative rarity or the complexity of their histological subtypes, cannot be satisfactorily investigated by any single centre. Its most important function remains the replication of research protocols in dispersed and dissimilar populations, so that findings can be subjected to the crucial epidemiologic test of reproducibility at an early stage in the development of the hypothesis.

The predominant mode of investigation has been the case–control study, although other forms of epidemiological study are not precluded. The IARC provides staff and resources commensurate with its central role and funds for travel between IARC and local centres for purposes of consultation, programme review, technology transfer and quality control. Each participating centre seeks local or national funds for the conduct of its own part of the study. Each SEARCH project is managed by a study group with one representative from each

participating centre attending regular meetings in Lyon with the responsible IARC staff and external experts. At an introductory planning meeting, the subject to be studied is reviewed by epidemiologists and laboratory scientists, hypotheses are proposed, discussed and formulated by those in attendance, and the logistics of undertaking the study outlined. Each centre undertakes to collect common items of data relevant to the hypotheses under study which it transmits to Lyon for central analysis. Each centre is at liberty to collect additional pieces of information and is strongly encouraged to undertake analysis of its own data as well as participating actively in the central analysis.

#### 1.3.1.1 *Cancers of the pancreas, gallbladder and bile duct*

(P. Boyle and P. Maisonneuve; in collaboration with P. Baghurst, Adelaide, Australia; H.B. Bueno de Mesquita, Bilthoven, Netherlands; P. Ghadirian, Montreal, Canada; G.R. Howe, Toronto, Canada; and W. Zatonski, Warsaw, Poland; A.J. McMichael, A.B. Miller and A.M. Walker continue to participate in this study group)

The first SEARCH study began in 1983 with a series of pilot studies designed to ascertain the feasibility of obtaining data relating to lifestyle factors in the etiologies of cancers of the pancreas, gallbladder and bile duct. The first full analysis, performed on a provisional dataset, was outlined at a meeting in Lyon in April 1989. Subsequently more detailed analyses have been performed on the complete data-set and the results from the individual participating centres have been published[51], as well as the overall results of the combined study.

Cancer of the pancreas is a fairly common and rapidly fatal form of cancer in Western society, where little is known about the etiology apart from an elevation in risk associated with cigarette smoking. In the present study, ever-smokers have been found to be at an increased risk of pancreas cancer compared to never-smokers in each strata of sex, response status and centre.

Risk of pancreas cancer was found to increase with increasing lifetime consumption of cigarettes, and the overall trend of increasing risk with total lifetime consumption, calculated omitting the never-smoking group, was highly significant; the association was found in each strata of age, response status and participating centre (Table 7). Similar patterns of risk were observed for cancers arising in the head, body and tail of the pancreas (Table 7). For cumulative amount smoked within the 15 years immediately before diagnosis or interview, compared to never-smokers (in whom the odds ratio was fixed at 1.0), there was a statistically significant increase in the risk of pancreas cancer with increasing amount smoked, rising to 4.34 in the highest quartile. By comparison, when smoking 15 or more years before diagnosis or interview

[51] Baghurst, P., McMichael, A.J., Slatvotnic, A., Baghurst, K., Walker, A.M. & Boyle, P. (1991) *Am. J. Epidemiol.*, **134**, 167–179
Bueno de Mesquita, B., Moerman, C.J., Runia, S. & Maisonneuve, P. (1990) *Int. J. Cancer*, **46**, 435–444
Bueno de Mesquita, B., Maisonneuve, P., Runia, S. & Moerman, C.J. (1991) *Int. J. Cancer*, **48**, 544–549
Ghadirian, P., Simard, A. & Baillergeon, J. (1991) *Cancer*, **67**, 2664–2670
Ghadirian, P., Simard, A., Baillergeon, J., Maisonneuve, P. & Boyle, P. (1991) *Int. J. Cancer*, **47**, 1–6
Howe, G.R., Jain, M. & Miller, M. (1990) *Int. J. Cancer*, **45**, 604–608
Howe, G.R., Jain, M., Burch, J.D. & Miller, A.B. (1991) *Int. J. Cancer*, **47**, 323–328
Jain, M., Howe, G.R., St Louis, P. & Miller, A.B. (1991) *Int. J. Cancer*, **47**, 384–389
Zatonski, W., Przewozniak, K., Howe, G.R., Maisonneuve, P., Walker, A.M. & Boyle, P. (1991) *Int. J. Cancer*, **48**, 390–394
Zatonski, W., Boyle, P., Przewozniak, K., Maisonneuve, P., Drosik, K. & Walker, A.M. (1991) (submitted for publication)

Table 7. Pancreatic cancer risk[a] and total lifetime cigarette consumption

| | Lifetime consumption[b] (thousands of cigarettes) | | | | | |
|---|---|---|---|---|---|---|
| | Never smoked | 0–83 849 | 83 850–193 449 | 193 450–319 875 | >319 875 | Chi-square[c] |
| Adelaide | 1.0 | 0.99 | 0.88 | 1.56 | 1.51 | 1.36 |
| Toronto | 1.0 | 1.45 | 2.11* | 2.96* | 4.15* | 10.86 |
| Utrecht | 1.0 | 1.47 | 1.29 | 1.99 | 2.69* | 2.08 |
| Opole | 1.0 | 0.93 | 2.45 | 1.98 | 1.42 | 0.13 |
| Montreal | 1.0 | 0.94 | 2.85* | 3.34* | 3.76* | 5.97 |
| Head of pancreas | 1.0 | 1.32 | 1.69* | 2.53* | 2.64* | 11.47 |
| Body of pancreas | 1.0 | 2.82* | 3.00* | 5.47* | 9.65* | 8.47 |
| Tail of pancreas | 1.0 | 1.37 | 3.14 | 7.48* | 10.62 | 7.69 |
| Entire pancreas | 1.0 | 0.73 | 1.53 | 1.21 | 1.24 | 0.34 |
| Pancreas NOS | 1.0 | 0.94 | 1.79 | 1.69 | 3.26* | 8.33* |
| All subjects[d] | 1.0 | 1.26 (0.91, 1.75) | 1.73* (1.25, 2.38) | 2.34* (1.69, 3.23) | 2.88* (2.08, 3.99) | 20.28 |

*Statistically significant at least at 5% level

[a]After adjustment for age, sex, centre, schooling and response status

[b]Cut-points based on quartile distribution of lifetime cigarette consumption measured among smokers. Reference category represents lifetime non-smokers

[c]Chi-square for trend excludes never-smokers category

[d]Figures in parentheses are lower and upper bounds of 95% confidence interval

was examined, no trend in the risk was visible. The results are considered consistent with a causal role for cigarette smoking in the etiology of pancreas cancer[52].

The data on lifetime intake of coffee and tea did not indicate that either habit increases the risk of pancreas cancer. No association was found with different forms of coffee consumption (caffeinated versus decaffeinated or instant versus regular), and there was no evidence of an interactive effect of lifetime coffee consumption and cigarette consumption. Relative to ever-drinkers, never-drinkers of both tea and coffee had a significantly elevated risk of pancreas cancer (OR = 4.76, 95% CI 2.03, 11.13). Those individuals who drank coffee on its own before breakfast were consistently found to have an elevated risk of pancreas cancer; drinking coffee at other times of the day was associated with no change in risk.

Comprehensive diet histories were completed for a total of 802 cases and 1669 controls in this study. Positive associations were observed between pancreatic cancer risk and intake of carbohydrates and cholesterol and inverse associations with dietary fibre and vitamin C intake. These relationships were fairly consistently found among the five study centres and showed statistically significant and generally monotonic relationships between level of intake and risk of pancreas cancer. The relative risks for highest versus lowest quintiles of intake were for carbohydrate intake 2.57 (95% CI 1.64, 4.03), cholesterol intake 2.68 (95% CI 1.72, 4.17), dietary fibre intake 0.45 (95% CI 0.30, 0.63) and vitamin C intake 0.53 (95% CI 0.38, 0.76). The

[52] Boyle, P., Maisonneuve, P., Bueno de Mesquita, B., Ghadirian, P., Howe, G.R., Zatonski, W., Baghurst, P., Moerman, C.D., Simard, A., Burch, D.J., Przewozniak, K., McMichael, A.J., Hsieh, C.-c. & Walker, A.M. (1991) (submitted for publication)

consistency, strength and specificity of these associations suggests that they may be indicative of underlying causal relationships[53].

Another interesting finding from this study was the strong and consistently observed protective effect of asthma, eczema or hay fever for pancreatic cancer.

A total of 196 cases of gallbladder cancer and 1515 controls (who had not reported cholecystectomy) were available for a combined analysis from the participating centres. After adjusting for potential confounding factors (age, sex, centre, response status, years of schooling, alcohol intake and lifetime cigarette consumption), a history of symptoms of gallbladder disease was the major risk factor associated with this form of cancer (OR = 4.4, 95% CI 2.6, 7.5). This association was present even in subjects where symptoms predated the cancer for as long as twenty years (OR = 6.2, 95% CI 2.8, 13.4). Other variables associated with gallbladder cancer risk included high body mass index, total energy intake or carbohydrate intake (after adjustment for energy intake) and chronic diarrhoea, all of which have previously been shown to be associated with gallstone disease. A number of dietary items were shown to be protective including vitamins C and E and dietary fibre. Alcohol consumption history and lifetime cigarette smoking did not appear to be associated with the risk of gallbladder cancer. The findings are consistent with a major role of gallstones in the etiology of gallbladder cancer[54].

In aggregate over the five study centres, a total of 95 patients with bile duct cancer were interviewed and compared with 1679 controls. Risk of bile duct cancer was elevated among those who reported having a gallbladder condition requiring medical attention (OR = 3.63, 95% CI 2.2, 6.0). Findings were similar in male and females, in direct and proxy respondents and over the five centres. Patients who had their gallbladder removed were at increased risk compared to those with no gallbladder disease and reporting no gallstones. No association was found with a number of variables including allergy, gastrectomy, oral contraceptive use and tonsillectomy. Cigarette smoking was associated with an increased risk of bile duct cancer, with the risk in the highest quintile of lifetime consumption 2.49 (95% CI 1.2, 5.0) compared with the referent group of lifetime never-smokers. There was no association with intake of tea, coffee or alcohol. Dietary fibre intake appeared to be associated with a reduced risk of bile duct cancer: the odds ratio in the highest quartile compared to the lowest quartile was 0.38 (95% CI 0.16, 0.89). There was no association with intake of fat or protein but increased carbohydrate intake and increased cholesterol intake were associated with an increased risk of extrahepatic bile duct cancer.

### 1.3.1.2 *Brain tumours in children*

(P. Boyle, J. Little and P. Maisonneuve; in collaboration with N.W. Choi, Winnipeg, Canada; S. Cordier, Paris, France; G. Filippini, Milan, Italy; E. Holly, San Francisco, CA, USA; M. McCredie, North Ryde, Australia; R. Peris-Bonet, Valencia, Spain; S. Preston-Martin, Los Angeles, CA, USA; and J. Stanford, Seattle, WA, USA)

Brain tumours in children are sufficiently uncommon to make their study in any single centre difficult, and for this reason little is known about their etiology. What little that is has been incorporated into this study, the main hypothesis of which has been suggested by laboratory findings; *viz.* the role of nitrosamines, nitrosatable substances and inhibitors of nitrosation in the

[53] Howe, G.R., Ghadirian, P., Bueno de Mesquita, H.B., Zatonski, W., Baghurst, P.A., Miller, A.B., Simard, A., Baillargeon, J., de Waard, F., Przewozniak, K., McMichael, A.J., Hsieh, C.-c., Maisonneuve, P., Boyle, P. & Walker, A.M. (1991) (submitted for publication)

[54] Zatonski, W., Lowenfels, A.B., Boyle, P., Maisonneuve, P., Bueno de Mesquita, B., Ghadirian, P., Jain, M., Przewozniak, K., Baghurst, P., Moerman, C.D., Simard, A., Howe, G.R., McMichael, A.J., Hsieh, C.-c. & Walker, A.M. (1991) (submitted for publication)

risk of this disease. These include exposure to nitrosamines and/or their precursors as a result of passive smoking, certain dietary sources as well as intake of nitrate and nitrite from food and water, with information also collected about vitamin C intake, which has been demonstrated in man as being able to inhibit nitrosamine formation from amino substrates.

The protocol for this study was developed at IARC by Dr S. Preston-Martin and was subsequently incorporated into the SEARCH programme. Data collection has been completed in Milan, Paris, Valencia, Manitoba and Sydney, and will continue until 1992 in three US centres—Los Angeles, San Francisco and Seattle Puget Sound.

Analyses have been made of the data collected by the first five centres and a preliminary pooled analysis is being performed. Several interesting findings have already emerged, particularly relating to the mother's dietary practices during the pregnancy with the index child. Analysis of all the available data sets will be completed by the end of 1992.

### 1.3.1.3 *Adult brain tumours*

(P. Boyle, J. Little and P. Maisonneuve; in collaboration with A. Ahlbom, Stockholm, Sweden; N. Choi, Winnipeg, Canada; R. Gurevicius, Vilnius, USSR; G.R. Howe, Toronto, Canada; A.J. McMichael, Adelaide, Australia; F. Ménégoz, Meylan, France; B. Modan, Tel-Hashomer, Israel; M. Salzburg, Melbourne, Australia; and J. Wahrendorf, Heidelberg, Germany)

The inaugural meeting of this SEARCH study group was held in Lyon in January 1986. The study is now under way in Toronto (Canada), Isère (France), Lithuania (USSR), Stockholm (Sweden), Manitoba (Canada), Heidelberg (Germany), Adelaide and Melbourne (Australia) and Israel. At the current rate of case acquistion, it is estimated that between 2000 and 2500 cases will be recruited from the participating centres in the course of the study.

The strength of this study lies in the reasonable number of focused hypotheses to be addressed, thus requiring a questionnaire which takes around one hour to administer to cases and controls alike. While interviewing and data cleaning will continue in some centres until the middle of 1992, initial results are already becoming available for publication[55].

The computer program BRAINCHECKER written by Patrick Maisonneuve is being used in all the centres for data validation and to ensure speedy data transfer between centres and IARC.

### 1.3.1.4 *Cancers of the breast and colorectum*

(P. Boyle, J. Little, P. Maisonneuve and H. Bartsch; in collaboration with H.B. Bueno de Mesquita, Bilthoven, Netherlands; H.J.A. Collette and F. de Waard, Utrecht, Netherlands; S. Franceschi, Aviano, Italy; P. Ghadirian, Montreal, Canada; E. Hietanen and J.T. Salonen, Kuopio, Finland; W.P.T. James, Aberdeen, UK; F. Kadlubar, Jefferson, AR, USA; K. Katsouyanni, Athens, Greece; N. Lang, Little Rock, AR, USA; C. La Vecchia, Milan, Italy; R.E. Leake, Glasgow, UK; B. MacMahon and D. Trichopoulos, Boston, MA, USA; J.M. Martin-Moreno, Granada, Spain; N. O'Higgins, Dublin, Ireland; P. Pietinen, Helsinki, Finland; and D.G. Zaridze, Moscow, USSR)

There is an increasing accumulation of epidemiological evidence suggesting that among women, breast cancer and colorectal cancer (particularly ascending colon) share a number of

[55] Schlehofer, B., Kunze, S., Sachsenheimer, W., Blettner, M., Niehoff, D. & Wahrendorf, J. (1990) *Cancer Causes Control*, **1**, 209–216

common etiological risk factors including an increased risk among family members, associations with dietary intake, fibre and vegetables, consumption of alcohol, and similar associations with aspects of reproductive history such as parity and age at first birth. Some important questions addressed in this study include the effect of alcohol intake on breast cancer risk and the roles of dietary intake of fat, fibre and vegetables in breast and colorectal cancer etiology. Data collection is at an advanced stage in Spain, Montreal, Athens and Dublin. Pilot studies have successfully been completed in Moscow, and in Italy there has been an extensive validation study of the dietary questionnaire. The questionnaire is being translated and pilot-tested in Lithuania and Warsaw. Other centres are at various stages of advancement and it is expected that data collection will continue throughout 1992 and 1993.

#### 1.3.1.5 *Childhood leukaemia and other related haematological malignancies*

(P. Boyle, J. Little and P. Maisonneuve; in collaboration with R.A. Cartwright, Leeds, UK; J.-P. Collet, Lyon, France; J. Elwood, Dunedin, New Zealand; R.P. Gallagher, Vancouver, Canada; R. Gurevicius, Vilnius, USSR; M. Linet, Bethesda, MD, USA; P. McKinney, Edinburgh, UK; F. Mitelman, Lund, Sweden; G.T. O'Conor, Maywood, IL, USA; L. Robison, Minneapolis, MN, USA; and D.G. Zaridze, Moscow, USSR)

A protocol has been approved for a multicentre case–control study on the etiology of leukaemia and related haematological malignancies in children, in collaboration with the European Organization for Research and Treatment of Cancer (EORTC).

In the proposed study a strong emphasis will be placed on medical and other written records for validation of interview-derived exposure data, for evaluation of possible recall bias, and for evaluation of risk factor association with biological subgroups of cases defined morphologically, immunologically and by cytogenetic characterization.

Investigation will focus on four specific aims: (i) to determine whether perturbations in the normal development of the immune response in infancy or early childhood are linked with specific subtypes of childhood leukaemia and lymphoma (the "Greaves hypothesis"); (ii) to examine possible associations of certain parental occupational exposures with specific subtypes of childhood leukaemia and lymphoma; (iii) to determine whether various postnatal residential exposures are associated with specific subtypes of childhood leukaemia and lymphoma; (iv) to examine a number of hypotheses regarding links of specific subtypes of childhood leukaemia and lymphoma with childhood use of chloramphenicol; parental prenatal and postnatal smoking; diagnostic radiation exposure (parental or postnatal); and other recent findings.

A detailed comparison has been made of published data on childhood haematological malignancies and the results of epidemiological studies on congenital malformations[56]. Preliminary work on reported clustering of childhood leukaemia cases has led to methodological research to assess different statistical techniques for identifying clusters (see below).

#### 1.3.1.6 *Endocrine tumors*

(P. Boyle)

In order to evaluate the possibility of SEARCH conducting a multicentre case–control study of the rare endocrine tumours, a survey of European cancer registry data for the period 1980 to 1985 inclusive was undertaken. For males and females respectively, the age-standardized

[56] Elwood, J.M., Little, J. & Elwood, P.C. (1991) *The Epidemiology of Congenital Malformations*, Oxford, Oxford University Press

incidence rates per 100 000 per annum, based on 530 million person-years of risk, were 0.05 and 0.03 for malignant tumours of the endocrine pancreas, 0.05 and 0.06 for malignant adrenocortical tumours, 0.03 and 0.02 for malignant phaeochromocytoma and 0.01 in each sex for malignant pituitary tumours. Interestingly, the age–incidence curves obtained appeared to resemble those of more common epithelial tumours. The rarity of these tumours seems to exclude their study even in an extremely large population.

### 1.3.1.7 *Technical support for collaborators*

Within the SEARCH programme activities, an important component is the provision of technical or informational support for collaborators. This involves, for example, participation in the preparation of research grant submissions by collaborators, advising at various stages of the data collection process and providing facilities, in terms of both hardware, software and personnel, for data analysis and interpretation. Training of personnel from the participating centres in techniques of conducting case–control studies may be provided, particularly in the form of periods of 'hands-on' training in statistical methods for the analysis of studies at the IARC in Lyon. These training activities have been supported both directly by the SEARCH programme budget and also by national sources of funding and international fellowship programmes such as that of the International Union Against Cancer (UICC).

### 1.3.1.8 *Method development*

During the course of conducting SEARCH studies, methodological problems have been identified which have resulted in collaborative research to propose solutions.

Little attention has been paid to the analysis of continuous outcome variables in epidemiological studies and this is a particularly important problem in view of recent developments in nutritional epidemiology. A meeting was convened to discuss the statistical analysis of nutritional data in case–control studies and allowed guidelines to be developed which have been followed in analysing the results from the pancreas cancer case–control study. Following this, and recognizing that current thinking in epidemiology recommends that continuous variables should be transformed and analysed as ordered categorical variables, it was shown that the optimal method of selecting cut-points for the categories was on the basis of the combined distribution of cases and controls[57]. Proceeding further with the analysis of continuous variables, it was shown that particular patterns, notably an apparent quadratic risk pattern, could be spuriously found in data where the only difference between cases and controls was in the variance of the variable under consideration[58]. The role of differential measurement error in influencing the apparent findings from studies has also been investigated and it has been clearly demonstrated that, even when no real difference exists between cases and controls with respect to the exposure variable, substantial odds ratios can be produced simply by differences in unbiased measurement error between cases and controls[59].

Much interest has been demonstrated in the statistical literature recently on the examination and identification of influential covariate patterns on the effects being measured. This work has been extended to logistic regression for case–control studies (it also holds for cohort studies) and a suite of GLIM macros has been developed to assist in this process and in other aspects of the

[57] Hsieh, C.-C., Maisonneuve, P., Boyle, P., Macfarlane, G.J. & Robertson, C. (1991) *Epidemiology*, **2**, 137–140
[58] Robertson, C., Boyle, P., Hsieh, C.-c., Macfarlane, G.J. & Maisonneuve, P. (1991) (submitted for publication)
[59] Marshall, J.R., Macfarlane, G.J., Hsieh, C.-c. & Boyle, P. (1991) *Am. J. Epidemiol.* (in press)

analysis of epidemiological studies[60]. The effects of misclassification of covariates have also been examined and their influence on the estimates of risk obtained has been quantified in a variety of circumstances[61]. An important consideration in many epidemiological studies is the effect of cessation of exposure on the risk of disease. This has been shown to be uninterpretable in case–control studies due, in essence, to the multicollinearity of the time-related variables measured and the explicit matching, or adjustment, for current age and the implicit matching on time period in the study design[62]. This finding has relevance to the mechanistic interpretation of information from epidemiological studies.

The collaborative study of childhood haematological neoplasms provides an opportunity to examine the hypothesis of spatial clustering of this disease in a number of different populations, because many of the individual studies are population-based. In order to identify the best statistical methodology to test a data-set for spatial clustering, researchers who have published and employed statistical tests of spatial clustering were invited to participate in a project designed to be a fair, comparative test of their methodologies. Sixty data-sets were generated based on the population characteristics of Yorkshire (UK) and on the number of cases of childhood leukaemia observed over a ten-year period in that region: these were analysed and interpreted by each of the five participating groups blind to the actual pattern within the data. It has proved possible to obtain a better insight into how each of the methods works and the results of the study will be published in the IARC Scientific Publications series[63].

### 1.3.2 Nasopharyngeal carcinoma

(G. Bouvier, S. Poirier, C. Malaveille, H. Ohshima, I. Brouet and H. Bartsch; in collaboration with G.W. Bornkamm and A. Polack, Munich, Germany; G. de-Thé, Paris, France; M. Hergenhahn, Heidelberg, Germany; Y.M. Shao and Y. Zeng, Beijing, China)

As different classes of substances are involved in mutagenicity and in Epstein–Barr virus (EBV)-inducing activity of preserved foods from areas where risk for nasopharyngeal carcinoma (NPC) is high (e.g. southern China, North Africa and Greenland)[64], the active principles in certain high-risk foodstuffs (Tunisian spice mixture) are geing characterized. EBV-inducing activity is measured in a new test by the induction of the EBV-DR promoter which regulates the bacterial chloramphenicol-acetyltransferase (CAT) gene in an autoreplicative plasmid transfected into Raji cells[65]. EBV-inducing activity was found in the aqueous phase of the spice extract. Work is in progress to characterize these active substances, which activate protein kinase C, as shown by a human granulocyte/chemiluminescence assay.

In order to assess the role of endogenous nitrosation in NPC development, twelve-hour urine samples were collected in 1990 from inhabitants of districts of high and low risk for NPC in

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[60] Maisonneuve, P., Boyle, P., Lemeshow, S., Hsieh, C.-c., Macfarlane, G.J. & Walker, A.M. (1991) (submitted for publication)

[61] Hsieh, C.-c. & Walter, S.D. (1988) *Stat Med.*, **7**, 1073–1085
Cox, B. & Elwood, J.M. (1991) *Am. J. Epidemiol.*, **133**, 202–207
Hsieh, C.-c. (1991) *Stat. Med.*, **10**, 361–374

[62] Maisonneuve, P., Boyle, P., Hsieh, C.-c., Saracci, R. & Walker, A.M. (1991) (submitted for publication)

[63] Alexander, F.E. & Boyle, P., eds (1992) *Statistical Methods in Cancer Research*, Vol. 4, *Detecting Localized Clusters of Disease*, Lyon, International Agency for Research on Cancer (in press)

[64] Poirier, S., Bouvier, G., Malaveille, C., Ohshima, H., Shao, Y.M., Hubert, A., Zeng, Y., de Thé, G. & Bartsch, H. (1989) *Int. J. Cancer*, **44**, 1088–1094

[65] Bouvier, G., Poirier, S., Shao, Y.M., Malaveille, C., Ohshima, H., Polack, A., Bornkamm, G.W., Zeng, Y., de Thé, G. & Bartsch, H. (1991) In: O'Neill, I.K., Chen, J. & Bartsch, H. eds, *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105) Lyon, International Agency for Research on Cancer, pp. 204–209

southern China who were being subjected to the nitrosoproline test. Samples were analysed for urinary nitrosamino acids, nitrate and creatinine and the results show a higher nitrosation potential in the high-risk subjects.

### 1.3.3 Oesophageal cancer

As a complement to the epidemiological studies described below, a long-term carcinogenicity study of the effect of hot drinks in causing oesophageal cancer in rats has been initiated (section 1.7.10). Genetic lesions in oesophageal tumours are being examined at the molecular level (sections 1.7.6.2–5).

#### 1.3.3.1 *Precancerous lesions of the oesophagus in China*

(N. Muñoz; in collaboration with J. Claude, R. Raedsch and J. Wahrendorf, Heidelberg, Germany; P. Correa, New Orleans, LA, USA; M. Crespi, Rome, Italy; H. Shimada, Tokyo, Japan; D. Thurnham, Cambridge, UK; and Yang Guan-Rei and Qui Song-Liang, Zhengzhou, China)

The main results of the 1988 epidemiological survey have been published and the data from the micronuclei studies have been analysed. No association was found between the prevalence of micronuclei in oesophageal cells and the prevalence of smoking or the consumption of scalding hot beverages or fresh fruits. This is in contrast with previous observations in the same study subjects showing that the consumption of very hot beverages, smoking and low intake of fresh fruits were the main risk factors for chronic oesophagitis.

#### 1.3.3.2 *Case–control studies of oesophageal cancer in high-risk populations of Latin America*

(N. Muñoz and J. Estève; in collaboration with R. Castelletto and J. Iscovich, La Plata, Argentina; E. de Stefani, Montevideo, Uruguay; P.A. Rolón, Asunción, Paraguay; and C. Victora, Pelotas, Brazil)

Case–control studies in Brazil and Uruguay have identified tobacco smoking, alcohol drinking and drinking of hot mate as the main risk factors for this cancer. Validation studies conducted in Brazil and Uruguay to verify the accuracy and precision of the perceived and reported information on the temperature at which mate is drunk have now been completed. A random sample of 542 daily mate drinkers from the cities of Pelotas and Montevideo were asked to prepare the mate and judge its temperature; the reported temperatures were compared with measured temperatures. Reported temperatures were subject to considerable error and grossly distort the odds ratio, such that in the worst case, a true odds ratio of 3.8 would be estimated as one of only 1.2. Studies using the reported temperatures must therefore yield considerable underestimates of the true associations.

Data from a case–control study including 131 cases and 262 controls from La Plata, Argentina, have been analysed, and again show tobacco smoking and alcohol drinking as the main risk factors for this cancer. The adjusted relative risk (RR) for those who smoked more than 15 cigarettes per day was 3.9 (95% CI 1.7–8.8) and for those drinking more than 200 ml of alcohol per day it was 5.8 (95% CI 2.6–13.0), while for those smoking more than 15 cigarettes per day and also drinking more than 200 ml of alcohol per day the RR was 14.2 (95% CI 4.5–40.6). The risk for smokers of black tobacco was double that of smokers of blond tobacco. Concerning dietary habits, as in Brazil and Uruguay, an increased risk for daily versus non-daily consumption was associated with frequent consumption of barbecued meat (adjusted RR 2.4,

95% CI 1.4–4.9) and decreased risk associated with low consumption of fruits (RR 0.5, 95% CI 0.3–0.9). However, in contrast to the findings in Brazil and Uruguay, no association with the habit of mate drinking was observed.

Data collection in the case–control study conducted in Paraguay, where mate is also drunk but mainly cold, was terminated in March 1991. A total of 123 cases and 369 controls were interviewed; data are being entered into the computer.

### 1.3.4 Stomach cancer

Stomach cancer remains one of the commonest cancers worldwide, but its detailed etiology is still unclear. Epidemiological studies of precancerous lesions and cancer of the stomach are described in this section. Nutritional factors are thought to play an important role, especially in relation to endogenously formed nitroso compounds and the protective effects of vitamin C (section 1.5.7). The latter aspect is being exploited in a new preventive trial in Venezuela in which administration of vitamins C and E and β-carotene will be combined with a treatment against *Helicobacter pylori* (section 2.3.2). A screening programme for early gastric cancer in the same population is already being evaluated (section 2.2.2).

#### 1.3.4.1 *Cohort study on chronic atrophic gastritis and intestinal metaplasia in Slovenia*

(N. Muñoz, S. Teuchmann and M. Benz; in collaboration with M.I. Filipe, London, UK; and A. Jutersek and I. Matko, Ljubljana, Yugoslavia)

Linking of the cohort of 1996 patients with the three main types of intestinal metaplasia (IM) to the population registry and to the Cancer Registry of Slovenia up to 1 April 1988 allowed 1496 individuals (75.1%) to be traced. A cohort analysis has been carried out using two end-points, morbidity and mortality from gastric cancer. Expected numbers were calculated using national mortality for Yugoslavia (WHO mortality data bank) for the periods 1965–69, 1970–74, 1975–79, 1980–84 and 1985–89 and incidence rates from the Slovenian Cancer Registry for the periods 1956–60, 1961–65, 1968–72, 1973–76 and 1978–81. A total of 226 cases of stomach cancer and 214 cancers at other sites were identified in this cohort. The standardized mortality ratios (SMR) for the subgroups of IM patients are given in Table 8.

A five-fold increase in gastric cancer risk was detected for the whole cohort when the period between gastric biopsy and cancer death was ≥1 year and this increase was greater for patients with IM-III. A similar analysis using incidence data is being completed.

Table 8. Standardized mortality ratios in patients with three types of intestinal metaplasia

| Risk interval[a] (years) | IM-O[b] | IM-I | IM-II | IM-III | Total |
|---|---|---|---|---|---|
| <1 | 57.5 | 61.4 | 75.5 | 88.7 | 70.6 |
| 1–2 | 19.7 | 13.3 | 21.0 | 22.7 | 18.3 |
| 3–4 | 4.8 | 1.7 | 5.1 | 8.6 | 4.7 |
| ≥5 | 1.2 | 1.1 | 1.5 | 3.9 | 1.9 |
| ≥1 | 4.2 | 2.9 | 4.8 | 7.7 | 4.7 |

[a] Period between gastric biopsy and death from gastric cancer

[b] Originally diagnosed as IM by local pathologist but not confirmed at review

### 1.3.4.2 *Case–control study in Tachira, Venezuela*

(N. Muñoz, D.M. Parkin and S. de Sanjosé; in collaboration with N. Alvarez, W. Oliver, S. Peraza and J. Vivas, San Cristobal, Venezuela; and E. Buiatti, Florence, Italy)

A case–control study to identify the main risk factors and to evaluate the efficacy of a screening programme for gastric cancer in Tachira state, Venezuela, has been initiated (see section 2.2.2). All new and histologically confirmed cases of stomach cancer diagnosed at the two main hospitals in San Cristobal since January 1991 are being included as well as two controls per case, one from the same hospital and the other from the same neighbourhood as the case and matched by sex and age. Cases and controls must have resided in Tachira state for at least five years. Information on diet is collected by personal interview using a dietary history questionnaire focused on usual diet one year before the disease. Dietary habits when the study subject was 15–20 years old are also being recorded. Information on screening will be retrieved from the records of the Cancer Control Centre. Serum samples to measure antibodies to *Helicobacter pylori* and selected micronutrients are being collected in cases and controls; biopsies from tumoural and non-tumoural gastric mucosa are being collected from the cases to look for genetic alterations. Nineteen cases and 19 hospital controls have been recruited and interviewed and sera and tissue specimens collected from them. It is planned to include 300 cases and 300 controls in each control group.

### 1.3.4.3 *Stomach cancer in Poland*

(H. Ohshima, D. Shuker, I. Brouet and H. Bartsch; in collaboration with K. Miki, Tokyo, Japan; A.S. Peña, Leiden, Netherlands; and W. Zatonski, Warsaw, Poland)

Following a feasibility study[66], urine and blood samples have been collected from 70 healthy subjects living in high- and low-risk areas for stomach cancer in Poland. Urine specimens collected before or after ingestion of 500 mg proline were analysed for sodium chloride and for nitrosamino acids and nitrate as exposure markers of endogenous nitrosation. Blood samples were examined for antibodies to *H. pylori* and analysed for pepsinogen isozymes and pro-oxidant status. The data are now being statistically evaluated.

### 1.3.4.4 *European correlation study (EUROGAST)*

(M.P. Coleman, P. Roy, C.P. Wild and R. Montesano; in collaboration with D. Forman, Oxford, UK)

Agency staff are collaborating in an EEC-funded study (EUROGAST; principal investigator D. Forman) designed to estimate the population-level correlation between the incidence and mortality from gastric cancer and the prevalence of various markers of chronic gastritis, a precursor lesion for "intestinal" adenocarcinoma, the most frequent type of gastric cancer. The study involves 17 centres in seven EEC countries and in Algeria, Japan, Iceland, Poland, USA and Yugoslavia, covering a 10-fold range of cancer incidence. Each centre has obtained questionnaire data and blood from 50 men and 50 women sampled randomly from the general population in each of the age groups 25–34 years and 55–64 years. Serum levels of biological markers of chronic gastritis have been measured (serum pepsinogen, antibodies to *H. pylori*),

[66] Zatonski, W., Ohshima, H., Przewozniak, K., Drosik, K., Mierzwinska, J., Krygier, M., Chmielarczyk, W. & Bartsch, H. (1989) *Int. J. Cancer*, **44**, 823–827

together with levels of nitrosamine-induced DNA adducts in lymphocytes (see section 3.3.4.2). Despite the indirect nature of the assocation being studied, initial analyses suggest a clear correlation between prevalence of *H. pylori* seropositivity and gastric cancer rates. Complete analyses will be published in 1992.

### 1.3.5 Liver cancer

Liver cancer is a serious public health problem especially in regions where aflatoxin contamination of foods is common and/or infection with the hepatitis B virus is endemic. Epidemiological research into the respective roles of these agents is being complemented by mechanistic studies of the etiology of liver cancer (section 1.7.6), which are also providing improved tools for exposure measurement (section 1.7.2). The Gambia Hepatitis B Intervention Study (section 2.3.1) is assessing the long-term effect of neonatal vaccination against the virus.

Vinyl chloride-induced liver cancer has been studied epidemiologically (section 1.2.2.1) and at the molecular level (section 3.3.2).

#### 1.3.5.1 *Cohort studies on hepatitis B virus, aflatoxin and other risk factors*

(N. Muñoz, F.X. Bosch and J. Estève; in collaboration with H.P. Lee, J. Lee and Tan Tah-Chew, Singapore; and S. Puribahat and P. Srivatanakul, Bangkok, Thailand)

In Singapore, linkage of the cohort of 15 782 Chinese males (of whom 1273 are carriers of HBsAg) to the Cancer Registry and death registry revealed that 41 cohort members have developed hepatocellular carcinoma (HCC). Statistical analysis of a nested case–control study will be carried out in 1991. Unfortunately, most of the serum samples collected at recruitment from each cohort member have been spoiled due to a breakdown of the freezers and therefore assays of aflatoxin–albumin adducts will no longer be possible.

In Bangkok, a total of 1972 male HBsAg carriers over 30 years of age were recruited up to December 1990. For each subject a questionnaire eliciting information on exposure to risk factors for HCC has been completed, blood and urine specimens have been collected and laboratory and ultrasound examinations to detect early signs of liver disease have been performed. Follow-up examinations including ultrasound, liver function tests, $\alpha$-fetoprotein and clinical examination are performed every 3–6 months in subjects in whom liver abnormalities are detected and every year in those found normal. A total of 436 subjects have been examined twice, 297 three times, 142 four times and 174 have had five or more follow-up examinations. Fifteen cases of HCC have been diagnosed in this cohort and tumour and non-tumour tissue specimens have been collected from most of them. A nested case–control analysis based on these cases and five controls per case will be carried out.

#### 1.3.5.2 *Follow-up of a cohort of HBsAg-positive blood donors in Catalonia*

(F.X. Bosch, N. Muñoz and S. Teuchmann; in collaboration with M. Casas, M. Gallen, J.M. Hernandez, A. Plasencia and M.C. Rodriguez, Barcelona, Spain)

A cohort of 2486 HBsAg carriers has been identified from the records of the major blood banks recruiting blood donors from all parts of Catalonia. Follow-up of the cohort has been updated using the census of 1990, and the mortality files up to 1989–1990. Preliminary analysis of the data indicated that 38 deaths have occurred, of which over one quarter (10/38) were primarily due to liver cirrhosis (nine cases) or liver cancer (one case). Two cases were attributed

to pancreatic cancer and one to a tumour of unknown origin. The detailed analysis of this follow-up is being conducted.

#### 1.3.5.3 *Liver cancer etiology in Thailand*

(D.M. Parkin, M. Khlat, H. Bartsch, H. Ohshima, D. Shuker and C.P. Wild; in collaboration with N. Ito, Nagoya, Japan; and P. Srivatanakul and W. Thamavit, Bangkok, Thailand)

The analyses of the correlation and case–control studies of liver cancer in Thailand have been completed. The very striking geographic variation in incidence of cholangiocarcinoma is closely related to the prevalence of *Opisthorchis viverrini* infection[67], and in high-incidence areas infected individuals show evidence of endogenous synthesis of nitrosamines[68,69]. There is little regional variation in hepatocellular carcinoma, and no obvious correlation with prevalence of markers of infection with hepatitis B virus nor with urinary aflatoxin.

To examine the mechanism(s) of the effect of liver fluke on endogenous nitrosation, Syrian golden hamsters infested with *O. viverrini* were given an oral dose of thiazolidine 4-carboxylic acid or $d_6$-amidopyrine with or without nitrite. Urine samples are being analysed for *N*-nitrosothiazolidine 4-carboxylic acid or $d_3$-3-methyladenine as markers for endogenous nitrosation, and for changes in hepatic drug-metabolizing and nitric oxide synthesizing enzymes.

In the case–control study of cholangiocarcinoma[70], an elevated antibody titre to *O. viverrini* was associated with a relative risk of 5.0, and chewing of betel nut (OR 6.4) emerged as an independent risk factor. In the parallel study of hepatocellular carcinoma[71], chronic carriage of HBsAg was associated with a relative risk of 15.2 and elevated alcohol intake (OR 3.4) and betel chewing (OR 11.0) were found to be independent risk factors. Hepatitis C virus appears to be unimportant as a cause of liver cancer in Thailand. The level of albumin-bound aflatoxin in serum was no different in cases of liver cancer (hepatocellular or cholangiocarcinoma) from that in control subjects.

### 1.3.6 Laryngeal and pharyngeal cancer

#### 1.3.6.1 *Geographical variations in laryngeal cancer*

(J. Nectoux and D.M. Parkin; in collaboration with D.J. Jussawalla, Bombay, India; A.P. Mirra, São Paulo, Brazil; P. Schaffer, Strasbourg, France; and S. Schraub, Besançon, France)

Data submitted for *Cancer Incidence in Five Continents* have shown interesting geographic differences in the sub-site distribution of cancers of the larynx and hypopharynx. Geographic

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[67] Srivatanakul, P., Parkin, D.M., Jiang, Y.-Z., Khlat, M., Kao-Ian, U., Sontipong, S. & Wild, C.P. (1991) *Cancer* (in press)

[68] Srivatanakul, P., Ohshima, H., Khlat, M., Parkin, M., Sukarayodhin, S., Brouet, I. & Bartsch, H. (1990) In: O'Neill, I.K., Chen, J. & Bartsch, H., eds, *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105) Lyon, International Agency for Research on Cancer, pp. 88–95

[69] Srivatanakul, P., Ohshima, H., Khlat, M., Parkin, M., Sukaryodhin, S., Brouet, I. & Bartsch, H. (1991) *Int. J. Cancer* (in press)

[70] Parkin, D.M., Srivatanakul, P., Khlat, M., Chenvidhya, D., Chotiwan, P., Insiripong, S., L'Abbé, K.A. & Wild, C.P. (1991) *Int. J. Cancer*, **48**, 323–328

[71] Srivatanakul, P., Parkin, D.M., Khlat, M., Chenvidhya, D., Chotiwan, P., Insiripong, S., L'Abbé, K.A. & Wild, C.P. (1991) *Int. J. Cancer*, **48**, 329–332

correlation between incidence rates of glottic, supraglottic and pyriform sinus cancers, the incidence of other cancers related to tobacco and alcohol, and data on per capita consumption of tobacco and alcohol have suggested that the patterns of incidence are the best explained by alcohol intake[72].

A more detailed study of the descriptive epidemiology of these cancers is being carried out with four cancer registries which have submitted data for the main sub-sites of laryngeal and hypopharyngeal cancers, where the point of origin of each case is recorded.

### 1.3.7 Lung cancer

By far the greatest fraction of lung cancer in humans is due to tobacco smoking. The degree to which environmental tobacco smoke is responsible for the disease in non-smokers remains to be established, and a major epidemiological study of the question is in progress (section 1.2.3.1). Biochemical studies of the constituents of tobacco smoke are reported in section 1.2.3, and inter-individual differences in metabolism of such compounds, due at least in part to genetic effects, that lead to high susceptibility to lung cancer, are being intensively explored (section 1.6.3). Repair of DNA damage in smokers' and non-smokers' lung tissue and blood cells is also being studied (section 1.7.4.1).

Epidemiological investigations of various proposed occupational lung carcinogens have continued, in relation to exposures in gold mining, the man-made mineral fibre industry, slate quarrying, and the paper and pulp, lead and steel industries (sections 1.2.1 and 1.2.2).

#### 1.3.7.1 *Indoor air pollution and lung cancer in Guangzhou, China*

(A. J. Sasco and E. Riboli; in collaboration with M.X. Hu and L. Qing, Guangzhou, China)

A case–control study of lung cancer has been conducted in Guangzhou, China. In addition to active and passive smoking, the study evaluated the influence of the indoor environment. Exposure to cooking fumes was associated with an increased risk of lung cancer. Detailed analysis of several variables describing house and kitchen ventilation showed a decreasing trend in lung cancer risk with improved ventilation[73].

### 1.3.8 Malignant melanoma

#### 1.3.8.1 *Diagnostic criteria*

(C.S. Muir, J. Nectoux, G.J. Macfarlane and P. Maisonneuve; in collaboration with H. Bharucha, Belfast, UK; J. Briggs and R. Philipps, Bristol, UK; R.A. Cooke and J.H. Little, Brisbane, Australia; A.G. Dempster, Dunedin, New Zealand; W.B. Essex, P. Ironside and K. Schafler, Melbourne, Australia; P.A. Hofer, Umeå, Sweden; A.F. Hood and R.S. Pfau, Baltimore, MD, USA; T.E. Larsen, Oslo, Norway; M. Prade, Villejuif, France; K.M. Pozharisski, Leningrad, USSR; F. Rilke, Milan, Italy; and E.P. van der Esch, Amsterdam, Netherlands)

The results of this study, which suggest that changes in criteria for classifying naevi as malignant have contributed little to the increasing incidence, have now been published[74].

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[72] Nectoux, J. & Parkin, D.M. (1990) *Bull. Cancer*, **77**, 137–146

[73] Liu, Q., Sasco, A.J., Riboli, E. & Hu, M.X. (1991) (submitted for publication)

[74] Van der Esch, E.P., Muir, C.S., Nectoux, J., MacFarlane, G., Maisonneuve, P., Bharucha, H., Briggs, J., Cooke, R.A., Dempster, A.G., Essex, W.B., Hofer, P.A., Hood, A.F., Ironside, P., Larsen, T.E., Little, J.H., Philipps, R., Pfau, R.S., Prade, M., Pozharisski, K.M., Rilke, F. & Schafler, K. (1991) *Int. J. Cancer*, **47**, 483–490

#### 1.3.8.2 *Etiological factors of plantar melanoma in Paraguay*

(D.M. Parkin and M. Khlat; in collaboration with P.A. Rolón, Asunción, Paraguay)

Data collection in this study has continued throughout 1990 and the target of 50 cases and 200 controls was achieved during 1991. The use of shoes, history of trauma, thermal injury, and presence of plantar naevi have been recorded for all subjects, as well as the history of exposure to UV light (important in cutaneous melanoma in European populations). Analysis will start during 1991.

### 1.3.9 Breast cancer

Breast cancer etiology is still an area of much uncertainty, and is being explored in a multinational project within the SEARCH programme (section 1.3.1.4). Nutritional factors thought to be involved are being considered both in this project and in others reported in section 1.5. Since breast cancer has been observed to have a familial component, the genetic study of the disease has been actively pursued and a gene that appears to be responsible has been localized on chromosome 17 (see section 1.6.1.3).

#### 1.3.9.1 *Breast cancer and reproductive and endocrine factors in premenopausal Chinese women*

(A.J. Sasco, E. Riboli and R. Saracci; in collaboration with M.X. Hu and L. Qing, Guangzhou, China)

The aim of this study is to evaluate the relationship between hormonal profiles and breast cancer incidence in women. The hormonal hypothesis for breast cancer etiology would provide a coherent explanation of epidemiological associations with various reproductive factors as well as with other hormone-dependent cancers, such as cancer of the ovary, endometrium and colon.

The study is using a case–control approach. Incident cases, all of them pre-menopausal, have been pair-matched to control women on the basis of age and residence. Women taking contraceptive pills or any other hormonal treatment, reserpine or tranquillizers were excluded, as well as women having or having had in the preceding twelve months a pregnancy (whether carried to full term or ending in a spontaneous or induced abortion), women having lactated in the preceding six months and women having documented hormonal disease, gynaecological conditions or chronic debilitating conditions.

A detailed questionnaire, administered to cases and controls, covered the following items: personal identification data, details of diagnosis, reproductive and contraceptive life history, personal history of diseases, family history of cancer, diet history and other factors. Saliva and blood specimens were collected between days 20 and 24 of the menstrual cycle.

Enrolment of cases and controls started in late 1987 in Guangzhou. Due to very restrictive inclusion criteria, recruitment of study subjects has progressed slowly and was only completed in late 1989. Preliminary results of analysis of the questionnaire data show a positive association of breast cancer with late age at first full-term birth, early age at menarche, university education and some aspects of diet. Analysis of the biological samples and further statistical analysis will be carried out in 1992.

#### 1.3.9.2 *European case–control study of male breast cancer*

(A.J. Sasco and R. Saracci; in collaboration with F. Berrino and P. Muti, Milan, Italy; M. Delendi, Udine, Italy; and A.B. Lowenfels, Valhalla, NY, USA)

In view of the rarity of male breast cancer and the exploratory nature of the present study, which is aimed at testing several hypotheses regarding the etiology of the disease, an

international case–control approach has been chosen. The study will evaluate the role of reproductive life, personal history of diseases and drug use, family history of cancer, tobacco and alcohol consumption, nutritional habits, body build and hepatic function. Evaluation of the etiological role of hormones is of particular interest.

A literature review on male breast cancer is being prepared and the protocol for the study is now being finalized.

Several case–control groups will be assembled in participating centres (Czechoslovakia, France, Greece, Italy, the Netherlands, Yugoslavia). The aim is to enrol about 200 incident breast cancer cases over a two-year period, and three age-matched controls per case. Data will be obtained by questionnaire and blood samples will be collected.

### 1.3.9.3 *Survey of breast cancer in the Département du Rhône*

(A.J. Sasco; in collaboration with B. Fontanière, J. Fabry and V. Sciortino, Lyon, France)

No population cancer registry exists for the Département du Rhône. To evaluate the descriptive epidemiology of breast cancer in this region, a comprehensive survey of all treatment institutions, anatomopathological laboratories and social security claims has been conducted. This led to the identification of 791 female and 10 male incident breast cancer cases in the resident population of the Rhône in 1985. The incidence of breast cancer is elevated (standardized incidence rate of 80.29 cases per 100 000 woman-years), higher than in some other French departments for which information is available, but similar to the incidence in Geneva. Most tumours were diagnosed at a rather advanced stage and in 1985 only 3% of the cancers were found as a result of mammographic screening.

An interesting feature of this study is the description of the pattern of care for breast cancer and the demonstration of the scattering of patients over a wide range of public and private treatment institutions[75].

### 1.3.9.4 *Descriptive epidemiology of breast cancer*

(D.M. Parkin and J. Nectoux)

In most countries breast cancer incidence and mortality rates have been increasing. Changes have been most marked in regions where westernization of lifestyle has been most marked, such as Latin America, Singapore and the Philippines. Changes in incidence are greater than those in mortality, possibly due to programmes of early detection and more effective therapy. Correlation studies have been used to examine the importance, at the population level, of diet (per capita consumption of fat) and patterns of childbearing (fertility rates, age of first birth). Dietary differences can account for variation in post-menopausal rates internationally, while fertility appears to be an important determinant of variation within countries in the pre-menopausal age group[76,77].

The descriptive epidemiology of male breast cancer is also being studied. In contrast with female breast cancer, no temporal increase in incidence is evident. Correlations with other cancer sites that may have etiological factors in common (e.g., colon, prostate), as well as with per capita intake of dietary items are under study.

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[75] Sasco, A.J., Fontanière, B., Charbaut-Lagarde, M.O., Kliebsch, U., Hamandjian, P., Cornu-Lugrin, A.E., Schnebelen, J.P., Sciortino, V. & Fabry, J. (1991) (submitted for publication)

[76] Parkin, D.M. & Nectoux, J. (1991) In: Stoll, B.A., ed., *Approaches to Breast Cancer Prevention*, Dordrecht, Kluwer, pp. 15–53

[77] Parkin, D.M. (1989) *Eur. J. Cancer Clin. Oncol.*, **25**, 1917–1925

## 1.3.10 Cervical cancer

### 1.3.10.1 *Sexual behaviour and human papillomavirus in high- and low-risk areas for cervical cancer*

(N. Muñoz, F.X. Bosch, S. de Sanjosé, N. Charnay, D. Magnin and S. Teuchmann; in collaboration with P. Alonso de Ruiz, Mexico City, Mexico; N. Aristizabal and L. Tafur, Cali, Colombia; N. Ascunce, Pamplona, Spain; M. Gili, Seville, Spain; L.C. Gonzalez, Salamanca, Spain; E. Guerrero and K. Shah, Baltimore, MD, USA; I. Izarzugaza, Vitoria, Spain; I. Lind, Copenhagen, Denmark; P. Moreo, Zaragoza, Spain; C. Navarro, Murcia, Spain; J. Orfila, Amiens, France; M. Santamaria, Pamplona, Spain; P. Viladiu, Gerona, Spain; and B. Wahren, Stockholm, Sweden)

This case–control study was designed to evaluate risk factors for cervical neoplasia (invasive cancer and cervical intraepithelial neoplasia, CIN III) in Colombia and Spain, two countries with extreme incidence rates of cervical cancer (age-adjusted annual incidence rates are 50 per 100 000 in Cali, Colombia, and less than 5 per 100 000 in Spain). All incident cases of cervical neoplasia occurring in pre-defined populations were identified and invited to participate before any treatment. Controls for invasive cancers were a representative sample of the residents in the province or city and controls for CIN III cases were individually matched to the cases by age and centre. The latter were recruited among women participating in screening programmes or submitting a cytological specimen to the same laboratory where each case was identified and showing no signs of cervical neoplasia. Husbands of cases and controls were also invited to participate. The total number of subjects interviewed was close to 3000 (918 cases, 912 controls and 1073 husbands of cases and controls).

Exposure to common sexually transmitted agents has been assessed by serological assays for herpes simplex virus types 1 and 2 (HSV 1, 2), hepatitis B virus (HBV) and cytomegalovirus (CMV) (Dr B. Wahren, Stockholm), for *Chlamydia* (Dr J. Orfila, Amiens) and for syphilis and gonorrhoea (Dr I. Lind, Copenhagen).

An important component of the study is the evaluation of the role of various types of human papillomavirus (HPV) as determined by hybridization tests on DNA material obtained from exfoliated cells from the cervix uteri and from the penis. Three different assays have been used, the commercially available Virapap™, Southern blot and hybridization following HPV DNA amplification using the polymerase chain reaction (PCR) technique.

Levels of vitamin A, $\beta$-carotene and vitamin E are being measured in a subsample of the specimens.

Data analysis indicated that early age at first sexual intercourse or at first birth, high number of sexual partners, low level of education and practice of prostitution were the main risk factors in women. The husbands' high number of lifetime sexual partners and contacts with prostitutes were risk factors in Spain but not in Colombia. The results shown in Table 9 clearly demonstrate a strong statistical association between detection of HPV DNA and invasive cervical cancer. The table also shows that the estimates of the relative risk are highly dependent on the method used to detect the viral DNA. Detailed analyses are being conducted to estimate the relative validity of each of the techniques used and to make recommendations for future studies.

