WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

BIENNIAL REPORT

1988 – 1989

FOR THE PERIOD 1 JULY 1987 TO 30 JUNE 1989

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
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1989

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INTRODUCTION

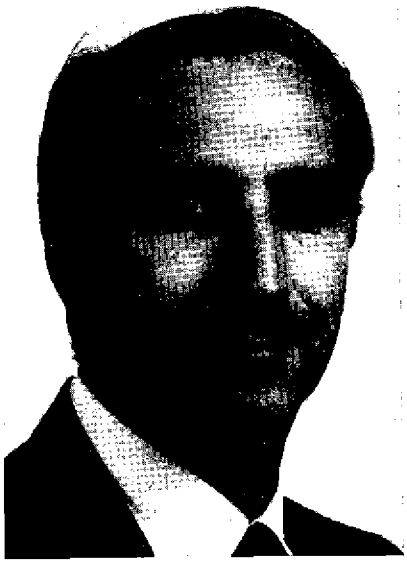
Over the years, the Agency's activities have continued to be oriented towards cancer etiology and the generation, collection and dissemination of information useful for the prevention of human cancer.

The choice of this orientation was the result of the consensus among the founders of the Agency (GC/1/R6) and was thereafter confirmed by several Governing Councils (GC/4/R6, GC/12/R1, GC/12/5). When the Agency was created, the view that it should have a scientific structure and research activities clearly prevailed. It was thus agreed that in its approach to the cancer problem the main emphasis should be put on research into causes of cancer, with a view to applying research results to cancer prevention, and on the evaluation of the efficacy of preventive interventions. Research was to be conducted both within the Agency's own premises and externally through a prominent coordinating and catalytic role at the international level, and in harmony with the public health orientation of WHO Headquarters in Geneva.

Almost 25 years after the creation of the Agency, many expectations have been fulfilled, but while there is broad agreement on the main orientation towards cancer etiology and prevention, there are differing views regarding the respective roles of laboratory research versus epidemiological studies. This is partly because laboratory research often requires the long-term pursuit of projects for which practical applications are not immediately evident. Nevertheless, for years the Agency has aimed at a progressively closer integration between laboratory and epidemiological activities in the search for clues to the origin of human cancer. Indeed, some of its most important projects have been, from its earliest days, clear examples of this close collaboration, such as the seroepidemiological studies of Burkitt's lymphoma, the project on etiological clues to oesophageal cancer in Iran, and more recently, the studies on the role of endogenous and exogenous *N*-nitroso compounds in the origin of certain human tumours, on the role of hepatitis B virus infection and aflatoxins in the origin of liver cancer, on second primary tumours due to cytostatic drugs, some of the projects on nutrition and cancer and those on genetics and cancer.

In this sense, the Agency has definitely contributed to, and to a considerable extent has opened the way to, a new type of epidemiology now often referred to as metabolic or molecular epidemiology. Clearly, this would not have been possible without the presence under the same roof of expert epidemiologists and laboratory scientists. Similarly, without the coexistence of, and cooperation between, scientists active in different areas of research, it would not have been possible for the Agency to initiate and successfully develop the programme on the evaluation of carcinogenic risk to humans that has generated the well-known Monographs series, which is an example of a truly multidisciplinary international collaboration.

In the last two years, between July 1987 and June 1989, the Agency has attracted an increasing number of visiting scientists and fellows, as well as senior scientists on sabbatical leave who have actively participated in various Agency programmes. The training of junior scientists who will take back to their home institutes the experience gained during the period spent in Lyon, and the expansion and consolidation of international networks of collaborating national institutes, are important components of the Agency's activities and fulfil part of its statutory duties. They also help to considerably amplify the Agency's role within the international scientific community in spite of its relatively small size and the limited in-house facilities. The Agency's staff has so far succeeded in accommodating, in terms of both working hours and space, this growing number of visiting scientists, but the shortage of space is increasingly a

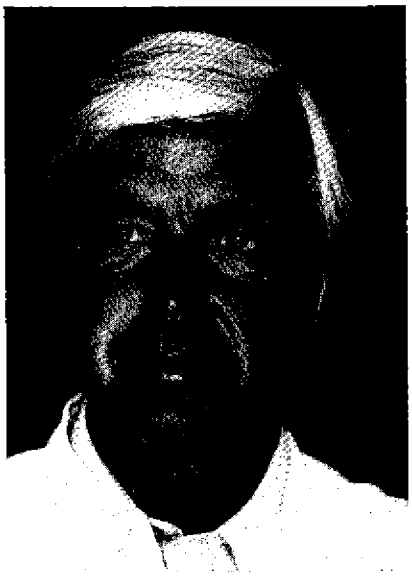


Professor L. Chieco-Bianchi

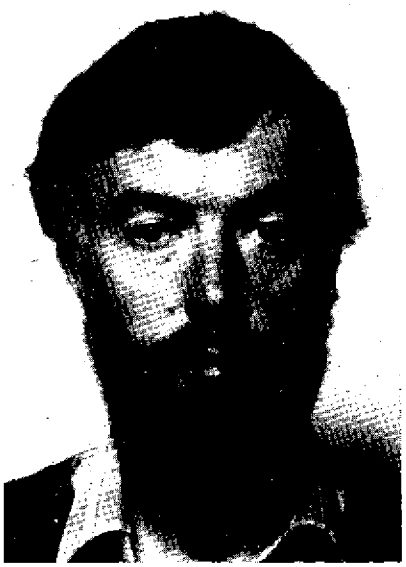
Professor O. H. Iversen

Professor U. Pettersson

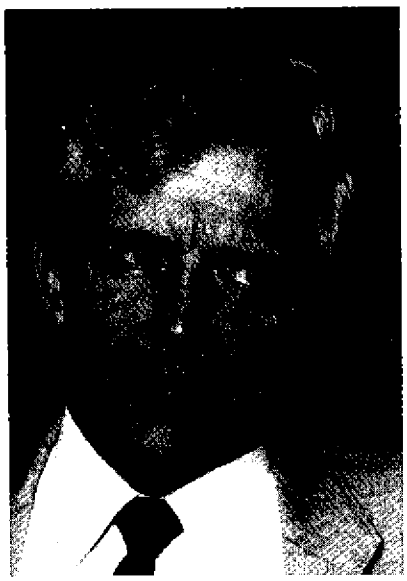
Fig. 1a. New members of the Scientific Council, 1988–1991



Professor E. J. Saksela



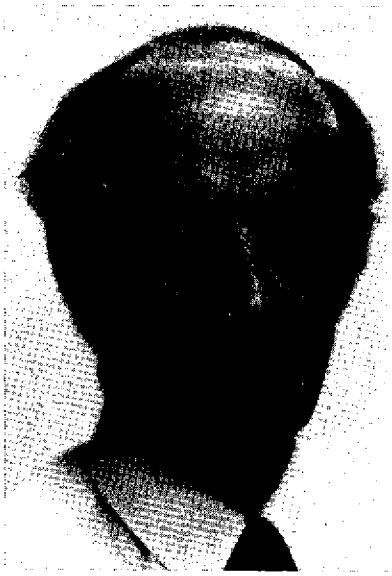
Dr P. G. Smith



Professor H. zur Hausen

Fig. 1a. (*Continued*)

Professor J. Klastersky



Professor A. J. McMichael

Dr S. Takayama

Fig. 1b. New members of the Scientific Council, 1989–1992

constraint. The recently built Sasakawa Memorial Hall, which was made possible through a generous donation by the Japan Shipbuilding Industry Foundation and which is in constant use for meetings, workshops and lectures, has allowed the reshaping of parts of the tower into a few badly needed offices. While bearing in mind the limitations imposed by its approved budget, it is essential to contemplate a possible expansion of the Agency's facilities. Such an expansion would enhance the Agency's effectiveness as a pivot of international activities, as well as providing less constricted, and therefore also safer, conditions for the laboratories which are expected to play a key role in the development of future epidemiological studies.

The past biennium has seen the successful development of several projects as well as the inception of new ones. Some of the results obtained are highlighted below, while more detailed descriptions can be found in the body of the report.

Descriptive epidemiology

In the first half of 1989, planning began for the sixth volume of *Cancer Incidence in Five Continents,* which is expected to include data from up to 30 new centres, including registries in Africa and the USSR. The data collected in Volume V have been used to prepare illustrations depicting the international range and patterns of cancer incidence. The resulting publication, *Patterns of Cancer in Five Continents,* shows the range of rates for each site among selected populations and the different patterns of incidence by age for selected sites.

The information from *Cancer Incidence in Five Continents* and from various other sources has been used to estimate the global burden of cancer in the world and to predict possible changes in occurrence over the next decade. From a parallel study aimed at measuring the public health impact of cancer, cancer appears as a leading cause of loss of years of life before age 70 in women in most of the countries considered, while among men it comes more often in second position, after cardiovascular diseases.

While particular attention has been given to promoting cancer registration and the analysis and interpretation of the data in several developing countries, a new series of studies on migrant populations has been initiated. Such studies are valuable for the formulation of hypotheses on the relative importance of environmental factors and on the stage of carcinogenesis at which they may act. Past studies of migrants have mainly involved Japanese migrants to the USA and British migrants to Australia or South Africa. In the present studies, the cancer experience of Jewish migrants to Israel and of migrants from a variety of European countries to Australia and to South America are being analysed.

A detailed analysis of geographic and ethnic differences for particular childhood cancers is also in progress, on the basis of the recently published data compilation on the incidence of cancer in childhood for more than 50 countries. In parallel, a collaborative project involving 17 European countries has been initiated to follow geographic and temporal trends in the incidence of childhood leukaemia in Europe from 1980 to the mid-1990s. This study will allow the evaluation of whether any changes are related to exposures consequent to the accident at Chernobyl in 1986.

The important role that post-mortem findings can play in epidemiology was stressed at an international symposium jointly organized by IARC and the Institute of Morbid Anatomy of the University of Trieste, held in Trieste in June 1989.

Occupational cancer

The Agency maintains its keen interest in the identification of occupational hazards. Studies in progress include a cohort study on workers exposed to silica, and two international cohort studies on vinyl chloride and on styrene-exposed workers. In addition, a multicentre cohort

study is aimed at analysing cancer risk in welders, subdivided into shipyard welders, mild steel, stainless steel and predominantly stainless steel welders. Available data indicate an increased lung cancer mortality in all of these subgroups.

The international study of cancer risk in biology research laboratory workers is being started with a retrospective historical cohort study. The feasibility of a long-term follow-up of identifiable cohorts is also being examined, with funding from the Europe Against Cancer programme of the EEC. The possible cancer risk of chronic low exposure to ionizing radiation in workers in the nuclear industry is being analysed in a collaborative study involving scientists from 11 countries. The continuous registration of persons exposed to phenoxy-acid herbicides and contaminants is being used for a multicentric follow-up cohort study in collaboration with the National Institute for Environmental Health Sciences of the USA and with the participation of 10 countries.

Second malignancy following chemotherapy

The growing relevance of the study of cancer risks following chemotherapy is related to the improved survival of certain categories of cancer patients treated with cytostatic drugs and to the possibility of reducing the long-term adverse effects of the therapy while at the same time improving its efficacy. Among the first results of this study is the demonstration of the role of chemotherapy, as opposed to radiotherapy, as the primary leukaemogenic agent. A 14-fold increase in risk for leukaemia was found when therapy of the MOPP type for Hodgkin's disease was continued for more than six treament cycle. By active collaboration between epidemiologists, clinicians and experimentalists, it should become possible to identify what specific type and extent of DNA damage induced by the alkylating agents is responsible for, on the one hand, the chemotherapeutic effect, and, on the other, the long-term adverse effects. The possibility that germ cell damage may be produced by the compounds used for cancer therapy and thus may have adverse effects in the offspring is also being investigated.

Nutrition and cancer

In spite of the general consensus on the importance of dietary factors in the origin and development of human tumours, the justification for initiating large-scale interventions is hampered by the limited knowledge available on the actual factors involved in the initiation/promotion or inhibition of neoplastic growth. The studies now being planned in Sweden as well as in six other European countries, sponsored by the Europe Against Cancer programme, are therefore of the greatest relevance for elucidating the role of various dietary components for their adverse or protective effects, that have been reported by many, often contradictory, case–control studies. This will become possible through an integrated epidemiological and laboratory effort over a long period. The recent joining of two further countries, namely the UK and Denmark, into this coordinated effort extends the present participation to nine European countries, covering over half a million individuals. An important component of these studies is the storing of biological samples which may allow precise documentation of specific intakes and exposures as well as the establishment of possible links with the development and possible prevention of diet-related diseases other than cancer. The study also allows for the monitoring of dietary habits to identify and measure possible changes through time.

In parallel with the planning and investigation of the long-term follow-up studies, two case–control studies have been conducted in the south of Europe, that have indicated no association between alcohol intake and colon tumours, positive correlations between high meat intake and risk of colon cancer and between a high intake of dairy products and rectal cancer, as well as a protective effect for both cancer types of large consumption of cruciferous vegetables.

Another case–control study was conducted in Singapore, where major changes in lifestyle have occurred in recent years. Here again the protective effects of cruciferous vegetables and the increased risk due to high meat consumption have been confirmed.

Tobacco smoking

Although the importance of tobacco smoking in causing lung cancer is conclusively established, there are still alarming increases in smoking, especially among young people, among women and in developing countries. The Agency has set up a major investigation of the possible carcinogenic effect of passive smoking looking at populations in 18 locations spread throughout Europe, Asia and North America. There remains great scope for effective education and intervention programmes for primary prevention of tobacco-related cancers, and the Agency is collaborating closely with WHO Headquarters and the European Regional Office in projects to promote and monitor such activities.

Surveillance of environmental aspects related to cancer (SEARCH) programme

This international collaborative programme was established in order to carry out studies of cancer epidemiology that cannot satisfactorily be conducted within a single centre, and to ensure that similar research protocols are widely applied. The aim is to generate reliable, consistent results that will provide sound evidence on the relevant etiological hypotheses.

The first SEARCH study, on cancer of the pancreas, gallbladder and bile duct, has been recently completed. The role of tobacco smoking in increasing the risk of pancreatic cancer was consistently shown. At the same time a rather puzzling, but consistent, finding has been the negative correlation between pancreatic cancer risk and asthma, eczema or hay fever. The analysis of data on gallbladder and bile duct cancer is well advanced.

Four other studies are at different stages of development, namely on brain tumours in children, adult brain tumours, cancer of the breast and colon, and childhood leukaemia and other related haematological malignancies. For the first three of these studies, results should become available during 1990, 1991 and 1992 respectively. The study on childhood leukaemia and related haematological malignancies is still in the organizational phase, following the approval of a protocol which will be applied in collaboration with the European Organization for Research and Treatment of Cancer.

Risk factors for cervical cancer

This study, designed to identify and assess the possible role of risk factors for cervical cancer, is being conducted in Columbia, where incidence of cervical cancer is very high and Spain, which has a low incidence. The recruitment of cases has been completed and all cytological smears and histological slides are carefully controlled to ensure the accuracy of the diagnosis. At the same time, they are screened for the presence of human papillomavirus (HPV) using a commercial dot blot kit. Southern blot analysis is used to retest all samples found positive for HPV, as well as a proportion of those found negative. The preliminary evaluation of data concerning female and male sexual behaviour and its role in modulating the risk for cervical cancer indicates that the prevalence of the known risk factors is higher in Colombia than in Spain and that the role of the male partner may be less strong than was expected.

A repository of cervical cancer tissue and of sera from cervical cancer patients has been created at IARC within the International Biological Study on Cervical Cancer in collaboration with Professor Julian Peto. Samples and questionnaires are being collected from 20 countries.

N-Nitroso compounds and human cancer

This project is aimed at assessing the role of *N*-nitroso compounds (NOC) as DNA-damaging agents in the origin of human cancer, either by themselves or in conjunction with other factors. Exposure to NOC may occur through exposure to preformed compounds or endogenous formation of NOC by nitrosation of amine precursors in the stomach, or at other body sites where nitrosation can be mediated by activated macrophages or bacteria. The first test for quantitatively estimating endogenous nitrosation in humans was developed at IARC and has been applied to epidemiological investigations. The possible role of NOC in the development of gastric, oesophageal, bladder and liver cancer is under study with the dual aim of better understanding the mechanisms involved and of finding measures that would help in preventing the progression of the malignant process. The tenth International Meeting on *N*-Nitroso Compounds will be held in Lyon in September 1989 with emphasis on a multidisciplinary approach to investigating the role of NOC in the occurrence of cancer at various sites in humans.

The IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Within the period July 1987 to June 1989, four Monograph volumes (Vols. 43, 44, 45, 46) and Supplements Nos. 6 and 7 have been published while three other volumes are in press or in the final editing phase (volumes 47, 48, 49). In volume 43, the risks to humans of exposure to man-made mineral fibres and radon were evaluated, and it was concluded that there was sufficient evidence that radon and its decay products are carcinogenic to humans, while for glass wool, rockwool and slag wool an overall evaluation was made of possible carcinogenicity to humans (Group 2B) on the basis of limited or inadequate evidence of carcinogenicity from epidemiological studies and sufficient or limited evidence from long-term animal studies. The overall evaluation of alcoholic beverages made in volume 44, on the basis of epidemiological studies showing a causal relationship between tumours of the oral cavity, pharynx, larynx and oesophagus and consumption of alcoholic beverages, is that the latter are carcinogenic to humans. The risks which may derive from occupational exposure in petroleum refining, and from exposures to crude oil and major petroleum fuels have been evaluated in volume 45. Gasoline, marine diesel fuel and residual heavy fuels oils were assigned to group 2B, possibly carcinogenic to humans. The carcinogenic risks of engine exhausts and of 15 selected nitroarenes were evaluated in volume 46. Diesel engine exhausts were assigned to group 2A (probably carcinogenic to humans), while gasoline engine exhaust and 6 nitroarenes were assigned to group 2B (possibly carcinogenic to humans).

In volume 47, the carcinogenicity of some organic solvents, resin monomers, pigments, and the occupational risks in paint manufacture and painting were evaluated. While occupational exposure in paint manufacture could not be classified as to its carcinogenicity to humans (Group 3), occupational exposure as a painter was considered carcinogenic to humans and assigned to group 1. Some flame retardants and textile chemicals were evaluated in Volume 48. Work in the textile manufacturing industry was considered possibly carcinogenic (Group 2B). Chlorinated paraffins, disperse blue 1, chlorendic acid and nitrilotriacetic acid were also assigned to group 2B, while *para*-chloro-*ortho*-toluidine and its strong acid salts were assigned to group 2A. Chromium, nickel and welding were evaluated in June 1989. Chromium (VI) and nickel compounds were considered carcinogenic to humans (Group 1), while metallic nickel and occupational exposure to welding fumes were considerably possibly carcinogenic to humans (Group 2B).

Within this same period, two *ad hoc* working groups of experts have also been convened. The first, in November 1988, was held to advise the Agency on how to proceed in the difficult issue of evaluating mixtures and groups of chemicals. The guidelines formulated by this group were first

adopted in the evaluations made in volume 49. A second working group was convened in April 1989 to set priorities for evaluation in future IARC Monographs. A list of high- and low-priority agents to be evaluated is now available.

Research in cancer prevention

The most important initiative in this area is the Gambia Hepatitis Intervention Study (GHIS), now in its fourth year of implementation. This study, entirely funded by the Italian Government, and conducted in collaboration with the Gambian Government and the MRC Unit in Fajara, is designed to evaluate the effectiveness of hepatitis B vaccination in the prevention of chronic liver disease and hepatocellular carcinoma, and at the same time assist the Government of The Gambia in maintaining a strong immunization programme. The coverage achieved in vaccination in the Gambia is probably the highest in Africa. Such high coverage is related to all the antigens provided through the Expanded Programme of Immunization which has been considerably potentiated with the support provided through the GHIS.

By early 1990, the vaccination against hepatitis B (HB) will be extended to all newborns in the Gambia. Results available to date indicate that 94% of children receiving at least three doses of HB vaccine developed antibody response that in 98% of them was above the recommended protective level.

Among several ancillary studies, those on the epidemiology of hepatitis delta virus, on risk factors for chronic liver disease, on HBV transmission, on the causes of non-response to HB vaccine and on assessment of the role of aflatoxins in the etiology of primary liver cancer are well advanced. In particular, improved methodology for aflatoxin exposure assessment now allows recent past exposures to be measured, based on the levels of aflatoxin–albumin adducts; these techniques may be applicable to epidemiological studies. The possible role of aflatoxin in the origin of liver cancer is being investigated in parallel also in Singapore and Thailand.

Cancer registration has been implemented throughout The Gambia and some data on cancer incidence at all sites and for the liver are already available. It is intended that the registry will continue as a long-term surveillance system which will be used to monitor the effectiveness of the intervention measures and to indicate different emerging priorities for primary or secondary prevention.

The Agency has continued to assist in the evaluation of early detection programmes, for example in China and in the Philippines with regard to cervical cancer, in Czechoslovakia with regard to lung cancer, and in Venezuela with regard to stomach cancer. In parallel, the Agency has collaborated with the UICC in reviewing the results of various intervention studies in an attempt to assess their effectiveness in reducing cancer risks. The resulting publication *Evaluating Effectiveness of Primary Prevention of Cancer* is appearing as IARC Scientific Publication No. 103.

A chemoprevention trial for precancerous lesions of the stomach using certain vitamins is under consideration in a high-risk population in Venezuela.

Genetics and cancer

While it has been accepted for a long time that cancer risks are related to variations in exposure to environmental factors as well as to individual variations in susceptibility to the carcinogenicity of a variety of agents, it is only recently that studies on the nature and extent of individual genetic differences have started to become possible. The use of molecular markers such as cloned genes and DNA polymorphism markers should now allow the identification of genetic factors that contribute to the development of cancer. The Agency's involvement in this fast-developing and competitive area of research has focused initially on two fairly uncommon

syndromes: X-linked lymphoproliferative syndrome (XLP) and multiple endocrine neoplasia type IIa (MEN IIA). Results from the XLP project have indicated that the XLP locus is in the chromosomal region Xq25–q26 and further investigations are in progress to locate it more precisely. Within the project on MEN IIa, 80 affected families have been identified. The gene predisposing to MEN IIa has been traced to a locus on chromosome 10. Although maximum accuracy in the prediction of cancer risk is assured when the conventional endocrine challenge methods are also used in parallel, the results so far obtained point to the possibility of predicting the carrier state in symptomless members of MEN families by RFLP analysis and thus also to the usefulness of genetic screening for identifying individuals at risk. The collection of families with frequent breast and ovary cancer is continuing and lymphoblastoid cell lines from ten such families, which will provide an adequate source of DNA for linkage studies, have been established.

Variations in individual susceptibility to cancer are also being investigated by analysing and measuring individual capacity to metabolize carcinogens. Preliminary results from the analysis of human lung samples indicate that the levels of inducibility of pulmonary Ah-locus-controlled enzymes in tobacco smokers may be related to cancer risk. The use of probe drugs, namely warfarin, debrisoquine and antipyrine, may also allow the non-invasive investigation of P450 isozyme patterns, providing valuable information on individual capacity to metabolize carcinogens.

Mechanisms of carcinogenesis

Laboratory investigations carried out partly in house and to a very considerable extent in collaboration with national institutions, and linked, whenever possible, to epidemiological studies, are directed to the elucidation of the role of viruses and cytogenetic anomalies in the etiology of human cancer, the role of alteration of gene expression, of genetic damage and DNA repair processes and of cell-to-cell communication in the progression of the carcinogenic process.

The Agency has continued to collect and maintain large numbers of cell lines and sera which are used for studies of tumours related to Epstein–Barr virus (EBV) and specifically on Burkitt's lymphoma, nasopharyngeal carcinoma and B-cell neoplasia. Studies are being conducted to identify the EBV genes involved in the process of cellular immortalization and the association of the EBV genome in nasopharyngeal carcinoma epithelial cells. The pathogenesis of lymphoma occurring in AIDS patients is being studied in particular for its possible independence, at least in some instances, from EBV infection or the HIV-induced T-cell immunodeficiency.

In a study on the prevalence of human T-cell leukaemia virus type 1 (HTLV-1) in the far east of the USSR, seropositivity for HTLV-1 infection was detected in about 2.0% of the population considered. In the same area, some viral types appear to exist that are related, but not identical, to HTLV-1.

Measurements of DNA adducts in human tissues are now being assessed as markers of exposure, and their biological significance is being explored. Experimentally it was shown that levels of DNA adducts after either single or repeated exposure(s) to *N*-nitrosodimethylamine are similar in the liver and in circulating lymphocytes. If this remains true following a chronic exposure to much lower levels of the carcinogen, it would open up its full applicability to human studies.

Within the studies aimed at investigating if patterns of oncogene activation may be related to exposures to environmental carcinogens that may vary in different parts of the world, preliminary results have revealed a significant amplification of the K-*ras* gene in some oesophageal tumours. In parallel, attempts to isolate transforming sequences in oesophageal tumour cells continue. Investigations on oncogene activation following prenatal exposure to a

chemical carcinogen suggest that the same mutation may be involved in the development of tumours produced by a chemical carcinogen in several, although not necessarily all, target organs. A specific H-*ras* mutation was found, for instance, in liver and skin, but not in lung, tumour cells following prenatal exposure of mice to dimethylbenzanthracene.

The possible role that the inhibition of gap-junctional intercellular communication (GJIC) may play in tumour promotion is the object of investigations aimed on the one hand at clarifying the underlying mechanisms of action, and on the other at developing a short-term screening test to detect environmental chemicals with promoting activity. Initial results using human cells suggest that there is a correlation between reduced intercellular communication and malignant transformation. The availability of molecular probes is now allowing the study of gene expression and localization of gap junctions in experimental animals and human tissue samples.

Statistical methodology

In addition to providing assistance and active participation in many of the Agency's experimental and epidemiological projects, the Unit of Biostatistics Research and Informatics has been prominent in supporting and disseminating statistical expertise, essential for the conduct of cancer research. Among areas of specific interest are research on measurement error in epidemiology and on the methodological problems of correctly quantifying cancer risks. Some important aspects of risk quantification are being analysed within the investigation on second malignancies following cytostatic therapy and some methods for taking into account temporal factors have been proposed. Another important activity is the development of methods for measuring relative survival which can be used by cancer registries to study survival of cancer patients.

Fellowships, courses and publications

A total of 28 fellowships were awarded to young scientists from among 92 eligible applicants in the biennium 1988–89, of which eight were in epidemiology and biostatistics, seven in cell biology and cytogenetics, five in viral carcinogenesis, four in molecular biology and four in chemical carcinogenesis. Eight of the 28 fellowships were tenable at the Agency.

During this biennium a total of ten courses were held, of which six were in epidemiology (in Paraguay, Spain, USSR, Italy and Colombia), one on the role of viruses in human cancer (Lyon), one on molecular biology for cancer epidemiologists (Norway), one on statistical methods in the design and analysis of long-term animal experiments (Lyon) and one on the detection of health hazards in human populations exposed to chemical mutagens and carcinogens (Mexico).

As well as the Monographs volumes mentioned above, thirteen volumes have appeared during 1988–89 within the IARC Scientific Publications Series and four have appeared in IARC Technical Reports. The Advisory Committee on Publications continues to exert a critical surveillance of the proposed publications to ensure their suitability for inclusion in the programme on the basis of their scientific quality.

The regular budget of the Agency for the biennium 1988–1989 was US $25 200 000.

On 30 June 1989, the Agency's staff consisted of 56 scientists, 53 technicians and 72 administrative and secretarial staff.

Lorenzo Tomatis, M.D
Director

I. STUDIES ON ETIOLOGY AND PREVENTION

1. STUDIES ON GEOGRAPHICAL DISTRIBUTION, TIME TRENDS AND SPECIAL GROUPS

(a) *Cancer Incidence in Five Continents*, Volumes V and VI (Dr C.S. Muir, Dr D.M. Parkin, Ms S. Whelan, Mr M. Smans and Mr J. Ferlay; in collaboration with Dr J.A.H. Waterhouse and Ms J. Powell, Birmingham and West Midlands Regional Cancer Registry, UK; Dr T.M. Mack, University of Southern California, Los Angeles, CA, USA; and Professor Y.T. Gao, Shanghai Cancer Institute, People's Republic of China)

Volume V of *Cancer Incidence in Five Continents*, published in 1987, presented compilations of cancer morbidity data provided by 105 registries, covering 137 populations in 36 countries. As for each previous volume in the series, the latest issue contains information from more countries and populations than the previous one, although for the first time, it was unfortunately not possible to obtain suitable data from Africa. Cancer incidence data covering more than 20 years are now available for certain parts of the world.

Planning for the sixth volume, which will cover the years 1982–87, began in the first half of 1989. It is evident that, in common with its predecessors, the next volume will cover a greater proportion of the world than has hitherto been possible. Some 30 new potential contributors are being invited to submit data, including registries in Africa and in the USSR. Volume V ran to nearly 1000 pages, so that methods of saving space were on the agenda of the first editorial meeting. It is probable that when data are available for every registry in a country, or cover a reasonable proportion of a country, Volume VI will present the age-specific rates for the combined data only. Summary tables will give the crude rates for all ages, the cumulative rates for ages 0–64 and 0–74, the world standardized rates, and the relative frequencies, for the individual populations within a country. The full data would be made available on computer medium.

It has also been decided to discontinue the urban and rural breakdowns because of the lack of international comparability in definitions, and the problems created and time consumed by the processing of these data.

Registries contributing to Volume V were invited to send data in the form of an anonymous case-listing instead of the traditional tabular format (by site, sex and five-year age group). Only a small minority of contributors took advantage of this possibility, but with the rapid increase in computerization worldwide, it is hoped that most of the data will now be submitted in the form of a case listing on tape or diskette.

Data are being requested for March 1990, and will be processed throughout 1990 and the first half of 1991, with the aim of sending Volume VI to press in September 1991.

(b) *Patterns of Cancer in Five Continents* (Ms S. Whelan, Dr D.M. Parkin and Mr E. Masuyer)

The *Cancer Incidence in Five Continents* series presents data on cancer incidence in a standardized format for every area in the world from which it is possible to obtain reliable figures.

Preparation of a publication depicting the data from Volume V (see section I.1.*a*) in a graphic format was initiated in 1988. This form of presentation allows easier appreciation of the range and patterns of incidence internationally, and highlights the interesting variations for the different cancer sites. Histograms of the world standardized rates illustrate the range in incidence for 40 geographically representative populations by cancer site and by sex, with the addition of bars showing the highest and lowest rates for each site among all the populations included in Volume V (see Fig. 1). Pie charts show the proportions of the top ten cancer sites within each of the 137 populations (see Fig. 2), and a series of graphs for 24 populations show the different patterns of incidence by age for 47 cancer sites.

Patterns of Cancer in Five Continents will be published in early 1990.

(c) Global burden of cancer (Dr D.M. Parkin and Dr C.S. Muir; in collaboration with Dr E. Läärä, University of Oulu, Finland)

Information from Volume V of *Cancer Incidence in Five Continents* and from various other sources was used to produce estimates of the numbers of new cases of cancer at 16 different sites,

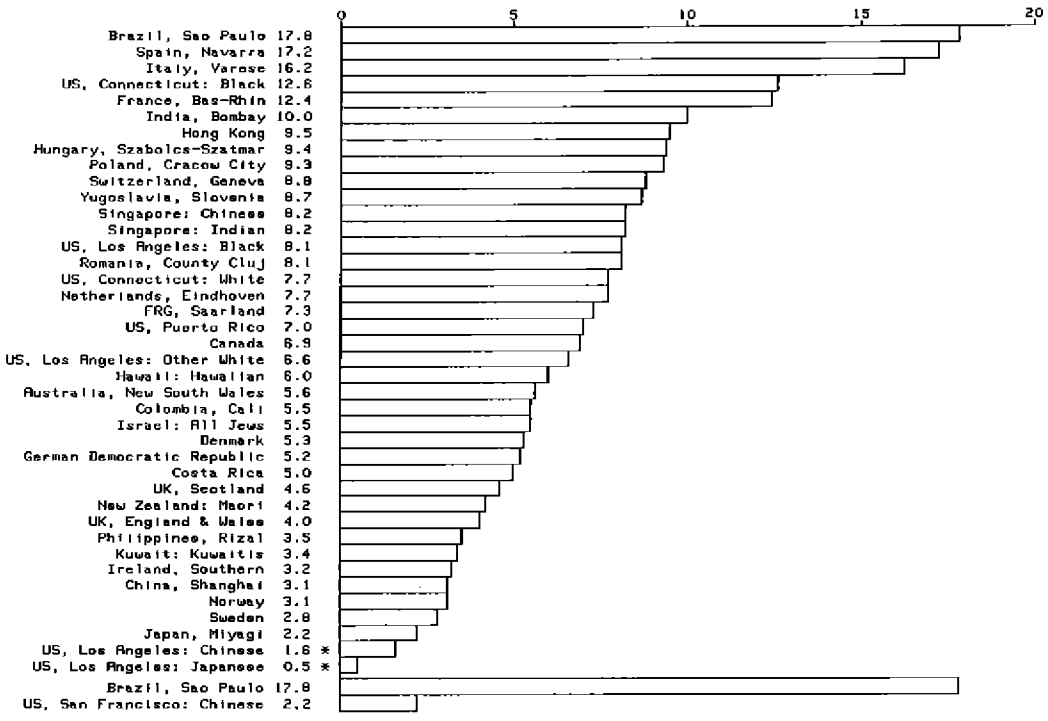


Fig. 1. World age-standardized rates for cancer of the larynx among males

Rates based on less than 10 cases

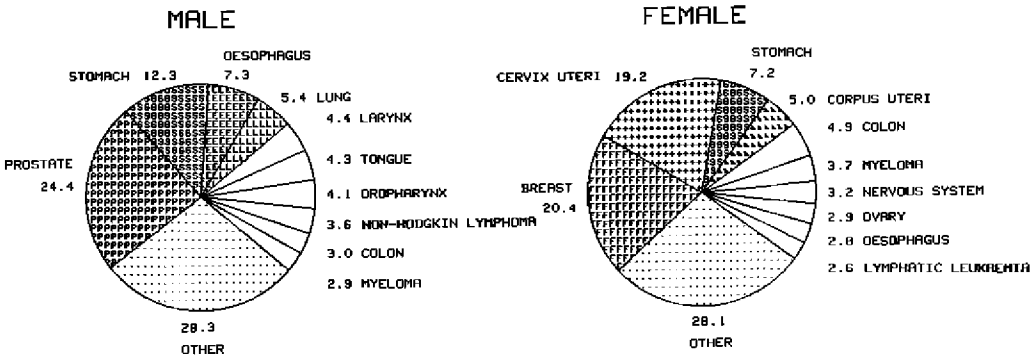


Fig. 2. Relative proportions of the 10 top ranking cancer sites in Martinique

for 24 areas of the world[1]. In 1980, there were estimated to be 6.35 million new cancer cases, fairly evenly shared between the developed and developing countries, although the distribution by site is very different (see Fig. 3). Although stomach cancer remained numerically the most important cancer in 1980, it is probable that, with the declining incidence rates of this cancer, and the rise in those for cancer of the lung, the latter will have become the most common cancer in the world by the end of 1981.

It is proposed to use data on recent changes in morbidity and mortality for some common tumours to predict the likely changes in occurrence up to the year 2000 and beyond. This will use the results from the study of time trends in incidence and mortality (see section I.1.*f*). Most of these data are from the developed countries of the world. For developing countries, projections of the future cancer burden require the use of assumptions concerning the probable shape of age–incidence curves for different cancers, population projections by age and sex, and such information as exists about current cross-sectional trends in incidence and mortality.

(*d*) Person-years of life lost due to cancer (Dr M. Khlat, Dr D.M. Parkin and Mr A. Bieber)

'Years of life lost' now constitute a widely used indicator of the public health impact of disease, since this measure weights deaths occurring at younger ages more heavily than those occurring in older populations.

An analysis has been carried out with mortality data from 34 countries and (whenever possible) three time periods—around 1960, 1970 and 1980. Both crude and age-standardized death rates and years of life lost for major causes of death and for major cancer sites have been calculated. The two mortality indicators are compared, and the contribution of cancer, and of individual cancers, to person-years of life lost (PYLL) in different countries, as well as the changes over time, are demonstrated. The results will be published in 1990.

In Table 1 cancer is compared with five other broad categories of cause of death—infectious and parasitic diseases, cerebrovascular disorders, circulatory and respiratory diseases, and injuries and poisoning—in terms of numbers of deaths and of person-years of life lost under the age of 70, for nine countries in different areas of the world. In general, cancer is less important as a cause of death in men under the age of 70 than in women; in women, it is the leading cause of death in eight of these nine countries. For men, circulatory diseases are usually the leading cause of death.