Type-specific analysis indicated that HPV-16 was the predominant HPV type in both countries. For cases of carcinoma *in-situ* and controls, only the ViraPap analysis has been completed, showing an $RR_a$ of 27.2 (9.7–76.1) in Spain and 73.8 (10.1–539.0) in Colombia. For other STDs, significantly increased risks were observed for invasive cancers in Spain and CIN

**Table 9. Relative risks for cervical cancer associated with presence of HPV as detected by various methods**

| | Adjusted relative risk[a] (95% confidence interval) | | |
|---|---|---|---|
| | ViraPap test | Southern blot | PCR |
| Spain | 26.2 (9.3–73.5) | 10.1 (4.3–23.6) | 45.3 (17.9–114.8) |
| Colombia | 77.5 (10.6–568) | 10.4 (3.8–28.6) | 14.6 (6.4–33.2) |

[a]Adjusted for age, centre and number of sexual partners

lesions in Colombia in those positive for HSV-2 antibodies. Seropositivity for *Chlamydia* was associated with an increased risk for *in-situ* cancer lesions in both countries and seropositivity for *Neisseria gonorrhoeae* with an increased risk for invasive cancer in Spain only.

1.3.10.2 *Prevalence survey of CIN lesions among prostitutes from Spain and Colombia*
(S. de Sanjosé, N. Muñoz and F.X. Bosch; in collaboration with N. Aristizabal and L. Tafur, Cali, Colombia; V. Palacio and S. Vazquez, Oviedo, Spain)

The primary purpose of this survey is to assess and compare the prevalences of CIN lesions in prostitutes from areas of high and low risk for cervical cancer. Secondarily, prostitutes will be investigated as a potential reservoir of the viral infections associated with cervical cancer.

In Cali (Colombia), 363 women reported themselves as prostitutes and 1904 non-prostitutes who participated in screening programmes during 1988–89 were identified. In addition, 603 women (mostly non-prostitutes) attending other screening programmes were identified and the results of their first recorded Pap smears were reviewed.

In Oviedo (Spain), information on the results of Pap smears of 758 prostitutes attending a dermatology and sexually transmitted disease clinic during the period 1985–90 were extracted from medical records. Data on 1203 women attending a family planning clinic at the same hospital for the first time were also reviewed.

Unexpectedly, the prevalence rates of CIN among prostitutes in Spain were 50% higher than those observed among prostitutes in Cali (2.5% versus 1.6%, $p > 0.05$). In Spain, the prevalence of CIN lesions increased from 2.2% for women having practised prostitution for less than six years to 4.4% for those having practised for longer. The prevalence of CIN lesions among non-prostitutes was also higher in Spain (1.2%) as compared to Cali (0.8%).

The risk of having a CIN lesion was about twice as high among prostitutes as among non-prostitutes, irrespective of the country (in Spain age-adjusted relative risk = 2.1 (95% CI 1.7–4.3), in Cali relative risk = 1.9 (95% CI 0.6–2.2)).

1.3.10.3 *International biological study on cervical cancer (IBSCC)F*
(F.X. Bosch, N. Muñoz, N. Charnay and D. Magnin; in collaboration with E. Alihonou, Cotonou, Bénin; Th. M. Barry, Conakry, Guinea; S. Bayo, Bamako, Mali; H. Cherif Mokhtar, Sétif, Algeria; R. Crespo de Britton, Panama; A. Daudt, Pelotas, Brazil; P. Gauthier and P. Ghadirian, Montreal, Canada; J.N. Kitinya, Dar es Salaam, Tanzania; M.O.A. Malik, Khartoum, Sudan; J. Peto, London, UK; Ll.M. Puig Tintoré, Barcelona, Spain; J.L. Rios-Dalenz, La Paz, Bolivia;

P.A. Rolón, Asunción, Paraguay; L. Tafur, Cali, Colombia; A.R. Teyssie, Buenos Aires, Argentina; M. Torroella, Habana, Cuba; A. Vila Tapia, Concepción, Chile; H.R. Wabinga, Kampala, Uganda; and W. Zatonski, Warsaw, Poland)

The purpose of the International Biological Study on Cervical Cancer (IBSCC) is to assess at the international level the variation in the prevalence of type-specific markers of HPV in specimens of cervical cancer. For this purpose a repository of cervical cancer tissue and of sera from cervical cancer patients has been created. Over 700 samples of invasive cervical cancer have already been collected in 15 countries with varying incidence rates of cervical cancer and collection is continuing in another five. DNA hybridization methods will be used to assess the prevalence of specific types of HPV, all assays being performed in the same reference laboratory. Serological assays will be performed to assess exposure to common sexually transmitted agents and a brief questionnaire is used to assess subjects' exposure to other known risk factors for cervical cancer.

Data and specimen collection started in 1989 and should be complete by the end of 1991. Laboratory work will be initiated in 1992.

#### 1.3.10.4 *Multicentre case–control studies on cervical cancer*

(F.X. Bosch, N. Muñoz, S. de Sanjosé, D. Magnin and N. Charnay; in collaboration with S. Bayo, Bamako, Mali; N. Chaouki, Rabat, Morocco; Saibua Chichareon, Hat Yai, Thailand; J. Eluf-Neto, São Paulo, Brazil; C. Ngelangel, Manila, Philippines; P.A. Rolón, Asunción, Paraguay; and K. Shah, Baltimore, MD, USA)

This multicentre study aims at exploring risk factors for cervical cancer in areas of the world where the incidence of the disease is high and in which very few studies have been completed so far. Particular attention is devoted to aspects of sexual behaviour or practices for which the epidemiological evidence is limited or contradictory. These include the role of the male as a vector of the relevant sexually transmitted agent(s), the implications of the practice of prostitution and the effects of practices such as polygamy. The most recent techniques to detect the presence of HPV DNA and other markers of sexually transmitted diseases will be used. The studies were initiated in 1990–1991 and are at different stages of implementation in the various countries. Data collection has been completed in Brazil and included 200 cases of invasive cervical cancer and 203 controls. In Thailand 62 cases and 24 controls had been interviewed up to April 1991. In the Philippines 42 cases and 21 controls have been recruited, in Mali data collection started in February 1991 and in Morocco the study was initiated in May 1991.

### 1.3.11 Thyroid cancer

(M.P. Coleman; in collaboration with B. Pettersson and H.-O. Adami, Uppsala, Sweden; and E. Schifflers, Namur, Belgium)

Analyses of trends in the incidence of the different histological types of thyroid cancer have been published[78] for Sweden for the period 1958–81. The mean annual increase over this period for all thyroid cancer was 1.9% for women and 1.2% for men, but the variation by histological type was marked: 4.9% and 2.1% for papillary, 0.9% and 2.1% for follicular and −1.0% and −2.1% for anaplastic carcinoma. The age-cohort models from which these trends were obtained

[78] Pettersson, B., Adami, H.-O., Wilander, E. & Coleman, M.P. (1991) *Int. J. Cancer*, **48**, 28–33

suggest that rates of papillary cancer have been increasing for those born since 1919, and for follicular cancer for those born since 1939, while anaplastic cancer has declined for those born since 1924. A report of analyses of regional variation in incidence in relation to iodine consumption is in preparation.

### 1.3.12 Leukaemia

(P. Roy and M.P. Coleman)

A review of the etiology of adult acute lymphoblastic leukaemia (ALL) has been prepared[79]. It has been estimated from French cancer registry data that some 600 cases of ALL a year could be expected in France.

Leukaemia etiology is a subject of research in the SEARCH programme (section 1.3.1.5) and in the programme on effects of electromagnetic and ionizing radiation (section 1.2.5).

## 1.4 *Childhood Cancer*

Childhood cancer is of particular interest in that cancers usually have long induction times, and their occurrence in children suggests that a genetic lesion may have been inherited from a parent. In addition to the descriptive study detailed below, IARC projects are examining the etiology of childhood leukaemia and brain tumours by a case–control approach within the SEARCH programme (section 1.3.1) and attempting to estimate the fraction of cases of childhood cancer that are due to inherited mutations (section 1.6.1.4).

### 1.4.1 Descriptive epidemiology of childhood cancer

(D.M. Parkin and J. Ferlay; in collaboration with G.J. Draper and C. Stiller, Oxford, UK)

The large data-base collected for the study of the international incidence of childhood cancer[80] is being used to produce more detailed analyses of geographic and ethnic differences of the common childhood cancers.

The results of these analyses for lymphoma[81] and renal tumours[82] have been published, and analyses for neuroblastoma, retinoblastoma, bone tumours and liver tumours are under way.

The age-distribution of Hodkgin's disease in childhood appears to be related to levels of socio-economic development but the total incidence seems to be determined more by ethnic and environmental factors (Figure 8). The highest incidence of Burkitt's lymphoma occurred in tropical Africa and Papua New Guinea. Elsewhere, Burkitt's lymphoma was rare, though the incidence was higher in Spain, North Africa and the Middle East than in other areas. There was no consistent pattern in the incidence of other non-Hodgkin lymphomas except for a tendency towards higher rates around the Mediterranean and in some Latin American registries.

As regards renal tumours, Wilms' tumour is sometimes considered to be an "index cancer of childhood" but in fact there is at least threefold difference in incidence between the age-standardized annual rates of over 10 per million in the Black populations in the United States and Nigeria and those of around three per million in several East Asian populations. This variation along ethnic rather than geographical lines suggests that genetic predisposition is important in its etiology.

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[79] Roy, P. & Coleman, M.P. (1991) (submitted)

[80] *IARC Biennial Report 1988/89*, p. 9

[81] Stiller, C.A. & Parkin, D.M. (1990) *Paediat. Perinatal Epidemiol.*, **4**, 303–324

[82] Stiller, C.A. & Parkin, D.M. (1990) *Br. J. Cancer*, **62**, 1026–1030

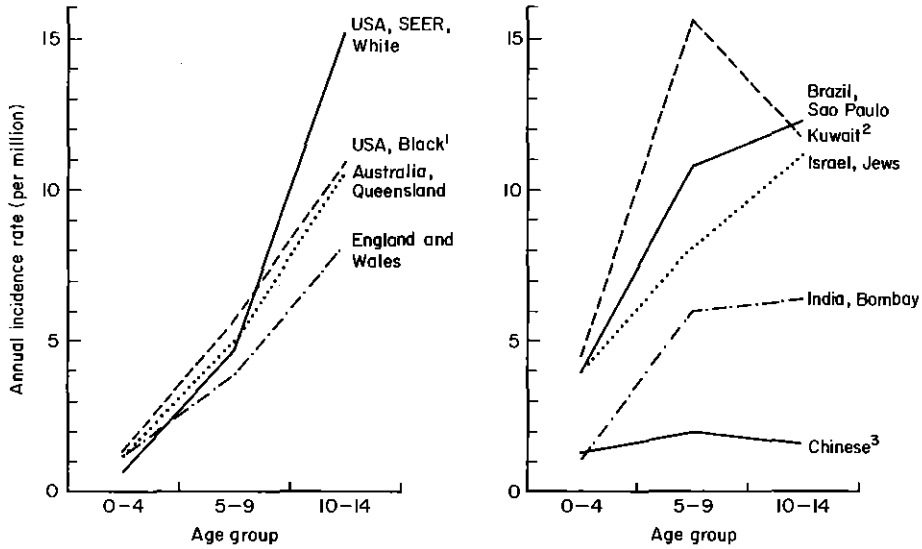


**Fig. 8. Incidence of Hodgkin's disease in childhood by five-year age group (from Stiller & Parkin, 1990[81])**

*[1]Los Angeles, New York and SEER data combined; [2]Kuwaiti and non-Kuwaiti combined; [3]Shanghai, Taipei, Hong Kong and Singapore data combined.*

## 1.5 *Nutrition and Cancer*

An increasing range of epidemiological studies demonstrate influences of dietary factors, either causative or protective, on various cancers. However the complex variety of components in human diets and the difficulty of obtaining precise information on consumption over the periods involved in cancer induction make convincing evidence of specific associations difficult to obtain. Many of the research projects at IARC now include consideration of possible dietary effects. Those studies specifically aimed at analysing such effects are described in this section. Other projects that are providing valuable relevant information are described in section 1.3.1 on the SEARCH programme, in relation to pancreas, brain, breast and colorectal cancers, and in sections 1.3.4 and 1.3.9 on stomach and breast cancers respectively. The effects of drinks such as alcoholic beverages and mate in the etiology of oesophageal cancer are being examined (section 1.3.3). Mycotoxins are common food contaminants in certain areas of the world that are believed to have a role in inducing liver and kidney tumours (sections 1.7.2 and 1.2.7 respectively). Methods for studying endogenously formed carcinogens in the gastrointestinal tract by the use of microcapsules are being developed (section 3.3.5).

### 1.5.1 Prospective studies on nutrition and cancer

(E. Riboli, R. Saracci, R. Kaaks, N. Slimani, C. Casagrande and B. Hémon)

The general objective of the programme of prospective studies on nutrition and cancer is to investigate the relation between diet, nutritional status, diet-related biochemical indicators and risk for cancer at several sties. The rationale of conducting large prospective cohort studies on diet-related factors and cancer is based on several considerations:

(1) The prospective approach provides an opportunity to overcome some of the main weaknesses of retrospective studies, because (*a*) measurements of individual diet (focused on current diet rather than on past diet) are much more reliable and repeated measurements (say every three or four years) allow changes in individual diet to be monitored, and (*b*) dietary information collected in healthy subjects who are followed up prospectively is not affected by biases due to differential recall between cases and controls.

(2) Biological samples can be stored at very low temperatures and analysed at a later stage for only those subjects who eventually develop cancer and a suitable group of matched controls without cancer. Measurements done on samples collected years before the onset of cancer have the advantage of not being affected by the pathological consequences of the disease, as may be the case for samples collected from cancer patients.

(3) The prospective approach can provide data on several cancers, on total cancer incidence and mortality, and on total (all causes) mortality. This information is crucial for deciding on public health interventions on diet, as it can indicate not only whether a given component of diet is related to a decreased or increased risk of one particular disease, but also whether it is related to longer or shorter life expectancy.

The main practical disadvantages of prospective studies compared to the case–control approach are (*a*) the need for very large numbers of subjects, and (*b*) the long time period required before results are obtained. The solution to these two problems that has been adopted is to set up a network of collaborative projects in different countries so as to provide a large enough study size and to yield meaningful results in a shorter time. An added advantage of this approach is the possibility of making comparisons between countries.

Table 10. Summary of recruitment for the European Prospective Study on Nutrition, Cancer and Health

| Country | Geographical area | Target population | No. of subjects | Sex | Age |
|---|---|---|---|---|---|
| France | Nationwide | Mainly teachers, members of health insurance plan | 70 000[a] | F | 40–65 |
| Italy | North (Turin, Varese) | Blood donors and breast | 25 000 | M | 40–65 |
| | Centre (Florence) South (Ragusa) | cancer screening | 35 000[b] | F | 35–65 |
| Spain | North (Asturias, Basque Country, Navarra) | Blood donors and civil servants | 30 000 | M | 40–65 |
| | South-east (Murcia, Granada) | | 20 000 | F | 35–65 |
| UK | Nationwide and Cambridge region | General population and breast cancer screening | 35 000 | M | 40–65 |
| | | | 45 000 | F | 35–65 |
| Greece | Nationwide | Teachers | 25 000 | M | 35–60 |
| | | | 25 000 | F | 35–60 |
| Germany | Nationwide | National health insurance | 25 000 | M | 35–60 |
| | | | 25 000 | F | 30–60 |
| Netherlands | Regional | General population and breast cancer screening | 20 000[c] | M | 40–60 |
| | | | 30 000 | F | 50–69 |

[a]100 000 subjects already answered a first mailed questionnaire and will receive a dietary questionnaire next year. Compliance of 70% is expected

[b]10 000 of the 35 000 women were already enrolled during 1988–90 in a prospective study on hormones and diet, conducted in Varese province by Dr F. Berrino and his colleagues, which will be merged into the European project

[c]Extension of an on-going cohort study on monitoring of risk factors in which about 20 000 men and women have already been enrolled

The project of European Prospective Studies on Nutrition, Cancer and Health was started in 1988 with the support of the "Europe Against Cancer Programme" combined with national and IARC resources, and it initially involved researchers from four countries (France, Italy, Spain and the UK). Studies on the validity of dietary questionnaires and pilot field tests had already begun in these four countries, when researchers from three additional countries (Germany, Greece and the Netherlands) joined the project in 1990. The general features of the projects are summarized in Table 10.

It is planned to include 50 000 to 70 000 subjects per country and to collect data from each subject on reproductive history, oral contraceptives, hormone replacement therapy, physical activity, tobacco smoking, brief occupational history, previous illnesses and anthropometry. In addition, blood samples will be collected. For security, the samples from each subject will be split in two, half being stored locally and half at IARC. Storage will be in large liquid nitrogen containers.

Table 11 provides estimates of the numbers of cancer cases which are expected to occur in the four countries where data collection is planned to start in 1992. The total number of expected cases, which is already large, will be increased by about 60% once the project is extended to Greece, Germany and the Netherlands.

In view of the possibility of later carrying out valid comparisons and combinations with results from other studies, cooperation is maintained with prospective studies in Denmark and in Sweden.

The development of the EEC-supported project was in fact preceded by the direct involvement of IARC in the methodological phase and the planning of a project in the Swedish town of Malmö. In 1991 this project reached the phase of starting data collection from 40 000 subjects.

### *Methodological pilot phase of the European project*

The methodological pilot studies have been designed with three main aims:

(1) To study the validity of questionnaires prepared for use in the prospective studies with a reference method of proven validity. The reference methods were the 24-h weighed diet record

Table 11. Expected numbers of cancer cases[a] computed on the assumption that recruitment will be spread over two to four years and follow-up will be ten years on average (8–12 years depending on cohort and year of enrolment)

| Cancer site | Women | | | | Men | | | Total |
|---|---|---|---|---|---|---|---|---|
| | France 70 000 | Italy 35 000 | Spain 20 000 | UK 40 000 | Italy 25 000 | Spain 30 000 | UK 40 000 | 260 000 |
| Stomach | 220 | 120 | 130 | 110 | 290 | 280 | 130 | 1280 |
| Colon | 320 | 130 | 50 | 190 | 120 | 60 | 200 | 1070 |
| Rectum | 110 | 50 | 40 | 80 | 110 | 70 | 160 | 620 |
| Breast (women) | 1030 | 490 | 400 | 690 | — | — | — | 2610 |
| Lung | 460 | 130 | 60 | 490 | 510 | 310 | 830 | 2790 |
| Larynx | 80 | 40 | 20 | 20 | 170 | 170 | 110 | 610 |
| Bladder | 120 | 60 | 10 | 70 | 180 | 100 | 310 | 850 |
| Prostate | — | — | — | — | 130 | 70 | 260 | 460 |
| Endometrium | 210 | 100 | 80 | 130 | — | — | — | 520 |

[a]Figures are rounded to the nearest ten

repeated for four days once every three months during one year (in the UK) and the 24-h diet recall repeated one day a month for one year (in Spain, France, Italy and Greece).

(2) To compare questionnaire data with biochemical markers of diet measured in urine and blood samples collected during the study period. In particular, the average excretion of urinary nitrogen measured in four to eight 24-h urine collections was used to evaluate protein intake estimated by the reference method and by dietary questionnaires. In addition, average levels of vitamins C, E and carotenoids were used to validate vitamin intake estimated by questionnaires.

(3) To evaluate the logistic aspects of the project, response rate from invited subjects, acceptability of the questionnaires and procedures for collecting biological specimens.

At each centre the pilot study included 100–150 subjects for a total of about 650 subjects in the four countries, similar for age and gender to the subjects whom we expect to enrol in the main project.

Preliminary results on the concordance between the reference method and tested questionnaire in estimating intake of some main foods groups are reported in Table 12. Overall there are fairly good correlations between the two methods, suggesting that the questionnaires designed for the study are generally well adapted to local foods and dietary habits. Modifications of some sections of the questionnaire for which the results were not as good as expected (e.g., fruits and cheese in Italy, legumes in France, etc.) are being considered, and the revised versions will be retested by the end of 1991.

#### 1.5.1.1 *France*

(in collaboration with N. Andrieu, A. Auquier, F. Clavel, H. Goulard and S. Villeminot, Villejuif)

The Mutuelle Générale de l'Enseignement Nationale, a private health insurance scheme for employees of the Department of Education (mainly teachers), has about 500 000 members in the age range 40–65. A baseline questionnaire on reproductive history, height, weight, etc. was mailed to all female participants in June 1990, and almost 100 000 (residing all over France) returned it, agreed to cooperate and gave permission for access to their medical data.

A questionnaire on diet will be mailed in 1992 to these women. Blood samples and anthropometric measurements will be collected either directly (from women living in large metropolitan areas) or by asking the subjects to have the blood measurements taken locally by a doctor or nurse.

#### 1.5.1.2 *Italy*

(in collaboration with F. Berrino and P. Pisani, Milan; E. Buiatti and D. Palli, Florence; F. Faggiano and P. Vineis, Turin; L. Gafà and R. Tumino, Ragusa)

The study will be based in four regions: two in the north (Turin and Varese), one in the centre (Florence) and one in the south (Ragusa in Sicily). The study will enrol 27 000 women among those attending a breast cancer screening programme in Varese and Florence, and 8000 women and 25 000 men among regular blood donors, members of the two national associations of blood donors in Turin, Florence and Ragusa.

In Varese, 10 000 women of these 27 000 have already been enrolled in a prospective cohort study on hormones and diet (ORDET) started by Dr Berrino and his colleagues. Data on diet, reproductive history, contraception, anthropometry, blood pressure, pulse rate and samples of blood and urine have already been collected. This study has provided very valuable scientific and practical experience for the design and planning of the present project.

An invitation to join the project will be sent to subjects who either attended breast cancer screening or donated blood. Information will be collected mainly through self-administered

Table 12. Correlation coefficients found between dietary questionnaires under evaluation and the reference method

(*a*) United Kingdom

| Nutrient | 7-day diary | Single 24-h recall | Food frequency questionnaire |
|---|---|---|---|
| Energy | 0.54 | 0.36 | 0.41 |
| Protein | 0.44 | 0.12 | 0.20 |
| Fat | 0.52 | 0.28 | 0.32 |
| Carbohydrate | 0.67 | 0.60 | 0.46 |
| Sugars | 0.73 | 0.69 | 0.44 |
| Fibre/non-starch polysaccharides | 0.73 | 0.56 | 0.52 |
| Vitamin C | 0.61 | 0.48 | 0.38 |
| Carotene | 0.45 | 0.38 | 0.42 |

(*b*) France, Italy and Spain

| Food group | France | Italy | Spain |
|---|---|---|---|
| Potatoes | 0.38 | 0.39 | 0.56 |
| Vegetables | 0.48 | 0.31 | 0.47 |
| Legumes | 0.17 | 0.46 | 0.58 |
| Fruits | 0.55 | 0.33 | 0.67 |
| Dairy products | 0.53 | 0.58 | 0.66 |
| Cheese | 0.59 | 0.55 | 0.43 |
| Cereals | 0.38 | 0.29 | 0.51 |
| Bread | 0.59 | 0.30 | 0.66 |
| Meat | 0.35 | 0.39 | 0.67 |
| Fish | 0.17 | 0.41 | 0.61 |
| Eggs | 0.40 | 0.32 | 0.60 |
| Sugar | 0.51 | 0.75 | 0.66 |
| Cakes and pastry | 0.37 | 0.44 | 0.43 |
| Soft drinks | 0.46 | 0.27 | 0.84 |
| Alcoholic beverages | 0.67 | 0.89 | 0.88 |
| Coffee | 0.69 | 0.41 | 0.46 |
| Tea and herbal teas | 0.74 | 0.62 | |

questionnaires in the north and the centre, while subject interview is planned in Sicily. On the basis of the pilot study results, very high compliance is expected from blood donors (around 90%) and women attending breast cancer screening (70%).

### 1.5.1.3 *Spain*

(in collaboration with M.L. Carcedo and J.R. Quíros, Oviedo; A. Del Moral, Pamplona; M. Domonsoro, I. Izarzugaza and N. Larrañage, San Sebastian; N. Fariol, C.A. González and M. Torrent, Mataró; G. López-Abente, Madrid; C. Martinez, Granada; I. Moreno, C. Navarro, P. Parra and M.-J. Tormo, Murcia)

The study is coordinated by the Unit of Epidemiology of the Hospital of Mataró (in the Barcelona Metropolitan area) and will be based in five regions of Spain: Asturias, Basque Country, Navarra, Murcia and Granada. It is planned to include in the study about 40 000 to

45 000 blood donors and 5000 to 10 000 civil servants, making a total of about 50 000 subjects.

Subjects will be invited by letter and personally contacted when donating blood. Part of the information will be collected by self-administered questionnaire. An appointment will be made to collect blood samples and anthropometric measurements.

#### 1.5.1.4 *United Kingdom*

(in collaboration with S. Bingham, N.E. Day and K.-T. Khaw, Cambridge; and D. Forman and T.J.A. Key, Oxford)

This study will combine two complementary approaches planned by the Imperial Cancer Research Fund Epidemiology Unit in Oxford and the Medical Research Council Biostatistics Unit and the University Department of Community Medicine in Cambridge.

The Cambridge component aims to recruit 10 000 women participating in breast cancer screening as well as 10 000 men and 10 000 women selected in collaboration with local general practitioners (GPs). In the latter group, GPs will be assisted by nurses who will take care of interviewing and blood collection.

The Oxford component will base recruitment on several hundred GPs from all over Britain. Each GP will be asked to recruit subjects from among those agreeing to take part in a national health screening programme for a total of 50 000 subjects. The GP will be asked to provide the subject with a self-administered questionnaire and to collect a blood sample.

#### 1.5.1.5 *Greece*

(in collaboration with K. Katsouyanni, A. Trichopoulou and D. Trichopoulos, Athens)

It is planned to include about 50 000 primary and secondary school teachers, men and women. A national programme of health education for teachers was started with the collaboration of the Department of Nutrition of the University of Athens, and it is planned to nest the recruitment of study subjects in this on-going programme.

#### 1.5.1.6 *The Netherlands*

(in collaboration with H.J.A. Collette and P. Peeters, Utrecht; and H.B. Bueno de Mesquita and D. Kromhout, Utrecht)

The project will be based on two components:

(*a*) A cohort of about 25 000, to be recruited from among women attending a breast cancer screening programme at the Preventicon Centre in Utrecht.

(*b*) A cohort of men and women (about 25 000) to be enrolled from subjects participating in the on-going study on monitoring of risk factors which was started in two areas of the Netherlands by the National Institute of Public Health and Environmental Protection and which will be extended to two or three additional areas.

Collection of data by a combination of interview and self-administered questionnaire and blood samples will be combined with the regular activities in these cohorts.

#### 1.5.1.7 *Germany*

(in collaboration with H. Boeing and J. Wahrendorf, Heidelberg)

The study will be based on members of a general health insurance plan (Allgemeine Ortskrankenkasse, AOK) which is open to the general population. Most AOK members belong to the manual work force, although some are students, unemployed or retired. It is planned to recruit subjects for the cohort in three regions which differ in socio-cultural aspects: (*a*) a medium-sized town, (*b*) a highly industrialized area, and (*c*) a rural area. The study should include 50 000 to 60 000 subjects, about half men and half women.

### 1.5.2 Case–control study on diet and colorectal cancer in Majorca

(F.X. Bosch and N. Muñoz; in collaboration with E. Benito and M. Mulet, Mallorca, Spain; V. Moreno, Barcelona, Spain; A. Obrador, Palma de Mallorca, Spain; and A. Stiggelbout, Amsterdam, Netherlands)

A population-based case–control study on diet and colorectal cancer was conducted in the island of Majorca during the period 1984–1988. The project included 286 cases of colorectal cancer, 295 population controls and 203 hospital controls. A food frequency questionnaire was used and the results by food groups, food items and dietary risk scores have been published[83]. The main findings were a protective effect of cruciferous vegetables for cancers of the colon and rectum, an increased risk associated with fresh meat consumption for colon cancer and increased risk associated with consumption of dairy products for rectal cancer. When colorectal cancer was considered, the consumption of cereals, particularly of white bread and pasta, also significantly increased the risk.

An analysis of the data by nutrients showed an increased risk for total calorie intake and intake of cholesterol and a protective effect linked to the intake of fibre—mostly due to the fibre from legumes (pulses)—and folic acid[84]. Of the main energy-supplying nutrients, the risk seemed more specifically linked to consumption of animal proteins and carbohydrates, whereas no effect was found for consumption of lipids or saturated fats.

### 1.5.3 Case–control study on diet and colorectal polyps in Majorca

(F.X. Bosch and N. Muñoz; in collaboration with E. Benito, E. Cabeza and M. Mulet, Ciutat de Mallorca, Spain; J. Costa, Lausanne, Switzerland; V. Moreno, Barcelona, Spain; and A. Obrador, Palma de Mallorca, Spain)

A case–control study on diet and colorectal polyps was conducted in Majorca between 1988 and 1990. All newly diagnosed cases at the gastroenterology unit of the largest hospital in the island were included and compared to a population-based sample. A food frequency questionnaire previously used in the study on colorectal cancer described above was used. The study group included 101 cases and 242 controls. Data analysis is in progress. Preliminary results indicate that the risk of developing colorectal polyps is related to the consumption of sugar and cakes. Consumption of vegetables and fresh fruits acted as protective factors irrespective of the fibre content of the vegetables. Among non-dietary factors, a strong protective effect was found for physical activity in the workplace (the job that was done for the longest period of time).

As a complement to the above studies, samples of tumour tissue, polypoid tissue and normal mucosa were analysed for allele loss on chromosomes 5 and 17. C-Ki-*ras* and p53 gene mutations were also studied[85]. The p53 gene was not mutated in any of the tissue from polyps but it was mutated in 52% of the cancer samples (13/25). *Ras* mutations were found in 48% of the cancers (11/23) and in six cases both mutations were present. The linkage of these results with data from the dietary questionnaires is in progress.

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[83] Benito, E., Obrador, A., Stiggelbout, A., Bosch, F.X., Mulet, M., Muñoz, N. & Kaldor, J.M. (1990) *Int. J. Cancer*, **45**, 69–76

[84] Benito, E., Stiggelbout, A., Bosch, F.X., Obrador, A., Kaldor, J., Mulet, M. & Muñoz, N. (1991) *Int. J. Cancer* (in press)

[85] Shaw, P., Tandy, S., Costa, J., Benito, E. & Obrador, A. (1991) *Oncogene* (in press)

### 1.5.4 Family studies on diet and colorectal cancer in Majorca

(F.X. Bosch, N. Muñoz, A. Rogatko and J. Estève; in collaboration with E. Benito and M. Mulet, Ciutat de Mallorca, Spain; V. Moreno, Barcelona, Spain; and A. Obrador, Palma de Mallorca, Spain)

This study was undertaken to evaluate the association between dietary factors and colorectal cancer in a case–control study which uses the sibs of the cases as controls. This approach attempts to take account of the known increased susceptibility to colorectal cancer currently observed among first-degree relatives of colorectal cancer cases. A second objective of this project is to identify high-risk families for colorectal cancer.

A pilot phase was conducted from January to June 1990 and confirmed the feasibility of such a study. Recruitment continued until June 1991, at which time 93 index cases and 202 controls have been identified and interviewed. An analysis of the dietary questionnaires is in progress.

Pedigree charts have been constructed for the family of each case of colorectal cancer identified and 17 high-risk families (defined as families in which two or more cases have occurred among first-degree relatives) have been identified. It is intended to offer to these families endoscopic screening for colorectal lesions and to obtain blood and tissue samples which will be analysed to look for genetic markers.

### 1.5.5 Case–control studies of diet and cancer in Singapore

(J. Estève, in collaboration with L. Gourley, H.P. Lee and J. Lee, Singapore; and N.E. Day and S.W. Duffy, Cambridge, UK)

The ethnic origin of the population and the change in lifestyle which occurred in recent years in Singapore probably have major roles in producing the cancer incidence pattern observed there[86]. The large variance in risk factor distributions resulting from these rapid changes gives the opportunity for highly informative epidemiological studies. Three studies have been carried out to investigate effects of nutrition on colorectal[87], breast[88] and nasopharyngeal cancer. The study of colorectal cancer confirmed the importance of the balance between meat and vegetable consumption and the protective effect of cruciferous vegetables. The breast cancer study showed, among other results, a protective effect of consumption of soya products, which is consistent with the richness of these foods in phyto-estrogens that have been suggested to contribute to inhibition of hormone-dependent carcinogenesis[89]. The nasopharyngeal cancer study is still in progress and will be completed at the end of 1991.

### 1.5.6 Effect of dietary constitutents on lipid peroxidation and foreign compound metabolism and its role in tumour initiation and progression

(E. Hietanen, Turku, Finland; A.-M. Camus, J.-C. Bérézíat, P. Boyle and H. Bartsch; in collaboration with O. Eremin, and W.P.T. James, Aberdeen, UK)

Results from a completed long-term study in rats kept on diets of different fat compositions and given *N*-nitrosodimethylamine (NDMA) as initiating carcinogen, yielded the following

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[86] Lee, H.P., Day, N.E. & Shanmugaratnam, K., eds (1988) *Trends in Cancer Incidence in Singapore 1968–1982* (IARC Scientific Publications No. 91), Lyon, International Agency for Research on Cancer

[87] Lee, H.P., Gourley, L., Duffy, S.W., Estève, J., Lee, J. & Day, N.E. (1989) *Int. J. Cancer*, **43**, 1007–1016

[88] Lee, H.P., Gourley, L., Duffy, S.W., Estève, J., Lee, J. & Day, N.E. (1991) *Lancet*, **337**, 1197–1200

[89] Barnes, S., Grubbs, C., Setchell, K.D.R. & Carlson, J. (1990) In: Pariza, M.W., ed., *Mutagens and Carcinogens in the Diet*, New York, Wiley-Liss, pp. 239–253

results[90]: (*a*) dietary fat promoted chemically-induced liver carcinogenesis; (*b*) a high content of $\omega-6$ unsaturated fatty acids in the diet was more effective than saturated fatty acids in enhancing hepatocarcinogenesis; (*c*) high levels of dietary fat, especially polyunsaturated, increased lipid peroxidation in a dose-related manner; (*d*) NDMA was a potent initiator of lipid peroxidation[91], independently of the diet, and indomethacin in the diet prevented this increase in lipid peroxidation, especially in rats that did not develop a tumour later; (*e*) a higher level of fat in the diet increased the level of $O^6$-methyldeoxyguanine in liver DNA of NDMA-treated animals, while DNA repair enzymes were unaffected[92].

We are now investigating whether oxidative stress, lipid peroxidation and anti-oxidant defence also have a role in some human cancers where dietary factors and the pro-oxidant changes may be involved in the etiology. Two approaches are being pursued: (1) to develop methods applicable to humans for non-invasive measurement of lipid peroxidation products and for the assay of enzymes and substances related to lipid peroxidation and anti-oxidant defence in blood; (2) to test, in pilot studies, the validity of enhanced lipid peroxidation and/or decreased antioxidant defence as related to certain human cancers.

We have carried out cross-sectional studies in human breast and colon cancer cases to study the role of pro-oxidant state in carcinogenesis, and in particular the hypothesis that patients with colon and breast cancers have altered pro-oxidant state and anti-oxidant defence. Laboratory analyses have been completed and the data are under evaluation.

Dietary factors linked to the regulation of lipid peroxidation and anti-oxidant defence are also being evaluated in a group of volunteers who, as part of another study, consumed consecutively different diets with varying degrees of fat saturation (in collaboration with M. Mutanen, Department of Nutrition, University of Helsinki, Finland). Laboratory analyses of this study have been completed, and results are under evaluation.

### 1.5.7 Endogenously formed carcinogens in human cancer etiology

The aim of this project is to assess the role of *N*-nitroso compounds (NOC) and other DNA-damaging agents in the etiology of human cancers[93] in connection with other factors such as dietary habits, lifestyle (section 1.2.3), bacterial flora (section 1.7.3), precancerous conditions and inflammatory status (section 1.3.5.3). Particular emphasis is directed towards the development, application and evaluation of biomarkers which can be exploited in subsequent epidemiological and intervention studies.

Current activities concentrate on (i) the identification of unknown DNA-damaging agents and their precursors; (ii) factors that affect the extent of endogenous formation of carcinogens.

#### 1.5.7.1 *Diet, lifestyle and cancer mortality in China*

(H. Ohshima, B. Pignatelli, D. Shuker and H. Bartsch; in collaboration with C. Campbell, Ithaca, NY, USA; J. Chen and C. Wu, Beijing, China; R. Peto, Oxford, UK; and a network of collaborating laboratories)

A multi-centre ecological study on diet, lifestyle and cancer mortality in China (similar to a

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[90] Hietanen, E., Bartsch, H., Bérézíat, J.-C., Ahotupa, M., Camus, A.-M., Cabral, J.R.P. & Laitinen, M. (1990) *Int. J. Cancer*, **46**, 640–647

[91] Bartsch, H., Hietanen, E. & Malaveille, C. (1989) *Free Radical Biol. Med.*, **7**, 637–644

[92] Camus, A.-M., Bérézíat, J.-C., Shuker, D.E.G., Hietanen, E., Wild, C.P., Montesano, R. & Bartsch, H. (1990) *Carcinogenesis* **11**, 2093–2095

[93] Bartsch, H., Ohshima, H., Pignatelli, B. & Calmels, S. (1989) *Cancer Surveys: Nitrate, Nitrite and Nitroso Compounds in Human Cancer*, **8**, 335–362

previous one[94,95]) is being conducted using data from a recent cancer mortality survey and study subjects from 69 counties with contrasting cancer mortality. Urine and other biological specimens were collected in 1990. Among many markers for carcinogen exposure, nutritional deficiency and disease state being measured, the IARC laboratory will analyse markers for NOC exposure (such as nitrosamino acids, alkylpurines, and specific mercapturic acids).

### 1.5.7.2 *Availability of dietary nitrate for endogenous nitrosation*

(H. Ohshima and H. Bartsch; in collaboration with D. Forman, Oxford, UK)

To assess the availability of normal dietary nitrate for endogenous nitrosation of L-proline, subjects were given a meal containing about 170 mg nitrate with or without a loading dose of proline. A significant increase in urinary *N*-nitrosoproline (NPRO) excretion followed ingestion of the meal plus proline, indicating intragastric nitrosation of proline by meal-derived nitrate.

In a second study, the mean urinary NPRO level was significantly decreased by inclusion of ascorbic acid in the meal, showing that proline nitrosation is inhibited by dietary vitamin. Significant interindividual differences in nitrosating ability appeared to be associated with variation in salivary conversion of nitrate to nitrite[96].

### 1.5.7.3 *Levels of nitrite, nitrate,* N*-nitroso compounds, ascorbic acid and total bile acids in gastric juice of patients with and without precancerous conditions of the stomach*

(B. Pignatelli, P. Thuillier and H. Bartsch; in collaboration with A.T.R. Axon, M.F.Dixon and G.M. Sobala, Leeds, UK)

Simultaneous measurements were performed of ascorbic acid, vitamin C (sum of ascorbic acid and dehydroascorbic acid), nitrate, nitrite, total NOC and total bile acids in gastric juice, and of vitamin C in plasma from 56 subjects from a gastroenterology unit in Leeds, UK. Significantly lower ascorbic acid and vitamin C levels were observed in gastric juice of chronic gastritis patients, in particular those with intestinal metaplasia, that were not associated with higher concentrations of nitrite and NOC. Plasma levels of vitamin C did not significantly differ in patients with and without precancerous conditions of the stomach. These results[97] imply a lowered anti-oxidant defence state and lowered levels of nitrosation inhibitors in the stomachs of chronic gastritis patients.

### 1.5.7.4 *Levels of* N*-nitroso compounds, precursors and nitrosation-dependent mutagens in human gastric juice*

(B. Pignatelli, C. Malaveille, C.S. Chen, A. Rogatko, N. Muñoz, A. Hautefeuille, P. Thuillier and H. Bartsch; in collaboration with A.T.R. Axon and G. Sobala, Leeds, UK; F. Berger, H. De Montclos, R. Lambert and B. Moulinier, Lyon, France; P. Correa, New Orleans, LA, USA; B. Ruiz, Cali, Colombia; supported in part by NIH grant no. CA 47591)

Patients with precancerous conditions such as chronic atrophic gastritis are at an elevated risk of stomach cancer. To examine whether this elevated risk is associated with higher levels of

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[94] Chen, J., Ohshima, H., Yang, H., Li, J., Campbell, T.C., Peto, R. & Bartsch, H. (1987) In: Bartsch, H., O'Neill, I.K. & Schulte-Hermann, R., eds, *The Relevance of* N*-Nitroso Compounds to Human Cancer: Exposures and Mechanisms* (IARC Scientific Publications No. 84), Lyon, International Agency for Research on Cancer, pp. 511–517

[95] Chen, J., Campbell, C., Li Junyar & Peto, R., eds (1990) *Diet, Life-Style and Cancer Mortality in China*, Oxford, Oxford University Press; Ithaca, NY, Cornell University Press; Beijing, People's Medical Publishing House

[96] Knight, T.M., Forman, D., Ohshima, H. & Bartsch, H. (1991) *Nutr. Cancer*, **15**, 195–203

[97] Sobala, G.M., Pignatelli, B., Schorah, C.J., Bartsch, H., Sanderson, M., Dixon, M.F., Shires, S., King, R.F.G. & Axon, A.T.R. (1991) *Carcinogenesis*, **12**, 193–198

NOC, their precursors and nitrosation-dependent mutagens in gastric juice, we compared patients with or without precancerous lesions of the stomach and living in three areas where risk of gastric cancer differs up to three-fold (France, UK and Colombia)[98,99].

Patients were classified according to histologically confirmed diagnosis: normal gastric mucosa, superficial gastritis, reflux gastritis, diffuse interstitial gastritis, chronic gastritis without atrophy, chronic atrophic gastritis, dysplasia, cancer. The level of nitrite in the gastric juice (range <1–472 μmol/l) increased with pH, and was also dependent on location (France, UK and Colombia). NOC levels (range <0.01–8.0 μmol/l) were not affected by sex, country of collection or diagnosis. The levels of NOC in gastric juice increased with nitrite concentration, but at a higher rate for acidic samples than for more basic ones (pH > 4). These data suggest that NOC are formed in gastric juice predominantly by acid-catalysed nitrosation; bacterial-mediated nitrosation appears less important.

Genotoxicity of gastric juice samples (expressed as SOS inducing potency (SOSIP) per 100 μl of juice) after acid-catalysed nitrosation was found to be dependent on the original pH of the sample in the patients from France and Colombia. The precursors of the nitrosation-dependent genotoxins appear to belong to similar classes of chemicals, and characterization of some constituents is being attempted.

### 1.5.7.5 *Food items associated with gastric cancer risk*

#### *Genotoxicity, tumour-initiating and -promoting effects of smoked foods and wood smoke condensates*

(H. Ohshima, M. Friesen and H. Bartsch; in collaboration with C. Furihata and T. Matsushima, Tokyo, Japan; N. Ito and M. Tatematsu, Nagoya, Japan; G. Klopman and H. S. Rosenkranz, Pittsburgh, PA, USA)

Epidemiological studies have associated the consumption of smoked fish and meat products with an increased risk of stomach cancer. The structural basis of the genotoxicity (quantitative structure–activity relationship, QSAR) of nitrosatable phenols and derivatives present in smoked food products was investigated using the CASE methodology[100]. Structural features were identified and revealed that genotoxicity is dependent upon the ease of formation of the reactive phenyldiazonium intermediate, and is influenced only secondarily by the nature of the mutagen or its ease of entry into the cell. With this data-base, CASE predicted the genotoxicity, following nitrosation, of a number of phenolic compounds including naturally occurring pesticides present in edible plants.

Hickory smoke condensate contains substances which have potential tumour-initiating and/or promoting activity, that after reaction with nitrite could act as tumour-initiators in the rat glandular stomach[101]. This was confirmed when groups of WkY rats were treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and hickory smoke condensate. The number of pepsinogen I-altered pyloric glands (a marker for gastric carcinogenesis) was significantly

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[98] Pignatelli, B., Malaveille, C., Chen, C.-S., Hautefeuille, A., Thuillier, P., Muñoz, N., Moulinier, B., Berger, F., de Montclos, H., Ohshima, H., Lambert, R. & Bartsch, H. (1991) In: O'Neill, I.K., Chen, J. & Bartsch, H., eds, *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105), Lyon, International Agency for Research on Cancer, pp. 172–177

[99] Pignatelli, B., Malaveille, C., Rogatko, A., Hautefeuille, A., Thuillier, P., Muñoz, N., Moulinier, B., Berger, F., de Montclos, H., Lambert, R., Correa, P., Ruiz, B., Sobala, G., Axon, A.T.R. & Bartsch, H. (submitted for publication)

[100] Rosenkranz, H.S., Klopman, G., Ohshima, H. & Bartsch, H. (1990) *Mutat. Res.*, **230**, 9–27

[101] Ohshima, H., Furihara, C., Matsushima, T. & Bartsch, H. (1989) *Fd. Chem. Toxicol.*, **27**, 511–516

increased in the group receiving both agents, as compared to animals treated with MNNG alone[102].

These results provide an interpretation of findings from a recent case–control study in southern Germany, in which the consumption of meat home-preserved by smoking was associated with a relative risk of 4.6 for stomach cancer as compared to consumption of meat not so preserved[103].

#### 1.5.7.6 *Direct-acting mutagens, N-nitroso compounds and tumour-promoter-like substances in fermented fish products*

(C.S. Chen, B. Pignatelli, C. Malaveille, D.E.G. Shuker, A. Hautefeuille and G. Bouvier; in collaboration with R.F. Fang, Beijing, China)

We have investigated the levels and nature of NOC and mutagens present, before and after nitrosation, in 49 fish sauce samples (pooled into six samples) from villages with high gastric cancer risk in Fujian, China. The concentrations of total NOC ranged from 0.2 to 16 $\mu$mol/l, and after nitrosation at pH 2 and pH 7, rose by up to 4800- and 100-fold, respectively. In the nitrosated samples, 40–50% of total NOC was not extractable into organic solvents, volatile *N*-nitrosamines accounted for 1–2% and *N*-nitrosamino acids for 8–16% of total NOC.

About 80% of the genotoxic activity in fish sauce was recovered in only three HPLC fractions; the precursors of the genotoxic substances are now being identified. This genotoxicity has been partly ascribed to the formation of nitrite-derived arene diazonium cations that were partially characterized[104]. The presence of nitrite-dependent mutagens and tumour promoter-like substances supports the hypothesis that fish sauce consumption is a risk factor for gastric cancer.

## 1.6 *Genetics and Cancer*

The Agency is contributing to the study of genetic susceptibility to cancer using three approaches:

(a) by identifying genetic predisposing conditions within the general population; the goal is to evaluate the role of inherited conditions predisposing to cancer through molecular, familial and population-genetic approaches, and finally, to establish how molecular genetics can be used to better define the genetic make-up of individuals in epidemiological surveys;

(*b*) by investigating variations in host susceptibility to carcinogenic agents, and in particular identifying subjects who are at increased risk for cancer, due to either inherited or acquired host susceptibility factors, and defining the contribution of environmental versus genetic risk factors to some tobacco- and diet-related cancers, namely of the lung, pancreas and urinary bladder.

(*c*) by developing statistical methods for use in genetic epidemiology.

The role of genetic factors in the etiology of human cancer can now be studied using newly developed molecular biological tools. The genetic make-up of individuals (cancer patients and controls) can be examined by directly analysing nucleic acid primary structure using various

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[102] Shichino, Y., Tatematsu, M., Ohshima, H., Bartsch, H., Furihata, C. & Ito, N. (submitted for publication)

[103] Boeing, H., Frentzel-Beyme, R., Berger, M., Berndt, V., Göres, W., Körner, M., Lohmeier, R., Menarcher, A., Männl, H.F.K., Meinhardt, M., Müller, R., Ostermeier, H., Paul, F., Schwemmle, K., Wagner, K.H. & Wahrendorf, J. (1991) *Int. J. Cancer*, **47**, 858–864

[104] Chen, C.S, Pignatelli, B., Malaveille, C., Bouvier, G., Shuker, D., Hautefeuille, A., Zhang, R.F. & Bartsch, H. (submitted for publication)

DNA probes, which may correspond either to randomaly characterized DNA polymorphic markers, or to specific genes including the recently characterized "cancer genes" (oncogenes).

The second approach involves genetic variations in the metabolism of carcinogens. Cytochrome P450 isozymes and their respective mRNAs and genes responsible for carcinogen activation are being characterized in terms of their catalytic properties and structures and the regulation of gene expression. The variability in enzyme activity, gene structure and expression in humans that can lead to variation in carcinogen metabolism is being assessed and correlated with differences in cancer susceptibility, to examine whether increased cancer risk (lung, urinary bladder and pancreas in tobacco smokers) can be predicted based on metabolic phenotypes. A study of the significance of genetic polymorphism in the enzymes metabolizing ochratoxin A is described in section 1.2.7.2.

Statistical methodology for use in genetic epidemiology of cancer is being assessed and developed, as described in section 3.2.4.

### 1.6.1 Genetic predisposition to cancer

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.

The programme on the study of genetic predisposition to cancer through a genetic linkage approach is now actively involved in the study of three genetic conditions: X-linked lymphoproliferative syndrome (XLP), medullary thyroid cancer (MTC) and familial breast cancer. For all these conditions, active mapping of disease loci is in progress, while for thyroid cancer, the use of genetic screening with polymorphic DNA probes now permits early detection of a gene carrier.

#### 1.6.1.1 *Studies on the X-linked lymphoproliferative syndrome*

(B.S. Sylla, Q. Wang, S. Pauly and G. Lenoir; in collaboration with C.T. Caskey and D. Nelson, Houston, TX, USA; P. Goodfellow, H. Lehrach and D. Nizetic, London, UK; D. Hayoz, Fribourg, Switzerland; D. Le Palier, Paris, France; and J. Skare, Boston, MA, USA)

The X-linked lymphoproliferative syndrome (XLP) is a rare recessive genetic disorder which affects boys carrying the mutated gene. The disease is characterized by either fatal infectious malignant lymphoma, acquired hypoglobulinaemia or malignant lymphoma, following primary Epstein–Barr virus (EBV) infection. XLP represents a very interesting model in humans, in which an infectious environmental agent (EBV) and a strong genetic predisposing condition lead to the development of malignant lymphoma.

Genetic linkage studies have indicated that the XLP locus is mapped at the Xq25–q26 region[105]. A collaborative study with J. Skare has shown that the responsible gene is situated close to the DXS37 genetic marker and proximal to the DXS42 marker (as illustrated in Figure 9).

Several approaches are being undertaken in order to physically map the chromosomal region of Xq25–q26 and to isolate and study the responsible gene. The methodology developed for this project will be applied in the breast cancer genetic project (see below) as soon as susceptibility loci have been clearly identified.

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[105] Sylla, B.S., Wang, Q., Hayoz, D., Lathrop, G.M. & Lenoir, G.M. (1989) *Clin. Genet.*, **36**, 459–462
Skare, J.C., Grierson, H.L., Sullivan, J.L., Nussbaum, R.L., Purtilo, P.T., Sylla, B., Lenoir, G., Reilly, D.S., White, B.N. & Milunsky, A. (1989) *Hum. Genet.*, **82**, 354–358

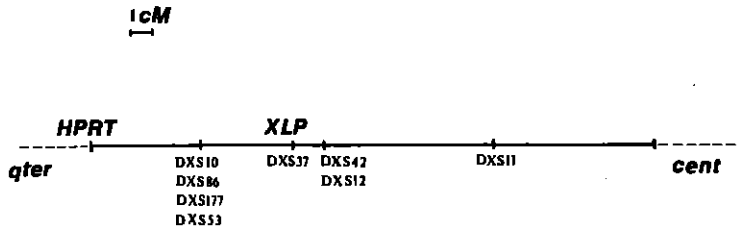


Fig. 9. Genetic map of the Xq24–q26 regions (Skare *et al.*, 1990; Sylla *et al.*, 1989)

*Search for new polymorphic markers in Xq25–q26*

New technology for physical mapping of genes is being developed. The use of an irradiation and fusion gene transfer technique has allowed us to obtain a panel of hybrid clones containing only small segments of the human X chromosome that include the Xq25–q26 region. One of these hybrid clones has been used to amplify specific human X chromosome sequences using a polymerase chain reaction (PCR) technique with human repetitive Alu sequences. The amplified sequences were then cloned in a plasmid vector and several clones have been analysed. Six probes were regionally mapped in the Xq23–q26 region by using a panel of cell hybrids containing various breakpoints on the X chromosome. Four probes cloned in lambda phage and mapped in the Xq23–q26 region were also characterized. None of these ten probes has shown a restriction fragment length polymorphism. A search for other DNA polymorphisms such as poly[dC–dA:dT–dG] polymorphic repeat or minisatellites in these cloned fragments is in progress. The clones are also being used to screen DNA libraries containing large fragments of human DNA, such as cosmid and yeast artificial chromosome (YAC) libraries, in order to isolate large inserts for physical mapping of the XLP region.

*Physical mapping of the Xq25–q26 region and search for candidate genes*

Several probes genetically mapped around the XLP locus have been used to screen three YAC libraries in Houston, Paris and Oxford and one cosmid library in London. No YAC containing 30Rib (DXS37) was obtained.

A search for candidate genes has been made by looking for the presence of potential HpaII tiny fragments (HTFs)—sections of DNA characterized by a cluster of CpG sequences generally found next to DNA coding sequences. The results are summarized in Figure 10.

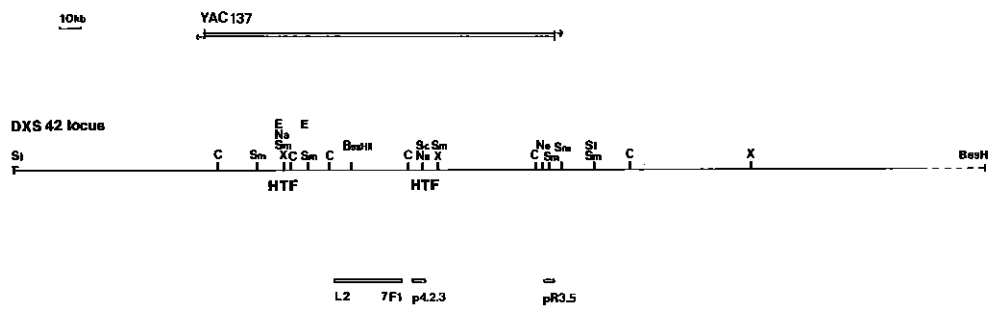


Fig. 10. Restriction maps of YAC 137 and DXS42 region in Xq25–q26. E, EagI, X, XhoI; C, ClaI, Sm, SmaI; Sc, SacI; Sl, SalI; Na, NarI; Ne, NaeI

A recent identification of an XLP patient with interstitial deletions in the Xq25 region (D. Purtilo, personal communication) constitutes an important step towards the isolation and study of the XLP gene. Four YACs and one lambda phage clone have been shown in Dr D. Nelson's laboratory to be deleted in this patient. We are now characterizing these clones for restriction mapping and for isolation of polymorphic markers. Identification of conserved sequences will be useful for screening cDNA libraries made from lymphoid cells. Any genes that are isolated will be tested as candidate genes involved in the XLP syndrome.

### 1.6.1.2 *Studies on multiple endocrine neoplasia (MEN)*

(H. Sobol, S. Narod, I. Schuffenecker, M.-F. Lavoué and G. Lenoir; in collaboration with the Group for the Study of Calcitonin Tumours: Secretariat, C. Calmettes, Paris, France; Y. Nakamura, Salt Lake City, UT, USA; and B. Ponder, Sutton, UK)

#### *Linkage studies on MEN type 2A*

MEN 2A is an autosomal dominant inherited cancer syndrome characterized by medullary carcinoma of the thyroid (MTC), phaeochromocytoma and hyperparathyroidism, accounting for at least 30% of medullary thyroid cancers. Almost all gene carriers will develop the disease (a very high penetrance of the gene), but their identification still relies on a screening test that detects an early stage of the malignancy. Through the Group for the Study of Calcitonin Tumours in France and contacts with various European institutions, over 100 families have been identified, and blood has already been collected from most members. Since the initial localization of the MEN 2A locus on the pericentromeric region of chromosome 10, mapping of the MEN 2A locus has been continued, by testing a new set of DNA polymorphic markers situated in this region of chromosome 10[106].

#### *Screening for individuals at risk*

MEN 2A has been shown to be genetically linked to a locus near the centromere of chromosome 10. The ability to predict the carrier state has been demonstrated to be much greater for restriction fragment length polymorphism (RFLP) analysis than for conventional endocrine challenge methods, but maximum accuracy is obtained when both methods are used. Following initial screening with DNA, testing for early neoplastic change can be directed towards those individuals determined to be at significant risk. Thus MEN type 2A is one of the first cancer syndromes for which genetic screening allows the identification of individuals at risk[107]. Analyses have been performed on three families, and prediction can be done in almost 50% of cases with the available markers. The availability of markers located on opposite sides of the MTC gene (flanking markers) makes the calculation of the risk much more precise[108].

#### *Genetic heterogeneity for familial medullary thyroid carcinoma*

Hereditary MTC appears in three forms: (1) in association with phaeochromocytomas and parathyroid hyperplasia (MEN 2A); (2) with phaeochromocytomas, neuromas of the mucous membranes and a marfanoid appearance (MEN 2B); and (3) without phaeochromocytoma. Despite these differences in presentation, age of onset and clinical severity, limited genetic

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[106] Schuffenecker, I., Narod, S.A., Ezekowitz, R.A.B., Sobol H. & Lenoir, G.M. (1991) *Cytogenet. Cell Genet.*, **56**, 99–102

[107] Sobol, H. and 21 others (1989) *New Engl. J. Med.*, **321**, 996–1001

[108] Narod, S.A., Sobol, H. & Schuffenecker, I. (1989) *Henry Ford Hosp. Med. J.*, **37**, Nos 3 & 4, 106–108

studies suggest that the three MTC variants may be due to inherited mutations at the same gene locus[108,109]. By testing 24 families with nine polymorphic markers spanning the centromere of chromosome 10, haplotypes have been constructed, and a segment was found to be shared by seven of these families, suggesting they have a common ancestor. The geographic distribution of some families sharing analogous haplotypes is given in Figure 11.

*Attempts to identify the responsible gene*

Two genes located in the centrometric region of chromosome 10 are being tested as candidate MEN genes. The first one, the human mannose binding protein, has already been excluded[106]. The second one, the oncogene *ret*, an oncogene originally isolated from a thyroid tumour, is under investigation[110].

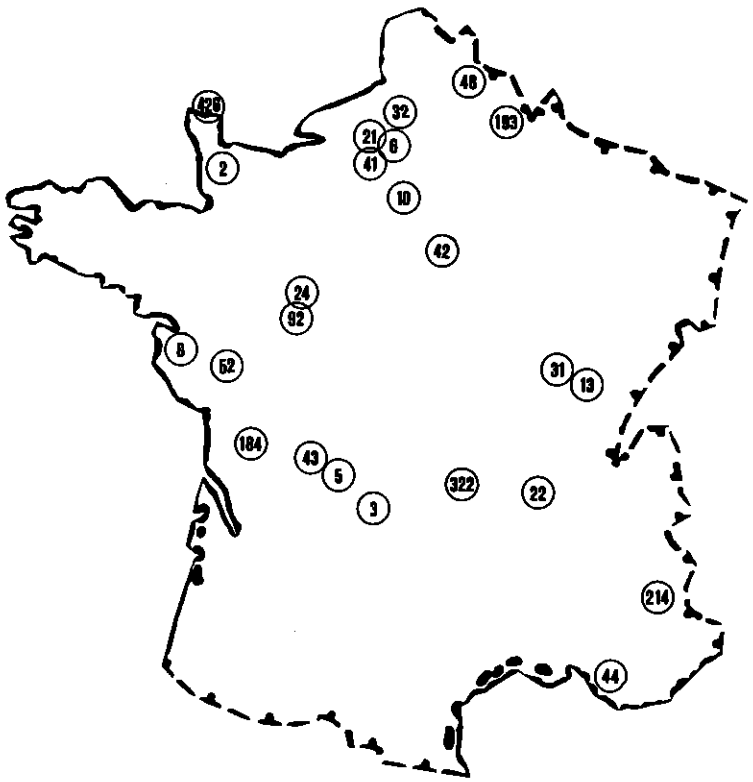


Fig. 11. The geographic origin of 24 French MEN 2A families. Families showing analogous haplotypes are highlighted

[109] Sobol, H., Narod, S.A., Schuffenecker, I., Amos, C., Ezekowitz, R.A.B., Lenoir, G.M. and the Groupe d'Etude des Tumeurs à Calcitonine (1989) *Henry Ford Hosp. Med. J.*, **37**, Nos 3 & 4, 109–111

[110] Norum, R.A., Lafrenière, R.G., O'Neal, L.W., Nikolai, T.F., Delaney, J.P., Sisson, J.C., Sobol, H., Lenoir, G.M., Ponder, B.A.J., Willard, H.F. & Jackson, C.E. (1990) *Genomics*, **8**, 313–317

### 1.6.1.3 *Hereditary breast cancer*

(S. Narod, J. Feunteun and G. Lenoir; in collaboration with C. Amos, Bethesda, MD, USA; H. Lynch, Omaha, NE, USA; and R. White, Salt Lake City, UT, USA)

The objectives of this project are to locate breast cancer susceptibility genes, to identify them, and to evaluate the biological significance of the genetic component in breast cancer disease.

The feasibility of applying the linkage approach to localizing a breast cancer gene was discussed at a workshop held on 28–29 November 1989 in Lyon. Members of several research groups from Europe and North America met to compare families in which several cases of breast cancer had occurred, and discussed the development of a linkage exclusion map. Since then this group has met regularly with the purpose of developing a network among which linkage data submitted by all interested groups will be tabulated, summarized and then redistributed to contributors.

Through a collaboration with Dr H. Lynch, 513 blood samples from members of 35 breast cancer families were shipped to Lyon during the period June 1989–June 1990. From these families, five in which breast and ovarian cancer were associated through several generations were selected; within these families, there are 169 affected individuals, including 30 living, which was estimated sufficient to permit the identification of a disease susceptibility locus in the absence of genetic heterogeneity[111]. Recently, linkage of early-onset dominant breast cancer to the D17S74 locus on the long arm of chromosome 17 has been reported[112] and among 23 breast cancer families having a mean age of onset below 46 years, 40% appeared to be linked. In an attempt to confirm these findings and to investigate their relevance to ovarian cancer, we have analysed our five families with hereditary breast–ovarian cancer with the D17S74 marker.

With the probe CMM86 at this locus, the maximum lod score for our largest family was 2.72 at a recombination fraction of 0.07 (Table 13 and Figure 12). This is the highest reported lod score for a single family with hereditary beast cancer and corresponds to odds of >500 to 1 in favour of linkage to locus D17S74. Of the remaining four families two showed evidence of linkage and two appeared to be unlinked.

Table 13. Two-point lod scores[a] for breast–ovary cancer families and locus D17S74

| Family | Recombination fraction | | | | | |
|---|---|---|---|---|---|---|
| | 0.01 | 0.05 | 0.10 | 0.15 | 0.20 | 0.30 |
| F1816 | 2.24 | 2.67 | 2.71 | 2.58 | 2.35 | 1.70 |
| F2090 | 0.99 | 0.89 | 0.79 | 0.68 | 0.57 | 0.35 |
| F2651 | −2.74 | −1.63 | −1.11 | −0.83 | −0.64 | −0.38 |
| F2770 | −2.80 | −1.99 | −1.42 | −1.05 | −0.77 | −0.35 |
| F2850 | 0.34 | 0.77 | 0.83 | 0.78 | 0.69 | 0.45 |
| Total | −1.94 | 0.72 | 1.79 | 2.16 | 2.20 | 1.78 |

[a] The lod score is a measure of the likelihood of the data if a particular recombination fraction ($\theta$) is assumed compared with the likelihood of the data under free recombination ($\theta = 0.50$). Generally, a lod score of 3.00 or greater is considered conclusive evidence of linkage.

[111] Narod, S., Feunteun, J., Lynch, H.T., Watson, P., Conway, T., Lynch, J. & Lenoir, G.M. (1991) *Lancet*, **338**, 82–83

[112] Hall, J.M., Lee, M.K., Newman, B., Morrow, J.E., Anderson, L.A., Huey, B. & King, M.C. (1990) *Science*, **250**, 1684–1689

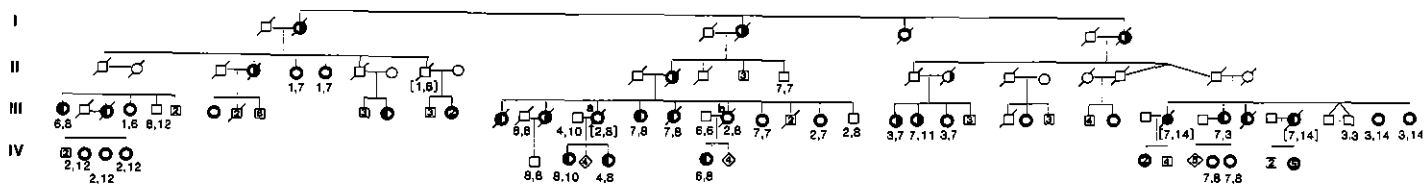


Fig. 12. Pedigree of breast–ovarian cancer family F1816. Left shading indicates breast cancer, right shading indicates ovarian cancer. Individual a had cancer at an unknown site and individual b was diagnosed to have omental cancer. Both are considered obligate carriers based on the appearance of very early onset breast cancer in their daughters. Numbers below the symbols indicate marker allele type, using the probe CMM86 (locus D17S74). Some genotypes have been unambiguously reconstructed from children and appear in brackets.

Our data strengthen the assignment of a breast cancer susceptibility locus to chromosome 17q12–q23. Furthermore, the mutation (or mutations) at the D17S74 locus appears to also predispose to tumours of the ovary.

Restricting the analysis to a phenotypically homogeneous condition did not mitigate the problem of locus heterogeneity, as two families present strong evidence of being unlinked.

These findings suggest that a high proportion of familial breast cancers map to the chromosome 17q12–q23 region. The mapping of the cancer susceptibility gene on chromosome 17 is currently imprecise and many polymorphic markers of the region are being typed in order to narrow down the genetic distance between markers and the disease susceptibility locus.

Fifteen additional families presenting either with breast and ovarian cancer or with breast cancer as the sole cancer have now been collected and are being typed for linkage at the 17q13 locus. In probably linked families, the breast cancer gene will be further mapped, while the unlinked families will be used to identify new breast cancer susceptibility loci by a similar approach.

#### 1.6.1.4 *Estimation of the heritable fraction of childhood cancer*

(G. Lenoir; in collaboration with S. Narod, Montreal, Canada; and C. Stiller, Oxford, UK)

The records of the 16 564 cases of childhood cancer diagnosed from 1971 to 1983 which were reported to the National Registry of Childhood Tumours in Great Britain have been reviewed for the presence of underlying genetic disease, in order to estimate the proportion resulting from inherited mutations. A genetic condition was listed for 508 patients, or 3.1% of the total number of tumours. When information about family history from published reports was incorporated, the total genetic fraction reached 4.4%. These analyses indicate that there is a clear genetic basis for a small minority of childhood cancers, but ethnic variation and the lack of known environmental determinants suggest that the total influence of heredity may be higher[113].

### 1.6.2 Genetic polymorphism in human CYP genes and cancer

(M. Lang, A.-M. Camus, J.-C. Béréziat and O. Geneste; in collaboration with E. Alhava, Kuopio, Finland; F. Stenbäck, Oulu, Finland; and C.R. Wolf, Edinburgh, UK)

CYP genes coding for cytochrome P450s are a superfamily of genes regulating the expression of enzymes oxidizing xenobiotics including the conversion of procarcinogens to their ultimate carcinogenic forms. The expression of CYP genes is regulated by environmental and host factors and most, if not all, have their individual patterns of regulation. Interindividual variation in the amount of certain gene products and activity may vary as much as several hundred-fold.

This new project has two main objectives: (*a*) to determine the roles of P450 isozymes (in particular of P450IIE1 and P450IIA3) in the activation of certain carcinogens to which humans are exposed and estimate interindividual differences in carcinogen activation in humans by the two isozymes; (*b*) to establish genotyping methods for analysing CYP gene polymorphisms of certain isozymes such as CYP2D6, CYP1A1 and CYP2E1, in order to demonstrate a possible association between CYP genotype and cancer susceptibility (in collaboration with on-going or planned epidemiological studies).

P450IIE1 is known to metabolically activate several carcinogens such as benzene, vinyl chloride and nitrosamines. Less is known about the role of P450IIA3, but similarities between

[113] Narod, S.A., Stiller, C. & Lenoir, G.M. (1991) *Br. J. Cancer*, **63**, 993–999

the two enzymes suggest that IIA3 is also involved in carcinogen activation. P450IIA3 is present in human liver in considerable quantities, with large interindividual variation, indicating its possible importance.

P450IIE1 and P450IIA3 have been purified from mouse liver and antibodies have been raised. Immunochemically cross-reacting proteins have been found in human livers. Studies with purified proteins and liver microsomal fractions have shown that the two proteins share some catalytic properties (e.g., aniline, ethanol and nitrosodiethylamine are substrates for both). Further studies are assessing the contributions of the two proteins in carcinogen activation.

The DNA coding for the two proteins has been isolated and characterized from mice as well as humans. cDNA will be used in population studies to determine interindividual differences in the expression of two proteins. A non-invasive method to determine P450IIA3 activity *in vivo* in humans has been developed.

Collaboration has been established with two university hospitals (Kuopio and Oulu) in Finland to obtain and analyse human liver samples for the two proteins. Other tissues will be obtained through the European tissue bank network.

### 1.6.3 Exposure and risk markers for some tobacco- or diet-associated cancers

The projects described below are aimed at defining the contribution of metabolic host-risk factors, notably, genetic polymorphism of human CYP genes, to the risk of tobacco-related lung and urinary bladder cancers. Simultaneous measurements of carcinogen exposure, macromolecular adducts and metabolic pheno(geno)typing should reveal the extent to which pharmacogenetic differences contribute to the risk of these malignancies. For these reasons, non-invasive phenotyping and genotyping assays are being set up that could later be applied to epidemiology studies. Other studies are investigating the role of increased pro-oxidant state as affected by dietary lipids in certain human cancers (see section 1.5.6).

#### 1.6.3.1 *Carcinogen metabolism and DNA adducts in human lung tissues as affected by tobacco smoking or metabolic phenotype: a case–control study on lung cancer patients*

Cigarette smoking is the strongest risk factor for lung cancer, but genetically determined variations in activities of pulmonary enzymes that metabolize tobacco-derived carcinogens may affect individual risk. To investigate whether these enzymes (e.g. P450IA-related) can serve as a marker for carcinogen–DNA damage, lung tissue specimens were taken during surgery from middle-aged men with either lung cancer or non-neoplastic lung disease and analysed for numerous biochemical and enzymatic parameters.

The results have demonstrated the pronounced effect of tobacco smoke on pulmonary xenobiotic metabolism and pro-oxidant state, and indicate the existence of a metabolic phenotype at higher risk for tobacco-associated lung cancer[114]. These findings are currently being confirmed in another group of patients with lung cancer related to smoking habits and asbestos exposure (see section 1.6.3.2).

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[114] De Flora, S., Petruzzelli, S., Camoirano, A., Bennicelli, C., Romano, M., Rindi, M., Ghelarducci, L. & Giuntini, C. (1987) *Cancer Res.*, **47**, 4740–4745
Petruzzelli, S., Camus, A.-M., Carrozzi, L., Ghelarducci, L., Rindi, M., Menconi, G., Angeletti, C.A., Ahotupa, M., Hietanen, E., Aitio, A., Saracci, R., Bartsch, H. & Giuntini, C. (1988) *Cancer Res.*, **48**, 4695–4700
Petruzzelli, S., De Flora, S., Bagnasco, M., Hietanen, E., Camus, A.-M., Saracci, R., Izzott, A., Bartsch, H. & Giuntini, C. (1989) *Am. Rev. Resp. Dis.*, **140**, 417–422
Bartsch, H., Petruzzelli, S., De Flora, S., Hietanen, E., Camus, A.-M., Castegnaro, M., Geneste, O., Camoirano, A., Saracci, R. & Giuntini, C. (1991) *Mutat. Res.* (in press)

*Prognostic value of pulmonary enzymes in patients operated on for tobacco-related lung cancer*

(H. Bartsch, A.-M. Camus, M. Castegnaro, O. Geneste and R. Saracci; in collaboration with C. Giuntini and S. Petruzzelli, Pisa, Italy; S. de Flora, Genoa, Italy; and E. Hietanen, Turku, Finland)

We have examined the value of pulmonary drug-metabolizing enzymes as prognostic markers for a group of male lung cancer patients, who were previously investigated for other reasons[115]. For a subset of 50 patients with lung cancer related to tobacco use, who had undergone thoracic surgery, data on the activity of parenchymal aryl hydrocarbon hydroxylase (AHH) and epoxide hydrolase (EH) in homogenates of non-neoplastic lung tissue were compared with the patients' survival after surgery. When the crude mortality percentages at one and two years by AHH or EH activity were calculated, lower mortality was related to lower enzyme levels. Subjects in the top and bottom quarters of the distribution showed significant differences in their one-year survival for AHH ($p = 0.05$) and EH ($p < 0.01$) activities. This relationship could not be accounted for by age, cumulative lifetime smoking, recent or continuing smoking, stage or histological type of disease.

*Pulmonary DNA adducts and P450 enzymes in lung cancer patients*

(M. Castegnaro, A.-M. Camus, O. Geneste and A. Shouft; in collaboration with C.A. Angeletti, C. Giuntini, P. Macchiarini and S. Petruzzelli, Pisa, Italy)

Activity of some drug-metabolizing enzymes, expressed by a particular metabolic phenotype or genotype, may reflect the rate of metabolic activation or inactivation of tobacco-related carcinogens in the lungs of smokers, and thus could serve as markers for the internal dose of DNA-reactive metabolites generated in target cells. In order to obtain support for this hypothesis, we have determined the levels of DNA adducts in lung parenchyma of smokers by $^{32}$P-postlabelling assays, to see whether they are correlated with the AHH activity in the same tissue. Subjects were smokers and ex-smokers who had undergone thoracic surgery for lung cancer and for non-malignant diseases at the University Hospital, Pisa, Italy[116].

The numbers of DNA adducts per $10^8$ unmodified nucleotides were determined by scintillation counting after $^{32}$P-postlabelling analysis. The microsomal fractions of the same lung specimens were assayed for AHH activity by a fluorimetric method. Autoradiograms of DNA adducts from the lungs of smokers revealed two distinct zones that were far less intense or absent in ex-smokers. The smokers had three-fold higher levels than ex-smokers. AHH activity was 2.5-fold higher ($p < 0.05$) in smokers who had smoked until one week before surgery than in those who had stopped smoking for more than seven days. A positive linear correlation between DNA adduct levels and AHH activity ($r = 0.69$; $p < 0.001$; $n = 19$) was found in smokers. Such a relationship could explain why AHH activity or inducibility (expressed by certain metabolic phenotypes or genotypes) appears to be a crude marker for lung cancer risk in smokers, as seen in our earlier study[117].

Because of the small number of patients investigated, another cohort of patients with lung cancer related to tobacco and asbestos expsoure is now being examined (see below).

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[115] Bartsch, H., Hietanen, E., Petruzzelli, S., Giuntini, C., Saracci, R., Mussi, A. & Angeletti, C.A. (1990) *Int. J. Cancer*, **46**, 185–188

[116] Geneste, O., Camus, A.-M., Castegnaro, M., Petruzzelli, S., Macchiarini, P., Angeletti, C.A., Giuntini, C. & Bartsch, H. (1991) *Carcinogenesis*, **12**, 1301–1305

[117] Petruzzelli, S., Camus, A.-M., Carrozzi, L., Ghelarducci, L., Rindi, M., Mencone, G., Angeletti, G.A., Ahotupa, M., Hietanen, E., Aitio, A., Saracci, R., Bartsch, H. & Giuntini, C. (1988) *Cancer Res.*, **48**, 4695–4700

### 1.6.3.2 *Phenotype and occupational exposures as risk modifiers in lung cancer patients*

(H. Vainio, H. Bartsch, A.-M. Camus, M. Castegnaro, C. Malaveille, K. Alexandrov, M. Rojas and A. Shouft; in collaboration with S. Anttila, L. Heikkilä, K. Husgafvel-Pursiainen, A. Karjalainen, Helsinki, Finland; H. V. Gelboin and S.S. Park, Bethesda, MD, USA; and E. Hietanen, Turku, Finland)

Surgical lung tissue samples (lobectomy or pulmonectomy) from patients with or without malignant lung disease are being collected from Helsinki University Hospital. Asbestos fibre content in the lung samples is measured by both scanning and transmission electron microscopy. Blood and urine samples are collected from the same individuals, and detailed smoking and occupational histories are taken through personal interview. Specimens from patients operated for lung cancer ($n = 50$) or non-malignant lung disease ($n = 6$) have already been collected and numerous parameters measured.

The main aims of this study are: (i) to develop, validate and apply methods for the analysis of genetic variations in relevant cytochrome P450 genes and their products, and (ii) to correlate the gene structure and expression with lung cancer susceptibility in smokers. Assays include P450 phenotyping of subjects by probe drugs *in vivo* (urinary caffeine metabolites), phenotyping of lung tissue *in vitro*, using P450-specific substrates, measuring carcinogen–DNA adducts in lung tissue by $^{32}$P-postlabelling and genotyping assays in lymphocytes. Several of these assays are being performed in each subject, allowing comparison of the different endpoints and selection of the most suitable non-invasive assays to identify metabolic pheno(geno)types at higher risk for smoking-associated lung cancer.

#### *Smoking and peripheral type of cancer are related to high levels of pulmonary cytochrome P450IA in lung cancer patients*

Pulmonary AHH activity showed a good correlation ($r = 0.59$; $p > 0.01$) with the intensity of immunohistochemical staining for cytochrome P450IA by a monoclonal antibody (raised against 3-methylcholanthrene-inducible rat P450s) in lung tissue sections from lung cancer patients. Smoking and peripheral type of lung cancer were positively related to high levels of pulmonary cytochrome P450IA species, probably reflecting high rates of induction. Cytochrome P450IA was detected mainly in the peripheral airways in type I and II alveolar epithelium and in ciliated columnar and cuboidal bronchiolar epithelium[118].

These data are consistent with independent findings that active smoking is positively correlated with the expression of CYP1A1 in human lung tissue; this gene expression was no longer detected six weeks after smoking was terminated[119].

These results reinforce previous evidence that recent cigarette smoke exposure induces pulmonary drug-metabolizing enzymes and that the inducibility of AHH activity (associated with a high level of cytochrome P450IA1) in the lungs of smokers is associated with lung cancer risk[120].

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[118] Anttila, S., Hietanen, E., Vainio, H., Camus, A.-M., Gelboin, H.V., Park, S.S., Heikkilä, L., Karjalainen, A. & Bartsch, H. (1991) *Int. J. Cancer*, **47**, 681–685

[119] McLemore, T.L., Adelberg, S., Liu, M.C., McMahon, N.A., Yu, S.J., Hubbar, W.C., Czerwinski, M., Wood, T.G., Storeng, R., Lubet, R.A., Eggleston, J.C., Boyd, M.R. & Hines, R.N. (1990) *J. Natl. Cancer Inst.*, **82**, 1333–1339

[120] Bartsch, H., Petruzzelli, S., de Flora, S., Hietanen, E., Camus, A.-M., Castegnaro, M., Geneste, O, Camoirano, A., Saracci, R. & Giuntini, C. (1991) *Mutat. Res.* (in press)

*Metabolism of (−)-benzo[a]pyrene-7,8-diol by lung microsomes and peripheral blood lymphocytes from lung cancer patients: effect of smoking*

We have measured the metabolism of (−)-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene (BP-7,8-diol) to corresponding tetrols (BP-tetrols) by human lung microsomes and peripheral blood lymphocytes from lung cancer patients[121]. In the lymphocytes, there was no statistically significant difference between smokers ($n = 6$), ex-smokers ($n = 4$) and non-smokers ($n = 3$).

Using lung microsomes from 19 lung cancer patients, recent smokers had four- and seven-fold higher levels ($p = 0.04$) of BP-tetrol fromation than ex-smokers and non-smokers, respectively. The lung microsomal AHH (CYP1A1) activity in smokers was much higher than in ex-smokers and non-smokers. Pulmonary AHH activity was correlated with tetrol formation ($r = 0.62$; $p < 0.1$ in smokers, and $r = 0.67$; $p < 0.01$ in all subjects). However, tetrol formation by lung microsomes was not correlated with that in lymphocytes. Despite the small number of study subjects, we can conclude that (i) lymphocytes cannot serve as a surrogate for lung microsomes in studies of metabolism of BP-7,8-diol; (ii) there was no difference in this metabolic step in lymphocytes from lung cancer patients, whether they were recent smokers or not; (iii) the higher tetrol formation observed in microsomes from recently smoking lung cancer patients is consistent with the higher pulmonary AHH activity and CYP1A1 expression.

*A new sensitive fluorometric assay for the metabolism of (−)-7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene by human hair follicles*

A new sensitive fluorometric assay was established to measure the stereospecific cytochrome P450-dependent formation of BP-tetrols from BP-7,8-diol by human hair follicles[122]. This simple assay requires 3–5 human hair follicles and a low (0.5–2.0 $\mu$m) substrate concentration and has a detection limit of 0.3 femtomoles of tetrols. Freshly isolated human hair follicles from 20 adult volunteers (10 non-smokers and 10 smokers) were assayed. While interindividual and seasonal variations were observed, the assay was found to be reproducible for a given subject. This rapid and non-invasive assay provides a new means for metabolic phenotyping of human subjects for their capacity to metabolize BP-7,8-diol to its carcinogenic form (+)-*anti*-BP diol-epoxide.

### 1.6.3.3 *Cytochrome P450 isozyme pattern is related to individual susceptibility to N-nitrosodiethylamine-induced liver cancer in rats*

(A.-M. Camus, E. Cardis and H. Bartsch; in collaboration with A. Aitio and M.L. Aitio, Helsinki, Finland)

In order to establish how variations in genetically determined mixed-function oxidase activities[123] are related to the susceptibility of individual animals of the same strain to a chemical carcinogen, outbred male Wistar rats were given various doses of *N*-nitrosodiethylamine (NDEA) for 20 weeks. Hepatic activities of mixed-function oxidase and conjugating enzymes, as well as of $O^6$-methylguanine-DNA-methyltransferase, were measured before the carcinogen treatment. In addition, the metabolic profiles of two model drugs, antipyrine and diisopyramide, were assessed to see whether there was a correlation with the carcinogen susceptibility.

The latency period of hepatocellular tumours in individual rats was negatively related to the activity of hepatic *N*-dealkylase and AHH activity and positively related to the amount of microsomal protein. Correlations between 11 other parameters and the susceptibility to NDEA-induced carcinogenesis were not consistent. Thus the pattern of cytochrome P450

[121] Alexandrov, K., Rojas, M., Camus, A.-M. & Bartsch, H. (1991) (submitted for publication)
[122] Alexandrov, K., Rojas, M., Goldberg, M., Camus, A.-M. & Bartsch, H. (1990) *Carcinogenesis*, **11**, 2157–2167
[123] Aitio, A., Aitio, M.-L., Camus, A.-M., Cardis, E. & Bartsch, H. (1991) *Jap. J. Cancer Res.*, **82**, 146–156

isoenzymes involved in nitrosamine metabolism is related to differences in individual susceptibility to nitrosamine-induced carcinogenesis. This relationship was most marked at the low dose levels. These results are consistent with a reported association between restriction fragment length polymorphism (RFLP) pattern of the human CYP2E1 gene and higher risk for lung cancer in smokers, who are exposed to tobacco smoke-derived nitrosamines[124].

### 1.6.3.4 *Carcinogen–haemoglobin and –DNA adducts, urinary mutagenicity and metabolic phenotype in active and passive cigarette smokers*

(C. Malaveille, A. Hautefeuille and H. Bartsch; in collaboration with N. Caporaso, Bethesda, MD, USA; F.F. Kadlubar and L. Unruh, Jefferson, AR, USA; M. Schamer and G. Talaska, Cincinnati, OH, USA; P. Skipper and S. Tannenbaum, Boston, MA, USA; and P. Vineis, Turin, Italy)

In 100 healthy volunteers, the relationship between (i) the type of air- or flue-cured tobacco used, (ii) number of cigarettes smoked, and (iii) various biomarkers potentially relevant to the risk of bladder cancer were examined[125,126]; these included the levels of 4-aminobiphenyl (ABP)–haemoglobin adducts (a marker of internal dose), urinary mutagenicity in *S. typhimurium* TA 98 and the *N*-acetylation and *N*-oxidation phenotype (putative markers of susceptibility). ABP is a potent bladder carcinogen which is *N*-acetylated as a detoxification step and *N*-oxidized as an activation step. Levels of the ABP-haemoglobin adduct were higher in smokers of black tobacco than in smokers of blond tobacco, confirming earlier results. Slow acetylators had higher levels of the adduct for the same type and quantity of cigarettes smoked; subjects who were both slow acetylators and fast *N*-oxidizers had the highest levels of ABP adducts. Urinary mutagenicity was also associated with the quantity of cigarettes smoked, but not with the acetylation phenotype. Convex dose–response relationships were found between the amount smoked and the levels of ABP–haemoglobin adducts and of urinary mutagenicity, reflecting the shape of dose–response curves for cigarette-induced bladder cancer. In non-smokers who reported exposure to environmental tobacco smoke, the urinary mutagenicity, but not ABP–haemoglobin adduct level, was found to be a specific exposure indicator.

The relationship between levels of carcinogen–DNA adducts in exfoliated urothelial cells and ABP–haemoglobin adducts and urinary mutagenicity has been investigated in the same group of volunteers[127]. The presence of covalent modifications in DNA from exfoliated urothelial cells of smokers and non-smokers was determined using $^{32}$P-postlabelling. At least four of the adducts detected appeared to be related to cigarette smoking, showing levels 2–9 times higher in the smokers than in non-smokers. Two were qualitatively very similar to adducts found previously in human bladder biopsy samples, of which one corresponded to *N*-(deoxyguanosin-8-yl)-ABP. Levels of these two adducts were correlated significantly with the levels of ABP–haemoglobin adducts and with the type and number of cigarettes smoked. In addition, levels of the putative *N*-(deoxyguanosin-8-yl)-ABP adduct were correlated with the mutagenic activity of the individual's urine. Levels of the two other carcinogen–DNA adducts that were increased in

[124] Uematsu, F., Kikuchi, H., Motomiya, M., Abe, T., Sagami, I., Ohmachi, T., Wakui, A., Kanamaru, R. & Watanabe, M. (1991) *Jap. J. Cancer Res.*, **82**, 254–256

[125] Vineis, P., Caporaso, N., Tannenbaum, S.R., Skipper, P.L., Glogowski, J., Bartsch, H., Coda, M., Talaska, G. & Kadlubar, F. (1990) *Cancer Res.*, **50**, 3002–3004

[126] Bartsch, H., Caporaso, N., Coda, M., Kadlubar, F., Malaveille, C., Skipper, P., Talaska, G., Tannenbaum, S.R. & Vineis, P. (1990) *J. Natl Cancer Inst.*, **82**, 1826–1831

[127] Talaska, G., Schamer, M., Skipper, P., Caporaso, N., Unruh, L., Kadlubar, F., Bartsch, H., Malaveille, C. & Vineis, P. (1991) *J. Natl Cancer Inst.* (in press)

cigarette smokers did not seem to be related to the amount or type of tobacco smoked, nor to the ABP–haemoglobin adduct level or urinary mutagenicity. One of these adducts displayed chromatographic behaviour similar to that reported for 2-amino-1-methyl-6-phenylimidazo-[4,5-*b*]pyridine (PhIP), and PhIP has been implicated as a major DNA-damaging agent[128] (see section 1.2.3.7).

## 1.7 *Studies on Mechanisms of Carcinogenesis*

During the last two years considerable effort has been devoted to the integration of biochemical and molecular biology techniques with epidemiological field studies. These studies have yielded promising insights into the etiology of some human cancers (liver and oesophagus) as well as clarifying their natural history. In particular, the examination of the spectra of mutations responsible for the inactivation of the human tumour suppressor gene p53 has provided valuable information on the etiology of some of these tumours (see section 1.7.6.2). The development of reliable markers of human exposure to aflatoxins has permitted the implementation of field studies to examine the interaction between this carcinogen and HBV infection in the etiology of liver cancer (see section 1.7.2). Parallel experimental studies have indicated the validity of this overall approach. Other such molecular epidemiological studies are being carried out, in collaboration with various national laboratories, by multidisciplinary teams.

Research is continuing into the role of cell-to-cell communication in cancer progression and the identification of substances that specifically affect such communication (see section 1.7.8). Studies on prenatal exposure to carcinogens have indicated that the activated oncogene detected in tumours that developed postnatally is specific for the type of tumours. Linkage studies have identified genetic markers that are informative in the identification of genetic susceptibility of breast cancer. These and other projects examining individual susceptibility to various cancers are described in detail in section 1.6.

### 1.7.1 Role of viruses in the etiology of human cancer

Laboratory investigations linked to epidemiological studies are being used to elucidate the role of viruses in the etiology of certain human cancers and to identify the molecular steps involved. The particular models of cancer being studied are Epstein–Barr virus (EBV)-associated lymphomas such as Burkitt's lymphoma (BL) (a cancer that shows great geographic variation in incidence) and lymphoma occurring in immunocompromised individuals.

Epidemiological research is continuing into the involvement of hepatitis B virus in liver cancer (section 1.3.5) and of human papillomavirus in cervical cancer (section 1.3.10). The effectiveness of vaccination against hepatitis B virus in prevention of liver cancer is being evaluated in the Gambia Hepatitis Intervention Study (section 2.3.1).

#### 1.7.1.1 *Collection of biological material related to Epstein–Barr virus and lymphoma* (G. Lenoir, C. Bonnardel, M. Vuillaume and S. Pauly)

As part of various Agency projects, we have collected for over 20 years a large and unique collection of sera, tumour material and cell lines (over 120 BL cell lines established in culture at the Agency, representing one of the largest collections of human tumour cell lines for a given

[128] Peluso, M., Castegnaro, M., Malaveille, C., Friesen, M., Garren, L., Hautefeuille, A., Vineis, P., Kadlubar, F. & Bartsch, H. (1991) *Carcinogenesis*, **12**, 713–717

cancer) which are used by institutions all over the world for studies of EBV, BL, nasopharyngeal carcinoma and B-cell neoplasia. During the period under review, 500 lymphoid cell lines, 30 biopsies, 90 sera and 60 probes were sent to 42 institutions in 13 countries in the form of live cells, frozen cells and samples of DNA, as well as various other materials, such as sera, biopsies and probes.

#### 1.7.1.2 *Studies on lymphomas occurring in AIDS patients*

(H.J. Delecluse and G. Lenoir; in collaboration with M. Raphaël, Paris (cooperative programme supported by the Agence Nationale de Recherches sur le Sida, Paris))

EBV can cause lymphoproliferative diseases in individuals with immune dysfunction. Most such lymphoproliferations are polyclonal B-cell proliferations classified as diffuse lymphoma, but are not of the Burkitt's type. They are very rare in the general population, but are a frequent cause of death in children with genetically determined immunodeficiencies. They also occur at relatively high incidence in individuals treated with immunosuppressive therapy for organ transplantation. The implication of EBV in these lymphomas is based on detection of markers for the virus within the proliferating cells. The importance of alterations of immune function in their genesis is stressed by the fact that they may regress when the immunosuppressive therapy is reduced or withdrawn. A similar lymphoma occurs in AIDS patients with severely altered immune characteristics. Some individuals positive for human immunodeficiency virus (HIV) also develop true Burkitt-type lymphoma, with characteristic chromosomal translocations, but in some cases, no detectable EBV sequences. This suggests that their pathogenesis is not directly related to the presence of EBV, nor to the HIV-induced T-cell immunodeficiency. A set of such tumours is being investigated at the molecular level in order to better define their biological characteristics. Correlation of the results with the clinical and pathological data from the cooperative study group may help in identifying the risk factors for the two types of lymphoma. The molecular analysis of a first set of 17 malignant non-Hodgkin lymphomas occurring in HIV-positive individuals indicates that the molecular approach is necessary complement to a morphological classification.

#### 1.7.1.3 *Molecular aspects of EBV-induced B-cell immortalization and transformation*

(A. Calender, M. Billaud, M. Cordier-Bussat and G. Lenoir; in collaboration with G. Bornkamm, Munich, Germany)

The importance of three latent EBV genes (those coding for EBV nuclear antigen-2 (EBNA2), latent membrane protein (LMP) and terminal protein) has been investigated. Through transfection experiments it was shown that both EBNA2 and LMP are critical for activation of cellular genes involved in cell proliferation (CD21, CD23)[129]. The expression of other cellular genes possibly involved in Burkitt's lymphoma pathogenesis has been investigated at the transcriptional level. We have demonstrated that expression of two lymphocyte function-associated molecules, LFA-1 and LFA-3, that are involved in intercellular adhesion and the T cytotoxic pathway, is strongly up-regulated by immortalizing EBV. These result suggest that EBNA2- and/or LMP-mediated deregulation of cellular genes, such as CD21, CD23 and LFA-3, could be part of the mechanisms of the EBV involvement in B cell immortalization.

The expression of cellular genes other than those coding for CD21 or CD23 activation antigens has been analysed. Following EBV infection, alteration of vimentin expression was

[129] Zimber–Strobl, U., Süntzenich, K.-O., Eick, D., Laux, G., Cordier, M., Calender, A., Billaud, M., Lenoir, G.M. & Bornkamm, G.W. (1991) *J. Virol.*, **65**, 415–423

consistently observed. A crucial observation was the activation by immortalizing EBV isolates of LFA-1 $\beta$ chain (CD18) and of LFA-3 (CD58)[130]. In collaboration with Dr D. Thorley-Lawson (Boston, MA, USA), we have shown that integration of EBV is a frequent event in EBV-converted Burkitt's lymphoma cells[131]. These results represent the first demonstration that integration can be a consistent mechanism of EBV maintenance upon infection *in vitro* of certain B cells. This raises the possibility that rare integration events could be involved in Burkitt's lymphoma and NPC genesis.

#### 1.7.1.4 *Prevalence of human T-cell leukaemia/lymphoma virus type 1 (HTLV-1) in the population of the far east of the USSR*

(V. Gurtsevitch, Moscow, USSR)

HTLV-1 seroprevalence among healthy individuals, including blood donors, in far eastern territories of the USSR has been studied. More than 1000 patients with lymphoproliferative malignancies from different regions of the USSR have also been tested. A cluster of HTLV-1-infected individuals was found in Sakhalin, and an HTLV-1-associated case of adult T-cell leukaemia (ATL) similar to those in Japan was detected for the first time in the USSR. Two HTLV-1-producing cell lines, from the ATL patient and from a seropositive healthy individual, have already been cultured for more than six months and have beome practically IL-2 independent.

#### 1.7.1.5 *Meeting on Viral–Chemical Interaction*

Viral infection plays a role in the etiology of several major malignancies. In addition, synergistic interactions between chemical carcinogens and viruses have been demonstrated in various model systems. A meeting was convened in Lyon on 3 and 4 June 1991, at which evidence on these issues at levels from molecular biological to epidemiological was reviewed.

Furthermore, on the day following this meeting, an ad-hoc *IARC Monographs* advisory group on viruses and other infective agents composed of most of the meeting participants was convened (see section 1.2.6.5).

### 1.7.2 The relative contributions of aflatoxin $B_1$ and hepatitis B virus in the etiology of liver tumours

(C.P. Wild, B. Chapot, L.A.M. Jansen and R. Montesano)

Knowledge of the relative contributions of hepatitis B virus (HBV) and aflatoxin to the occurrence of liver cancer is of importance, particularly in designing intervention strategies to reduce the incidence of this cancer. Assays to measure individual exposure to aflatoxin have been developed that complement the use of HBV markers in the examination of both factors in field studies. In parallel, animal models provide an opportunity to examine specific hypotheses regarding mechanisms of possible interaction between these two risk factors under controlled conditions. The ability to measure individual aflatoxin exposure also allows the investigation of the link between that exposure and genetic changes induced in somatic or tumour cells (see section 1.7.6.3).

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[130] Calender, A., Cordier, M., Billaud, M. & Lenoir, G.M. (1990) *Int. J. Cancer*, **46**, 658–663

[131] Hurley, E.A., Agger, S., McNeil, J.A., Lawrence, J.B., Calender, A., Lenoir, G.M. & Thorley-Lawson, D.A. (1991) *J. Virol.*, **65**, 1245–1254

### 1.7.2.1 *Human exposure assessment by assay of aflatoxin–albumin adducts*

The level of serum aflatoxin–albumin adducts has been shown to be an informative marker of relatively recent exposure to aflatoxin $B_1$ ($AFB_1$) and from studies in The Gambia and elsewhere using this marker, considerable information is now available concerning aflatoxin exposure (see below).

The aflatoxin exposure data in The Gambia and China are shown in relation to those from other countries in Table 14. The assay is clearly suitable for use in field studies, particularly prospective cohort studies (see for example section 1.3.5.1) aimed at clarifying the role of aflatoxin and HBV in the etiology of hepatocellular carcinoma. In addition, the geographical differences in exposure may be useful in clarifying the genetic alterations involved in liver carcinogenesis (section 1.7.6.2).

*The Gambia*

(in collaboration with S.J. Allen, A.J. Hall, H. Inskip, F. Rasheed and H. Whittle, Fajara, The Gambia)

Of some 400 individuals examined in The Gambia, over 95% had detectable levels of the aflatoxin–albumin adduct. There was no significant difference in levels between males and females nor any trend with age in studies of children aged 3–8 years[132]. In children, mean adduct levels were twice as high (with a much greater range) in the dry season (May) than in November, although there was little association between values at each survey in individual children.

Significant differences in adduct levels were measured in the three ethnic groups, with Wollofs being the highest and Mandinkas the lowest (see Table 15). These clear variations could be based on genetic differences in aflatoxin metabolism.

HBV surface antigen carriers had higher levels of adduct than non-carriers (see Table 15), an effect of borderline significance after allowing for confounding factors ($p = 0.05$). This result is

Table 14. Aflatoxin–albumin adducts in human sera

| Country[a] (no.) | No. of subjects with different adduct levels (pg $AFB_1$–lysine eq. per mg albumin) | | | | | |
|---|---|---|---|---|---|---|
| | <5[b] | 5–25 | 26–50 | 51–75 | 76–100 | >100 |
| The Gambia | | | | | | |
| May (323) | 7 | 53 | 76 | 49 | 40 | 98 |
| November (67) | 0 | 39 | 13 | 7 | 3 | 5 |
| Senegal (29) | 0 | 20 | 6 | 2 | 1 | 0 |
| Kenya (91) | 48 | 26 | 5 | 1 | 5 | 6 |
| China | | | | | | |
| Guanxi (93) | 28 | 35 | 13 | 6 | 2 | 9 |
| Shangdong (69) | 69 | 0 | 0 | 0 | 0 | 0 |
| Thailand (84) | 73 | 10 | 1 | 0 | 0 | 0 |
| France (44) | 44 | 0 | 0 | 0 | 0 | 0 |
| Poland (30) | 30 | 0 | 0 | 0 | 0 | 0 |

[a]Numbers in parentheses are numbers of subjects tested

[b]Limit of detection = 5 pg aflatoxin $B_1$

[132] Wild, C.P., Jiang, Y.-Z., Allen, S.J., Jansen, L.A.M., Hall, A.J. & Montesano, R. (1990) *Carcinogenesis*, **11**, 2271–2274

Table 15. Aflatoxin–albumin adducts in The Gambia

| | | Log aflatoxin conc. (pg AF–lysine/mg albumin) | |
|---|---|---|---|
| | *N* | Mean | SD |
| *By ethnic group* | | | |
| Fula | 145 | 4.05 | 1.10 |
| Mandinka | 89 | 3.70 | 1.14 |
| Wollof | 89 | 4.41 | 0.69 |
| Fula vs Mandinka, $t = 2.3$; $p = 0.02$. Wollof vs Fula, $t = 3.08$; $p = 0.002$ | | | |
| *By HBV status* | | | |
| HBsAg + | 25 | 4.41 | 0.95 |
| HBsAg − | 298 | 4.02 | 1.05 |
| HBsAg+ vs HBsAg−, $t = 1.78$; $p = 0.08$ | | | |

of relevance to the study of the interaction between HBV and aflatoxin in the etiology of liver cancer.

Some association appeared to exist between the presence of malaria parasitaemia in children and a higher aflatoxin–albumin adduct level ($p = 0.06$). At the same time, no correlation between aflatoxin exposure and T cell-mediated immunity *in vitro* was observed. The mechanism of the association between aflatoxin adduct levels and malaria parasitaemia remains unclear.

In a study of 30 paired, maternal venous and umbilical cord blood samples collected in the east of the country, 21 of the cord blood samples were positive for the adduct. A correlation was seen between the levels of adduct in the mothers' venous blood taken at the time of giving birth and in the cord blood (Figure 13). Levels in the mothers' venous blood were on average five times higher than in the cord blood. These data suggest that *in utero* exposure to aflatoxin occurs[133].

*China*

(in collaboration with W.J. Blot, Bethesda, MD, USA; J. Chen, Beijing, China; and Y. Shunzhang, Shanghai, China)

In a case–control study of 100 cases of primary hepatocellular carcinoma, aflatoxin exposure was measured by dietary analysis and aflatoxin–albumin adduct analysis. Since these adducts are only markers of recent exposure, a lack of difference in levels between cases and controls was not surprising. A good correlation was observed between the dietary exposure and aflatoxin–albumin adduct level in control subjects, but no such relationship was seen in the liver cancer cases. One explanation could be an altered aflatoxin metabolism in these patients.

A comparison of aflatoxin exposure in three villages in Guangxi Fusui Xian showed that the frequency and level of exposure were associated with corn being the staple food rather than rice. The levels of exposure in these three villages contrasted with a lack of any positive sera from Shandong in the north-east of the country.

[133] Wild, C.P., Rasheed, F.N., Jawla, M.F.B., Hall, A.J., Jansen, L.A.M. & Montesano, R. (1991) *Lancet*, **337**, 1602

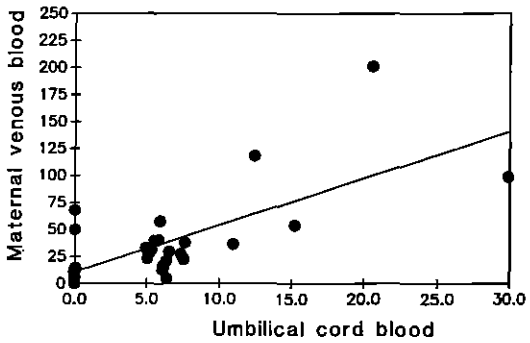


Fig. 13. Correlation between aflatoxin-albumin adduct levels (pg aflatoxin-lysine eq. per mg albumin) in maternal venous blood and umbilical cord blood

### 1.7.2.2 *The interaction of aflatoxin $B_1$ and hepatitis B virus in the Pekin duck*

in collaboration with L. Cova and C. Trépo, Lyon, France)

Aflatoxin $B_1$ was administered to newly hatched ducklings that were either uninfected or experimentally infected (day 3 post-hatching) with duck HBV. No difference in liver $AFB_1$ DNA adduct level was observed between the virally infected or uninfected groups. In addition, no significant change in viral replication occurred in ducklings treated with $AFB_1$ (days 2 to 9 post-hatching) compared to untreated birds, although this treatment did appear to lead to a higher level of DNA adduct formation when a further dose of $AFB_1$ was given on day 13 post-hatching.

### 1.7.2.3 *Aflatoxin–albumin adducts: a basis for comparative carcinogenesis between animals and man*

(in collaboration with R. Hasegawa and N. Ito, Nagoya, Japan)

In this study, serum albumin and liver DNA adduct levels are being compared in three strains of rat, as well as mice, hamsters and guinea-pigs treated chronically with $AFB_1$. This comparison should establish whether the albumin adduct levels reflect genotoxic damage in the target organ, and show if there is a correlation between the albumin adduct levels and differences in susceptibility to tumour induction in the different species.

### 1.7.2.4 *Studies of $AFG_1$–albumin adducts*

(in collaboration with G. Sabbioni, Würzburg, Germany)

Aflatoxin $G_1$ ($AFG_1$) is carcinogenic to animals and often present as a food contaminant along with $AFB_1$. It therefore needs to be taken into consideration in the molecular dosimetry of aflatoxin. The binding of $AFG_1$ to serum albumin in rats has been measured and found to be three to six times lower than binding of $AFB_1$, at equimolar doses. The $AFG_1$ adduct has not to date been observed in sera from humans with high levels of $AFB_1$–albumin adduct, even in individuals with $AFG_1$ in their food supply. $AFG_1$ may therefore make a minor contribution to aflatoxin–albumin adduct levels measured by immunoassay and could serve as an internal standard in such analyses[134].

[134] Sabbioni, G. & Wild, C.P. (1991) *Carcinogenesis*, **12**, 97–103

## 1.7.3 Mechanisms of nitrosation

### 1.7.3.1 *Biochemical studies on the bacterial nitrosating enzyme*

(S. Calmels, N. Dalla Venezia and H. Mower; in collaboration with M. Chippaux, Marseille, France; supported in part by NIH Grant No. CA 47591)

A number of studies have firmly established that the bacterial formation of nitrosamines from nitrite and secondary amines *in vitro* is enzyme-mediated[135,136,137]. Previous attempts to isolate the nitrosating activity in crude extracts of *Escherichia coli* or *Pseudomonas aeruginosa* after cell disruption were unsuccessful. However, we have recently succeeded in isolating the nitrosating enzyme from two denitrifying microorganisms: *P. aeruginosa* and *Neisseria mucosae,* when a specific copper-chelator (diethyldithiocarbamic acid ethyl ester) was present during the isolation procedure[138]. The soluble enzyme has a molecular weight of 66 kDa and a pH optimum of 7.25, and its biochemical characteristics are now being investigated. In non-denitrifying bacteria such as *E. coli,* nitrosation appears to be catalysed by a different enzyme.

In an attempt to establish whether subjects at high risk for gastric or bladder cancer harbour more of these nitrosation-proficient microorganisms, we are currently developing screening immunoassays for quantification of these proficient strains. Polyclonal antibodies raised against the nitrosating enzyme[139] have been used in a preliminary ELISA test which allowed the detection of bacterial nitrosating proficiency in 2 ml samples of human urine infected with $10^6$ cells of *P. aeruginosa* per millilitre.

In addition, monoclonal antibodies against the nitrosating enzyme from *P. aeruginosa* have been produced[139]. Although non-denitrifying enterobacteria have a lower nitrosating activity than denitrifying bacteria, they are more prevalent in the human microflora; thus it remains important to develop an assay for the nitrosating enzyme in *E. coli.*

### 1.7.3.2 *Catalysis of nitrosation by bacteria in a rat model of urinary tract infection*

(S. Calmels and J.-C. Béréziat)

To examine the role of urinary tract infection and inflammation as risk factors for bladder cancer, an abdominal incision was made in male Sprague–Dawley rats, and a stitch was inserted in the bladder wall to generate an inflammatory response; some of these animals received, in addition, $10^{11}$ cells of *Pseudomonas morganii* (previously isolated from a human urinary tract infection, exhibiting high nitrate-reductase and nitrosating activities) as an inoculate in the bladder. One week after surgery, the rats received an intraperitoneal dose of morpholine and 10 mM nitrate in the drinking water, and on the following day 5 mM nitrite. When rats were given nitrate or nitrite, urinary excretion of nitrate was highest in the animals with an inflamed bladder but no infection. This suggests that macrophages are involved in endogenous nitrate synthesis; the low levels of nitrate excretion in the infected animals is probably attributable to bacterial reduction of nitrate, which was confirmed by a higher urinary nitrite concentration in this group.