[1] Parkin, D.M., Läärä, E. & Muir, C.S. (1988) *Int. J. Cancer, 41*, 184–197

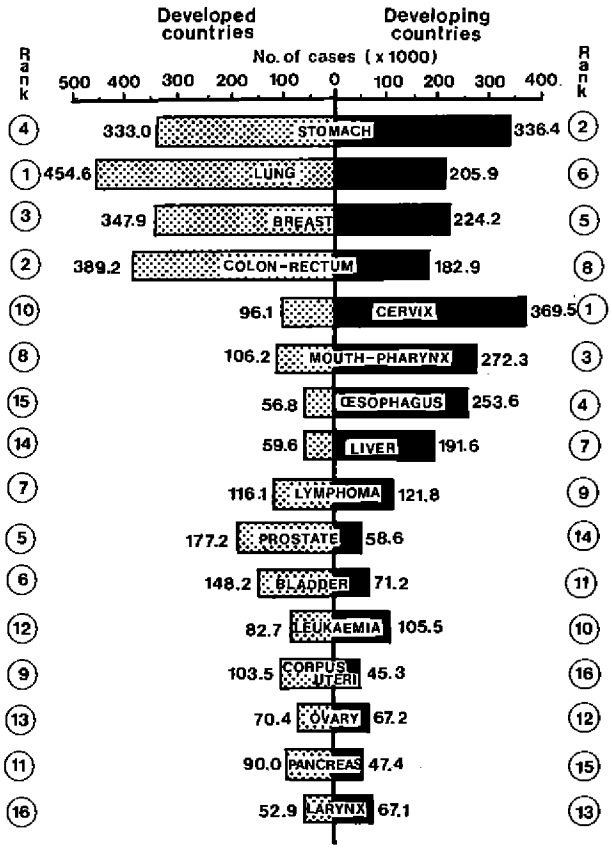


Fig. 3. Numbers of new cancer cases, and their ranking, in the developed and developing areas of the world (both sexes combined)

Cancer assumes less importance when examined as a cause of PYLL. The percentage contribution which cancer makes to the total falls in all countries and in people of each sex, and diseases affecting younger persons (infectious diseases, injury and poisoning) assume greater importance.

Comparisons of the three time periods show that the percentage of deaths and of PYLL due to cancer is increasing and this rise is independent of the ageing of the population over the 20-year period.

(e) Cancer in developing countries

In 1988/89, several special studies have been completed which analyse data from cancer registries of special interest.

(i) *Costa Rica* (Dr D.M. Parkin; in collaboration with Dr R. Sierra and Dr G. Muñoz Leiva, University of Costa Rica)

Table 1. Numbers of deaths and person-years of life lost in persons under age 70 for six major groups of causes; figures are % of total

	Cancer	Infectious/ Parasitic diseases	Cardio-vascular disorders	Circulatory diseases	Respiratory diseases	Injury/ poisoning	Other/ unknown
Males	DEATHS						
Australia	**24**	1	6	**35**	5	16	13
Chile	13	7	5	10	8	**23**	**34**
Hong Kong	**31**	**4**	10	13	13	12	17
Hungary	21	2	10	**29**	6	16	16
Japan	**29**	2	15	15	4	17	18
Kuwait	8	9	3	**21**	8	22	29
Spain	**24**	3	8	22	8	13	22
Sweden	23	1	5	**40**	**4**	15	12
USA	22	1	**4**	**34**	5	19	15
Females							
Australia	**32**	1	9	25	5	11	17
Chile	**20**	6	7	11	8	9	39
Hong Kong	**30**	3	12	14	10	**10**	21
Hungary	**27**	1	13	26	4	9	20
Japan	**35**	2	16	**14**	4	**10**	19
Kuwait	10	**14**	3	**14**	10	11	38
Spain	**29**	3	11	20	6	7	24
Sweden	**40**	1	7	22	4	10	16
USA	**32**	1	6	26	5	11	19
Males	PERSON-YEARS OF LIFE LOST						
Australia	16	1	3	20	4	**32**	24
Chile	7	9	2	5	10	**28**	39
Hong Kong	**23**	4	5	7	11	21	29
Hungary	15	1	6	20	6	**24**	28
Japan	21	2	10	11	4	**28**	24
Kuwait	5	13	2	11	10	**22**	37
Spain	16	5	4	14	7	**21**	33
Sweden	17	1	4	**24**	3	**29**	22
USA	13	1	2	19	4	**35**	27
Females							
Australia	**24**	1	5	12	**4**	20	34
Chile	10	10	3	5	12	**13**	**47**
Hong Kong	**21**	**4**	6	8	10	16	35
Hungary	**21**	1	7	15	5	13	38
Japan	**28**	2	9	9	5	17	30
Kuwait	5	**19**	1	8	13	11	43
Spain	**21**	6	5	11	7	11	39
Sweden	**33**	2	5	11	4	19	26
USA	**22**	2	**4**	14	4	20	34

Data relate to 1980 deaths. Bold type indicates the leading cause in each country

A monograph[2] and subsequent summary paper[3] have been published which analyse in detail the results from the national cancer registry for the years 1979–83, together with mortality data for 1973–82. Temporal changes in mortality and geographic variation in incidence were reviewed. The strikingly high incidence of gastric cancer, notably in the centre of the country, has stimulated studies of etiological factors (see section I.3.*d*.iv).

(ii) *Mali* (Dr D.M. Parkin; in collaboration with Professor S. Bayo, National Institute of Public Health, Bamako)

The results from the first two years of the cancer registry in Bamako, Mali, were published as an offset publication[4]. Improvements in methodology mean that there was a marked increase in coverage during the period; and results from 1988 suggest that this increase has continued. There is a very high incidence of liver cancer, and high rates also for cancers of the stomach and cervix.

(iii) *The Philippines* (Dr D.M. Parkin; in collaboration with Dr A.V. Laudico, University of the Philippines, Manila; and Dr D. Esteban, Rizal Medical Center, Manila)

The results from two cancer registries serving the city of Manila and the surrounding Rizal province (total population 6.3 million) were brought together and analysed for a three-year period (1980–82). The full results have been published as a monograph[5]. Notable findings include relatively high rates of lung cancer in males, and of breast cancer (the highest in Asia, other than Israel) and thyroid cancer in females.

(*f*) Time trends in cancer (Dr M.P. Coleman, Mr P. Damiecki, Miss H. Renard and Dr J. Estève; in collaboration with Professor E. Schifflers, University of Namur, Belgium)

Time trends in cancer incidence and mortality are being examined for 28 major cancers, using data covering a 25-year period from over 30 cancer registries and countries around the world. Incidence data are derived from the five volumes so far published of *Cancer Incidence in Five Continents*, and mortality data from the WHO mortality data banks. In order to avoid introducing artefacts in the analysis from the use of irregular population denominators, new statistical methods have been developed for the application of age, period and cohort models to the incidence data, and the development of statistical and graphical software has been completed. Analysis of data for malignant melanoma has begun, and will be followed shortly by examination of trends in cervical cancer and lung cancer.

The main analyses will be completed during 1989. Results will be presented in a monograph both graphically and in tables, in the form of trends by period of incidence or death, and by period of birth, showing data from each global region, separately, with results by sex and broad age-group.

(*g*) 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.

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[2] Sierra, R., Parkin, D.M., Barrantes, R., Bieber, C.A., Muñoz Leiva, G. & Muñoz Calero, N. (1988) *Cancer in Costa Rica* (IARC Technical Report No. 1), Lyon, International Agency for Research on Cancer

[3] Sierra, R., Parkin, D.M. & Muñoz Leiva, G. (1989) *Cancer Res.*, *49*, 717–724

[4] Bayo, S. & Parkin, D.M. (1988) *Le Cancer au Mali 1986–1987*, Lyon, International Agency for Research on Cancer

[5] 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

In such studies the risk of cancer in migrant populations 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 new 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 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.

(i) *Cancer incidence in Jewish migrants to Israel* (Dr D.M. Parkin, Mr A. Bieber, Dr M. Khlat and Dr J. Kaldor; in collaboration with Dr R. Steinitz and Dr L. Katz, Israel Center for Registration of Cancer and Allied Diseases, Jerusalem; and Dr J. Young, National Cancer Institute, Bethesda, MD, USA)

This study brings together data from the Israel Cancer Registry for a period of 21 years (1961–81). With 120 000 cases for analysis, it represents the largest study of cancer incidence in migrants ever published[6]. The incidence of different cancers is compared between Jews born in Israel, migrants from different countries, and with populations remaining in the countries of origin. Some of the methodological aspects of the analysis will be published separately[7], namely the log–linear modelling used to examine the importance of changes in risk due to duration of residence in Israel (or age at the time of migration) in the face of underlying temporal trends in incidence. The results in Table 2 indicate that, for malignant melanoma, there has been an increase in incidence with time for persons born in Europe and Africa (particularly between the first period, 1961–66, and later years). In addition, risks increase with longer duration of residence in Israel for European and Asian migrants, but there is no change in the low risk of Jews born in Africa.

Table 2. Relative risk of malignant melanoma (adjusted for age and sex) in Jewish migrants to Israel

Birthplace	Period of diagnosis (adjusted for duration of stay)			
	1961–66	1967–71	1972–76	1977–81
Israel	1.0	1.15	1.40	1.25
Asia	1.0	0.95	1.56	0.85
Africa	1.0	1.95	2.76	2.46
Europe	1.0	1.54	1.87	1.71

	Duration of stay in Israel—years (relative to born in Israel; adjusted for period of diagnosis)			
	0–9	10–19	20–29	30+
Asia	0.13	0.11	0.21	0.27
Africa	0.14	0.06	0.06	0.19
Europe	0.32	0.36	0.39	0.60

[6] Steinitz, R., Parkin, D.M., Young, J.L., Bieber, C.A. & Katz, L. (1989) *Cancer Incidence in Jewish Migrants to Israel, 1961–1981* (IARC Scientific Publications No. 98), Lyon, International Agency for Research on Cancer

[7] Kaldor, J., Khlat, M. & Parkin, D.M. (1989) *Int. J. Epidemiol.* (in press)

(ii) *Cancer incidence in second-generation migrants in Israel* (Dr D.M. Parkin and Dr M. Khlat; in collaboration with Dr L. Katz and Dr J. Iscovich, Israel Center for Registration of Cancer and Allied Diseases, Jerusalem)

The study of cancer in migrants to Israel is to be 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 (born in country of origin) and second generation (born in host country) migrants. Parental birthplace has been recorded in the population register of Israel since 1948. All cancer registrations for the years 1961–86, in individuals born in Israel and aged 0–29, are being matched with the population register in order to record parental birthplace. The study will concentrate upon those cancers with substantial incidence rates in young age groups and for which there are clear differences in incidence by country of birth (e.g., nasopharynx cancer, Ewing's sarcoma, lymphoma, lymphatic leukaemia).

(iii) *Mortality from cancer in migrants to Australia* (Dr. D.M. Parkin, Dr J. Kaldor and Dr M. Khlat)

Mortality records in Australia 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. Since mortality records are now available for a long period of time (1964–85), it will be possible to greatly extend earlier analyses[8] of cancer risk in different migrant populations in relation to their duration of stay in (or age at migration to) Australia. Analysis has begun in 1989.

(iv) *Cancer in Italian migrant populations* (Dr D.M. Parkin, Dr J. Kaldor and Dr M. Khlat; in collaboration with Dr E. Buiatti and Dr M. Geddes, Tuscany Cancer Registry, Florence, Italy)

This study examines incidence and/or mortality rates from cancer in populations born in Italy but resident in other countries. The objective of the study 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 remaining in Italy. Whenever data are available on time of migration, the effect of duration of residence in the host country will be studied. Incidence data will be included from the USA (Connecticut, New York, San Francisco), Australia (New South Wales), England and Wales, and Switzerland (Geneva). Mortality data are available for Australia, Canada, Brazil (São Paulo), Uruguay, Argentina, France and Great Britain.

Data analysis was started in 1989, and a meeting of collaborators to present and compare results will be held in February 1990.

(v) *Cancer in European migrants to South America* (Dr D.M. Parkin, Dr J. Kaldor and Dr M. Khlat; in collaboration with Dr E. Matos, University of Buenos Aires, Argentina; Dr A.P. Mirra, São Paulo Cancer Registry, Brazil; Dr H. Pracilio, National University of La Plata, Argentina; and Dr E. de Stefani, Oncology Institute, Montevideo, Uruguay)

Country of birth is recorded on death certificates in several South American countries, and in some, the mortality rates for cancer are sufficiently reliable to allow calculation by place of birth.

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[8] Armstrong, B.K., Woodings, T.L., Stenhouse, N.S. & McCall, M.G. (1983) *Mortality from Cancer in Migrants to Australia—1962 to 1971*, Nedlands, University of Western Australia

Data from three countries are available: Argentina (national data, and Buenos Aires province), Brazil (São Paulo) and Uruguay. The most important migrant populations are of European origin (Spain, Portugal, Italy). Mortality from cancer can be compared with that in the locally born, and in the country of origin. Data analysis will be completed in 1989 and the results published in 1990.

(*h*) Childhood cancers

(i) *International incidence of childhood cancer* (Dr D.M. Parkin and Mr A. Bieber; in collaboration with Dr G. Draper and Mr C. Stiller, Childhood Cancer Research Group, University of Oxford, UK; Professor B. Terracini, University of Turin, Italy; and Dr J. Young, National Cancer Institute, Bethesda, MD, USA)

This large collaborative project was completed in 1987, and the results were published in 1988[9,10]. The data assembled comprise information on the incidence of cancer in childhood from cancer registries in more than 50 countries, and cover for the most part the decade 1970–79, although several centres provided more recent data. For most of these centres, incidence rates (per million children) could be calculated, although for 17 centres (mainly in Africa and Asia) the absence of a defined population at risk means that only relative frequency of the different tumour types could be calculated. Tumours are classified into 12 major groups and 40 subgroups, primarily according to their histology, based upon a modification of the scheme of the Manchester Children's Tumour Registry, UK[11].

In addition to the detailed data for each centre, the monograph includes a commentary on the results, and references to previously published work. Summary tables compare the age-standardized rates for all the principal childhood cancers between the different participating centres.

As an example of the range of incidence rates recorded, Figure 4 illustrates the age-standardized rates for malignant kidney tumours for 22 of the participating registries. The majority of such cases were nephroblastomas (Wilms' tumour); there is a difference of a factor of at least three between the incidence rates observed in some black populations and those in certain eastern Asian registries. The old hypothesis that Wilms' tumour can be regarded as an 'index tumour' of childhood[12]—that is, as having a relatively constant incidence throughout the world—is clearly not valid.

(ii) *Selected childhood cancers* (Dr. D.M. Parkin and Mrs J. Nectoux; in collaboration with Dr G. Draper and Mr C. Stiller, Childhood Cancer Research Group, University of Oxford; UK; Dr J.W. Coebergh, Erasmus University, Rotterdam, the Netherlands; and Dr J.M. Birch, Christie Hospital and Holt Radium Institute, Manchester, UK)

The large data set collected for the study of international incidence of childhood cancer is being used to produce more detailed analyses of geographic and ethnic differences for particular cancers. A study of childhood lymphomas has been completed, and work on childhood leukaemias and bone tumours is in progress.

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[9] Parkin, D.M., Stiller, C.A., Draper, G.J., Bieber, C.A., Terracini, B. & Young, J.L., eds (1988) *International Incidence of Childhood Cancer* (IARC Scientific Publications No. 87), Lyon, International Agency for Research on Cancer

[10] Parkin, D.M., Stiller, C.A., Draper, G.J. & Bieber, C.A. (1988) *Int. J. Cancer, 42,* 511–520

[11] Birch, J.M. & Marsden, H.B. (1987) *Int. J. Cancer, 40,* 620–624

[12] Innis, M.D. (1972) *Med. J. Austral., 1,* 18–20

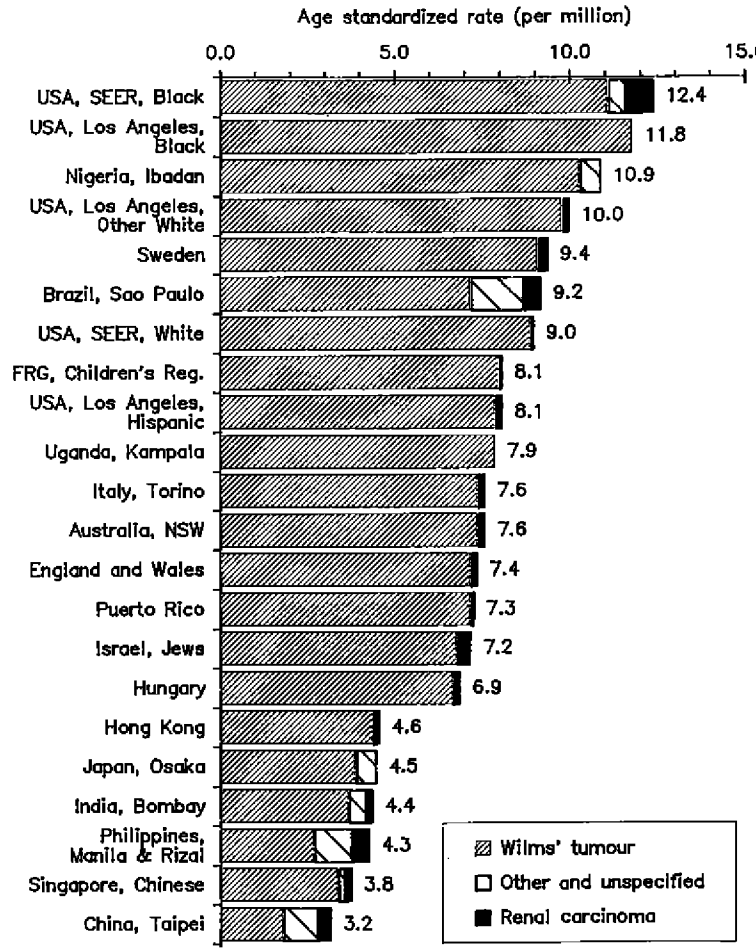

Fig. 4. Age-standardized incidence rates (per 10^6) of malignant kidney tumours in childhood, age 0–14 years (both sexes)

(i) **Long-term autopsy study on cancer mortality in Trieste** (Dr. E. Riboli, Dr A.J. Sasco and Dr R. Saracci; in collaboration with Dr G. Stanta, Dr M. Delendi and Professor L. Giarelli, Institute of Morbid Anatomy, University of Trieste, Italy)

Since the end of the 1960s, the Institute of Morbid Anatomy, under the direction of Professor L. Giarelli, has steadily increased the number of autopsies performed on patients who died in local hospitals. The proportion of all deaths coming to autopsy rose from 30% in early 1970 to 50% in 1975, and 70% in recent years. For all subjects autopsied, diagnoses are available based on clinical data reported on the death certificate and the diagnosis made at autopsy.

The work jointly undertaken consists in the retrieval and the analysis of all data concerning deaths where there was a diagnosis of cancer either at the clinical level or at autopsy, or both

The data are being analysed, focusing on the rate of concordance and on the type of error in cases of disagreement between the two diagnoses. Preliminary reports on specific findings regarding early gastric cancer and breast cancer have been published.

The prevalence at necropsy of invasive gastric cancer was 22 per 1000 in men and 16.7 per 1000 in women aged 30 and over. The prevalence of early gastric cancer was ten times lower than the prevalence of invasive cancer.

The prevalence of breast cancer at necropsy was 118 per 1000 women aged 35 and over, subdivided into previously known breast cancer (87 per 1000) or incidental necropsy findings of breast cancer that had been missed completely (14 per 1000) or misdiagnosed as breast lump (17 per 1000).

The overall prevalence of unsuspected colon cancer at necropsy was 8.46 per 1000 among men aged 40 and over, and 10.74 among women.

An extensive analysis of the data on over 30 000 autopsies is now in progress, focusing on false positive and false negative clinical diagnoses of cancers, on time trends of 'autopsy-corrected' cancer mortality and on the effect of the implementation of new diagnostic techniques on the rates of error.

A comparison of clinical (as reported on death certificates) and of autopsy diagnoses indicates that for some cancer sites (e.g. cancers of the breast and larynx), most if not all cases in which the cancer was the main cause of death were correctly diagnosed during life. On the other hand, for several cancer sites (e.g. cancers of the liver, gallbladder and pancreas), the proportion of misdiagnosed cases is quite high. A preliminary report was published on specific findings regarding latent tumours of the colon and rectum first discovered at autopsy[13]. More extensive results were presented at a symposium on the role of autopsy in epidemiology, medical research and clinical practice held in Trieste in June 1989. The symposium was jointly organized by IARC and the Institute of Morbid Anatomy of the University of Trieste.

2. DETERMINATION OF ENVIRONMENTAL AND OCCUPATIONAL HAZARDS

(*a*) Carcinogenic risk of inhalable particles (Dr L. Simonato, Dr R. Saracci, Ms R. Winkelmann and Mr G. Ferro)

(i) *Mesothelioma in Central Turkey* (in collaboration with Dr Y.I. Baris, Hacettepe University, Ankara; Dr P. Sébastien, Research Centre of Charbonnages de France, Verneuil-en-Halatte, France)

The results of further analysis of the dose–response relationship between exposure to erionite fibres and the pattern of mesothelial and bronchial cancer in the villages affected were presented at a meeting in Lyon in September 1987. The elevated mortality from pleural mesothelioma and lung cancer among residents of the villages of Karain and Sarihidir is highly correlated with cumulative fibre dose, as shown in Table 3. The regression equations are:

For pleural mesothelioma: $\text{rate}/10^5 = -245.3 + 1241$ fibres year/ml

For both sites combined: $\text{rate}/10^5 = 38.6 + 3029$ fibres year/ml

In addition to these etiological investigations, an intervention and surveillance programme concerning the population exposed is now under study.

[13] Delendi, M., Gardiman, D., Riboli, E. & Sasco, A.J. (1989) *Lancet* (in press)

Table 3. Age-specific mortality rates per 100 000 person-years for pleural mesothelioma and lung cancer in Karain and Sarihidir by cumulative exposure for both sexes combined[a]

Cumulative exposure (fibres, year/ml)	Mortality from pleural mesothelioma		Mortality from lung cancer		Mortality from both	
	Rate	Number	Rate	Number	Rate	Number
≤0.2	336	1	336	1	671	2
≤0.3	773	6	0	0	773	6
≤0.4	905	6	151	1	1056	7
>0.4	705	4	881	5	1587	9
Total	738	17	304	7	1041	24

[a] It is assumed that first exposure occurred at birth

(ii) *Silica exposure and lung cancer* (in collaboration with Dr W.H. Mehnert, Dr W. Staneczek and Dr M. Mohner, National Cancer Registry of the Central Institute for Cancer Research, East Berlin; Dr G. Konetzke and Dr B. Beck, Central Institute for Occupational Medicine of the GDR; Dr W. Muller and Dr W. Ahlendorf, Occupational Health Inspectorate, Gera, German DR)

The results of the cohort study on pottery workers in the UK and the mortality analysis of a study on slate quarry workers in the GDR have been completed, and will be included in a forthcoming IARC Scientific Publication together with previous contributions of other members of the working group on silica exposure and lung cancer. A noteworthy feature of this international endeavour is that it has allowed the assembly, as shown in Table 4, of a number of studies on workers exposed to silica in industries with little or no contamination from other known lung carcinogens.

(iii) *Cancer mortality among gold miners* (in collaboration with Dr B. Javelaud, Société des Mines et Produits Chimiques de Salsigne, Salsigne, France; Dr J.J. Moulin, National Institute of Research and Safety, Vandoeuvre-lès-Nancy, France)

A cohort of approximately 2000 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. Collection of mortality data has been completed and the analysis will be done by the end of 1989.

(*b*) Carcinogenic risk of occupational exposures

(i) *Exposure to vinyl chloride monomer* (Dr L. Simonato, Dr R. Saracci, Dr K.A. L'Abbé, Mr G. Ferro and Ms R. Winkelmann; in collaboration with Dr A. Andersen, Cancer Registry of Norway, Oslo; Dr S. Belli and Dr R. Pirastù, National Health Institute, Rome; Dr G. Engholm, Bygghälsan, Danderyd, Sweden; Dr L. Hagmar, University Hospital, Lund, Sweden; Dr I. Lundberg, Karolinska Hospital, Stockholm; Professor S. Langard, Telemark Central Hospital, Porsgrunn, Norway; Dr N. Tenkhoff, Leitender Werksarzt der Hüls AG, Marl, FR Germany; Dr P. Thomas, Employment Medical Advisory Service, Bootle, UK)

This pooling of the European studies of vinyl chloride workers is in the final stages of completion. Collaborators from France, Spain and the Federal Republic of Germany had

Table 4. Studies on workers exposed to silica in industries little or not contaminated by known lung carcinogens

Study population	Overall relative risk	Time since first exposure	Duration of exposure	Estimated dose
Granite workers				
(Koskela *et al.*)	1.56*	+	n.a.	n.a.
Slate quarry workers				
(Mehnert, 1989)	1.1	+	+	−
	1.8 silicotics	+		
	0.9 non-silicotics	+		
Ceramic workers				
(Lagorio *et al.*)	2.0*	n.a.	±	n.a.
	3.9* silicotics			
	1.4 non-silicotics			
Pottery workers				
(Thomas *et al.*)	1.2*			
	1.8* sanitary ware	−	−	+
Pottery workers				
(Winter *et al.*)	1.3*	n.a.	n.a.	±

*, statistically significant at 0.05 level

+, positive association; −, negative association

±, doubtful association; n.a., not available

Source: Simonato, L. & Saracci, R. (1989) In: Simonato, L., Fletcher, A.C., Saracci, R. & Thomas, T., eds, *Occupational Exposure to Silica and Cancer Risk* (IARC Scientific Publications No. 97), Lyon, International Agency for Research on Cancer (in press)

eventually to withdraw their participation due to organizational difficulties. The remaining study population, totalling about 14 000, will be analysed in late 1989. Past exposure levels have been estimated approximately and the results are being used for exposure–response investigations.

(ii) *Exposure to styrene* (Dr L. Simonato, Dr R. Saracci, Dr M. Kogevinas and Ms R. Winkelmann; in collaboration with Dr A. Andersen, Cancer Registry of Norway, Oslo; Dr A. Astrup-Jensen, Danish Institute of Technology, Taastrup, Denmark; Dr M. Biocca, Institute of Public Health, Rome; Dr R. Frentzel-Beyme, Institute for Epidemiology and Biometry, Heidelberg, FR Germany; Dr K. Kurppa, Institute of Occupational Health, Helsinki; Dr I. Lundberg, Karolinska Hospital, Stockholm; Dr E. Lynge, Danish Cancer Registry, Copenhagen; Dr B. Pannett, MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton, UK; Dr P. Thomas, Employment Medical Advisory Service, Bootle, UK)

A collaborative working group of researchers from seven European countries has been formed in order to collect and evaluate data on exposure to styrene, mainly in the glass-reinforced plastics industry. The total population suitable for the epidemiological study is approximately 20 000 workers. The feasibility study has been completed and during the second meeting of the research group (30–31 March 1989, Lyon), available exposure data were

evaluated and the study design discussed. All the cohorts will be followed for mortality while incidence information will be available only for some countries. Data collection is expected to be complete by the end of 1990.

(iii) *Carcinogenic risk among welders* (Dr L. Simonato, Ms R. Winkelmann, Mr G. Ferro and Dr R. Saracci; in collaboration with WHO EURO; the Commission of the European Communities; Dr A. Andersen, Cancer Registry of Norway, Oslo; Dr K. Anderson and Dr J. Peto, Institute of Cancer Research, Sutton, UK; Dr N. Becker and Dr. J. Claude, Institute for Epidemiology and Biometry, Heidelberg, FR Germany; Dr A.C. Fletcher and Dr C. Gray, University of Birmingham, UK; Dr M. Gérin, Montréal, Canada; Dr K. Kurppa, Institute of Occupational Health, Helsinki; Dr S. Langard, Telemark Central Hospital, Porsgrunn, Norway; Dr F. Merlo, National Institute for Research on Cancer, Genoa, Italy; Dr J.-J. Moulin and Mr P. Wild, National Institute of Research and Safety, Vandoeuvre-lès-Nancy, France; Dr M.L. Newhouse, London School of Hygiene and Tropical Medicine, London; Dr B. Sjögren, National Board of Occupational Safety and Health, Solna, Sweden; Dr K. Stagis-Hansen, Odense University Hospital, Odense, Denmark)

IARC has coordinated a multicentric cohort study, updating and aggregating the information on mortality and cancer incidence among welders. The population under study included 11 092 workers employed as welders in 135 companies located in eight European countries, and during the follow-up period 1093 deaths were observed. Mortality for the total cohort from all causes was low (SMR = 93). Increased mortality for all neoplasms was observed (obs. = 303, SMR = 113, 95% CI: 100–126) mainly due to the increased risk for lung cancer (obs. = 116, SMR = 134, 95% CI: 110–160). Considering the different characteristics of the working environment, four subgroups were identified: shipyard welders, mild steel welders, ever stainless steel welders (those who had at any time worked with stainless steel), and predominantly stainless steel welders. Lung cancer mortality was high in all subgroups (Table 5) and in the latter three, mortality increased with time since first exposure. No association was found with any other exposure parameter and analyses by cumulative dose of exposure to total fumes, total chromium, chromium[VI] and nickel failed to demonstrate an effect of these exposures on lung cancer mortality.

Table 5. Lung cancer mortality among welders by years since first exposure. Data are presented as standardized mortality ratios (SMR), with 95% confidence intervals in parentheses.

Subgroup	Years since first exposure				Total
	0–9	10–19	20–29	30+	
Shipyard welders	508 (165–1185)	141 (52–306)	161 (94–257)	63 (27–123)	126 (88–174)
Mild steel welders	135 (37–345)	162 (81–290)	186 (93–333)	207 (113–348)	178 (127–243)
Ever stainless steel welders	104 (34–243)	107 (55–186)	132 (70–226)	194 (89–369)	128 (91–175)
Predominantly stainless steel welders	64 (8–232)	88 (29–206)	126 (51–260)	312 (115–679)	123 (75–190)

(iv) *International Registry of Persons Exposed to Phenoxy Acid Herbicides and Contaminants* (Dr R. Saracci, Dr M. Kogevinas, Dr K.A. L'Abbé and Ms R. Winkelmann; in collaboration with NIEHS; Dr H. Becher, German Cancer Registry, Heidelberg, FR Germany; Dr P. Bertazzi, Clinica del Lavoro Luigi Devoto, University of Milan, Italy; Dr H. B. Bueno de Mesquita, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands; Dr D. Coggon, MRC Environmental Epidemiology Unit, Southampton, UK; Dr M. Fingerhut, National Institute for Occupational Safety and Health, Cincinnati, OH, USA; Ms L.M. Green, Ontario Hydro, Toronto, Canada; Dr T. Kauppinen, Institute of Occupational Health, Helsinki; Dr M. Littorin, University of Lund, Sweden; Dr E. Lynge, Danish Cancer Registry, Copenhagen; Dr J. D. Mathews, Menzies School of Health Research, Casuarina, Australia; Dr M. Neuberger, Institute of Environmental Hygiene, Vienna; Dr N. Pearce, Wellington School of Medicine, Wellington, New Zealand; Mr P. Thomas, Health and Safety Executive, Bootle, UK)

The overall objective of the project is to establish and maintain an international register, through joint IARC/NIEHS collaboration, of persons exposed to phenoxy acid herbicides and contaminants, principally chlorinated dibenzo-*p*-dioxins. This register serves as a basis for follow-up of possible long-term health effects, including cancers. Attention is being focused on occupational exposure and categories of subjects included are past and present workers in factories which have synthesized 2,4-D and 2,4,5-T and related herbicides, as well as users of these herbicides (e.g., sprayers in railroad work, agriculture and forestry). A total of 10 countries are currently participating in the project. A common protocol for acquisition of exposure and follow-up data is in use, and a preliminary analysis is being carried out. The registry was established in 1984 and now contains about 19 000 individuals.

(v) *International study of cancer risk in biology research laboratory workers* (Dr A.J. Sasco, Dr C.S. Muir and Dr R. Saracci)

The occurrence of a cluster of rare cancers at the Pasteur Institute in Paris led in May 1986 to the setting up of a Commission of Enquiry under the chairmanship of Professor Jean Bernard; the International Agency for Research on Cancer was invited to participate in the work of the Commission. Almost immediately, it became obvious that any relationship between laboratory work and specific cancers would be hard to establish with certainty, and impossible to refute, if only one research centre were studied. The IARC was therefore asked to explore the possibility of conducting an international collaborative study in a number of research centres around the world.

A preliminary meeting was held at the Agency in February 1987 to discuss the desirability of such a study. In preparation, a review of the literature[14] on health risks linked to work in laboratories showed the paucity of studies on cancer risk for populations of research workers with the exception of chemists, who have an increased risk of leukaemia and lymphoma. A three-step approach has been agreed upon:

—retrospective cohort study (to be started in 1990)
—prospective cohort study, with periodic reassessment of exposure and outcome (to be started in 1991 and pursued until 2016)
—case–control studies nested within the cohort

The proposed study is designed to assess whether there is indeed excess cancer mortality

[14] Sasco, A.J. (1989) *Médecine/Sciences* (in press)

and/or incidence among biology research workers, either overall or on a site-specific basis, with special attention being paid to histology and age at cancer occurrence. There is particular interest in new aspects of biological science such as molecular biology and recombinant genetics. This emphasis does not exclude consideration of other agents (chemical carcinogens, mutagens, radiation) also present in the laboratory setting, whose effects on human health (under the conditions of laboratory work) have not been fully evaluated.

Following funding from the 'Europe Against Cancer' programme of the EEC, a feasibility study has been in progress since September 1988. Its goals are:

(1) To better define past and present exposures within laboratories;

(2) To identify potential cohorts in each participating country and to find the best means of following up cohort members;

(3) To determine the best means of assessing cancer incidence and/or mortality.

A meeting was held at IARC in January 1989 to discuss the protocol of the feasibility study. It was attended by 15 external participants representing 11 countries (Australia, Canada, FR Germany, Finland, France, Ireland, Italy, Sweden, Switzerland, United Kingdom, United States of America). In addition, the Netherlands and Denmark had expressed the intention to collaborate in the study.

The results of the feasibility study will be available by the end of 1989, in time to allow the retrospective cohort study to be launched in 1990.

(*c*) Smoking and cancer

While the role of tobacco smoking in causing lung cancer is now indisputable, there remains much scope for further progress in understanding the importance of environmental tobacco smoke (passive smoking), in how to change people's smoking habits (see below and section I.7.*a*.ii), in elucidating the role of tobacco in other cancers (see sections I.3.*h*.i and I.3.*k*.i), in assessing individual susceptibilities (see section I.6) and in identifying mechanisms by which tobacco might be exerting its effects (see sections I.3.*c*.i and II.3.*h*).

(i) *Passive smoking and respiratory cancers* (Dr E. Riboli and Dr R. Saracci; in collaboration with Dr C. Gonzales, Hospital Sant Jaume i Santa Magdalena, Mataro (Barcelona), Spain; Dr G. Pershagen, National Institute of Environmental Medicine, Stockholm, Sweden; Dr N. Segnan, Department of Epidemiology, University of Turin, Italy; Dr F. Levi, Institute of Social and Preventive Medicine, Lausanne, Switzerland; Professor G.R. Howe, National Cancer Institute of Canada Epidemiology Unit, Toronto, Canada; Dr Y.T. Gao, Shanghai Cancer Institute, PR China; Professor D. Trichopoulo, Department of Hygiene and Epidemiology, University of Athens, Greece; Professor C. Vutuc, Institute of Social Medicine, University of Vienna, Austria; Dr S. Benhamou, INSERM (U 287), Gustave-Roussy Institute, Villejuif, France; Dr L. LeMarchand, Cancer Center of Hawaii, Honolulu, USA; Dr W. Ahrens, Bremen Research Institute for Preventive and Social Medicine, Bremen, FR Germany; Ms M. Blettner, Department of Community Health, University of Liverpool, UK; Dr L. Simonato, Centre of Environmental Carcinogenesis, University of Padua, Italy; Dr R. Mak, Faculty of Medicine, Ghent, Belgium; Dr S.C. Darby, Imperial Cancer Research Fund, Radcliffe Infirmary, Oxford, UK; Dr W. Zatonski, Curie-Sklodowska Institute of Oncology, Warsaw, Poland; Dr F.E. van Leeuwen, The Netherlands Cancer Institute, Amsterdam, The Netherlands; and Dr S.K. Jindal, Postgraduate Institute of Medical Education and Research, Chandigarh, India)

A methodological investigation of self-reported exposure to environmental tobacco smoke (ETS) and biological indicators of exposure was completed in 1987[15]. Results indicated that non-smokers can provide fairly accurate reports of their recent exposure to ETS. The proportion of self-reported non-smokers who were likely to have smoked in the few days preceding interview was very low (around 3%), according to the results of urinary cotinine measurements.

The study provided a valuable methodological background for the planning of a large collaborative study on lung cancer in non-smokers. Three meetings of researchers willing to collaborate in the project have taken place. A common questionnaire on exposure to ETS was adopted as well as a common basic protocol. The study will include subjects who have never smoked in all centres. In some of the centres, smokers too will be investigated.

Other potential risk factors being considered in the investigation are: occupation, intake of carotene and vitamin A, background radiation and air pollution. Table 6 summarizes some features of the studies in the centres which are involved. The study started in 1988–89 in Spain, FR Germany and Greece. Interview of cases and controls should start towards the end of 1989 in the other centres.

(ii) *Smoking and drinking habits of French adolescents* (Dr A.J. Sasco and Ms D. Pobel; in collaboration with Ms M. Jambon, Association de Lutte Etudiante contre le Cancer, Lyon, France)

A study is being carried out to evaluate the smoking habits of school children between the ages of 11 and 18. In 1985, 2600 pupils aged 11–15 in 16 representative high schools of Lyon and the surrounding area answered a detailed questionnaire describing their smoking habits, their reasons for smoking and their attitudes towards health education. Analysis of the data showed a high prevalence of smokers which increases consistently with age. The survey was repeated in early 1988 to evaluate trends in smoking habits of French adolescents. Some of these schools were then separated into two comparable groups which received a health education campaign according to a specified schedule, in order to evaluate the efficacy of the intervention. Results should be available in 1990.