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[135] Calmels, S., Ohshima, H., Vincent, P., Gounot, A.-M. & Bartsch, H. (1985) *Carcinogenesis,* **6**, 911–915

[136] Calmels, S., Ohshima, H., Crespi, M., Cattoen, C. & Bartsch, H. (1987) In: Bartsch, H., O'Neill, I.K. & Schulte-Hermann, R. (1987) *The Relevance of* N-*Nitroso Compounds to Human Cancer: Exposure and Mechanisms* (IARC Scientific Publications No. 84), Lyon, International Agency for Research on Cancer, pp. 391–395

[137] Calmels, S., Ohshima, H. & Bartsch, H. (1988) *J. Gen Microbiol.,* **134**, 211–226

[138] Calmels, S., Dalla Venezia, N. & Bartsch, H. (1990) *Biochem. Biophys. Res. Commun.,* **171**, 655–660

[139] Dalla Venezia, N., Calmels, S. & Bartsch, H. (1991) *Biochem. Biophys. Res. Commun.,* **176**, 262–268

The excretion of *N*-nitrosomorpholine was higher in animals with bladder infection than in those with only inflammation. Thus, in our model inflammation was not sufficient to markedly increase endogenous nitrosamine synthesis, but required the presence of bacteriuria. As a consequence, increased reduction of nitrate into nitrite and bacterial nitrosation occurred in the bladder. In the infected rats, the pH of urine was 7.8 as compared to 6.7 in those with inflammation only and in control animals, ruling out the possibility that nitrosamine formation occurred by acid-catalysed nitrosation in infected urine. Our results are consistent with previous studies that have reported higher nitrosamine and nitrite levels in urine from humans with urinary tract infections.

### 1.7.3.3 *Bacterial catalysis of nitrosation in the colonized stomach*

(S. Calmels, J.-C. Béréziat, H. Ohshima and H. Bartsch)

Although microorganisms isolated from the human achlorhydric stomach have been found to possess nitrate-reductase activity and a nitrosating enzyme, it remains unclear whether endogenous formation of NOC is increased in subjects with achlorhydria due to the presence of bacteria in the colonized stomach. We have therefore investigated the role of bacteria in catalysing intragastric formation of nitrosamines in a rat model[140]. Using omeprazole to selectively inhibit gastric $H^+/K^+$-ATPase under acidic conditions and thus induce gastric achlorhydria, we measured endogenous nitrosation of thiazolidine-4-carboxylic acid and morpholine by nitrate or nitrite, in the presence or absence of *E. coli* and *P. aeruginosa*, both nitrosation-proficient bacteria. Rats given thiazolidine-4-carboxylic acid, nitrate and $10^{11}$ cells of *E. coli* had a five times higher endogenous formation of *N*-nitrosothiazolidine-4-carboxylic acid as compared to controls. When rats were given morpholine and nitrite together with *E. coli* or *P. aeruginosa*, endogenous *N*-nitrosomorpholine formation was increased ~2.5-fold as compared to controls. Rats given morpholine, nitrate and *E. coli* or *P. aeruginosa* excreted a three times higher level of *N*-nitrosomorpholine as compared to controls. These results show that bacteria possessing nitrate-reductase and nitrosating enzymes contribute to intragastric NOC formation, in the presence of suitable precursors.

### 1.7.3.4 *Nitrosation by macrophages*

(H. Ohshima; in collaboration with H. Adachi, H. Esumi, T. Ogura, T. Sugimura and M. Tsuda, Tokyo, Japan)

Nitrosamines are formed in macrophage culture when appropriate amines are added and if macrophage stimulators such as lipopolysaccharide (LPS) and interferon-$\lambda$ (IFN-$\lambda$) are present[141]. Elucidation of the mechanism of this process has been hampered by the complexity of the culture medium, and to overcome this problem, we have set up a cell-free reaction system[142]. The $105\,000 \times g$ supernatant of macrophages from the cell line J774-1, activated with both LPS and IFN-$\lambda$, nitrosates morpholine to form *N*-nitrosomorpholine in the presence of L-arginine and NADPH under physiological conditions (optimal pH 7.5). Activation of macrophages by both LPS and IFN-$\lambda$ induced nitrosation activity by a factor of 500–600, compared to that of non-activated macrophages. Macrophages stimulated with LPS or IFN-$\lambda$ alone, or neither, exhibited much lower nitrosation activity. A combined sample of cytosols from macrophages activated with LPS alone and with IFN-$\lambda$ alone did not nitrosate morpholine as rapidly as did the cytosol of macrophages activated by the two compounds together. Heat-denatured cytosol lost

[140] Calmels, S., Béréziat, J.-C., Ohshima, H. & Bartsch, H. (1991) *Carcinogenesis*, **12**, 435–439
[141] Leaf, C.D., Wishnok, J.S. & Tannenbaum, S.R. (1989) *Cancer Surveys*, **8**, 323–334
[142] Ohshima, H., Tsuda, M., Adachi, H., Ogura, T., Sugimura, T. & Esumi, H. (1991) *Carcinogenesis*, **12**, 1217–1220

its ability to nitrosate amines. On the other hand, the formation of L-citrulline and nitrite/nitrate from L-arginine, which is catalysed by NO synthase, was markedly induced in macrophages cultured with either LPS alone or with both LPS and IFN-$\lambda$. These results suggest that for nitrosation, induction of NO synthase alone is not sufficient and that some additional factor(s) must be induced in macrophages. This factor, however, was not induced in macrophages by treatment with either LPS or IFN-$\lambda$ alone, but rather induced by both compounds in combination or synergistically.

The formation of nitrosomorpholine increased linearly with the protein concentration of cytosol under the conditions used. The presence of EDTA or EGTA decreased nitrosation activity; the addition of either $Mg^{2+}$, $Ca^{2+}$ or $Mn^{2+}$ restored activity.

The arginine analogues $N^G$-monomethyl-L-arginine, $N^G$-nitro-L-arginine and its methyl ester and L-canavanine inhibited L-arginine-dependent nitrosation, as did L-ascorbate and oxyhaemoglobin.

Substrate specificity for L-arginine-dependent nitrosation by macrophage cytosol was studied using seven secondary amines and one tertiary amine (aminopyrine). An inverse linear relationship was observed between the amounts of nitrosamine formed and the $pK_a$ value of the amine.

Use of anaerobic conditions decreased the yield of *N*-nitrosomorpholine markedly, indicating that NO generated from L-arginine is probably oxidized to a nitrosating agent. However, there was no significant difference in L-citrulline formation from L-argininge under anaerobic and aerobic conditions. The presence of superoxide dismutase enhanced the yield of nitrosomorpholine up to 240%.

These results, together with those previously reported, support the hypothesis of a three-step mechanism for macrophage-mediated nitrosamine formation: (i) NO is generated from L-arginine, catalysed by NO synthase; (ii) NO is oxidized by oxygen to form $NO_2$, either enzymatically or chemically; and (iii) the $NO_2$ generated exists in equilibrium with the potent nitrosating agents, $N_2O_3$ and $N_2O_4$, which react with amines to form nitrosamines.

### 1.7.4 Repair of DNA damage induced by alkylating agents

Alkylating agents are widespread in the environment and human exposure occurs for many of these agents, some of which have been shown to be carcinogens. The studies reported below are mainly centred on repair of DNA damage induced by methylating agents ($O^6$-methyldeoxyguanosine and 7-methyldeoxyguanosine), since human exposure to such agents can occur from various sources, such as nitrosamines (present in tobacco or endogenously formed) and various chemotherapeutic drugs (e.g. procarbazine, dacarbazine, nitrosourea derivatives).

#### 1.7.4.1 *Modulation of DNA repair enzymes in human tissues*

(J. Hall and H. Brésil; in collaboration with A. Likhachev and N. Loktionova, Leningrad, USSR)

To complement the studies on the detection of alkylated DNA bases in human tissues, measurement of various DNA repair enzymes is being carried out on numerous human tissues and cell types[143]. $O^6$-Alkylguanine-DNA alkyltransferase (AGT) was found in all tissues tested, with much the highest level in liver, as expected, and considerable inter-individual variation. The level in peripheral blood lymphocytes was higher than those in oesophagus, lung, placenta or

[143] Montesano, R., Hall, J., Hollstein, M., Mironov, N. & Wild, C.P. (1990) In: Sutherland, B.M. & Woodhead, A.D., eds, *DNA Damage and Repair in Human Tissues*, New York, Plenum Press, pp. 437–452

stomach. Repair activity of 7-methylguanine was very low, which makes it unlikely that this can be used as a biological marker of exposure to alkylating agents (see section 3.3.4.1).

The levels of AGT and methylpurine and formamidopyrimidine-DNA glycosylases have been measured in protein extracts from peripheral blood cells of blood donors (smokers and non-smokers) and lung tissues from cancer patients (smokers and non-smokers). No difference in the AGT activity was observed between smokers and non-smokers in either sample type (Table 16). A difference in methylpurine-DNA glycosylase was observed between smokers and non-smokers in lung tissue and in peripheral blood cells from blood donors. Interestingly, in this small sample set the level of formamidopyrimidine-DNA glycosylase, which also repairs 8-hydroxyguanine adducts in DNA, was found to be elevated in blood cell extracts from smokers but not in lung tissue extracts.

The modulation of AGT activity was followed in cancer patients treated with a single dose of *N*-nitroso-*N*-methylurea (NMU) (300 mg) (see section 3.3.4.4). In three cases complete loss of AGT activity was observed (the protein extract containing active methylpurine-DNA glycosylase) following this treatment, which produced $O^6$-MedG levels between 10 and 16 μmol per mole dG.

### 1.7.4.2 *Modulation of DNA repair enzymes following DNA damage by alkylating agents in rat liver*

(J. Hall, H. Brésil, M. Miele and C. Pezet)

The capacity of rat liver to repair $O^6$-methylguanine has been previously shown to be altered after either chronic or a single exposure to 20 mg/kg *N*-nitrosodimethylamine (NDMA). Following an initial depletion in the pool of the repair enzyme, a rapid reconstitution and increase in enzyme level to above control values was observed. A similar effect has subsequently been observed after single doses of 5 and 10 mg/kg NDMA. Increases in levels of formamidopyrimidine-DNA glycosylase (which repairs the imidazole ring-open form of 7-MeG and 8-hydroxyguanine) and the methylpurine-DNA glycosylase have also been observed in rat liver (Figure 14) following a single dose of NDMA (20 mg/kg). The effect of the dose schedule can modulate various DNA repair processes and this affects the carcinogenic dose-response in this system.

The repair mechanism for the promutagenic lesion $O^4$-methylthymine ($O^4$-MedT) has been investigated in rat liver epithelial cells in culture by correlating the level of AGT activity in the cells and the amounts of $O^6$-MedG and $O^4$-MedT formed in the cellular DNA at various times after treatment with the alkylating agent MNNG. Initial results suggest a correlation between the

Table 16. DNA repair activity (fmol/mg protein/h) in protein extracts from lung and peripheral blood cells

| | AGT | Methylpurine-DNA glycosylase | Formamidopyrimidine-DNA glycosylase |
|---|---|---|---|
| *Lung tissue* | | | |
| Smokers (20) | 76.1 ± 5 | 917.3 ± 78.8 | 46.0 ± 3 |
| Non-smokers (6) | 73.5 ± 6 | 652.2 ± 50.8 | 41.2 ± 3 |
| *Peripheral blood cells* | | | |
| Smokers | 164.9 ± 24.7 (17) | 890.2 ± 131.2 (16) | 50.1 ± 10.3 (10) |
| Non-smokers | 147.1 ± 17.6 (17) | 490.6 ± 104.7 (13) | 29.6 ± 3.6 (8) |

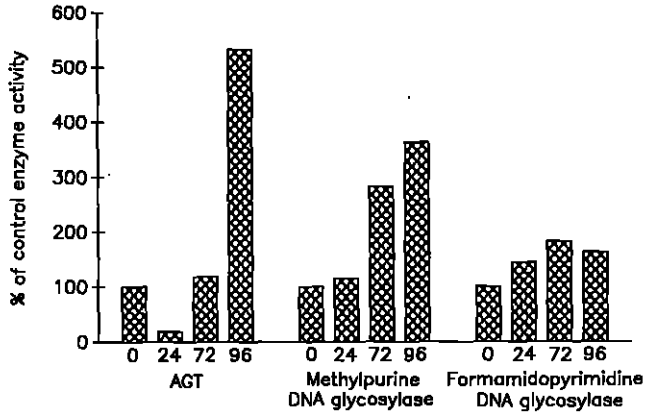


**Fig. 14. Variation in DNA repair enzymes after a single treatment with NDMA (20 mg/kg) in rat liver**

resynthesis of AGT and the loss of $O^4$-MedT, implicating this enzyme in the repair process of this modified base[144].

### 1.7.4.3 *Mechanisms of tolerance to the cytotoxic effects of alkylating agents in mammalian cells*

(J. Hall and C. Pezet; in collaboration with K. Wiebauer, Rome, Italy)

An increased resistance to the cell-killing effects of alkylating agents in mammalian cells can be observed in cells which express increased levels of AGT activity and thus enhanced repair of the cytotoxic lesion $O^6$-methylguanine. However, cytotoxic resistance and the AGT expression are not causally related, suggesting that some alternative tolerance mechanisms to DNA damage may exist. A series of Chinese hamster ovary, AGT-deficient, MNNG-resistant cell lines has been established which do not have detectable AGT activity nor significantly elevated levels of methylpurine-DNA glycosylase. All have elevated levels of glutathione-*S*-transferase and glutathione compared to the parental cell line. However, the initial levels of formation of $O^6$-methylguanine in cellular DNA after 0.1 mM MNNG treatment were similar in all but one cell line, suggesting that the acquired resistance to the cell-killing effect of MNNG is not due to a reduction in the formation of modified bases by the alkylating agent. All the resistant cell lines show cross-resistance to the cytotoxic effects of the alkylating agents NMU and methyl methanesulfonate and also to 6-thioguanine. In preliminary studies *in vitro* the levels of a specific DNA glycosylase involved in repairing G:T base-pair mismatches seem to be similar in parental and resistant cell lines, but the subsequent single nucleotide gap-filling reaction appears more efficient in the resistant cell lines. DNA polymerase $\beta$ is one of the enzymes involved in this later step and its possible involvement in this resistance phenotype is being further studied.

[144] Hall, J., Brésil, H., Serres, M., Martel-Planche, G., Wild, C.P. & Montesano, R. (1990) *Cancer Res.*, **50**, 5426–5430

#### 1.7.4.4 *Differential repair of* $O^6$*-methylguanine*

(N. Mironov, F. Bleicher, G. Martel-Planche and C.P. Wild; in collaboration with P.F. Swan, London, UK)

Carcinogenic N-nitroso compounds are thought to act via direct damage of DNA. Lesions at specific genomic sites can lead to corresponding local changes in nucleotide sequence, which could in turn cause the activation of proto-oncogenes or the inactivation of tumour-suppressor genes. Differences in capacity to repair damage in selected genomic regions may account for some of the profound differences seen in the carcinogenic response in different tissues or in comparison of different individuals.

A method has been developed which allows detection of $O^6$-MeG within a nucleotide sequence of a single gene in order to measure methylation and repair at specific base sites. The method is based on the fact that $O^6$-MeG:T mispairs can be formed during DNA replication by DNA-polymerases. During PCR amplification, $O^6$-MedG may be read as adenine, so that the $O^6$-MeG:C pair in the template DNA will be converted to an A:T pair in the product. In order to validate this method, three different DNA templates for PCR were constructed, each containing one $O^6$-MeG in a defined position. Preliminary experiments have confirmed that the $O^6$-MeG in the template is replaced by adenine in the PCR product.

At the same time, the distribution of $O^6$-MeG in the H-*ras* gene sequence in DNA treated with NMU was examined. After PCR, the product was cloned in phage M13 and the corresponding $O^6$-MeG to A transition analysed. A nonrandom distribution of this adduct was found with regard to DNA sequence, with no adducts found in triplets such as AGC or CGC, whereas the middle G in triplets AGA, GGA or GGC was often adducted. Calculation of the frequency of adduct in each triplet could give a basis for prediction of the action of NMU at a single gene level.

### 1.7.5 *In vitro* assay of capacity to repair UV-induced DNA damage: its use in molecular epidemiological studies for exposure assessment

(J. Hall; in collaboration with D. English, Perth, Australia; and L. Grossman, Baltimore, MD, USA)

A method for measuring DNA excision repair in human lymphocytes has been developed in the laboratory of Professor Grossman. The assay, as developed, measures the capacity of cells to repair cyclobutane–dithymidine DNA photoproducts formed by solar UV irradiation and benzo[*a*]pyrene adducts. The repair efficiency measured in a human population can be compared with that of known repair-proficient (normal human) and excision repair-deficient xeroderma pigmentosum lymphoblastoid cell lines. Prospective studies have been initated in a population based in Geraldton, Western Australia to assess the association between capacity to repair UV DNA damage and the risk for skin cancer.

### 1.7.6 Oncogenes and tumour suppressor genes as critical targets of environmental carcinogens

Cancer is the result of an accumulation of genetic alterations that disrupt control of cell growth and differentiation. The most common specific gene changes known to contribute to human carcinogenesis are point mutations in the p53 tumour suppressor gene and in *ras* oncogenes. More than half of the world cancer burden is made up of malignancies in which mutations at the p53 locus or in a *ras* gene, or both, have been detected[145,146]. Many known

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[145] Hollstein, M., Sidransky, D., Vogelstein, B. & Harris, C.C. (1991) *Science* **253**, 49–53

[146] Bos, J.L. (1989) *Cancer Res.*, **49**, 4682–4689

human carcinogens are efficient in inducing base substitutions such as those actually observed in cancer genes of humans tumors. *Ras* oncogenes and the p53 tumour suppressor genes are thus probably among the important targets of genetic damage for some of these agents. The mutation spectra in human tumours are being analysed, and may help in identifying the carcinogen exposures that elevate cancer risk. In addition, studies are being carried out in cultured cells and in animals to examine experimentally the interaction of carcinogens with oncogenes.

We are applying this approach to two major human cancers, carcinoma of the oesophagus and hepatocellular carcinoma, in parallel with refined measurements of individual carcinogen exposure developed at the IARC (sections 1.7.2 and 3.3.4). This approach represents a means of testing hypotheses generated by epidemiological studies of environmental risk factors.

### 1.7.6.1 *Chemical-specific induction of* ras *gene mutations; development of a sensitive method to detect a specific mutation*

(H. Nakazawa, A.M. Aguelon and H. Yamasaki)

When tumours are induced by administered carcinogens in rodents, the mutation patterns of *ras* genes detected in these tumours are often specific[147]; for example, A to T transversion in tumours induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) and G to A transition in those induced by ENU. It has been, therefore, assumed that different types of chemical induce *ras* mutations in specific manners. It is relatively easy to analyse oncogene mutations in tumour samples, since the majority, if not all, of the cells in a given tumour contain the same mutation. However, one requires a sensitive method to detect a mutation in an exposed cell population before a tumour develops, since very few cells have such a mutation. We have developed a sensitive method, by which we can detect a specific mutation (A to T transversion at the 61st codon of Ha- and Ki-*ras* genes) at a frequency as low as one mutant in $10^6$ cells[148].

In developing this method, we took advantage of the fact that the $A^{182}$ to T mutation at the 61st codon of Ha- or Ki-*ras* genes creates an additional cleavage site for the XbaI restriction enzyme. Using a PCR assay[149] (Figure 15) we found no Ha-*ras* $A^{182}$ to T mutation in unexposed cells. In order to examine whether this assay can detect a mutant Ha-*ras* sequence when mixed with a vast number of wild-type Ha-*ras* sequences, we mixed DNA samples from mouse skin carcinomas which contained homologous Ha-*ras* $A^{182}$ to T mutations with DNA samples from normal mouse epidermal cells, in various ratios. The results of the assay indicated clearly that the mutant and normal alleles are amplified to similar extents in the PCR step. Furthermore, it was possible to detect a mutation frequency of around $10^{-6}$. This level of sensitivity is sufficient to tell us whether DMBA induces the Ha-*ras* $A^{182}$ to T mutation in BALB/c 3T3 cells. The mutation was in fact detectable after 48 h of exposure to 100 ng/ml of DMBA, whereas it required 72 hours to obtain a similar level of mutation with 50 ng/ml. After two weeks of exposure of these levels of DMBA, the mutation frequencies reached $1.4 \times 10^{-4}$ and $0.8 \times 10^{-4}$, respectively.

In order to see whether other carcinogens also induce the same mutation, we exposed BALB/c 3T3 cells to 3-methylcholanthrene (MCA), MNNG, 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and ultraviolet-C radiation. All these carcinogens induce transformation in BALB/c 3T3 cells, but no Ha-*ras* $A^{182}$ to T mutation was detectable. Thus this mutation is specific to DMBA, among the agents tested, at least within the limits of detection.

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[147] Balmain, A. & Brown, K. (1988) *Adv. Cancer Res.*, **51**, 147–182

[148] Nakazawa, H., Aguelon, A.M. & Yamasaki, H. (1990) *Mol. Carcinog.*, **3**, 202–209

[149] Keohavong, P. & Thilly, W.G. (1989) *Proc. Natl. Acad. Sci. USA*, **86**, 9253–9275

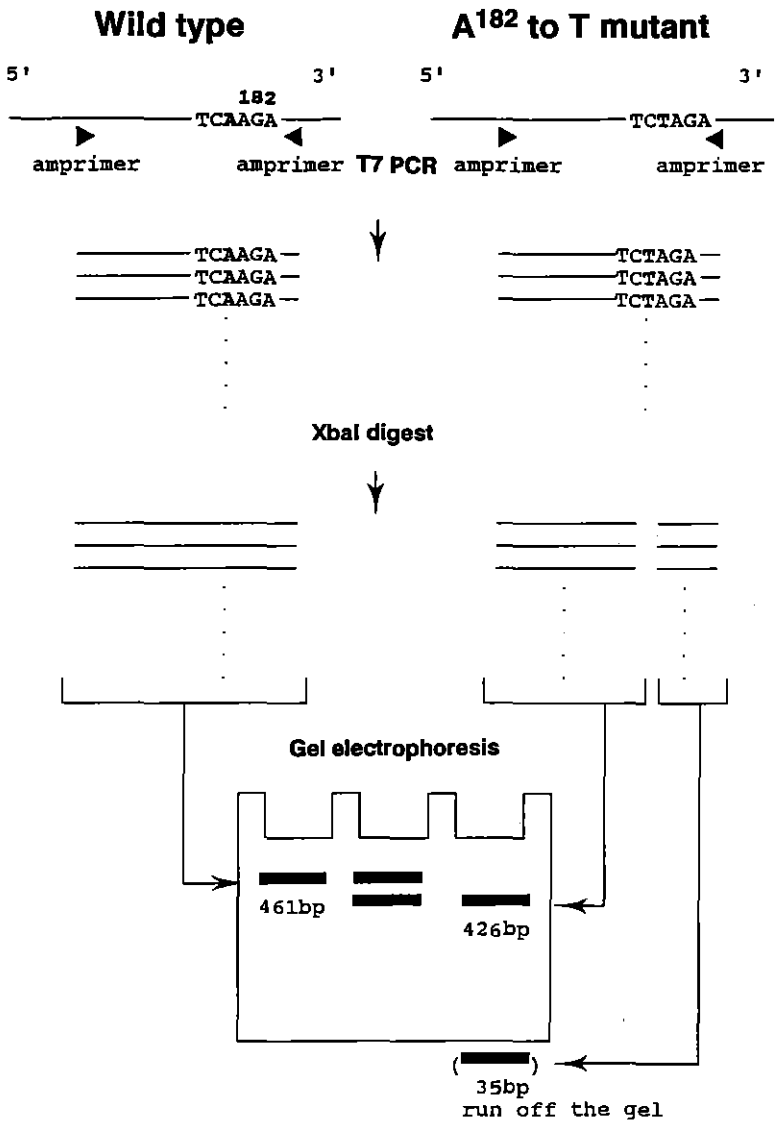


Fig. 15. Procedure for determination of Ha-*ras* mutation ($A^{182} \rightarrow T$) by PCR followed by RFLP analysis

### 1.7.6.2 *Involvement of* ras *gene mutations in human oesophageal tumours*

(C. Galiana, A. Fusco, Y. Oyamada, N. Martel and H. Yamasaki)

No mutations of *ras* oncogenes were detected in human oesophageal tumour samples from various geographical areas (see also section 1.7.6.3). Another 25 samples from France were also negative for mutations at codons 12, 13 and 61 of Ha-, Ki- and N-*ras* genes. We have studied seven established cell lines of human oesophageal tumours which show different degrees of

tumorigenicity in nude mice. An activating *ras* mutation was detected in three of these lines; two had G to A transition at the second position of codon 12 of Ki-*ras* and another had G to T transversion at the second position of codon 12 of Ha-*ras*. Since these cell lines were derived from Japanese tumour samples, it may be that some etiological agent(s) for oesophageal cancer specific to Japan can cause such mutations. In order to test this hypothesis, we have examined nine primary oesophageal tumours from Japan for *ras* mutations and found no mutation at codons 12, 13 or 61 of Ha-, Ki- and N-*ras* genes. The three mutated cell lines are more tumorigenic in nude mice than the four others, suggesting the involvement of the *ras* gene in the progression of oesophageal tumours. We therefore transfected mutated *ras* genes into the cell line which had the lowest tumorigenicity in nude mice. The transfectants selected for co-transfected *neo* gene expression were, however, no more tumorigenic than before *ras* transfection.

### 1.7.6.3 *Oncogene and tumour suppressor gene damage in human cancers*

(M. Hollstein, F. Bleicher, R. Montesano and C.P. Wild)

#### *Oesophageal cancer*

(in collaboration with C.C. Harris and R. Metcalf, Bethesda MD, USA; A.-M. Mandard, Caen, France; and L. Péri, Montevideo, Uruguay)

A major fraction of the world's cases of oesophageal cancer is attributable to tobacco and alcohol consumption, which suggests that some of the tumour mutations in cancer genes are directly or indirectly the result of exposure to these risk factors. In certain regions of the world, *N*-nitroso compounds in foodstuffs are thought to be important. Gene damage in oesophageal cancer patients belonging to different risk groups is being studied, to see if it reflects the genotoxicity of these carcinogens.

At the time of our study, sequence alterations in the p53 gene had been detected in human tumours of the brain, breast, lung and colon, but tumours of the oesophagus had not been examined. We tested four human oesophageal carcinoma cell lines and 14 human oesophageal squamous cell carcinomas by PCR amplification and direct sequencing for the presence of p53 mutations. Two cell lines and five of the tumour specimens contained a mutated allele (one frameshift and six missense mutations). The identification of aberrant p53 gene alleles in one third of the tumours suggested that mutations at this locus are common genetic events in the pathogenesis of carcinomas of the oesophagus[150].

Samples of oesophageal squamous cell carcinoma from 34 patients residing in Uruguay or in Normandy, France (15 from Normandy and 19 from Uruguay), were analysed for point mutations in the p53 tumour-suppressor gene. Most of these cancers are attributable to tobacco and/or alcohol consumption, and in Uruguay, to the drinking of hot mate tea as well. Point mutations in the p53 gene that result in amino acid substitutions or stop codons were identified in nearly half the samples by PCR amplification of exons 5–8 and direct sequencing[151]. The mutations were dispersed over the mid-region of the p53 gene in contrast to mutations reported in hepatocellular carcinoma samples, which were found almost exclusively at one base pair in the p53 coding sequence (see below).

No mutations in the *ras* gene family (Ha-, Ki- and N-*ras*) were found in 16 tumours from Uruguay by direct sequencing of exons in which transforming mutations are known to occur.

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[150] Hollstein, M.C., Metcalf, R.A., Welsh, J.A., Montesano, R. & Harris, C.C. (1990) *Proc. Natl. Acad. Sci. USA*, **87**, 9958–9961

[151] Hollstein, M.C., Péri, L., Mandard, A.-M., Welsh, J.A., Montesano, R., Metcalf, R.A., Bak, M. & Harris, C.C. (1991) *Cancer Res.* (in press)

Our previous study on *ras* mutations in oesophageal tumours from France was also negative[152], although p53 point mutations were found in almost half of these tumours. Studies by others on the occurrence of *ras* mutations in oesophageal squamous cell carcinomas of patients in Transkei and in China have also been negative[153,154].

Activating mutations in the Ha-, Ki- and N-*ras* genes are confined to a few critical sites, principally codons 12, 13 and 61. Possibly the mutational specificity of environmental factors contributing to oesophageal carcinogenesis in the populations studied is not directed towards potentially transforming *ras* sequences. Alternatively, in humans, *ras* mutations may not contribute to the growth of epithelial cells in the oesophagus *in vivo*.

*Analysis of p53 genetic and protein alterations in archival Chinese oesophageal tumour samples*

(in collaboration with W. Bennett and C.C. Harris, Bethesda, MD, USA; A. He, Shenyang, China; D. Lane and C. Midgley, Dundee, UK; and S. Zhu, Guangzhou, China)

In conjunction with a collaborative study investigating methods for analysis of p53 gene and protein alterations in paraffin-embedded tissues, we have analysed 20 tumours from Shenyang, China. More than half of the tumours contained elevated levels of the p53 protein as detected by immunohistochemical analysis. Sequence analysis was performed after PCR amplification of isolated DNA. Analysis of exons 5–8 in a subset of 20 tumours revealed missense point mutations in 8 out of 15 immunostain-positive tumours and a mutation encoding a stop codon in 1 of 5 immunostain-negative tumours. The data suggest that the occurrence of missense mutations is correlated with elevated levels of p53 protein[155].

*Hepatocellular carcinoma*

(in collaboration with L. Cova and C. Trépo, Lyon, France; A.-M. Mandard, Caen, France; K. Moussa, Conakry, Guinea; I.O. Oluybuyide, Ibadan, Nigeria; A. Ponzetto and M. Rizzetto, Turin, Italy; P. Srivatanakul, Bangkok, Thailand; and X.L. Xia and S.Y. Yu, Shanghai, China)

Activating *ras* mutations are rare in hepatocellular carcinomas (HCC) from both high- and low-incidence regions, whereas base substitutions in the p53 gene are seen in 40–50% of tumours from high-incidence regions. Mutations in tumour-suppressor genes are commonly found in most other human cancers also, but they are generally dispersed over the mid-region of the gene coding sequences, whereas the distinctive feature of p53 mutations in HCC is that in tumours from patients in the high-incidence regions tested so far, almost all mutations are G to T base substitutions at one base pair in codon 249[156,157], even though there are hundreds of possible sites at which a base substitution would affect the biological activity of the p53 protein.

G to T transversion is the substitution most likely to result from aflatoxin exposure and in these high-risk populations, dietary aflatoxin levels are high. Most HCC patients in these areas are also carriers of the hepatitis B virus, which could modulate mutation patterns. It is possible that the high frequency of codon 249 mutation is due to the specific nucleotide sequence in this region which makes aflatoxin–guanine adducts more likely to occur or less likely to be repaired (or perhaps both).

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[152] Hollstein, M., Smits, A.M., Galiana, C., Yamasaki, H., Bos, J.L., Mandard, A., Partensky, C. & Montesano, R. (1988) *Cancer Res.*, **48**, 5119–5123

[153] Jiang, W., Kahn, S.M., Guillem, J.G., Lu, S.H. & Weinstein, I.B. (1989) *Oncogene*, **4**, 923–928

[154] Victor, T., Dutoit, R., Jordaan, A.M., Bester, A.J. & van Helden, P.D. (1990) *Cancer Res.*, **50**, 4911–4914

[155] Bennett, W.P., Hollstein, M.C., He, A., Zhu, S.M., Resau, J., Trump, B.F., Metcalf, R.A., Welsh, J.A., Midgley, C., Lane, D.P. & Harris, C.C. (1991) *Oncogene* (in press)

[156] Hsu, I.C., Metcalf, R.A., Sun, T., Welsh, J., Wang, N.J. & Harris, C.C. (1991) *Nature*, **350**, 427–428

[157] Bressac, B., Kew, M., Wands, J. & Ozturk, M. (1991) *Nature*, **350**, 429–431

To investigate whether the codon 249 "hotspot" is a reflection of a sequence-specific activity of aflatoxin, and whether hepatitis B or C virus carrier state modulates the involvement of this gene lesion in the development of HCC, studies of human tumour samples are in progress, in parallel with animal model experiments.

HCC and normal tissue, as well as serum, have been collected in Nigeria, Thailand and China (see also section 1.7.2.1). The HBV status of each patient has been recorded, and detailed histopathological analysis of tumour samples performed. As aflatoxin exposure is considered a risk factor in these patient groups, levels of aflatoxin–macromolecular adducts have been measured.

Mutations in the p53 gene are being examined in DNA from malignant cells recovered from tissue sections prepared for histopathology, using PCR amplification and direct sequencing. The codon 249 mutation has already been detected in several samples.

In European countries, by contrast, the principal risk factors for HCC are consumption of alcoholic beverages and HBV infection. Another probable risk factor is infection or co-infection with the genetically unrelated hepatitis C virus, and smoking may also have a role. Patients in this study are therefore being grouped according to these factors, and tumours will be examined for the presence and nature of p53 mutations.

Two animal models have been used for the study of HCC, based on the isolation and characterization of hepadna viruses specific for the respective species (woodchucks and ducks) and these allow investigation of chemical and viral interactions believed to be important in the human situation. In ducks, tumours also appear following exposure to aflatoxin, particularly in animals chronically infected with the virus. HCC samples from untreated ducks and from ducks treated with aflatoxin and/or infected with duck hepatitis virus are being studied. We are examining the coding region of the duck p53 gene that corresponds to the area where most mutations are seen in human tumours, by amplification of short segments (100 to 300 base pairs) using degenerate primers designed from the chicken p53 nucleotide sequence.

### 1.7.6.4 *Comparison of p53 mutation pattern in oesophageal squamous cell carcinomas and hepatocellular carcinomas with those of other cancers*

(M. Hollstein; in collaboration with C.C. Harris, Bethesda, MD, USA; and B. Vogelstein, Baltimore, MD, USA)

Mutations in the p53 gene thought to interfere with control of cell proliferation are dispersed over several hundred base pairs in the mid-region of the gene in most human cancers. This region represents a broad target for mutation events in which specificities of exogenous chemical agents and endogenous cellular mutagenic processes can be examined. Studies using simple prokaryotic and eukaryotic organisms, as well as *in vitro* mutagenesis assays with mammalian cells, have shown that carcinogens produce "fingerprints" with respect to the type and location of point mutations they induce in a defined DNA sequence. Information on the patterns of base substitution mutations in specific types of tumour may offer new insights into the origins of genetic changes in human cancers.

We found that CpG to TpG transitions are far less prevalent in oesophageal than in colorectal tumours, whereas G to T transversions, rarely found in colon cancers, were found in a quarter of the samples of oesophageal squamous cell carcinoma. Base transversions at A:T pairs constitute a major fraction of p53 mutations in oesophageal tumor samples, in contrast to mutation patterns in most other types of solid tumour. Distinct etiological factors for different cancers are likely to play a role in generating these differences. Linking of patient exposure histories with patterns of p53 mutations in high-risk populations is being explored[158].

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[158] Hollstein, M., Sidransky, D., Vogelstein, B. & Harris, C.C. (1991) *Science*, **253**, 49–53

### 1.7.6.5 *Tumour-suppressor gene mutations as an early event in oesophageal carcinogenesis*

(M. Hollstein; in collaboration wtih W. Bennett and C.C. Harris, Bethesda, MD, USA)

p53 analysis of colon tumours has shown that in this tumour type mutations arise relatively late in the progression of the disease. In the development of oesophageal squamous cell carcinoma there may be greater variability in the timing of these events. In some instances at least, the mutation may be present in early neoplastic lesions of the oesophagus, since immunohistochemical staining of carcinoma *in situ* with a polyclonal antibody raised against the human p53 protein has been observed.

A number of early lesions in the oesophagus (carcinoma *in situ,* squamous intraepithelial neoplasia) of patients with carcinomas have been examined by immunohistochemistry and by direct sequencing of cells recovered from fixed tissue sections. In a preliminary study, we have found a mutation in an early oesophageal lesion of one patient who also harboured a malignant carcinoma with different mutation.

## 1.7.7 Transplacental and transgeneration carcinogenesis

(A. Loktionov, J.R.P. Cabral, M. Hollstein, O. Bertrand, D. Galendo, M.-P. Cros, M. Laval, N. Lyandrat, H. Yamasaki and L. Tomatis)

Studies on transplacental and multigeneration effects of carcinogens in experimental animals are being continued. During the past two years, special emphasis has been placed on the molecular analysis of tumours produced by these experimental protocols.

### 1.7.7.1 *Role of oncogene activation in transplacental carcinogenesis: tissue-specific activating mutation of* ras *genes*

Transplacental carcinogenesis represents a good model in which to study the involvement of tissue-specific oncogene activation in carcinogenesis, because a single exposure to a carcinogen induces tumours at various sites. We have tested transplacentally induced tumours of mouse skin, liver and lung for activation of *ras* genes. XbaI restriction fragment length polymorphism analysis has shown that exposure to DMBA in utero can generate an A to T transversion at the second position of codon 61 of the Ha-*ras* oncogene in skin and liver tumours, but not in lung tumours. Moreover, DNA samples isolated from spontaneous and DMBA-induced lung and liver tumours were analysed for mutations at the same position of the Ki-*ras* oncogene, using differential hybridization with specific oligonucleotides. Among five spontaneous lung tumours, three cases of A to G transition and one case of A to T transversion were found, whereas four out of ten DMBA-induced lung tumours were positive for the A to T mutation. No Ki-*ras* mutation was detected in one spontaneous and four DMBA-induced hepatomas. In two cases, we detected Ki-*ras* A to T mutation in a lung tumour and Ha-*ras* mutation in a liver tumour from the same animal. These results indicate first that DMBA treatment can induce A to T mutation at the second position of codon 61 both in Ha-*ras* and in Ki-*ras* and, second, that the role of different activated oncogenes in carcinogenesis may differ, depending on the tissue in which the tumour develops[159].

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[159] Loktionov, A., Hollstein, M., Martel, N., Galendo, D., Cabral, J.R.P., Tomatis, L. & Yamasaki, H. (1990) *Mol. Carcinog.*, **3**, 134–140

### 1.7.7.2 *Possible role of mutated* ras *genes in multigeneration transmission of carcinogenic risk*

(in collaboration with M. Zabezhinski, Leningrad, USSR)

Recent studies suggest that *de novo* mutation of the Rb gene in germ cells accounts for three quarters of hereditary retinoblastoma cases[160]. These results and those from experimental animal studies[161] suggest that environmental carcinogens can induce germ cell mutations in certain critical genes which may in turn play a critical role in transgeneration carcinogenesis. We have tested this hypothesis using an experimental animal model system.

Transgeneration transmission of the carcinogenic action of DMBA and the possible involvement of *ras* gene mutation was studied in two generations of mice using transplacental DMBA initiation followed by postnatal skin tumour promotion with TPA in the first generation (F0) and only promotion in the second generation (F1). Local application of TPA resulted in increased yields of skin tumours both in the mice exposed to DMBA *in utero* and in their progeny. These results suggest a transgeneration transfer of the effect of DMBA. An A to T mutation at the second base of codon 61 of the Ha-*ras* oncogene was found in skin tumours of DMBA-exposed mice, but not in tumours induced by TPA without initiation. In the progeny (F1) of the DMBA-exposed F0 mice, only a few skin tumour samples were available for oncogene analysis and none contained the Ha-*ras* mutation. The results confirm our previous finding that initiation of skin and lung tumorigenesis can be transmitted transgenerationally but suggest that *ras* gene mutation may not be critically involved in this transmission.

### 1.7.7.3 *Multigeneration effects of carcinogens after exposure of males*

(in collaboration with B.N. Hemsworth, Cleveland, UK; N.P. Napalkov, Leningrad, USSR; and V.S. Turusov, Moscow, USSR)

There is well documented evidence in both humans and experimental animals that exposure to diethylstilbestrol (DES) during pregnancy results in an increased incidence of tumours in the progeny. In this study, female CBA mice were treated with DES and their male offspring were mated with untreated females. In the second-generation offspring so obtained, the females (but not the males) showed a statistically significant increase in tumour incidence, in particular of uterine sarcomas, and also of benign ovarian tumours and of lymphomas.

Studies on the role of griseofulvin and analogues in the induction of liver porphyria and carcinogenesis in newborn mice have been conducted, and the slides are now being evaluated.

## 1.7.8 Cell transformation and mutagenesis: study on genotoxic and non-genotoxic events

(H. Nakazawa, C. Chiodino, J.-L. Klein, A.-M. Aguelon and H. Yamasaki)

Cell transformation systems have been studied at IARC laboratories as an in-vitro model of carcinogenesis. Major aims of the study are to examine genetic and non-genetic determinants of cell transformation and to see whether the test system can detect genotoxic as well as non-genotoxic carcinogens[162].

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[160] Yandell, D.W. (1991) *Proc. Am. Assoc. Cancer Res.*, **32**, 459–460

[161] Moser, A.R., Pitot, H.C. & Dove, W.F. (1990) *Science*, **247**, 322–324

[162] Fitzgerald, D.J., Piccoli, C. & Yamasaki, H. (1989) *Mutagenesis*, **4**, 286–291

### 1.7.8.1 *Identification of the critical gene involved in initiation of BALB/c 3T3 cell transformation*

When BALB/c 3T3 cells were transformed by exposure to DMBA, transformed foci invariably contained a specific Ki-*ras* mutation (A to T transversion at the 61st codon) while those transformed by other carcinogens (MCA, MNNG, NMU and UV-C radiation) did not. It therefore appears that this mutation is a prerequisite event for DMBA-induced cell transformation of BALB/c 3T3 cells. In order to test this hypothesis, we examined whether and to what extent DMBA induces this mutation, using the method described above (see section 1.7.6.1). DMBA did induce A to T mutation at the 61st codon of Ki-*ras*, and also induced the same mutation in Ha-*ras*.

The time course of Ha- and Ki-*ras* mutation induction by DMBA is shown in Figure 16. The number of cells with Ha-*ras* $A^{182}$ to T mutation reached a plateau after one week's exposure to DMBA, whereas the Ki-*ras* mutation frequency kept increasing. These results are consistent with the idea that Ki-*ras*, but not Ha-*ras*, mutation is a critical event for DMBA-induced BALB/c 3T3 cell transformation; only those cells with the Ki-*ras* mutation grew clonally to form foci and therefore the Ki-*ras* mutation frequency appeared to increase.

In order to see why cells with the Ha-*ras* mutation are not recruited into the transformation process, we examined the levels of expression of the Ha- and Ki-*ras* genes. Northern analysis showed that the level of Ki-*ras* mRNA was higher than that of Ha-*ras*. Furthermore, when cells were treated with 5-azacytidine (an inhibitor of 5-methylcytosine formation and stimulator of expression of certain genes) before DMBA exposure, some resultant transformed foci contained Ha-*ras* mutation. These results suggest that DMBA induces both Ha- and Ki-*ras* genes in BALB/c 3T3 cells and that Ki-*ras* gene mutation plays the role of initiation event because this gene is highly expressed.

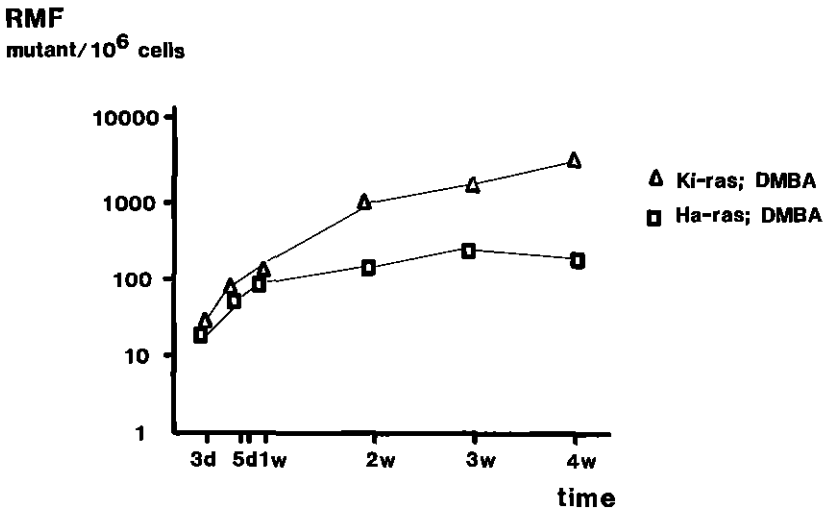


Fig. 16. DMBA-induced Ha- and Ki-*ras* $A^{182}$ to T mutation frequency in BALB/c 3T3 1-1 cells

### 1.7.8.2 *Quantitative relationship between "initiation" event and transformation frequency*

It has been reported that the frequency of mutations induced by carcinogens is lower than the transformation frequency in a given system[163]. This is paradoxical, since it is believed that cell transformation is a multistage process that requires more than a single mutation event. However, in these previous studies, mutation frequency was determined using such genes as HPRT and ATPase, that are not critically involved in cell transformation.

As we have now identified Ki-*ras* $A^{182}$ to T mutation as an initiating mutation of DMBA-induced BALB/c 3T3 cell transformation, we can compare more directly the initiating mutation and transformation frequencies[164]. This indicates that about 13% of "initiated" cells undergo morphological transformation, and when TPA is added after DMBA, about 30% of "initiated" cells become transformed. The results confirm that TPA does not induce *de novo* transformation, but rather help clonal expansion of "initiated" cells. This idea is represented schematically in Figure 17. This may serve as a useful model for measuring the contributions of "genetic" and "non-genetic" events as well as "initiation" and "promotion" stages of cell transformation, which may, in turn, provide useful information for quantitative risk estimation in multistage carcinogenesis.

### 1.7.8.3 *Modulation of cell transformation by growth factors*

In order to look for growth factors that influence cell transformation, we have examined the effect of human placental extracts, and found that such extracts contain tumour-suppressing factors which are not related to transforming growth factor $\beta$ (TGF$\beta$). One fraction (EAP) from the extracts inhibited growth, in soft agar, of Ha-*ras*-transformed BALB/c 3T3 cells and human squamous lung carcinoma A-2182 cells, but had no effect on the anchorage-dependent growth of these cells, although there was a slight mitogenic activity on nontransformed cells. These data together with those on plating efficiency indicated no significant cytotoxicity of EAP towards transformed cell lines. Although the EAP fraction contained TGF$\beta$, this cannot account for its inhibitory activity, since (*a*) pure TGF$\beta$ does not inhibit anchorage-dependent growth of Ha-*ras*-transformed BALB/c 3T3 cells, (*b*) EAP retains its inhibitory activity in the presence of neutralizing antibodies against TGF$\beta$ and (*c*) the inhibitory activity did not co-purify with TGF$\beta$. Partial characterization of our inhibitory factor suggests that it is a new tumour-growth inhibitor[165]. Further purification is in progress. In order to clearly define the effect of this factor and to extend the study to other human cell lines, we are establishing human oesophageal and mesothelioma cell lines which can grow in serum-free culture media.

## 1.7.9 Role of intercellular communication in carcinogenesis: detection of tumour-promoting agents and analysis of human and animal tumours

(V. Krutovskikh, D.J. Fitzgerald, M. Mesnil, S. Swierenga, W.M.F. Jongen, M. Oyamada, M. Asamoto, F. Katoh, C. Piccoli and H. Yamasaki)

The role of cell contact-mediated intercellular communication (IC) can be studied at the functional level as well as the gene and protein expression levels; expression vectors for gap

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[163] Barrett, J. C. & Elmore, E. (1985) In: Flamm, W.G. & Lorentsen, R.J., eds, *Advances in Modern Environmental Toxicology. Mechanisms and Toxicity of Chemical Carcinogens and Mutagens*, Princeton, Princeton Scientific Publishing, pp. 171–206

[164] Yamasaki, H., Aguelon, A.M. & Nakazawa, H. (1991) *Proc. Am. Assoc. Cancer Res.*, **32**, 135

[165] Klein, J.L., Hamel, E., Tayot, J.L. & Yamasaki, H. (1991) *J. Cancer Res. Clin. Oncol.*, **117**, 192–196

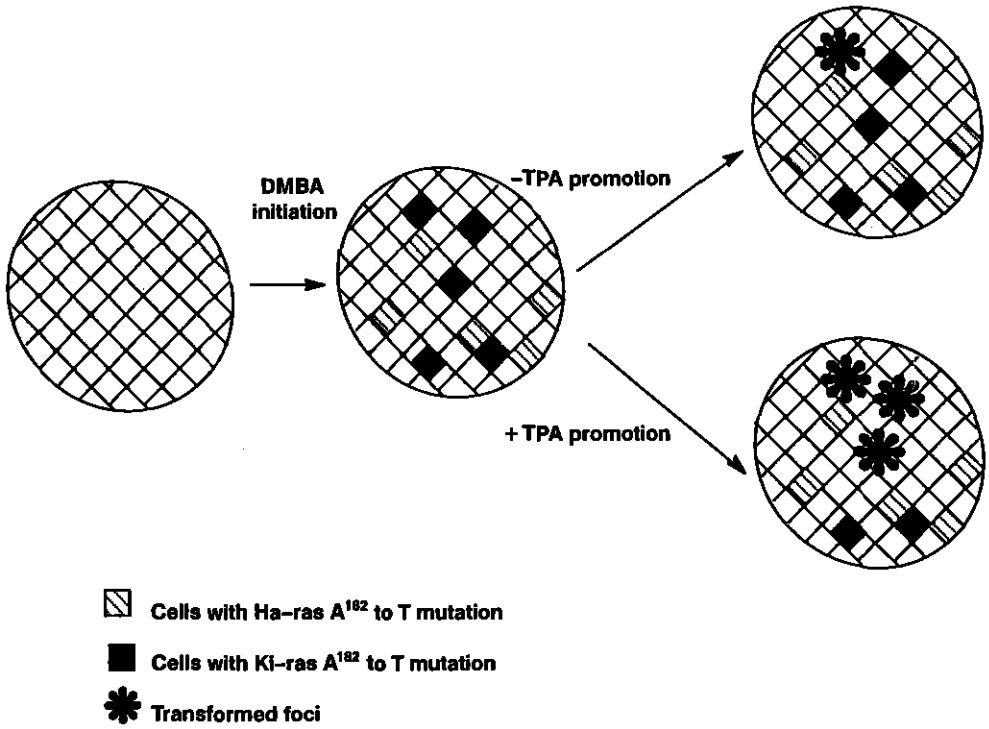


Fig. 17. Schematic view of *ras* gene involvement in BALB/c 3T3 cell transformation

junction (connexin) and cell adhesion molecule (CAM) genes are available. A dye-transfer assay to measure gap-junctional intercellular communication (GJIC) in tissue slices from animals and surgically removed human tissue samples has been developed. Emphasis is being placed on studying the role of IC in carcinogenesis *in vivo* (including in human tissues) and to exploring whether blocking of GJIC can be used as an assay to detect tumour-promoting activity of environmental carcinogens.

### 1.7.9.1 *Aberrant expression of connexin genes in primary human hepatocellular carcinomas*

(in collaboration with F. Berger and C. Partensky, Lyon, France)

The expression of connexin 32 (the major liver gap-junction progein) and connexin 43 (the major cardiac gap-junction protein) was examined in six surgically removed human hepatocellular carcinoma samples and surrounding non-tumorous tissue using specific rat connexin probes. No decrease in connexin 32 mRNA expression was found in carcinomas compared with the surrounding non-tumorous tissue. Morphometric analysis showed that in most of the carcinomas, the number of gap junction spots stained with connexin 32 antibody was no less than in the normal tissue. These results are in striking contrast to the significant reductions in connexin 32 mRNA and protein expression observed in rat primary liver tumours induced by chemicals. On the other hand, all of the six human hepatocellular carcinomas exhibited elevated levels of connexin 43 mRNA, which was expressed at a very low level in the surrounding non-tumorous

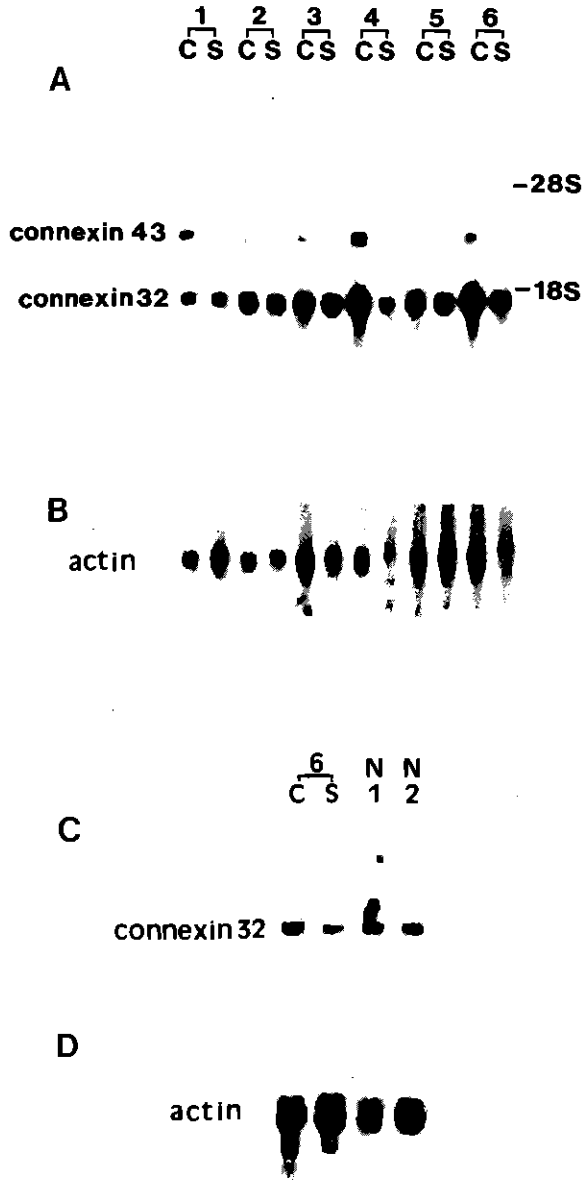


Fig. 18. Northern blot analysis of RNA from human HCCs, surrounding non-tumorous liver tissue and normal livers. Total RNAs (20 $\mu$g) were fractionated by electrophoresis in a 1% agarose-formaldehyde gel and blot-hybridized with $^{32}$P-labelled connexin 32 and 43 cDNA probes (A, C), and actin cDNA (B, D). C, hepatocellular carcinoma; S, surrounding non-tumorous tissue; N, normal liver

tissue (Figure 18). These carcinomas exhibited no detectable amplification of the connexin 43 gene. The present study suggests that GJIC is altered in human hepatocellular carcinomas by molecular mechanisms different from those in rat hepatocarcinogenesis[166].

### 1.7.9.2 *Measurement of gap-junctional intercellular communication in freshly removed human and rat liver tissue slices*

We have developed a simple method for measuring GJIC in freshly removed rat liver slices by means of a microinjection/dye transfer assay (Figure 19)[167]. This technique has also been successfully used to measure the communication capacity of slices of freshly removed human liver.

Using this method in conjunction with immunostaining of connexin 32, we studied sequential changes in GJIC during chemical hepatocarcinogenesis in male Fischer 344 rats under a modified Solt–Farber protocol (nitrosodiethylamine/2-acetylaminofluorene/partial hepatectomy, 25-day exposure regimen). Four weeks after the start of treatment, there was a substantial decrease in GJIC in the liver parenchyma which was free from focal lesions. This decreased GJIC persisted up to at least the 15th week, while a decrease in the number of immunoreactive connexin 32 spots was detected only at four weeks after the start of treatment. Most enzyme-altered (GST-P-positive) focal lesions showed markedly lower GJIC and a significantly lower number of connexin 32-positive spots than surrounding hepatocytes, and there was also a selective lack of GJIC with surrounding hepatocytes. Hepatocellular carcinomas that arose one year after the carcinogen treatment had significantly reduced GJIC and greatly decreased expression of connexin 32. These results suggest that a progressive decrease in both homologous and heterologous GJIC in preneoplastic lesions occurs during rat hepatocarcinogenesis, and that preneoplastic lesions with the most prominent disorders in GJIC may be more likely to develop into carcinomas[168].

In contrast, when GJIC capacity in primary human hepatocellular carcinomas was measured by the same method, there was no difference from surrounding non-cancerous tissue. It will be important now to examine whether tumour cells communicate with surrounding normal cells. Selective lack of intercellular communication between transformed and non-transformed cells *in vitro* has been described previously[169].

### 1.7.9.3 *Effect of carcinogens on intercellular communication in primary human epithelial cell cultures*

We have developed a method for culturing hair follicle cells in which to examine the effects of environmental chemicals on GJIC. This system is useful not only for screening of possible tumour-promoting agents, but also to determine genetic variations in individual intercellular communication ability and in their response to various agents[170].

TPA inhibited GJIC of primary cultured human hair follicle cells[168]. In addition, when two hair-staining compounds (HC blue 1 and HC blue 2) were tested on the human hair follicle cells, only the carcinogenic one (HC blue 1) inhibited the GJIC capcaity 24 h after the treatment.

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[166] Oyamada, M., Krutovskikh, V.A., Mesnil, M., Partensky, C., Berger, F. & Yamasaki, H. (1990) *Mol. Carcinog.*, **3**, 273–278

[167] Krutovskikh, V.A., Oyamada, M. & Yamasaki, H. (1991) *Carcinogenesis* (in press)

[168] Krutovskikh, V.A., Oyamada, M. & Yamasaki, H. (1991) *Carcinogenesis* (in press)

[169] Mesnil, M. & Yamasaki, H. (1988) *Carcinogenesis*, **9**, 1499–1502

[170] Swierenga, S.H.H., Fitzgerald, D.J., Yamasaki, H., Piccoli, C. & Goldberg, M. (1991) *Toxicology in Vitro* (in press)

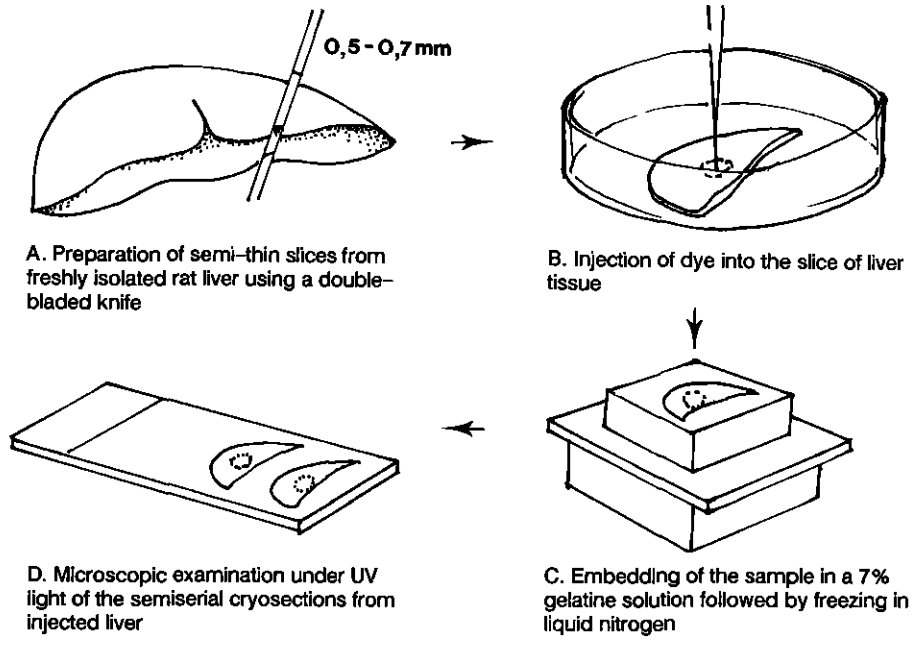


Fig. 19. Scheme for GJIC measurement method using dye-transfer assay in liver slices, and the results in normal and tumorous parts of rat liver. Note wider spread of the dye, due to higher GJIC, in normal than in tumorous liver cells

### 1.7.9.4 *Effects of polychlorinated biphenyl congeners on gap-junctional intercellular communication in cultured human keratinocytes and liver-derived cells* *in collaboration with N. Marceau, Quebec, Canada; and L. Robertson, Lexington, KY, USA)*

Several pure polychlorinated biphenyl (PCB) congeners with different toxicities and tumour-promoting activities in rat liver *in vivo* were tested for their effects on GJIC in cell lines derived from human liver and skin. 3,3′,4,4′-Tetrachlorobiphenyl (an MCA-type cytochrome P450 inducer and hepatotoxic tumour promoter) was inactive in all of the cells tested, suggesting that this promoter acts by other mechanisms. The phenobarbital-like enzyme inducer and less toxic promoter 2,2′,4,4′,5,5′-hexachlorobiphenyl inhibited GJIC in both liver and skin cells, whereas the 2,2′,5,5′-tetrachlorobiphenyl congener, which does not act as a promoter in rat liver, inhibited GJIC only in the skin cell types and in one of the liver cell strains thought to be of bile duct origin. 2,3,4,4′,5-Pentachlorobiphenyl, a mixed (phenobarbital plus MCA) inducer of cytochrome P450, inhibited GJIC in both liver and skin cells, suggesting that it may be a promoter *in vivo*. The results suggest that GJIC inhibition is associated with PCB congeners that show phenobarbital-like enzyme induction capabilities, and that there exist some tissue and cell type differences in sensitivity to these congeners[171].

### 1.7.9.5 *Effect of liver tumour-promoting agents on gap-junctional intercellular communication in rat liver* in vivo

Phenobarbital, clofibrate, DDT (dichlorodiphenyltrichloroethane), PCBs and ethynylestradiol are rat liver tumour promoters believed to have different modes of action. Fischer 344 rats were administered these chemicals by gavage and their livers were examined for their communication capacity and the presence of connexin proteins.

Using the functional dye-transfer assay described above, a significant decrease in GJIC was detected after only one week of treatment with all these compounds. The strongest effect was found in rats treated with PCBs and DDT. The decreased level of GJIC was associated with a substantial reduction in numbers of gap junctions in the liver, as measured by immunostaining for connexin 32.

These results confirm the effect of tumour-promoting agents on GJIC *in vivo* and suggest that GJIC inhibition may be a good assay system to detect tumour-promoting activity of chemicals.

### 1.7.9.6 *Cell adhesion molecules and gap-junctional intercellular communication* (in collaboration with D. Gros, Marseille, France; T.J. Slaga, Smithville, TX, USA; and M. Takeichi, Kyoto, Japan)

In cultured mouse epidermal cells, GJIC is mediated by a gap junction protein, connexin 43, and is dependent on the calcium concentrations in the medium, with higher GJIC in a high-calcium (1.2 mM) medium. In several mouse epidermal cell lines, we found a good correlation between the levels of GJIC and of immunohistochemical staining for E-cadherin, a calcium-dependent cell adhesion molecule, at cell–cell contact areas. The variant cell line P3/22 showed low levels of both GJIC and E-cadherin protein expression in low- and high-calcium media, and very low E-cadherin mRNA expression. When we tranfected the E-cadherin

[171] Swierenga, S.H.H., Yamasaki, H., Piccoli, C., Robertson, L., Bourgon, L., Marceau, N. & Fitzgerald, D.J. (1990) *Carcinogenesis*, **11**, 921–926

expression vector into P3/22 cells, all the transfectants expressed E-cadherin molecules at cell–cell contact areas in a calcium-dependent manner and showed calcium-dependent GJIC. These results suggest that the calcium-dependent regulation of GJIC in mouse epidermal cells is directly controlled by E-cadherin. Furthermore, several lines of evidence suggest that this control involves post-translational regulation (assembly and/or function) of the gap junction protein connexin 43[172].

### 1.7.10 Long-term carcinogenicity: effect of hot drinks on oesophageal carcinogenesis

(H. Yamasaki, J.R.P. Cabral, D. Galendo, M.-P. Cros and J. Garcia)

Consumption of very hot drinks is one of the major suspected risk factors for human oesophageal cancer[173]. We are examining this hypothesis by a long-term carcinogenesis study in BDVI rats, given water at a temperature comparable to that at which mate is drunk by humans. "Hot drinking" is being tested as a possible promoting agent, complete carcinogen or co-carcinogen. All organs and tumours will be examined histogically and some of the tumours will be analysed for oncogene activation and tumour-suppressor gene inactivation.

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[172] Jongen, W.M.F., Fitzgerald, D.J., Asamoto, M., Piccoli, C., Slaga, T.J., Gros, D., Takeichi, M. & Yamasaki, H. (1991) *J. Cell Biol.* (in press)

[173] Victora, C.G., Muñoz, N., Horta, B.L. & Ramos, E.O. (1990) *Cancer Res.*, **50**, 7112–7115

# PART 2. STUDIES ON PREVENTION

The majority of the IARC research activity is oriented towards, and contributes to, cancer control and, in particular, primary prevention through elucidation of cancer determinants. Some research topics, however, are more specifically and closely related to prevention activities; for instance, studies aimed at testing the effectiveness of chemoprophylactic interventions or of screening procedures for early diagnosis of cancers. Increasing knowledge of the etiology of cancer, as well as slow (real and perceived) progress in cancer control in most countries, fully warrants the singling out of research in prevention as a major programme worth a concentrated effort in the foreseeable future.

## 2.1 *Evaluation of Primary Prevention*

### 2.1.1 Evaluating effectiveness of intervention studies

(D.M. Parkin, M.P. Coleman and J. Kaldor; in collaboration with V. Beral, Oxford, UK; J.W. Cullen, Bethesda, MD, USA; and M. Hakama, Tampere, Finland)

The results of this project were published during 1990[1]. Preliminary discussions have been held concerning a possible review of chemoprevention trials in 1992/93.

## 2.2 *Evaluation of Early Detection Programmes*

### 2.2.1 Screening for cancer of the cervix

(D.M. Parkin; in collaboration with D. Estebán and C. Ngelangel, Manila, Philippines)

A limited screening programme has been in existence in certain municipalities of the greater Manila area for 15 years. As part of a case–control study of possible etiological factors (see section 1.3.10.4) information is being collected on previous screening history. The study protocol also requests information concerning knowledge of and attitudes to screening and preventive health care, so that the magnitude of any selection bias related to these additional variables can be estimated.

### 2.2.2 Screening for gastric cancer

(D.M. Parkin and N. Muñoz; in collaboration with N. Alvarez and W.E. Oliver, San Cristobal, Venezuela)

A programme of screening for early gastric cancer by photofluoroscopy, followed by endoscopy, has been in progress in the state of Tachira, Venezuela, since 1981. About

[1] Hakama, M., Beral, V., Cullen, J.W. & Parkin, D.M., eds (1990) *Evaluating Effectiveness of Primary Prevention of Cancer* (IARC Scientific Publications No. 103), Lyon, International Agency for Research on Cancer

12 000–14 000 examinations are carried out every year. A case–control study is being performed to evaluate the possible success of this programme. 250 deaths from gastric cancer during the years 1985–1989 form the case group. There are two groups of controls: (*a*) live individuals matched for age and sex, from the same residential area as the cases (2500), and (*b*) deaths from causes other than gastric cancer, matched by age, sex and residence (750). Screening histories have been recorded for cases and controls from records at the Cancer Control Centre. Analysis will be completed during 1991.

As part of the study of etiological factors (section 1.3.4.2), screening history is being recorded for cases and controls both by interview and by review of records; the evaluation of screening efficacy will consider only subjects with advanced gastric cancer, plus their matched controls. Some control for selection bias should be possible.

Since the present screening programme achieves only a modest coverage of the population, a proposal to implement it as a randomized controlled trial has been prepared, and funding for the implementation of such a project is being sought.

### 2.2.3 Screening for lung cancer

(D.M. Parkin and M. Khlat; in collaboration with M. Adamec, A. Kubik and J. Reissigova, Prague, Czechoslovakia; and S.D. Walter, Hamilton, Canada)

The analysis of a randomized controlled trial of lung cancer screening in Czechoslovakia has been completed[2]. The intervention group (screened every six months by chest X-ray and sputum cytology) had a rather higher incidence of diagnosed lung cancer than the controls (unscreened). There was no difference in mortality between the two groups and hence no detectable benefit from screening. Further work is in progress using the model developed by Walter and Day[3] to estimate the sensitivity of the screening test, and parameters of the natural history of lung cancer in this population (distribution and mean duration of pre-clinical detectable phase).

### 2.2.4 Screening for breast cancer

(D.M. Parkin; in collaboration with A.V. Laudico, C. Ngelangel and M.G. Reyes, Manila, Philippines)

Screening for breast cancer by mammography, with or without physical examination of the breast, has been shown to be effective in reducing mortality from breast cancer in women over 50 years of age. However, since the equipment is expensive, such programmes are inappropriate for developing countries, even where breast cancer incidence is moderately elevated. The Manila area of the Philippines is one such area[4], and a protocol has been developed for a randomized controlled trial of screening for breast cancer in 330 000 women aged 35–64, using physical examination by trained nurses as the sole screening modality. A pilot study with 12 000 women in the age range 35–64 began in 1991, to investigate various aspects of feasibility and compliance, and to estimate predictive value of physical examination in this population.

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[2] Kubik, A., Parkin, D.M., Khlat, M., Erban, J., Polak, J. & Adamec, M. (1990) *Int. J. Cancer*, **45**, 26–33

[3] Walter, S.D. & Day, N.E. (1983) *Am. J. Epidemiol.*, **118**, 865–886

[4] Laudico, A.V., Esteban, D. & Parkin, D.M. (1989) *Cancer in the Philippines* (IARC Technical Report No. 5), Lyon, International Agency for Research on Cancer

# 2.3 *Intervention Studies*

## 2.3.1 The Gambia Hepatitis Intervention Study (GHIS)

(H.M. Inskip, A.J. Hall, J. Chotard, M. Vall Mayans, A. Jack, M. Fortuin, C.S. Muir, B.K. Armstrong, F.X. Bosch, N. Muñoz, D.M. Parkin, J. Estève, R. Montesano, C.P. Wild, N. Charnay and H. Renard; in collaboration with A.B.H. N'jie, M. George, K. Cham and P.E. Crivelli, Banjul, The Gambia; B.M. Greenwood, H.C. Whittle, M. Mendy and E. Bah, Fajara, The Gambia; L. Chieco-Bianchi, Padua, Italy; F. Aiuti, Rome, Italy; M. Rizzetto, Turin, Italy; and R.L. Robertson, South Hadley, MA, USA)

The Gambia Hepatitis Intervention Study (GHIS) aims to evaluate the effectiveness of hepatitis B (HB) vaccination in the prevention of chronic liver disease and hepatocellular carcinoma (HCC) in a population at high risk. It has been funded by the Direzione Generale per la Cooperazione allo Sviluppo of the Italian Ministry for Foreign Affairs and is being conducted in collaboration with the Government of The Gambia and the laboratories of the Medical Research Council of the United Kingdom in Fajara.

In phase I of the project, conducted between 1986 and 1990, a cohort of 124 000 children was recruited. All study children received the usual vaccines administered under The Gambia's Expanded Programme of Immunization (EPI) and approximately half received HB vaccine in addition. Children were recruited into the study when they first registered at a health centre, and those given the HB vaccine received their first dose at the same time. Three further doses were given when the children returned to the clinics, the target ages being 2 months, 4 months and 9 months. Some children were not brought to the clinics regularly and thus the HB-vaccinated children each received a total of between one and four doses. Recruitment into the cohort ceased in February 1990 and the recording of the vaccines given to these children was stopped at the end of 1990, by which time all of the study children were scheduled to have received all their vaccinations. Since February 1990, the HB vaccine has been administered routinely within The Gambia's EPI (Figure 20).

Initially, only one health centre (Brikama) gave HB vaccine. Thereafter additional centres started to give the vaccine one after the other, the order being chosen randomly, until in February 1990, the last centre started to give HB vaccine and recruitment to the cohort ceased. The centres that, at any particular time, had not yet started to give the HB vaccine provided a control set of non-vaccinated subjects.

At the outset of the project in 1986, a national cancer registry was established for The Gambia to record the liver cancers occurring in the GHIS cohort. In this way it will be possible to assess whether the HB vaccine has been successful in preventing this cancer.

Three sub-groups of the main cohort are being studied in detail to assess the effectiveness of the vaccine in preventing infection with the hepatitis B virus and the carrier state.

Group 1 consists of 1000 children who received the HB vaccine, chosen from the first four centres to administer the vaccine. Blood samples have been taken annually from each child where possible, the third year follow-up being completed in August 1990. The fourth year follow-up is almost complete. Further follow-ups are planned for the fifth, seventh and ninth years after recruitment. This group provides valuable information on the protection afforded by vaccination and the decline in antibody concentrations.

Table 17 gives the main results for the first three years of the Group 1 follow-ups. By the third year 19 children has been infected but only five of these were HBsAg-positive and thus

Fig. 20. Hepatitis B vaccination in progress in the Gambia

potential carriers of the virus who would be at relatively high risk of liver cancer in later life. Antibody levels have fallen over the three years but only 29 uninfected children have levels that are considered to be unprotective. That 656 children (93%) remain uninfected by year three and still have protective levels of antibody is encouraging, as HB virus carriage tends to be determined by infection in early life.

Group 2 consists of 800 children in the same birth cohorts as the vaccinated children but who did not receive the HB vaccine, chosen from four areas in the country. A cross-sectional survey is being conducted during 1990 to 1991 to determine the prevalence of HB infection and chronic carriage in these children. Preliminary results using children in this group from the first three areas surveyed and the data for the three-year follow-up for Group 1 show that the effectiveness of the vaccine in preventing HBsAg-positivity is 94% (95% confidence interval 85% to 97%) and in preventing infection is 90% (84% to 94%). The effectiveness of the vaccine in preventing the carrier state cannot be determined until the HBsAg-positive children from Group 2 have been resurveyed one year later. Using other data on unvaccinated children from The Gambia, a comparison can be made with the Group 1 data, in terms of carriage and infection, which indicates that the vaccine appears to be highly effective (Figure 21).

Table 17. Hepatitis B status of children in group 1 in each of the first three years of follow-up

| | HBsAb+ HBcAb− | | HBsAb− HBcAb− | | HBsAb+ HBcAb+ | | HBsAb− HBcAb+ | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | |
| 1st year | 716 | 94* | 11 | 1 | 33 | 4 | 4 | 0.5** | 764 |
| 2nd year | 663 | 94 | 28 | 4 | 8 | 1* | 4 | 0.6** | 703 |
| 3rd year | 656 | 93 | 29 | 4 | 13 | 2* | 6 | 0.9**** | 704 |

*, one child (**, two children etc.) positive for HBsAg

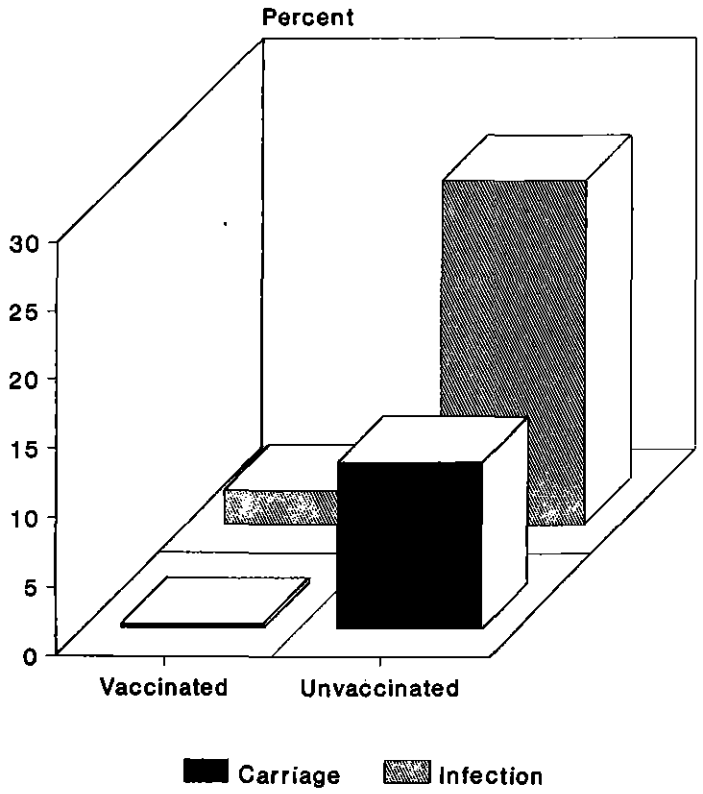


Fig. 21. Hepatitis B virus infection in vaccinated and unvaccinated Gambian children aged 3–4 years

Group 3 consists of groups of 100 children aged 12–17 months from fifteen areas in the country, who had received the HB vaccine as administered within the EPI. Cross-sectional surveys are being made of these groups to provide information on the continuing immunogenicity of the vaccine lots used and on the vaccination coverage achieved following introduction of the HB vaccine. Wide, and as yet unexplained, variation has been observed in the antibody response obtained in the fifteen geographical areas. Despite this, it appears that good antibody levels have been produced by successive lots of vaccine.

Data from 1986–1990 are available from the cancer registry. The incidence rates for cancers of the liver and cervix and all cancers are shown in Table 18 along with data from neighbouring registries and from northern Europe. The rates for liver cancer are much higher than those in northern Europe and of the same order as those observed in Mali and Senegal. That the rates are lower than those in Mali may indicate under-reporting in The Gambia. Efforts are continuing to increase the coverage of The Gambian registry, particularly in the eastern region of the country where there are fewer health facilities.

Progress of the GHIS is monitored annually by a Steering Committee made up of representatives of the Governments of The Gambia and Italy, the UK Medical Research Council, the WHO office in Banjul, the WHO Regional Office for Africa and the IARC. The fifth and sixth meetings of this committee took place in January 1990 and February 1991 respectively.

Table 18. Age-adjusted incidence of cancer per 100 000 person years[a]

| Cancer site (ICD-9) | The Gambia 1986–90 | | Mali 1987–88 | | Senegal 1969–74 | | Northern Europe 1970 | |
|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female |
| Liver (155) | 34.0 | 13.0 | 48.8 | 15.3 | 25.6 | 9.0 | <2 | <1 |
| Cervix (180) | | 11.0 | | 20.8 | | 17.2 | | 5–20 |
| All sites | 56.9 | 41.0 | 119.6 | 88.3 | 76.3 | 75.9 | >250 | >200 |

[a]Age-adjusted to world standard population
*One child (**, two children etc.) positive for HBsAg

A number of ancillary projects are being conducted within the GHIS. Some have been completed, whilst others are still in progress. They include the following:

1. An intervention study has shown that arthropods are not a major route of transmission of the HB virus. Other possible mechanisms of transmission which have been suggested, namely circumcision, scarification, immunizations and open wounds, were also examined in this study and also do not appear to account for much of the transmission of the virus.
2. The HB profile of the families into which a child is born has been shown to hardly influence the child's antibody response to the vaccine. This is encouraging, as children born into families where there are HB virus carriers are at greatest risk of becoming carriers themselves.
3. Follow-up of children who were vaccinated with HB vaccine before the GHIS began has shown that even those with poor antibody responses are protected against carriage of the virus.
4. Preliminary work has shown that aflatoxin exposure in The Gambia appears to be quite high (see section 1.7.2.1). Since aflatoxin is also thought to be a factor in the etiology of liver cancer, further work in this area is being planned.
5. An analysis of the cost-effectiveness of the HB vaccination has shown that, even with the currently high price of the vaccine, the cost of preventing a liver cancer is within the range of the costs of preventing deaths from the other diseases against which the EPI aims to protect.
6. Other studies that are reaching fruition include a case–control study of chronic liver disease, and a study of twins to examine the genetic contribution to the immune response to the EPI vaccines and also their mortality pattern in the first year of life. A study of the families of women who are HBeAg-positive and thus highly infectious is also in progress. A second case–control study of chronic liver disease is being planned in which hepatitis C is one of the factors of interest.
7. New work has begun on mutant HB viruses that have been identified elsewhere. These are a source of concern as the HB vaccine does not appear to protect against them.

### 2.3.2 Chemoprevention trial on precancerous lesions of the stomach in Venezuela

(N. Muñoz and S. de Sanjosé; in collaboration with N. Alvarez, O. Andrade, E. Cano, D. Castro, W.E. Oliver, S. Peraza, V. Sanchez and J. Vivas, San Cristobal, Venezuela; E. Buiatti, Florence, Italy; P. Correa, New Orleans, LA, USA; B. Rathbone, Leicester, UK; and G. Sobala, Bradford, UK)

An intervention study is being set up in Tachira state taking advantage of the infrastructure created for the screening programme for stomach cancer (see section 2.2.2). The aim of this double-blind randomized trial is to determine whether treatment for *Helicobacter pylori* infection followed by treatment with certain anti-oxidants ($\beta$-carotene, vitamins C and E) can interrupt

the gastric carcinogenic process by blocking the progression from chronic gastritis and intestinal metaplasia to dysplasia and cancer. A total of 3000 subjects 35–64 years of age will be recruited during the first year and randomized into two equal groups, one of which will receive anti-*H. pylori* treatment for two weeks and the other a placebo. One month after completion of this treatment, the subjects will be stratified into three groups according to the histological diagnosis of the gastric lesions and then randomized to receive anti-oxidant treatment or placebo during three years. The effect of the treatments will be assessed using histological, histochemical and biochemical endpoints.

Pilot studies carried out in 40 subjects with various degrees of gastritis have shown a prevalence of *H. pylori* infection of 90% in this population. Bacterial cultures from these patients revealed that the local *H. pylori* strains were sensitive to all antibiotics tested (amoxycillin, erythromycin, ciprofloxacin and nitrofurantoin) but resistant to metronidazole. In view of these results, it has been decided to use bismuth salts in combination with amoxycillin in the main trial.

Two anti-oxidant preparations, one containing 750 mg of conventional vitamin C and the other containing 500 mg of slow-release vitamin C, were compared with regard to their ability to raise levels of ascorbic acid in serum and gastric juice after one week of treatment. No significant difference was detected between the two treatments and therefore the preparation containing conventional vitamin C was chosen for the trial.

In addition, the questionnaire and protocols to be used for the endoscopic and histological examinations have been tested and final versions produced based on the results of these pilot studies.

It is planned to start recruitment of subjects in July 1991.

# PART 3. DATA COLLECTION AND DEVELOPMENT OF RESEARCH METHODS

## 3.1 *Support to Cancer Registries and Improvement of Epidemiological Data Collection*

### 3.1.1 Advice and support to registries

(D.M. Parkin, M.P. Coleman, S. Whelan and S. Olivier)

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 course of the biennium, and many individuals working in cancer registries have visited the unit for training or discussion. The Mersey Regional Cancer Registry (Director, R. Hussey) has acted as a collaborative centre in providing on-site training for registry staff from anglophone countries, and the cancer registries of Bas-Rhin (Director, P. Schaffer), Isère (Director, F. Ménégoz) and Doubs (Director, Professor S. Schraub) for francophone staff.

Registries are encouraged to send copies of any reports published to the Agency. An abstract of each such report is prepared for the International Association of Cancer Registries' Newsletters, and abstracts of all the reports have now been entered onto computer to facilitate retrieval of the information, and to permit searching for specific items by combining parameters of interest and interrogating the system.

Several commonly used computer programs are available to registries free of charge, including verification checks (e.g., tumour site versus age, sex, histology), an ICD-O to ICD-9 conversion program (based on a conversion devised by C. Percy in 1979) and conversion of ICD-O coded cases into the categories of the classification scheme for childhood cancer (see section 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.

AFRICA:

*Algeria, Algiers* (Principal investigators, L. Abid, Registre des Cancers Digestifs d'Alger and D. Hammouda, Institut National de Santé Publique). Consultant advice was provided both to the specialized Digestive Tract Tumour Registry for Algiers (Dr Abid), in existence since 1985, and to the National Institute of Public Health (Dr Hammouda), which is organizing a general population-based cancer registry for the city and its metropolitan area (the wilaya).

*Algeria, Oran* (Principal investigators, L. Mokhtari and A. Tadjeddine). Consultation has been provided to assist in planning the creation of a further population-based cancer registry covering an urban region in the west of the country, to complement those in Sétif (eastern, rural)

and Algiers (coastal, urban). Pilot studies involving retrospective data collection are in progress, and CANREG software has been supplied.

*Algeria, Sétif* (Principal investigator, M. Hamdi Cherif, CHU de Sétif). A pilot study was carried out in 1989, the results of which (for 1986–88) have been published (see section 1.1.3.3). Prospective data collection began on 1 January 1990.

*Guinea* (Principal investigator, M. Koulibaly, Centre National d'Anatomie Pathologique, Conakry). A research agreement was established in 1991 to inaugurate a cancer registry for the city of Conakry. A registrar has been appointed and a period of training is being arranged for 1991.

*Mali* (Principal investigator, S. Bayo, National Institute of Public Health, Bamako). Financial support for the registry has continued, together with additional training for the tumour registrar in computing methods. The initial data have been published (see Section 1.1.3.1).

*Rwanda* (Principal investigator, P.-J. Ngilimana, Butare Cancer Registry). The research agreement which had been in abeyance for two years was reactivated in May 1991. Plans for multi-source reporting were finalized and data collection was started.

*Tanzania* (Principal investigator, J.N. Kitinya, Muhimbili Medical Centre, Dar es Salaam). The registry is expanding from being pathology-based (only) to multi-source reporting. New staff were appointed in 1991 and underwent training in the UK and Lyon, and a computer-based system was installed (Figure 22).

*Uganda* (Principal investigators, R. Owor and H. Wabinga, Makerere University, Kampala). The registry restarted in 1988 and is now receiving notifications from several hospitals in Kyaddondo county. A cancer registrar has now been appointed but no computer is yet available.

*Zimbabwe* (Principal investigator, L.M. Levy, University of Zimbabwe, Harare). Registration is gradually becoming complete for the city of Harare; further technical difficulties were resolved during a visit in 1991. Future plans include incorporation of the Bulawayo registry (currently hospital-based).

ASIA:

*China.* In collaboration with Shanghai Cancer Institute (Y.T. Gao) and the Western Pacific

Fig. 22. Cancer registration in Dar es Salaam is now computerized

Regional Office of WHO, a training seminar for cancer registry personnel from throughout China was held in June 1990.

*Indonesia* (Principal investigator, Sarjadi, Diponegoro University, Semarang). The pathology-based registry in Semarang is being extended to become population-based. The principal investigator was awarded a four-week fellowship for training in Europe and Singapore.

*Philippines* (Principal investigators, A.V. Laudico, University of the Philippines, and D. Esteban, Rizal Medical Center, Manila). Support for registration activities was continued through technical assistance in the computerization and analysis of data.

*Thailand.* A one-day meeting was held in Bangkok in December 1990 at which the continued development of a common basic data set for the three existing population-based registries was agreed (Chiang Mai, Director N. Martin; Khon Kaen, Director V. Vatanasapt; and Songkhla, Director H. Sriplung). All three registries received technical support during the biennium 1990/91. Provisional plans were developed, in collaboration with the National Cancer Institute in Bangkok (Principal investigator, S. Sontipong) for a further registry in central Thailand. Plans for combined publication of the registries' data will be finalized during 1992.

*Vietnam* (Principal investigator, Pham Hoang Anh, Cancer Institute, Hanoi). Support by means of a collaborative research agreement continued. Two years' data and revised population estimates are now available. The first results will be published in 1991/92. Plans for a second registry in Ho Chi Minh City (Saigon) were discussed.

AMERICAS:

*Bolivia* (Principal investigator, J. Rios Dalenz, La Paz Cancer Registry). Support to recommence registration, using an extended data collection system, from 1 January 1988, has been provided. Results for three years (1988–90) are now available and confirm the previously noted elevated incidence of gallbladder and cervix cancer.

*Brazil, Goiana* (Principal investigator, M.P. Curado, Fundaçao Leide das Neves Ferreira). Support has been provided to the cancer registry serving the city of Goiana, the site of an accident involving population exposure to radioactive caesium (of medical origin) in 1987.

*Paraguay* (Principal investigator, P.A. Rolón, National University, Asunción). A population-based registry was established in January 1988, with comprehensive data collection (including death certificates), using the CANREG system. Analysis of data for 1988–89 has been completed.

*Peru* (Principal investigator, P.F. Albujar, Trujillo Cancer Registry). Following a consultant visit in March 1990, a collaborative research agreement was established to support a cancer registry for the city of Trujillo in northern Peru. Data collection and analysis were aided by the appointment of full-time registry staff and acquisition of a microcomputer. Data collection (at first retrospective) and analysis are now complete for 1984–87.

OCEANIA:

The longstanding collaborative research agreement with the cancer registry of Fiji was maintained until 1990. At that time, agreement was reached with the epidemiology department of the South Pacific Commission in Noumea (principal investigator, Dr F. Bach) to coordinate support for registration activities via a collaborative research agreement between the Commission and IARC. At present, permanent population-based registration covers three countries (New Caledonia, French Polynesia and Fiji), but a system of visiting cancer registrars permits data collection from several smaller countries also.

### 3.1.2 International Association of Cancer Registries

(C.S. Muir, D.M. Parkin and S. Whelan; in collaboration with O.M. Jensen, Copenhagen Denmark; and D.B. Thomas, Seattle, WA, USA)

The International Association of Cancer Registries was founded in Tokyo, Japan in 1966 and

so celebrates its 25th anniversary in 1991. The aims of the Association, to improve quality of data and comparability between registries by standardizing methods of registration, definitions and coding, and to disseminate information on the multiple uses of cancer registry data in the planning and evaluation of cancer prevention and therapy, and in epidemiological research, have been substantially realized over the years. The Association collaborates extensively with the Agency, which has provided a secretariat since 1973, in many of the epidemiological studies described in part 1 of this report, including the regular provision of comparable incidence data and the preparation of publications on methodology.

The 1989 scientific meeting of the Association, held in Maastricht, the Netherlands, featured keynote lectures on cancer in the host country to the year 2000, the role of the registry in cancer screening, and cancer registries and occupational risk. The 1990 meeting took place in Hamburg, Germany, and focused on the topic 'Urban Life and Cancer', with sessions on the general environment, lifestyle and occupation. Quito, Ecuador, is the setting for the 1991 meeting which will be held in October.

The Association has been a non-governmental organization in official relations with WHO for a decade, and collaboration was renewed for three years following a successful review by WHO in 1991. This agreement permits Association members to attend WHO meetings and so foster the strengthening of research on cancer.

Regular newsletters are prepared and distributed by the secretariat to keep members informed about developments in cancer registration worldwide, projects in collaboration with the Agency, scientific meetings and literature.

### 3.1.3 Cancer registration and cancer epidemiology in Latin countries

(J. Estève, A. Rivoire and A.J. Tuyns; in collaboration with L. Raymond, Geneva, Switzerland; and R. Zanetti, Turin, Italy)

IARC provides support to the "Groupe pour l'Epidémiologie et l'Enregistrement du Cancer dans les Pays de Langue Latine", in particular for the organization of the annual meeting and publication of the proceedings.

The 1990 meeting of the group was held in Fort-de-France (Martinique, France)[1] at the invitation of Dr Ph. Escarmant, Dr H. Azaloux, and Dr G. Le Mab, and the 1991 meeting in Lisbon (Portugal) at the invitation of Dr Limbert. Results from cancer registries and from epidemiological studies presented at these meetings are published in the IARC Technical Report series. Advice and training on statistical methodology are regularly given to members of the group by Agency scientists on the occasion of site visits or by organizing workshops. In 1991, a one-day seminar on survival was organized in Lisbon in collaboration with Dr A. da Costa Miranda.

### 3.1.4 *Cancer Registration: Principles and Methods*

(D.M. Parkin and C.S. Muir; in collaboration with O.M. Jensen, Copenhagen, Denmark; R. MacLennan, Brisbane, Australia; and R. Skeet, Hereford, UK)

This volume, produced in collaboration with the International Association of Cancer Registries, supersedes the old IARC Scientific Publication No. 21 *Cancer Registration and its Techniques*[2]. It is aimed at medical and scientific staff who wish to start or operate a population-based cancer registry. Chapters include purposes of registration, planning a registry,

[1] IARC Technical Report No. 9 (1991) *Epidémiologie du Cancer dans les Pays de Langue Latine* (XVth Meeting, Fort-de-France, 24–25 May 1990), Lyon, International Agency for Research on Cancer

[2] MacLennan, R., Muir, C., Steinitz, R. & Winkler, A., eds (1978) *Cancer Registration and its Techniques* (IARC Scientific Publications No. 21), Lyon, International Agency for Research on Cancer

data items collected, classification and coding of cancer, quality control, reporting of results, statistical methods for registries, analysis of survival, registries in developing countries, the hospital registry, and confidentiality and legal aspects. A series of appendices describe methods used in different registries.

Negotiations on Spanish, Italian and French translations have been started.

### 3.1.5 *Training Manual for Cancer Registry Personnel*

(S. Whelan and D.M. Parkin; in collaboration with D. Badger, Ottawa, Canada; D. Estebán and A.V. Laudico, Manila, Philippines; S. Gravestock, Liverpool, UK; and A.L. Maya, Miami, FL, USA)

The relatively few training manuals for clerical and technical registry personnel are often far too complex and specialized for the needs of cancer registration in developing countries. It is planned to produce a core book, in loose-leaf format, which can be added to by individual registries for their specific needs.

A first draft of the manual was completed in 1990, and extensively reviewed in a meeting of editors, collaborators and advisers at the end of the year. The contents cover the various steps involved in registering a case of cancer, from understanding the medical terminology, through how to find the information, what details should be abstracted and how, coding, input operations and finally how to present the data.

The English version of the manual will be published as an IARC Technical Report in 1991. It is hoped to produce French and Spanish versions later.

### 3.1.6 Confidentiality in the cancer registry

(M.P. Coleman and C.S. Muir; in collaboration with F. Ménégoz, Meylan, France)

A policy statement on maintenance of confidentiality in cancer registries was prepared as the basis for a recommendation adopted by the International Association of Cancer Registries at its annual meeting in Hamburg in August 1990. A small committee on confidentiality was formed after this meeting to prepare and publish a code of confidentiality for cancer registration on behalf of the IACR. The code will provide a set of principles and ideas which may be selected, adapted and reformulated, as necessary, as part of a registry's procedures to maintain confidentiality, and is not intended to be adopted *en bloc* as a rigid set of rules. A draft code has been circulated to 325 population-based registries and individual members of IARC, and the revised version incorporating their comments is being prepared.

### 3.1.7 CANREG computer software for cancer registries

(D.M. Parkin, M.P. Coleman and S. Olivier)

CANREG is a set of microcomputer programs designed to meet the needs of small to medium cancer registries. It is a self-contained system that is simple to use, and has proved suitable for many registries, including those in developing countries where registry personnel have little or no formal training in computing[3].

[3] Bieber, C.A., Coleman, M.P. & Parkin, D.M. (1989) *CANREG: Cancer Registration Software for Microcomputers* (IARC Internal Report No. 89/001), Lyon, International Agency for Research on Cancer

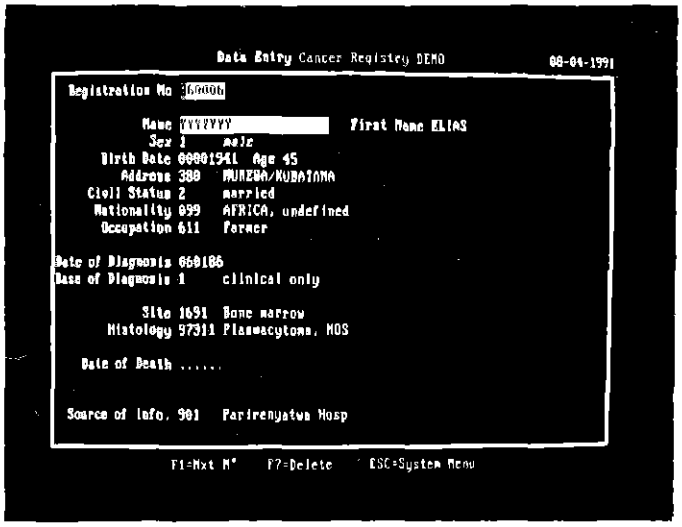


Fig. 23. A CANREG data-entry screen

The CANREG system permits entry of case data into a data-base specifically designed for cancer data (and hence incorporating a variety of in-built validations). The variables to be entered and the format of the data entry screen (Figure 23) are readily adapted to different installations. The system provides for the selection of subsets of cases for analysis. There are also tabulation facilities, and programs for the calculation of age-standardized incidence rates.

The CANREG system has been supplied to many centres. Registry personnel are sometimes able to visit IARC for a period of training; more often a staff member visits collaborating registries to modify the system to their requirements and train staff in its use.

The centres where the CANREG system has been installed include:

Africa: Algeria (3 centres), Burundi, Gabon, Gambia, Mali, Morocco, Rwanda, Tanzania, Zimbabwe.

Asia: Indonesia, Pakistan, Philippines (3 centres), Thailand (3 centres), Vietnam.

Americas: Bermuda, Bolivia, Colombia, Costa Rica, Paraguay, Peru.

Oceania: Fiji, French Polynesia, New Caledonia.

In addition to these installations in developing countries, the system has been supplied to several smaller cancer registries in Europe (notably in France, Italy and Spain).

Future development of the project includes the addition of more powerful programs for data verification (notably flagging unlikely site/histology combinations), for sorting of cases (by behaviour code), and enhanced analysis facilities (by interfacing with software for tabulation and plotting of descriptive data).

### 3.1.8 Revisions of the International Classification of Diseases

3.1.8.1 *Tenth revision of the International Classification of Diseases (ICD-10)*
(C.S. Muir and S. Whelan; in collaboration with J.W. Berg, Denver, CO, USA; P. Maguin, Le Vésinet, France; N.P. Napalkov, Leningard, USSR; G.T. O'Conor, Maywood, IL, USA; C. Percy and V. Van Holten, Bethesda, MD, USA; F. Rilke, Milan, Italy; L.H. Sobin, Washington, DC, USA; and D.H. Wright, Southampton, UK)

The Agency has been responsible for the revision of the neoplasms chapter of the 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-10). The draft proposals for ICD-10 were approved by the WHO Revision Conference held in Geneva in 1989, and accepted by the 1990 World Health Assembly.

Changes with significant implications include the transfer of neoplasms considered to be 'caused' by HIV to the chapter on infectious diseases, and the inclusion of CIN III with 'carcinoma *in-situ*' of the cervix (while 'severe dysplasia' remains with non-neoplastic diseases of the female genital tract).

In the Short Tabulation List, it was agreed that the most frequent sites of cancer worldwide which did not already figure on the list (e.g., stomach, prostate) should be added or replace sites which were felt to be unnecessary.

#### 3.1.8.2 *The International Classification of Diseases for Oncology*

(C.S. Muir; in collaboration with C. Percy, Bethesda, MD, USA)

The second edition of the International Classification of Diseases for Oncology (ICD-O), developed by the Agency in collaboration with the US National Cancer Institute, was published in 1990[4]. The topography codes are given according to the ICD-10 alphanumeric classification.

Innovations include the addition of several new histological types, a complete revision of the section on non-Hodgkin lymphoma, and expansion of the sixth digit code for histological grading and differentiation in order to identify T- and B-cell involvement for lymphomas and leukaemias.

## 3.2 *Development of Statistical Methodology*

### 3.2.1 Statistical methods in descriptive epidemiology

(J. Estève, M. Smans, P. Damiecki, H. Renard and A. Arslan; in collaboration with O.M. Jensen and H. Møller, Copenhagen, Denmark)

New methodological approaches have been set up for studies of estimation of incidence[5], prediction of cancer mortality in the year 2000 (Figure 24) and time trends (see section 1.1.4). Thorough analyses of the problem of the detection of spatial aggregation of cancer incidence and mortality have been carried out, and in particular the properties of the various statistics established for that purpose, including that used in the atlas of cancer incidence in Scotland (IARC Scientific Publications No. 72) have been studied[6].

Drafting of a monograph on statistical methods in descriptive epidemiology has now been completed; this will be published in 1992.

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[4] Percy, C., Van Holten, V. & Muir, C.S., eds (1990) *International Classification of Diseases for Oncology*, second edition, Geneva, World Health Organization

[5] Møller Jensen, O., Estève, J., Møller, H. & Renard, H. (1990) *Eur. J. Cancer*, **26**, 1167–1256

[6] Smans, M. & Estève, J. (1991) In: Elliott, P., Cuzick, J. & English, D., eds, *Geographical and Environmental Epidemiology: Methods for Small Area Studies*, Oxford, Oxford University Press (in press)

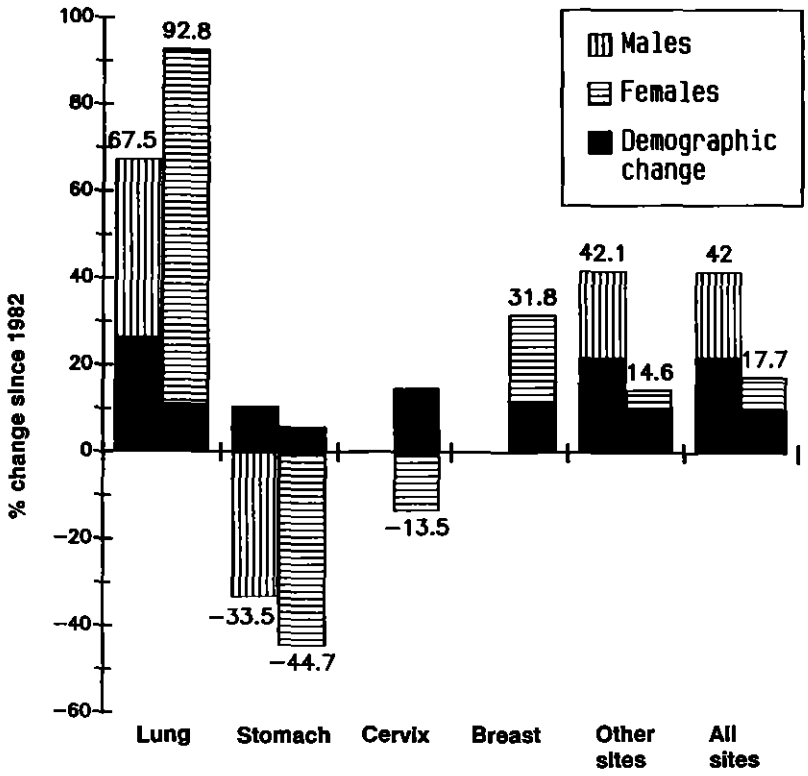


Fig. 24. Cancer mortality in the European Community in the year 2000: projected changes since 1982

### 3.2.2 Study of interaction and synergism

(J. Estève and P. Roy)

In order to assess the real impact of carcinogenic exposures on a population, it is essential to understand the interactions between the effects of different agents. Multiplicative models have generally been applied in this context and only exceptionally have other models been examined. Pursuing the exploration of models which are mixtures of additive and multiplicative effects[7], we have compared the performance of three models proposed by Thomas[8], Breslow and Storer[9] and Guerrero and Johnson[10] for studying combined effects. The model of Thomas is the most discriminant in the neighbourhood of additivity, while the model of Guerrero and Johnson is more discriminant in the neighbourhood of multiplicativity; the Breslow and Storer model occupies an intermediate position. Applying this approach to alcohol and tobacco exposures as risk factors for oesophageal and larynx cancer, it was demonstrated that the synergy (the

[7] Estève, J. & Tuyns, A.J. (19881) In: Feo, F., Pani, P., Columbano, A. & Garcea, R., eds, *Chemical Carcinogenesis* (Proceedings of the Fourth Sardinian International Meeting, 23–27 October 1987, Alghero, Italy), New York, Plenum, pp. 649–655

[8] Thomas, D.C. (1981) *Biometrics*, **37**, 673–686

[9] Breslow, N.E. & Storer, B.E. (1985) *Am. J. Epidemiol.*, **122**, 149–162

[10] Guerrero, V.M. & Johnson, R.A. (1982) *Biometrika*, **69**, 309–314

proportion of cases exposed to both agents which would not have occurred in the presence of only one) was the same for these two cancer sites despite large risk differences for alcohol consumption.

### 3.2.3 Study of survival

(J. Estève, P. Roy and P. Grosclaude; in collaboration with M. Croasdale, Halesowen, UK; L. Raymond, Geneva, Switzerland; A. Douglas, A. Swerdlow, and B. Vaughan Hudson, London, UK; F. Berrino and M. Sant, Milan, Italy; E. Benhamou, Villejuif, France; and M. Mercier, Besançon, France)

Practical applications of a model developed for the study of survival[11] are being made in collaboration with the EUROCARE programme and are being used in a study of survival of Hodgkin's disease patients. The goal is to develop a satisfactory methodology for studying survival from cancer registry data. This effort is directly related to the work undertaken in the framework of the European network of cancer registries (see section 1.1.7).

### 3.2.4 Statistical methods in genetic epidemiology

(A. Rogatko, H. de Solages, K. Zaid and J. Estève; in collaboration with T. Bishop, Leeds, UK; G. Bonney, Washington, DC, USA; R.C. Elston and B. Keats, New Orleans, LA, USA; J. Hopper, Carlton, Australia; D.V. Lindley, Minehead, UK; S. Narod, Montreal, Canada; N. Risch, New Haven, CT, USA; S. Sherman, Atlanta, GA, USA; J. Williamson, Boulder, CO, USA; and S. Zacks, New York, USA)

Statistical methods for inferring the order of genes in a chromosome are being developed. Information on the relative location of a gene for susceptibility to cancer and corresponding markers is essential for risk prediction. These methods will be used to construct genetic maps for genes related to, for example, breast cancer and multiple endocrine neoplasia type 2. The complete theory will include different sampling techniques (sperm typing and pedigrees), design (fixed sample or sequential), and three-point or multi-point data.

Methods to evaluate the precision of risk prediction in genetic counselling, when linked DNA markers are available, are being developed. Methods for one or several markers are being applied to families with a simple pedigree structure of multiple endocrine neoplasia type 2.

Graphical methods for the diagnosis of Hardy–Weinberg equilibria are under development. Since the analysis of familial data is based on assumption of the Hardy–Weinberg equilibrium, statistical methods that can be used in any sample size are being developed to evaluate how plausible it is to accept the hypothesis of equilibrium for monogenic diallelic autosomic, sex-linked inheritance, or multiallelic systems.

The results of segregation analysis depend on the method of ascertainment employed for sampling families. Methods to provide better solutions to the ascertainment problem are under investigation. The theoretical framework for a Bayesian approach is being studied for recessive inheritance. Generalizations for other types of inheritance, nuclear family and pedigree sampling will also be studied.

The gain in power from using relatives as controls in case-control studies when the disease depends both on exposure and on a genetic factor is under investigation.

A monograph on statistical methods in genetic epidemiology is being prepared as the fifth volume of the Statistical Methods in Cancer Research series. It will present the most recent

[11] Estève, J., Benhamou, E., Croasdale, M. & Raymond, L. (1990) *Stat. Med.*, **9**, 529–538

approaches in linkage and segregation analysis in a manner suitable for epidemiologists with a good background in statistics.

One of the main goals of this programme is to improve methods for studying the interaction of genetic and environmental factors. Lung cancer is particularly suited for the investigation of this problem. We are therefore planning the feasibility phase of a case-control study aimed at determining the role of several metabolic markers in predicting the risk of lung cancer among smokers (see section 1.6.3). This study should provide a basis for selecting families at very high risk of lung cancer which could then be studied by segregation and linkage analysis.

### 3.2.5 Training and consultation

An important part of the statistical methodology programme is devoted to training (see also section 5.1.2) and consultation which can be given to groups inside or outside the Agency[12]. The unit of statistical research hosts many visitors (often with financial help from the UICC), who may thus acquire expertise in a particular statistical domain.