In 1988–1989, another survey was conducted among older pupils aged 15–18 years in five representative *lycées* of the Lyon region, to evaluate not only smoking habits but also the consumption of alcoholic beverages and illegal drugs. Data will be analysed in late 1989.

***(d)* Second malignancies following chemotherapy** (Dr J. Kaldor and Mrs A. Arslan; in collaboration with Dr P. Band, Cancer Control Agency of British Columbia, Vancouver, BC, Canada; Dr J. Bell, Thames Cancer Registry, Sutton, UK; Ms V. Blair, Northeastern Cancer Registry, Manchester, UK; Dr R. Cartwright, Yorkshire Regional Cancer Organization, Leeds, UK; Professor N.W. Choi, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada; Dr E.A. Clarke, Ontario Cancer Treatment and Research Foundation, Toronto, Ontario, Canada; Dr J. Cuzick, Imperial Cancer Research Fund, London; Dr N.E. Day, Medical Research Council, Cambridge, UK; Dr M. Fiorentino, Padua Civic Hospital, Padua, Italy; Dr P. Fraser, London School of Hygiene and Tropical Medicine, London; Dr M. Hakama and Dr S. Karjalainen, Finnish Cancer Registry, Helsinki; Dr M. Henry-Amar, Gustave-Roussy Institute, Villejuif, France; Dr M. Koch, Cancer Registry, Edmonton, Alberta, Canada; Dr F. Langmark, Norwegian Cancer Registry, Oslo; Dr W.H. Mehnert, National Cancer

[15] Saracci, R. & Riboli, E. (1989) *Mutat. Res.*, *22*, 117–127

Table 6. Outline of studies in the IARC international project on lung cancer in non-smokers

Place	Year of start	Duration (years)	Study subjects (M = male, F = female)		Expected no. of non-smoking cases		Type of controls	Matching criteria[a]	No. of controls per case
			Smokers	Non-smokers	Per year	Total[b]			
Barcelona Spain	1989	2	F	M + F	70	140	Population, hospital	Area	2
Stockholm Sweden	1989	3	—	M + F	30	90	Population	Area	3
Turin Italy	1989	2	M + F	M + F	70	140	Population (hospital)	Area	2
Lausanne Switzerland	1989	3	—	M + F	30	90	Hospital, population	Hospital	2
Canada	1990	5	—	M + F	50	250	Population	Area	2
Shanghai China	1989	2	—	M + F	250	500	Population	Area	1
Athens Greece	1989	2	F	M + F	50	100	Hospital, hospital visitors	No matching	2
Vienna Austria	1989	2	—	F	50	100	Hospital (population)		2
Paris France	1989	2	F	M + F	40	80	Hospital	Area	2
Hawaii USA	1989	3	—	M + F	100	300	Population	Ethnic group	2
Bremen FR Germany	1988	2	M + F	M + F	40–50	80–100	Population		1
Padua Italy	1989	3	M + F	M + F	130	390	Population		2
Ghent Belgium	1988	3	M + F	M + F	30	90	Hospital, hospital visitors		2–4
Warsaw Poland	1990	3	—	M + F	45	135	Population		2
Netherlands	1990	3	—	M + F	100	300	Population	Area	2
Chandigarh India	1990	2	M + F	M + F	60	120	Hospital visitors	Religion, age, sex	2

[a] Cases and controls will be matched by age and gender in all centres except Greece.

[b] The figures for non-smokers include occasional smokers.

Registry, Berlin-Johannisthal; Dr F. Neal, Weston Park Hospital, Sheffield, UK; Dr F. Petterson, Karolinska Hospital, Stockholm; Dr R. Pfeiffer, University Clinic, Essen, FR Germany; Dr V. Pompe-Kirn, Cancer Registry of Slovenia, Ljubljana, Yugoslavia; Dr P. Prior, Birmingham Cancer Registry, Birmingham, UK; Dr C. Sebban and Dr D. Assouline, Edouard Herriot Hospital, Lyon, France; Dr M. Stovall and Dr S. Smith, University of Texas, Houston, TX, USA; Dr H.H. Storm, Danish Cancer Registry, Copenhagen; Dr F. van Leeuwen, Netherlands Cancer Institute, Amsterdam)

(i) *Case–control studies of second malignancies*

The data collection in the international collaborative case–control studies of second cancers following cytostatic chemotherapy was completed during 1988, and the statistical analyses were begun. In studies of leukaemia following ovarian cancer and Hodgkin's disease[16], over 270 cases of leukaemia and three matched controls per case were identified, and the role of the therapy for the first cancer in the etiology of the leukaemia was investigated. Both studies clearly demonstrated the role of chemotherapy, as opposed to radiotherapy, as the primary leukaemogenic agent (Table 7).

In the study of leukaemia following Hodgkin's disease, combination chemotherapy of the MOPP type (including procarbazine and nitrogen mustard but no other alkylating agents) was associated with an increase in risk of five-fold for up to six treatment cycles, and 14-fold for more than six cycles. In contrast to some earlier studies, no substantial synergy was detected between radiotherapy and chemotherapy. However, among patients treated with chemotherapy, the risk of leukaemia among those who received between 10 and 20 Gy to the active bone marrow was about three times higher than the risk for patients who received either less than 10 Gy or more than 20 Gy. Other findings from the study were the two-fold increase in leukaemia risk associated with splenectomy, and the persistence of risk increased up to eight years after the last chemotherapy.

Leukaemia following ovarian cancer was clearly associated with five different alkylating agents which had been given alone in the treatment of the ovarian tumour. Of these agents, melphalan, cyclophosphamide, treosulphan and chlorambucil had already been identified as human leukaemogens in previous studies. The fifith, thio-TEPA, had not previously been demonstrated to cause leukaemia in humans. The combination of adriamycin and cisplatin was also associated with an increase in leukaemia risk. For all five drugs identified individually as leukaemogenic, there was a clear gradient in risk between two categories of total dose defined by the median in controls (Table 8).

Table 7. Relative risk of acute or non-lymphocytic leukaemia by category of treatment for first cancer (number of cases in parentheses)

First cancer	Treatment			
	Surgery only	Radiotherapy; no chemotherapy	Chemotherapy; no radiotherapy	Radiotherapy and chemotherapy
Hodgkin's disease	—	1.0 (11)	9.0* (30)	7.7* (108)
Ovarian cancer	1.0 (6)	1.6 (15)	12.0* (41)	9.8* (39)

* $p < 0.001$ compared to reference category

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

Table 8. Relative risk[a] for leukaemogenic drugs used in treatment of ovarian cancer, by categories of total dose (numbers of cases in parentheses)

Drug	Low-dose[b] group	High-dose[b] group
Chlorambucil	14* (2)	23** (5)
Cyclophosphamide	2.2 (4)	4.1 (8)
Melphalan	12* (9)	2.3** (17)
Thio-TEPA	8.3* (4)	9.7** (5)
Treosulphan	3.6 (1)	33** (7)

[a] Compared to no chemotherapy

[b] Defined by median dose in controls

* $p < 0.05$ (2-sided)

** $p < 0.01$ (2-sided)

Statistical analyses are continuing on the case–control studies of lung cancer following Hodgkin's disease and of bladder cancer following ovarian cancer. Also in progress are further analyses of the leukaemia studies, to evaluate the predictive value of bone marrow toxicity as an indicator of subsequent leukaemia risk, and to study temporal aspects of the leukaemia risk.

(ii) *Studies of DNA damage following chemotherapy* (see also section II.3.*i*.i) (Dr J. Kaldor and Dr C. Wild; in collaboration with Dr A.M. Fichtinger-Schepman, TNO Medical Biological Laboratory, Rijswijk, The Netherlands; Dr R. Somers and Dr F.E. van Leeuwen, Netherlands Cancer Institute, Amsterdam, The Netherlands; Dr A. Hagenbeek and Dr G. Stoter, Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands; Dr D. Bron, Jules Bordet Institut, Brussels; Dr P. Carde, Gustave Roussy Institute, Villejuif, France; Dr G. ten Bokkel Huinink, Antoni Van Leeuwenhoek Hospital, Amsterdam, The Netherlands; Dr W. Jones, Cookridge Hospital, Leeds, UK; Dr S. Kaye, Gartnavel General Hospital, Glasgow, UK; Dr D. Sleijfer, Groningen, The Netherlands)

The reaction between alkylating chemotherapeutic agents and cellular DNA is probably the main pathway to both their cytotoxic and their carcinogenic effects. Recently developed biochemical and cytogenetic techniques provide means of directly evaluating DNA damage *in vivo* in peripheral lymphocytes and other tissues, and studying the relationship between DNA damage and the long-term effects of chemotherapy. Collaborative studies have been set up with the lymphoma and genitourinary groups of the European Organization for the Research on Treatment of Cancer (EORTC), to study respectively methyl adducts in Hodgkin's disease patients, and cis-platinum adducts in testicular cancer patients, and the extent to which adduct levels can predict the clinical outcome of chemotherapy.

(iii) *Genetic effects in the offspring of cancer patients* (Dr J. Kaldor; in collaboration with Dr J.J. Mulvihill, National Cancer Institute, Bethesda, MD, USA; Dr G.J. Draper, University of Oxford, UK; and Dr S.J. Durako, Westat Inc., Rockville, MD, USA)

The recent successes in treating cancers of young people through radiotherapy and chemotherapy with mutagenic agents has raised the question of possible germ cell damage and adverse effects in the offspring of survivors. Answers to this question are of primary interest for

counselling patients, but also for evaluating human susceptibility to germ cell mutagenesis. In order to adequately study this issue, large numbers of patients must be investigated and international cooperation is the only way this can be achieved. A protocol for a collaborative study has been drafted and a meeting of potential participants took place in Lyon in May 1989. As a result, the protocol is being finalized and study funding sought.

(*e*) ***N*-Nitroso compounds: exposure assessment and carcinogenicity** (Dr H. Ohshima, Dr. B. Pignatelli, Dr S. Calmels, Dr C. Malaveille, Dr M. Friesen, Dr. D. Shuker, Ms V. Prévost, Mrs I. Brouet, Miss F. El-Ghissassi, Dr C.-S. Chen, Mrs A. Hautefeuille, Mr P. Thuillier, Dr D.M. Parkin, Dr M. Khlat, Dr. N. Muñoz, Miss S. Teuchmann, Mr G. Bouvier, Ms S. Poirier and Dr H. Bartsch; in collaboration with external institutions as cited below) (supported in part by NIH grant IRO1-CA47591)

The aim of this project is to assess the role of DNA-damaging agents in the etiology of human cancers in connection with other factors such as dietary habits, life-style, bacterial flora, precancerous conditions and inflammatory status. Particular emphasis is directed towards:

(1) the development, application and evaluation of biomarkers which can be associated with exposure to carcinogens in specific organs—such markers would be exploited in subsequent epidemiological and intervention studies and be used in the development of early detection procedures in highly exposed individuals;
(2) the identification of unknown DNA-damaging agents or their precursors;
(3) an understanding of the factors that affect the extent of endogenous formation of carcinogens, particularly relating to bacterial and parasitic infection of the stomach, urinary bladder or liver.

The major effort continues to be directed towards the identification of the role of *N*-nitroso compounds (NOC) but the relevance of other etiological agents, particularly those which result in oxidative damage in this process, is also considered.

Although NOC have been shown to induce tumours in 40 animal species and in most organs of the body, proof that NOC are carcinogenic in man is lacking. Humans are exposed to these carcinogens both through ingestion or inhalation of preformed compounds and through nitrosation of amine precursors in the body, mostly in the stomach. In addition, activated macrophages can synthesize nitrite, nitrate and nitrosating agents and a number of bacterial strains that enzymatically synthesize nitrosamines from precursors at neutral pH have been isolated from human infections. Such macrophage- or bacteria-mediated nitrosation can occur at sites remote from the stomach and could lead to NOC exposure at sites of infection or inflammation.

Endogenous formation of NOC from ingested precursors has for some years been suspected of being the largest single source of exposure to these compounds for the general population. Such exposure has been associated with an increased risk of cancer of the stomach, oesophagus and bladder, but convincing epidemiological evidence is lacking. One reason has been the absence of reliable methods for estimating the extent of *in vivo* NOC formation. In addition, any nitrosation reaction occurring *in vivo* is influenced by many factors. The simple and sensitive *N*-nitrosoproline (NPRO) test developed at IARC provided the first quantitative estimation of endogenous nitrosation in humans. It is based on the fact that certain nitrosamino acids such as NPRO are excreted unchanged almost quantitatively in the urine. This NPRO test has for the first time allowed the study of the kinetics and factors affecting nitrosation *in vivo* in human subjects and in animals. In addition, immunoassay methods are now being developed to quantitate 3-alkyladenines in urine and to monitor human exposure to alkylating nitroso compounds from the environment and from cancer therapy.

In order to evaluate the possible role of NOC in human cancer at specific sites, the following

projects are being undertaken: (i) to measure endogenous nitrosation rates in healthy human subjects in order to collect data on geographic and inter-individual variation; (ii) to study dietary and host factors that affect nitrosation, in particular to elucidate the molecular mechanism by which bacteria are involved in this process; (iii) to compare NOC exposure in subjects with precancerous conditions of the stomach with subjects without such lesions; (iv) to compare NOC exposure in asymptomatic subjects from high- and low-risk areas for oesophageal and stomach cancer and subjects with different exposure to NOC precursors (e.g. tobacco users). Data on NOC exposure are then evaluated in relation to epidemiological and clinical observations.

(i) *Tenth International Meeting on N-Nitroso Compounds, Tobacco Smoke and Mycotoxins* (Dr I.K. O'Neill and Dr H. Bartsch; in collaboration with Dr J.-S. Chen and Dr S.H. Lu, Chinese Academy of Preventive Medicine and with the support of the US National Cancer Institute, the US National Institute of Environmental Health Sciences and the International Programme for Chemical Safety)

The tenth meeting of this series was arranged for July 1989 in Beijing, PR China. The programme was organized with a multi-disciplinary approach to major cancer sites associated with the title substances, with sessions focused on exposure, biological mechanisms and preventive measures and a workshop on biological monitoring procedures for assessing recent exposure. Because of domestic disturbances in the People's Republic of China, the meeting was rescheduled to be held in Lyon in autumn 1989. The proceedings will be published in the IARC Scientific Publications series.

(ii) *N-Nitroso compounds, genotoxins and their precursors in gastric juice from humans with or without precancerous lesions of the stomach* (in collaboration with Dr R. Lambert, Dr B. Moulinier and Dr J. Forichon, Edouard Herriot Hospital, Lyon, France, and Dr P. Correa, Louisiana State University Medical Center, New Orleans, LA, USA)

The relationship is being investigated between levels of total NOC, genotoxic activity (before and after nitrosation), degree of bacterial colonization in gastric juice and the degree of severity or absence of precancerous lesions of the stomach (diffuse interstitial gastritis, chronic atrophic gastritis, dysplasia).

Total NOC in gastric juice were determined by a group-selective method using chemical denitrosation and a thermal energy analyser[17]. Mean levels were similar in the different groups of patients, but higher in acidic juide than in that with pH > 4.5; the latter samples lacked abundant gastric flora. Acid-catalysed nitrosation of gastric juice *in vitro* increased the concentration of total NOC by a factor of up to several thousand, with a maximum value of 1330 µmol/l. The difference in levels of nitrosatable precursors in gastric juice may be pH-related.

The genotoxicity of gastric juice, measured in a modified SOS chromotest[18], was detectable for only 20% of the samples tested, and this was not related to their pH. After acid-catalysed nitrosation, all samples showed genotoxic activity, with mean SOS-inducing potency (SOSIP) increased 4- to 7-fold compared with untreated samples. No association was seen between mean SOSIP and the severity of precancerous lesions. Mean SOSIP of neutral or basic gastric juices

[17] Pignatelli, B., Richard, I., Bourgade, M.-C. & Bartsch, H. (1987) *Analyst, 112,* 945–949

[18] Malaveille, C., Vineis, P., Estève, J., Ohshima, H., Brun, G., Hautefeuille, A., Gallet, P., Ronco, G., Terracini, B. & Bartsch, H. (1989) *Carcinogenesis, 10,* 577–586

was slightly higher than that of acidic samples. Assuming that the genotoxic activity measured could be attributable to NOC, SOSIP expressed per nmol of NOC were compared with those of known carcinogenic NOC. For all nitrosated juices, the values were higher than that of *N*-nitroso-*N*-methylurea and for 32% of the samples, they were similar to or higher than that of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. All of these 32% were acidic samples (pH 1.5–3.5), although basic pH favours the presence of higher concentrations of both NOC and genotoxins. Such findings suggest that pH of gastric juice affects quantitatively and qualitatively the precursors of genotoxic NOC. This may explain the observed lack of correlation between level of NOC and genotoxic activity in gastric juice.

To explore the nature of nitrosatable substrates in gastric juice and factors that influence formation of their *N*-nitroso derivatives, we carried out nitrosations of acidic, neutral and basic gastric juice *in vitro*.

After 1 h nitrosation, volatile nitrosamines (VNA) were extracted with dichloromethane and analysed by gas chromatography. The aqueous phase was acidified and *N*-nitrosamino acids were extracted with 10% methanol in dichloromethane, methylated with diazomethane and analysed by GC. Other NOC were extracted from the acidic aqueous phase with ethyl acetate. The levels of total NOC present in the samples were measured in the reaction mixture, in all organic solvent extracts and in the remaining aqueous phase after organic solvent extractions[19]. About 40–50% of total NOC was not extractable in organic solvents. The detailed analysis of the results reveals a preponderance of non-volatile, unknown NOC with varying polarity formed in nitrosated gastric juice. Our results suggest that only pH determines the nature and level of NOC precursors and nitrosation-dependent genotoxins in gastric juice. Work is in progress to complete this study and to elucidate the structure of some of these substances. Gastric juice samples have now also been collected from inhabitants of a high-risk area for gastric cancer in Colombia, and are being investigated similarly.

(iii) *Nitrosation catalysis by bacteria in the rat stomach*

A number of disorders of the gastrointestinal tract are accompanied by gastric achlorhydria, allowing the bacterial colonization of the stomach. Some of the microorganisms isolated from the achlorhydric stomach possess a nitrate-reductase and a nitrosating activity, so the enhanced gastric formation of *N*-nitroso compounds (NOC) has been intensively studied, particularly in the light of increased risk of gastric cancer in some hypochlorhydric groups, but a causal relationship is not proven.

In this study, the effect of bacterial colonization of the stomach on endogenous nitrosation has been investigated in rats treated with omeprazole, a substituted benzimidazole of a new class of antisecretory agents that function by inhibiting selectively the H^+,K^+-ATPase, the gastric proton pump of the gastric mucosa. Six-week-old male Sprague–Dawley rats were given omeprazole (4 mg/rat), to reduce gastric secretion sufficiently to allow the intragastric survival of a bacterial suspension (*E. coli* A10 and/or *Pesudomonas aeruginosa* D3375: nitrosation-proficient strains). Thiazolidine-4-carboxylic acid (TCA) (20 μmol) was given by gavage with or without nitrite (20 μmol) or nitrate (20 μmol–1.6 mmol) in the presence or absence of bacteria. Endogenous nitrosation was quantified by the urinary level of *N*-nitrosothiazolidine-4-carboxylic acid (NTCA). When rats were given both TCA and nitrate, higher endogenous formation of NTCA ($p < 0.005$) was observed in those receiving *E. coli* A10 suspension. When nitrite

[19] Pignatelli, B., Chen, C.-S., Thuillier, P. & Bartsch, H. (1989) In: O'Neill, I.K., Chen, J., Lu, S.H. & Bartsch, H. *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105) (in press)

(20 μmol) was administered together with TCA, there was no significant change of endogenous nitrosation between controls and omeprazole-treated rats in presence or absence of bacteria; chemical nitrosation of TCA appeared to totally mask the contribution of bacterial nitrosation in the achlorhydric rat stomach.

Similar experiments were performed with morpholine, studying the endogenous formation of *N*-nitrosomorpholine (NMOR) and its metabolite *N*-nitrosohydroxyethylglycine (NHEG) in urine. The amount of endogenously formed NMOR, estimated from the level of NHEG excretion in the urine, was increased ($p < 0.05$) in omeprazole-treated rats given morpholine (20 μmol) and nitrite (20 μmol) together with bacteria. A higher excretion ($p < 0.05$) of unchanged NMOR was also observed in urine. When rats were given morpholine (20 μmol) and nitrate (1.6 mmol), higher levels of unchanged NMOR ($p < 0.01$) were excreted in urine of rats gavaged with omeprazole and bacteria. Thus as shown in this model, bacteria efficiently reduced nitrate into nitrite and catalysed nitrosation of morpholine with nitrate/nitrite, resulting in an increased formation of NOC in the achlorhydric stomach. The metabolism of NMOR differed in rats with induced achlorhydria; whether this is generally true for other NOC needs to be further investigated.

(iv) *Biochemical studies on the bacterial nitrosating enzyme*

It has been demonstrated that the nitrosating activity of *E. coli* is directly linked to the presence of an intact *nar* G,H,I structural gene coding for the nitrate-reductase. When this gene was deleted in *E. coli* MC 4100, the resulting strain LCB330 had no nitrosating activity; this activity was restored with the nitrate-reductase activity after the insertion of a plasmid carrying *nar* Z (a gene coding for a cryptic nitrate-reductase) into the deleted strain. In denitrifying bacteria such as *Pseudomonas aeruginosa,* the analysis of various genetic mutants did not show real evidence for a link between nitrosating activity and the nitrate/nitrite-reductase activities. However, experiments are in progress to isolate the nitrosating enzyme in *Pseudomonas* and *Neisseria* which exhibited their nitrosating activity in the supernatant after sonication. Further purification of the enzyme is in progress, with the aim of developing rapid immuno-screening tests.

(v) *Genotoxicity and possible tumour-initiating and -promoting effects of smoked foods* (in collaboration with Drs T. Matsushima, C. Furihata, N. Ito, M. Tatematsu and M. Hirose, Nagoya City University Medical School, Nagoya, Japan)

Epidemiological studies have associated the consumption of smoked fish and meat products with an increased risk of stomach cancer. Therefore, the reaction of smoked foods with nitrite under acidic conditions was investigated and was shown to produce potent direct-acting genotoxic substances as detected by the SOS chromotest[20]. Similar genotoxic activity was observed in nitrosated samples of wood-smoke condensates. Simple phenolic compounds such as phenol, 3-methoxycatechol, catechol and vanillin were identified as the precursors of the genotoxic substances. These phenolic compounds also exhibited direct-acting genotoxicity after nitrosation. The major genotoxic substances formed after nitrosation of phenol were isolated and identified as 4- and 2-hydroxyphenyldiazonium ions. Nitrosation of various wood-smoke condensates was found to generate the same type of diazonium compounds, which in part account for the genotoxicity of nitrosated smoked foods.

[20] Ohshima, H., Friesen, M., Malaveille, C., Brouet, I., Hautefeuille, A. & Bartsch, H. (1989) *Food Chem. Tox.*, 27, 193–203

In order to assess the potential of wood smoke condensate to act as a glandular stomach carcinogen, the induction of ornithine decarboxylase, replicative and unscheduled DNA synthesis, and DNA single-strand breaks were measured in the pyloric mucosa of rat stomach after oral administration of hickory smoke condensate (HSC) with or without nitrite[21]. The results indicate that HSC contains substance(s) which have potential tumour-initiating and/or -promoting activity and that reaction with nitrite generates new substance(s) which could act as tumour-initiators in the rat glandular stomach. Middle- and long-term carcinogenicity experiments with HSC are now planned.

(vi) *Stomach cancer in Costa Rica* (in collaboration with Dr R. Sierra, Institute of Health Research, University of Costa Rica, San José, Costa Rica)

Stomach cancer is the most common cause of death from cancer in Costa Rica. In order to study whether endogenous nitrosation occurring in early life plays a crucial role in its etiology, samples of 12 h overnight urine (after dosing proline and vitamin C or proline alone) were collected from about 50 children (aged 8–14 years) living in a high- and a low-risk area for stomach cancer (incidence rates 61.3 versus 18.7 per 100 000). Levels of *N*-nitrosoproline (NPRO; range of median values 0.28–0.84 μg/12 h) or sum of nitrosamino acids (0.75–1.75 μg/12 h in these samples) were much lower than those in urine samples from adults from Japan, China or Poland. However, the NPRO level after proline ingestion was significantly higher in the children from the high-risk area than in those from the low-risk area ($p < 0.04$), but was much reduced ($p < 0.05$) if ascorbic acid was ingested simultaneously with the proline. The urinary nitrate level was also lower than that of adult urine samples analysed in different studies. NPRO levels on the day of proline intake, however, were correlated well with the nitrate levels ($\alpha = 0.580$, $p < 0.001$). These results indicate that children in a high-risk area in Costa Rica have higher endogenous nitrosation potential.

In these children, the prevalence of infection with *Campylobacter pylori* has been studied (see section I.3.*d*.iv).

Beans consumed frequently in Costa Rica were collected and analysed for nitrate, total NOC and mutagens before and after nitrosation *in vitro*. Amounts of total NOC and genotoxins detected by the SOS chromotest were increased markedly after chemical nitrosation under acidic conditions simulating those of the human stomach.

(vi) *Stomach cancer in Poland* (in collaboration with Dr W. Zatonski, Department of Cancer Control and Epidemiology, Curie-Sklodowska Institute of Oncology, Warsaw)

Following a feasibility study conducted in a high-risk rural area and a low-risk urban area for stomach cancer in Poland[22] and a study on children in Costa Rica (see above), 12-h overnight urine and fasting, morning blood samples are being collected from 70 healthy subjects (male and female; 35 aged 8–13 yrs and 35 aged 30–60 yrs) living in a high- and a low-risk area for stomach cancer. Urine specimens (with or without 500 mg proline ingestion) will be analysed for nitrosamino acids, nitrate and 3-methyladenine as exposure markers of endogenous nitrosation. Blood samples will be used for serological examination for *C. pylori* antibodies and analyses for pepsinogen isozymes and pro-oxidant status.

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[21] Ohshima, H., Furihata, C., Matsushima, T. & Bartsch, H. (1989) *Food Chem. Tox.* (in press)

[22] Zatonski, W., Ohshima, H., Prewozniak, K., Drosik, K., Mierzwinska, J., Krygier, M., Chmielarczyk, W. & Bartsch, H. (1989) *Int. J. Cancer* (in press)

(viii) *Liver cancer in Thailand* (in collaboration with Dr P. Srivatanakul, National Cancer Institute, Bangkok, Dr W. Thamavit, Mahidol University, Bangkok, and Drs M. Moore and N. Ito, Nagoya City University Medical School, Japan)

Cholangiocarcinoma is one of the commonest cancers in north-east Thailand and has been associated with infestation by the liver fluke *Opisthorchis viverrini* (see section I.3.*a*.iv). About 100 inhabitants in five areas of contrasting incidence for cholangiocarcinoma and hepatocellular carcinoma were dosed with 500 mg proline and 200 mg ascorbic acid or 500 mg proline alone and overnight urine was collected and analysed for nitrosamino acids, nitrate and creatinine. Blood samples from the same subjects were examined serologically for hepatitis B virus infection and *O. viverrini* infestation. The incidence of cholangiocarcinoma or hepatocellular carcinoma was not correlated with the amount of NPRO or other nitrosamino acids, endogenous nitrosation potential (difference of NPRO levels between proline dose and proline + vitamin C dose), or nitrate level. However, in the high-risk areas (Ubon and Korat), the subjects who were positive for *O. viverrini* antibody (titre $\geq 1:40$) excreted significantly higher levels ($p < 0.01$) of NPRO ($12.3 \pm 18.7\,\mu g/12\,h$) after proline ingestion than did negative subjects (titre $< 1:40$) ($3.5 \pm 3.2\,\mu g/12\,h$). After ingestion of vitamin C, the NPRO levels were significantly reduced to $2.4 \pm 2.0\,\mu g/12\,h$, suggesting that endogenous nitrosation of proline was inhibited. Thus, endogenous nitrosation potential was significantly higher in the subjects positive for *O. viverrini* antibody. No significant difference of endogenous nitrosation, however, was observed between subjects who were negative and positive for hepatitis B surface antigen (HBsAg).

In order to study the mechanism(s) for the increased nitrosation in the patients with liver fluke, studies in a Syrian golden hamster model with *O. viverrini* infestation are in progress. The urine samples after an oral dose of thiazolidine 4-carboxylic acid or aminopyrine with or without nitrite are being analysed for *N*-nitrosothiazolidine 4-carboxylic acid and 3-methyladenine as markers for endogenous nitrosation. Further, the livers from control and infected hamsters which received *N*-nitrosodimethylamine are being examined immunohistochemically for the presence of O^6- and 7-methyldeoxyguanosine (in collaboration with Dr C. Wild, IARC).

(ix) *Liver cancer in The Gambia* (in collaboration with Dr A.J. Hall, Medical Research Council, Fajara, The Gambia)

As an ancillary study to the Gambia Hepatitis Intervention Study (see section I.7.*a.i*), urine samples are being collected in The Gambia from (*a*) hepatitis B surface antigen (HBsAg) carriers with active hepatitis, (*b*) HBsAg carriers without active hepatitis and (*c*) controls, using a protocol similar to that described for the study in Poland (see section vii above). Samples will be analysed for nitrate, *N*-nitrosamino acids and 3-methyladenine as exposure markers, to test the hypothesis that activated macrophages, reported to synthesize nitrosating agents, could play an important role for endogenous nitrosation in inflammatory diseases such as hepatitis.

(x) *Nasopharyngeal cancer etiology* (in collaboration with Dr G. de-Thé and Dr A. Hubert, Faculty of Medicine A. Carrel, Lyon, France; Dr Y.M. Shao and Professor Y. Zeng, Institute of Virology, Chinese Academy of Preventive Medicine, Beijing; Dr A. Polack and Dr G.W. Bornkamm, Institute of Virology, Freiburg, FR Germany)

Nasopharyngeal carcinoma (NPC) has been associated with Epstein–Barr virus (EBV) and with environmental and genetic factors. Case–control studies have shown that traditional dietary habits, such as consumption of salted and dried Cantonese-style fish, could be a risk factor for NPC. To examine the relevance of such associations, we have analysed some preserved foods

collected in high-risk areas for NPC (Southern China, Tunisia and Greenland). These frequently consumed foods were previously screened for volatile nitrosamines (VNA)[23]. Aqueous extracts of some Cantonese-style salted and dried fish from China, *qaddid* (dried mutton preserved in oil) and *harissa* (a spice mixture) from Tunisia showed EBV-inducing activity in a latently infected Raji cell line[24]. A further sixteen traditional preserved foods were tested for mutagenicity before and after nitrosation *in vitro*. Out of 16 food samples 13 showed a weak direct-acting genotoxicity in the SOS chromotest in at least one of the aqueous, n-hexane or ethyl acetate extracts of the food samples, but only one sample from Greenland was weakly mutagenic in the *Salmonella* assay. The chemical nitrosation of most aqueous extracts increased genotoxicity detected by the SOS chromotest, and levels of VNA, i.e. *N*-nitrosodimethylamine (NDMA), *N*-nitrosopiperidine (NPIP) and *N*-nitrosopyrrolidine (NPYR). Highest levels ranging from 1190 μg/kg for NDMA to 3840 μg/kg for NPYR were found in hard salted and dried fish from China and spice mixture (*harissa*) from Tunisia, respectively. The increased levels of VNA correlated well with increased mutagenicity, but the presence of VNA and of genotoxic activity was not correlated with EBV-inducing activities. These results suggest that different classes of substances are involved in mutagenicity and in EBV-inducing activity. Therefore, these substances either present in foods or formed endogenously by nitrosation, could be etiological factors in NPC pathways[25].

In order to assess the role of endogenous nitrosation in NPC development, urine samples were collected in early 1989 from inhabitants in high- and low-risk areas for NPC in south China. However, samples were unfortunately spoiled during transport from China to Lyon, so a repeat sample collection is being planned.

EBV-inducing activity is now being screened[26] using as a new marker of activation the induction of the EBV 'DR' promoter, an early promoter of the virus which regulates the bacterial chloramphenicol-acetyltransferase (CAT) gene in an autoreplicative plasmid in Raji cells. The advantage of this method is that the CAT assay is much more precise than detection of EBV early antigen induction by an immuno-enzymatic method, giving a much lower background and more reproducible results. Preliminary results show that there is a good correlation between the results from the two methods. Using the new procedure, work is in progress to isolate and characterize the EBV-inducing substance from *harissa,* which was found to show the strongest EBV-inducing activity.

(xi) *Oesophageal cancer in China* (in collaboration with J. Wahrendorf and J. Claude, Institute of Epidemiology and Biometry, German Cancer Research Centre, Heidelberg, FR Germany)

Urine samples collected in a high-risk region for oesophageal cancer in China as a part of a case–control study for the etiology of precancerous lesions of the oesophagus have been analysed for nitrate, nitrosamino acids and 3-methyladenine (3-MeAde) (see below). A moderate correlation between NPRO and 3-MeAde levels indicates that 3-MeAde may be present as a result of endogenous methylating NOC formation. The final analysis of the data is in progress.

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[23] Poirier, S., Ohshima, H., de-Thé, G., Hubert, A., Bourgade, M.C. & Bartsch, H. (1987) *Int. J. Cancer, 39,* 293–296

[24] Shao, Y.M., Poirier, S., Ohshima, H., Malaveille, C., Zeng, Y., de-Thé, G. & Bartsch, H. (1988) *Carcinogenesis, 9,* 1455–1457

[25] Bouvier, G., Poirier, S., Shao, Y.M., Malaveille, C., Ohshima, H., Polack, A., Bornkamm, G.W., Zeng, Y., de-Thé, G. & Bartsch, H. (1989) In: O'Neill, I.K., Chen, J., Lu, S.H. & Bartsch, H., eds, *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins* (IARC Scientific Publications No. 105) (in press)

[26] Bouvier, G., Polack, A., Traub, B., Bornkamm, G.W., Ohshima, H., Bartsch, H. & de-Thé, G. (1989) In: *Epstein-Barr Virus and Human Disease,* Humana Press, Clifton, NJ (in press)

(xii) *Urinary alkylated purine bases as markers of human exposure to carcinogens* (in collaboration with Dr P. Farmer, MRC Toxicology Unit, Carshalton, UK; supported by NIH grant CA 48473)

The major DNA reaction products of many alkylating carcinogens are the unstable 7-alkyldeoxyguanosine and 3-alkyldeoxyadenosine adducts. These adducts break down, either spontaneously or under the influence of glycosylases, to give the corresponding alkyl-purines which are usually excreted intact in urine[27]. This phenomenon has been used to develop a totally non-invasive technique to monitor human exposure to alkylating carcinogens.

The measurement of urinary 3-methyladenine (3-MeAde) has been proposed as a technique for monitoring exposure to methylating carcinogens[28] such as *N*-methyl-*N*-nitroso compounds[29]. Antibodies have been raised against 3-MeAde, but its direct determination in urine by ELISA was hindered by cross-reacting compounds[30]. However, the use of immunoaffinity chromatography (in which the antibody is immobilized on a support gel) to extract 3-MeAde before determination by GC–MS[31] or by ELISA with a monoclonal antibody (MAb) to 3-MeAde (developed in collaboration with Professor S.R. Tannenbaum, MIT, Cambridge, MA, USA) allows reliable and rapid assay of urinary 3-MeAde.

It now appears that much of the urinary 3-MeAde may be of dietary origin and extremely variable levels of urinary 3-MeAde were observed in different population groups. Only weak correlations were observed between 3-MeAde and variables such as smoking. Higher homologues of 3-MeAde are unlikely to be present to any significant extent in food and, thus, the possibility of detecting other 3-alkyladenines by using a similar approach is now being explored. A recently developed MAb against 3-ethyladenine has the interesting property of being able to recognize a wide range of 3-alkyladenines (collaboration with Professor M. Rajewsky and Dr. G. Eberle, Institute for Cell Biology, University of Essen, FR Germany). Use of this MAb in making immunoaffinity columns capable of extracting a range of 3-alkyladenines from urine samples followed by GC–MS analyses is being examined.

The determination of urinary 7-methylguanine (7-MeGua) as a monitor of methylation is confounded by the presence of a large amount of RNA-derived 7-MeGua. However, the recently developed antiserum to 7-MeGua has proved useful in the determination of methylated adducts in DNA[32]. In addition, as for 3-alkyladenines, it seems unlikely that higher homologues of 7-MeGua would be naturally present in urine, and methods for the determination of urinary 7-alkylguanines are currently being developed (e.g. adducts from cyclophosphamide).

(xiii) *Development of methods for biological monitoring of exposure to nitrogen oxides (NOx) and endogenous nitrosating agents produced by activated macrophages*

Sensitive methods for biological monitoring of exposure to nitrogen oxides (NOx) and endogenous nitrosating agents are being developed by analysing as exposure markers nitrotyrosine (NTYR) in serum and tissue proteins, and deaminated DNA bases such as xanthine and

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[27] Shuker, D.E.G. (1989) *Arch. Toxicol.* (in press)

[28] Shuker, D.E.G., Bailey, E., Parry, A., Lamb, J. & Farmer, P.B. (1987) *Carcinogenesis, 8*, 959–962

[29] Shuker, D.E.G. (1989) *Cancer Surveys* (in press)

[30] Shuker D.E.G. & Farmer, P.B. (1988) In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 92–96

[31] Friesen, M.D., Shuker, D.E.G., Garren, L. & Prévost, V. (1989). Proceedings of the 37th ASMS Conference on Mass Spectrometry and Allied Topics, East Lansing, MI, American Society for Mass Spectrometry, pp. 82–83

[32] Shuker, D.E.G. (1988) In: Bartsch, H., Hemminki, K. & O'Neill, I.K., *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, pp. 296–300

hypoxanthine in tissues. NTYR and its urinary metabolites are determined using a gas chromatograph (GC) combined with a thermal energy analyser (TEA) in a number of *in vitro* and *in vivo* studies now under way. These have shown that (*a*) NTYR is formed much more rapidly (~50 times) than nitrosoproline *in vitro*, (*b*) NTYR is formed in blood proteins incubated *in vitro* with sodium nitrite or tetranitromethane, a well known nitrating agent and lung carcinogen in rats and mice, and (*c*) NTYR is formed dose-dependently in both plasma proteins and haemoglobin in rats after i.p. injection of different doses of tetranitromethane. Major urinary metabolites of NTYR given orally to rats were identified as 3-nitro-4-hydroxyphenylacetic acid (NHPA) and 3-nitro-4-hydroxyphenyllactic acid. About 44 and 5% of an oral dose of NTYR (100 μg/rat), respectively, were excreted as these metabolites. In 11 human urine samples analysed by GC-TEA after ethyl acetate extraction and HPLC purification, amounts of NHPA ranging from 0 to 7.9 μg/24 h (mean ± SD, 2.8 ± 2.3) were detected. Levels of NTYR in plasma proteins and haemoglobin and of urinary metabolites are currently being compared in smokers and non-smokers.

In addition, rabbit antiserum was raised against NTYR-containing protein and is being used for immunocytochemical detection of this protein in the lungs of animals exposed to NOx or in inflamed tissues.

(xiv) *Group-selective determination of total N-nitroso compounds in nitrate-containing human urine samples*

The group-selective method developed at IARC for the determination of total *N*-nitroso compounds (NOC)[33] has been adapted for analysing human urine samples. Nitrate is first removed from urine by an anion exchange procedure which did not lead to significant loss of various added reference NOC nor of unidentified urinary NOC. Total NOC are then determined by injecting the urine sample (nitrate content < 1 mmol/l) or anion exchange eluate treated by sulfamic acid into refluxing ethyl acetate containing either (*a*) acetic acid or (*b*) hydrogen bromide. An NO-sensitive thermal energy analyser provides an estimate of all heat- or acetic-acid-labile compounds in the acetic acid-treated solution, while NOC are cleaved only in the HBr-treated solution and are therefore estimated from the difference between the two measurements.

When added to human urine samples spiked with nitrate (5–6 mmol/l) at concentrations ranging from 2.9 to 5.4 μmol/l, seven different standard NOC, including two *N*-nitrosamino acids (NAA) were recovered satisfactorily (73–99%) after anion exchange chromatography. Ten urine samples containing <1 mmol/l of nitrate, that had been analysed for total NOC, were spiked with nitrate up to 6 mmol/l. The recoveries of urinary NOC (range 0.20 to 2.63 μmol/l) after anion exchange chromatography were over 75% in most samples.

No artefactual nitrosation during up to two months of storage at −20°C was observed in NaOH- or sulfamic acid-treated urine samples ($n = 12$) spiked with nitrite (500 μmol/l), 2,6-dimethylmorpholine (500 μmol/l) or both. The stability of urinary NOC in the same samples as a function of time and storage conditions was quite good. Loss of urinary NOC, which was similar after treatment with either NaOH or sulfamic acid, was 5 to 10% after 1 month and <30% after 3 months. Stabilization of urine samples with NaOH has the advantage that nitrate and nitrite are stable under these conditions and can be determined. Anion exchange chromatography is not required for urine samples containing <1 mmol/l of nitrate.

Fifteen urine samples collected from volunteers dosed with proline were analysed for total NOC and NAA. Although human subjects were given 500 mg proline (with vitamin C for one subject), *N*-nitrosoproline usually accounted for less than 10% of total NOC and never for more

[33] Pignatelli, B., Richard, I., Bourgade, M.-C. & Bartsch, H. (1987) *Analyst, 112*, 945–949

both colony-forming efficiency and clonal growth rate of epithelial cells to less than 50% at 10 µg/ml. Exposure to higher concentrations also caused both dose-dependent depletion of thiols and formation of single strand breaks in DNA. Of eight areca nut-associated compounds investigated, *N*-nitroso-3-(methylamino)propionaldehyde (MNPA) was the most potent agent for causing these effects in cells.

(vi) *Immunohistochemical staining for carcinogen–DNA adducts* (Dr U. Nair and Miss I. Richard)

Using polyclonal antibodies for O^6-MeG and 7-MeG (in collaboration with Dr C. Wild), staining procedures have been set up using frozen rat liver sections from NDMA-treated rats. Modifications are being tested to detect alkyl-purines in paraffin-embedded tissue sections.

(vii) *Antibodies against MNPA-modified epitopes in mice exposed to the areca nut alkaloid, arecoline* (Dr G. Maru, Dr A. Barbin and Dr U. Nair)

As our earlier studies have shown that MNPA is a potent and direct-acting areca nut-specific nitrosamine, human serum albumin has been modified *in vitro* with MNPA. The modified and unmodified albumin is being used to assess whether an antibody response is observed in serum of mice exposed to arecoline and sodium nitrite, by an enzyme-linked immunosorbent assay (ELISA).

Serum samples from treated Swiss mice (i.p. treatment with 1 mg arecoline hydrobromide + 1 mg sodium nitrite per day per mouse, seven days a week, for total of 43 days) and corresponding controls have been collected. Conditions for ELISA are being optimized using these samples.

(viii) *Assays for alkylation damage to DNA* (Dr M. Friesen, Dr D.E.G. Shuker and Dr G. Maru)

A rapid method using immunoaffinity clean-up and gas chromatography–mass spectrometry (see section I.2.*e*.xii) has been developed for the determination of 3-MeAde in urine as a measure of exposure to methylating agents. The method is being applied to the analysis of 3-MeAde in the urine of rats treated with tobacco- and areca nut-specific nitrosamines. Once this method has been validated, it may serve as a marker of humans exposed to methylating agents present in betel quid and tobacco.

(*g*) Aflatoxins: exposure assessment and carcinogenicity (Dr C.P. Wild, Miss B. Chapot, Mrs Y.Z. Jiang, Dr R. Montesano and Dr F.X. Bosch)

The elucidation of the role of aflatoxins in the etiology of liver cancer has been hindered by the lack of a method to measure individual exposure. Such methods are needed for studies to assess the interaction of aflatoxins and hepatitis B virus in the development of primary hepatocellular carcinoma (see section I.3.*a*) and to monitor exposure during the Gambia Hepatitis Intervention Study.

To complement the epidemiological studies being carried out in various countries, experiments are being conducted on various aspects of the carcinogenic effects of aflatoxins and their interaction with hepadnaviruses and other environmental factors.

(i) *Methodological developments* (in collaboration with Dr G. Sabbioni, Toxicological Institute, University of Würzburg, FR Germany)

Sensitive and specific assays, suitable for use in large-scale epidemiological studies, have been established for aflatoxin (AF) bound to albumin and for aflatoxin metabolites in urine[36]. For

[36] Wild, C.P., Jiang, Y.Z., Sabbioni, G. & Montesano, R. (1989) *Cancer Res.* (in press)

urine analysis, aflatoxins are extracted by antibody affinity chromatography followed by quantitation in ELISA. For albumin analysis, the aflatoxin can be detected by immunoassay either directly on the intact albumin molecule or in a hydrolysed albumin sample. In addition, on a hydrolysed sample, the specific presence of the aflatoxin B_1 (AFB_1)–lysine adduct can be established by HPLC with fluorescence detection. Comparison of these methods with animal samples suggested that a combination of the hydrolysis–immunoassay method with confirmation by HPLC–fluorescence is optimal. These methods can be performed on as little as 50 µl of serum or plasma and less than 1 ml of urine.

(ii) *Thailand* (in collaboration with Dr D.M. Parkin and Dr M. Khlat, IARC, and Dr Petcharin, National Cancer Institute, Bangkok)

Urine and serum samples were collected from 50–100 healthy donors in each of five regions of Thailand for a geographical correlation study aimed at examining the roles of various environmental factors in the etiology of liver cancer[37]. The frequency of urine samples detected as positive for aflatoxin was highest in the north-east (Ubon, 23% positive) and Bangkok (23%), intermediate in the north (Chiang Mai, 14%), whilst the south (Songkla, 10%) and central regions (Korat, 7%) were the areas where least aflatoxin was observed. The frequency of positive serum samples as measured directly on albumin was lower than that for urine in each region but the relative frequencies among these areas were the same as for the urine data. The levels of aflatoxin in the urine ranged from 0.06 to 4.78 ng AFB_1 equivalent per ml urine, whilst the serum albumin levels were up to 376 ng aflatoxin equivalent per gram albumin. The levels found in the positive urine and serum samples did not differ between the regions.

(iii) *The Gambia* (in collaboration with Dr A.J. Hall, IARC, Fajara, The Gambia; Dr H. Whittle, Medical Research Council, Fajara, The Gambia; Mr G. Hudson, Dunn Nutrition Unit, Medical Research Council, Cambridge, UK; Dr J.D. Groopman, Boston University School of Public Health, Boston, MA, USA; and Dr G.N. Wogan, Massachussetts Institute of Technology, Cambridge, MA, USA)

A study was performed in October 1988 in Keneba, The Gambia, to correlated dietary intake of aflatoxin with the various markers of aflatoxin exposure in urine, serum albumin and breast milk. Ten pairs of individuals were selected in whom one of each pair was chronically infected with HBV and one not. Food samples were collected over eight days, urine samples from day 4 to 8, and a blood sample on days 1 and 8. Breast milk from five lactating women was also collected on days 4 to 8.

Each individual showed a large variation in urinary levels of aflatoxin over the four-day period (a range of >60-fold in one subject). This demonstrates that urinary excretion reflects only the exposure over the previous day. In contrast, when the total urinary aflatoxin excretion over the four days was compared with aflatoxin albumin adduct levels on day 8, a highly significant correlation was observed (Fig. 5) (correlation coefficient 0.73 with 18 individuals). The albumin data therefore gave an integration of exposure over a longer period of time. Initial analyses show that the level of aflatoxin in food is well correlated with these biological markers of exposure.

These findings indicate that detection of albumin–aflatoxin B adducts provides a sensitive, specific marker of aflatoxin exposure that is readily applicable in field studies.

[37] Wild, C.P., Jiang, Y.Z., Montesano, R., Parkin, M., Khlat, M. & Srivatanakul, P. (1989) *Proc. Am. Assoc. Cancer Res., 30,* 317

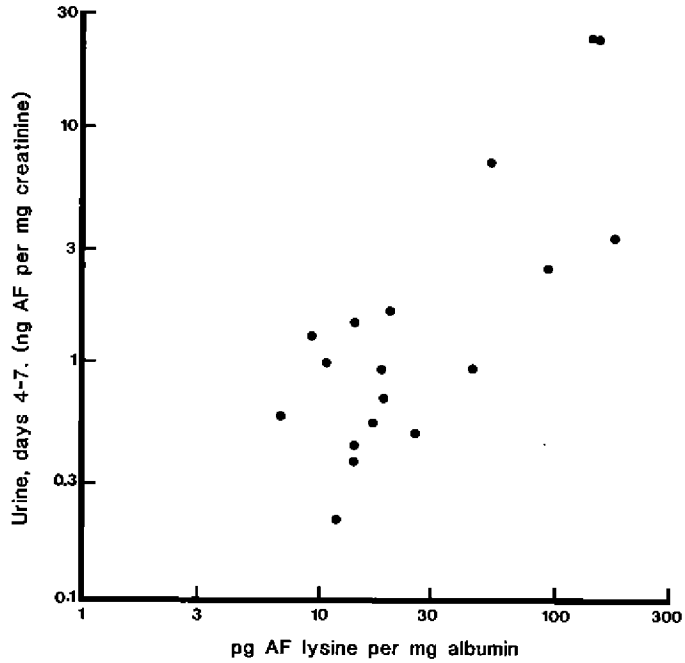

Fig. 5. Correlation between total 4-day urinary excretion of aflatoxin and serum aflatoxin–albumin adducts in man

(iv) *Kenya* (in collaboration with Dr D. Forman, Imperial Cancer Research Fund, Oxford, UK; and Dr G.W. Lachlan, Presbyterian Church Hospital, Chogoria, Kenya)

In the region of Chogoria in Kenya, an unusually high incidence of chronic gastritis in young people was reported, with patients presenting with bouts of epigastric pain. This condition was common in specific inland rural areas of the country and appeared to be rare in coastal regions. High maize consumption was implicated as having a possible etiological role and a mycotoxin involvement was suspected. Therefore serum albumin and urines were analysed from about 20 individuals in each of three groups: (*a*) patients from Chogoria (with bouts of epigastric pain), (*b*) volunteers from Chogoria, and (*c*) volunteers from the coastal region (Fig. 6). There was a good agreement between the albumin and urine data, with higher levels of exposure over recent weeks or months in Chogoria subjects compared to coastal subjects and also patients from Chogoria compared to volunteers from the same area. The relevance of the increased exposure to aflatoxins or other mycotoxins to the etiology of the disease is being further investigated.

The pattern of urinary metabolites in HBV chronic carriers is now being compared to that of non-carriers to examine whether there are differences in metabolism of AFB_1 in these individuals.

(v) *Experimental studies on the possible modification of aflatoxin excretion by environmental factors* (in collaboration with Dr G.E. Neal, Medical Research Council Laboratories, Carshalton, UK; and Dr K. Makarananda, Mahidol University, Faculty of Science, Bangkok)

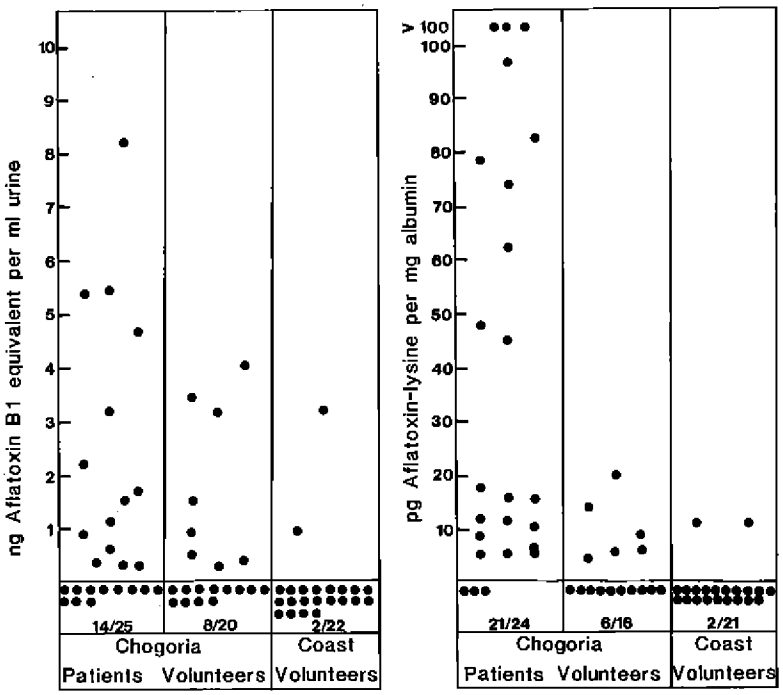

Fig. 6. Levels of aflatoxin in serum of Kenyan individuals in a study of chronic atrophic gastritis

In order to validate the observations obtained in field studies, animal models are being used to examine the effect of dose of aflatoxin and presence of liver fluke on the urinary excretion of the markers of aflatoxin exposure that are being measured in human samples[38].

These studies are important because although the antibodies used quantitate total aflatoxin metabolites in the urine, each metabolite has a different affinity for the antibody. Thus, if the pattern of metabolites is altered by a factor such as liver fluke or hepatitis B virus, a given level of dietary exposure could nevertheless lead to different measurements of aflatoxin in the urine.

In rats, over a 400-fold dose range of [^{14}C]AFB_1 (3–1200 µg/kg), no difference was observed in the pattern of excretion of urinary metabolites. It appears, therefore, that the exposure level itself is unlikely to result in an altered pattern of excretion in man.

In contrast, in hamsters infected with *Opisthorchis viverrini,* more polar aflatoxin metabolites were excreted compared to non-infected hamsters. Comparable changes are being sought in urine samples from Thailand from individuals infected or uninfected with this same liver fluke.

(vi) *Comparative studies on the effects of aflatoxin M_1 (AFM_1) and aflatoxin B_1 (AFB_1) in newborn rats* (in collaboration with Dr T. Shirai, Dr J.R.P. Cabral, Mrs. M.P. Cros and Mrs D. Galendo, IARC; and Dr G.E. Neal, Medical Research Council Laboratories, Carshalton, UK)

[38] Makarananda, K., Wild, C.P. & Neal, G.E. (1989) In: O'Neill, I.K., Chen, J., Lu, S.H. & 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 (in press)

These experiments were designed to assess the carcinogenicity of aflatoxins in newborn rats and specifically (*a*) to compare the effect of AFM_1 received in dams' milk during lactation with that of a single intraperitoneal injection and (*b*) to compare the effects of AFB_1 and AFM_1 when given as a single intraperitoneal injection in one-week-old rats. All rats were killed at 120 weeks of age and the tumour frequency and number of liver foci are being examined in the various groups. In addition, measurements of the relative AFM_1 and B_1 DNA adduct levels in liver are available after the single doses of these agents and will be compared with the neoplastic response.

(vii) *Contribution of aflatoxin B_1 and duck hepatitis B virus infection in the induction of liver tumours* (Dr J.R.P. Cabral, Dr T. Shirai, Dr V.S. Turusov, Dr C.P. Wild, Dr R. Montesano and Dr L. Tomatis; in collaboration with Dr C. Trépo and Dr L. Cova, Research Unit (U271) on Hepatitis and the Role of Hepatotropic Viruses in Oncogenesis, National Institute for Health and Medical Research, Lyon, France; Dr R. Mehrotra, King George's Medical College, Lucknow, India)

The study of two major risk factors in the development of hepatocellular carcinoma (HCC), persistent hepatitis virus infection and exposure to dietary aflatoxins, has been hampered by lack of an experimental system. To this end we have used a Peking duck model to examine the effect of congenital duck hepatitis B virus (DHBV) infection and aflatoxin B_1 (AFB_1) exposure in the induction and development of liver cancer. AFB_1 was administered to DHBV-infected or non-infected ducks at two doses (0.08 mg/kg and 0.02 mg/kg) by i.p. injection once a week from the third month after hatching until they were sacrificed (2.3 years later). Two control groups of ducks not treated with AFB_1 (one of which was infected with DHBV) were observed for the same period. Each experimental group included 13–16 ducks. Higher mortality was observed in ducks infected with DHBV and treated with AFB_1 compared to non-infected ducks treated with AFB_1 and other control ducks (Table 9). In the groups of non-infected ducks treated with high and low doses of AFB_1, liver tumours developed in 3/10 and 2/10 ducks; in infected ducks

Table 9. Frequency of liver tumours in ducks infected or uninfected with duck hepatitis B virus (DHBV) and treated with aflatoxin B_1 (AFB_1)

Groups	Treatment[a]		No. of ducks		No of ducks with liver tumours	No. and type of tumours
	AFB_1[b]	DHBV	Initial	Effective		
1	0.08	–	13	10	3	3 HCC, 1 adenoma
2	0.02	–	13	10	2	1 HCC, 1 adenoma
3	0.08	+	15	6	3	3 HCC[c]
4	0.02	+	15	13	0	—
5	—	+	16	15	0	—
6	—	–	15	12	0	—

[a] Peking ducks (*Anas domesticus*) were naturally infected at birth with DHBV (French strain) and received AFB_1 intraperitoneally once weekly starting at 3 months of age for a period up to 27 months.

[b] mg/kg. Total dose/year: 4.15 and 1.05 mg

[c] One with multiple liver cancer

treated with the high dose, 3/6 liver tumours were observed and none at the low dose of AFB_1. No liver tumours were observed in the two control groups. Ducks infected with DHBV and treated with AFB_1 showed more pronounced periportal inflammatory changes, fibrosis and focal necrosis compared to other groups. All DHBV carrier ducks showed persistent viraemia throughout the observation period. An increase of viral DNA titres in livers and sera of AFB_1-treated animals compared to infected controls was frequently observed. No DHBV DNA integration into the host genome was observed, although in one HCC from an AFB_1-treated duck, an accumulation of viral multimer DNA forms was detected. The metabolism of AFB_1 in infected and non-infected duck liver was also examined. The study on the role of HBV infection and AFB_1 in this experimental system may help to clarify the etiopathogenesis of liver tumours[39].

Related studies to understand the mechanisms of action of the interaction between these two risk factors are under way, in collaboration with Dr C.R. Wolf (Imperial Cancer Research Fund, Edinburgh, UK). These studies examine the role of hepatitis B virus infection on the metabolism of AFB_1 in the liver of Peking duck and man and the characterization of the P450 enzyme responsible for AFB_1 metabolism. In addition, the effect of hepatitis B virus on the metabolism of various carcinogens is being explored in a woodchuck model (see section I.6.*d*). These studies have relevance to epidemiological investigations of liver cancer in Thailand (sections ii above and I.3.*a*.iv), The Gambia (section iii) and Singapore (section I.3.*a*.i).

(*h*) Role of ochratoxin A exposure in relation to Balkan endemic nephropathy and bladder cancer

The aim of this project is to confirm the etiological role of ochratoxin A (OA) and other mycotoxins in Balkan endemic nephropathy (BEN) and related urinary tract tumours. In addition, studies in experimental animal systems and in human tissues or body fluids are being carried out in order to investigate how these mycotoxins induce nephrotoxicity and carcinogenicity.

A predisposing genetic susceptibility factor for the disease(s) has been associated with the oxidation polymorphism of debrisoquine, both in human study subjects and in rodent models.

(i) *Environmental exposure to OA and cytogenetic effects* (Dr M. Castegnaro, Mr J.-C. Béréziat, Dr V. Maru and Dr H. Bartsch; in collaboration with Dr I.N. Chernozemsky, Dr G. Manolov, Dr L. Parvanova, Dr T. Petkova-Bocharova, Dr I. Nikolov and Dr D. Todorov, Institute of Oncology, Sofia)

To confirm the etiological role of OA in BEN, the sampling and analysis of food for OA has been continued, some very high levels of OA being detected in samples collected in late spring 1986 from the 1985 crop in the endemic area. The results obtained confirm previous ones, in that cereals and beans consumed by affected families were contaminated to a greater extent than those consumed by non-affected households either from the endemic area or from control regions. A pilot study to determine the levels of citrinin, another nephrotoxic agent which increases the carcinogenic potential of OA[40], has been initiated. The preliminary data suggest a higher number of citrinin-positive samples in staple food (maize and beans) from families with BEN patients than from disease-free families, and higher levels of this compound (see Table 10).

Sampling and analysis of blood of BEN-affected people and controls for OA has been

[39] Cova, L., Wild, C.P., Mehrotra, R., Turusov, V., Shirai, T., Lambert, V., Jacquet, C., Tomatis, L., Trépo, C. & Montesano, R. (1989) (submitted for publication)

[40] Kanisawa, M. (1984) In: Kurata, H. & Ueno, Y., *Toxigenic Fungi—Their Toxins and Health Hazard* (Developments in Food Science, vol. 7), Amsterdam, Elsevier; Tokyo, Kodansha, pp. 245–254

Table 10. Citrinin contamination of consumed by families with or without members affected by Balkan endemic nephropathy

Families	Beans					Maize				
	No. of samples	No. positive	%	Citrinin levels (μg/kg)		No. of samples	No. positive	%	Citrinin levels (μg/kg)	
				Range	Average[a]				Range	Average[a]
Affected	58	20	34.5	20–1000	67.0	58	21	36.2	50–1500	122
Unaffected	34	3	8.8	100–120	9.7	34	5	14.7	100–300	29

[a] Average values over all samples tested.

continued, confirming previous results[41]. The method for analysis of OA and its 4-hydroxy metabolite (4-hydroxy-OA) in human urine, has been improved, lowering detection limits to 10 ng of OA and 20 ng of 4-hydroxy-OA. Analysis of OA and 4-hydroxy-OA in urine samples, from the endemic and control areas has been performed. OA has been detected more often and at higher levels in members from affected families than in ones from control areas (see Table 11). No 4-hydroxy-OA was detected in the samples.

To study the mechanisms of OA-induced carcinogenesis, kidney DNA from rats treated with OA has been analysed for DNA adducts by the ^{32}P-postlabelling technique of Randerath *et al*[42].

Table 11. Urinary excretion of ochratoxin A (OA) by subjects suffering from endemic nephropathy (EN) or urinary system tumours (UST) and by healthy persons

Group	No. of samples	No. positive	%	OA levels (range; ng/l)
EN/UST patients	36	14	38.9	5–604
EN suspected	25	9	36	5–32
Family members of EN patients	25	12	48	5–33
Healthy persons from healthy families in endemic villages	32	11	44	5–43
Healthy persons from unaffected villages in endemic area	31	4	12.9	17–41
Healthy persons from villages in non-endemic area	3	0	—	—

[41] *IARC Biennial Report* 1986/1987, p. 36

[42] Randerath K., Reddy, M.V. & Gupta, R.C. (1981) *Proc. Natl. Acad. Sci. USA, 78*, 6126–6129

Even with the intensifying techniques of Gupta[43] and of Reddy and Randerath[44], no adducts were detected, confirming negative results from *in vitro* binding studies with [^{3}H]OA.

36 tumour samples (kidney, urinary tract) have been collected from operated BEN patients. DNA extracted from these samples will be screened for adducts using the same postlabelling techniques. Peripheral lymphocytes of 16 patients with BEN have been analysed cytogenetically. None of these patients had an entirely normal karyotype in 100% of the cells. Numerical and structural chromosome aberrations were found in 14 of the individuals showing defined break points and the other two patients had numerical aberrations only; chromosomes 1, 2, 3, 4 and X were mainly involved. In human peripheral lymphocytes, in the presence or absence of a kidney microsomal metabolic activation system, OA was found to induce aberrations on X chromosomes of similar types to those in lymphocytes of BEN patients[45].

Among patients with BEN and children from endemic families, the frequency of spontaneous sister chromatid exchanges (SCE) was no higher than in controls. However, after *in vitro* treatment with mitomycin C, the level of SCE doubled only in lymphocytes from both patients and clinically healthy children from affected families. Preliminary data from analysis of SCE in lymphocytes treated with OA and S9 seem to indicate that OA causes an increase in SCE. Work is in progress to confirm these data using OA alone and after metabolic activation.

Exfoliated urinary cells have been collected from urine of patients and controls. Slides have been prepared for analysis of micronuclei.

(ii) *Drug metabolism in rat strains phenotyped as poor and extensive metabolizers of debrisoquine and ochratoxin A* (Dr M. Castegnaro, Dr E. Hietanen, Dr C. Malaveille, Mr J.-C. Béréziat and Ms A.-M. Camus)

Debrisoquine 4-hydroxylation *in vivo* has been proposed as a probe to assess individual oxidative drug-metabolizing capacity and to classify humans into poor metabolizers (PM) and extensive metabolizers (EM). PM appear to be at lower risk than the EM phenotype for certain types of environmentally induced cancer, including that of BEN/UST.

In DA and Lewis rat strains, PM and EM strains also differ with respect to ochratoxin A metabolizing capacity *in vitro*[46] and *in vivo*[47]. Since hepatic and renal ochratoxin A 4-hydroxylase activity *in vitro* was much lower in DA than in Lewis rats[48], a study has been carried out *in vivo* using the same rat strains. Rats were treated with 1.5 mg/kg body weight of ochratoxin A, five times a week for eight weeks. The ratio of the parent compound to its 4-hydroxy metabolite excreted in urine was at all times greater in DA than in Lewis rats, confirming the results obtained *in vitro*: female DA rats have a two- to four-fold lower 4-hydroxylase activity than Lewis rats.

We are now characterizing the cytochrome P450 isozymes catalysing the OA hydroxylation using antibodies (from Dr H.V. Gelboin, National Cancer Institute, Bethesda, USA) against various cytochrome P450 isozymes in various mouse strains to explore a possible association with

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[43] Gupta, R.C. (1985) *Cancer Res., 45,* 5656–5662

[44] Reddy, M.V. & Randerath, K. (1986) *Carcinogenesis, 7,* 1543–1551

[45] Manolova, Y., Manolova, G., Parvanova, L., Petkova-Bocharova, T., Castegnaro, M. & Chernozemsky, I.N. (submitted for publication)

[46] Hietanen, E., Malaveille, C., Camus, A.-M., Béréziat, J.-C., Brun, G., Castegnaro, M., Michelon, J., Idle, J.R. & Bartsch, H. (1986) *Drug Metab. Disp., 14,* 118–126

[47] Castegnaro, M., Bartsch, H., Béréziat, J.-C., Arvela, P., Michelon, J. & Broussolle, L. (1989) *Xenobiotica, 19,* 225–230

[48] Hietanen, E., Bartsch, H., Castegnaro, M., Malaveille, C., Michelon, J. & Broussolle, L. (1985) *J. Pharmacol. Clin., 4,* 71–78

the genes regulating debrisoquine hydroxylation and methylcholanthrene-inducible forms of cytochrome P450.

(iii) *Mechanism of ochratoxin A-induced toxicity and carcinogenicity* (Dr A.D. Rahimtula, Memorial University of Newfoundland, St Johns, Canada, Mr J.-C. Béréziat, Mrs V. Bussacchini-Griot and Dr H. Bartsch)

The mechanism of the toxicity and carcinogenicity of ochratoxin A (OA) is not known, but may involve oxidative stress, as no covalent binding to DNA has been demonstrated. Incubation of OA with rat liver microsomes and NADPH results in a large increase in lipid peroxidation[49,50] and a substantial level of covalent binding to microsomal proteins. NADPH-dependent lipid peroxidation in kidney microsomes is similarly enhanced by OA. The process requires the presence of trace amounts of iron but cytochrome P450 and reactive oxygen species appear not to be involved. The efficiency of several ochratoxins (A, B, C, α and *O*-methyl-C) in enhancing lipid peroxidation is related to their toxicity in chicks.

Furthermore, administration of OA led to a substantial elevation in the rate of ethane exhalation in Lewis but not DA rats. These results suggest that lipid peroxidation may play a role in the toxicity of ochratoxin A, while cytochrome P450-mediated metabolism may modify this effect. ATP-dependent calcium uptake was inhibited by 42–45% in liver microsomes from OA-intoxicated rats. In the presence of NADPH, addition of 2.5 to 100 µM of OA causes a concentration-dependent inhibition of calcium uptake of 28 to 94% in untreated rat liver microsomes[51].

Together, these results suggest that OA disrupts microsomal calcium homeostasis by an impairment of the endoplasmic reticulum membrane, probably due to enhanced lipid peroxidation.

(*i*) Radiation

(i) *Extremely low-frequency electromagnetic fields* (Dr M.P. Coleman, Dr E. Cardis, Dr P. Boyle and Dr R. Saracci)

An international meeting was held in May 1988 to review current knowledge on the association between exposure to extremely low-frequency (ELF) electromagnetic fields and human cancer risk, and to develop better epidemiological study designs, particularly in the area of exposure assessment. Principal investigators from 12 major studies currently planned or in progress were represented, and broad agreement was reached on the choice of exposure parameters and on the methods of data collection and storage, in order to enhance the eventual comparability of the results. The results of the meeting will be published[52].

Exposure to ELF fields will be included in the SEARCH study of childhood leukaemia (see section I.3.*k*.v), and IARC staff participated in a workshop organized by the Electric Power Research Institute (USA) in Baltimore in February 1989, at which a single ELF field exposure assessment protocol was developed for the three major case–control studies of childhood leukaemia now in the planning stage (SEARCH, NCI/Childhood Cancer Study Group (USA) and a Canadian national study).

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[49] Rahimtula, A.D., Béréziat, J.-C., Bussacchini-Griot, V. & Bartsch, H. (1988) *Biochem. Pharmacol.*, 37, 4469–4477

[50] Rahimtula, A.D., Castegnaro, M., Béréziat, J.-C., Bussacchini-Griot, V., Broussole, L., Michelon, J. & Bartsch, H. (1989) In: Bach, P.H. & Lock, E.A., eds, *Nephrotoxicity: Extrapolation from* in vitro *to* in vivo, *and Animals to Man*, London, Plenum Press, pp. 617–622

[51] Khan, S., Martin, M., Bartsch, H. & Rahimtula, A.D. (1989) *Biochem. Pharmacol.*, *38*, 67–72

[52] Coleman, M. & Cardis, E., for the Ad Hoc Working Group (1989) *Bioelectromagnetics* (in press)

(ii) *European Childhood Leukaemia Incidence Study* (Dr J. Kaldor and Dr D.M. Parkin; in collaboration with Dr J. Michaelis, Johannes Gutenberg University Clinic, Mainz, FR Germany; Dr W.H. Mehnert, National Cancer Registry, Berlin-Johannisthal, German Democratic Republic; Dr H.H. Storm, Danish Cancer Registry, Copenhagen; Dr S. Karjalainen, Finnish Cancer Registry, Helsinki; Dr T. Gunnarson, Swedish Cancer Registry, Stockholm; Mr L. Raymond, Geneva Cancer Registry, Switzerland; Dr A. van der Does-van den Berg, The Hague; Dr G.J. Draper, University of Oxford, UK; Dr J.-M. Lutz, Cancer Registry of Department of Isère, Meylan, France; Dr B. Terracini, University of Turin, Italy; Dr J. Keleti, Semmelweiss University Medical School, Budapest; Dr V. Pompe-Kirn, Cancer Registry of Slovenia, Ljubljana, Yugoslavia; Dr I. Plesko, Cancer Registry of Slovakia, Bratislava Czechoslovakia; Dr R. Schulte-Hermann, University of Vienna; Dr F. Langmark, Norwegian Cancer Registry, Oslo; and Dr W. Zatonski, Polish Cancer Registry, Warsaw)

This collaborative project was started in 1988 following a series of discussions organized by WHO Regional Office for Europe, and involves the participation of representatives from cancer registries in 17 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.

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

The first meeting of project collaborators was held in March 1988, and following circulation of drafts, a final Protocol (IARC Internal Report 89/002) was agreed. Data collection from registries was started in spring 1989, and a preliminary analysis of incidence (for the period 1980–86) will be completed during the year.

(iii) *Chronic low-dose exposures to ionizing radiation* (Dr J. Estève, Dr E. Cardis, Dr J. Kaldor and Dr R. Saracci; in collaboration with Dr E. Gilbert and Dr J. Fix, Battelle, Pacific Northwest Laboratories, Richland, WA, USA; Dr G. Howe, National Cancer Institute of Canada Epidemiology Unit, University of Toronto, Ontario, Canada; Dr V. Beral, Dr L. Carpenter, Dr A. Douglas and Dr P. Smith, London School of Hygiene and Tropical Medicine, London, UK; Mr L. Salmon, United Kingdom Atomic Energy Authority, Harwell, Didcot, UK; Dr G. Cowper, Deep River, Ontario, Canada; Dr S. Fry, Centre for Epidemiological Research, Oak Ridge Associated Universities, Oak Ridge, TN, USA; Dr G.L. Voelz and Dr L. Wiggs, Los Alamos National Laboratory, Los Alamos, NM, USA)

Current radiation risk estimates are based primarily on studies of atomic bomb survivors and medically irradiated individuals, who were exposed to high doses of ionizing radiation over short periods. These studies, however, do not provide direct information on the effects in humans of long-term exposure to low levels of radiation. A more direct assessment of such effects comes from studies of cancer risk among workers in the nuclear industry, many of whom have been continuously exposed to above background levels of ionizing radiation over several decades, and whose exposures are carefully monitored through the use of dosimeters.

A meeting was held at IARC in June 1988 to review completed epidemiological studies of nuclear workers which have been carried out over the last decade and discuss the need for further studies of existing data and new studies of additional cohorts of workers, in order to correctly assess the cancer risk, if any, associated with occupational low-level exposure to ionizing radiation[53].

Aggregated data were sent by several investigators before the meeting, so that preliminary pooled analyses of cancer risk at various sites, taking into account exposure level and time since first exposure, could be carried out. The results were presented at the meeting. The data from Hanford (the largest study) and from Sellafield (the study with the largest number of subjects with exposure greater than 50 mSv) greatly influenced the results of the pooled analyses. A dose-related increase in risk of multiple myeloma, particularly when exposure was lagged by 10 and 15 years, was observed. No significant overall dose-related increase in all cancer mortality or in mortality from leukaemia was seen.

The following studies are currently being developed as a result of this meeting:

Combined analyses of data from existing studies

A protocol was prepared (IARC Internal Report 89/005), in collaboration with the investigators of the original studies of cancer mortality among nuclear workers, to carry out combined analyses of their data. It addresses various methodological problems including choice of study population (because of differences in monitoring practices between facilities) and comparability of dose estimates (see below).

If approval is obtained from appropriate authorities, the data will be sent to IARC in early 1990. The analyses, which will predominantly include studies of radiation effects and calculation of risk estimates for comparison with current risk estimates proposed by regulatory agencies, are expected to take approximately one year.