## 3.3 *Methods for Detection of Carcinogens and DNA Damage, and Applications in Human Biomonitoring*

### 3.3.1 International network of carcinogenicity testing

(J. Wilbourn, H. Vainio, E. Cardis and J.R.P. Cabral)

The Agency, in collaboration with the WHO-ILO-UNEP International Programme on Chemical Safety (IPCS), continues to coordinate a network of laboratories involved in the long-term testing of chemicals for carcinogenicity in rodents and in studies of transplacental carcinogenesis. Studies on ftorafur (a chemotherapeutic agent) in mice and simazine (a herbicide) in rats are in progress, as well as transplacental studies on diethylstilbestrol in mice. Studies on ethanol and mancozeb have been terminated and the results of histopathological findings analysed. Results of studies on atrazine, deltamethrin and fenvalerate have been published[13,14,15]. IARC support is given through research agreement which are renewed periodically.

### 3.3.2 Development of methods for biological monitoring of vinyl chloride exposure

(A. Barbin, F. Ciroussel, L. Poncet, F. El-Ghissassi, Y. Guichard and H. Bartsch; in collaboration with J.-C. Contassot, M.-J. Marion and C. Trépo, Lyon, France; H.V. Gelboin, Bethesda, MD, USA; A.T. Natarajan, Leiden, Netherlands; G. Eberle and M.F. Rajewsky, Essen, Germany; J. Swenberg, Chapel Hill, NC, USA (supported in part by a contract with the Groupe de Recherche sur les Hépatites, Cirrhoses et Cancers du Foie (INSERM, Lyon) and ATOCHEM (Paris) and by the Weisbrem–Beneson Foundation (Fondation de France, Paris))

Occupational exposure to vinyl chloride (VC) has been associated with the development of

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[12] Hours, M., Cardis, E. & Fabry, J. (1990) Surveillance épidémiologique et toxicologique des populations résidant autour des décharges industrielles. Rapport de l'Agence Nationale pour la Récupération et l'Elimination des Déchets (ANRED), Paris

[13] Pinter, A., Török, G., Börzsönyi, M., Surjàn, A., Csik, M., Keleczényi, Z. & Kocsis, Z. (1990) *Neoplasma*, **37**, 533–544

[14] Cabral, J.R.P., Galendo, D., Laval, M. & Lyandrat, N. (1990) *Cancer Lett.*, **49**, 147–152

[15] Cabral, J.R.P. & Galendo, D. (1990) *Cancer Lett.*, **49**, 13–18

hepatic angiosarcoma (see section 1.2.2.1). The aims of this project are to develop methods for biological monitoring of humans exposed to VC and to elucidate the molecular mechanisms of angiosarcoma induction and development.

The formation and persistence of the DNA adducts 3,$N^4$-ethenodeoxycytidine ($\varepsilon$CdR) and 1,$N^6$-ethenodeoxyadenosine ($\epsilon$AdR), have been investigated in preweanling CD rats exposed to 600 ppm VC by inhalation. The concentrations of $\varepsilon$CdR and $\varepsilon$AdR in DNA hydrolysates from several organs have been measured, using a combination of HPLC and competitive radioimmunoassay[16]. In tissues of rats killed immediately after exposure, the concentrations of both adducts were over three times higher in liver than in lung and kidney. Measurements in rats killed at days 3, 7 or 14 following the end of exposure indicate that $\varepsilon$CdR and $\varepsilon$Adr are stable in liver DNA for at least 14 days. $N^2$,3-Ethenoguanine ($\varepsilon$G) also appears to be stable in liver DNA, whereas 7-(2-oxoethyl)guanine has a reported half-life of 62 hours[17]. $\varepsilon$G, $\varepsilon$CdR and $\varepsilon$AdR have been considered as promutagenic lesions, and their stability in DNA suggests that they are not repaired or only poorly, and could be involved in the initiation of VC-induced carcinogenesis. Thus, these DNA adducts could be used as markers of VC exposure in molecular dosimetry studies.

A more sensitive method of analysis for the ethenoadducts is being developed based on separation of the ethenodeoxyribonucleotides by immunoaffinity and $^{32}$P-postlabelling. This method will be applied in a study of the kinetics of accumulation and persistence of VC-DNA adducts in tissues of adult rats exposed to VC for various durations and killed either immediately after the end of exposure or after intervals of several weeks. These experiments should indicate whether ethenoadducts formed in DNA are repaired *in vivo*.

The possibility of detecting circulating antibodies directed against VC-modified epitopes of serum albumin has been examined. Using an ELISA methodology and native or chemically-modified serum albumin as the antigen, we failed to detect such antibodies in blood from retired workers who were heavily exposed to VC in their employment, from workers currently exposed to low levels of VC (8-h average concentration in the range of 0.05 to 1 ppm) or from rats exposed to 500 ppm VC[18].

Genetic damage in blood cells from retired workers heavily exposed to VC before 1975 was measured by scoring micronuclei in binucleated lymphocytes and haemoglobin mutants (haemoglobin S and haemoglobin San José) in erythrocytes. No significant increase in the frequency of either of these biological end-points was detected in VC-exposed individuals, as compared to control values.

To get further insight into interindividual variation in the ability to activate VC, we are characterizing the P450 isozymes implicated in VC oxidation and investigating their induction by VC. A previously developed *in vitro* assay[19] has been adapted to measure VC activation in the presence of microsomal suspensions. The activity of particular P450 isozymes is inhibited by adding specific substrates or monoclonal antibodies to the incubation medium.

Using the polymerase chain reaction/oligonucleotide hybridization technique, VC-associated human liver angiosarcomas have been analysed for activation of *ras* genes. In five out of six tumours analysed, an activated Ki-*ras* gene has been found with a GC→AT transition at the second base of codon 13[20]. This type of base-pair substitution is consistent with the mutational specificity of VC in bacteria[21].

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[16] Ciroussel, F., Barbin, A., Eberle, G. & Bartsch, H. (1990) *Biochem. Pharmacol.*, **39**, 1109–1113

[17] Fedtke, N., Boucheron, J.A., Walker, V.E. & Swenberg, J.A. (1990) *Carcinogenesis*, **11**, 1287–1292

[18] Ciroussel, F. (1990) Ph.D. Thesis, Lyon University

[19] Rinkus, S.J. & Legator, M.S. (1985) *Anal. Biochem.*, **150**, 379–393

[20] Marion, M.-J., Froment, O. & Trépo, C. (1991) *Mol. Carcinog.* (in press)

[21] Barbin, A., Besson, F., Perrard, M.H., Béréziat, J.-C., Kaldor, J., Michel, G. & Bartsch, H. (1985) *Mutat. Res.*, **152**, 147–156

The role of oncogene activation in the genetics of VC-associated tumours in rats is being investigated. Tumour DNA is being analysed by the polymerase chain reaction/oligonucleotide technique and with the NIH 3T3 transfection/nude mouse tumorigenicity assay.

The factor VIII-related antigen (von Willebrand factor, vWF), a known marker for endothelial cells, has been analysed in the serum of VC-exposed workers (active or retired) and in three patients with hepatic angiosarcoma associated with VC exposure. As compared to a control group, the serum level of vWF was markedly elevated in the patients with angiosarcoma and was raised in some of the VC-exposed subjects. Although a rise in the plasma or serum level is observed in various diseases associated with angiopathy, an elevated level in VC-exposed subjects, in the absence of other clinical symptoms, may reflect early endothelial cell damage or increased activity, predictive of an angiosarcoma[22].

### 3.3.3 New approaches to predicting the carcinogenic potency of alkylating carcinogens

(A. Barbin and H. Bartsch; in collaboration with H.S. Rosenkranz, Pittsburgh, PA, USA; and E.W. Vogel, Leiden, Netherlands)

DNA-damaging agents exhibit a remarkable range of carcinogenic activities in rodents: their $TD_{50}$ values ($TD_{50}$ = dose of carcinogen required to reduce by one half the probability of the animal being tumour-free throughout a standard lifetime) cover seven orders of magnitude[23]. For a series of direct-acting, monofunctional alkylating agents, a linear correlation was observed between the carcinogenic potency in rodents (log of $TD_{50}$ estimate) and nucleophilic selectivity (Swain–Scott constant *s* or DNA alkylation pattern); in contrast, several multifunctional anti-tumour drugs did not follow this relationship[24,25]. Similar results have been obtained in a comparison of mutagenic action in *Drosophila* (hypermutability of excision repair-deficient strains) with the *s* constants of 30 monofunctional or cross-linking alkylating agents[26]. These two approaches have now been combined and applied to a larger series of 60 DNA-damaging agents. In addition, the relative clastogenic efficiency of these agents in *Drosophila* (ratio of chromosomal aberrations to sex-linked recessive lethal mutations in a wild-type strain) has been compared with their nucleophilic selectivity and cross-linking activity. This multi-endpoint analysis has permitted the classification of genotoxic carcinogens into two major classes with different mechanisms of action: the monofunctional and the cross-linking agents[27]. It also allowed the categorization of procarcinogens and of chemicals of unknown *s* or $TD_{50}$ value.

The analysis of quantitative structure–activity relationships is now being extended to other carcinogenic chemicals to which humans are exposed. In addition, an attempt is being made to correlate the carcinogenic potency, genotoxic activities in *Drosophila* and nucleophilic selectivity of alkylating agents with molecular descriptors, using the CASE programme developed by Rosenkranz and Klopman[28].

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[22] Froment, O., Marion, M.-J., Lepot, D., Contassot, J.-C. & Trépo, C. (1991) *Cancer Lett.* (in press)

[23] Gold, L.S., Sawyer, C.B., Magaw, R., Backman, G.M., de Veciana, M., Levinson, R., Hooper, N.K., Havender, W.R., Bernstein, L., Peto, R., Pike, M.C. & Ames, B.N. (1984) *Environ. Health Perspect.*, **58**, 9–319

[24] Bartsch, H., Terracini, B., Malaveille, C., Tomatis, L., Wahrendorf, J., Brun, G. & Dodet, B. (1983) *Mutat. Res.*, **110**, 181–219

[25] Barbin, A. & Bartsch, H. (1989) *Mutat. Res.*, **215**, 95–106

[26] Vogel, E.W. (1989) *Carcinogenesis*, **10**, 2093–2106

[27] Vogel, E.W., Barbin, A., Nivard, M.J. & Bartsch, H. (1990) *Carcinogenesis*, **11**, 2211–2217

[28] Rosenkranz, H.S. & Klopman, G. (1990) *Mutat. Res.*, **228**, 105–124

### 3.3.4 Markers of human exposure to alkylating carcinogens: adducts in DNA and urine

The major reaction products of many alkylating carcinogens with DNA are the 7-alkyldeoxyguanosine (7-alkyldG) and 3-alkyldeoxyadenosine (3-alkyldA) adducts. 7-AlkyldG, such as 7-methyldeoxyguanosine (7-MedG) are relatively persistent in DNA and are being exploited as markers of alkylation exposure in readily accessible samples such as DNA from lymphoyctes or buccal tissue. 3-AlkyldA adducts are unstable and break down either spontaneously or by the action of glycosylases, to give the corresponding alkylpurines which are usually excreted intact in urine. This phenomenon has been used to develop a totally non-invasive technique to monitor human exposure to alkylating carcinogens. Mechanistic studies of DNA adduct repair are reported in section 1.7.4.

#### 3.3.4.1 *Analytical methods for DNA adducts*

(C.P. Wild, F. Bianchini, G. Martel-Planche, M. Miele, A. Munnia, D. Shuker and N. Mironov)

A previously developed radioimmunoassay to quantitate $O^6$-methyldeoxyguanosine ($O^6$-MedG) in human tissues[29] that required relatively large quantities of DNA (>1 mg) has been modified to a microassay that can detect as little as 50 fmol $O^6$-MedG. Second, an alternative approach has been developed to measure this adduct based on the capacity of the test DNA to compete with the repair of $O^6$-MedG present in the oligonucleotide substrate[30]. This method requires only 0.1–10 $\mu$g of DNA, and has a detection limit of 0.8 fmol of $O^6$-MedG per $\mu$g DNA.

7-Methyldeoxyguanosine (7-MedG) is the major DNA adduct resulting from exposure to alkylating agents and thus its measurement could be a very sensitive indicator of human exposure. However, its determination is more problematic than for $O^6$-MedG, demanding the elimination of 7-methylguanosine, a normal minor component of RNA. To provide an analytical method complementary to our previous approach[31] using antibodies to the imidazole ring-opened form of 7-MedG, antibodies to the free base (7-methylguanine) have been used to immunopurify the adduct before chromatography and quantitation in an enzyme-linked immunosorbent assay (ELISA). The specificity of this assay is dependent upon selective hydrolytic release of the adduct from DNA but not from RNA. The detection limit is of the order of 1 pmol per sample, or one adduct per $10^6$ unmodified parent bases in 1 mg DNA.

#### 3.3.4.2 *Detection of methylation adducts in human cells*

(C.P. Wild, F. Bianchini and A. Munnia)

*Smokers and non-smokers*

(in collaboration with A. Likhachev and N. Loktionova, Leningrad, USSR)

Peripheral blood cells were obtained from a series of 23 blood donors and analysed for the presence of 7-MedG. Of samples from 16 smokers, eight contained detectable levels of adduct, five individuals having >15 $\mu$mol per mole dT. Levels in samples from seven non-smokers were all below 15 $\mu$mol per mole dT. This indication of higher levels of methylation adducts in some smokers could reflect exposure to tobacco-specific nitrosamines.

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[29] *IARC Biennial Report 1988/89*, pp. 114–115

[30] Mironov, N.M., Martel-Planche, G. & Wild, C.P. (1991) *Proc. Am. Assoc. Cancer Res.*, **32**, 110

[31] *IARC Biennial Report 1988/89*, pp. 112–113

*EUROGAST*

(in collaboration with D. Forman and the EUROGAST study group)

This is a cross-sectional study of risk factors for gastric cancer in 13 countries where the incidences of this cancer vary ten-fold (see also section 1.3.4.4). Peripheral blood cells have been collected for measurement of 7-MedG levels in different populations. Initial results have shown detectable levels of 7-MedG in non-smoking subjects, when the DNA from 10 ml of blood was used. Further studies are required to establish the source of the DNA adducts induced and to look for possible variations in levels in the different countries.

### 3.3.4.3 *Urinary excretion of 3-methyladenine in subjects on controlled diets*

(D.E.G. Shuker and V. Prevost; in collaboration with S.R. Tannenbaum, Cambridge, MA, USA)

Previous results[32] indicated that 3-methyladenine (3-MeAde) was present in human urine at relatively high and variable levels. However, by use of pre-analysed liquid diets, the amount of exogenous 3-MeAde excreted can be reduced to such a level that methylation due to carcinogen exposures (e.g. <10 cigarettes) can be detected (Figure 25). Immunoaffinity column–monoclonal

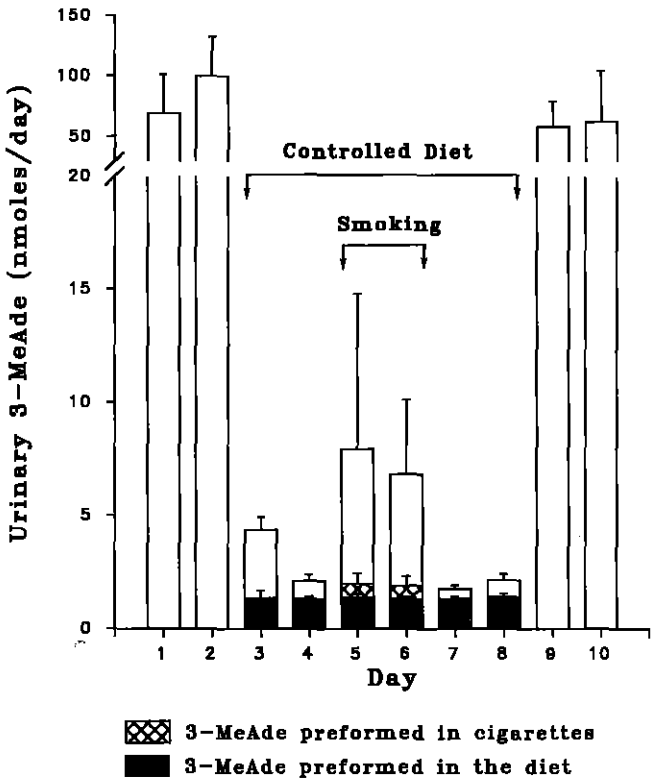


Fig. 25. Urinary excretion of 3-methyladenine by three smokers on a controlled diet

[32] Shuker, D.E.G., Bailey, E., Parry, A., Lamb, J. & Farmer, P. (1987) *Carcinogenesis*, **8**, 959–962

antibody ELISA was used to provide a rapid and sensitive assay of urinary 3-MeAde[33]. An immunoaffinity column/GC–MS procedure has also been developed[34] and agreement between the results obtained by the two methods has been excellent.

3.3.4.4 *DNA adducts and urinary alkylpurines in chemotherapy patients*
(C.P. Wild, F. Bianchini, A. Munnia, D.E.G. Shuker and V. Prevost; in collaboration with A.I. Arkhipov, M. Gershanovich, O.I. Kazanova, A. Likhachev, N. Loktionova and R.I. Wagner, Leningrad, USSR, and with J. Estève and the EORTC Lymphoma Group)

*N*-Nitroso-*N*-methylurea (NMU) is occasionally used as a chemotherapeutic agent to treat patients with melanoblastoma, lymphoblastic lymphoma or lymphogranulomatosis. In a series of such patients in Leningrad, average levels of $O^6$-MedG in peripheral blood cell DNA were 10–16 $\mu$mol per mole dG and 17–35 $\mu$mol per mole dG in patients given single doses of 300 mg and 600 mg NMU respectively. 7-MedG levels were generally between five and 20-fold higher than those of $O^6$-MedG. In patients receiving several doses of NMU over a period of 12–14 days, no marked accumulation of either adduct was observed.

In the same patients, urinary 3-MeAde levels exhibited a dose–response relationship. Increased excretion of 3-MeAde was observed in all patients following treatment with NMU. Current work is aimed at establishing the relationship between methyl adducts in lymphocyte DNA and urinary 3-MeAde in the same patients.

In the context of the study of second cancers in chemotherapy patients (see section 1.2.4), a protocol to examine DNA adduct formation, repair and mutation induction in peripheral blood cells in relation to therapeutic response has been established and recruitment of patients is in progress. In this study the drug of interest is procarbazine used as part of the MOPP drug combination in treatment of Hodgkin's disease.

3.3.4.5 *Preparation and characterization of an immunoaffinity column for 3-alkyladenines*
(D.E.G. Shuker and V. Prevost; in collaboration with G. Eberle and M.F. Rajewsky, Essen, Germany)

Monoclonal antibody EM-6-47[35] cross-reacts with a wide range of 3-alkyladenines. Immunoaffinity columns were prepared by covalently binding this antibody to Protein A-Sepharose CL4B gel (~100 $\mu$g/ml gel). A simple competitive binding assay was developed in which tritiated 3-MeAde with high specific activity was bound to the column and increasing amounts of 3-alkyladenines were eluted through the column. 3-Ethyl-, 3-hydroxyethyl-, 3-benzyl-adenine and tricanthine were equally well retained, while adenine and other purines were not retained at all. Use of these immunoaffinity columns has allowed the development of a GC–MS procedure for the simultaneous quantification of several 3-alkyladenines.

3.3.4.6 *Determination of urinary 3-alkyladenines by immunoaffinity purification and GC–MS*
(D.E.G. Shuker and V. Prevost; supported by a grant from the US National Cancer Institute, CA-48473)

In order to quantify various 3-alkyladenines by GC–MS, $d_3$-3-MeAde, $d_5$-3-ethyladenine,

[33] Prevost, V., Shuker, D.E.G., Bartsch, H., Pastorelli, R., Stillwell, W.G., Trudel, L. & Tannenbaum, S.R. (1990) *Carcinogenesis*, **11**, 1747–1751
[34] Friesen, M.D., Garren, L., Prevost, V. & Shuker, D.E.G. (1991) *Chem. Res. Toxicol.*, **4**, 102–106
[35] Eberle, G., Glüsenkamp, K.H., Drodziok, W. & Rajewsky, M. (1990) *Carcinogenesis*, **11**, 1753–1759

$d_4$-3-hydroxyethyladenine and $d_7$-3-benzyladenine were synthesized as internal standards. The metabolism of 3-alkyladenines was studied in two human volunteers who ingested 10 pmol of each of the deuterium-labelled alkyladenines. In urine collected up to 48 h after the dose, excretion of unchanged 3-MeAde and 3-hydroxyethyladenine was >90% and of 3-ethyladenine 70%, confirming results of animal experiments in which 3-alkyladenines were largely excreted unchanged. The exception was 3-benzyladenine which showed only 20–25% excretion unchanged by humans.

The effect of controlling diet on the excretion of background levels of 3-MeAde, 3-ethyladenine and 3-hydroxyethyladenine has been studied in human volunteers. Background excretion of 3-MeAde of 60–90 nmol per 24 h was reduced to levels of 2.4–2.9 nmol per 24 h in volunteers on the controlled diet.

The background levels of the longer-chain 3-alkyladenines were 10–100-fold lower than those of 3-MeAde, and much less susceptible to changes in diet. Preliminary results with a smoker suggest that the level of 3-ethyladenine increases with number of cigarettes. Current work is aimed at developing methods for the detection of characteristic 3-alkyladenines derived from tobacco-specific nitrosamines.

### 3.3.4.7 *Fluorescence postlabelling of DNA adducts*

(D.E.G. Shuker and M.-J. Durand)

7-Alkylguanines react with phenylmalondialdehyde to produce highly fluorescent derivatives[36]. As part of a project to develop methods for the identification of genotoxic substances in biological fluids (such as gastric juice) or foods, this reaction is being used to determine 7-alkylguanines in DNA ("probe DNA") which has been incubated with samples of interest.

In order to purify 7-alkylguanines as a group before the reaction with phenylmalondialdehyde, antibodies have been prepared against antigens synthesized from 7-(2-carboxyethyl)guanine and carrier proteins. Immunoaffinity columns have been prepared with these antibodies and [$^{14}$C]-7-ethylguanine of high specific activity has been synthesized in order to examine the characteristics of the immunoaffinity columns. Preliminary results show that a number of 7-alkylguanines are retained by the columns. Optimal conditions for the derivatization of 7-alkylguanines by phenylmalondialdehyde are being developed; good separation of the derivatives of the N7-methyl, ethyl and hydroxyethyl adducts of guanine can be obtained on reversed phase HPLC.

### 3.3.4.8 *Metabolic and dosimetry studies on* N-*nitroso*-N-*benzylmethylamine*

(M. Friesen, C. Malaveille, D. Shuker and H. Bartsch; in collaboration with H.V. Gelboin and S.S. Park, Bethesda, MD, USA; and D. Lin, Fuzhou, China)

Exposure to *N*-nitroso-*N*-benzylmethylamine (NBzMA) has been suggested to be involved in human oesophageal carcinogenesis in northern China. We previously investigated the relative contributions of methylation and benzylation to mutagenicity of NBzMA in bacteria[37]. Benzylcarbonium cations formed after P450-mediated hydroxylation of the methyl group were implicated in this mutagenicity. Experiments with specific monoclonal antibodies have specified the contributions of various P450 isozymes to NBzMA demethylation at low and high substrate concentrations. A GSH-dependent reduction of NBzMA mutagenicity of up to 100% was found with liver S9 from untreated Wistar rats, but this effect of GSH was less pronounced in livers from BDVI or Fischer 344 rats.

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[36] Sabbioni, G., Tannenbaum, S.R. & Shuker, D.E.G. (1986) *J. Org. Chem.*, **51**, 3244–3246

[37] Lin, D.X., Malaveille, C., Park, S.S., Gelboin, H.V. & Bartsch, H. (1990) *Carcinogenesis*, **11**, 1653–1658

We have confirmed that benzylmercapturic acid is excreted in the urine of rats treated with NBzMA, and have developed a GC-MS method to determine urinary levels[38]. The amount of urinary benzylmercapturic acid increased with the dose of NBzMA (up to 5 mg/kg b.w.) and varied between rat strains. Most was excreted with 24 h. Work is in progress to improve the sensitivity of the method using specific antibodies for clean-up and chemical ionization mass spectrometry for possible applications in human biomonitoring studies.

### 3.3.5 Development and use of microencapsulated trapping agents for carcinogens in the gastrointestinal tract

(I.K. O'Neill, A. Ellul and A. Shah; in collaboration with S.A. Bingham, Cambridge, UK; supported by a grant from the US National Cancer Institute, CA-39471)

Semi-permeable magnetic microcapsules have been developed for trapping carcinogen metabolites during gastrointestinal (GI) transit[39], providing the first method for GI biomonitoring. Three aspects are being studied: (*a*) validation of various microcapsule end-points for alkylating agents, cross-linking agents[40], nitrosating agents, apparent precursors of oxidative damage[41], and desorbable carcinogens having planar molecular structure[42], (*b*) the identification of endogenous DNA-damaging agents and their sources and (*c*) use of sets of human diets[43] for human and animal consumption to distinguish the GI effects of epidemiologically-identified colorectal cancer dietary risk factors, as an approach to systematic screening of possible modulators of risk.

#### 3.3.5.1 *Further development of microcapsule structure and carcinogen trapping*

(with B. Inçaurgarat; in collaboration with M. Ashwell and B. Golding, Newcastle, UK)

Relatively large polyethyleneimine (PEI) microcapsules (mean diameter 70–120 μm) were prepared in order to have microcapsules that are more magnetic for easier recovery from faeces and also to preclude any absorption into human GI structures. These microcapsules were shown to survive GI transit, to trap [$^{14}$C]BP and [$^{14}$C]PhIP *in vivo*, and to trap endogenous nitrosating agents 60 times more effectively than proline present in a 10-fold higher mass. A deoxyguanosine-simulating target[44] intended for covalent attachment inside the microcapsules has been shown to react with NMU at the same ratio and to yield the same $O^6$/N7 methylation ratio as deoxyguanosine. Microcapsules based on poly(vinyl alcohol) and triethylenetetramine were prepared as a non-competing vehicle for GI transport of this target, and were shown to have relatively low nucleophilicity and improved capacity to trap BP in the microcapsule core during GI transit.

#### 3.3.5.2 *Microcapsules containing double-stranded DNA*

(in collaboration with T. Alexakis, R. Neufeld and D. Poncelet, Quebec, Canada)

An obvious target material for encapsulation is DNA, but earlier microencapsulation techniques would have led to extensive DNA damage during the interfacial polymerization

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[38] Lin, D.X., Friesen, M., Malaveille, C., Shuker, D.E.G. & Bartsch, H. (1991) *Cancer Lett.*, **57**, 193–198
[39] Povey, A.C., Brouet, I., Bartsch, H. & O'Neill, I.K. (1987) *Carcinogenesis*, **8**, 825–831
[40] Ellul, A., Povey, A.C. & O'Neill, I.K. (1990) *Carcinogenesis*, **11**, 1577–1582
[41] Bingham, S., Shah, A., Ellul, A. & O'Neill, I.K. (1991) (submitted for publication)
[42] Povey, A.C. & O'Neill, I.K. (1990) *Carcinogenesis*, **11**, 1989–1993
[43] O'Neill, I.K., Bingham, S., Povey, A.C., Brouet, I. & Béréziat, J.-C. (1990) *Carcinogenesis*, **11**, 599–607
[44] Ashwell, M., Bleasdale, C., Golding, B.T. & O'Neill, I.K. (1990) *J. Chem. Soc. Chem. Commun.*, 955–956

process used to produce the membrane. A recently developed microencapsulation process with a non-biodegradable polymer (Chitosan) has been adapted to produce microcapsules containing double-stranded calf thymus DNA, that are stable to GI transit for magnetic recovery and were shown to trap electrophiles from [$^{14}$C]BP *in vivo*.

### 3.3.5.3 *Endogenous substances in the human gastrointestinal tract as precursors of radical oxidizing and cross-linking agents*
(in collaboration with J. Cummings, Cambridge, UK)

Microcapsules covalently labelled with $^{14}CH_3$ have provided a simple means of evaluating the faecal excretion of microcapsules[45]; such labelled microcapsules contained in gelatin capsules, together with radio-opaque marker controls, were swallowed by volunteers. The faecal excretions of radioactivity and of the radio-opaque markers were highly correlated ($r = 0.96$), indicating that gut transit time of the microcapsules is similar to that of larger objects. There was a 4–17% deficit of faecal $^{14}$C that appeared inversely related to breath $^{14}$C. Microcapsules incubated anaerobically with stool also lost radiolabel; microcapsules treated with hydrogen peroxide showed a dose-dependent loss of core but not membrane label. These data indicate that low-molecular-weight agents enter microcapsules in the GI tract and probably react with the magnetite iron to generate hydroxyl radicals that cause oxidative demethylation of N-$^{14}CH_3$ groups; recent hypotheses on colorectal cancer etiology[46,47] and experimental modulation by iron or iron chelators of 1,2-dimethylhydrazine-induced colorectal tumorigenesis[48,49] have invoked the intermediacy of Fe-dependent formation of hydroxyl radicals. In Fischer 344 rats, label loss was shown to be dependent on components of human diets (bran fibre and beef) that have been suggested to modulate development of colorectal cancer by this mechanism[47]. Microcapsules recovered from volunteers also showed extensive cross-linking unrelated to label loss. As many cross-linking agents are carcinogens, such a finding may also be of significance for GI cancer.

### 3.3.5.4 *Diet modulation of entrapment by microcapsules in volunteers*
(with F. El-Ghissassi)

In contrast to the above results found with humans on unrestricted diets, volunteers resident long-term in a clinical nutritional suite (Cambridge, UK) were given a series of three diets (4 weeks on each diet) that provided a systematic range of bran fibre and beef protein intake, before microcapsule administration. Three types of microcapsule were used simultaneously to identify dietary modulations of GI cancer-relevant agents: (*a*) $^{14}CH_3$-labelled microcapsules assessed for label loss; (*b*) unlabelled microcapsules assayed for *N*-nitrosation during a nitrosoproline test[50] for comparison of the efficacy of proline and microcapsules as nitrosation substrates; (*c*) microcapsules labelled with copper phthalocyanine functions[51] to trap protein pyrolysate products that are formed at high temperature in the grilling of beef-steaks. In prior work with F344 rats, endogenous nitrosation of microcapsule PEI was found to be ~600-fold greater w/w than of proline, and microcapsule entrapment of metabolites of $^{14}$C-radiolabelled

[45] Povey, A.C., Godeneche, D. & O'Neill, I.K. (1988) *J. Pharm. Pharmacol.*, **40**, 431–433
[46] Graf, E. & Eaton, J.W. (1985) *Cancer*, **56**, 717–718
[47] Babbs, C.F. (1990) *Free Radical Biol. Med.*, **8**, 191–200
[48] Siegers, C.P., Bumann, D., Baretton, G. & Younes, M. (1989) *Cancer Lett.*, **41**, 251–256
[49] Ullah, A. & Shamsuddin, A.M. (1990) *Carcinogenesis*, **11**, 2219–2222
[50] Ohshima, H. & Bartsch, H. (1981) *Cancer Res.*, **41**, 3658–3662
[51] Povey, A.C. & O'Neill, I.K. (1990) *Carcinogenesis*, **11**, 1989–1993

PhIP and IQ (a food pyrolysis product) was shown to be highly dependent on the diet being consumed.

### 3.3.5.5 *Effects of human dietary components on microcapsule trapping and related biochemical parameters*

(with C. Malaveille, F. El-Ghissassi and M. Rojas-Moreno; in collaboration with M. Goldberg, Guelph, Canada; K. Randerath, Houston, TX, USA; and I. Rowland and S. Rumney, Carshalton, UK)

Human diets formulated for isocaloric consumption and used in a number of rodent experiments[52,53] gave results greatly different from the chow or semi-purified diets in laboratory use worldwide. Changing the proportions of four colorectal cancer risk factors (fibre, beef, fat and calorific intake) in these diets led to alterations in GI transport, enterohepatic circulation, DNA adduct levels or small intestinal P450-related enzyme activity. (*a*) *Increased dietary fibre* (measured as non-starch polysaccharide) led to (i) decreased binding of electrophiles to microcapsules, by bulking and not by competitive adsorption, (ii) decreased systemic absorption, and (iii) increased conversion of IQ to 7-hydroxy-IQ by human microflora in rats; (*b*) *beef replacing vegetable protein* led to (i) increased binding of BP electrophiles to microcapsules and free radical activation of BP in low-fat but not high-fat diets, (ii) increased systemic DNA damage by BP, (iii) increased colonic DT diaphorase; (*c*) *a high-fat diet* (45% versus 15% available calories) (i) increased liver-DNA indigenous (I)-spots, and (ii) increased β-glucuronidase activity of human microflora in rats; (*d*) *40% decreased calorific intake* (i) increased microcapsule binding by BP and (ii) increased systemic absorption of BP.

Use of germ-free F344 rats showed that gut microflora (i) increased microcapsule binding of BP electrophiles, (ii) increased liver-DNA I-spots, and (iii) increased systemic DNA damage by BP. These data are consistent with dietary fibre non-starch polysaccharide minimizing contact with small intestine mucosa through bulking and hastening transit distally, with beef protein enhancing P450 activities in the small intestine and liver and also free radical oxidation, and with fat enhancing microfloral enzyme activity and enterohepatic circulation. By contrast, B57/C6 mice adapted to a set of human diets and administered BP and microcapsules had diet-dependent levels of nuclear aberrations in colorectal mucosa at 24 h that were also decreased by beef and fat intake[54]. Although the patterns and levels of BP metabolites trapped by faecally-excreted microcapsules were consistent with alterations occurring in (enzymatic or non-enzymatic) conversion of BP, the time- and species-dependence of microcapsule trapping and DNA adduction need to be elucidated. When [$^3$H]BP and [$^{14}$C]BP were administered together by gavage to rats given four large separate microcapsule doses, the $^3$H/$^{14}$C ratio in both microcapsules and urine was altered by the amount of microcapsules used, possibly because excessive microcapsule use resulted in interference with BP metabolism in the small intestine.

### 3.3.5.6 *Correlation between microcapsule trapping and GI or systemic DNA adduct formation*

(with B. Inçaurgarat and M. Klaude)

[$^{14}$C]BP was administered by gavage and [$^3$H]BP was given intraperitoneally 2 h after PEI microcapsules to F344 rats adapted to either rat chow or human diets with high or low levels of dietary fibre; different diets changed the levels of DNA- and microcapsule-binding of BP over 10-fold. In rats sacrificed at 24 h, large bowel DNA adduct levels were correlated with those on

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[52] O'Neill, I.K., Bingham, S., Povey, A.C., Brouet, I. & Béréziat, J.-C. (1990) *Carcinogenesis* **11**, 599–607

[53] O'Neill, I.K., Povey, A.C., Bingham, S. & Cardis, E. (1990) *Carcinogenesis*, **11**, 609–616

[54] O'Neill, I.K., Goldberg, M., El-Ghissassi, F. & Rojas-Moreno, M. (1991) *Carcinogenesis*, **12**, 175–180

microcapsules removed from large bowel contents ($r = 0.86$, $p > 0.005$), although microcapsule adducts were 1000-fold greater. The time-dependence of adduct levels on colorectal mucosal DNA differed greatly between tritiated and $^{14}C$-labelled adducts, and the level of DNA adducts in the small intestine mucosa was relatively high, indicating that colorectal DNA adducts arise from transit of DNA-damaging metabolites through the cavity (and not the bloodstream), possibly following predominantly duodenal metabolism.

### 3.3.6 Safe handling of carcinogens and destruction of their wastes

With the support of the Office of Safety of the US NIH, eight volumes have been published in this field dealing with laboratory decontamination and destruction of carcinogenic wastes, for various classes of compound. With further support from the French Ministry of the Environment, two more volumes have now been prepared. In addition, several courses have been held to train hospital and laboratory personnel in the safe handling of carcinogens and cytostatics.

#### 3.3.6.1 *Use of potassium permanganate for oxidative destruction of carcinogenic substances*

(M. Castegnaro; in collaboration with M. Laget and M. de Méo, Marseille, France)

Potassium permanganate ($KMnO_4$) combined with sulfuric acid, a strongly oxidizing mixture, has been recommended for the destruction and the decontamination of various mutagens/carcinogens[55]. Presence of direct-acting mutagens was detected in $KMnO_4$/sulfuric acid solutions with *Salmonella typhimurium* strain TA 102 without S9 mix. In addition, DNA damage in human peripheral blood lymphocytes was measured for one of the mixtures by the single cell gel assay (SCGA): samples of $KMnO_4/H_2SO_4$ induced DNA damage in a dose–response related fashion. The major mutagenic agent generated by the permanganate solutions was found to be the $Mn^{2+}$ ion. Both $MnSO_4$ and $MnCl_2$ gave dose–response curves in strain TA 102 and $MnCl_2$ induced DNA damage in human lymphocytes as determined by SCGA. Use of an alkaline $KMnO_4$ solution, which does not produce mutagenic species, offers alternative means for the degradation of genotoxic compounds.

#### 3.3.6.2 *Destruction of some mycotoxins and some polycyclic heterocyclic compounds*

(with support of the French Ministry of the Environment and of the Office of Safety of the US National Institutes of Health)

Methods for the degradation of mycotoxins (citrinin, ochratoxin A, patulin and sterigmatocystin) and some polycyclic heterocyclic compounds (dibenzacridines and dibenzocarbazoles) have been investigated. This project involves: collection and evaluation of published data on degradation techniques and the chemistry of the carcinogenic substances considered; laboratory evaluation and development of the proposed methods; collaborative studies to ascertain the efficiency of the methods; final description of the method by a meeting of experts, and publication in the IARC Scientific Publications series.

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[55] De Méo, M., Laget, M., Castegnaro, M. & Duménil, G. (1991) *Mutat. Res.*, **260**, 295–306

### *Mycotoxins*

(M. Castegnaro and J. Michelon; in collaboration with J.M. Fremy, Paris, France; M. Laget and M. de Méo, Marseille, France; and E.B. Sansone, Frederick, MD, USA)

Residues from degradation of citrinin, ochratoxin A and sterigmatocystin by various methods have been tested for mutagenic activity using four *S. typhimurium* strains with and without metabolic activation. Mutagenicity was detected for most residues generated by $KMnO_4/H_2SO_4$ treatments, presumably due mainly to the mutagenic $Mn^{2+}$ ion (see above); in addition degradation of sterigmatocystin by sulfuric acid led in some experiments to mutagenic residues[56].

Alkaline $KMnO_4$, which does not give mutagenic $Mn^{2+}$ residues, degraded the four mycotoxins, as well as four aflatoxins, and no mutagenic activity was detected in the residues.

Destruction of patulin in animal litter and in other types of waste using ammoniation was investigated. No residual mutagenic activity from any of the treatments was detected in four *S. typhimurium* strains, with or without metabolic activation.

Six methods for the degradation of mycotoxins were finally retained for validation by seven laboratories: (i) sodium hypochlorite for the degradation of ochratoxin A or citrinin; (ii) ammoniation at 100°C for the degradation of citrinin; (iii) sodium hypochlorite followed by acetone treatment for the degradation of sterigmatocystin; (iv) ammoniation in autoclave of patulin-contaminated litter; (v) ammoniation in autoclave of patulin in various wastes; and (vi) oxidation of the mycotoxins by alkaline $KMnO_4$. At a meeting of collaborators held in March 1991, all six methods were found acceptable for publication[57].

### *Polycyclic heterocyclic compounds*

(M. Castegnaro; in collaboration with U. Kirso, Tallinn, USSR; and E.B. Sansone, Frederick, MD, USA)

The residues from degradation of two dibenzacridines and two dibenzocarbazoles by several methods were tested for mutagenicity in *S. typhimurium* strains. Because of residual mutagenicity due to $Mn^{2+}$ from $KMnO_4/H_2SO_4$, the destruction of the hydrocarbons to non-mutagenic residues could not be proven. Instead, alkaline $KMnO_4$ completely degraded the two dibenzocarbazoles tested and dibenz[*a,j*]acridine in three hours, although dibenz[*a,h*]acridine was poorly degraded. Oxidative degradation by $KMnO_4$ alone at neutrality led to complete degradation of the same three compounds in six hours, but not dibenz[*a,h*]acridine.

Hydrogen peroxide and $FeCl_2$ gave complete degradation of all four aza-arenes, giving residues that were non-mutagenic in four *S. typhimurium* strains with or without metabolic activation.

A fourth method using concentrated sulfuric acid degraded dibenzocarbazoles but not dibenzacridines. The residues from degradation of the two dibenzocarbazoles were non-mutagenic in four *S. typhimurium* strains with or without metabolic activation.

Four methods for degradation of aza-arenes were retained for validation by seven laboratories: (i) oxidation by potassium permanganate alone; (ii) oxidation by potassium permanganate in alkaline medium; (iii) by Fenton reagents; and (iv) treatment by concentrated sulfuric acid. At a meeting of collaborators held in March 1991, all four methods were found acceptable for publication[58].

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[56] De Méo, M.P., Miribel, V., Botta, A., Laget, M. & Duménil, G. (1988) *Mutagenesis*, **3**, 277–283

[57] Castegnaro, M., Barek, J., Frémy, J.-M., Lafontaine, M., Miraglia, M., Sansone, E.B. & Telling, G.M., eds (1991) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Mycotoxins* (IARC Scientific Publications No. 113), Lyon, International Agency for Research on Cancer (in press)

[58] Castegnaro, M., Barek, J., Jacob, J., Kirso, U., Lafontaine, M., Sansone, E.B., Telling, G.M. & Vu Duc, T., eds, (1991) *Laboratory Decontamination and Destruction of Carcinogens in Laboratory Wastes: Some Polycyclic Heterocyclic Hydrocarbons* (IARC Scientific Publications No. 114), Lyon, International Agency for Research on Cancer (in press)

#### 3.3.6.3 *Safe handling of genotoxic substances*

(M. Castegnaro and W. Davis, in collaboration with A. Nagcotte, Lyon, France; and X. Rousselin, Paris, France)

A course on handling cytostatic drugs in hospitals was held in Lyon in March 1990 (see section 5.2). In order to complement this theoretical course, an agreement was signed with the Hospices Civiles de Lyon for practical training of private nurses.

A similar course is planned to be held in Bordeaux in September 1991 with the support of the ANFH Aquitaine.

A course on handling genotoxic substances in laboratories held in March 1990 was attended by more than eighty scientists, staff physicians and regulators.

### 3.3.7 Analysis of environmental carcinogens and analytical quality assurance

#### 3.3.7.1 *International Mycotoxin Check Sample Programme*

(M. Friesen, L. Garren and E. Bayle; supported by the Joint FAO/WHO Food Contamination Monitoring Programme and the Mycotoxin Working Group of the IUPAC Commission on Food Chemistry)

Since 1979, the IARC has provided laboratories around the world with a yearly service of analytical quality assurance for the analysis of mycotoxins in foods. Participants analyse identical portions of a homogeneous food sample for mycotoxins using methods of their choice. Participants are then provided with the distribution of the results from all participants, with which they can compare their own results. In 1989, 201 laboratories in 47 countries participated in the analysis of aflatoxins B and G in maize and peanuts, 130 laboratories in 39 countries in the analysis of aflatoxin $M_1$ in milk.

#### 3.3.7.2 *International N-nitrosamine check sample programme*

(M. Castegnaro and Z. Schneider)

The second check sample survey for determination of *N*-nitrosamines in beer and malt has been initiated. Each laboratory received four samples: two beers, from a same batch, spiked respectively with 0.5 µg/l *N*-nitrosodimethylamine (NDMA) and 4 µg/l NDMA plus 30 µg/l *N*-nitrosoproline (NPRO) and two naturally contaminated malts. Sixteen laboratories out of 18 were able to provide the results of their analyses. The statistical evaluation of the results of this study[59], as compared to the previous one[60], demonstrated an improved analysis of NDMA in beer and malt, but no improvement for two other common contaminants of beer and malt, *N*-nitrosopyrrolidine and NPRO. The method of Sen *et al.*[61] for NPRO in beer is expected to be more reliable.

#### 3.3.7.3 *Environmental Carcinogens: Methods of Analysis and Exposure Measurement*

(I.K. O'Neill and B. Dodet; in collaboration with L. Fishbein, Washington, DC, USA; A. Mackenzie-Peers, St-Alvère, France; C. Rappe, Umeå, Sweden; B. Seifert, Berlin, Germany; partly supported by the Netherlands Ministry of the Environment and the French Ministry of the Environment)

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[59] Castegnaro, M. (1991) *Food Add. Contam.* (in press)

[60] Castegnaro, M. (1988) *Food Add. Contam.*, **5**, 283–288

[61] Sen, N.P., Teissier, L. & Seanan, S.N. (1983) *J. Agric. Food Chem.*, **32**, 1033–1035

Progress was made towards completing volumes 11 (dioxins and polychlorinated dibenzofurans) and 12 (contaminants of indoor air). The future continuation of this series is now being reviewed in view of the need for greater resources to complete volumes in a more acceptable period. Volume 11 will be published in 1991 and volume 12 in 1992.

### 3.3.8 Meeting series on Biomonitoring and Susceptibility Markers in Human Cancer and on Relevance of Nitroso Compounds in Human Cancer

(H. Bartsch and I.K. O'Neill)

The previous meetings since 1969 (in particular those held in Helsinki in 1987[62] and in Lyon in 1989[63]) have stressed the multi-disciplinary aspects of research needs in environmental carcinogenesis and molecular/metabolic epidemiology. Although the first meetings were mainly focused on nitroso compounds, the emphasis of these conferences has gradually shifted to a wide range of carcinogens and to dosimetry methods for individual susceptibility and (dietary) modulating factors, and their applications to cancer etiology and prevention. The main aims of the meetings are to strengthen the link between human cancers and suspected etiological agents, and to encourage the development and application of validated methods to identify high-risk subjects in biochemical and molecular epidemiology studies.

The tenth meeting of this series, that was arranged for July 1989 in Beijing, China, was rescheduled to Lyon, 23–25 September 1989 (in collaboration with J. Chen and S.H. Lu, Beijing, and with support of the US NCI and NIEHS and the IPCS). 120 participants presented 118 papers. The programme was organized with a multi-disciplinary approach to major cancer sites associated with the title substances, and with sessions focused on exposure, biological mechanisms and preventive measures and a workshop on biological monitoring[63].

The next two meetings will be held in Kona, Hawaii, USA between 27 October and 2 November 1991, and are entitled (*a*) Biomonitoring and Susceptibility Markers in Human Cancer: Applications in Molecular Epidemiology and Risk Assessment, and (*b*) Nitroso Compounds; Biological Mechanisms, Exposures and Cancer Etiology.

## 3.4 *Surveys of On-Going Carcinogenicity Testing and of Epidemiological Studies*

### 3.4.1 *Directory of Agents Being Tested for Carcinogenicity*

(M.J. Ghess, J. Wilbourn and H. Vainio)

The Directory (formerly *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*) was initiated in 1973 in collaboration with the US National Cancer Institute. The title has been changed to allow agents other than chemicals to be included. The Directory of

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[62] Bartsch, H., Hemminki, K. & O'Neill, I.K., eds (1988) *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention* (IARC Scientific Publications No. 89), Lyon, International Agency for Research on Cancer

[63] O'Neill, I.K., Chen, J. & Bartsch, H., eds (1991) *Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105), Lyon, International Agency for Research on Cancer

Agents No. 14, published in June 1990, gives information on 922 chemicals or agents being tested for carcinogenicity from 80 institutes in 20 countries; a total of 298 published reports on 242 chemicals or agents are listed.

### 3.4.2 *Directory of On-Going Research in Cancer Epidemiology*

(M.P. Coleman, E. Démaret, A.-M. Beh and S. Whelan; in collaboration with H.-J. Baur, K. Schlaefer and J. Wahrendorf, Heidelberg, Germany; partially supported by Contract No. NO1-CO-55195 (until 15 August 1988) and then by NO1-CO-84340 with the National Cancer Institute, USA)

The Directory is a compilation of abstracts of current, unpublished research in cancer epidemiology. It has been published annually since 1976 in collaboration with the German Cancer Research Centre in Heidelberg. The 1989/90 edition, published in January 1990, contained abstracts of 1300 projects being carried out in 86 countries. The 1991 edition, published in January 1991, contained information on 1147 projects. Eight indexes (by investigator, key-word, cancer site, study type, chemical, occupation, country and cancer registry) facilitate access to the information.

Electronic searching of the Directory has been provided since the 1989/90 volume in the form of a diskette for IBM-compatible microcomputers. The diskette contains seven of the eight indexes and easy-to-use software. Complex searches can be done quickly, in particular when key-words from several indexes are being combined. Plans are in hand to make the entire Directory content available in electronic form (see section 5.3.1). Starting in 1989, a cancer registry index has identified over 300 projects in which registries are involved, and all cancer registries actively involved in research are identified.

Biological material is increasingly being used (or stored for later use) in epidemiological studies, and a special effort has been made to expand coverage of these collections. The 1991 Directory gives details of 322 banks of biological materials.

One of the main activities in the last year has been the development of a data-base management system (EPIBASE) to manage the mailing, compilation and preparation of the Directory entirely on microcomputer. This system is now operational and is being used to prepare the 1992 Directory, which will contain descriptions of some 1150 projects.

# PART 4. TECHNICAL SUPPORT

## 4.1 *Computing and Biostatistical Support*

(M. Smans, B. Charnay, P. Damiecki, X. Nguyen-Dinh, A. Arslan, H. Renard, D. Magnin, B. Kajo, E. Cardis, A. Rogatko and J. Estève)

A careful study of the Agency's computer configuration was undertaken in 1989 in order to assess the feasibility of applying a more decentralized approach. The adoption of cluster technology will permit greater flexibility in responding to evolving demands. The most obsolete part of our equipment, a VAX 8300, has been replaced in summer 1991 by a VAX 4000–300, which will be better suited to serving the cluster at present composed of six VAX 3100s. In this configuration, each research group has its own computing resources, and overloading in one group does not affect the other groups. At the same time, all groups use the same technology, enabling the central computer group to carry out maintenance, back-up and user support smoothly.

Office automation has reached an advanced stage, with a wide range of non-scientific staff using computer-supported tools. The main computerized work in the office is still word-processing, with some 50 concurrent users connected to the central system for several hours each day. The capacity of this system has been increased to meet the growing demand, and new software capabilities have been introduced.

The Agency is now a full member of the BITNET/EARN network (Node FRIARC51), and many scientists at the Agency are regular users of this system.

The biostatistics and computer group regularly provides assistance to users at various levels of expertise, on topics such as selection and testing of software, choice of statistical techniques, design of databases, and the computerization of applications in various fields (library, inventory, publications, and others).

## 4.2 *Library and Bibliographic Information*

(H. Miido, M. Coudert and L. Ossetian)

The Library received 225 journals including serials and free-of-charge titles. The present stock of bound journals is approximately 9800. The total number of library books is almost 9000, including WHO publications and annual reports.

The Library now has Medline from 1966 and Cancerlit from 1987 available on CD-ROM, to facilitate searching and reduce the heavy connection charges for use of external data-bases. During the two-year period 1989–1991, these were used in performing 97 selective bibliographic updates per year, an increase of 13% over the previous two-year period, and an increase of 39% over the previous year. Other database searches totalled 1058, a decrease of 47% from the

previous two-year period, caused by the disruption resulting from the temporary relocation of the Agency. The acquisition of 3392 photocopies of articles not available in the IARC library constituted an increase of 37% over the previous two-year period.

## 4.3 *Common Laboratory Services*
## (J.R.P. Cabral, H. Yamasaki, M. Laval and N. Lyandrat)

These services include animal breeding and maintenance of the animal house, the histology laboratory and the glass-washing service. The Agency's scientists use animals bred in-house for the majority of their work, since they now have considerable detailed knowledge of the spontaneous tumour rates in the strains used—BDIV and BDVI rats, C57BL/6 and CD1 mice. Facilities for the maintenance of nude mice are also available. The histology laboratory processes all the histological material from experimental animals in the Agency as well as biopsy material sent by Agency researchers doing field work abroad. The glass-washing facility is a unified service for the experimental work carried out in chemistry, biochemistry and cell culture.

In 1990, these services were considerably disrupted due to the relocation of the laboratories and the activities were necessarily reduced.

# PART 5. EDUCATION AND TRAINING

## 5.1 *Research Training Fellowships*
(R. Montesano)

### 5.1.1 The Fellowships Selection Committee

The Fellowships Selection Committee met twice in Lyon over the period to review applications; the members of the Committee were:

| | |
|---|---|
| Dr J.P. Allison (1990–1991) | Cancer Research Laboratory, University of California, Berkeley, CA, USA (UICC representative) |
| Dr V.N. Anisimov (1991) | Laboratory of Experimental Tumours, N.N. Petrov Research Institute of Oncology, Leningrad, USSR |
| Dr J. Cairns (1990–1991) | Harvard School of Public Health, Boston, MA, USA |
| Dr A. Likhachev (1990) | Laboratory of Biophysics, N.N. Petrov Research Institute of Oncology, Leningrad, USSR |
| Dr B. Mansourian (1990–1991) | Office of Research Promotion and Development, WHO, Geneva, Switzerland |
| Dr J. Pontén (1990–1991) | University of Uppsala, Department of Pathology, Uppsala, Sweden |
| Dr B. Terracini (1990–1991) | Department of Biomedical Science & Human Oncology, University of Turin, Turin, Italy |
| Dr S. Watanabe (1990–1991) | National Cancer Centre Research Institute, Division of Epidemiology, Tokyo, Japan |

The Agency representatives were Dr R. Montesano, Dr N. Muñoz (1990–1991) and Dr H. Vainio (1990–1991).

In 1990, a total of 13 fellowships were awarded out of 46 applications; in 1991, 13 out of 42 eligible candidates received fellowships. In 1990, two fellowships were tenable at the IARC and in 1991 four.

The distribution of fellowships awarded by discipline is given in Table 19; the list of fellows is given in Table 20.

The 'Associazione Italiana per la Ricerca sul Cancro' provided US$100 000 in 1990–1991 in support of the Fellowships Programme.