In parallel, a descriptive study of dosimetric methods is being carried out with the aim of standardizing radiation exposure estimates between facilities, on the basis of a detailed questionnaire completed for each facility involved. Particular problems to be addressed are conversion to common units and the treatment of missing or threshold dose values.

Feasibility of new studies of nuclear industry workers

Table 12 is a summary of a preliminary assessment of the levels of exposure and of the sizes of previously unstudied nuclear worker populations. Eleven countries have agreed to participate in the feasibility phase of a study of these workers. The aim of this phase is to verify the amount, type and quality of information, the need for additional data collection and the feasibility of a follow-up of the workers for cancer incidence or mortality. Particular attention will also be given to differences in radiation monitoring practices and reporting regulations over time, availability of information on potential confounders and choice of study population (monitored workers, contract workers, etc.).

(*j*) **IARC Monographs on the Evaluation of Carcinogenic Risks to Humans** (Dr A. Aitio, Dr T. Kauppinen, Mrs C. Partensky, Mrs I. Peterschmitt, Dr L. Shuker, Dr A. Tossavainen and Mr J. Wilbourn. The following members of other units have contributed to this programme: Dr E. Cardis, Dr M. Coleman, Dr J. Estève, Dr. J. Kaldor, Dr M. Khlat, Dr M. Kogevinas, Dr K. L'Abbé, Dr C.S. Muir, Dr E. Riboli, Dr

[53] Cardis, E. (1988) *Report on Meeting on Cancer Risk among Nuclear Industry Workers, Lyon, June 9–10, 1988* (IARC Internal Technical Report 88/001)

Table 12. Characteristics of cohorts of nuclear industry workers not yet studied for cancer incidence

	Person years	Collective dose (person Sv)	Year of start of industry
Canada	<10 000	<100	1962
Finland	≥25 000	25	1977
France	600 000[a]	1 000	1947
FR Germany	200 000	700[a]	1965
Italy	18 600	50	1963
Japan	250 000[c]	500[c]	1966
Spain	6 500[a]	[b]	1968
Sweden	[b]	25	1972
Switzerland	[b]	[b]	1969
UK	200 000[a]	375	1960
USA	1–2 000 000	5 900[a]	1960

[a] Includes contractors

[b] Not available at present

[c] Since 1982

R. Saracci and Dr L. Simonato for expertise in epidemiology and statistical aspects of data analysis; Dr H. Bartsch, Dr J.R.P. Cabral, Dr R. Montesano, Dr V. Turusov and Dr H. Yamasaki in experimental pathology, toxicology and mutagenesis; Dr M. Friesen, Dr I.K. O'Neill and Dr D. Shuker in analytical chemistry)

During the period July 1987 to June 1989, volumes 42–49 and Supplements 6 and 7 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* were published or in preparation. Descriptions of the meetings concerning Volume 42 and Supplements 6 and 7 were provided in the 1986/87 Biennial Report (pp. 40–41).

Volume 43

An IARC Working Group was convened in June 1987 to consider data relevant to the evaluation of carcinogenic risks to humans from exposures to man-made mineral fibres and radon. A summary of the evaluations of carcinogenicity to humans and animals, and the overall classifications of carcinogenicity to humans are given in Table 13.

Volume 44

In October 1987, an IARC Working Group considered data relevant to the evaluation of carcinogenic risks to humans from alcohol drinking. The Working Group's evaluation was that there is *inadequate evidence* for the carcinogenicity of ethanol and of alcoholic beverages in experimental animals and that there is *sufficient evidence* for the carcinogenicity of alcoholic beverages in humans. The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver was considered causally related to the consumption of alcoholic beverages. The overall evaluation was that alcoholic beverages are carcinogenic to humans (Group 1).

Volume 45

In March 1988, an IARC Working Group considered data relevant to the evaluation of carcinogenic risks to humans from occupational exposures in petroleum refining, and from

Table 13. Carcinogenicity of man-made mineral fibres and of radon and its decay products

Agent	Degree of evidence for carcinogenicity		Overall evaluation[a]
	Humans	Animals	Group
Glass wool	Inadequate	Sufficient	2B
Rock wool	Limited	Limited	2B
Slagwool		Inadequate	2B
Glass filaments	Inadequate	Inadequate	3
Ceramic fibres	No data	Sufficient	2B
Radon and its decay products	Sufficient	Sufficient	1

[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, Group 4: Probably not carcinogenic to humans.

crude oil and major petroleum fuels. The Working Group's evaluation was that: There is *limited evidence* that working in petroleum refineries entails a carcinogenic risk. This limited evidence applies to skin cancer and leukaemia. There is *sufficient evidence* for the carcinogenicity in experimental animals of light and heavy vacuum distillates, of light and heavy catalytically-cracked distillates and of cracked residues derived from the refining of crude oil. There is *limited evidence* for the carcinogenicity in experimental animals of light strain-run naphtha, of straight-run kerosene, of hydrotreated kerosene and of light catalytically-cracked naphtha. An overall evaluation was made that: Occupational exposures in petroleum refining are probably carcinogenic to humans (Group 2A). Table 14 summarizes the Working Group's evaluations on crude oil and petroleum fuels.

Table 14. Carcinogenicity of crude oil and petroleum fuels

Agent	Degree of evidence for carcinogenicity		Overall evaluation[a]
	Humans	Animals	Group
Crude oil	Inadequate	Limited	3
Gasoline[b]	Inadequate		2B
Unleaded automotive gasoline		Limited	
Jet fuel	Inadequate	Inadequate	3
Diesel fuels	Inadequate		
Distillate (light) diesel fuels			3
Marine diesel fuel[b]		Limited	2B
Fuel oils	Inadequate		
Distillate (light) fuel oils			3
—fuel oil No. 2		Limited	
Residual (heavy) fuel oils		Sufficient	2B

[a] See footnote to Table 13.

[b] Other relevant data described in the monographs influenced the making of the overall evaluations.

Table 15. Carcinogenicity of engine exhausts and some nitroarenes

Agent	Degree of evidence for carcinogenicity		Overall evaluation[a]
	Humans	Animals	Group
Diesel engine exhaust	Limited		2A
Whole diesel engine exhaust		Sufficient	
Gas-phase diesel engine exhaust (with particles removed)		Inadequate	
Extracts of diesel engine exhaust particles		Sufficient	
Gasoline engine exhaust	Inadequate		2B
Whole gasoline engine exhaust		Inadequate	
Condensates/extracts of gasoline engine exhaust		Sufficient	
Engine exhaust (unspecified as from diesel or gasoline engines)	Limited		
3,7-Dinitrofluoranthene	No data	Limited	3
3,9-Dinitrofluoranthene	No data	Limited	3
1,3-Dinitropyrene	No data	Limited	3
1,6-Dinitropyrene	No data	Sufficient	2B
1,8-Dinitropyrene	No data	Sufficient	2B
7-Nitrobenz[*a*]anthracene	No data	Limited	3
6-Nitrobenzo[*a*]pyrene	No data	Limited	3
6-Nitrochrysene	No data	Sufficient	2B
2-Nitrofluorene	No data	Sufficient	2B
1-Nitronaphthalene	No data	Inadequate	3
2-Nitronaphthalene	No data	Inadequate	3
3-Nitroperylene	No data	Inadequate	3
1-Nitropyrene	No data	Sufficient	2B
2-Nitropyrene	No data	Inadequate	3
4-Nitropyrene	No data	Sufficient	2B

[a] See footnote to Table 13

Volume 46

In June 1988, an IARC Working Group considered data relevant to the evaluation of carcinogenic risks to humans of engine exhausts and 15 selected nitroarenes, most of which have been identified in engine exhausts. The resulting monographs will be published as Volume 46 in the Monographs series. Table 15 summarizes the Working Group's evaluations on engine exhausts and some nitroarenes.

Volume 47

In October 1988 an IARC Working Group was convened to evaluate some organic solvents, resin monomers and related compounds, pigments, and occupational exposures in paint manufacture and painting. The Working Group considered that the available data provided *sufficient evidence* for the carcinogenicity in experimental animals of phenyl glycidyl ether and antimony trioxide (Group 2B, possibly carcinogenic to humans) and *limited evidence* for 1,2-epoxybutane, bis(2,3-epoxycyclopentyl)ether, bisphenol A diglycidyl ether, antimony trisulfide and titanium dioxide (Group 3, not classifiable as to their carcinogenicity to humans). For dimethylformamide there was *limited evidence* for carcinogenicity in humans (Group 2B). Petroleum solvents, toluene, xylene, phenol, cyclohexanone and morpholine were not classi-

fiable as to their carcinogenicity to humans (Group 3). Occupational exposure as a painter was considered to be carcinogenic to humans (Group 1) but occupational exposure in paint manufacture could not be classified as to its carcinogenicity to humans (Group 3).

Volume 48

In February 1989 an IARC Working Group was convened to evaluate some flame retardants and textile chemicals and exposures in the textile manufacturing industry. The evaluations have been summarized in Table 16.

Volume 49

An IARC Working Group to consider chromium, nickel and welding was convened in June 1989. The Working Group concluded that chromium[VI] compounds are carcinogenic to humans (Group 1) and that metallic chromium and chromium[III] compounds are unclassifiable as to their carcinogenicity to humans (Group 3). In relation to metallic nickel and nickel compounds, the Working Group concluded that nickel compounds are carcinogenic to humans (Group 1) and that metallic nickel is possibly carcinogenic to humans (Group 2B). A monograph on occupational exposures in welding was also prepared and it was concluded that welding fumes are possibly carcinogenic to humans (Group 2B).

Special meetings

The IARC Monographs Programme was started by making evaluations on single chemicals, and the evaluation scheme was generated and further developed for this purpose. More recently, complex mixtures, such as coal tars, polychlorinated biphenyls, therapeutic combinations and industrial exposures have been evaluated. Even more recently the carcinogenicity of complex life-style factors and cultural habits such as tobacco smoking and alcohol drinking have been evaluated. In November 1988 an *ad hoc* meeting was convened to recommend general guidelines for the evaluation of mixtures and groups of chemicals. The deliberations of this Working Group have now been published as IARC Internal Technical Report No. 88/002. Specifically the Working Group made a series of procedural recommendations and in addition recommended changes to the preamble of the *IARC Monographs*.

Ad hoc working groups were convened in 1979 and 1984 to set priorities for agents to be evaluated in the monograph series. Out of the 110 agents that the 1984 priority-setting meeting regarded as high priority, 84 will have been evaluated by the end of 1989. Methods to set priorities have advanced markedly and more information on use and exposures has become available. A further *ad hoc* Working Group was therefore convened in April 1989 to select priorities for evaluation in future IARC Monographs. The report has been published as IARC Internal Report No. 89/004. The distribution in categories by use and level of priority for the agents nominated is given in Table 17. Additional topics discussed by the Working Group were: model carcinogens and non-carcinogens, dietary factors and biological agents such as viruses and parasites.

(*k*) International workshop on experimental and epidemiological approaches to cancer risk assessment of complex mixtures

Both the testing and the risk evaluation of human exposure to complex mixtures present difficult scientific problems. To better define the toxicity of complex mixtures, and thus to give a more precise and reliable risk assessment, there is a need for extensive experimental research as well as development of risk assessment strategies. An international workshop was held in Espoo, Finland, on 14–16 May 1989, organized jointly by the Institute of Occupational Health of Finland, the International Agency for Research on Cancer and the US National Institute of Environmental Health Sciences, at which the lines of exploration likely to yield the most relevant and practically useful information were discussed.

Table 16. Carcinogenicity of some flame retardants and textile chemicals and exposures in the textile manufacturing industry

Agent	Degree of evidence for carcinogenicity		Overall evaluation[a]
	Humans	Animals	Group
Agents and groups of agents			
Chlorendic acid	No data	Sufficient	2B
Decabromodiphenyl oxide	No data	Limited	3
Dimethyl hydrogen phosphite	No data	Limited	3
Tetrakis(hydroxymethyl)phosphonium salts	No data	Inadequate	3
Tris(2-chloroethyl)phosphate	No data	Inadequate	3
para-Chloro-*ortho*-toluidine and its strong acid salts			2A
para-Chloro-*ortho*-toluidine	Limited		
para-Chloro-*ortho*-toluidine hydrochloride		Sufficient	
Disperse Blue 1	No data	Sufficient	2B
Disperse Yellow 3	No data	Limited	3
Vat Yellow 4	No data	Limited	3
5-Nitro-*ortho*-toluidine	No data	Limited	3
Nitrilotriacetic acid and its salts	No data		2B
Nitrilotriacetic acid and its sodium salts		Sufficient	
Mixtures			
Chlorinated paraffins	No data		
Chlorinated paraffins of average carbon chain length C_{12} and average degree of chlorination approximately 60%			2B
—A commercial chlorinated paraffin product of average carbon chain length C_{12} and average degree of chlorination 60%		Sufficient	
A commercial chlorinated paraffin product of average carbon chain length C_{23} and average degree of chlorination 43%		Limited	
Exposure circumstances			
Working in the textile manufacturing industry	Limited		2B

[a] See footnote to Table 13.

Table 17. Priorities for evaluation of carcinogenic risks to humans

Class of agents	High priority	Low priority	Deleted	Testing Recommended
Chemicals	54	40	9	21
Pesticides	20	10	4	4
Drugs	11	14	5	2
Fibres and particulates	—	1	1	4
Occupational exposures and industries	4	2	5	1
Physical agents	2	—	1	—
Naturally occurring substances	4	3	3	—
Food additives	11	8	1	—
Life-style and environmental factors	2	1	2	—

The approaches for improved risk assessment include more effective use of epidemiology (including molecular epidemiology), health surveillance and biological monitoring (*in vivo* data on exposed humans) as well as *in vivo* toxicological studies supplemented with the relevant *in vitro* experiments and knowledge on chemistry.

The proceedings of the workshop will be published in the IARC Scientific Publications series.

3. SITE-ORIENTED STUDIES

(*a*) Liver cancer

Projects bearing upon liver cancer are largely related to the roles of aflatoxins and hepatitis B virus in hepatocellular carcinoma, especially in tropical countries. A number of studies specifically concerning aflatoxins as risk factors are described in section I.2.*g*. In relation to cholangiocarcinoma, a factor that appears to be involved is infestation with the parasite *Opisthorchis viverrini*, possibly in conjunction with enhanced endogenous nitrosation (see section I.2.*e*.vi and section iv below). In view of the strength of evidence for the role of hepatitis B virus, the Gambia Hepatitis Intervention Study has been set up to monitor any preventive effect for liver cancer of the vaccination programme for hepatitis (see section I.7.*a*.i).

(i) *Cohort studies on hepatitis B virus, aflatoxin and other risk factors* (Dr N. Muñoz, Dr F.X. Bosch and Dr J. Estève; in collaboration with Professor H.P. Lee, Dr N.P. Fong and Dr J. Lee, Department of Social Medicine and Public Health, University of Singapore; and Dr P. Srivatanakul and Dr P. Punthumchiuda, National Cancer Institute, Bangkok)

In Singapore, a total of 15 782 Chinese males in the age group 35–65 years were enrolled into this study up to March 1987, of whom 1273 (8%) were found to be positive for HBsAg (Table 18). 25 cases of hepatocellular carcinoma (HCC) have been identified by linking this cohort to the Cancer Registry records up to December 1988. A case–control study nested in the cohort will be carried out once 30 cases of HCC have been identified, to try to relate aflatoxin adducts to albumin in the serum collected at recruitment to the presence of HCC.

Table 18. Cohort study of HBsAg carriers in Singapore

Source of cohort members	Number of serum specimens collected	Serum specimens positive for HBsAg	
		Number	%
Hospitals	11 220	1 087	9.7
Blood bank	3 580	93	2.6
Others	982	93	9.5
Total	15 782	1 273	8.1

In Bangkok, 984 male HBsAg carriers over the age of 30 have been recruited from the blood bank and the outpatient clinic of the National Cancer Institute from July 1987 to May 1989. For each subject, a questionnaire on risk factors for HCC was completed, blood and urine specimens were collected, and physical and ultrasound examinations performed to detect signs of liver disease. Patients in whom liver abnormalities are detected by ultrasound, α-foetoprotein or liver function tests, are re-examined every 1, 2, 3 or 6 months and those without liver abnormalities are being followed up every year. Blood and urine specimens are also collected at each follow-up examination. Up to May 1989, chronic hepatitis and other liver abnormalities have been detected in 249 subjects (25.3%), in six of whom HCC has been diagnosed. Recruitment of subjects into this cohort will continue until 2000 HBsAg carriers have been assembled.

(ii) *Follow-up of a cohort of HBsAg-positive blood donors in Catalonia* (Dr F.X. Bosch, Dr N. Muñoz, and Ms S. Teuchmann; in collaboration with Dr M.C. Rodriguez, Dr M. Casas and Dr A. Plasencia, Municipal Health Department, Barcelona, Spain; Dr J.M. Hernandez, Blood Bank of the Residencia Vall d'Hebro, Barcelona, Spain; and Dr M. Gallen, Hospital del Mar, Barcelona, Spain)

The first analysis in this project was conducted in 1987. The total number of HBsAg-positive blood donors identified and traced up to 1985 was 2486. Nineteen deaths were registered (18 males and 1 female) against 29 expected according to general mortality. Cancer-specific mortality among males and expected number of cases by selected causes are shown in Table 19.

The observed numbers of cases for the major cancer sites did not differ from the expected numbers, except for an unexpected excess of colon cancer. No case of liver cancer has been identified but only 0.5 were expected. It is now planned to link this cohort to the next census

Table 19. Cancer-specific mortality among males in Catalonia and expected number of cases by selected causes

Cause of death	ICD-9	Number observed	Rate per 10^5	Number expected	Ratio O/E	*P* value
Lung cancer	1620–1629	4	45.6	2.1	1.9	0.2
Colon cancer	1530–1539	3	34.2	0.3	10.9	0.003
Stomach cancer	1510–1519	1	11.4	0.7	1.4	0.5
Cerebrovascular accident	4360–4369	2	22.8	0.8	2.5	0.2
Liver cirrhosis	5710–5719	1	11.4	1.8	0.5	0.8
Liver cancer	1550–1559	0	0.0	0.5	0.0	1.0

which will take place in 1990 and to death certificates to reassess the risk of cancer among HBsAg carriers.

(iii) *Descriptive studies of HCC as a clue to its etiology* (Dr N. Muñoz and Dr A. Chalkias; in collaboration with Dr D. Trichopoulos, Department of Hygiene and Epidemiology, School of Medicine, Athens, Greece; supported by EEC grant No. ST2–403)

In order to understand the reasons for the male predominance of HCC, an analysis of the sex ratios in various populations was undertaken. A positive correlation was found between the sex ratios and the age-adjusted incidence rates of HCC. The male predominance was greater in the high-risk populations than in the low-risk ones in the age group 30–60 years. The relative contributions of HBV, aflatoxin, smoking and alcohol to the higher risk of HCC among males was investigated. No statistically significant correlation was found between the sex ratio of HCC and the sex ratios of alcohol consumers, cigarette smokers and HBsAg carriers, suggesting that other factors such as hormonal factors play a role in the male predominance of HCC.

(iv) *Liver cancer etiology in Thailand* (Dr D.M. Parkin, Dr M. Khlat, Dr H. Bartsch, Dr H. Ohshima, Dr R. Montesano and Dr C. Wild; in collaboration with Dr P. Srivatanakul, National Cancer Institute, Bangkok)

A preliminary descriptive analysis of liver cancer in Thailand showed considerable regional variation, particularly for cholangiocarcinoma, which comprised about 40% of registered cases[54]. In five areas of the country with widely different risks for hepatocellular carcinoma and cholangiocarcinoma, the prevalence of risk factors in a sample of the normal adult population has been carried out (markers of infection with hepatitis B virus and *Opisthorchis viverrini*, urine aflatoxin and *N*-nitrosamines). The risk for cholangiocarcinoma clearly correlates with prevalence of *O. viverrini* infection, and in high-incidence areas individuals with evidence of infection demonstrate an increase in endogenous formation of nitrosamines (see section I.2.*e*.viii). The regional variation in incidence of hepatocellular cancer is much less, and not clearly related to prevalence of markers of infection with hepatitis B virus, nor to urinary aflatoxin.

A case–control study investigating risk factors for hepatocellular carcinoma and cholangiocarcinoma in residents of north-east Thailand has also been completed. One hundred cases of primary hepatocellular carcinoma and 100 cases of cholangiocarcinoma were recruited in two hospitals in north-east Thailand and in Bangkok, and controls matched for age and sex were drawn from patients attending the same hospitals. Cases and controls were interviewed in relation to dietary history, smoking, alcohol and contraceptive use, and specimens obtained for investigation of markers of infection with hepatitis B virus and *O. viverrini*. Specimens of blood from cases and controls are being examined to measure concentrations of albumin-bound aflatoxin (see section I.2.*g*.ii). Preliminary results confirm that chronic infection with the virus of hepatitis B confers a high risk for hepatocellular carcinoma, and that serological evidence of infection with *O. viverrini* is strongly associated with cholangiocarcinoma.

Analyses of both studies will be completed during 1989.

[54] Srivatanakul, P., Sontipong, S., Chotiwan, P. & Parkin, D.M. (1988) *J. Gastroenterol. Hepatol.*, *3*, 413–420

(*b*) Oesophageal cancer

(i) *Precancerous lesions of the oesophagus in China* (Dr N. Muñoz; in collaboration with Dr J. Wahrendorf and Dr J. Claude, German Cancer Research Centre, Heidelberg, FR Germany; Dr Qui Song-Liang and Dr Yang Guan-Rei, Henan Institute of Medical Sciences, Zhengzhou, Henan, PR China; Professor M. Crespi, Regina Elena Institute, Rome; Dr R. Raedsch, University of Heidelberg, FR Germany; Dr D. Thurnham, MRC Dunn Nutrition Unit, Cambridge, UK; and Dr P. Correa, Louisiana State University Medical Center, New Orleans, LA, USA)

An epidemiological/endoscopic survey to investigate the prevalence and risk factors of precancerous lesions of the oesophagus among young persons in Huixian, Henan Province, was carried out in May 1988. A total of 887 subjects aged 15–25 years were identified from case households (homes in which one or more cases of oesophageal cancer have been diagnosed since 1981) and from control households. Of these, 545 (62%) accepted to participate in the study and 538 of them underwent upper endoscopy. Young adults from case households have a two-fold increase in risk of chronic oesophagitis as compared to those from control households, and this excess risk was present mainly in males. The strongest risk factor for chronic oesophagitis was the consumption of beverages at scalding temperatures. Other risk factors included low intake of green vegetables, fresh fruits and animal protein, tobacco smoking, use of cotton-seed oil for cooking and use of wood as fuel (Table 20). The results of micronuclei tests and on blood levels of vitamins are not yet available.

(ii) *Case–control studies of oesophageal cancer in high-risk populations of Latin America* (Dr N. Muñoz, Dr J. Estève and Ms S. Teuchmann; in collaboration with Dr C. Victora, Federal University of Pelotas, Brazil; Dr E. de Stefani, Oncology Institute, Montevideo; Dr R. Castelletto, National University, La Plata, Argentina; Dr J. Iscovich, San Martin Hospital, La Plata, Argentina; and Dr P.A. Rolón, Cancer Registry, National University, Asunción)

In Latin America, the highest rates of oesophageal cancer are observed in an area which includes southern Brazil, Uruguay and north-eastern Argentina. These high-risk populations provide a unique opportunity for assessing the role of thermal injury in the causation of oesophageal cancer, because a considerable proportion of the population (about 80%) has the habit of drinking *maté*, a very hot infusion made of *Ilex paraguayensis*, and there is a well

Table 20. Risk factors for chronic oesophagitis among young males adults in Huixian, China

Variables	Relative risk (95% confidence interval)[a]
Consumption of very hot beverages	5.8 (1.6–20.4)
Cigarettes/day: 1–15	1.6 (0.7–3.6)
>15	2.6 (0.7–6.3)
Being member of case household	1.9 (0.9–3.8)
Frequent use of cotton-seed oil	1.9 (0.9–3.8)
Wood as fuel in early 1970s	1.8 (0.8–4.2)
Fresh fruits ≥ 1 time/week	0.5(0.2–1.1)

[a] Multiple logistic regression using a model in which all variables of interest are included.

defined unexposed group (about 20%) who do not drink *maté* at all. To assess the role of thermal injury and of other known risk factors for oesophageal cancer, such as alcohol and tobacco, case–control studies have been carried out in these countries. The Brazilian one revealed that alcohol and tobacco are the main risk factors for this cancer and that there is a weak association with *maté* drinking. In addition, an endoscopic survey carried out in Brazil showed that *maté* drinkers have a two-fold increase of chronic oesophagitis as compared to non-drinkers, after adjusting for the effects of alcohol and tobacco. The case–control study in Uruguay showed strong associations for not only alcohol and tobacco but also for *maté* drinking. The main results of this study are shown in Tables 21, 22 and 23.

Table 21 shows that alcohol and tobacco appear to act in a multiplicative way. The risk for those who smoke black tobacco was about three times higher than the risk for the smokers of blond tobacco. Table 22 shows a clear protective effect associated with the frequent consumption of fruits and vegetables but with a dose–response relationship only for fruits. A strong association for *maté* drinking and clear relationships with the amount of *maté* drunk daily and duration of the habit are seen in Table 23[55]. In Argentina a total of 131 cases and 262 controls were interviewed and data analysis has just started. A pooled analysis of the three case–control studies from Brazil, Uruguay and Argentina will be carried out in a final phase.

As a complement to these investigations, validation studies to evaluate the accuracy and the precision of the perceived and reported information on the temperature at which *maté* is drunk were initiated in May 1988 in Pelotas, Brazil and Montevideo, Uruguay. Regular *maté* drinkers were interviewed about recent smoking and drinking habits, and especially about the way he or she drank *maté*. The actual temperature at which the *maté* was drunk was then registered with a high-quality thermometer. The data are now undergoing statistical analysis.

Table 21. Relative risks (RR) for oesophageal cancer of combined consumption of alcohol and tobacco[a]

Alcohol (ml per day)	Cigarettes per day				Total RR for alcohol
	0–7	8–14	15–24	25+	
0–49	1 (7)	2.0 (12)	3.3 (16)	4.5 (19)	1 (54)
50–149	2.7 (7)	2.4 (5)	6.1 (17)	6.5 (21)	1.6 (50)
150–249	3.9 (3)	8.2 (4)	21.4 (17)	15.1 (22)	4.1 (46)
250–349	10.4 (1)	16.1 (2)	13.5 (7)	30.0 (6)	5.1 (16)
350+	22.7 (3)	18.1 (5)	22.5 (5)	22.6 (20)	6.7 (33)
Total RR for cigarette	1 (21)	1.8 (28)	2.9 (62)	3.1 (88)	(199)

[a] Relative risks are adjusted for age and region; the deviance of the full model is 667.32 and the deviance of the multiplicative model is 673.7. The difference of 6.4 is rather smaller than expected. (Actual numbers in parentheses)

[55] de Stefani, E., Muñoz, N., Estève, J. *et al.* (1989) *Cancer Res.* (in press)

Table 22. Relative risks for oesophageal cancer of consumption of certain foodstuffs[a]

Food	Current frequency of consumption				
	<once a week	1–3 times/ week	>3 times/ week	Daily	Trend (χ)
Meat	1	0.30 (0.1–0.8)	0.38 (0.2–1.0)	0.61 (0.2–1.5)	2.11
Fat	1	1.03 (0.7–1.6)	2.07 (1.2–3.5)	1.44 (1.02–2.2)	2.27
Vegetables	1	0.49 (0.3–0.7)	0.48 (0.3–0.8)	0.56 (0.3–1.0)	−2.45
Barbecue	1	0.86 (0.6–1.2)	1.04 (0.6–1.9)	2.66 (1.3–5.5)	1.73
Fruit	1	0.60 (0.4–0.9)	0.48 (0.3–0.8)	0.33 (0.2–0.5)	−4.58

[a] 95% confidence intervals are given in parentheses.

There are two possible mechanisms through which *maté* drinking could increase the risk of oesophageal cancer. First, the leaves could contain carcinogenic or promoting substances. However, laboratory assays at IARC have failed to reveal any mutagenic or promoting activity. Second, thermal injury caused by hot *maté* drinking could increase the susceptibility of the oesophagus to carcinogens. This possibility is supported by the findings of the endoscopic survey among *maté* drinkers and non-*maté* drinkers in Brazil referred to above and by the results of the study on precancerous lesions of the oesophagus among young adults in China described in section i above.

A direct test of this hypothesis is now being carried out in Paraguay, where *maté* is widely drunk but mainly cold. A case–control study using a similar protocol and questionnaire to the one used in Brazil, Uruguay and Argentina was initiated in Paraguay in January 1988. Up to May

Table 23. Risk for oesophageal cancer of *maté* drinking

Daily amount (litres/day)	Relative risk	Confidence interval	No. of cases
0	1	—	5
0.01–0.49	2.52	0.8–8.4	11
0.50–1.49	3.60	1.3–9.9	133
1.50–2.49	6.07	2.1–17.3	78
2.50+	12.21	3.8–39.6	34
Duration (years)			
0–14	1	—	7
15–29	3.67	1.1–11.8	11
30–44	4.44	1.7–11.4	58
45–59	2.65	1.1–6.5	101
60+	6.40	2.6–16.4	84

1989, a total of 62 cases and 186 controls had been interviewed. The study was designed to include a total of 100 cases and 300 controls.

(c) Laryngeal and pharyngeal cancer

(i) *Case–control study in south-western Europe* (Dr J. Estève, Dr E. Riboli and Dr A.J. Tuyns; in collaboration with Dr A. Zubiri, Cancer Registry of Zaragoza, Spain; Dr A. del Moral and Dr N. Ascunce, Health Department of Navarra, Pamplona, Spain; Dr B. Terracini, Institute of Pathology, Turin, Italy; Dr F. Berrino, National Cancer Institute, Milan, Italy; Mr L. Raymond, Geneva Cancer Registry, Switzerland; Dr W. Lehmann, Geneva University Hospital, Switzerland; and Dr H. Sancho-Garnier and Dr E. Benhamou, Gustave-Roussy Institute, Villejuif, France)

A multinational population-based case–control study of cancer of the larynx and hypopharynx carried out in France, Italy, Spain and Switzerland permitted a detailed study of the risk from smoking and alcohol drinking for cancer at various subsites of the larynx and hypopharynx[56]. The information on alcohol drinking was obtained through a detailed dietary questionnaire, which also allowed evaluation of the protective effect of β-carotene, vitamin C and vitamin E and of high consumption of polyunsaturated fatty acids relative to saturated fatty acids. The four factors showed a clear dose–response relationship with the risk of larynx cancer and hypopharynx cancer; the strongest association was observed for vitamin C from fruit and vegetables and hypopharynx/epilarynx cancer, with a relative risk of 2.03 (1.53–2.70) for those who consumed less than 40 mg relative to others, after adjustment for alcohol and tobacco consumption[57].

This study also recorded a complete occupational history for each case and control. These have been reviewed by a panel of industrial hygienists and epidemiologists who were not aware of the disease status of the subject, in order to evaluate exposure to asbestos, polycyclic aromatic hydrocarbons, arsenic and dust; the evaluation took into account the type of industry and the dates of employment in which the occupation was exercised. This exposure evaluation is now complete, and the analysis of the risk is in progress.

(ii) *Geographical variations in laryngeal cancer* (Mrs J. Nectoux and Dr D.M. Parkin; in collaboration with Dr S. Wilson, Birmingham and West Midlands Regional Cancer Registry, UK; Dr M. Cotter, Cancer Registry of Wales, Cardiff, UK; Dr A.P. Mirra, São Paulo Cancer Registry, Brazil; Dr D.J. Jussawalla, Bombay Cancer Registry, India; Professor S. Schraub, Doubs Cancer Registry, Besançon, France; Dr P. Schaffer, Bas-Rhin Cancer Registry, Strasbourg, France; Dr R. Gurevicius, Lithuanian Cancer Research Institute, Vilnius, USSR; and Professor J. Gaillard, Croix Rousse Hospital, Lyon, France)

Data submitted for *Cancer Incidence in Five Continents* (see section I.1.*a*) show interesting geographic differences in the sub-site distribution of cancers of the larynx and hypopharynx. A geographic correlation between incidence rates of glottic, supraglottic and pyriform sinus cancers, incidence of others cancers related to tobacco and alcohol, and data on per capita consumption of tobacco and alcohol, suggest that the patterns of incidence are best explained by alcohol intake. A more detailed study of the descriptive epidemiology of these cancers has been

[56] Tuyns, A.J. *et al.* (1988) *Int. J. Cancer, 41,* 483–491
[57] Estève, J., Péquignot, G., Riboli, E. *et al.* (1989) (submitted for publication)

started, involving seven cancer registries that show different rates for the main sub-sites of laryngeal and hypopharyngeal cancers. Otorhinolaryngologists in each centre are now assessing the point of origin of each case being registered.

(*d*) Stomach cancer

Dietary factors are strongly implicated in the etiology of stomach cancer, and a new study of such factors is being conducted in Spain (see section I.4.*c*). *N*-Nitroso compounds, either ingested in foodstuffs or formed endogenously in the stomach, seem to be important in this respect (see section I.2.*e*). Gastric bacteria also influence carcinogenesis, some being known to have effects on nitrosation, and *Campylobacter pylori* is associated with stomach disorders that may constitute precancerous lesions. The risk associated with such precancerous lesions is also being studied. Another dietary factor being investigated in etiological studies is the possible protective role of certain micronutrients.

(i) *Precancerous lesions of the stomach in Huixian, China* (Dr N. Muñoz and Ms S. Teuchmann; in collaboration with Dr Lu Jian-Bang, Henan Cancer Institute, Zhengzhou, Henan, PR China; Professor M. Crespi and Dr A. Grassi, Regina Elena Institute, Rome; Dr D. Thurnham, MRC Dunn Nutrition Unit, Cambridge, UK; and Dr P. Correa, Louisiana State University Medical Center, New Orleans, LA, USA)

During the intervention study on precancerous lesions of the oesophagus carried out in Huixian (see section I.3.*b*.i), gastroscopy and gastric biopsies were performed on 248 of the 566 subjects. The histological slides were read independently and blindly by three pathologists. As was the case for the oesophagus, no significant difference in the prevalence of the various precancerous lesions of the stomach was observed between the group that had received retinol, riboflavin and zinc for one year and the placebo group. However, a subsequent logistic regression analysis revealed that increases in blood retinol levels from the initial to the final survey were associated with a reduced prevalence of chronic atrophic gastritis and that there was a tendency for increased blood β-carotene levels to be associated with a lower prevalence of gastric dysplasia.

All histological slides from gastric biopsies were stained with Warthin-Starry stain for *Campylobacter pylori* (a bacterium associated with various types of gastritis). The results are summarized in Table 24. The strongest associations for *C. pylori* are observed for diffuse antral gastritis and gastric dysplasia, although strong associations were also observed for chronic atrophic gastritis and intestinal metaplasia. Those biopsies positive for intestinal metaplasia (IM) were also stained for the various kinds of mucin. Sulfomucins were detected in 17% of IM without dysplasia and in 50% of IM with dysplasia, giving relative risk of 8.5 after adjusting for sex, age and treatment group.

(ii) *Cohort study on chronic gastritis and intestinal metaplasia in Slovenia* (Dr N. Muñoz and Ms S. Teuchmann; in collaboration with Dr I. Matko and Dr A. Jutersek, University Clinical Centre of Ljubljana, Yugoslavia; and Dr M.I. Filipe, School of Medicine, Guy's Hospital, London)

To assess the risk of gastric cancer associated with three types of intestinal metaplasia (IM) defined by the presence or absence of sialo- and sulfomucins, a cohort study was initiated in Slovenia in September 1985. Over 10 000 gastric biopsies taken between 1967 and 1976 were reviewed to identify those with IM. IM was found in at least one gastric biopsy in 1684 patients. Histological evaluation of over 5000 slides from 1876 patients has been completed, and the

Table 24. Association between *Campylobacter pylori* infection and various gastric lesions in Huixian, China

Histological diagnosis	Total number		Positive for *C. pylori*		
	Number	%	Number	%	RR[a]
Normal gastric mucosa or superficial gastritis (reference group)	24	10.5	3	12.5	—
Diffuse antral gastritis	21	9.2	17	81.0	40.4
Chronic atrophic gastritis (CAG) (without intestinal metaplasia (IM))	140	61.1	90	64.3	13.6
CAG + IM	32	14.0	19	59.4	9.4
CAG + IM + dysplasia	12	5.2	8	66.6	34.0
Total	229	100.0	137	59.8	15.2

[a] Relative risk adjusted for sex, age and treatment group.

Table 25. Distribution of intestinal metaplasia (IM) types among gastric biopsies in Slovenia

Year of diagnosis	IM-0	IM-I	IM-II	IM-III	I or II and III	Total
1967	38	16	3	4	4	65
1968	35	10	4	6	3	58
1969	27	15	6	3	4	55
1970	38	20	6	11	7	82
1971	27	33	16	25	15	116
1972	37	83	28	39	13	200
1973	27	108	35	39	23	232
1974	50	143	55	34	26	308
1975	65	119	57	42	23	306
1976	107	182	65	51	49	454
Total	451	729	275	254	167	1876
%	25	40	15	12	8	100
Stomach cancer 1 year after IM biopsy	10	9	12	10	2	43
%	2.4	1.3	4.8	5.0	1.4	2.6
Stomach cancer total	18	25	22	31	13	109
%	4.0	3.4	8.0	12.2	7.8	5.8

preliminary results are shown in Table 25. The proportion of IM type III (20%) is higher than that reported from other European populations (about 10%). Cases of gastric cancer and other malignant tumours occurring in this cohort have been identified by matching them to cancer registry files up to December 1984. A total of 109 cases of stomach cancer were identified but 66 of them were diagnosed within one year of the diagnosis of IM and only 43 were diagnosed after longer intervals. A cohort analysis of these data is in progress.

(iii) *Etiology and chemoprevention of stomach cancer in Venezuela* (Dr N. Muñoz and Dr D.M. Parkin; in collaboration with Dr W.E. Oliver and Dr N. Alvarez, Cancer Control Centre, San Cristobal, Venezuela; and Dr P. Correa, Louisiana State University Medical Center, New Orleans, LA, USA)

High mortality rates for gastric cancer similar to those in Colombia and Costa Rica have been reported in the Andean states of Venezuela. A case–control study to identify the main risk factors is being planned in conjunction with a study to evaluate the efficacy of a screening programme for gastric cancer. It will include 300 cases and two groups of 300 controls each (hospital and neighbourhood controls), matched by sex and age. Exposure to the risk factors will be investigated by means of a questionnaire enquiring about life-style, in particular dietary factors, and consideration will be given to measuring selected markers of exposure in serum (antibodies to *C. pylori*), in DNA from lymphocytes (adducts to nitroso compounds) and in urine (NaCl/creatinine ratio).

A chemoprevention trial is also planned to take advantage of the infrastructure created for the screening programme (see section I.7.*b*.ii). A double blind randomized trial will be carried out to determine whether three years' treatment with certain micronutrients, for which there is some evidence of protective effects in experimental and epidemiological studies (vitamin C, β-carotene, vitamin E), blocks or decreases the progression of intestinal metaplasia to dysplasia, as compared to a group receiving a placebo. A total of 800 subjects with intestinal metaplasia will be included.

(iv) *Etiology of stomach cancer in Costa Rica* (Dr N. Muñoz and Ms S. Teuchmann; in collaboration with Dr R. Sierra and Dr S. Hernandez, Health Research Institute, University of Costa Rica; Dr A.S. Peña, Department of Gastroenterology, Leiden University Hospital, Leiden, Netherlands)

Costa Rica has one of the highest incidences of stomach cancer in the world, but little is known about the risk factors in this population. The role of *N*-nitroso compounds and other mutagens is being investigated (see section I.2.*e*.vi). In addition, a prevalence survey of *C. pylori* antibodies has been carried out in 276 young volunteers from a high-risk community (Turrubares) and a low-risk one (Hojancha) for gastric cancer. IgG and IgA antibodies to *C. pylori* were measured using a modified ELISA technique. The results are summarized in Figure 7. An increase in the prevalence of *C. pylori* antibodies with increasing age is observed, in particular in the low-risk area and for IgA antibodies which might be a marker of more recent *C. pylori* infection. Although no significant difference was observed in the prevalence of either antibody between the two areas, the very high prevalence, even in the youngest age-group (7–10 years), is noteworthy. The overall prevalence in both populations was 71.7%, whereas it is below 10% in children in developed countries.

(v) *European correlation study (EUROGAST)* (Dr M.P. Coleman, Dr C.P. Wild and Dr R. Montesano; in collaboration with Dr D. Forman, Imperial Cancer Research Fund, Oxford, UK)

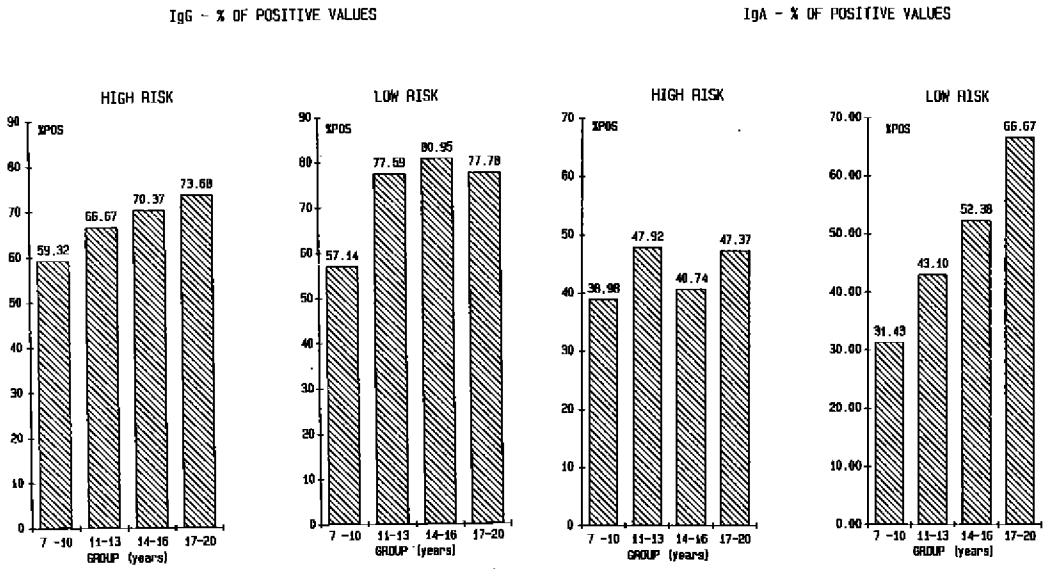

Fig. 7. Prevalence of *Campylobacter pylori* antibodies in Costa Rica children and adolescents

Agency staff are collaborating in an EEC-funded study (EUROGAST: principal investigator Dr D. Forman) designed to estimate the population-level correlation between various markers of chronic gastritis and the incidence and mortality from gastric cancer. Chronic atrophic gastritis is thought to be a precursor lesion for the most frequent type of stomach cancer, the 'intestinal' type of adenocarcinoma. Fourteen centres in six EEC countries and in Algeria, Iceland, Poland and Yugoslavia will participate, covering a 2.6-fold range of stomach cancer incidence. Each centre will provide blood samples from 200 persons, 50 men and 50 women sampled randomly from the general population in the age-groups 25–34 years and 55–64 years. Serum levels of three markers of chronic atrophic gastritis (serum pepsinogen I and II, and antibodies to *C. pylori*) will be measured, together with the levels of nitrosamine-induced DNA adducts in peripheral blood cells, and these will be correlated with incidence and mortality rates from cancer of the stomach and several other major sites in the same countries or regions.

(*e*) Colon cancer (Mrs J. Nectoux and Dr D.M. Parkin)

Although data on cancer incidence and mortality are often presented for the large bowel as whole, it seems reasonably clear that cancers of different parts of the colon and rectum have distinct etiologies.

A review of the geographic variation in sub-site distribution of colon cancer in the data submitted for *Cancer Incidence in Five Continents* is being carried out, together with an investigation of the trends over three time periods, for the same areas, in populations at different levels of adoption of 'western' cultural and dietary habits.

(*f*) Cervical cancer

(i) *Male sexual behaviour and human papillomavirus in high- and low-risk areas for cervical cancer* (Dr N. Muñoz, Dr F.X. Bosch, Dr J. Kaldor, Dr S. de Sanjosé, Ms

N. Charnay, Ms D. Magnin and Ms S. Teuchmann; in collaboration with Dr L. Tafur and Dr N. Aristizabal, Department of Medicine, University of Valle, Cali, Colombia; Dr P. Alonso de Ruiz, General Hospital, Mexico City; Dr N. Ascunce, Institute of Public Health, Pamplona, Spain; Dr K.F. Gey, Hoffmann-La Roche, Basle, Switzerland; Dr M. Gili, Faculty of Medicine, Seville, Spain; Dr L.C. Gonzalez, Office of Social Welfare, Salamanca, Spain; Dr I. Izarzugaza, Department of Health and Consumption, Vitoria, Spain; Dr I. Lind, Statens Seruminstitut, Copenhagen; Dr C. Martos, Department of Health, Zaragoza, Spain; Dr C. Navarro, Department of Health, Murcia, Spain; Dr J. Orfila, Laboratory of General Bacteriology and Immunology, Amiens, France; Dr M. Santamaria, Provincial Hospital of Navarra, Pamplona, Spain; Dr K. Shah and Dr E. Guerrero, Johns Hopkins University, Baltimore, MD, USA; Dr P. Viladiu, St Catarina Hospital, Gerona, Spain; and Dr B. Wahren, National Bacteriological Laboratory, Stockholm)

This study was designed to evaluate risk factors for cervical cancer in two countries with extreme incidence rates (age-adjusted annual incidence rates are 50 per 100 000 in Cali, Colombia, and less than 5 per 100 000 in Spain). Evaluation of the role of female and male sexual behaviour is based on questionnaire responses and the measurement of various biological markers of exposure to sexually transmitted diseases. An important component of the study is the evaluation of the role of various types of human papillomavirus (HPV).

The field part of the study was conducted in Spain from June 1985 to June 1986 (pilot study in Gerona and Zaragoza) and from June 1986 to December 1987 in all nine provinces (Gerona, Zaragoza, Seville, Alava, Guipouzcoa, Vizcaya, Navarra, Salamanca and Murcia). In Colombia the study was initiated in June 1985 and recruitment of cases continued until June 1989. The total number of subjects interviewed and the number of specimens collected are shown in Table 26.

A panel of three cytopathologists (Dr N. Aristizabal, Dr P. Alonso de Ruiz and Dr M. Santamaria) has started the blind review of the cytological smears taken from the subjects (male and female) upon enrolment in the study and the histological slides on which the original diagnosis of cervical cancer was based. Morphological signs of various sexually transmitted infectious agents are also being recorded. Cases for which there is disagreement will be reviewed by the panel during a meeting to be held in Lyon before the end of 1989. For each subject a consensus diagnosis will be reached.

Hybridization tests for HPV DNA have been carried out in the laboratory of Dr K. Shah, all exfoliated cytological samples being screened using the Virapap commercial dot blot kit (Life Technology, Inc.) with probes against HPV 6, 11, 16, 18, 31, 33 and 35. All positive samples for

Table 26. Study of male sexual behaviour and human papillomavirus in relation to cervical cancer: number of subjects interviewed and number of specimens collected

	Number of subjects interviewed			Number of specimens		
	Cases [*in situ*; invasive]	Controls	Male partners	Serum	Cytology (frozen sample)	Biopsy (cases only)
Spain	476 [250; 226]	480	636	1519	1358	179
Colombia	442 [265; 177]	432	437	1242	110	202
Total	918 [515; 403]	912	1073	2761	2468	381

HPV and a fraction of the negatives are being retested using Southern blot analysis under different conditions of stringency. All filters used in the Virapap analysis will be retested using 10–12 additional HPV probes. 2290 cytological samples have already been analysed using the Virapap kit; nearly 20% of samples from females are positive for the HPV types tested and only 2.3% of those from males.

Exposure to sexually transmitted agents is also being assessed by serological assays for Herpes simplex virus types 1 and 2, HPV and cytomegalovirus (Dr B. Wahren, Stockholm) and for *Chlamydia* (Dr J. Orfila, Amiens). Antibodies for syphilis and gonorrhoea are being measured by Dr I. Lind in Copenhagen.

Levels of vitamin A, β-carotene and vitamin E are being measured by Dr K.F. Gey, in Basle.

By June 1989, 2903 questionnaires had been received and processed at IARC, and preliminary analyses have been carried out.

In Spain, about 70% of the women interviewed had a husband or partner at the time of interview, but only 50% in Colombia. Because of this, the field part of the study was extended in Colombia until June 1989 in order to recruit a sufficient number of monogamous women with a current partner to estimate the contribution of the male role. The proportion of married persons (both sexes combined) is 44% in Colombia and 83% in Spain, while for those cohabiting it is 31% in Colombia and 4% in Spain. Among females, the proportion of monogamous women (one lifetime sexual partner) is 51% in Colombia and 80% in Spain. In both countries controls are more often monogamous than cases.

Among males, the proportion with fewer than five sexual partners is 5% in Colombia and 62% in Spain. This proportion was greater for controls than for cases only in Spain. The mean age at first sexual intercourse for females was 18 years in Colombia and 22 years in Spain, and cases tend to start earlier than controls in both countries. In Colombia, 9% of the women reported having practised prostitution, frequently or occasionally, while in Spain only 2% did. The proportion of cases in this category was greater than among controls in both countries. The proportion of males who had had intercourse with prostitutes at least once was 82% in Colombia and 64% in Spain. This proportion was higher among cases than among controls only in Spain (72 versus 55%). Among females the proportion of regular smokers was 20% in Colombia and 27% in Spain. In both countries this proportion was higher among cases than among controls. The proportion of women without any education was 9% in Colombia and 19% in Spain, and it tended to be higher for cases than for controls.

These preliminary findings tend to show that the prevalence of the various risk factors for cervical cancer is higher in Colombia than in Spain, and it is usually higher for cases than for controls. The role of the male seems to be less strong than expected, especially in Colombia. Further interpretation of the questionnaire data will be made when full results of the various laboratory assays are available.

(ii) *Prevalence of risk factors for cervical cancer among prostitutes and young males in Spain and in Colombia* (Dr S. de Sanjosé, Dr F.X. Bosch, Dr N. Muñoz; in collaboration with Dr L. Tafur and Dr N. Aristizabal, Department of Medicine, University of Valle, Cali, Colombia; Dr N. Ascunce, Institute of Public Health, Pamplona, Spain; Dr I. Izarzugaza, Department of Health and Consumption, Vitoria, Spain; Dr L.C. Gonzalez, Office of Social Welfare, Salamanca, Spain; and Dr V. Palacio, Principado de Asturias, Oviedo, Spain)

As an extension to the case–control study on cervical cancer in Spain and Colombia, samples will be obtained from prostitutes and young sexually active males in both countries in order to

assess the prevalence of infectious agents regarded as possible risk factors for cervical cancer, and questionnaires will be used to obtain additional data on exposure to possible risk factors.

A protocol and questionnaires are being developed at IARC. The first meeting of collaborators took place in June 1989 and the field part of the project is expected to begin in 1990.

(iii) *International Biological Study on Cervical Cancer (IBSCC)* (Dr F.X. Bosch, Dr. N. Muñoz, Dr J. Kaldor, Ms N. Charnay; in collaboration with Dr J. Peto, Institute of Cancer Research, Sutton, UK; Dr M. Agapitos, University of Athens, Ampelokipi-Athens, Greece; Dr E. Alihonou, National University of Bénin, Cotonou; Professor S. Bayo, Institut National de Recherche en Santé Publique, Bamako, Mali; Dr J.-Y. Bobin, Centre Léon Bérard, Lyon, France; Dr H. Cherif Mokhtar, Centre Hospitalo-Universitaire, Setif, Algeria; Dr D. Dargent, Edouard Herriot Hospital, Lyon, France; Dr A. Daudt, Federal University of Pelotas, Brazil; Dr M.M. Galasso, Hospital San Filippo Neri, Rome; Dr P. Ghadirian and Dr P.Gauthier, Hôtel-Dieu de Montréal, Canada; Dr B. Guijon, University of Manitoba, Winnipeg, Canada; Dr M. Gurgel Carlos da Silva, Ceara Cancer Registry, Fortaleza-Ceara, Brazil; Dr M.O.A. Malik, University of Khartoum, Sudan; Dr B. Modan, Chaim Sheba Medical Center, Tel-Hashomer, Israel; Dr Ll. M. Puig Tintoré, Hospital Clinic i Provincial, Barcelona, Spain; Dr J.L. Rios-Dalenz, Cancer Registry of La Paz, Bolivia; Dr A.R. Teyssie, National Institute of Microbiology, Buenos Aires; Dr D. Raudrant, Hôtel Dieu, Lyon, France; Dr P.A. Rolón, National Register of Tumour Pathology, Asunción; Dr A. Schneider, University Clinic, Ulm, FR Germany; Dr R. Testa Paredes, National Oncology Institute, Panama; Dr M. Torroella, National Cancer Institute, Habana; Dr A. Vila Tapia, Regional Clinical Hospital, Ministry of Health, Concepción, Chile; Dr W. Zatonski, M. Sklodowska-Curie Memorial Cancer Centre, Warsaw)

The International Biological Study on Cervical Cancer (IBSCC) is creating at IARC a repository of cervical cancer tissue and of sera from cervical cancer patients for use in studying markers of exposure to known or suspected risk factors. Samples of invasive cervical cancer will be collected in about 20 countries with a broad range of incidence rates of cervical cancer. Initially, DNA/RNA hybridization methods will be used to assess the prevalence of specific types of HPV, all assays being performed in one reference laboratory. A brief questionnaire will also be used to assess subjects' exposure to other known risk factors for cervical cancer. It is envisaged to organize a collection of exfoliated cervical cells from appropriate samples of healthy women in some of the same countries.

Countries participating in this project are shown in Table 27 grouped according to their incidence rates of cervical cancer and by broad regions of the world. Data and specimen collection started in 1989.

(iv) *Risk factors for cervical cancer in rural China* (Dr D.M. Parkin and Dr J. Estève; in collaboration with Dr Zhang Z.F. and Professor Yu S.Z., School of Public Health, Shanghai Medical University, PR China)

Data collected in the course of a population screening programme for cervical cancer, in Jing-An county, Jiangxi province, China, were used to study the importance of different risk factors in this population[58]. One hundred and nine cases of invasive squamous cell carcinoma

[58] Zhang Z.F., Parkin, D.M., Yu S.Z., Estève, J. & Yang X.Z. (1989) *Int. J. Epidemiol., 43,* 762–767

Table 27. Collaborating countries in the International Biological Study on Cervical Cancer, and age-adjusted incidence rates of cervical cancer per 100 000

Region	Country	Incidence	Region	Country	Incidence
N. America	Canada	9–20	Europe	UK	9–16
				France	12–16
Central	Cuba	17		Spain	5–7
America	Panama	>35		Italy	9–10
				FR Germany	12–20
South	Brazil	>35		Greece	10–20[a]
America	Colombia	>35		Poland	12–20
	Chile	>35			
	Bolivia	>35	Middle East	Israel	3–5
	Paraguay	>35			
	Argentina	10–28	Africa	Mali	15
				The Gambia	20–35[a]
South-East				Benin	20–35[a]
Asia	Thailand	12		Sudan	20
				Algeria	24

[a] Estimated

occurred in women aged 35–85 years during a 12-year period, and five controls per case matched for age and residence were selected from the same population. Important risk factors in this population are the number of sexual partners of the woman and her husband (as found in other studies), but poor genital hygiene emerged as a risk factor more clearly than in studies of western populations (odds ratios were 4.8 for absence of daily genital washing, relative to washing every day, and 0.3 for the use of sanitary napkins).

(v) *Workshop on human papillomavirus and cervical cancer*

To review the state of the evidence on the association between cervical cancer and human papillomavirus and to discuss how it might be improved, a multidisciplinary meeting was held in Copenhagen from 1 to 3 March 1988 under the auspices of the IARC and the Danish Cancer Registry, with additional support from the Danish Cancer Society. It was agreed that the epidemiological evidence for the association remained inconclusive, and a number of problems needing attention were highlighted. The working papers and discussions formed the basis for a meeting report[59] and an IARC Scientific Publication[60].

(*g*) Breast cancer

The main hypotheses on the etiology of breast cancer relate to hormonal and dietary factors. In addition to the studies reported in this section, a major multifactorial study is in progress within the SEARCH programme (see section I.3.*k*.iv), and specifically diet-oriented studies in Italy (see section I.4.*c*) and Argentina (see section III.3.*b*.v) have been completed. Further-

[59] Armstrong, B., Jensen, O.M., Muñoz, N. & Bosch, F.X. (1988) *Lancet, i*, 756–758

[60] Muñoz, N., Bosch, F.X. & Jensen, O.M., eds (1989) *Human Papillomavirus and Cervical Cancer* (IARC Scientific Publications No. 94), Lyon, International Agency for Research on Cancer

more, genetic aspects are under investigation with the help of families in whom unusual frequencies of breast cancer have occurred (see section I.5.*c*).

(i) *Breast cancer and reproductive and endocrine factors in premenopausal Chinese, Chinese American and Caucasian American women* (Dr A.J. Sasco, Dr E. Riboli and Dr R. Saracci; in collaboration with Professor Meng Xuan Hu and Dr Liu Qing, Sun Yat Sen University of Medical Sciences, Guangzhou, PR China; Dr D.P. Rose and Dr N.J. Haley, American Health Foundation, Valhalla, NY, USA)

The aim of the study is to evaluate the relationship between hormonal profiles and breast cancer incidence in females. The hormonal hypothesis for breast cancer etiology would provide a coherent explanation of epidemiological evidence of increased risk for nulliparous women, women with a late first birth, with anovulatory cycles, early menarche and late menopause, as well as the observed association of breast cancer with other hormone-dependent cancers, such as cancer of the ovary, endometrium and colon.

This study is using a case–control approach and will also permit comparisons of control women among population groups with contrasting incidence of the disease. Study groups have been selected from the population of Guangdong province in the People's Republic of China, the Chinese population of New York City in the USA, and the Caucasian population of New York City.

Incident cases, all of them pre-menopausal, have been selected from each population group. Control women were pair-matched to the cases on the basis of age (±2 years). Women taking contraceptive pills or any other hormonal treatment, reserpine or tranquillizers have been 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 has been administered to cases and controls, including 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 have been collected between days 20 and 24 of the menstrual cycle. The American Health Foundation (New York) will analyse the samples for testosterone, estradiol, progesterone, prolactin and growth hormone.

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 will be completed in late 1989.

(ii) *European case–control study of male breast cancer* (Dr A.J. Sasco and Dr R. Saracci; in collaboration with Professor D. Trichopoulos, University of Athens Medical School, Athens; and Dr D.P. Rose and Dr N.J. Haley, American Health Foundation, 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.

Several case–control groups will be assembled in participating European centres (Czechoslovakia, France, Greece, Italy, the Netherlands, Yugoslavia). The aim is to enrol about 200

incident breast cancer cases over a two-year period. The matching ratio will be three controls per case. Cases and controls will be matched with the cases for age (±2 years).

A detailed questionnaire will be administered to cases and controls, covering the following items: personal identification data, data on diagnosis, reproductive and sexual life history, life-long history of use of hormones, personal history of diseases, family history of cancer, nutritional and personal habits and body build.

Blood samples will be collected for determination of hormonal profiles (androgens and estrogens) and hepatic function.

A meeting of collaborators was held at IARC in March 1989 to discuss the protocol of the study. A pilot phase will be conducted in summer 1989 and subject recruitment is planned to start in late 1989.

(iii) *Survey of breast cancer in the 'Département du Rhône'* (Dr A.J. Sasco; in collaboration with Dr B. Fontanière, Centre Léon Bérard, Lyon, France; Professor J. Fabry, Université Claude Bernard, Lyon, France; and Dr V. Sciortino, Securité Sociale, 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. Analyses allow determination of incidence rate, distribution of stage at diagnosis, histology, as well as evaluation of some selection factors for place and mode of diagnosis.

Preliminary results indicate that 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 its demonstration of the scattering of patients over a wide range of public and private treatment institutions.

(*h*) Bladder cancer

(i) *Bladder cancer and multiple risk factors in Spain* (Dr E. Riboli; in collaboration with Dr C. Gonzales, Unit of Epidemiology and Biostatistics, Hospital Sant Jaume i Santa Magdalena, Mataro (Barcelona), Spain; Dr G. Lopez-Abente, Unit of Preventive Medicine, Centro Ramon y Cajal, Madrid; Dr A. Escolar Pujolar, Public Health Service, Cadiz, Spain; Dr M. Errezola, State Public Health Service, Basque Government, Vitoria, Spain; Dr A. Companys, Municipal Health Service, Barcelona, Spain)

A multicentre case–control study was started in 1985 in four areas (Barcelona, Cadiz, Madrid and the Basque Country), with the participation of 13 hospitals. The study was aimed at investigating the association between the risk of bladder cancer and a number of potential risk factors: diet, coffee, occupational exposures, tobacco smoking, passive smoking exposure, medical history of diabetes and urinary infections.

The collection of data was completed at the end of 1986 with the inclusion of 497 cases and 1114 controls. Controls were matched to cases for sex, age and residence. Half of the controls

were recruited from patients discharged from the hospitals where the cases were hospitalized and half were healthy subjects living close to the cases. All cases and controls were interviewed at home.

Statistical analyses on occupational exposure confirmed the findings from an earlier Spanish study of an increased risk of bladder cancer among textile industry workers[61]. Preliminary results indicate a four-fold increased risk for smokers and a reduced risk for ex-smokers compared to current smokers. Analysis for history of urinary infections provides support for the hypothesis that past infections may increase the risk of bladder cancer. Analyses are also being completed for the association with diet.

(ii) *Bladder cancer in Tarragona (Spain) and Uruguay* (Dr F.X. Bosch, Dr E. Cardis, Dr J. Estève, Dr H. Bartsch and Dr N. Muñoz; in collaboration with Dr E. de Stefani, Oncology Institute, Montevideo; Dr J. Borras, Dr A. Lafuerza and Dr C. Galceran, Spanish Cancer Society, Tarragona, Spain; and Dr V. Moreno, Autonomous University of Barcelona, Spain)

The Cancer Registry in Tarragona has repeatedly reported very high incidence of bladder cancer among males (age-adjusted incidence rate 23.7 per 10^5 in 1980–83). In contrast, the incidence of lung cancer is relatively low (age-adjusted incidence rate 30.5 per 10^5 in 1980–83). Analysis of world cancer incidence data indicates that in the registry of Tarragona, the ratio of bladder cancer to lung cancer incidence is exceptionally high (0.78) (Figure 8).

Data from a hospital-based registry in Montevideo (Uruguay) indicate that bladder cancer is, here again, one of the most frequent cancers in males, but the ratio of bladder to lung cancers is only 0.35.

A protocol is being prepared for a study which initially will take place in Uruguay and Tarragona of the role of cigarette smoking history in bladder cancer, with possibly a concurrent study on lung cancer. Detailed tobacco smoking histories, including information on temporal patterns of exposure, changes in smoking habits and type of tobacco (black vs. blond) will be analysed to expand the understanding of the mechanisms of tobacco-induced bladder carcinogenesis. Collaboration will be established with relevant laboratories so that information on biological markers of exposure to tobacco compounds and other chemicals can be integrated into the study.

A meeting will take place in 1990 to review the epidemiological evidence on the risk for cancers of the lung, oral cavity, pharynx and larynx, oesophagus and bladder from different types of tobacco, and will include experts in the field of biological markers. The protocol of the study will be finalized during this meeting.

(iii) *DNA adducts in urinary bladder and excretion of urinary mutagens in tobacco smokers* (Dr C. Malaveille, Dr M. Castegnaro, Dr M. Friesen, Dr M. Peluso, Mrs L. Garren, Mrs A. Hautefeuille and Dr H. Bartsch; in collaboration with Dr P. Vineis, University of Turin, Italy; Dr F. Kadlubar, National Center for Toxicological Research, Jefferson, AR, USA; Dr S.R. Tannenbaum, Massachusetts Institute of Technology, Cambridge, MA, USA; and Dr N. Caporaso, National Cancer Institute, Bethesda, MD, USA)

Epidemiological studies have identified cigarette smoking as a risk factor in bladder carcinogenesis, with a 2.5 times higher risk among smokers of black tobacco than among

[61] Gonzalez, C.A., Lopez-Abente, G., Errozola, M., Escolar, A., Riboli, E., Izarzugaza, I. & Nebot, M. (1989) *Int. J. Epidemiol.* (in press)

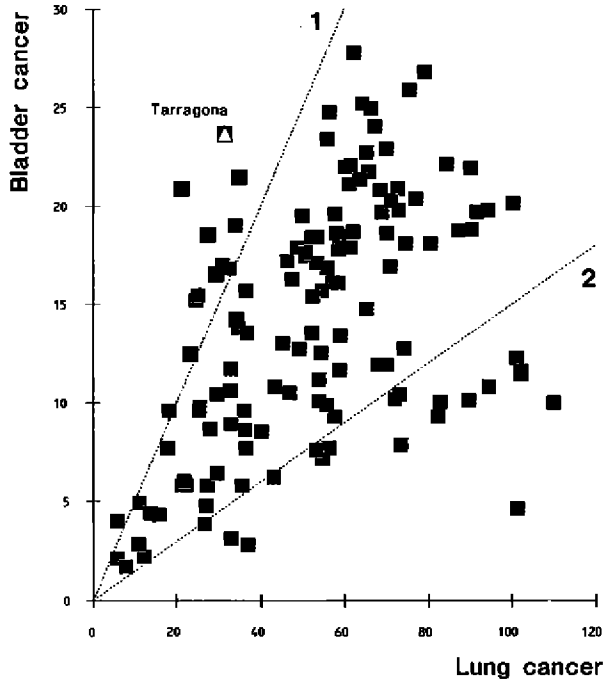

Fig. 8. Correlation between age-adjusted incidence rates of lung and bladder cancer in 131 cancer registries

Line 1: Ratio of bladder cancer incidence/lung cancer incidence = 0.5
Line 2: Ratio of bladder cancer incidence/lung cancer incidence = 0.15
Source: Cancer Incidence in Five Continents, *Vol. V*

smokers of blond tobacco. In this project, mutagenicity in urine from smokers of black tobacco was found to be twice the level in that from blond tobacco smokers after adjustment for the same nicotine uptake[62]; the former also had a higher level of 4-aminobiphenyl residues bound to haemoglobin[63].

Previous work has shown that urinary mutagens excreted by smokers of black and blond tobacco are planar molecules and specifically induce frameshift mutations in *S. typhimurium* strain TA98, which is known to be responsive to aromatic amines. The mutagenicities of urinary extracts were compared after treatment with or without sodium nitrite in the presence of hypophosphorous acid; this procedure deaminates aromatic amines to the parent hydrocarbon. After 1 min of reaction with sodium nitrite, the S9-mediated mutagenicity of urinary extract disappeared completely, showing that primary aromatic amines are indeed the mutagens.

In order to characterize the tobacco-derived mutagens excreted by black-tobacco smokers, ^{32}P-postlabelling techniques have been applied to examine the DNA adducts formed with calf

[62] Malaveille, C., Vineis, P., Estève, J., Ohshima, H., Brun, G., Hautefeuille, A. Gallet, P., Ronco, G., Terracini, B. & Bartsch, H. (1989) *Carcinogenesis, 10,* 577–586

[63] Bryant, M.S., Vineis, P., Skipper, P.C. & Tannenbaum, S.R. (1988) *Proc. Natl. Acad. Sci. USA, 85,* 9788–9791

thymus DNA in the presence of a metabolic activation system. 2-Naphthylamine and 4-aminobiphenyl are bladder carcinogens that are thought to contribute to the carcinogenic effects of tobacco smoke both in experimental animals and in humans. However, the adducts did not correspond on the autoradiograms to those formed by *N*-hydroxy-2-amino-3-methylimidazolo[4,5-*f*]quinoline, *N*-hydroxy-2-naphthylamine or *N*-hydroxy-4-aminobiphenyl. The comparison of the autoradiograms revealed that none of the reference aromatic amines is responsible for the adduct pattern produced by the urinary mutagens although they could be derived from C-oxygenated metabolites of one or more of these aromatic amines.

As a follow-up to this study, work is in progress to isolate and characterize mutagenic substance(s) from urine of black tobacco smokers. Another multicentre study is examining whether the acetylator phenotype of cigarette-smoking subjects affects their DNA adduct levels in the urinary bladder, haemoglobin adduct levels or excretion of mutagens.

(*i*) Malignant melanoma

(i) *Diagnostic criteria* (Dr C.S. Muir, Mrs J. Nectoux, Dr G.J. Macfarlane and Mr P. Maisonneuve; in collaboration with Dr H. Bharucha, Institute of Pathology, Queen's University of Belfast, UK; Dr J. Briggs, Frenchay Hospital, Bristol, UK; Dr R.A. Cooke, North Brisbane Hospital Board, Brisbane, Australia; Dr A.G. Dempster, Department of Pathology, University of Otago, Dunedin, New Zealand; Dr E.P. van der Esch, Netherlands Cancer Institute, Amsterdam, The Netherlands; Dr W.B. Essex, Alfred Hospital, Prahran, Victoria, Australia; Dr P.A. Hofer, Institute of Pathology, University of Umeå, Sweden; Dr A.F. Hood, John Hopkins Medical Institutions, Baltimore, MD, USA; Dr P. Ironside, Peter MacCallum Hospital, Melbourne, Australia; Dr T.E. Larsen, Ulleval Sykehus, Oslo, Norway; Dr J.H. Little, Princess Alexandra Hospital, Brisbane, Australia; Dr R.S. Pfau, Johns Hopkins Medical Institutions, Baltimore, MD, USA; Dr R. Philipps, Department of Epidemiology and Community Medicine, University of Bristol, UK; Dr K.M. Pozharisski, Petrov Research Institute of Oncology, Leningrad, USSR; Dr M. Prade, Gustave Roussy Institute, Villejuif, France; Dr F. Rilke, National Institute for the Study and Treatment of Tumours, Milan, Italy; and Dr K. Schafler, Queen Victoria Medical Centre, Melbourne, Australia)

To assess whether the increase in malignant melanoma incidence could be due, at least in part, to changes in histological criteria of malignancy, pathologists in nine countries reviewed diagnoses of 50 pigmented naevi (40 junctional and compound; 10 intradermal) and 20 malignant melanoma made in each centre around 1930, around 1955 and around 1980, totalling 2667 cases. Overall 2.8% of cases originally reported as benign or dubious benign (B/DB) were reviewed as dubious malignant or malignant (DM/M), while 4.4% of the DM/M diagnoses were held to be B/DB. These shifts in diagnostic category in a study designed to give maximum attention to these lesions—the junctional and compound naevi—in which a change in opinion as to malignancy would be most likely to arise, were considered unlikely to be responsible for the continuous increase observed in malignant melanoma incidence, and other explanations must be sought, such as an increase in the frequency of precursor lesions.

(ii) *Etiological factors of plantar melanoma in Paraguay* (Dr D.M. Parkin and Dr M. Khlat; in collaboration with Dr P.A. Rolón, National University, Asunción, Paraguay)

Data from Paraguay indicate that melanoma of the sole of the foot is relatively common (as it is in African countries). The situation in Paraguay, where the entire population of approximately

4 million is well covered by hospital services, is particularly favourable for a study of etiological factors, which has never been attempted previously. A case–control study has been started, which examines currently suspected factors of importance, such as wearing shoes, presence of plantar naevi, trauma and thermal injury, and also collects information on the risk factors for cutaneous melanoma in European populations.

After a pilot phase, the main study began in December 1988. The aim is to recruit 50 cases, with four controls per case, matched by age and sex and residence.

The study is planned to terminate in 1991.

(*j*) Thyroid cancer (Dr M.P. Coleman and Mr A. Bieber; in collaboration with Dr B. Pettersson and Dr H.-O. Adami, University of Uppsala, Sweden; and Professor E. Schifflers, University of Namur, Belgium)

Thyroid cancer incidence data, by histological type and sex, for the period 1958–81 have been reviewed by Dr Pettersson (principal investigator). Time trends are being examined by age, period and cohort modelling and geographic differences in incidence related to the presence of water supplies deficient in iodine (before the regular supplementation of the water supply, which began in the 1960s). Preliminary results suggest that time trends have differed for the main histological types in Sweden as a whole, and that trends in iodine-deficient regions are distinct from those elsewhere; for papillary adenocarcinoma, the effect of residence in an iodine-deficient region appears to be different for the two sexes. Further analysis of the complex interaction between histological type, sex and geographic region is expected to throw further light on the role of iodine deficiency in the etiology of thyroid cancer.

(*k*) Case–control studies network (the SEARCH programme) (Dr P. Boyle and Dr R. Saracci)

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 and thereby improve prospects for prevention.

SEARCH, as a collaborative, international programme, offers a number of advantages to participating centres in providing: 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 be able to undertake in isolation. In promoting local input into all these studies, IARC recognizes the importance of this aspect for both the quality of research locally and for the IARC.

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. However, the most important function of the SEARCH collaborative network 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.

SEARCH also aims to promote cancer epidemiology in centres where, for example, trained investigators exist in isolation who would benefit from exposure from experts in their field. Involving such centres in study groups containing recognized experts provides valuable training for epidemiologists. The present structure of SEARCH favours participation by centres from

affluent countries; mechanisms are now being investigated to bring into the SEARCH network, centres from rapidly developing countries where aspects of the historic fact of poverty may still play an important role in determining cancer incidence.

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 a regular meeting in Lyon with the responsible IARC staff and external experts. The initial meeting is an introductory, planning meeting where the subject to be studied is reviewed by epidemiological and laboratory scientists, hypotheses are proposed, discussed and formulated, 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 will transmit to Lyon for central analysis. Each centre, however, it is at liberty to collect whatever other pieces of information it wishes and, at the end of the study, is strongly encouraged to undertake analysis of its own data as well as participating actively in the central analysis.

The work of the SEARCH programme can be considered under two main headings: the studies at various stages of development (summarized in Figure 9), and technical support for collaborators.