### 5.1.2 Visiting Scientist Awards

In 1991, this Award was given to Dr P. Ryan (Department of Community Medicine, University of Adelaide, Adelaide, South Australia), who spent a period of one year in the Unit of Analytical Epidemiology and in 1991 to Dr Q.-s. Wang (Tianjin Cancer Institute, Tianjin, China), who will spend one year in the Unit of Descriptive Epidemiology.

Table 19. Distribution of Research Training Fellowships awarded by discipline

| Scientific discipline | No. of fellowships | | |
|---|---|---|---|
| | 1990 | 1991 | 1966–91 |
| Epidemiology and biostatistics | 4 | 3 | 86 |
| Chemical carcinogenesis | 0 | 2 | 24 |
| Viral carcinogenesis | 2 | 2 | 17 |
| Cell biology, cell differentiation and cell genetics | 3 | 3 | 48 |
| Biochemistry and molecular biology | 4 | 3 | 61 |
| Others | 0 | 0 | 152 |
| Total | 13 | 13 | 388 |

## 5.2 *Training Courses*
(J. Cheney and W. Davis)

Twelve courses were held during the period under review.

### 5.2.1 **Advanced statistical methods in epidemiology,** 19–26 July 1989, IARC, Lyon, France

This course was the sixth in a very successful series held in the Agency's premises. The programme was coordinated by Dr John Kaldor. There were 66 participants coming from 24 countries.

### 5.2.2 **Epidemiological aspects of occupational cancer,** 18–26 September 1989, Ljubljana, Yugoslavia

At the request of the Institute of Oncology (Director: Professor Z. Rudolf), the Agency organized this course with the help of Dr Lorenzo Simonato (University of Padua, Italy) as programme coordinator. There were 27 participants coming from 6 countries.

### 5.2.3 **Cancer epidemiology** (in French), 20 November–1 December 1989, IARC, Lyon, France

In collaboration with the French National Institute for Medical Research (INSERM) (Director: Dr Philippe Lazar), the Agency organized this course, the first in a series, with the help of Dr Jacques Estève (IARC) and Dr Denis Hémon (INSERM) as programme coordinators. 46 participants coming from 11 countries attended this course.

### 5.2.4 **Safe handling of cytostatic drugs for health workers** (in French), 13–14 March 1990, IARC, Lyon, France; and **Safe handling of genotoxic substances in research laboratories** (in French), 15–16 March 1990, IARC, Lyon, France

The French Ministry of Health is currently evaluating available knowledge and wishes to propose recommendations for safe handling of genotoxic substances. At the request of the French National Institute for Research and Security (INRS), the Agency organized these two courses for the training of nurses and of public health and laboratory workers. Dr Xavier

Table 20. Fellowships awarded in 1990 and 1991

| Name | Institute of origin | Host institute |
|---|---|---|
| **1990** | | |
| ABERDAM, D. | Weizmann Institute of Science<br>Department of Molecular Genetics and Virology<br>Rehovot, Israel | University of Nice, INSERM U273<br>Biochemical Centre<br>Nice, France |
| BILLAUD, M. | IARC<br>Unit of Mechanisms of Carcinogenesis<br>Lyon, France | MGH Cancer Center<br>Harvard Medical School<br>Charlestown, MA, USA |
| CHITLARU, T. | Weizmann Institute of Science<br>Department of Molecular Genetics and Virology<br>Rehovot, Israel | Johns Hopkins University<br>School of Medicine<br>Department of Molecular Biology and Genetics<br>Baltimore, MD, USA |
| EVTUSHENKO, V. | Central Research Institute of Roentgenology and Radiology<br>Leningrad, USSR | National Cancer Institute<br>Laboratory of Molecular Oncology<br>Frederick, MD, USA |
| FRIEDENREICH, C. | University of Toronto<br>NCIC Epidemiology Unit<br>Toronto, Ontario, Canada | IARC<br>Unit of Analytical Epidemiology<br>Lyon, France |
| KEMP, C. | McArdle Laboratory for Cancer Research<br>Department of Oral Biology<br>Madison, WI, USA | Beatson Institute for Cancer Research<br>Glasgow, Scotland, UK |
| KOIFMAN, S. | National School of Public Health<br>Osvaldo Cruz Foundation<br>Department of Epidemiology<br>Rio de Janeiro, Brazil | McGill University<br>School of Occupational Health<br>Montreal, PQ, Canada |
| LANDI, M. | Institute of Occupational Health<br>University of Milan<br>Milan, Italy | NCI Environmental Epidemiology Branch<br>Family Studies Section<br>Bethesda, MD, USA |
| MAZIN, A. | Institute of Cytology and Genetics<br>Novosibirsk, USSR | CNRS<br>Enzymology Laboratory<br>Gif-sur-Yvette, France |
| PASQUALINI, R. | Ludwig Institute for Cancer Research<br>São Paulo, Brazil | Harvard Medical School<br>Department of Pediatrics<br>Boston, MA, USA |
| QI, Y. | Beijing Medical University<br>Laboratory of Gene Engineering<br>Department of Biochemistry<br>Beijing | CRC Human Cancer Genetics Research Group<br>Cambridge University<br>Department of Pathology<br>Cambridge, UK |
| TYCZYNSKI, J. | Oncological Centre<br>Department of Cancer Control and Epidemiology<br>Warsaw | IARC<br>Unit of Biostatistics Research and Informatics<br>Lyon, France |
| ZHANG, Z. | Henan Medical University<br>Henan Institute of Medical Sciences<br>Zhengzhou, Henan, China | Massachusetts General Hospital Cancer Center<br>Molecular Hepatology Laboratory<br>Charlestown, MA, USA |

Table 20—*contd*

| Name | Institute of origin | Host institute |
|---|---|---|
| **1991** | | |
| BIKFALVI, A. | INSERM U118<br>Gerontological Research Unit<br>Paris | New York University Medical School<br>Department of Cellular Biology<br>New York, NY, USA |
| CASTELLSAGUÉ, X. | Yale University<br>Department of Pediatrics<br>New Haven, CT, USA | IARC<br>Unit of Field and Intervention Studies,<br>Lyon, France |
| IOTSOVA, V. | Institute of Cell Biology and Morphology<br>Bulgarian Academy of Sciences<br>Sofia | Pasteur Institute<br>INSERM/CNRS Molecular Oncology Unit<br>Lille, France |
| KATOH, O. | National Cancer Centre Research Institute<br>Genetics Division, Tokyo | Institute of Cancer Research<br>Leukaemia Research Fund Centre<br>London |
| KIRBY, G. | University of Guelph<br>Department of Pathology<br>Guelph, Ontario, Canada | IARC<br>Unit of Environmental Carcinogens and Host Factors, Lyon, France |
| KUIJTEN, R. | Emma Children's Hospital<br>Department of Paediatric Oncology<br>Amsterdam<br>Netherlands | Children's Hospital of Philadelphia<br>Cancer Research Center<br>Division of Oncology<br>Epidemiology Section<br>Philadelphia, PA, USA |
| MINVIELLE, S. | CHU Saint-Antoine<br>INSERM U113, CNRS UA 163<br>Paris | National Cancer Institute<br>Laboratory of Human Carcinogenesis<br>Bethesda, MD, USA |
| NOPHAR, Y. | Weizmann Institute of Science<br>Department of Molecular Genetics and Virology<br>Rehovot, Israel | National Institute of Child Health and Human Development (NIH)<br>Laboratory of Mammalian Genes and Development<br>Bethesda, MD, USA |
| OGUNBIYI, O. | University of Ibadan<br>College of Medicine<br>Department of Pathology<br>Ibadan, Nigeria | IARC<br>Unit of Mechanisms of Carcinogenesis,<br>Lyon, France |
| OKPALA, I. | University College Hospital<br>Department of Haematology<br>Ibadan, Nigeria | Royal Postgraduate Medical School<br>MRC/LRF Leukaemia Unit<br>London |
| PHAM, A.T.H. | Hanoi Cancer Institute<br>Hanoi | London School of Hygiene and Tropical Medicine<br>Department of Epidemiology<br>London |
| SEROVA, O.M. | N.N. Petrov Research Institute of Oncology<br>Molecular Genetics Cancer Unit<br>Leningrad, USSR | IARC<br>Programme on Viral & Hereditary Factors<br>Unit of Mechanisms of Carcinogenesis,<br>Lyon, France |
| XU, Shiqiong | Shanghai Chest Hospital<br>Lung Cancer Research Centre<br>Shanghai, China | Osaka University Research Institute for Microbial Diseases<br>Department of Oncogene Research,<br>Osaka, Japan |

Rousselin (INRS) and Dr Marcel Castegnaro (IARC) coordinated the two programmes. For the session on cytostatic drugs, the 65 participants came from France, apart from one who came from Belgium, while for the session on genotoxic substances, the 84 participants came from France, Italy and Switzerland.

### 5.2.5 **Modern methods in cancer epidemiology,** 7–18 May 1990, Shanghai, China

The Agency organized this course in collaboration with the Shanghai Medical University (President: Professor Tang Zhao You) and the Shanghai Cancer Institute (Director: Dr Gao Yu-Tang). Professor Tony McMichael (University of Adelaide, Australia) coordinated the programme. A popular innovation was practical instruction in microcomputer techniques used in epidemiology. 38 participants from 7 different countries attended the course.

### 5.2.6 **European Educational Programme in Epidemiology—Third Residential Summer Course,** 18 June–6 July 1990, Florence, Italy

As a follow-up to the first two successful courses held in 1988 and 1989, IARC provided administrative support for the organization by the European Education Programme in Epidemiology of its third residential summer school in the same premises (CISL Study Centre, Florence) with Dr Rodolfo Saracci from IARC acting as course director. There were 51 participants coming from 20 different countries.

### 5.2.7 **Molecular biology for cancer epidemiologists,** 18–27 September 1990, IARC, Lyon, France

This third course on molecular biology for cancer epidemiologists, with Dr R. Montesano (IARC) and Professor J. Cairns (Harvard University) as programme coordinators, was the first event to be held in the new Villemanzy International Residence, in Lyon. Laboratory sessions were held in the Alexis Carrel Faculty of Medicine of the University of Lyon. The course was attended by 47 participants from 20 different countries.

### 5.2.8 **Epidemiological methods in cancer control,** 15–26 October 1990, Manila, Philippines

In collaboration with the World Health Organization Regional Office for the Western Pacific (WPRO) and with the sponsorship of the Department of Health, Philippines and the University of the Philippines, Manila, the Agency organized a course on epidemiological methods in cancer control in the WPRO headquarters and a significant part of the teaching was conducted by local faculty members. Dr Max Parkin (IARC) coordinated the programme. 32 students from 12 different countries attended the course.

### 5.2.9 **Cancer epidemiology** (in Spanish), 11–22 March 1991, Havana, Cuba

In collaboration with the Pan American Health Organization and the National Institute of Oncology and Radiobiology (INOR), Havana, the Agency organized a course on cancer epidemiology, in Spanish. Dr Xavier Bosch from IARC coordinated the programme with the local help of Dr Adolfo Valdivia (INOR). 46 students coming from 9 Latin American countries and Spain attended the course.

### 5.2.10 **Cancer epidemiology** (in French), 8–19 April 1991, IARC, Lyon, France

As a follow-up to the successful course held in 1989 in collaboration with the French National Institute for Medical Research (INSERM), the Agency organized a second course in the series with Dr Jacques Estève (IARC) and Dr Denis Hémon (INSERM) acting as programme coordinators. 36 participants from 8 countries attended the course.

### 5.2.11 **Scientific basis of carcinogenicity testing,** 29 May–4 June 1991, Moscow, USSR

In collaboration with and sponsorship of the National Institute for Environmental Health Sciences (NIEHS), USA and the Environmental Health Directorate, Health & Welfare, Canada, the Agency organized a short course on the scientific basis of carcinogenicity testing at the All-Union Cancer Research Centre (Director: Professor N.N. Trapeznikov) in Moscow, with the local support of Drs Vladimir Turusov and David Zaridze. Drs Christopher Portier (NIEHS) and Hiroshi Yamasaki (IARC) coordinated the programme. In addition to 43 participants from the Soviet Union, another three travelled from Canada, Japan and the United Kingdom.

### 5.2.12 **European Educational programme in Epidemiology—Fourth Residential Summer Course,** 24 June–12 July 1991, Florence, Italy

This series being now well established, with one course each year since 1988, IARC again provided its administrative support to the programme. The course was held at Hotel Ambasciatori, in Montecatini Terme, for the first week, the usual premises (STUDIUM Study Centre, Florence) being available only for the last two weeks. Dr Walter Davis coordinated the administrative arrangements for the course, which was directed by Dr Rodolfo Saracci. 61 participants from 17 different countries attended the course.

## 5.3 *Publications*
(J. Cheney)

All proposals for IARC publications are critically reviewed by the Advisory Committee on Publications (chaired by the Deputy Director) to ensure scientific quality and compatibility with the Agency's overall programme.

Notable features of the programme during the biennium were the issue of the 50th volume in the IARC Monographs series (on pharmaceutical drugs) and the completion of two long-awaited items in the IARC Scientific Publications series, No. 95, *Cancer Registration: Principles and Methods,* a unique reference work for the establishment and running of cancer registries, and No. 100 *Cancer: Causes Occurrence and Control,* a comprehensive review of cancer incidence and etiology and the possibilities for prevention.

The Agency's best-sellers continue to be volumes I and II of Statistical Methods in Cancer Research, of which sales now exceed 7500 and 5000 copies, respectively.

An advanced desktop publishing system has been installed to facilitate the typographic make-up of publications and other documents.

Illustrations for IARC publications and for journal articles, lectures and poster presentations by the scientific staff, as well as for other purposes are prepared by a draughtsman and a photographer. Photographic work is also carried out in connection with various laboratory activities. A computerized graphics system with a variety of software is used to produce both slides and printed illustrations.

### 5.3.1 Electronic publication

(M.P. Coleman, H. Vainio, J. Cheney, E. Démaret, J. Wilbourn and M.-J. Ghess)

An extension of the conventional publishing activities was the issue of the indexes for the Directory of On-going Research in Cancer Epidemiology in electronic form on a microcomputer diskette, starting with the 1989/1990 edition. Electronic publication of the complete Directory along with other IARC information resources on CD-ROM (Compact Disk, Read-Only Memory) is being explored in order to improve the dissemination of information compiled by the Agency. A full-text version of the Directory of On-going Research in Cancer Epidemiology was produced in 1989 on CD-ROM in a successful pilot study. A project has been started to create a CD-ROM with powerful search software to provide full-text access to the entire series of IARC Monographs, together with the Directories of Agents Being Tested for Carcinogenicity and of On-going Research in Cancer Epidemiology. This CD-ROM is planned to also include the Cross-Index of Synonyms and Trade Names and the Compound Data-base, which contains key data on all the animal experiments used for evaluations of carcinogenicity in the Monographs programme.

Cancer incidence and mortality data for Europe (EUROCIM) have also been prepared for electronic publication, together with statistical and graphical software, as part of the European Network of Cancer Registries project (see section 1.1.7).

Software has been developed to make the next volume of *Cancer Incidence in Five Continents* available in parallel in electronic form (see section 1.1.1).

### 5.3.2 New publications

During the period covered by this report, the following publications have appeared:

*Cancer Registration: Principles and Methods* (IARC Scientific Publications No. 95)

*Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96)

*Occupational Exposure to Silica and Cancer Risk* (IARC Scientific Publications No. 97)

*Cancer Incidence in Jewish Migrants to Israel, 1961–1981* (IARC Scientific Publications No. 98)

*Pathology of Tumours in Laboratory Animals*, Second Edition, Volume I, *Tumours of the Rat* (IARC Scientific Publications No. 99)

*Cancer: Causes, Occurrence and Control* (IARC Scientific Publications No. 100)

*Directory of On-going Research in Cancer Epidemiology 1989/90* (IARC Scientific Publications No. 101)

*Patterns of Cancer in Five Continents* (IARC Scientific Publications No. 102)

*Evaluating Effectiveness of Primary Prevention of Cancer* (IARC Scientific Publications No. 103)

*Complex Mixtures and Cancer Risk* (IARC Scientific Publications No. 104)

*Relevance to Human Cancer of* N-*Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105)

*Directory of On-going Research in Cancer Epidemiology 1991* (IARC Scientific Publications No. 110)

*Autopsy in Epidemiology and Medical Research* (IARC Scientific Publications No. 112)

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 46, *Diesel and Gasoline Engine Exhausts and some Nitroarenes*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 47, *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 48, *Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 49, *Chromium, Nickel and Welding*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 50, *Pharmaceutical Drugs*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 51, *Coffee, Tea, Mate, Methylxanthines and Methylglyoxal*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol 52, *Chlorinated Drinking-Water*; *Chlorination By-products*; *Some Other Halogenated Compounds*; *Cobalt and Cobalt Compounds*

*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 8, *Cross-Index of Synonyms and Trade Names in Volumes 1 to 46 of the IARC Monographs*

*Directory of Agents Being Tested for Carcinogenicity*, No. 14

*La Genèse du Centre International de Recherche sur le Cancer* (IARC Technial Report No. 6)

*Epidémiologie du Cancer dans les Pays de Langue Latine* (IARC Technical Report No. 7)

*Annex 1*

# PARTICIPATING STATES AND REPRESENTATIVES AT THE THIRTY-FIRST SESSION OF THE IARC GOVERNING COUNCIL 3–4 May 1990

*Australia*

Dr D. De Souza
Minister (Health)
Australian High Commission
London

*Belgium*

Mr D. van Daele
Secretary General
Ministry for Public Health and the Environment
International Relations
Brussels

*Canada*

Dr E. Somers
Director-General
Drugs Directorate
Department of National Health and Welfare
Ottawa

Professor R. Simard
Vice-Rector
University of Montreal
Montreal

*Denmark*

Mr S. Loiborg
Head of Division
Ministry of Health
Copenhagen

Dr N. Rosdahl
Chief of Division
National Board of Health
Copenhagen

*Finland*

Dr M. Ruokola
Director-General
National Board of Health
Helsinki

Professor J.K. Huttunen (*Vice-Chairman*)
Director-General
National Public Health Institute
Helsinki

*France*

Professor M.R. Tubiana
Honorary Director
Gustave Roussy Institute
Villejuif

Dr Angelé
Ministry of Health
Paris

Mrs I. Royer
Ministry of Foreign Affairs
Paris

*Germany*

Mr H. VOIGTLÄNDER
Director, International Health Relations Section
Federal Ministry for Youth, Family Affairs, Women and Health
Bonn

*Italy*

Dr P. MALARA
Ministry of Health
Rome

Dr G. SALVO
National Institute of Health
Rome

Professor L. SANTI
Director, Institute of Oncology
University of Genoa

*Japan*

Dr F. IRIYAMA
Director-General, Statistics and Information Department
Ministry of Health and Welfare
Tokyo

Dr T. TOGUCHI
Deputy-Director, International Affairs Division
Ministry of Health and Welfare
Tokyo

*Netherlands*

Professor R. KROES
Deputy Director-General
National Institute of Public Health and Environmental Protection
Bilthoven

Mr F.H. DE MAN
Deputy Head, International Health Affairs Division
Ministry of Welfare, Health and Cultural Affairs
Rijswijk

*Norway*

Mr O.J. SANDVAND
Director, Medical Research Council
Norwegian Research Council for Science and the Humanities
Oslo

*Sweden*

Professor H. DANIELSSON (*Chairman*)
Secretary-General
Swedish Medical Research Council
Stockholm

*Switzerland*

Professor B. ROOS
Director
Federal Office of Public Health
Bern

*Union of Soviet Socialist Republics*

Professor N.N. TRAPEZNIKOV
Director
All-Union Cancer Research Centre
Academy of Medical Sciences
Moscow

*United Kingdom of Great Britain and Northern Ireland*

Dr D.C. EVERED
Second Secretary
Medical Research Council
London

Dr H. MARKOWE
Director, Department of Health
Central Health Monitoring Unit
London

*United States of Anerica*

Dr F. WELSCH (*Rapporteur*)
Associate Director for International Affairs
National Cancer Institute
Bethesda, MD

Mr N.A. BOYER
Director, Health and Transportation Programs
Bureau of International Organization Affairs
Department of State
Washington, DC

*World Health Organization*

Dr H. NAKAJIMA
Director-General

Dr N.P. NAPALKOV
Assistant Director-General

Mr E.E. UHDE
Acting Assistant Director-General and Director, Division of Budget and Finance

Dr C.-H. VIGNES
Legal Counsel

*Observers*

Professor A.J. MCMICHAEL
Incoming Chairman, Scientific Council

Professor E.J. SAKSELA
Outgoing Chairman, Scientific Council

Mr A.J. TURNBULL
Executive Director, UICC

*Experts*

Mr A. IMBRUGLIA

Mr T. VITTERY
Medical Research Council
London
UK

# PARTICIPATING STATES AND REPRESENTATIVES AT THE THIRTY-SECOND SESSION OF THE IARC GOVERNING COUNCIL
## 2–3 May 1991

*Australia*

Dr D. DE SOUZA
Minister (Health)
Australian High Commission
London

Dr CATHERINE MEAD
Medical Services Adviser
Communicable Disease and International Health Branch
Australian Department of Community Services and Health
Canberra, ACT 2601

*Belgium*

Mr D. VAN DAELE
Secretary General, Ministry for Public Health and the Environment
Brussels

*Canada*

Dr E. SOMERS
Director-General
Drugs Directorate
Department of National Health and Welfare
Ottawa

*Denmark*

Mr S. Loiborg
Head of Division
Ministry of Health
Copenhagen

*Finland*

Professor J.K. Huttunen (*Chairman*)
Director-General
National Public Health Institute
Helsinki

Dr J. Eskola
Director, Department for Promotion and Prevention
Ministry of Health and Social Affairs
Helsinki

*France*

Professor M.R. Tubiana
Honorary Director
Gustave Roussy Institute
Villejuif

Mrs A. Cukierman
Directorate for United Nations and International Organizations
Ministry of Foreign Affairs
Paris

Dr Marie-France Veran-Peyret
Regional Directorate for Health and Social Affairs
Lyon

*Germany*

Mr H. Voigtländer (*Vice-Chairman*)
Director, International Health Relations Section
Bonn

*Italy*

Dr Marta di Gennaro
Director
Office of International Relations
Ministry of Health
Rome

Dr G. D'Agnolo
Director, Laboratory of Cell Biology
Institute of Health
Rome

Professor L. Santi
Director, Institute of Oncology
University of Genoa
Genoa

*Japan*

Dr F. Iriyama
Director-General
Statistics and Information Department
Ministry of Health and Welfare
Tokyo

Mr K. Itoi
Deputy Director
International Affairs Division
Ministry of Health and Welfare
Tokyo

Dr T. Toguchi
Medical Officer and Deputy-Director
International Affairs Division
Ministry of Health and Welfare
Tokyo

*Netherlands*

Professor R. Kroes
Deputy Director-General
National Institute of Public Health and Environmental Protection
Bilthoven

Dr J.W. Hartgerink
Head, Research Coordination Unit
Ministry of Welfare, Health and Cultural Affairs
Rijswijk

Dr Alice Verwers
Ministry of Welfare, Health and Cultural Affairs
Rijswijk

*Norway*

Mr O.J. SANDVAND (*Rapporteur*)
Assistant Director General
Norwegian Research Council for Science and the Humanities
Oslo

Dr BERIT MØRLAND
Director, Council for Medical Research
Norwegian Research Council for Science and the Humanities
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Dr T. SCHERSTEN
Swedish Medical Research Council
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*Switzerland*

Dr T. ZELTNER
Director, Federal Office of Public Health
Bern

Dr STÉPHANIE ZOBRIST
International Organizations
Federal Office of Public Health
Bern

*Union of Soviet Socialist Republics*

Dr A.M. MOSKVICHEV
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Ministry of Health
Moscow

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Director-General
All-Union Cancer Research Centre
Academy of Medical Sciences
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Second Secretary
Medical Research Council
London

Mr A. VITTERY
Medical Research Council
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*United States of America*

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Department of State
Washington, DC

*World Health Organization*

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Dr N.P. NAPALKOV
Assistant Director-General

Dr H. DANIELSSON
Chief, Office of Cancer Programme Coordination

Dr J. STJERNSWÄRD
Chief, Cancer and Palliative Care

Mr E.E. UHDE
Director, Division of Budget and Finance

Dr C.-H. VIGNES
Director, Office of the Legal Counsel

*Observers*

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China

Dr J.G. ENRIQUEZ
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Madrid
Spain

Dr J.R.R. CAMPOS
Ministry of Health and Consumer Affairs
Madrid
Spain

Professor A. J. MCMICHAEL
Chairman, Scientific Council

Professor N. ODARTCHENKO
UICC

*Annex 2*

# MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS TWENTY-SIXTH SESSION 22–25 January 1990

Professor E.J. SAKSELA (*Chairman*)
Department of Pathology
University of Helsinki
Finland

Professor H. zur Hausen (*Vice-Chairman*)
Director, German Cancer Research Center
Heidelberg
Germany

Professor A. J. MCMICHAEL (*Rapporteur*)
Department of Community Medicine
University of Adelaide
Australia

Professor L. CHIECO-BIANCHI
Director, Institute of Oncology
University of Padua
Italy

Professor F. de WAARD
Preventicon
Utrecht
The Netherlands

Professor S. GRAHAM
Department of Social and Preventive Medicine
University of Buffalo
School of Medicine
Buffalo, NY
USA

Professor K.P. HANSON
Chief, Laboratory of Biochemistry
N.N. Petrov Institute of Oncology
Leningrad
USSR

Professor L.G. ISRAELS
Executive Director
Manitoba Cancer Treatment and Research Foundation
Winnipeg
Canada

Professor O.H. IVERSEN
Institute of Pathology
University of Oslo
Norway

Professor J. KLASTERSKY
Free University of Brussels
Jules Bordet Institute
Belgium

Professor J.-P. LÉVY
Laboratory for Immunology and Oncology of Retroviral Diseases
Cochin Hospital
Paris
France

Professor U. PETTERSSON
Department of Medical Genetics
Biomedical Center
Uppsala
Sweden

Professor P.G. SMITH
Head, Tropical Epidemiology Unit
London School of Hygiene and Tropical Medicine
London
UK

Dr S. TAKAYAMA*
Director, National Cancer Centre Research Institute
Tokyo
Japan

*World Health Organization*

Dr N.P. NAPALKOV
Assistant Director-General

*International Union Against Cancer*

Dr N. ODARTCHENKO
Epalinges sur Lausanne
Switzerland

# MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS TWENTY-SEVENTH SESSION

Professor A.J. MCMICHAEL (*Chairman*)
Department of Community Medicine
University of Adelaide
Australia

Professor U. PETTERSSON (*Vice-Chairman*)
Department of Medical Genetics
Biomedical Center
Uppsala
Sweden

Dr P.A. CERUTTI
Department of Carcinogenesis
Swiss Institute for Experimental Cancer Research
Epalinges sur Lausanne
Switzerland

Professor P. KLEIHUES (Alternate)
University of Zurich
Switzerland

Professor L. CHIECO-BIANCHI
Director, Institute of Oncology
University of Padua
Italy

Professor K.P. HANSON
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N.N. Petrov Institute of Oncology
Leningrad
USSR

Dr C.C. HARRIS
Chief, Laboratory of Human Carcinogenesis
National Cancer Institute
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USA

Professor L.G. ISRAELS
Executive Director
Manitoba Cancer Treatment and Research Foundation
Winnipeg
Canada

Professor O.H. IVERSEN
Institute of Pathology
University of Oslo
Norway

Dr O.M. JENSEN
Director, Danish Cancer Registry
Copenhagen
Denmark

* Unable to attend.

Professor J. KLASTERSKY
Jules Bordet Institute
Free University of Brussels
Belgium

Professor R. MONIER (Alternate)
Director, Laboratory of Molecular Oncology
Gustave Roussy Institute
Villejuif
France

Professor G.R. MOHN
National Institute of Public Health and Environmental Protection
Bilthoven
Netherlands

Professor E.J. SAKSELA
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Helsinki
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Professor H. ZUR HAUSEN
Director, German Cancer Research Center
Heidelberg
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*World Health Organization*

Professor H. DANIELSSON
Chief, Office of Cancer Programme Coordination

Dr N.P. NAPALKOV,
Assistant Director-General

*International Union Against Cancer*

Dr S. ECKHARDT
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Dr LU SHIH-HSIN
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Beijing
China

*Annex 3*

# STAFF AT IARC
## 1 July 1989–30 June 1991

**Office of the Director**

| | |
|---|---|
| Director, IARC | Dr L. Tomatis |
| Deputy Director | Dr C.S. Muir (until 24.12.90)<br>Dr B.K. Armstrong (from 2.4.91) |
| Administrative Assistants | Mr C. Augros<br>Mrs M. Davis<br>Mrs A. Geser<br>Mrs E. Riviere |
| Secretaries | Mrs C. Dechaux<br>Miss A. Dufournet<br>Mrs W. Fevre-Hlaholuk |

*Gambia Hepatitis Intervention Study*

| | |
|---|---|
| Project Leader/Epidemiologist | Dr A.J. Hall (until 31.8.90) |
| Statistician/Programmer | Dr H.M. Inskip<br>(Acting Project Leader from 1.12.90) |
| Medical Officers | Dr J. Chotard<br>Dr M. Fortuin (from 16.7.90)<br>Dr A. Jack (from 1.7.90)<br>Dr M. Vall-Mayans (until 30.6.90) |
| Secretary | Miss S. Cotterell |

*Editorial, Translation and Publication Services*

| | |
|---|---|
| Head, Editorial & Publications Services/Editor | Dr J. Cheney |
| Translator | Mrs L. Eydoux (from 21.8.89) |
| Laboratory Technician (Photography) | Mr G. Mollon |
| Secretaries | Mrs E. El Akroud<br>Mrs A.C. Moret |
| Clerks | Mr J. Dechaux<br>Mrs M. Mainaud (half time) (from 11.3.1991)<br>Mrs A. Romanoff<br>Mrs J. Thevenoux |

*Education and Training*

| | |
|---|---|
| Chairman, Fellowships Selection Committee | Dr R. Montesano |
| Administrative Assistant | Mrs M. Davis |
| Secretaries | Mrs C. Dechaux |
| | Mrs E. El Akroud |

*Library*

| | |
|---|---|
| Librarian | Mrs H. Miido |
| Technical Assistant (Search Analyst) | Mrs M. Coudert |
| Assistant (Library) | Mrs L. Ossetian |

**Division of Scientific Activities**

*Unit of Analytical Epidemiology*

| | |
|---|---|
| Chief | Dr R. Saracci |
| Scientists | Dr P. Boffetta (from 4.2.90) |
| | Dr P. Boyle (Head, SEARCH Programme) |
| | Dr E. Kogevinas |
| | Dr J. Little (from 31.8.89) |
| | Dr E. Riboli (Head, Programme of Nutrition and Cancer) |
| | Dr A.J. Sasco (on secondment from INSERM) |
| Assistants (Statistics) | Mr G. Ferro (from 1.6.90) |
| | Mr B. Hemon (from 15.2.90) |
| | Mr P. Maisonneuve |
| | Miss R. Winkelmann |
| Secretaries | Mrs A. Hanss-Cousseau (from 28.8.89) |
| | Miss S. Haver (from 1.12.89) |
| | Miss A. Shannon |
| | Mrs S. Somerville |
| | Mrs S. Stallard |
| | Mrs A. Zitouni (until 31.8.89) |

*Unit of Biostatistics Research and Informatics*

| | |
|---|---|
| Chief | Dr J. Esteve |
| Scientists | Dr J.M. Kaldor (until 14.11.90) |
| | Dr E. Cardis |
| | Dr A. Rogatko (from 1.7.90) |
| Computer Systems Manager | Mr M. Smans |
| Computer Analysts | Ms B. Charnay |
| | Mr P. Damiecki |
| | Mr X. Nguyen-Dinh |
| Assistants (Statistics) | Mrs A. Arslan |
| | Miss D. Magnin |
| | Miss H. Renard |
| | Mr K. Zaid (from 7.2.90) |

| | |
|---|---|
| Secretaries | Mrs B. ANDRIEUX (half-time from 11.12.89) |
| | Miss J. GIBERT (from 1.11.89 until 14.12.90) |
| | Mrs J. NYAIRO (until 31.8.89) |
| | Mrs A. RIVOIRE |
| Clerk (Computer Operator) | Mrs B. KAJO |

*Unit of Field and Intervention Studies*

| | |
|---|---|
| Chief | Dr N. MUÑOZ |
| Scientist | Dr F.X. BOSCH |
| Assistant (Statistics) | Miss S. TEUCHMANN (until 17.5.91) |
| Secretary | Mrs H. BIEHE |

*Unit of Descriptive Epidemiology*

| | |
|---|---|
| Chief | Dr D.M. PARKIN |
| Scientists | Dr M.P. COLEMAN |
| | Dr M. KHLAT (until 31.5.90) |
| Assistants (Statistics) | Mr J. FERLAY |
| | Mr E. MAZUYER (from 1.1.90) |
| | Mr S. OLIVIER (from 1.4.90) |
| Technical Assistants | Mrs E. DEMARET |
| | Mrs J. NECTOUX |
| | Miss S. WHELAN |
| Secretaries | Miss O. BOUVY |
| | Miss M. GEESINK |
| Clerk | Mrs F. PETIT (half-time) |
| Clerk-stenographer | Mrs A.-M. BEH |

*Unit of Environmental Carcinogens and Host Factors*

| | |
|---|---|
| Chief | Dr H. BARTSCH |
| Scientists | Dr A. BARBIN |
| | Dr S. CALMELS-ROUFFET (from 18.12.89) |
| | Dr M. CASTEGNARO |
| | Dr M. FRIESEN |
| | Dr E. HIETANEN (until 2.9.89) |
| | Dr M. LANG (from 21.1.90) |
| | Dr C. MALAVEILLE |
| | Dr I.K. O'NEILL |
| | Dr H. OHSHIMA |
| | Dr B. PIGNATELLI |
| | Dr D. SHUKER |
| Laboratory Research Assistants | Mr J.-C. BEREZIAT |
| | Mrs G. BRUN |
| | Miss A.-M. CAMUS |
| | Mrs L. GARREN |
| Laboratory Technicians | Mrs I. BROUET |
| | Mrs A. ELLUL |

| | |
|---|---|
| | Mrs A. HAUTEFEUILLE |
| | Miss J. MICHELON |
| | Miss I. RICHARD (until 23.2.90) |
| | Mr A. SCHOUFT (from 1.7.90) |
| | Mr P. THUILLIER (from 2.10.89) |
| Secretaries | Mrs E. BAYLE |
| | Mrs P. COLLARD (from 1.10.89) |
| | Miss Y. GRANJARD (half-time) |
| | Mrs L. NEYRET (until 30.9.89) |
| | Mrs Z. SCHNEIDER (half-time) |
| | Mrs M. WRISEZ |

*Unit of Mechanisms of Carcinogenesis*

| | |
|---|---|
| Chief | Dr R. MONTESANO |
| Scientists | Dr J.R.P. CABRAL |
| | Dr C. DREVON (until 31.1.91) |
| | Dr D.J. FITZGERALD (until 2.6.90) |
| | Dr J. HALL |
| | Dr M. HOLLSTEIN |
| | Dr V. KRUTOVSKIKH |
| | Dr G.M. LENOIR (Head, Programme of Viral & Hereditary Factors in Carcinogenesis) (until 31.12.90) |
| | Dr A. LOKTIONOV |
| | Dr N. MIRONOV |
| | Dr H. NAKAZAWA |
| | Dr B. SYLLA |
| | Dr C.P. WILD |
| | Dr H. YAMASAKI (Head, Programme of Multistage Carcinogenesis) |
| Technical Assistant | Miss C. BONNARDEL |
| Laboratory Research Assistants | Mrs A.-M. AGUELON-PEGOURIES |
| | Miss H. BRESIL |
| | Mrs D. GALENDO |
| | Mr F. KATOH |
| | Miss M. LAVAL |
| | Mrs M.-F. LAVOUE |
| | Miss N. MARTEL |
| | Mrs G. MARTEL-PLANCHE |
| | Mrs C. PICCOLI |
| | Mrs M. VUILLAUME |
| Laboratory Technicians | Miss B. CHAPOT |
| | Mrs M.-P. CROS |
| | Mr J. GARCIA |
| | Mrs N. LYANDRAT |
| | Miss A. MUNNIA |
| | Mrs S. PAULY |

| | |
|---|---|
| Secretaries | Mrs C. Fuchez |
| | Mrs A.M. Maillol (from 1.1.90) |
| | Mrs E. Perez (half-time) |
| | Mrs A. Trochard |
| Equipment Operator | Mr F. Faria |
| Laboratory Aides | Mr J. Cardia-Lima |
| | Mr R. Dray |
| | Mrs M. Essertel |
| | Mrs N. Grandclaude |
| | Miss M. Maranhao |
| | Mrs S. Veyre |

*Unit of Carcinogen Identification and Evaluation*

| | |
|---|---|
| Chief | Dr H. Vainio |
| Scientist/Officer in Charge | Dr A. Aitio (until 4.7.89) |
| Scientists | Dr D. McGregor (from 2.9.89) |
| | Dr L. Shuker (until 31.12.90) |
| | Mr J. Wilbourn |
| | Mrs I. Peterschmitt (half-time) |
| Technical Editor | Mrs C. Partensky |
| Technical Assistants | Mrs J. Cazeaux |
| | Mrs M.-J. Ghess |
| | Mrs D. Mietton |
| Secretary | Miss S. Reynaud |
| Clerk | Mrs M. Lezere |

**Division of Administration and Finance**

| | |
|---|---|
| Director | Mr K. Saita (from 3.7.89 until 31.12.90) |
| | Mr H.R. Crockett (from 1.1.91) |
| Administrative Assistant | Mrs J. Martinez |

*Personnel*

| | |
|---|---|
| Personnel Officer | Mrs A. Escoffier |
| Clerk | Mrs C. Mogenet (from 1.3.90) |

*Budget and Finance*

| | |
|---|---|
| Budget and Finance Officer | Mr M.P. Johnson |
| Finance Officer | Mr S. Sapra |
| Assistant (Accounting) | Mrs M. Herin |
| Assistant (Payments) | Mrs F. Romagnan |
| Secretary | Mrs D. Marcou-Hansson |
| Clerk (Cashier) | Mr D. Hornez |
| Clerk (Accounts) | Mrs D. Lombardo |
| Clerks (Finance) | Mrs F. Florentin (half-time) |
| | Miss A. Milone (half-time) |

*Administrative Services*

| | |
|---|---|
| Administrative Services Officer | Mr B. BORGSTRØM (until 31.12.89)<br>Mr G. GUILLERMINET (from 15.1.90) |
| Administrative Assistant | Mrs R. SEXTIER |
| Clerk | Mrs M. LEPETIT (half-time) (from 1.10.89) |
| Switchboard Operator | Mrs R. KIBRISLIYAN |
| Driver | Mr J.-F. DURAND-GRATIAN |
| Usher (Messenger) | Mr D. LAGARDE |
| Assistant (Building Maintenance) | Mr E. CATHY (until 31.3.90) |
| Maintenance Technicians | Mr M. BARBIEUX<br>Mr M. BAZIN<br>Mr J.-P. BONNEFOND<br>Mr G. THOLLY |
| Assistant (Registry) | Mrs M. GREENLAND (from 1.4.90) |
| Clerk (Registry) | Mrs L. VIGIER |
| Assistant (Supplies) | Mrs J. POPOFF |
| Clerks (Supplies) | Mrs M. FILIPPI<br>Mrs L. GRAVIER (half-time)<br>Mr M. PRAT |
| Equipment Operators (Reproduction) | Mr D. GRAIZELY<br>Mr M. JAVIN |

*Documents and Stenographic Pool*

| | |
|---|---|
| Assistant | Mrs J. BORGSTRØM (until 31.12.89)<br>Mrs M.-H. CHARRIER (from 1.1.90) |
| Clerk | Mrs M.-B. D'ARCY |
| Clerk-stenographers | Mrs M. CAMPBELL (from 1.1.91)<br>Miss B. GEOFFRE<br>Miss C. HUGHES (from 24.12.90)<br>Miss W. KINUTHIA (until 31.8.90)<br>Miss G. RAWLING (from 1.12.89) |

## SHORT-TERM STAFF (CONSULTANTS AND TEMPORARY STAFF) 1 July 1989–30 June 1991

**Office of the Director**

| | |
|---|---|
| Consultant | Professor R. SOHIER* |
| Social Adviser | Mrs P. MALINDINE (part-time) |

* Still on short-term employment on 30 June 1991

*Editorial, Translation and Publication Services*

| | |
|---|---|
| Clerk | Mrs E. Brussieux |

*Education and Training*

| | |
|---|---|
| Consultant | Dr W. Davis* |

**Division of Scientific Activities**

*Unit of Analytical Epidemiology*

| | |
|---|---|
| Technical Officers | Dr B. Cox |
| | Mr R. Kaaks* |
| | Dr R. McGinn |
| | Ms N. Slimani* |
| Clerks (Statistics) | Mr G. Ferro |
| | Miss C. Casagrande* |
| Clerk | Mrs M. Lepetit |

*Unit of Biostatistics and Informatics*

| | |
|---|---|
| Consultant | Dr D. English |

*Unit of Field and Intervention Studies*

| | |
|---|---|
| Consultants | Dr P. Alonso de Ruiz |
| | Dr C.N. Aristizabal-Payan |
| | Dr M. Santamaria |
| Clerk | Miss M. Dodet (part-time) |

*Unit of Descriptive Epidemiology*

| | |
|---|---|
| Consultant | Mr A. Bieber |
| Technical Officer | Dr C. Bouchardy (part-time) |
| Technical clerks | Miss B. Fischer |
| | Mr E. Masuyer |

*Unit of Environmental Carcinogens and Host Factors*

| | |
|---|---|
| Consultants | Dr M. Ashwell |
| Scientists | Dr S. Calmels-Rouffet |
| | Dr N. Dalla Venezia |
| | Dr A.B. Shah* |
| | Dr J. Nair |
| Technical Officer (Bibliographic Research) | Mrs B. Dodet (part-time) |
| Laboratory Technicians | Miss F. El Ghissassi* |
| | Mr P. Thuillier |

*Unit of Mechanisms of Carcinogenesis*

| | |
|---|---|
| Consultant | Dr D.J. Fitzgerald |

* Still on short-term employment on 30 June 1991

| | |
|---|---|
| Scientists | Dr M. Asamoto |
| | Dr A. Fusco |
| | Dr T. Shirai |
| Laboratory Technicians | Miss B. Chambe* |
| | Mrs L. Fournier* |
| | Miss C. Pezet |
| Laboratory Aides | Miss L. Fraissinet-Tachet |
| | Mr C. Mariotto* |
| | Mr S. Sebaoui |

*Unit of Carcinogen Identification and Evaluation*

| | |
|---|---|
| Consultant | Dr J. Maki-Paakanen |
| Scientists | Dr M. Marselos |
| | Dr E. Matos* |
| | Dr G. Nordberg |
| Technical Officer (Bibliographic Research) | Mrs B. Dodet (part-time) |
| Secretary | Mrs J. Atherton* (half-time) |
| Clerks | Mr J. Cereda* (part-time) |
| | Miss S. Ruiz* |

**Division of Administration and Finance**

*Administrative Services*

| | |
|---|---|
| Consultant | Mr A. Sayour |

*Budget and Finance*

| | |
|---|---|
| Consultant | Mr A. Imbruglia |

*Documents and Stenographic Pool*

| | |
|---|---|
| Clerk-stenographers | Miss B. Geoffre |
| | Miss J. Gibert |
| | Miss C. Hughes |
| | Miss S. Lille* |
| | Miss G. Rawling |

*Personnel*

| | |
|---|---|
| Social Adviser | Mrs M. A. Viot-Coster* (part-time) |

*Supplies*

| | |
|---|---|
| Clerk | Miss V. Berthet |

* Still on short-term employment on 30 June 1991

*Annex 4*

# VISITING SCIENTISTS, FELLOWS AND TRAINEES

**Scientists and fellows**

Dr L. Abid, Unit of Descriptive Epidemiology (13–18 December 1990)

Ms T. Alexakis, Unit of Environmental Carcinogens and Host Factors (17 June–20 July 1991)

Dr K. Alexandrov, Unit of Environmental Carcinogens and Host Factors

Dr A. Aminzadeh, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (18 March–22 March 1991)

Dr K. Athanasiou, Programme of Multistage Carcinogenesis, Fellowship from the European Science Foundation (8 January–22 June 1990)

Dr D. Balzi, Unit of Descriptive Epidemiology (25–29 September 1989 and 4–15 December 1990)

Dr T. Bandaletova, Unit of Mechanisms of Carcinogenesis, Special Training Award (from 4 February 1991)

Dr G.A. Bannikov, Unit of Mechanisms of Carcinogenesis (7–14 March 1990)

Miss F. Barbeillon, Unit of Carcinogen Identification and Evaluation, Temporary adviser (15 April–15 July 1991)

Dr F. Bianchini, Unit of Mechanisms of Carcinogenesis, Fellowship from the Commission of the European Communities (from 1 December 1990)

Mr C.A. Bieber, Unit of Descriptive Epidemiology (until 7 July 1989)

Dr R. Black, Unit of Descriptive Epidemiology (24 January–2 February 1990)

Dr V. Blair, Unit of Descriptive Epidemiology (13–17 November 1989)

Dr F. Bleicher, Unit of Mechanisms of Carcinogenesis, Special Training Award (from 8 January 1990)

Dr C. Bouchardy, Unit of Descriptive Epidemiology, IARC Research Training Fellowship (2 October 1989–30 September 1990)

Mr G. Bouvier, Unit of Environmental Carcinogens and Host Factors

Dr M. Caperle, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (22–26 April 1991)

Dr C. S. Chen, Unit of Environmental Carcinogens and Host Factors (until 31 December 1989)

Dr C. Chiodino, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Fellowship from the Commission of the European Communities (from 1 January 1991)

Miss S. Chutimataewin, Unit of Mechanisms of Carcinogenesis, Special Training Award (from 1 March 1991)

Dr S. de Sanjosé Llongueras, Unit of Field and Intervention Studies, Fellowship from the Commission of the European Communities and Special Training Award (January 1989–February 1991)

Dr E. De Stefani, Unit of Descriptive Epidemiology (29 January–7 February 1990)

Miss N. Dube, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (28 August–24 September 1989)

Miss M.-J. Durand, Unit of Environmental Carcinogens and Host Factors (from 2 January 1990)

Dr D. Esteban, Unit of Descriptive Epidemiology (14–19 April 1991)

Dr C.M. Friedenreich, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology, IARC Research Training Fellowship (from 1 October 1990)

Dr A. Fusco, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis (25 February–1 March 1991)

Dr D. Garcia Sanchez, Unit of Analytical Epidemiology, Fellowship from the Commission of the European Communities (8 January–8 May 1990)

Dr M. Geddes, Unit of Descriptive Epidemiology (25–29 September 1989 and 4–15 December 1990)

Dr K. Goodtzova, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (11 March–10 May 1991)

Dr L. Grossman, Unit of Mechanisms of Carcinogenesis (6–13 May 1990)

Dr P.C. Gupta, Unit of Descriptive Epidemiology (11–29 September 1989)

Dr N.J. Haley, Unit of Analytical Epidemiology (16–23 April 1990 and 20–24 May 1991)

Dr M. Hamdi Cherif, Unit of Descriptive Epidemiology (23–27 October 1989)

Mr G. Hu, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (25 September–20 October 1989)

Dr J. Iscovich, Unit of Descriptive Epidemiology (1–12 October 1990)

Mr L. Jansen, Unit of Mechanisms of Carcinogenesis, Fellowship from the Commission of the European Communities (8 January 1990–22 August 1990)

Dr Y.-Z. Jiang, Unit of Mechanisms of Carcinogenesis, Fellowship from the Association pour la Recherche sur le Cancer (until 27 October 1989)

Dr E. Johnson, Unit of Analytical Epidemiology (13–28 February 1990)

Dr W.M.F. Jongen, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Fellowship from the Commisssion of the European Communities (until 30 November 1989)

Dr T. Kauppinen, Unit of Analytical Epidemiology (4–8 June 1990)

Professor T. Kuroki, Unit of Mechanisms of Carcinogenesis (17–22 September 1989)

Dr D. Lin, Unit of Environmental Carcinogens and Host Factors (until 31 July 1990)

Dr J.P. Lob-Levyt, Unit of Descriptive Epidemiology (7 July–4 August 1989)

Dr N. Loktionova, Unit of Mechanisms of Carcinogenesis (5 June 1989–29 January 1991)

Dr S.H. Lu, Unit of Mechanisms of Carcinogenesis (3 February–2 March 1991)

Professor H.G. Mandel, Unit of Environmental Carcinogens and Host Factors (20 October–8 November 1989)

Dr E. Matos, Unit of Descriptive Epidemiology (8 January–3 February); Fellowships from the International Cancer Research Technology Transfer Programme (3 July–4 August 1989) and the Italian League Aginst Cancer (14 November 1990–20 January 1991)

Dr F. Merletti, Unit of Analytical Epidemiology (28 May–1 June 1990 and 9–13 July 1990)

Dr M. Mesnil, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award (1–31 July 1989, and from 2 January 1991)

Dr M. Miele, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellowship (26 July 1989–10 June 1990); EEC DNA Repair Network Fellowship (15–30 November 1990); IARC Research Training Fellowship (7 January–15 April 1991)

Dr A.-M. Mikheev, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellowship (6 February 1990–15 February 1991)

Dr F. Minervini, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (5 November–1 December 1990)

Dr H.F. Mower, Unit of Environmental Carcinogens and Host Factors (15 February to June 1991)

Mr N'G. Mukendi, Unit of Mechanisms of Carcinogenesis (19–23 November 1990)

Dr J. Nair, Unit of Environmental Carcinogens and Host Factors (29 July–3 September 1989)

Dr U. Nair, Unit of Environmental Carcinogens and Host Factors (until 31 December 1989)

Dr S.A. Narod, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (25 February–1 March 1991)

Dr Nguyen Thi Hanh, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (10–14 July 1989)

Mr B. Noble, Unit of Descriptive Epidemiology, Editorial, Translation and Publications Services, and Unit of Biostatistics Research and Informatics (25 February–1 March 1991)

Dr Y. Oyamada, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellow (until September 1989); voluntary worker (until 1 September 1990)

Dr M. Oyamada, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award (until 30 November 1989); Visiting Scientist Award (1 December 1989–30 November 1990)

Dr S. Pavanello, Unit of Environmental Carcinogens and Host Factors (21 August–22 October 1989)

Dr M. Peluso, Unit of Environmental Carcinogens and Host Factors (until 15 April 1990)

Dr B. Pettersson, Unit of Descriptive Epidemiology (30 October–3 November 1989)

Dr C.B. Pinto, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (3 July–2 August 1989)

Dr D. Pobel, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (2 May–31 October 1991)

Dr G. Potapova, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (29 January–26 February 1990)

Miss V. Prevost, Unit of Environmental Carcinogens and Host Factors (from 1 January 1991)

Dr Liu Qing, Unit of Analytical Epidemiology, IARC Research Training Fellowship (1 March 1990–28 February 1991)

Mr D.N. Rao, Unit of Descriptive Epidemiology, WHO Fellowship (8–17 May 1990)

Miss R. Razdan, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (27 January–15 March 1990)

Dr E. Rivedal, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (23 January–23 February 1990 and 1–14 March 1991)

Dr V. Rodrigues, Fellowship from the International Cancer Research Technology Transfer Programme (14–31 May 1991)

Dr M. Rojas-Moreno, Unit of Environmental Carcinogens and Host Factors

Dr Sarjadi, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (9–21 May 1991)

Dr Y.-F. Shao, Unit of Mechanisms of Carcinogenesis, Yamagiwa–Yoshida Memorial Grant (19 December 1990–19 March 1991)

Dr M. Siddiqi, Unit of Mechanisms of Carcinogenesis, Fellowship from the Commission of the European Communities (from 8 April 1991)

Dr L. Simonato, Unit of Analytical Epidemiology (28 January–2 February 1991 and 11–15 March 1991)

Dr C. A. Stiller, Unit of Descriptive Epidemiology (21–27 September 1989)

Dr S. Swierenga, Unit of Carcinogen Identification and Evaluation, Temporary adviser (3 September–28 December 1991)

Dr S. Szmigielski, Unit of Carcinogen Identification and Evaluation, Temporary adviser (14 January–20 February 1991)

Mr W. Tarkowski, Unit of Descriptive Epidemiology (3 April–16 May 1991)

Dr J. Tyczynski, Unit of Biostatistics Research and Informatics, IARC Research Training Fellowship (from 31 January 1991)

Dr A.P. Vizcaino, Unit of Descriptive Epidemiology (23–30 March 1991); Fellowship from the Commission of the European Communities (8 January–7 December 1990)

Dr J. Wahrendorf, Units of Descriptive Epidemiology, Field and Intervention Studies, and Analytical Epidemiology (3–7 September 1990)

Dr Y. Wu, Unit of Environmental Carcinogens and Host Factors (from 5 April 1991)

Dr J.H. Youngson, Unit of Descriptive Epidemiology (17–28 July 1989)

Professor S. Zacks, Unit of Biostatistics Research and Informatics (8–13 April 1991)

Dr S.Y. Zhao, Unit of Analytical Epidemiology, Fellowship from the Association pour la Recherche sur le Cancer, France (1 September 1989–31 August 1990), Special Training Award (1 September–30 September 1990)

**Trainees**

Ms V. Benhaïm, Unit of Analytical Epidemiology, Special Training Award (from 1 April 1991)

Miss M. Benz, Unit of Field and Intervention Studies, Special Training Award (from 4 March 1991)

Mr O. Bertrand, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award

Dr H. Bruné, Unit of Analytical Epidemiology, Special Training Award (1 July 1989–28 February 1990)

Dr A. Calender, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award

Ms M.C. Chapot, Unit of Biostatistics Research and Informatics, Special Training Award (8 April–21 June 1991)