(i) *Cancers of the pancreas, gallbladder and bile duct* (Dr P. Boyle and Dr R. Saracci; in collaboration with Dr H.B. Bueno de Mesquita, National Institute for Public Health, Bilthoven, The Netherlands; Professor N.W. Choi, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada; Dr P. Baghurst, Commonwealth Scientific and Industrial Research Organization, Adelaide, Australia; Professor G. R. Howe, National Cancer Institute of Canada Epidemiology Unit, Toronto, Ontario, Canada; Dr P. Ghadirian, Montreal Cancer

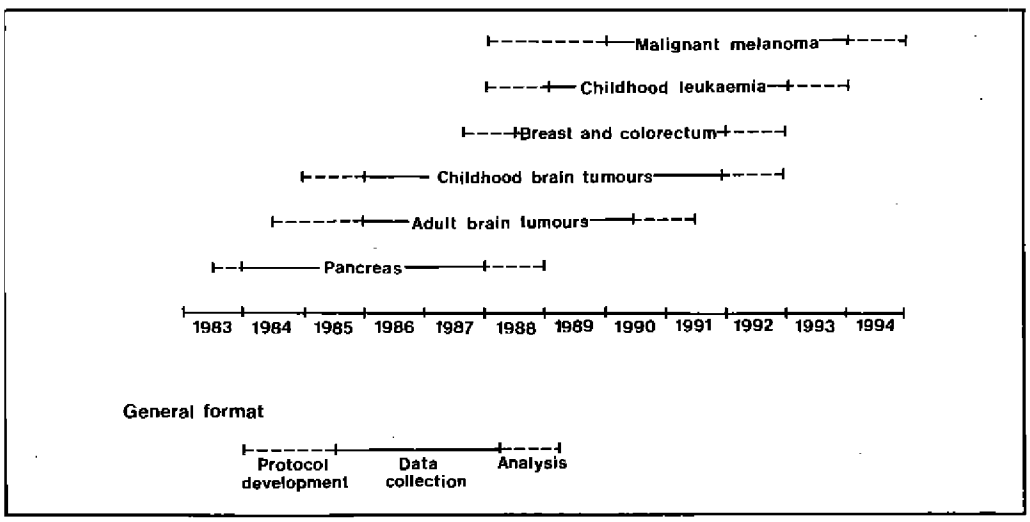

Fig. 9. Schedule of studies being conducted within the SEARCH programme

Institute, Quebec, Canada; and Dr W. Zatonski, Institute of Oncology, Warsaw; Professor A.J. McMichael, Professor A.B. Miller and Dr 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 life-style factors in the etiologies of cancers of the pancreas, gallbladder and bile duct. In December 1987, provisional results were presented to the collaborators and the first full analysis outlined to participants at a meeting convened in Lyon in April 1989. The final results and manuscripts of journal articles and an IARC Scientific Publication will be substantially available at the final meeting of collaborators at IARC in November 1989.

Cancer of the pancreas is a fairly common and rapidly fatal form of cancer in western society, but little is known about the etiology apart from an elevation in risk associated with cigarette smoking. A number of hypotheses were determined as important for investigation by the initial study group meeting in January 1983. Specifically, these related to the role of fats and other personal habits (consumption of alcohol, tobacco, coffee and artificial sweeteners) and occupational exposure to certain chemicals in the etiology of this disease and also to the role of cholecystectomy and pre-existing diabetes. The role of elevated protein consumption, thought to increase pancreatic cancer risk, was considered important to investigate in view of a demonstrated association relating to chronic stimulation of pancreatic enzyme production. Finally, it was decided to investigate the importance of specific agents which stimulate the release of gut hormones such as cholecystokinin (pancreozymin), which at that time were suspected from laboratory findings of being of potential importance in pancreatic carcinogenesis.

The initial results of this study clearly demonstrate an increase in pancreatic cancer risk with increasing consumption of cigarettes (see Table 28); there was absolutely no evidence of any heterogeneity in this finding between the different centres. Another interesting finding from this study was the strong and consistently found protective effect of asthma, eczema or hay fever. There were also consistent findings associating pancreatic cancer risk with various aspects of dietary intake, particularly from animal sources.

The results from the collaborative studies of gallbladder cancer and bile duct cancer are now being analysed.

Table 28. Pancreatic cancer risk[a] and total lifetime cigarette consumption

Centre	Non-smokers	Lifetime cigarette consumption		
		1000–149 999	150 000–299 999	300 000 +
Adelaide	1.00	0.79	1.52	1.71
Toronto	1.00	1.49	2.83	3.76
Utrecht	1.00	1.36	1.86	2.62
Warsaw	1.00	1.41	3.20	1.48
Montreal	1.00	1.97	1.94	3.61
Overall[b]		1.46 (1.12, 1.91)	2.37 (1.78, 3.15)	2.86 (2.12, 3.86)

[a] Adjusted for age, sex and response status; overall adjustment for centre also (95% confidence intervals in parentheses)

[b] Chi-square for trend is 47.04 (1 d.f.)

(ii) *Brain tumours in children* (Dr S. Preston-Martin, Dr P. Boyle and Dr R. Saracci; in collaboration with Dr R. Peris-Bonet, National Register of Childhood Tumours, Valencia, Spain; Dr N.W. Choi, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada; Dr S. Cordier, National Institute for Health and Medical Research, Paris; Dr G. Filippini, C. Besta Neurological Institute, Milan, Italy; Dr E. Holly, Northern California Cancer Center, San Francisco, CA, USA; Dr M. McCredie, New South Wales Central Cancer Registry, North Ryde, Australia; and Dr J. Stanford, University of Washington, Seattle, USA)

Brain tumours in children are sufficiently uncommon to make their study in any single centre difficult. In view of this, it is not surprising that little is known about their etiology. The main hypothesis tested in this study has been suggested by laboratory findings; this relates to the role of nitrosamines, nitrosatable substances and inhibitors of nitrosation in the risk for this disease. Data on possible exposure to nitrosamines and/or their precursors as a result of passive smoking, from certain dietary sources and through intake of nitrate and nitrite from food and water are being collected, along with information about vitamin C intake, which has been demonstrated to be able to inhibit nitrosamine formation from amino substrates in man.

Details of a collaborative study of childhood brain tumours were first circulated by IARC in 1983 and the study protocol was developed by Dr S. Preston-Martin. Subsequently, the study was incorporated into the SEARCH programme. Data collection has now been completed in Milan, Paris and will terminate in early 1990 in Valencia, Manitoba and Sydney. A study has been funded in three centres in the USA—Los Angeles, San Francisco and Seattle Puget Sound, where data collection will continue until 1992.

A full analysis of the first five data sets will be conducted at IARC by the middle of 1990, although the final result from the study will not be available until at least the end of 1992, when the US part of the study is scheduled to be completed.

(iii) *Adult brain tumours* (Dr P. Boyle and Dr R. Saracci; in collaboration with Dr A. Ahlbom, National Institute of Environmental Medicine, Stockholm; Dr N. Choi, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada; Professor G. R. Howe, National Cancer Institute of Canada Epidemiology Unit, Toronto, Ontario, Canada; Dr R. Gurevicius, Lithuanian Cancer Research Institute, Vilnius, Lithuanian SSR, USSR; Professor A.J. McMichael, Department of Community Medicine, University of Adelaide, Australia; Dr F. Menegoz, Cancer Registry of the Département de l'Isère, Meylan, France; Dr M. Salzburg, Department of Social and Preventive Medicine, Monash Medical School, Melbourne, Australia; Professor D. Trichopoulos, Department of Hygiene and Epidemiology, University of Athens Medical School, Athens; and Professor J. Wahrendorf, German Cancer Research Centre, Heidelberg, FR 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 (FR Germany), Adelaide and Melbourne (Australia).

By the time of a participants' meeting held in Lyon in February 1989, approximately 1000 cases had been interviewed with an appropriate number of control subjects. Subject enrolment in all but two of the centres is expected to extend to towards the end of 1990.

A major strength of this study lies in the reasonable number of focused hypotheses to be addressed, thus requiring a questionnaire which takes an average of approximately one hour to administer to cases and controls alike. Interviewing will continue until the middle of 1990, and results should become available in a form for publication by the middle of 1991. It is estimated that between 2000 and 2500 cases will be recruited from the participating centres in the course of the study.

To help centres with data validation, a computer program BRAINCHECKER has been written by Mr P. Maisonneuve (IARC) for use by the centres. This has been field-tested successfully by the Adelaide group (Dr Ryan, Professor McMichael) and has been sent to each participating centre.

(iv) *Cancers of the breast and colorectum* (Dr P. Boyle and Dr H. Bartsch; in collaboration with Dr H.B. Bueno de Mesquita, National Institute of Public Health, Bilthoven, The Netherlands; Dr H. Collette and Professor F. de Waard, Preventicon, Utrecht, The Netherlands; Dr S. Franceschi, Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano, Italy; Dr P. Ghadirian, Hôtel-Dieu de Montréal, Canada; Dr S. Gonzalez, National Institute of Oncology and Radiobiology, Havana; Dr E. Hietanen, Department of Community Health, University of Kuopio, Finland; Professor G. R. Howe, National Cancer Institute of Canada Epidemiology Unit, Toronto, Canada; Professor W.P.T. James, Rowett Research Institute, Aberdeen, UK; Dr F. Kadlubar, National Center for Toxicological Research, Jefferson, AR, USA; Dr K. Katsouyanni, Department of Epidemiology, University of Athens Medical School, Greece; Dr N. Lang, Department of Surgery, Veteran's Hospital, Little Rock, AR, USA; Dr C. La Vecchia, 'Mario Negri' Institute, Milan, Italy; Dr R.E. Leake, Department of Biochemistry, University of Glasgow, UK; Dr B. MacMahon, Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; Dr J.M. Martin-Moreno, School of Public Health, Granada, Spain; Professor Niu Shiru, Institute of Environmental Health, Beijing; Professor N. O'Higgins, St Vincent's Hospital, Dublin; Dr P. Pietinen, National Public Health Institute, Helsinki; Dr J. Potter, University of Minnesota, Minneapolis, MN, USA; Dr I. Romieu, Institute of Public Health, Mexico City, Mexico; Professor J.T. Salonen, Department of Community Health, University of Kuopio, Finland; Professor E. Schifflers, University of Namur, Belgium; Professor D. Trichopoulos, Department of Hygiene and Epidemiology, University of Athens Medical School, Athens; Professor S.Z. Yu, Institute of Public Health, Shanghai, PR China; and Dr D.G. Zaridze, Institute of Carcinogenesis, All-Union Cancer Research Centre, Moscow)

A meeting of the SEARCH Advisory Group in May 1987 encouraged the SEARCH programme staff to develop a protocol to study cancers of the breast and large bowel. An expert group comprising Professor B. MacMahon, Professor G. Howe, Professor D. Trichopoulos, Dr J. Potter and Dr P. Boyle has been established to supervise the design and analysis of this study.

There is an increasing accumulation of epidemiological evidence suggesting that among women, breast cancer and colorectal cancer (particularly ascending colon) share a number of common etiological risk factors, including a genetic element and dietary factors, such as fibre, vegetables and alcohol, and similar associations with aspects of reproductive history such as parity and age at first birth. Epidemiological issues such as the association with dietary factors and alcohol consumption can be best addressed in a variety of population settings. Some

important research questions to be studied therefore include the role of alcohol intake on breast cancer risk and the role of dietary intake of fat, fibre and vegetables on risk of breast and colorectal cancer. Questionnaires have been developed and food lists prepared in each participating centre. It is expected that data collection on this study will continue throughout 1990 and 1991. Further information regarding participation in this study is available on request from IARC.

(v) *Childhood leukaemia and other related haematological malignancies* (Dr P. Boyle; in collaboration with Dr R.A. Cartwright, Leukaemia Research Fund Centre, Leeds, UK; Dr J.-P. Collet, Neuro-cardiological Hospital, Lyon, France; Dr R.P. Gallagher, Cancer Control Agency of British Columbia, Canada; Dr R. Gurevicius, Lithuanian Cancer Research Institute, Vilnius, Lithuania, USSR; Dr M. Linet, National Cancer Institute, Bethesda, MD, USA; Dr R. Mitelman, Department of Clinical Genetics, University Hospital, Lund, Sweden; Dr G.T. O'Conor, Loyola University, IL, USA; Dr L. Robison, University of Minnesota, Minneapolis, MN, USA; Professor D. Skegg, University of Otago, Dunedin, New Zealand; Dr J. Urquhart, Information and Statistics Division, Scottish Health Services, Edinburgh, UK; and Dr D.G. Zaridze, Institute of Carcinogenesis, All Union Cancer Research Centre, Moscow)

A protocol has been finalized 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). The study protocol has been written by Dr M.S. Linet, Dr R.A. Cartwright, Dr F. Mitelman, Dr G.T. O'Conor, Dr L. Robison, Dr L. Simonato and Dr P. Boyle. Requests for collaboration are still being considered by the IARC and copies of the protocol for the study are available.

The proposed study will differ from most previous epidemiological research in the field of childhood haematological malignancies in several ways: 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:

(1) 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').

(2) To examine possible associations of certain parental occupational exposures (to agents including benzene, toluene, xylene, styrene, other solvents, pesticides, gasoline, diesel exhaust, pharmaceuticals, heavy metals, ionizing and non-ionizing radiation, ethylene dibromide, ethylene oxide and formaldehyde, as well as employment in specific occupations and industries) with specific subtypes of childhood leukaemia and lymphoma.

(3) To determine whether a number of postnatal domestic exposures (including various solvents, pesticides and (optionally) radon and low-frequency electromagnetic radiation) are associated with specific subtypes of childhood leukaemia and lymphoma.

(4) To confirm a number of hypotheses generated by recent studies including links of specific subtypes of childhood leukaemia and lymphoma with childhood use of chloramphenicol; parental prenatal and postnatal smoking; diagnostic radiation exposure (pre-conception both parents, maternal prenatal, and children postnatal); and other recent findings.

The final study design, logistics and protocol will be finalized at a meeting of collaborators in November 1989.

(vi) *Malignant melanoma of the skin* (Dr P. Boyle; in collaboration with Professor J.M. Elwood, Hugh Adam Cancer Epidemiology Unit, University of Otago, Dunedin, New Zealand; Dr R.P. Gallagher, Cancer Control Agency of British Columbia, Canada; Dr O.M. Jensen, Danish Cancer Registry, Copenhagen; Dr F. Lejeune, Jules Bordet Institute, Brussels; Dr A. Osterlind, Danish Cancer Registry, Copenhagen; and Dr S. Walter, McMaster University, Ontario, Canada)

The SEARCH Advisory Group recommended that priority be given to an international study to investigate risk factors in malignant melanoma, both in the skin and in other tissues. A protocol has been prepared by SEARCH staff together with the external collaborators; further details are available on request.

The aim of this series of studies is to examine the relationship between malignant melanoma and a wide variety of factors such as eye, skin and hair colour; history, number, type and distribution of naevi on the body; sun exposure including history of sunburn; occupation, leisure and sport activities; exposure to artificial light and fluorescent light; family history of malignant melanoma and naevi; specific occupations such as printing; substances used to promote suntan; sun-screen use; diet; previous relevant medical history of skin conditions and treatments and a variety of factors including age, sex, height, weight, socio-economic status, ethnic origin, smoking, alcohol history, reproductive factors, and use of oral contraceptives and replacement estrogens. This case–control study will also serve as a vehicle to investigate the possibilities for preventive education against relevant exposure. While the central goal is to conduct a replicated study of malignant melanoma of the skin, both intra-ocular malignant melanoma and mucosal malignant melanoma will also be investigated.

(vii) *Technical support for collaborators*

In conjunction with the SEARCH programme, a number of projects have been or are being carried out with the goal of providing needed technical or informational support for collaborators. Such activities have been listed in previous reports and new activities include:

(1) Production of guidelines for the analysis of nutritional data in epidemiology.

(2) Preparation of critical reviews of the literature in relation to breast cancer risk factors and to pancreas cancer risk factors.

(3) Collaboration with Professor G.R. Howe (Toronto) and international groups of epidemiologists in an overview analysis of previously conducted studies of breast cancer and nutritional factors.

(4) Collaboration with Dr J. Cuzick (London) and Dr C. La Vecchia (Milan) in assembling data from all epidemiological studies of pancreas cancer with a view to conducting an overview analysis once the SEARCH programme study is completed.

(5) Collaboration with Dr F. Li (Boston), Dr L. Robison (Minnesota), Dr J. Buckley (Minnesota), Professor B. Terracini (Turin), Dr G. Draper (Oxford) and Dr J. Birch (Manchester) in preparing an overview of all epidemiological studies of acute lymphocytic leukaemia and brain tumours in children.

(6) In collaboration with Dr H. Storm (Copenhagen), conducting a survey of the incidence of endocrine tumours to evaluate the feasibility of conducting etiological studies.

(7) Updating correlations of per capita food disappearance data (available from the Food and Agriculture Organization) from time periods since 1960 with cancer mortality data.

(8) In collaboration with Dr F. Alexander (Leeds), Dr J. Cuzick (London), Dr J. Kaldor and Dr J. Estève (IARC), evaluating suitability of statistical methodologies for detecting clustering, to be used in (population-based) case–control studies of childhood leukaemia.

(9) In collaboration with Dr C. Robertson (Glasgow), Dr C.-C. Hsieh (Boston), Dr G.J.

Macfarlane (Glasgow) and Dr J. Marshall (Buffalo), development of methodologies for analysis of case–control studies, particularly for continuous data.

4. NUTRITION AND CANCER

Several studies conducted at IARC, both in epidemiology and in the laboratory, include directly or indirectly some aspects of diet and nutrition. Some of these studies focus on possible carcinogenic chemicals which occur in foods as contaminants, e.g., aflatoxins (section I.2.*g*), ochratoxin (section I.2.*h*) and nitrosamines (section I.2.*e*). The role of alcohol and alcoholic beverages in the etiology of cancer has been investigated in a number of epidemiological studies in different populations around the world. On existing evidence, the IARC Monograph programme has evaluated that alcoholic beverages are carcinogenic to humans (see section I.2.*j*). Further studies are in progress in relation to the role of alcohol in cancer of the liver, oesophagus, pharynx, larynx, breast, pancreas, colon and rectum, as detailed under the respective sites in part I.3.

Other studies address the role of dietary habits and cancer risk in relation to the intake of fat, protein, carbohydrates and energy. These include (a) case–control studies on specific cancer sites for which several other risk factors are investigated at the same time, in particular, those within the SEARCH programme (section I.3.*k*) or (b) laboratory studies investigating possible mechanisms by which particular constituents of diet can intervene in tumour initiation and progression (section I.6.*f*). The present section includes only epidemiological investigations which are designed to investigate diet at the main research objective.

(*a*) **Programme of prospective studies on diet and cancer in Europe** (Dr E. Riboli, Dr R. Saracci and Mr R. Kaaks; in collaboration with Dr F. Clavel, INSERM (U. 287), Gustave Roussy Institute, Villejuif, France; Dr C. Gonzalez, Mataro Hospital, Barcelona, Spain; Dr F. Berrino, National Cancer Research and Treatment Centre, Milan, Italy; Dr P. Vineis, Cancer Epidemiology Department, University of Turin, Italy; Professor H. Collette, Preventicon, Utrecht, The Netherlands; Professor D. Kromhout, National Institute of Public Health and Environmental Protection (RIVM), Utrecht, The Netherlands; Professor J. Wahrendorf, Institute of Epidemiology and Biometrics, German Cancer Research Centre, Heidelberg, FR Germany; Professor A. Trichopoulou, Department of Nutrition and Biochemistry, University of Athens, Greece; Ms E. Callmer, Department of Medical Nutrition, Huddinge Hospital, Sweden; and Professor G. Berglund, Department of Medicine, University of Lund, Malmö, Sweden)

The methodological study on dietary assessment methods and related biochemical parameters in Malmö was completed and the first results were presented in an internal report to the IARC Scientific Council in September 1987. Data analyses are being completed and major results will be ready for publication towards the end of 1989. The collaboration with Swedish scientists for the planning of a prospective study in Malmö was continued during 1988 and 1989. It is foreseen that the study will be based on 55 000 middle-aged men and women from Malmö, with enrolment of subjects starting towards the end of 1990.

In 1988 the proceedings of an international meeting held at IARC in January 1987 on 'Diet, Hormones and Cancer: Methodological Issues for Prospective Studies' were published as an IARC Technical Report[64]. In 1988 a project in collaboration with three EEC countries, namely

[64] Riboli, E. & Saracci, E., eds (1988) *Diet, Hormones and Cancer: Methodological Issues for Prospective Studies* (IARC Technical Report No. 4) Lyon, International Agency for Research on Cancer

France, Italy and Spain, was launched within the 'Europe Against Cancer' programme. In 1989 researchers from Greece, The Netherlands and Germany also decided to join the project. The planning phase is aimed at identifying the appropriate methodology for:

(*a*) Dietary assessment methods suitable for large prospective studies;

(*b*) Collection and storage of biological samples to be used at a later stage for laboratory analyses of markers of diet as well as indicators of exposure to environmental carcinogens;

(*c*) Measurement of anthropometric characteristics and body composition in terms of fat and lean body mass.

Working groups on specific methodological issues have been created and will build upon the large experience on dietary and nutritional investigations carried out at IARC as well as in other European research institutions.

In addition to the projects in the six European countries, which are coordinated by IARC, and the project in Sweden which was started and developed as a collaborative activity between Swedish researchers and IARC, close scientific cooperation has been established with researchers involved in similar projects in the UK and Denmark. Participation in the working groups organized by IARC has therefore been extended to a total of nine European countries. Table 29 summarizes the main features of the projects as they appear at this preliminary stage.

The planning phase for Spain, France and Italy is expected to be completed during the first half of 1990, and the actual studies should start at the end of 1990. The studies in Greece, The Netherlands and Germany will probably start in 1991.

(*b*) Cancer of the large bowel in southern Europe

(i) *Marseilles* (Dr E. Riboli; in collaboration with Dr J. Cornée, Unit of Research on Digestive Pathology, INSERM U-31, Marseilles, France)

Two case–control studies were started in parallel during 1979–80 in the Marseilles metropolitan area, the first on cancers and the second on adenomatous polyps of the colon and rectum. The study on cancers was completed in 1985. It included 399 cases and 399 matched controls. Data collection for the study on adenomatous polyps was completed in 1986. It investigated the differences in usual past diet between 252 subjects with newly diagnosed adenomatous or villous polyps of the colon and rectum and a group of 238 hospital controls. Cases and controls were interviewed in hospital by three nutritionists using a dietary history questionnaire focused on the diet during the preceding year[65].

History of consumption of alcoholic beverages was collected as part of the dietary history method. Original data reported on 1278 questionnaires were reviewed, coded and added to the data-base of the study. The data on alcohol included age at start of consumption and up to six periods characterized by different patterns of consumption of wine, beer, aperitifs, liqueurs and spirits. Statistical analyses were completed in 1989. The results indicated no association between alcohol intake and risk of either cancers or polyps of the colon and/or rectum.

(ii) *Majorca* (Dr F.X. Bosch, Dr J. Kaldor and Dr N. Muñoz; in collaboration with Dr E. Benito and M. Mulet, Cancer Registry of Majorca, Ciutat de Mallorca, Spain; Dr A. Obrador, Hospital Son Dureta, Palma de Mallorca, Spain; and Ms A. Stiggelbout, Netherlands Cancer Institute, Amsterdam, The Netherlands)

This population-based case–control study was conducted in the island of Majorca during the period 1984–88. The project included 286 cases of colorectal cancer, 295 population controls and

[65] Macquart-Moulin, G., Riboli, E., Cornée, J., Kaaks, R. & Berthezène, P. (1987) *Int. J. Cancer, 40,* 179–188

Table 29. Programme of prospective studies on diet and cancer

Country	Target population	No. of subjects	Sex	Age	Location	Diet questionnaire	Biological samples	Phase
Projects coordinated by IARC within the framework of the EEC programme 'Europe Against Cancer'								
France	Members of health insurance schemes, mainly teachers	50 000	F	40–65	National	S.A.	t.b.d.	Pilot
Italy:								
Varese	Breast cancer screening	20 000	F	35–69	Regional	S.A.	b + u	Pilot
Turin	Blood donors	13 000 5 000	M F	35–64	Regional	S.A.	b	Pilot
Ragusa	Blood donors General population	5 000 5 000	M F	35–64	Regional	Int.	b	Pilot
Spain	General population	50 000	M + F	35–64	2–3 provinces	Int.	b	Pilot
UK	Breast cancer screening	100 000	F	50–64	Regional	S.A.	b	Pilot
Greece	Teachers	40 000	M + F	25–60	National	S.A.	t.b.d.	Planning
FR Germany	General population	12 300	M + F	26–69	National	S.A.	t.b.d.	Pilot
Netherlands	Breast cancer screening	30 000	F	50–69	Regional	S.A.	t.b.d.	Planning
	Existing cohort on cardiovascular diseases	20 000	M + F	40–60	Regional	?	b	Planning
Project developed in scientific collaboration with IARC								
Sweden	General population	55 000	M + F	50–69	Regional	Diary	b	Pilot
Projects with which IARC maintains scientific contact								
Australia: Victoria State	Australian born	20 000	M + F	40–69	Regional	S.A.	b	Pilot
	Italian, Greek, migrants	30 000	M + F	40–69	Regional	S.A.	b	Pilot
Denmark	General population	100 000	M + F	40–60	National	S.A.	t.b.d.	Planning

S.A., self administered; Int., interview; b, blood; u, urine; t.b.d., to be defined

203 hospital controls. A food frequency questionnaire was used and the results were presented by food groups, food items and dietary risk scores. The data have been analysed at IARC and the main findings are summarized in Table 30.

These results are compatible with an effect of some of the components of the diet in colorectal cancer. Thus there is a protective effect of cruciferous vegetables for both colon and rectum, an increased risk associated with fresh meat consumption for colon cancer and an increased risk associated with consumption of dairy products for rectal cancer. For cancer of the colon and rectum together, the consumption of cereals, particularly of white bread and pasta, was also significantly linked to risk.

An analysis of nutrients is being completed.

Table 30. Adjusted relative risk[a] for cancers of the colon and rectum and consumption of selected food groups

Food group	Colon					Rectum				
	Level of consumption[b]				χ^2 trend	Level of consumption[b]				χ^2 trend
	1	2	3	4		1	2	3	4	
Cereals	1.00	1.36	1.45	1.86	2.9	1.00	1.39	1.46	1.89	2.53
Potatoes	1.00	3.32	2.87	2.13	2.0	1.00	3.08	2.34	2.26	2.47
Cruciferous vegetables	1.00	0.92	0.53	0.48	7.4**	1.00	0.67	0.44	0.50	4.28*
Meat	1.00	1.97	1.99	2.87	6.8**	1.00	1.98	2.05	2.42	2.80
Dairy products	1.00	0.86	0.98	1.07	0.0	1.00	1.58	1.48	3.08	8.41**
Eggs	1.00	1.77	1.62	2.28	2.5	1.00	1.95	1.90	1.96	1.16

[a] Adjusted for age, sex, weight 10 years before the interview, number of years of education, job classification, physical activity on the job, number of meals per day, and food groups listed in the table

[b] Level 1 indicates non-consumption or very low consumption and 4 indicates high consumption

* $p < 0.05$

** $p < 0.01$

(*c*) **Case–control study on diet and gastric cancer in four regions of Spain** (Dr E. Riboli, Dr R. Montesano and Dr C. P. Wild; in collaboration with Dr C. Gonzales, Epidemiology Unit, Mataro Hospital; Dr M. Sans, Soria Hospital; Dr G. Marcos, University Hospital, Zaragoza; and Dr S. Pita, Seguridad Social, La Coruña, Spain)

Some epidemiological studies have shown that the two main histological types of stomach cancer, the diffuse and the intestinal ones, have different geographical distributions and different time trends. The two types may also be differently related to dietary factors but no studies have analysed the effect of diet separately by histological type.

A case–control study on diet and gastric cancer was started in 1988 in four areas of Spain. Cases are patients hospitalized for the first time for stomach cancer in one of the 12 collaborating hospitals. Only cases with histologically confirmed gastric cancer are included. Controls are patients in the same hospital, matched by age and sex.

Information on diet is collected by personal interview using a dietary history questionnaire focused on usual diet two or three years before. A simple food frequency questionnaire is used to estimate the consumption of selected foods twenty years before. About 300 cases and 300 controls have been interviewed. In a subsample of 50 cases and 59 controls blood samples were taken. Lymphocytes and red blood cells were isolated and stored at −80°C, and will be used to explore the presence of alkylated DNA bases and of haemoglobin adducts of tobacco-derived nitrosamines.

Data collection will be completed by the end of 1989, and laboratory analysis will be carried out during 1990.

(*d*) **Breast cancer and diet in Northern Italy** (Dr E. Riboli; in collaboration with Dr P. Toniolo, New York University, New York, USA)

A study on breast cancer and diet, alcohol consumption, reproductive history and other potential risk factors was completed in 1986 in the province of Vercelli in northern Italy. The

study was based on 250 incident cases and 499 controls matched by age and area of residence within the province. All subjects were interviewed at home. Information on diet was collected by means of a dietary history method structured by meals and focused on usual diet during the year preceding diagnosis for cases and during an equivalent period for controls. Daily intake of energy, energy-providing nutrients and vitamins was computed with specially prepared food tables.

The results indicated that the risk of breast cancer was higher in women reporting greater intake of saturated fat and animal protein. No increase in risk was observed for unsaturated fat and for vegetable protein. Adjustment for calorie intake did not materially modify the association with fat and protein[66]. The study was conducted in an area where wine consumption is widespread; wine is commonly consumed during meals even by most women.

The case–control analyses indicated that there was no increase in the risk of breast cancer for consumption of less than 30 g/day of alcohol, which corresponds to about 250 ml/day (i.e. three glasses) of wine. The risk of breast cancer was increased to 2.1 for consumption of 40 g/day or more. Adjustment for energy intake (total energy minus energy from alcohol) reduced the statistical significance of the association with alcohol, but did not substantially modify the estimated relative risk[67].

(e) **Diet-related case–control studies in Singapore** (Dr J. Estève and Ms D. Magnin; in collaboration with Dr H.P. Lee, Dr L. Gourley and Dr J. Lee, Singapore Cancer Registry; Dr S.W. Duffy and Dr N.E. Day, MRC Biostatistics Unit, Cambridge, UK)

The change in life-style that has occurred in recent years in Singapore probably explains the major changes in the pattern of cancer observed there over the last 20 years[68]. Two case–control studies have been conducted to investigate the role of diet in causing part of the observed increase in colorectal cancer and breast cancer. A total of 203 cases and 425 controls were included in the colorectal study, which demonstrated a protective effect of high consumption of cruciferous vegetable and a predisposing effect of a high ratio of meat to vegetable consumption. No consistent trend was noted for fat or fibre intake for either colon or rectal cancer[69]. 200 cases and 227 controls have been interviewed for the breast cancer study. The target of 400 controls will be reached at the end of 1989, enabling analysis to be done in the first half of 1990. A case–control study on nasopharyngeal cancer has been set up to test various dietary hypotheses, paying particular attention to the consumption of salted fish, and will proceed during 1990.

5. GENETICS AND CANCER

Variations in cancer incidence are often considered to result mainly from variation in exposure to environmental factors. However, it is clear that there are individual variations in susceptibility to the carcinogenic effects of these agents. Such individual genetic differences are still poorly understood, and a molecular genetic approach is being applied to assess the importance of genetic predisposing conditions in the etiology of human cancer. Until recently, only a few cancer types had been shown to have a clear genetic component, and the identification of genetic risk factors for other cancers occurring in the general population was

[66] Toniolo, P., Riboli, E., Protta, F., Charrel, M. & Cappa, A.P.M. (1989) *J. Natl Cancer Inst., 81,* 278–286

[67] Toniolo, P., Riboli, E., Protta, F., Charrel, M. & Cappa, A.P.M. (1989) *Cancer Res.* (in press)

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

[69] Lee, H.P., Gourley, L., Duffy, S.W., Estève, J., Lee, J. & Day, N.E. (1989) *Int. J. Cancer* (in press)

almost impossible. However, recombinant DNA technology has provided new sources of molecular markers (for example, cloned genes or oncogenes, DNA polymorphic markers) which may be used to identify the genetic factors that contribute to the development of cancer. This approach could also permit better identification of the environmental factors associated with a given cancer. Pharmacogenetic studies related to individual response to carcinogens are covered in section I.6.

(*a*) Studies of the X-linked lymphoproliferative syndrome (Dr B.S. Sylla, Ms Q. Wang, Ms S. Pauly and Dr G. Lenoir; in collaboration with Dr D. Hayoz, Fribourg, Switzerland; Dr J. Skare, Center for Human Genetics, Boston University, Boston, MA, USA; and Dr P. Goodfellow, Imperial Cancer Research Fund Laboratories, London)

The X-linked lymphoproliferative syndrome (XLP) is a recessive genetic disorder linked to the X chromosome which affects boys carrying the gene that confers susceptibility. It is a very rare disease, characterized by a fatal chronic infectious mononucleosis, acquired hypogammaglobulinaemia, or malignant lymphoma, following 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 development of malignant lymphomas. A genetic linkage study is being carried out, identifying cosegregation between the susceptible gene(s) of XLP and a marker(s) displaying restriction fragment length polymorphism (RFLP).

We have identified four families affected by XLP, of which the largest kindred was found in Switzerland[70].

(i) *Genetic linkage*

The genetic linkage study has permitted location of the XLP locus in the chromosomal region Xq25–q26 defined by the DNA polymorphic marker DXS37[71]. A multipoint linkage analysis performed on the Swiss family under investigation has indicated that the XLP locus is situated between the DXS11 marker and the hypoxanthine phosphoribosyl transferase gene, with 13 and 10% recombination respectively (see Figure 10)[72].

(ii) *Mapping of the Xq25-q26 region*

Another approach taken to map more precisely the XLP locus was the irradiation and fusion gene transfer technique (IFGT). This technique involves irradiating with gamma rays human lymphocytes or human rodent hybrid cells which contain a single human chromosome, and fusing the irradiated cell with a recipient hamster cell. The resulting hybrid cell clones contain human chromosome fragments of various sizes. The use of human/rodent cell hybrids gives the advantage of producing hybrid clones containing different fragments from a single human chromosome. Starting with a human/hamster hybrid cell line containing a single human X chromosome, we have generated about 200 clones containing different portions of the X chromosome. DNAs extracted from these clones were tested with various probes isolated from

[70] Hayoz, D., Lenoir, G.M., Nicole, A., Pugin, P. & Regamey, C. (1988) *Am. J. Med., 84,* 529–534

[71] Skare, J.C., Grierson, H.L., Sullivan, J.L., Nussbaum, R.L., Purtilo, D.T., Sylla, B.S., Lenoir, G.M., Reilly, D.S., White, B.N. & Milunsky, A. (1989) *Hum. Genet., 82,* 354–358

[72] Sylla, B.S., Wang, Q., Hayoz, D., Lathrop, G.M. & Lenoir, G.M. (1989) *Clin. Genet.* (in press)

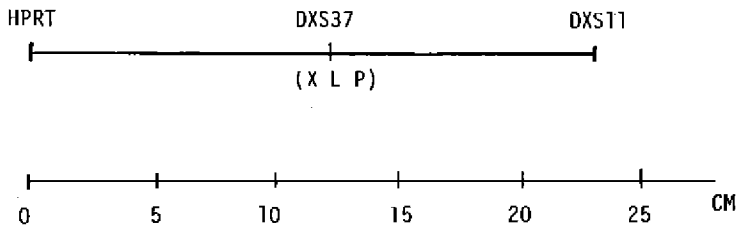

Fig. 10. A linkage map of markers in Xq25-q-26

The distance between the DXS loci is indicated
The DCS37 locus shows no recombination with XLP.
A multipoint linkage analysis performed in the Swiss family to map the XLP locus relative to the hypoxanthine phosphoribosyl transferase gene (HPRT), and the anonymous RFLP markers DXS37 and DXS11. The DXS37 locus shows no recombination with XLP. The gene order showed on the map indicates that the XLP locus is distal to DXS11 at 10 centimorgans (CM), but proximal to the HPRT gene at 13 CM. At the molecular level, 1 cm is approximately equivalent to 10^6 base pairs.

human X chromosomes. The analysis of the results should lead to the building up of a good physical map of the human X chromosome.

Out of the 200 clones tested, eight contained specific DNA markers provisionally shown to be linked to the XLP locus were identified. These characterized clones are being used to construct genomic DNA libraries by the 'Alu PCR' method, a technique which allows direct amplification of human DNA present in a cell hybrid. Using such libraries, new polymorphic markers will be isolated for use in fine genetic and physical mapping of the XLP region. It will be possible also to identify unique sequences which have been well conserved during evolution. The relationship between these sequences and the XLP disease will be established by expression studies in affected and healthy individuals.

(*b*) Studies on multiple endocrine neoplasia (MEN) (Dr H. Sobol, Dr S. Narod, Ms I. Schuffenecker, Ms M-F. Lavoué and Dr G. Lenoir; in collaboration with the Group for the Study of Calcitonin Tumours: Secretariat, Dr C. Calmettes, Saint-Antoine Hospital, Paris; Dr B. Ponder, Royal Cancer Hospital, Sutton, UK; and Dr Y. Nakamura, Howard Hughes Medical Institute, Salt Lake City, UT, USA)

(i) *Linkage studies on MEN type IIa*

MEN IIa is an autosomal dominant inherited cancer syndrome characterized by medullary carcinoma of the thyroid, 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 80 families have been identified, and blood has already been collected from most members.