Miss S. Chapuis, Unit of Mechanisms of Carcinogenesis (19 March–20 April 1990)

Mrs F. Ciroussel, Unit of Environmental Carcinogens and Host Factors (until 30 September 1990)

Ms M. Cordier, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award and supported by La Fondation Mérieux

Ms K. de Bruin, Unit of Analytical Epidemiology, Special Training Award (1 December 1990–31 July 1991)

Miss M. de Jesus, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis (3 June–12 July 1991)

Mr H. de Solages, Unit of Biostatistics Research and Informatics, Special Training Award (from 5 March)

Dr H.J. Delecluse, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (until May 1991)

Miss C. Duinat, Unit of Mechanisms of Carcinogenesis (2 April–7 May 1991)

Mr J.F. Gaillard, Unit of Biostatistics Research and Informatics, Special Training Award (14 May–14 August 1990)

Mrs C. Galiana, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award (until 31 December 1990); Fellowship from the Association pour la Recherche sur le Cancer (from 1 January 1991)

Dr D. Gardiman, Unit of Analytical Epidemiology (24 January–24 April 1989)

Miss S. Gazzo, Unit of Mechanisms of Carcinogenesis (from 3 June 1991)

Mr O. Geneste, Unit of Environmental Carcinogens and Host Factors (from 1 September 1989)

Miss L. Giroldi, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award (until 31 December 1989)

Miss H. Gour, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (9–13 April 1990)

Ms P. Grosclaude, Unit of Biostatistics Research and Informatics, Special Training Award (22 April–25 October 1991)

Mr D. Guerra, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (9–13 April 1990)

Mr Y. Guichard, Unit of Environmental Carcinogens and Host Factors (from 8 October 1990)

Mr M. Hertog, Unit of Mechanisms of Carcinogenesis, Special Training Award (5 June–31 August 1989)

Mr C. Heuer, Unit of Biostatistics Research and Informatics, Special Training Award (4 March–31 May 1991)

Miss B. Inçaurgarat, Unit of Environmental Carcinogens and Host Factors (until 10 November 1989)

Miss M. Klaude, Unit of Environmental Carcinogens and Host Factors (until 11 August 1989)

Mr J.L. Klein, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Fellowship from Fondation Marcel Mérieux (GERP) (until 1 October 1990); Special Training Award (from 1 October 1990)

Ms F. Kreuger, Unit of Analytical Epidemiology, Special Training Award (1 September 1989–28 February 1990)

Mr J. Lamartine, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (from 3 September 1990)

Miss P. Lamude, Unit of Mechanisms of Carcinogenesis (5 March-6 April 1990)

Ms C. Lange, Unit of Biostatistics Research and Informatics, Special Training Award (1 March–31 August 1990)

Mr J.C. Lozano, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award (from 1 November 1989)

Ms C. Lucas, Unit of Biostatistics Research and Informatics, Special Training Award (21 May–21 August 1991)

Ms T. Mathiesen, Unit of Descriptive Epidemiology, Special Training Award (from 24 September 1990)

Miss I. Morand, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis (15 April–10 May 1991)

Dr I. Moreno, Unit of Analytical Epidemiology (2 April–15 June 1990 and 23 July–28 September 1990)

Miss T. Mpanza, Unit of Mechanisms of Carcinogenesis (25–29 March 1991)

Ms M.N. Napp, Unit of Biostatistics Research and Informatics, Special Training Award (14 May–14 August 1990)

Mr C. Pepin, Unit of Descriptive Epidemiology, Special Training Award (3–21 July 1989)

Ms D. Pobel, Unit of Analytical Epidemiology, Special Training Award (1 November 1989–31 October 1990)

Miss V. Prevost, Unit of Environmental Carcinogens and Host Factors (until 31 December 1990)

Dr P. Roy, Unit of Descriptive Epidemiology (1 November 1989–31 October 1990) and Unit of Biostatistics Research and Informatics (from 1 November 1990)

Mr R. Sauze, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (2 April–2 May 1991)

Ms C. Schrijvers, Unit of Analytical Epidemiology, Special Training Award (1 February–30 June 1990)

Miss H. Schunk, Unit of Environmental Carcinogens and Host Factors (until 31 July 1989)

Miss F. Tall, Unit of Mechanisms of Carcinogenesis (19–30 March 1990)

Mr A. Vail, Unit of Descriptive Epidemiology, Special Training Award (17 July–1 September 1989)

Mr T. van Barneveld, Unit of Analytical Epidemiology, Special Training Award (1 February–31 August 1990)

Ms A.L. van Kappel, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (29 April–31 October 1991)

Ms M.L. Varrault, Unit of Biostatistics Research and Informatics, Special Training Award (21 May–21 August 1991)

Ms L. Vergnais, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (10 June–10 July 1991)

Miss S. Vincent, Programme of Multistage Carcinogenesis, Unit of Mechanisms of Carcinogenesis (2 January–9 February 1990)

Dr Q. Wang, Programme of Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis, Special Training Award

*Annex 5*

# RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS
## 1 July 1989–30 June 1991

**Cancer registries**

| | |
|---|---|
| DEB/73/16 | International Association of Cancer Registries<br>(Provision of a secretariat and other supporting services) |
| DEB/85/32 | Ministry of Health, Harare, Zimbabwe<br>(Cancer registry of Harare) |
| DEB/85/41 | Department of Anatomo-pathology, Faculty of Medicine, University of Rwanda, Butare, Rwanda<br>(Cancer registry of Butare) |
| DEB/85/42 | Ministry of Health, Suva, Fiji<br>(Provision of a cancer registry service for the Fiji Islands) |
| DEP/87/02 | National Institute of Public Health, Bamako, Mali<br>(Cancer registry of Mali) |
| DEP/87/01 | Hanoi Cancer Institute, Hanoi, Viet Nam<br>(Cancer registry of Hanoi) |
| DEP/87/04 | Srinararind Hospital, Faculty of Medicine, Khon Kaen, Thailand<br>(Population-based cancer registry of Khon Kaen Province) |
| DEP/87/07 | College of Medicine, University of the Philippines, Manila<br>(Preparation of training manuals for registry personnel in developing countries) |
| DEP/87/09 | La Paz Cancer Registry, Oncological Society of Bolivia, La Paz, Bolivia<br>(La Paz Cancer Registry) |
| DEP/88/02 | Chiang Mai Cancer Registry, Faculty of Medicine, Chiang Mai, Thailand<br>(Chiang Mai Cancer Registry) |
| DEP/88/05 | Cancer Registry of Tanzania, Pathology Department, Muhimbili Medical Centre, University of Dar-es-Salaam<br>(Cancer Registry of Tanzania) |
| DEP/89/02 | Cancer Registry, Department of Pathology, National University, Asunción, Paraguay<br>(Cancer Registry of Asuncion) |
| DEP/89/03 | National Cancer Registry of Cuba, National Cancer Institute, Havana, Cuba<br>(National Cancer Registry of Cuba) |

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| DEP/89/04 | Kampala Cancer Registry, Department of Pathology, Makerere University Medical School, Kampala, Uganda<br>(Kampala Cancer Registry) |
| DEP/89/10 | Department of Pathology, National University of Trujillo, Trujillo, Peru<br>(Cancer Registry of Trujillo) |
| DEP/89/11 | Department of Epidemiology and Preventive Medicine, University Hospital, Sétif, Algeria<br>(Cancer Registry of Sétif) |
| DEP/89/13 | Foundation "Leide das Neves Ferreira", Goiana, Brazil<br>(Cancer Registry of Goiana) |
| DEP/90/02 | Faculty of Medicine, Prince of Songkla University, Hat-Yai, Songkla, Thailand<br>(Population-based cancer registry of Songkla Province) |
| BRI/91/01 | Danish Cancer Registry, Copenhagen, Denmark<br>(European Network of Cancer Registries) |
| DEP/91/02 | South Pacific Commission, Noumea, New Caledonia<br>(Cancer registration in the Pacific area) |
| DEP/91/04 | National Centre of Anatomo-Pathology, Faculty of Medicine, University of Conakry, Conakry, Guinea<br>(Cancer registry of Conakry) |

**Collaborating centres**

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|---|---|
| DEB/74/03 | Institute of Epidemiology and Biometry, German Cancer Research Centre, Heidelberg, Germany<br>(Clearing-house for on-going research in cancer epidemiology) |
| AEP/87/05 | Research Group in Morbid Anatomy, University of Trieste, Italy<br>(Assessment of the value of autopsy diagnosis for the purpose of epidemiological research, in particular, cancer studies) |
| AEP/88/01 | Institute of Environmental Health and Engineering, Chinese Academy of Preventive Medicine, Beijing, China<br>(To explore the feasibility of conducting case-control studies in Beijing, within the SEARCH programme of the IARC) |

**Incidence studies**

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|---|---|
| DEB/85/37 | All-Union Cancer Research Centre, Academy of Medical Sciences, Moscow, USSR<br>(Descriptive epidemiology of cancer in the USSR) |
| DEP/87/05 | Israel Center for Registration of Cancer and Allied Diseases, Jerusalem, Israel<br>(Cancer risk in second generation migrants to Israel) |

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| DEP/88/03 | Foundation Doctor Pedro Belou, Faculty of Medical Sciences, National University, La Plata, Argentina<br>(Cancer risk in migrants to Buenos Aires Province) |
| DEP/89/07 | New South Wales Central Cancer Registry, Macquarie Hospital, North Ryde, Australia<br>(Study on Italian migrants) |
| DEP/89/09 | Department of Community Medicine, University College London & Middlesex Hospital Medical School, London, UK<br>(Cancer risk in migrants to England and Wales) |
| DEP/91/01 | Israel Center for Registration of Cancer and Allied Diseases, Jerusalem, Israel<br>(Cancer risk in second-generation migrants to Israel: Phase II) |

**Second cancers and DNA damage following chemotherapy**

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| BRI/89/03 | Rotterdam Cancer Institute, Rotterdam, The Netherlands<br>(Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients) |
| BRI/89/04 | Department of Oncology, University Hospital Antwerpen, Edegem, Belgium<br>(Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients) |
| BRI/89/05 | Gartnavel General Hospital, Glasgow, UK<br>(Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients) |
| BRI/89/06 | Cookridge Hospital, Leeds, UK<br>(Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients) |
| BRI/89/07 | TNO Medical Biological Laboratory, Rijswijk, The Netherlands<br>(Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients) |
| BRI/89/08 | Doctor Daniel den Hoed Clinic, Rotterdam, The Netherlands<br>(Pilot study for the detection of methylation adducts in lymphoma patients) |
| BRI/89/09 | Biological Research Center, National Hellenic Research Foundation, Athens, Greece<br>(Detection of methylation adducts in Hodgkin's disease patients) |
| BRI/89/10 | Department of Radiation Genetics and Chemical Mutagenesis, Sylvius Laboratories, State University of Leiden, Leiden, The Netherlands<br>(Measurements of micronuclei in lymphocytes as an indication of DNA damage following chemotherapy in Hodgkin's disease patients) |
| BRI/89/11 | Gustave Roussy Institute, Villejuif, France<br>(Pilot study for the detection of methylation adducts in lymphoma patients) |

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| BRI/89/12 | Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands<br>(Pilot study for the detection of methylation adducts in lymphoma patients) |
| BRI/89/13 | Jules Bordet Institute, Brussels, Belgium<br>(Pilot study for the detection of methylation adducts in lymphoma patients) |
| BRI/91/02 | Lymphoma Clinic, University of Athens School of Medicine, Athens, Greece<br>(Pilot study for the detection of methylation adducts, oncogene mutation, micronuclei and DNA repair in Hodgkin's disease patients treated with MOPP/ABV chemotherapy) |

**Studies on breast cancer**

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| DEB/86/10 | Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, USA<br>(Breast cancer and hormonal profile in Chinese and Chinese-American women) |
| DEB/86/14 | Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, USA<br>(Biochemical analyses for studies of (*a*) urinary levels of oestrogens and progesterone in relation to passive smoking in nonsmoking women, and (*b*) breast cancer and hormonal profile in males) |
| DEP/91/03 | Clinical Epidemiology Unit, College of Medicine, University of the Philippines, Manila<br>(Pilot study into the feasibility of screening for breast cancer in the population of metropolitan Manila) |

**Studies on cervical cancer**

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|---|---|
| DEB/85/17 | Foundation for Higher Education, Cali, Colombia<br>(Case-control study on risk factors for cervical cancer) |
| FIS/88/01 | Department of Immunology and Infectious Diseases, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA<br>(Human papilloma virus (HPV) and cervical cancer: analysis of specimens for HPV–DNA) |
| DEP/89/06 | College of Medicine, University of the Philippines, Manila<br>(Pilot case-control study on cervix cancer in Rizal Province) |
| FIS/89/02 | Department of Social Medicine, Faculty of Medicine, Federal University of Pelotas, Brazil<br>(International biological study on cervical cancer) |
| FIS/89/03 | Cancer Registry, Department of Pathology, National University, Asunción, Paraguay<br>(International biological study on cervical cancer) |

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| FIS/89/04 | Department of Pathology, School of Medicine, University of Athens, Greece<br>(International biological study on cervical cancer) |
| FIS/89/05 | Faculty of Health Sciences, Cotonou, Benin<br>(International biological study on cervical cancer) |
| FIS/89/06 | National Institute of Public Health, Bamako, Mali<br>(International biological study on cervical cancer) |
| FIS/89/07 | Department of Oncology, Regional Hospital, Ministry of Health, Concepcion, Chile<br>(International biological study on cervical cancer) |
| FIS/89/08 | National Cancer Institute, Havana, Cuba<br>(International biological study on cervical cancer) |
| FIS/89/10 | Department of Epidemiology and Preventive Medicine, University Hospital, Sétif, Algeria<br>(International biological study on cervical cancer) |
| FIS/89/12 | Department of Virology, National Bacteriological Laboratory, Stockholm, Sweden<br>(Herpes simplex virus (HSV) and cytomegalovirus (CMV) and cervical cancer) |
| FIS/90/01 | Department of Public Health, Oviedo, Spain<br>(Prevalence of cervical lesions among prostitutes in Oviedo and Gijon, Spain) |
| FIS/90/02 | La Paz Cancer Registry, Oncological Society of Bolivia, La Paz, Bolivia<br>(International biological study on cervical cancer) |
| FIS/90/03 | Ministry of Public Health, Conakry, Guinea<br>(International biological study on cervical cancer) |
| FIS/90/04 | Department of Social Medicine, Faculty of Medicine, Federal University of Pelotas, Pelotas, Brazil<br>(Multicentric case–control study on cervical cancer) |
| FIS/90/05 | WHO Collaborating Centre for the Community Control of Hereditary Diseases, Department of Human Genetics and Teratology, National Institute of Hygiene, Budapest, Hungary<br>(Cytogenetic studies) |
| FIS/90/06 | Department of Histopathology and Morbid Anatomy, Muhimbili Medical Centre, University of Dar es Salaam, Dar es Salaam, Tanzania<br>(International biological study on cervical cancer) |
| FIS/90/07 | Department of Pathology, Makerere University Medical School, Kampala, Uganda<br>(International biological study on cervical cancer) |
| FIS/90/08 | Faculty of Medicine, Prince of Songkla University, Hat–Yai, Thailand<br>(Multicentric case–control study on cervical cancer) |

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| FIS/90/09 | National Institute of Public Health Research, Bamako, Mali<br>(Multicentric case–control study on cervical cancer) |
| FIS/90/10 | Clinical Epidemiology Unit, College of Medicine, University of the Philippines, Manila<br>(Multicentric case–control study on cervical cancer) |
| FIS/90/11 | Department of Pathology, Ministry of Health, Asunción, Paraguay<br>(Multicentric case–control study on cervical cancer) |
| FIS/90/13 | National Institute of Oncology, Rabat, Morocco<br>(Multicentric case–contol study on cervical cancer) |

**Studies on cancers linked with herpesviruses**

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|---|---|
| DEC/83/09 | Cytogenetics Laboratory, Blood Transfusion Centre, St Etienne, France<br>(Characterization of cytogenetic anomalies observed in Burkitt-type lymphoma cells) |
| MCA/87/01 | All-Union Cancer Research Centre, Academy of Medical Sciences, Moscow, USSR<br>(Prevalence of anti-HTLV-I antibodies in the population of the USSR from different geographic areas) |

**Studies on liver cancer**

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|---|---|
| DIR/86/01 | Medical Research Council, London, UK<br>(Gambia Hepatitis Intervention Study) |
| FIS/87/01 | National Cancer Institute, Bangkok, Thailand<br>(Cohort study of HBsAg carriers in Bangkok) |
| FIS/88/02 | Institute of Oncology, University of Padua, Italy<br>(Natural history of human retrovirus infections in the Gambia) |
| FIS/88/03 | Division of Gastroenterology, Hospital San Giovanni Battista, Turin, Italy<br>(Causes of non-response to hepatitis B vaccine) |
| FIS/88/04 | Department of Clinical Immunology, University of Rome, Italy<br>(Causes of non-response to hepatitis B vaccine) |
| FIS/88/05 | Department of Social Medicine and Public Health, University of Singapore, Singapore<br>(Cohort study of hepatitis B carriers and liver cancer) |
| FIS/89/09 | Mount Holyoke College, South Hadley, MA, USA<br>(Cost effectiveness of addition of hepatitis B virus vaccination to expanded programme on immunization in the Gambia) |
| MCA/89/02 | Department of Preclinical Veterinary Studies, University of Zimbabwe, Harare, Zimbabwe<br>(Aflatoxin exposure and its interaction with other associated factors in the etiology of liver cancer in Zimbabwe) |

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| MCA/89/03 | Institute for Toxicology, University of Würzburg, Germany<br>(Development, validation and evaluation of methods to detect aflatoxin–protein adducts for monitoring human exposure to aflatoxins) |

**Studies on malignant melanoma**

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| DEP/87/08 | Cancer Registry, Department of Pathology, National University, Asunción, Paraguay<br>(Case–control study of etiological factors of plantar melanoma in Paraguay) |

**Studies on nutrition and on cancer of the gastrointestinal tract**

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|---|---|
| DEB/84/01 | Singapore Cancer Registry, Department of Pathology, University of Singapore, Singapore<br>(Development of methodology for the conduct of diet-directed case–control studies in Singapore) |
| FIS/87/05 | Cancer Registry, Department of Pathology, National University, Asunción, Paraguay<br>(Case–control study on oesophageal cancer in Paraguay) |
| AEP/88/02 | Department of Epidemiology and Statistics, Hospital San Jaume i Santa Magdalena, Mataro, Spain<br>(Case–control study on stomach cancer and diet) |
| AEP/89/01 | Rowett Research Institute, Aberdeen, UK<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| AEP/89/02 | Department of Epidemiology and Statistics, Hospital San Jaume i Santa Magdalena, Mataro, Spain<br>(Planning phase of a project on prospective studies on diet and cancer) |
| ECH/89/02 | Bejing Institute for Cancer Research, China<br>(Interrelationships between total *N*-nitroso compounds in gastric juice, genotoxicity and severity of precancerous lesions of the stomach) |
| AEP/89/03 | Unit of Epidemiology, National Institute for the Study and Treatment of Cancer, Milan, Italy<br>(Planning phase of a project on prospective studies on diet and cancer) |
| AEP/89/04 | Gustave Roussy Institute, Villejuif, France<br>(Planning phase of a project on prospective studies on diet and cancer) |
| ECH/89/04 | Institute of Medical Science, University of Tokyo, Japan<br>(Study on evaluation of vicine/divicine as a possible glandular stomach carcinogen in short-term *in vivo* assays) |

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| AEP/89/05 | Institute of Anatomy, University of Turin, Italy<br>(Planning phase of a project on prospective studies on diet and cancer) |
| DEP/89/05 | Cancer Control Centre, San Cristobal, Venezuela<br>(Case–control study to investigate the effect of screening by X-ray examination in preventing death from gastric cancer) |
| AEP/89/07 | School of Public Health, Granada, Spain<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| ECH/89/07 | Foundation for Higher Education, Cali, Colombia<br>(Interrelationships between total *N*-nitroso compounds in gastric juice, genotoxic activity and severity of precancerous lesions of the stomach) |
| AEP/89/08 | St Vincent Hospital, Dublin, Ireland<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| AEP/89/09 | National Institute of Public Health and Environmental Hygiene, Bilthoven, The Netherlands<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| AEP/89/10 | Unit of Epidemiology, Oncological Centre, Aviano, Italy<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| ECH/89/10 | The General Infirmary, Gastroenterology Unit, Leeds, UK<br>(Relationship between gastric juice ascorbic acid levels and NOC concentrations in patients with normal gastric histology and those with chronic gastritis) |
| AEP/89/11 | Department of Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| FIS/89/11 | Institute of Oncology, Ljubljana, Yugoslavia<br>(Precancerous lesions of the stomach in Slovenia) |
| AEP/89/13 | Department of Biochemistry, University of Glasgow, UK<br>(Nutrititional assessment component of EEC breast and colorectal cancer study) |
| FIS/89/13 | Unit of Epidemiology, Cancer Registry of Majorca, Spain<br>(Family studies on diet and colorectal cancer: pilot study) |
| AEP/89/22 | University Institute of Social and Preventive Medicine, Lausanne, Switzerland<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |
| AEP/89/23 | Unit of Cancerology and Haematology, University Hospital, Luxembourg<br>(Nutritional assessment component of EEC breast and colorectal cancer study) |

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| AEP/89/24 | Italian League against Cancer, Ragusa, Italy<br>(Planning phase of a project on prospective studies on diet and cancer) |
| AEP/90/01 | Institute of Epidemiology and Biometry, German Cancer Research Centre, Heidelberg, Germany<br>(Planning phase of a project on prospective studies on diet and cancer) |
| AEP/90/02 | National Institute of Public Health and Environmental Hygiene, Bilthoven, The Netherlands<br>(Planning phase of a project on prospective studies on diet and cancer) |
| ECH/90/02 | Nagoya City University Medical School, Nagoya, Japan<br>(Studies on endogenous formation of carcinogenic *N*-nitroso compounds and their precursors in hamsters infected with *Opisthorchis viverrini,* and medium-term animal experiments to assess carcinogenicity of nitrosated hickory smoke concentrate) |
| AEP/90/03 | Department of Nutrition and Biochemistry, School of Public Health, Athens, Greece<br>(Planning phase of a project on prospective studies on diet and cancer) |
| AEP/90/05 | "Preventicon", Utrecht, The Netherlands<br>(Planning phase of a project on prospective studies on diet and cancer) |
| FIS/90/12 | Cancer Control Center, San Cristobal, Venezuela<br>(Etiology and prevention of stomach cancer in Venezuela) |

**Studies on occupational cancer**

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|---|---|
| DIR/87/02 | Department of Biomedical Science and Human Oncology, University of Turin, Italy<br>(Study on early lesions produced by low environmental exposures [passive smoking and pollution] and by low levels of occupational exposures) |
| AEP/89/14 | Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |
| AEP/89/16 | National Institute of Health and Medical Research (INSERM), Villejuif, France<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |
| AEP/89/17 | Institute of Occupational Health, Helsinki, Finland<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |

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| AEP/89/18 | College of Physicians and Surgeons of Columbia University, New York, USA<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |
| AEP/89/19 | National Institute of Agronomical Research (INRA), Paris, France<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |
| AEP/89/20 | TEAGASC, Agricultural and Food Development Authority, Dublin, Ireland<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |
| AEP/89/21 | National Institute of Public Health, Rome, Italy<br>(Feasibility phase of an international study of cancer risk in biology research laboratory workers) |
| AEP/89/25 | Institute of Anatomy, University of Turin, Italy<br>(Non-occupational exposure to asbestos and mesothelioma) |
| AEP/89/26 | Norwegian Cancer Registry, Norwegian Radium Hospital, Oslo, Norway<br>(Multicentric study of workers exposed to styrene) |
| AEP/90/04 | National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands<br>(IARC international register of workers exposed to phenoxy acid herbicides and their contaminants) |
| AEP/90/06 | Department of Epidemiology, London School of Hygiene and Tropical Medicine, London, UK<br>(Lung cancer mortality among iron and steel workers in the steel valley of South-East Brazil) |
| AEP/90/07 | National Centre for Scientific Research (CNRS), Paris, France<br>(International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/08 | National Institute for Research and Security (INRS), Vandoeuvre, France<br>(International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/09 | Institute of Epidemiology and Biometry, German Cancer Research Centre, Heidelberg, Germany<br>(International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/10 | United Kingdom Co-ordinating Committee on Cancer Research, London, UK<br>(International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/12 | Institute of Pathology, University of Oslo, Oslo, Norway<br>(International study of cancer risk in biology research laboratory workers in Europe) |

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| AEP/90/13 | Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/14 | TEAGASC, Agriculture and Food Development Authority, Dublin, Ireland (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/15 | National Institute of Public Health, Rome, Italy (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/16 | National Institute of Health and Medical Research (INSERM), Villejuif, France (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/17 | National Institute of Agronomical Research (INRA), Paris, France (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/90/18 | Netherlands Cancer Institute, Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/91/01 | Atomic Energy Agency, Paris, France (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/91/02 | Institute of Occupational Health, Helsinki, Finland (International study of cancer risk in biology research laboratory workers in Europe) |
| AEP/91/03 | National Institute of Health and Medical Research, Le Vesinet, France (International study of cancer risk in biology research laboratory workers in Europe) |

**Studies on the effects of active and passive smoking**

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| AEP/87/02 | Department of Epidemiology and Statistics, Hospital San Jaime i Santa Magdalena, Mataro, Spain (International collaborative study on lung cancer in non-smokers) |
| AEP/87/03 | Department of Hygiene and Epidemiology, School of Medicine, University of Athens, Athens, Greece (International collaborative study on lung cancer in non-smokers) |
| AEP/87/04 | Maria Sklodowska-Curie Memorial Centre, Institute of Oncology, Warsaw, Poland (International collaborative study on lung cancer in non-smokers) |

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| AEP/89/15 | Department of Chest Diseases, Postgraduate Institute of Medical Education and Research, Chandigarh, India (International collaborative study on lung cancer in non-smokers) |
| DEP/89/12 | 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**

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|---|---|
| DEC/79/06 | Institute of Medical Sciences, University of Tokyo, Japan (Mutagenesis and neoplastic transformation *in vitro* of cultured cells by environmental chemicals) |
| DEC/79/10 | All-Union Cancer Research Centre, Academy of Medical Sciences, Moscow, USSR (Investigation of the development of cellular and biochemical markers of in-vitro transformation of epithelial cells in culture) |
| DEC/81/02 | Cancer Institute, Chinese Academy of Medical Sciences, Beijing, China (Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines) |
| DEC/81/09 | Oncological Institute of the Ministry of Health, Vilnius, Lithuanian SSR, USSR (Long-term carcinogenicity testing of environmental chemicals) |
| DEC/81/35 | National Institute of Hygiene, Budapest, Hungary (Long-term carcinogenicity testing of environmental chemicals) |
| DEC/83/01 | Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK (Preparation and characterization of antibodies against DNA modifications induced by nitrosamines to be used for the determination of human exposure to that group of carcinogens) |
| DEC/83/11 | Institute of Oncology, Medical Academy, Sofia, Bulgaria (Mycotoxins and individual oxidative susceptibility in relation to endemic nephropathy and tumours of the urinary system) |
| DEC/84/01 | Research Department, National Board of Occupational Safety and Health, Solna, Sweden (Long-term carcinogenicity testing of environmental chemicals) |
| DEC/85/06 | N.N. Petrov Research Institute of Oncology, Leningrad, USSR (Study on $O^6$-alkylguanine-DNA methyltransferase activities in human tissues) |
| CIE/86/07 | Laboratory of Carcinogenic Substances, Oncological Research Centre, Moscow, USSR (Role of prezygotic events in increasing cancer risk in subsequent generations) |
| ECH/87/04 | Cancer Research Institute, Tata Memorial Centre, Bombay, India (Study on DNA damage as marker of exposure to betel quid/tobacco) |

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|---|---|
| ECH/87/06 | Laboratory of Microbiology, Faculty of Pharmacy, Marseille, France<br>(Studies of methods for degradation of chemical carcinogens) |
| ECH/88/04 | Department of Organic Chemistry, University of Newcastle-upon-Tyne, UK<br>(Nucleotide modifications in recoverable microcapsules) |
| MCA/88/01 | Department of Pathology, Sapporo Medical College, Sapporo, Japan<br>(Molecular and cellular mechanisms of cultured liver cell transformation) |
| MCA/88/02 | Human Molecular Genetics Laboratory, Imperial Cancer Research Fund Laboratories, London, UK<br>(Study of the human X-chromosome by the irradiation and fusion gene transfer method) |
| CIE/89/01 | Vijskumny Ustav Preventivneho Lekarstva, Bratislava, Czechoslovakia<br>(Studies for testing the transplacental carcinogenicity of Mancozeb (Novozir) in Wistar rats) |
| MCA/89/01 | Institute of Pathology and Experimental Cancer Research, Semmelweis Medical University, Budapest, Hungary<br>(Characterization of glycosaminoglycans and other membrane components in human liver and renal tumours) |
| MCA/89/04 | Centro de Estudio Integral de la Enfermedades Digestivas (CEIED), Hospital de Clinicas "Dr Manuael Quintala" Montevideo, Uruguay<br>(Molecular epidemiology of oesophageal cancer—detection of *ras* oncogene mutations) |
| MCA/89/05 | Life Science Laboratory, Teesside Polytechnic, Cleveland, UK<br>(Carcinogenic effects in the offspring of male Swiss mice treated with NMU or ENU before mating) |
| MCA/89/06 | The Maria Sklodowska–Curie Memorial Institute, Gliwice, Poland<br>(Research project on the level of DNA adducts in white blood cells of urban and rural population) |
| MCA/89/07 | Department of Biochemistry, University of Kashmir, Srinagar, India<br>(Detection of DNA alkylation adducts and oncogene activation in human tissues) |
| ECH/89/01 | N.N. Petrov Institute of Oncology, Leningrad, USSR<br>(Urinary excretion of 3-methyladenine in NMU-treated patients: correlations with DNA methylation) |
| ECH/89/03 | MRC Toxicology Unit, Carshalton, UK<br>(Characterization and analysis of alkylpurines in urine by mass spectrometry) |
| ECH/89/05 | School of Dentistry, University of Khartoum, Sudan<br>(Identification of carcinogenic agents in tomback in the Sudan) |

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| ECH/89/06 | Department of Surgery, University of Aberdeen, UK<br>(Lipid peroxidation, antioxidant defence and human cancer) |
| ECH/89/08 | Medical Research Council, London, UK<br>(Mass spectrometry of nucleotide modifications and adducts in recoverable microcapsules) |
| ECH/89/11 | Department of Genetics, University of Essen, Germany<br>(DNA damage as marker of exposure to betel quid in Papua New Guinea) |
| ECH/90/01 | Department of Organic Chemistry, University of Newcastle-upon-Tyne, UK<br>(Nucleoside analogue modifications in recoverable microcapsules) |

**Support to meetings**

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| DEP/90/01 | Hamburg Cancer Registry, Hamburg, Germany<br>(Annual meeting of the International Association of Cancer Registries, Hamburg, 13–15 August 1990) |
| AEP/91/04 | Institute of Internal Medicine, Naples, Italy<br>(European prospective study on nutrition, cancer and health—opportunities for cardiovascular studies: proceedings of meeting held in Naples on 4–6 February 1991) |

*Annex 6*

# MEETINGS AND WORKSHOPS ORGANIZED BY IARC
## July 1989–June 1991

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| Working group meeting to discuss biochemical markers for prospective studies on diet and cancer in Europe | Lyon<br>3–5 July 1989 |
| Advanced statistical methods course | Lyon<br>19–26 July 1989 |
| Meeting of the International Association of Cancer Registries | Maastricht, Netherlands<br>17–20 September 1989 |
| Course on epidemiological aspects of occupational cancer | Ljubljana, Yugoslavia<br>18–26 September 1989 |
| Meeting on the European Childhood Leukaemia Incidence Study | Maastricht, Netherlands<br>21 September 1989 |
| 10th international meeting on *N*-nitroso compounds, mycotoxins and tobacco smoke: relevance to human cancer | Lyon<br>25–27 September 1989 |
| Scientific Council Peer Review meeting | Lyon<br>5–6 October 1989 |
| IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Volume 50: Some pharmaceutical drugs (II) | Lyon<br>17–24 October 1989 |
| Meeting on the case–control studies of second cancers | Padua, Italy<br>21–22 October 1989 |
| Working group on cancer incidence and mortality data-base | Lyon<br>30 October 1989 |
| Final meeting for the collaborators in the vinyl chloride study | Lyon<br>2–3 November 1989 |
| Workshop on multistage carcinogenesis | Lyon<br>4 November 1989 |
| Advisory Group on Cancer Prevention | Lyon<br>7–9 November 1989 |
| Course on cancer epidemiology (in French) | Lyon<br>20 November–1 December 1989 |
| Meeting of the collaborators in the international study on lung cancer in non-smokers and passive smoking | Venice, Italy<br>20–22 November 1989 |

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| Workshop on linkage studies in hereditary breast cancer | Lyon<br>28–29 November 1989 |
| Meeting of the international study of cancer risk in research laboratory workers | Lyon<br>7–8 December 1989 |
| Working Group of collaborators in the prospective studies on diet and cancer in Europe | Mataró, Spain<br>13–14 December 1989 |
| SEARCH breast and colorectal cancer study collaborators meeting | Lyon<br>13–15 December 1989 |
| Programme committee meeting for the third European Educational Programme in Epidemiology Residential Summer Course | Lyon<br>19–20 December 1989 |
| Working group of collaborators in the IARC MMMF study | Lyon<br>8–9 January 1990 |
| Meeting of collaborators in prospective studies on diet and cancer | Turin, Italy<br>9–10 January 1990 |
| IARC Scientific Council | Lyon<br>22–25 January 1990 |
| 5th Steering committee and Peer Review meeting for the Gambia Hepatitis Intervention Study | Lyon<br>25–26 January 1990 |
| Advisory group on nutrition and cancer | Lyon<br>27 January 1990 |
| Analysis and interpretation of spatial aggregation of disease | Lyon<br>29–30 January 1990 |
| Meeting on Small Area Health Statistics | Lyon<br>29–31 January 1990 |
| Meeting on methodology in detecting disease clusters | Lyon<br>30–31 January 1990 |
| Working group on cancer in Italian migrants | Lyon<br>31 January–2 February 1990 |
| Working group on cancer incidence and mortality data base | Lyon<br>13–14 February 1990 |
| Editorial Board meeting for the proceedings of the IPCS/CEC/FRG/ICOH workshop on immunotoxicology and immunotoxicity of metals | Lyon<br>19–20 February 1990 |
| Final review meeting of the cervical cancer study cytopathologists panel | Mexico City<br>19–23 February 1990 |
| Working group of collaborators in the SEARCH childhood leukaemia study | Lyon<br>20–22 February 1990 |
| Meeting of the International Register of workers exposed to phenoxy-acid herbicides and contaminants | Lyon<br>22–23 February 1990 |
| IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Volume 51: Coffee, tea, mate, methylxanthines and methylglyoxal | Lyon<br>27 February–6 March 1990 |

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| Meeting to discuss pilot phase of prospective studies on diet and cancer in Germany, Greece and The Netherlands | Lyon<br>1–2 March 1990 |
| Meeting of the subcommittee for dosimetry and combined analyses of data on cancer among nuclear industry workers | Lyon<br>12–13 March 1990 |
| Training course on safe handling of cytostatic drugs for health workers | Lyon<br>13–14 March 1990 |
| Training course on safe handling of genotoxic substances in research laboratories | Lyon<br>15–16 March 1990 |
| Group discussion on the evaluation of carcinogenic risks | Lyon<br>19 March 1990 |
| Coordinating committee on prospective studies on diet and cancer to discuss progress of pilot phase | Lyon<br>19–21 March 1990 |
| Réunion de travail sur les méthodes d'enquêtes alimentaires | Lyon<br>29 March 1990 |
| SEARCH collaborative study of cancers of the pancreas, gall bladder and bile ducts—collaborators meeting | Lyon<br>27–29 March 1990 |
| Working group on cancer incidence and mortality data-base | Copenhagen<br>30 April–1 May 1990 |
| IARC Governing Council | Lyon<br>3–4 May 1990 |
| Course on modern epidemiological methods | Shanghai, China<br>7–18 May 1990 |
| Working group on cancer incidence and mortality data-base | Lyon<br>8–9 May 1990 |
| L'Environnement electromagnétique et le cancer | Lyon<br>11 May 1990 |
| IARC Fellowships Selection Committee | Lyon<br>22–23 May 1990 |
| XVth Meeting of the 'Groupe pour l'Epidémiologie et l'Enregistrement du Cancer dans les Pays de Langue Latine' | Fort-de-France<br>Martinique,<br>24–25 May 1990 |
| Second meeting of industrial hygienists for the IARC multicentric cohort study of workers exposed to styrene | Bologna, Italy<br>4–5 June 1990 |
| Coordinating committee on prospective studies on diet and cancer to discuss nested investigations on risk factors other than diet | Lyon<br>7–8 June 1990 |
| Third European Educational Programme in Epidemiology Residential Summer Course | Florence, Italy<br>18 June–7 July 1990 |
| IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Volume 52: Chlorinated drinking-water, chlorination by-products, some other halogenated compounds; cobalt and cobalt compounds | Lyon<br>12–19 June 1990 |
| Working group for the international study of cancer risk in biology research laboratory workers | Lyon<br>18–20 June 1990 |

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| Steering committee of the Cancer Registries Network | Copenhagen<br>11 August 1990 |
| IACR Annual Meeting | Hamburg, Germany<br>13–15 August 1990 |
| Meeting of coordinators of the cervical cancer case–control study | Murcia, Spain<br>3–7 September 1990 |
| Genetic epidemiology meeting | Lyon<br>11–12 September 1990 |
| Course on molecular biology for cancer epidemiologists | Lyon<br>18–27 September 1990 |
| Working group to finalize the protocol for male breast cancer study | Lyon<br>24–26 September 1990 |
| International course on epidemiology and cancer control | Manila<br>15–26 October 1990 |
| IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Volume 53: Some pesticides and occupational exposures in pesticide applications | Lyon<br>16–23 October 1990 |
| Editorial Board Meeting for *Cancer Incidence in Five Continents*, Vol. VI | Lyon<br>26–29 November 1990 |
| Meeting of agronomical sector in the international study of cancer risk in biology research laboratory workers | Paris<br>26 November 1990 |
| Review meeting for the Gambia Hepatitis Intervention Study | Rome<br>4 December 1990 |
| Meeting of French collaborators in the international study of cancer risk in biology research laboratory workers | Villejuif<br>17 December 1990 |
| Meeting to prepare a training manual for cancer registry personnel | Lyon<br>10–14 December 1990 |
| SEARCH meeting on clustering | Lyon<br>7–9 January 1991 |
| Meeting of the working group of collaborators in the European prospective study on nutrition, cancer and health | Lyon<br>9–11 January 1991 |
| EEC workshop on research on geographic correlation of biological risk factors with gastritis and gastric cancer (EUROGAST) | Lyon<br>14–18 January 1991 |
| National coordinating committee meeting on the prospective study on diet and cancer | Pamplona, Spain<br>15–17 January 1991 |
| SEARCH working group for the study of childhood leukaemia and related neoplasms | Lyon<br>28–31 January 1991 |
| Working Group of collaborators in the European prospective study on nutrition, cancer and health | Lyon<br>29 January–1 February 1991 |
| Advisory group on studies on cardiovascular diseases nested in the programme on prospective studies on diet and cancer | Naples, Italy<br>4–6 February 1991 |

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| 6th Steering Committee and Peer Review meeting for the Gambia Hepatitis Intervention Study | Fajara, The Gambia<br>12–13 February 1991 |
| Meeting of the European Network of Cancer Registries | Lyon<br>27 February–1 March 1991 |
| EC/STEP Nongenotoxic Group Meeting | Lyon<br>1 March 1991 |
| Steering committee meeting for the European Network of Cancer Registries | Lyon<br>28 February–1 March 1991 |
| Meeting to revise the volume on decontamination of mycotoxins | Lyon<br>4–5 March 1991 |
| Meeting on the future of human radiation research (in collaboration with the Commission of the European Community and the Radiation Effects Research Foundation) | Schloss Elmau, Germany<br>4–8 March 1991 |
| Meeting to revise the volume on decontamination of polycyclic heterocyclic compounds | Lyon<br>6–7 March 1991 |
| Course on cancer epidemiology, in collaboration with PAHO | Havana, 11–22 March 1991 |
| SEARCH working group for childhood brain tumours study | Lyon<br>18–19 March 1991 |
| SEARCH working group for adult brain tumours study | Lyon<br>20–21 March 1991 |
| Meeting of the collaborators of the study on cancer risk in the private sector of biological and medical research | Lyon<br>25 March 1991 |
| Working group meeting of the European collaborators of the international study of cancer risk in research laboratory workers | Lyon<br>4–5 April 1991 |
| Course on cancer epidemiology, in collaboration with INSERM | Lyon, 8–19 April 1991 |
| First meeting of the working group of the IARC study on cancer risk in the pulp and paper industry | Lyon, 22–23 April 1991 |
| Workshop on black and blond tobacco related cancers | Tarragona, Spain,<br>24–27 April 1991 |
| IARC Fellowships Selection Committee | Lyon, 25–26 April 1991 |
| IARC Governing Council | Lyon, 2–4 May 1991 |
| XVIth Meeting of the "Groupe pour l'Epidémiologie et l'Enregistrement du Cancer dans les Pays de Langue Latine" | Lisbon, Portugal<br>9–10 May 1991 |
| Workshop on HPV and cervical cancer | Lyon<br>28–31 May 1991 |
| Course on the scientific basis of carcinogenicity testing | Moscow<br>28 May–4 June 1991 |

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| Viral–chemical interactions in human cancers | Lyon<br>3–4 June 1991 |
| Meeting on the monograph on statistical methods in genetic epidemiology | Lyon<br>3–6 June 1991 |
| Ad hoc advisory group on viruses and parasites | Lyon<br>5 June 1991 |
| International meeting on mycotoxin-associated nephropathy and urinary tract tumours | Lyon<br>6–8 June 1991 |
| IARC Working Group on the use of mechanistic data to evaluate the carcinogenicity of chemicals to humans | Lyon<br>11–18 June 1991 |
| Editorial Board meeting for *Cancer Incidence in Five Continents*, Vol. VI | Lyon<br>17–20 June 1991 |
| Editorial Board meeting for the Manual on Rat Tumour Morphology | Lyon<br>19 June 1991 |
| Working Group on food coding systems and food composition data-bases | Lyon<br>20–21 June 1991 |
| EEC workshop on research on geographic correlation of biological risk factors with gastritis and gastric cancer (EUROGAST) | Lyon<br>27–28 June 1991 |

*Annex 7*

# VISITORS TO IARC
## 1 July 1989–30 June 1991

A total of 1269 persons from 54 countries visited the Agency during the period under review. The following gave lectures:

Dr R.J. Albertini, Vermont Cancer Center, Vermont, USA
Hprt-mutations in T-cells arising *in vivo* in humans

Dr V.N. Anisimov, N.N. Petrov Research Institute of Oncology, Leningrad, USSR
5-Bromodeoxyuridine-induced carcinogenesis in rats

Professor P. Band and Ms A. Keefe, Cancer Control Agency of British Columbia, Vancouver, BC, Canada
The British Columbia Cancer Agency

Dr G.A. Bannikov, All-Union Cancer Research Centre, Moscow
Embryonic and tumour cell invasion: specific changes in cytoskeletal and extracellular matrix components

Dr J. Baron, Dartmouth Medical School, New Hampshire, USA
Cigarette smoking and estrogen-related disorders in women

Dr R. Bedwani, Alexandria Cancer Registry, Medical Research Institute, Alexandria, Egypt
Description of the activities in the Alexandria Cancer Registry

Professor Z.S. Beniashvili, Oncological Research Centre, Tbilisi, USSR
Experimental tumours in monkeys

Dr R. Benigni, National Institute of Health, Rome
Exploration of genotoxicity data: methods and facts

Sir Walter Bodmer, Imperial Cancer Research Fund Laboratories, London
Genetics and biology of colorectal cancer

Dr L. Brinton, National Cancer Institute, Bethesda, MD, USA
Etiologic factors for invasive cervical cancer in four Latin American countries

Dr N. Colburn, NCI Frederick Cancer Research Facilities, Frederick, MD, USA
Genes and signal transduction in tumour production

Dr A. Columbano, Institute of Pharmacology and Biochemical Pathology, Cagliari, Italy
Cell proliferation and cell death in multistage chemical hepatocarcinogenesis

Dr C.J. Conti, MD Anderson Cancer Centre, Smithville, TX, USA
Cytogenetic and molecular events in chemically induced skin cancer

Dr M.G. Deo, Cancer Research Institute, Tata Memorial Centre, Bombay
Oncogenes and oral cancer

Dr R. Di Lauro, European Molecular Biology Laboratory, Heidelberg, Germany
Cloning of the cDNA for a thyroid specific transcription factor: its expression in normal and transformed thyroid cells

Dr H.J. Evans, MRC Human Genetics Unit, Western General Hospital, Edinburgh, UK
Ionizing radiations from nuclear establishments and childhood leukaemias—an enigma

Dr A. Fusco, II Faculty of Medicine, Naples, Italy
Oncogenes and human thyroid carcinogenesis

Dr M. Gérin, Montreal University, Canada
The Montreal multisite case–referent study of occupational: an update and further research on the validity of job exposure matrices

Dr L. Grossman, Johns Hopkins University, Baltimore, MD, USA
Assays for measuring human DNA repair as a basic factor in environmentally induced diseases

Professor F. Guijon, University of Manitoba, Canada
HPV, genital infections and cervical neoplasia

Dr L.D. Hamilton, Brookhaven National Laboratory, Upton, Long Island, NY, USA
Assessment of health impact of various energy sources

Professor K.P. Hanson, N.N. Petrov Research Institute of Oncology, Leningrad, USSR
Mechanisms of radiation-induced carcinogenesis

Dr M. Hayashi, National Institute of Hygiene Sciences, Tokyo
Attempts to automatize micronuclei tests

Dr E. Helsing, WHO Regional Office for Europe, Copenhagen
Food and nutrition policy: translating scientific knowledge into political practice. WHO/EURO Nutrition Programme

Dr M. Hergenhahn, Institute of Biochemistry, German Cancer Research Centre, Heidelberg, Germany
Short-term test for tumour promoters

Dr A. Hirsch, Saint-Louis Hospital, Paris
Rôle des médecins généralistes dans la lutte contre le tabagisme

Dr J.L. Hopper, University of Melbourne, Carlton, Victoria, Australia
Approaches to measuring and interpreting familiar aggregation: application to breast cancer

Dr T. Ishikawa, Japanese Foundation for Cancer Research, Tokyo
Expression of *E. coli* DNA repair gene ($O^6$-methylguanine DNA methyltransferase) in transgenic mice

Dr P. Jäppinen, Occupational Health Centre, Imatra, Finland
Cancer risk in the forestry industry

Dr J.M. Jongen, Agricultural University, Wageningen, The Netherlands
E cadherin—intercellular communication regulator?

Professor S. Kamiyama, Akita University School of Medicine, Akita, Japan
Factors to regulate familial accumulation of cancer

Dr H. Kasai, National Cancer Center Research Institute, Tokyo
Formation, inhibition of formation and repair mechanisms of an oxidative DNA damage, 8-hydroxyguanine

Dr P. Kleihues, Institute of Pathology, Zurich, Switzerland
Cell-specific tumour induction in fetal brain transplants by retrovirus-mediated oncogene transfer

Professor Y. Konishi, Nara Medical College, Nara, Japan
Pancreatic carcinogenesis in animals and humans

Dr T. Kuroki, Institute of Medical Science, University of Tokyo
Signal transduction and gene expression during the stage of tumour promotion in mouse skin carcinogenesis

Dr K.A. L'Abbé, University of Toronto, Canada
Results from a collaborative cohort study of workers exposed to vinyl chloride

Dr J. Laval, Gustave Roussy Institute, Villejuif, France
Repair of secondary lesions induced in DNA by alkylating agents

Dr A. Leclerc and Dr D. Luce, INSERM U.88, Paris
The Franch case–control study on sinonasal cancer

Dr T. Lindahl, Clare Hall Laboratories, Potter's Bar, UK
Molecular deficiencies in human chromosome breakage syndromes

Dr Liu Qing, Sun Yat Sen University, Guangzhou, China
Air pollution and risk of lung cancer in China

Dr E. Matos, University of Buenos Aires
Cancer in Argentina. Patterns by place of residence and place of birth

Dr M.A. Moore, Nagoya City University, Nagoya, Japan
Dehydroepiandrosterone—a modulator of the neoplastic process

Dr A.W. Murray, Flinders University of South Australia, Bedford Park, Australia
Protein kinase C activated turnover of ether-linked phospholipids: a possible new signalling pathway

Dr S. Narod, Montreal General Hospital, Canada
Hereditary fraction of childhood cancer

Dr D.W. Nebert, National Institute of Child Health and Human Development, Bethesda, MD, USA
Cellular response to oxidative stress

Professor M. Oshimura, Tottori University School of Life Sciences, Tottori-ken, Japan
Lessons learned from studies on tumour suppression via microcell-mediated chromosome transfer

Dr M. Ozturk, Massachusetts General Hospital, Harvard Medical School, Charleston, MA, USA
Hot spot p53 mutation in primary liver cancer

Dr F.P. Perera, Columbia University, NY, USA
Molecular epidemiology of cancer

Dr D.H. Phillips, Royal Marsden Hospital, Sutton, Surrey, United Kingdom
DNA adduct formation in animals and humans exposed to complex mixtures of carcinogens

Dr C. Pourcel, Pasteur Institute, Paris
Souris transgéniques pour l'ADN du virus de l'hépatite B

Dr P. Rakoczy, University of Western Australia, Nedlands, Australia
Time trends in the prevalence of HPV infection in archival Pap smears

Dr A. Rogatko, Memorial Sloan–Kettering Cancer Center, New York, USA
Statistical inference in multipoint linkage

Professor H.S. Rosenkranz, Case Western University School of Medicine, Cleveland, OH, USA
Application of artificial intelligence to chemical carcinogenesis

Dr G. Rouleau, Montreal General Hospital, Canada
Molecular genetics of neurofibromatosis

Dr L. Samson, Harvard University School of Public Health, Boston, MA, USA
The expression of prokaryotic DNA repair function in eukaryotic cells and vice–versa

Dr A. Sergeant, Ecole Normale Supérieure de Lyon, France
Activation of the Epstein–Barr putative lytic cycle switch gene by the tumour promoter TPA

Dr K. Shah, Johns Hopkins University, Baltimore, MD, USA
Biology and disease potential of HPV

Dr J.A. Swenberg, Glaxo Research Laboratory, Chapel Hill, NC, USA
Molecular dosimetry of DNA adducts in carcinogenesis

Dr S. Szmigielski, Centre for Radiobiology, Warsaw
Electromagnetic fields and neoplasms

Dr R. Schäfer, Zurich University, Switzerland
Reversion of the transformed phenotype in Ha-ras transfected tumorigenic cells by transfer of a candidate suppressor gene

Dr D. Stéhelin, Pasteur Institute, Lille, France
Angiogenèse, extension tumorale et implication du proto-oncogène *etsl*

Dr R. Snyder, Rutgers Medical School, Rutgers, NJ, USA
The role of benzene metabolism in the production of adverse health effects

Dr W. Thilly, MIT Centre for Environmental Health Sciences, Cambridge, MA, USA
Mutation spectra in human cells

Dr D.B. Thomas, University of Southern California, Los Angeles, CA, USA
WHO collaborative study of neoplasia and steroid contraceptives

Dr S.P. Tong, c/o Professor C. Trépo, INSERM U.271, Lyon, France
Hepatitis B virus variants with defective precore-region

Dr V.B. Vasiliev, Institute of Experimental Medicine, Leningrad, USSR
Copper-containing proteins in free radical turnover, ageing and cancer

Dr A. Visconti, Institute of Toxins and Mycotoxins of Vegetal Parasites, Bari, Italy
Cytotoxicity and immunotoxicity of *Fusarium* mycotoxins: considerations on the structure–activity relationship

Professor B. Wahren, National Bacteriological Laboratory, Stockholm
T-cell activation by HIV peptides

Dr S. Watanabe, National Cancer Center Research Institute, Tokyo
A population-based cohort study with biological markers

Professor J. Williamson, University of Colorado at Boulder, CO, USA
Genetic linkage under an incorrect model

*Annex 8*

# INTERNAL REPORTS

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| IARC Internal Report 89/006 | Person–Years (PYRS)—A Fortran Programme for Cohort Study Analysis, Lyon, September 1989 |
| IARC Internal Report 89/007 | Mortality and cancer incidence results of the European multicentric cohort study of workers employed in the vinyl chloride industry |
| IARC Internal Report 89/008 | A mortality study of miners and factory workers at the "Société des Mines et Produits Chimiques de Salsigne", France |
| IARC Internal Report 89/009 | Etude de mortalité parmi les salariés de la "Société des Mines et Produits Chimiques de Salsigne", France |
| IARC Internal Report 90/001A | International Collaborative Study of Cancer Risk among Nuclear Industry Workers. Protocol of the Feasibility Study. E. Cardis and J. Estève |
| IARC Internal Report 90/001B | International Collaborative Study of Cancer Risk among Nuclear Industry Workers. Questionnaire of the Feasibility Study. E. Cardis and J. Estève |
| IARC Internal Report 90/002 | Epidemiological Studies of Melanocytic Naevi: Protocol for Identifying and Recording Naevi. D. English |

*Annex 9*

# PAPERS PUBLISHED BY IARC STAFF AND FELLOWS


Ad Hoc Working Group (Coleman, M.P., Cardis, E., Boyle, P., Saracci, R., Ahlbom, A., Feychting, M. and 18 others) (1990) Extremely low-frequency electric and magnetic fields and risk of human cancer. *Bioelectromagnetics*, **11**, 91–99

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