Following recent reports[73,74] on the assignment of the MEN IIa predisposing gene to chromosome 10, we were able to confirm the data on our set of families[75] and, through collaboration with the London and Salt Lake City groups, to further map the chromosomal region[76].

(ii) *Screening for individuals at risk*

Now that MEN IIa has been shown to be genetically linked to a locus near the centromere of chromosome 10, the availability of polymorphic DNA probes for the region has permitted the evaluation of restriction fragment length polymorphism (RFLP) analysis in the identification of gene carriers for this cancer syndrome. DNA probes were used in a genetic linkage study of 130 members of eleven families of our panel. In these families there were no instances of recombination between the mutation causing multiple endocrine neoplasia type IIa and two of the three probes used. All 11 families were informative for at least one of the three markers, and linkage information was adequate to offer genetic counselling to eight families. The ability to predict the carrier state was demonstrated to be much greater for RFLP analysis than for conventional endocrine challenge methods, especially in younger individuals, 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 multiple endocrine neoplasia type IIa is one of the first cancer syndromes for which genetic screening allows the identification of individuals at risk[77].

(iii) *Genetic heterogeneity in MEN IIa*

In MEN type IIa, family members are at high risk for developing medullary carcinoma of the thyroid and other tumours, especially phaeochromocytoma. Several families have also been identified in which medullary thyroid carcinoma is inherited, but a phaeochromocytoma is not seen. The two syndromes may be related to genes in the same or different loci. We have analysed 18 families, 9 with MEN IIa and 9 with medullary carcinoma of the thyroid without phaeochromocytomas, with probes specific for the pericentromeric region of chromosome 10. The linkage analysis has indicated that the genes for the two presentations are located close together. Genetic heterogeneity of the susceptibility locus was not seen among this sample of 18 families. The genetic mutation for medullary carcinoma was in disequilibrium with the marker alleles of the two closely linked probes, IRBPH4 and MCK2. These data suggest that different mutant alleles of the same gene or closely linked mutations account for the variation in penetrance of phaeochromocytoma in families with hereditary medullary thyroid carcinoma[78].

(iv) *Further mapping of the MEN IIa locus*

In an attempt to detect genetic alteration at the MEN IIa locus and if possible to identify the responsible gene, further mapping of this locus is being carried out using pulse field gel

[73] Mathew, C.G.P., Chin, K., Easton, D.F., Thorpe, K., Carter, C., Liou, G.I., Fong, S.L., Bridges, C.D.B., Haak, H., Nieuwenhuijzen Kruseman, A.C., Schifter, S., Hansen, H.H., Telenius, H., Telenius-Berg, M. & Ponder, B.A.J. (1987) *Nature, 328,* 527–528

[74] Simpson, N.E., Kidd, K.K., Goodfellow, P.J., McDermid, H., Myers, S., Kidd, J.R., Jackson, C.E., Duncan, A.M.V., Farrer, L.A., Brasch, K., Castiglione, C., Gend, M., Gertner, J., Greenberg, C.R., Gusella, J.F., Holden, J.J.A. & White, B.N. (1987) *Nature, 28,* 528–530

[75] Sobol, H., Salvetti, A., Bonnardel, C. & Lenoir, G.M. (1988) *Lancet, i,* 62

[76] Nakamura, Y., Mathew, C.G.P., Sobol, H., Easton, D.F., Telenius, H., Bragg, T., Chin, K., Clark, J., Jones, C., Lenoir, G.M., White, R. & Ponder, B.A.J. (1989) *Genomics, 5,* 199–203

[77] Sobol, H., Narod, S.A., Nakamura, Y. *et al.* (1989) *New Engl. J. Med. 321,* 996–1001

[78] Narod, S.A., Sobol, H., Nakamura, Y. *et al.* (1989) *Hum. Genet.* (in press)

electrophoresis. One affected individual of each of our MEN families has now been investigated. No structural anomalies have been detected so far.

(*c*) **Breast cancer** (Dr S. Narod, Dr H. Sobol and Dr G. Lenoir; in collaboration with Dr H. Lynch, Creighton University, Omaha, NB, USA; Dr R. White, Howard Hughes Medical Institute, Salt Lake City, UT, USA; and Dr C. Amos, Howard University, Washington, DC, USA)

A collection of families in which breast and ovarian cancer are associated through several generations has been compiled. Lymphoblastoid cell lines are now being established from blood samples from members of ten such families to provide a source of DNA for forthcoming linkage studies. Beginning at the end of 1989, a set of RFLP markers spanning the entire human genome will be used to search for the chromosomal location of the susceptibility gene believed to be transmitted in these families. In preparation for the proposed gene mapping study, computer simulation has been employed to estimate the statistical power to detect linkage in breast cancer families[79]. This technique has permitted the evaluation of the expected effects of sporadic cases and of multiple gene loci on the power of the proposed studies and has also been used to evaluate the relative efficiency of various RFLP markers available for screening.

(*d*) **Constitutional c-*myc* gene anomaly** (Dr C. Drevon)

Following our identification of a constitutional *c-myc* gene duplication in Algeria, attempts have been made to identify rare *c-myc* alleles occurring in other populations. The results have so far been negative using an RFLP approach, indicating that the *c-myc* locus is highly conserved in the human population. New strategies are being developed using the polymerase chain reaction technique in order to identify limited nucleotide variations, in particular around the first exon.

6. BIOCHEMICAL AND METABOLIC PARAMETERS AS INDICATORS OF INDIVIDUAL SUSCEPTIBILITY TO CANCER

The projects below are aimed at defining the contribution of metabolic host-risk factors, e.g., in relation to lung cancer in cigarette smokers and to diet-related malignancies. The approach which has been chosen is the simultaneous measurement in human subjects of carcinogen exposure and metabolic phenotype to reveal the extent to which pharmacogenetic differences contribute to these malignancies.

Over the past decade, IARC has developed non-invasive methods to assess carcinogen exposure and carcinogen metabolism in man that can now be applied in human pilot studies.

With our increasing knowledge about the mechanisms of pharmacogenetic disorders at a molecular level and the availability of new probe drugs (e.g., warfarin or caffeine) that permit selective and non-invasive determination of the metabolic phenotype of human subjects, the following questions can now be addressed:

(1) How large are the genetic versus environmental contributions to individual cancer risk?
(2) How great is the genetic variability between individuals?
(3) Is it possible to detect these differences using a routine assay?
(4) Is it feasible to screen populations to determine the risk?
(5) Can these differences be explained on a molecular basis?

[79] Narod, S.A. & Amos, C. (1989) *Am. J. Hum. Genet.* (in press)

(*a*) Metabolic parameters predicting individual susceptibility to lung cancer (Dr E. Hietanen, Miss A.-M. Camus, Dr M. Castegnaro, Dr R. Saracci and Dr H. Bartsch; in collaboration with Dr S. Petruzzelli and Professor C. Giuntini, National Research Council, University of Pisa, Italy; Dr H. Vainio, Institute of Occupational Health, Helsinki, Finland; Dr H.V. Gelboin, National Cancer Institute, Bethesda, MD, USA; and Dr A. Poland, McArdle Laboratory for Cancer Research, Madison, WI, USA)

Lung samples from a group of smokers (and ex-smokers), undergoing surgery for either lung cancer or non-malignant lung disease were assayed for several enzyme activities and markers for antioxidant defence[80,81]. The enzyme activities were measured in lung parenchyma, due to a better availability of parenchymal than bronchial tissue. We showed that both mutagenicity of several carcinogens mediated by lung tissue fractions and enzyme activities correlated well between the healthy parenchymal and bronchial tissues[82]. In smoking lung cancer patients, aryl hydrocarbon hydroxylase (AHH) and ethoxycoumarin *O*-deethylase (ECDE) activities were induced relative to the enzyme levels found in smoking or non-smoking patients operated for benign lung diseases. This enzyme induction was seen only in smokers who had stopped smoking within 30 days before surgery. There was a linear inverse correlation between the time elapsed from smoking before operation and the AHH, ECDE and UDGPT activities, while a positive correlation was found for glutathione transferase (GST) activity showing a long-lasting effect of smoking (Table 31). Thus these results reinforce previous circumstantial evidence from lymphocyte studies that the inducibility of pulmonary Ah-locus-controlled enzymes in tobacco smokers is related to cancer risk.

The AHH activity in lung samples showed good correlation with immunohistochemical

Table 31. The time after stopping smoking required for enzyme activity levels to return to the basal level (i.e. that found in non-smoking patients) in lung cancer patients

	Duration of induced state (days)	Induction factor[a]
AHH	59	2
ECDE	90	7
EH	108	2.5
UDPGT	67	1.6
GST	40[b]	0.7[b]

EH = epoxide hydrolase. For other abbreviations, see text

[a] Induction level in lung cancer patients who smoked until one day before surgery

[b] Inhibition

[80] Ahotupa, M., Camus, A.-M., Giuntini, C., Aitio, A., Hietanen, E., Petruzzelli, S., Carrozzi, L., Ghelarducci, L., Rindi, M., Menconi, G.F., Angeletti, C.A., Saracci, R. & Bartsch, H. (1987) In: Sotaniemi, E., ed., *Enzyme Induction in Man*, London, Taylor & Francis, pp. 61–65

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

[82] Petruzzelli, S., De Flora, S., Bagnasco, M., Hietanen, E., Camus, A.-M., Saracci, R., Izzotti, A., Bartsch, H. & Giuntini, C., (1989a) *Am. Rev. Resp. Dis.* (in press)

staining of the cytochrome P450IA isozyme and both were related to the time patients had abstained from smoking before surgery[83].

In preliminary studies we have found that the ^{32}P-postlabelling technique is able to detect typical cigarette-smoke related spots and radioactive diagonal zone in thin-layer plates and further, that the intensity of the spot/zone is related to the number of cigarettes smoked and the time that elapsed since smoking before surgery[84]. In the same series of patients, the parenchymal malondialdehyde concentration (as a measure of lipid peroxidation) was much elevated in recently smoking lung cancer patients and the concentration was correlated negatively with the time elapsed since stopping smoking[81]. This suggests that in cigarette smoke there are compounds (perhaps *N*-nitroso compounds) that can initiate free radical reactions and consequent lipid peroxidation[85]. Similarly, asbestos exposure may be related to elevated malondialdehyde levels as a potent inducer of lipid peroxidation[86]. Further, in our study the degree of small airway obstruction was related to the level of lipid peroxidation[87], suggesting either that these phenomena are causally related or that they have a common etiological background.

Current research activities are directed towards establishing methods for assaying Ah-receptor levels and quantifying P_1450 isozymes using either immunohistochemical staining or specific substrates. Preliminary analyses have suggested that some of the parameters measured (Ah-linked enzymes) may serve as prognostic markers of survival of lung cancer patients[88]. These data will be correlated with DNA adduct measurements and more relevant non-invasive methods are to be developed for use in non-diseased populations for risk estimation.

***(b)* Use of probe drugs to estimate individual cancer risk** (Dr E. Hietanen, Dr M.-L. Aitio, Dr H. Bartsch and Mr J.-C. Bérézíat; in collaboration with Dr P. Arvela, Department of Pharmacology, University of Oulu, Finland; Dr H.V. Gelboin, National Cancer Institute, Bethesda, MD, USA; and Professor M. Lang, Department of Pharmacology and Toxicology, University of Kuopio, Finland)

Although many methods have been developed to assess individual risk to chemical carcinogens, e.g. lymphocyte AHH inducibility, the metabolic profiles of antipyrine, debrisoquine and caffeine, these methods have often, as a disadvantage, their limited representativeness of whole metabolic capacity, although they are useful to study genetic polymorphism. To avoid the limits of a single drug, some 'drug cocktails' have been developed. Warfarin, long used in clinical medicine, is metabolized to various compounds (Fig. 11) which may reflect the activities of different cytochrome P450 isozymes showing isomeric specificity[89]. This suggests the possibility of using warfarin as a probe drug to study non-invasively the P450 isozyme pattern of liver, giving insight into the individual capacity to metabolize carcinogens. The excretion of warfarin metabolites in urine has already been used, to study the specificity of P450 isozyme induction by other drugs in man[90,91].

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[83] Hietanen, E., Bartsch, H. & Camus, A.-M. (1989) 10th Annual Symposium Finnish Society of Toxicology, Abstracts, p. 33

[84] Hietanen, E., Castegnaro, M., Bartsch, H., Anttila, S., Nikkilä, L., Vainio, H., Gelboin, H.V. & Park, S.S. (1989) *Proceedings of the 2nd Conference on Pneumopathies, Paris, 14–15 March, 1989*

[85] Bartsch, H., Hietanen, E., & Malaveille, C. (1989) *Free Radical Biol. Med.*, (in press)

[86] Cerutti, P.A. (1985) *Science, 227,* 375–381

[87] Petruzzelli, S., Hietanen, E., Bartsch, H., Camus, A.-M., Mussi, A., Angeletti, C.A., Saracci, R. & Giuntini, C. (1989) (submitted for publication)

[88] Bartsch, H., Hietanen, E., Petruzzelli, S., Giuntini, C., Mussi, A., Angeletti, C.A. (1989) (submitted for publication)

[89] Kaminsky, L.S., Dunbar, D.A., Wang, P.P., Larrey, D., Guengerich, F.P., Schnellmann, R.G. & Sipes, I.G. (1984) *Drug Metab. Disp., 12,* 470–477

[90] Toon, S., Low, L.K., Gibaldi, M., Trager, W.F., O'Reilly, R.A., Motley, C.H. & Goulart, D.A. (1986) *Clin. Pharmacol. Ther., 39,* 15–24

[91] Heimark, L.D. & Trager, W.F. (1987) *Clin. Pharmacol. Ther., 39,* 15–24

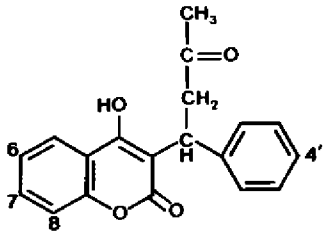

Fig. 11. The structure of warfarin. Sites of hydroxylation by the cytochrome P-450 isozymes are shown by numbers

For the first part of this study, rats were treated with nitrosodiethylamine and phenobarbital. Following a subsequent dose of warfarin, the metabolites were analysed by HPLC[92] using reference metabolites (donated by Dr A.O. Obaseki) and warfarin enantiomers (donated by Professor D.V. Parke). The data showed that the amounts of *S*-isomer of 7-hydroxywarfarin correlated well *in vitro* vs *in vivo*, while other metabolites were less significantly correlated. The total liver microsomal cytochrome P450 concentration was associated with the metabolite formation *in vitro*. The microsomal metabolite patterns and urinary excretion patterns were also, to some extent, correlated suggesting that warfarin may be a useful tool for assessing individual metabolic capacity. Similar comparisons are being made using debrisoquine and antipyrine.

In the second part of the study, the roles of different cytochrome P450 isozymes are being studied using mice treated with different inducers of cytochrome P450 isozymes and inhibiting the metabolic conversion of warfarin into metabolites by various monoclonal and polyclonal antibodies towards P450 isozymes. This study will provide information on the specific metabolite(s) produced by various isozymes and should allow particular metabolite(s) and isozyme(s) to be related to the metabolism of carcinogens.

For the next phase of the studies, human urine samples have been collected for development of assay methods for warfarin metabolites. First attempts have been made to develop methods for the separate analysis of enantiomers of warfarin metabolites in humans given the racemic drug for therapeutic purposes.

(*c*) Use of human hair follicles in carcinogenesis studies

Human hair follicles offer great potential for studies of the genetics of susceptibility to carcinogenesis and of individual differences in metabolism of carcinogens, because (1) they are readily accessible and can be obtained from human volunteers in a non-invasive and painless fashion; (2) they contain cytochrome P450 enzymes; (3) they are highly mitotically active; (4) they are an epithelial tissue and the majority of human tumours arise from epithelial tissues[93,94,95]. Hair follicles are also being used as the basis for a new mutation assay system (see section II.6.*b*).

(i) *Measurement of* (−)-*BP-7,8-diol activation* (Dr M. Goldberg, Dr M. Rojas-Moreno and Dr K. Alexandrov)

[92] Fasco, M.J., Piper, L.J. & Kaminsky, L.S. (1977) *J. Chromatogr., 131,* 365–373
[93] Ghadially, F.N. (1961) *Cancer* (Philadelphia), *14,* 801–816
[94] Burns, F.J., Sinclair, I.P., Albert, R.E. & Vanderlaan, M. (1976) *Radiat. Res., 67,* 474–480
[95] Aldaz, C.M., Conti, C.J., Gimenez, I.B., Slaga, T.J. & Klein-Szanto, A.J.P. (1985) *Cancer Res.*, 2753–2759

Using hair follicles, a non-invasive method has been developed to assess an individual's capacity for metabolizing carcinogens, using benzo[*a*]pyrene (BP) as a probe. Recently, it has been shown that human hair follicles possess aryl hydrocarbon hydroxylase[96], epoxide hydrolase[97] and ethoxyresorufin-*O*-deethylase[98] activities, enzymes involved in metabolism of carcinogens. We are now developing an HPLC/fluorescence assay to measure the profile of enantiomeric metabolites produced from (−)-BP-7,8-diol by a few human hair follicles. Reverse-phase HPLC profile of tetrols and other products formed from (−)-[^{14}C]BP-7,8-diol after incubation with human hair follicles. 75 pmol in our studies, 75 pmol of (−)-[^{14}C]BP-7,8-diol was incubated for 24 h at 37°C with three human hair follicles in 150 µl modified Eagle's medium. The whole medium was injected onto HPLC. I-1 and I-2 are *anti*-BP-diol epoxide tetrols, I-3 is a triol derived from *anti*-BP-diol epoxide, II-1 and II-2 are *syn*-BP-diol epoxide tetrols and A is an unknown product (Fig. 12). The *anti*-BP diol epoxide is formed nearly exclusively (>99%). Thus human hair follicles show very high stereoselectivity in the metabolism of (−)-BP-7,8-diol.

This assay is now being applied to lung cancer patients and controls and also to samples from a population at risk of cancer due to occupational exposure or smoking habits. The patterns of metabolism will be correlated with other end-points, measured in the same subject (see section I.6.*a*).

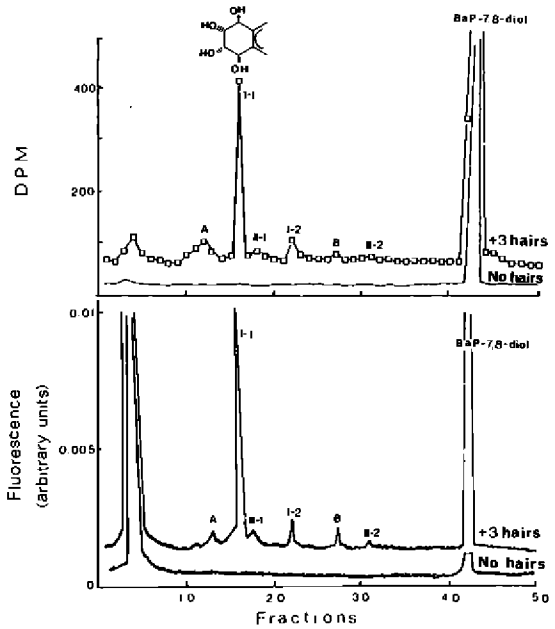

Fig. 12. Reverse-phase HPLC profile of formation of tetrol and other products after (−)[^{14}C]BP-7,8-diol epoxidation by human hair follicles. I-1 and I-2 are *anti*-BP-diol epoxide tetrols, II-1 and II-2 are *syn*-BP-diol epoxide tetrols and A and B are unknown products

[96] Merk, H.F., Mukhtar, H., Kaufmann, J., Das, M. & Bickers, D.R. (1987) *J. Invest. Dermatol., 88*, 71–76

[97] Hukkelhoven, M.W.A.C., Vromans, E.W.M., Vermorken, J.M. & Bloemendal, H. (1982) *FEBS Lett., 144*, 104–108

[98] Merk, H.F., Mukhtar, H., Schutte, B., Kaufman, I., Das, M. & Bickers, D.R. (1987) *Biochem. Biophys. Res. Comm., 148*, 755–761

(ii) *Immunohistochemical studies of enzymes in human and mouse hair follicles* (Miss A.-M. Camus, Dr M.T. Goldberg, Mr J.-C. Béréziat, Miss M. Laval, Mrs N. Lyandrat)

Hair follicles were obtained from mice pretreated with Aroclor 1254, an inducer of P450 activity. Hairs were also obtained from human volunteers and incubated for 24 h in the presence of benzo[*a*]pyrene 7,8-diol (see above). After fixation, paraffin blocks were made and sections were then subjected to immunohistochemical staining, using both monoclonal and polyclonal antibodies to specific types of cytochrome P450. Both phenobarbital-inducible and 3-methylcholanthrene-inducible types of P450 were detected in Aroclor-induced mice. The areas of highest concentration corresponded to the sebaceous glands and hair follicles. These results will be compared with the BP metabolite profile obtained with hairs from the same subject.

(*d*) **Hepatitis B virus infection as a predisposing factor to chemical carcinogenesis** (Dr E. Hietanen, Dr H. Bartsch, Mr J.-C. Béréziat and Miss A.-M. Camus; in collaboration with Professor S. De Flora, Institute of Hygiene and Preventive Medicine, University of Genoa, Italy; and Dr H.V. Gelboin, National Cancer Institute, Bethesda, MD, USA)

The metabolism of chemical carcinogens has been investigated in liver preparations from woodchucks (*Marmota monax*). Some animals were naturally infected with the woodchuck hepatitis virus (WHV), and some also had primary hepatocellular carcinoma (PHC). Twenty-nine parameters were investigated in liver subcellular fractions, including cross-reactivity with HBsAg and biochemical parameters such as levels of γ-glutamyl transpeptidase, cytochrome P450 and microsomal monooxygenases (aryl hydrocarbon hydroxylase, ethoxycoumarin and ethoxyresorufin deethylases, aminopyrine and nitrosodimethylamine demethylases, and testosterone 7α-, 16α- and 6β-hydroxylases), uridine 5'-diphosphoglucuronosyl transferase, glutathione and related enzymes (peroxidase, reductase and *S*-transferase), as well as other cytosolic enzyme activities (glucose 6-phosphate and 6-phosphogluconate dehydrogenases, NADPH- and NADH-dependent diaphorases and DT diaphorase). In addition, liver preparations were used to quantify the metabolic activation into bacterial mutagens of five procarcinogens (aflatoxin B_1, the protein pyrolysis products Trp-P-2 and MeIQ, 2-aminofluorene and nitrosodimethylamine) and the decrease of potency of three direct-acting mutagens (sodium dichromate, ICR 191 and 4-nitroquinoline 1-oxide). WHV infection produced a significant stimulation of carcinogen metabolism, as shown by the simultaneous change in detoxication parameters (GSH depletion) and activation indices (enhancement of microsomal monooxygenases and of procarcinogen activation into mutagenic metabolites[99]). A larger proportion of ethoxyresorufin *O*-deethylase activity was inhibited by monoclonal antibody 1-7-1 towards methylcholanthrene-inducible cytochrome P450 in those WHV-infected livers having cancers than in livers from animals with or without infection and no liver tumours[100].

These results, together with previous data from humans, revealed that metabolic factors may play a role in the synergism between viral hepatitis and chemical hepatocarcinogens in the etiopathogenesis of primary hepatocellular carcinoma.

As a next step, the cytochrome P450 isozyme composition of woodchuck livers will be studied by the Western blot technique and immunohistochemical techniques will be developed for the analysis of P450 isozyme composition in infected human livers, with the aid of antibodies

[99] DeFlora, S., Hietanen, E., Bartsch, H., Camoirano, A., Izzotti, A., Bagnasco, M. & Millman, I. (1989) *Carcinogenesis, 10,* 1099–1106

[100] Hietanen, E., Bartsch, H., Camus, A.-M., Béréziat, J.-C., DeFlora, S., Park, S.S. & Gelboin, H.V. (1989) In: Schuster, I., ed., *Cytochrome P-450: Biochemistry and Biophysics,* London, Taylor & Francis, pp. 511–514

towards various cytochrome isozymes (in collaboration with Dr C.R. Wolf, ICRF, Edinburgh, UK). Parallel studies of the interaction of hepatitis B virus infection and aflatoxins in the genesis of liver tumours are being carried out in Peking duck (see section I.2.*g*.vii).

(*e*) **Cytochrome P450 IIE1-mediated activation of *N*-nitrosamines into mutagens** (Dr C. Malaveille, Mrs G. Brun and Dr H. Bartsch; in collaboration with Dr H.V. Gelboin, National Cancer Institute, Bethesda, MD, USA; and Professor U. Mohr, School of Medicine, Hanover, FR Germany)

Previous studies have shown the utility of monoclonal antibodies (MAb) against particular cytochrome P450 isozymes for the analysis of P450-dependent reactions[101,102,103]. The inhibitory effect of MAb 1-91-3 and MAb 1-98-1 against ethanol-induced rat liver P450 was measured in rat liver microsome-mediated genotoxicity assays and with *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA) or *N*-nitrosomorpholine (NMOR) as substrates. The contribution of the epitope-defined ethanol-inducible P450 to the activation of these nitrosamines in liver S9 from untreated, ethanol-, pyrazole-, phenobarbital- and pregnenolone 16α-carbonitrile (PCN)-treated BDVI rats was determined at low (5 mM) and high (50 mM) nitrosamine concentrations. The SOS chromotest (*E. coli* PQ37) and the *Salmonella* assay (*S. typhimurium* TA1530) were used for experiments at low and high substrate concentration, respectively. The inhibitory effect of MAb 1-91-3 was measured on the *N*-demethylation of NDMA by human liver microsomal preparations.

Ethanol- or pyrazole-treatment increased the liver S9-mediated genotoxicity of the three nitrosamines up to 2.3-fold when assayed at low concentration (5 mM). As MAb 1-91-3 strongly inhibited their metabolic activation, P450 II E1 (and/or epitope-related P450s) is implicated in these reactions in liver S9 from untreated rats, but other P450s contributed significantly to these reactions. Similar inducibility and immunoinhibition were observed with NMOR at 50 mM concentration. Ethanol treatment decreased 2-fold and pyrazole treatment did not change the liver S9-mediated mutagenicity of NDMA at 100 mM concentrations; MAb 1-91-3 was strongly inhibitory.

In liver S9 from phenobarbital-treated rats, P450 II E1 (and/or epitope-related P450s) did not contribute markedly to NDMA, NDEA and NMOR activation at low and high nitrosamine concentration. Similar results were obtained with liver S9 from PCN-treated rats, except for NDMA (at 5 mM concentration) which was activated predominantly by P450 II E1 (and/or epitope related P450s).

The *N*-demethylation of 5 mM NDMA by human liver preparations (11 samples) was only weakly or not inhibited by MAb 1-91-3; at 100 mM no inhibition was observed.

Our data indicate that (*a*) P450 II E1 (and/or epitope-related P450s) catalyse the activation of aliphatic (NDMA, NDEA) and cyclic (NMOR) nitrosamines in rat liver; and (*b*) MAb 1-91-3 against rat liver P450 II E1 is useful for studying metabolic reactions of nitrosamines in rat but not in human liver, suggesting that the corresponding epitope is either absent or inaccessible in human liver P450 II E1.

(*f*) **Effect of dietary constituents on lipid peroxidation and foreign compound metabolism and its role in tumour initiation and progression** (Dr E. Hietanen, Dr H. Bartsch, Dr M. Ahotupa, Mr J.-C. Bérézíat, Mrs V. Bussachini-Griot and Miss A.-M. Camus)

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[101] Hietanen, E., Malaveille, C., Friedman, F.K., Park, S.S., Bérézíat, J.C., Brun, G., Bartsch, H. & Gelboin, H.V. (1986) *Cancer Res., 46,* 524–531

[102] Malaveille, C., Brun, G., Park, S.S., Gelboin, H.V. & Bartsch, H. (1987) *Carcinogenesis, 8,* 1775–1779

[103] Bartsch, H., Hietanen, E. & Malaveille, C. (1989) *Free Radical Biol. Med, 7,* (in press)

This study is investigating whether oxidative stress, lipid peroxidation and anti-oxidant defence have a role in human cancers, where dietary factors may be involved and these prooxidant changes may be the underlying mechanism for tumour development. Two approaches have been adopted: (1) to develop methods applicable to humans for measurement of lipid peroxidation products non-invasively and for the assay of enzymes and substances related to lipid peroxidation and antioxidant defence in blood; (2) to test, in cross-sectional studies, the validity of enhanced lipid peroxidation and/or decreased antioxidant defence as related to certain human cancers.

In order to identify possible links between lipid peroxidation, drug metabolism and the development of tumours, we have studied long-term changes in numerous metabolic parameters caused by dietary lipids alone or in combination with a chemical carcinogen, together with the appearance of tumours in rodents. We also changed the dietary fat content both qualitatively and quantitatively.

Free radical-related reactions are known to initiate lipid peroxidation. As a consequence, cell membranes are damaged through a detectable loss of membrane polyunsaturated fatty acids, increased diene conjugation, formation of other lipid peroxidation products and cholesterol oxidation. Lipid peroxidation has been chosen for monitoring the formation of free radical and active oxygen species and related cell damage due to the relative stability of peroxidation products. Some initiating carcinogenic nitrosamines have been found to cause lipid peroxidation and changed antioxidant status in short-term, long-term and *in vitro* studies[104,105,106].

Groups of male Wistar rats, after weaning, were fed diets containing 2%, 12.5% or 25% by weight of either saturated fat (SF; lard) or polyunsaturated fatty acids (PUFA; sunflower oil). Possible auto-oxidation of dietary lipids was checked routinely by analysing the malondialdehyde (MDA) content. One group of rats on the 25% polyunsaturated fat diet was also given indomethacin in the diet (50 mg/kg). After ten weeks, each dietary group was divided, and one received intragastric doses of *N*-nitrosodimethylamine (NDMA, 200 µg/rat) dissolved in 1 ml of water on 5 days per week for 30 weeks.

NDMA produced mainly hepatic haemangiosarcomas (Table 32). Up to 12.5% fat in the diet resulted in similar frequency of tumours, whether the diet contained SF or PUFA. However, when the dietary fat content was 25%, the group of rats on PUFA had more liver tumours than the group on the SF diet. In the group fed 25% PUFA, indomethacin at 50 mg/kg diet resulted in a decreased tumour incidence.

Ethane exhalation, as a measure of total body lipid peroxidation, in different groups of rats was monitored 10, 20–27 and 43 weeks after the start of feeding. When the amount of SF or PUFA in the diet was raised from 2% to 12.5%, the rate of ethane exhalation increased. A further increase in the level of dietary fat did not, however, further augment ethane production: animals receiving either 12.5% or 25% fat in the diet exhaled at similar rates. With the exception of rats on 2% dietary fat, animals consuming PUFA produced more ethane than those on SF diets. Within all dietary groups, administration of NDMA elevated ethane production by two to four times, and the increase was more pronounced than the variation in dietary lipid content. The presence of 0.005% indomethacin in the 25% PUFA diet diminished ethane production to

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[104] Ahotupa, M., Bérézíat, J.-C., Bussachini, V., Camus, A.-M., Hietanen, E. & Bartsch, H. (1987) In: *Lectures and Symposia of the XIV International Cancer Congress, Budapest, August 1986*, Budapest, Akademiai: Kiado, Vol. 4, 3–8

[105] Bartsch, H., Hietanen, E., Ahotupa, M., Camus, A.-M. & Bérézíat, J.-C. (1988) In: Feo, F., Pani, P., Columbano, A. & Garcea, R., eds, *Chemical Carcinogenesis Models and Mechanisms*, New York, Plenum Press, pp. 609–617

[106] Hietanen, E., Ahotupa, M., Bérezíat, J.-C., Bussachini, V., Camus, A.-M. & Bartsch, H. (1987) *Toxicol. Pathol., 15*, 93

Table 32. The effect of 50 weeks' feeding of various fat diets on the number of NDMA-induced liver tumours. The effect of indomethacin in the diet is also shown.

Per cent fat in diet	Polyunsaturated fat		Saturated fat	
	No. of rats with liver tumours (%)	No. of haemangio-sarcomas	No. of rats with liver tumours (%)	No. of haemangio-sarcomas
2	5 (42%) 1 early	4	6 (43%)	5 1 early
12.5	9 (64%)	7 2 early	9 (69%)	5 4 early
25	12 (80%)*	10 2 early	10 (67%)	9 1 early
25 plus indomethacin	9 (64%)	9		

* $p < 0.05$ in comparison with 2% fat diet

less than that seen with 2% fat, and in rats treated with NDMA, indomethacin suppressed the increase in ethane exhalation (Fig. 13).[107]

Our results indicate that the amount and composition of dietary lipids modify the oxidative state in experimental animals *in vivo*, as measured by lipid peroxidation.

We have started cross-sectional human studies in selected breast and colon cancer cases (in collaboration with Dr P. Boyle, IARC, and Professor O. Eremin, University of Aberdeen and Professor P.D. James, Rowett Research Institute, Aberdeen) to study the role of pro-oxidant state in carcinogenesis. Dietary factors for the regulation of lipid peroxidation and antioxidant defence are also being evaluated (in collaboration with the Department of Nutrition, University of Helsinki, Finland), in a group of volunteers who consumed consecutively different diets varying the degree of fat saturation.

7. INTERVENTION AND CANCER SCREENING STUDIES

(*a*) Evaluation of primary prevention programmes

(i) *The Gambia Hepatitis Intervention Study* (Dr A.J. Hall, Dr H.M. Inskip, Dr J. Chotard, Dr M. Vall Mayans, Dr C.S. Muir, Dr F.X. Bosch, Dr N. Muñoz, Dr D.M. Parkin, Dr J. Estève, Dr R. Montesano, Ms N. Charnay and Ms H. Renard; Dr A.B.H. N'jie and Dr K. Cham, Ministry of Health of The Gambia, Dr B.M. Greenwood and Dr H.C. Whittle, Medical Research Council, Fajara, The Gambia; in collaboration with Professor L. Chieco-Bianchi, University of Padua, Italy; Professor F. Aiuti, University of Rome, Italy; Professor M. Rizzetto, Hospital S. Giovanni Battista, Turin, Italy; and Professor R.L. Robertson, Mount Holyoke College, Massachusetts, USA)

[107] Bartsch, H., Hietanen, E. & Malaveille, C. (1989) *Free Radical Biol. Med.* (in press)

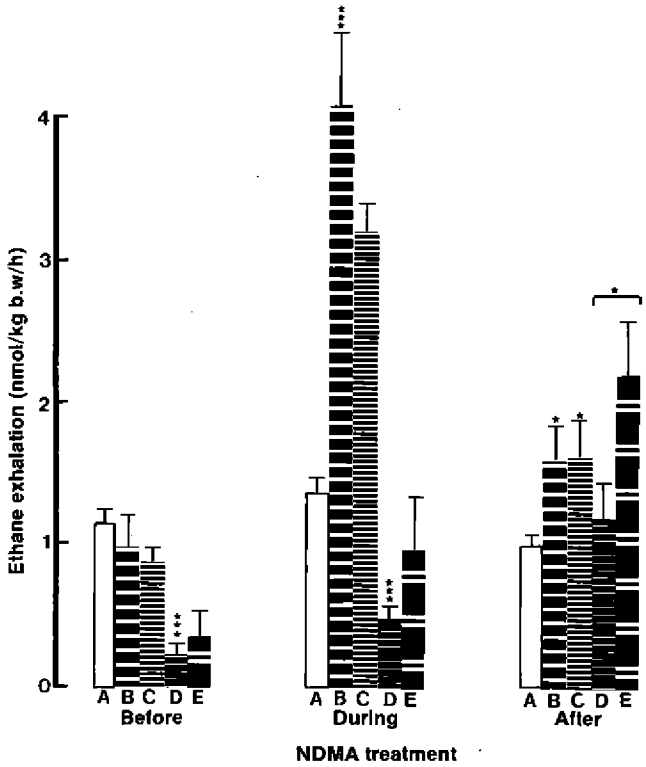

Fig. 13. Ethane exhalation as a measure of lipid peroxidation in male rats given *N*-nitrosodimethylamine (NDMA)

*Male Wistar rats were given NDMA in saline intragastrically, from the age of 10 to 40 weeks at a dose of 200 µg/rat on five days/week. The three sets of columns represent data obtained before NDMA treatment, during treatment and 10 weeks after NDMA treatment. Rats fed 25% fat diet were killed at 50 weeks, and the presence of liver tumours (haemangiosarcomas) was noted. One group of rats also received indomethacin in the diet (50 mg/kg diet) from weaning until the end of the study. A: no NDMA treatment, no tumours present (n = 14); B: NDMA treated, without tumours (n = 13); C: NDMA treated, with tumours (n = 16); D: NDMA treated, having indomethacin in the diet, without tumours (n = 6); E: NDMA treated, having indomethacin in the diet, with tumours (n = 5). Means ± SE are shown; statistical comparisons were made using untreated group (A) as reference, unless otherwise shown. Significance: *: $p < 0.05$; ***: $p < 0.001$*

The Gambia Hepatitis Intervention Study (GHIS) is designed 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. A cohort of at least 120 000 infants registered at health centres between July 1986 and February 1990 will be recruited into the study, of whom approximately half will have received the standard Expanded Programme of Immunization (EPI) vaccines and the rest will have received, in addition, between one and four doses of HB vaccine (10 µg per dose intramuscularly in the deltoid). Figure 14 shows the timetable of the project. The

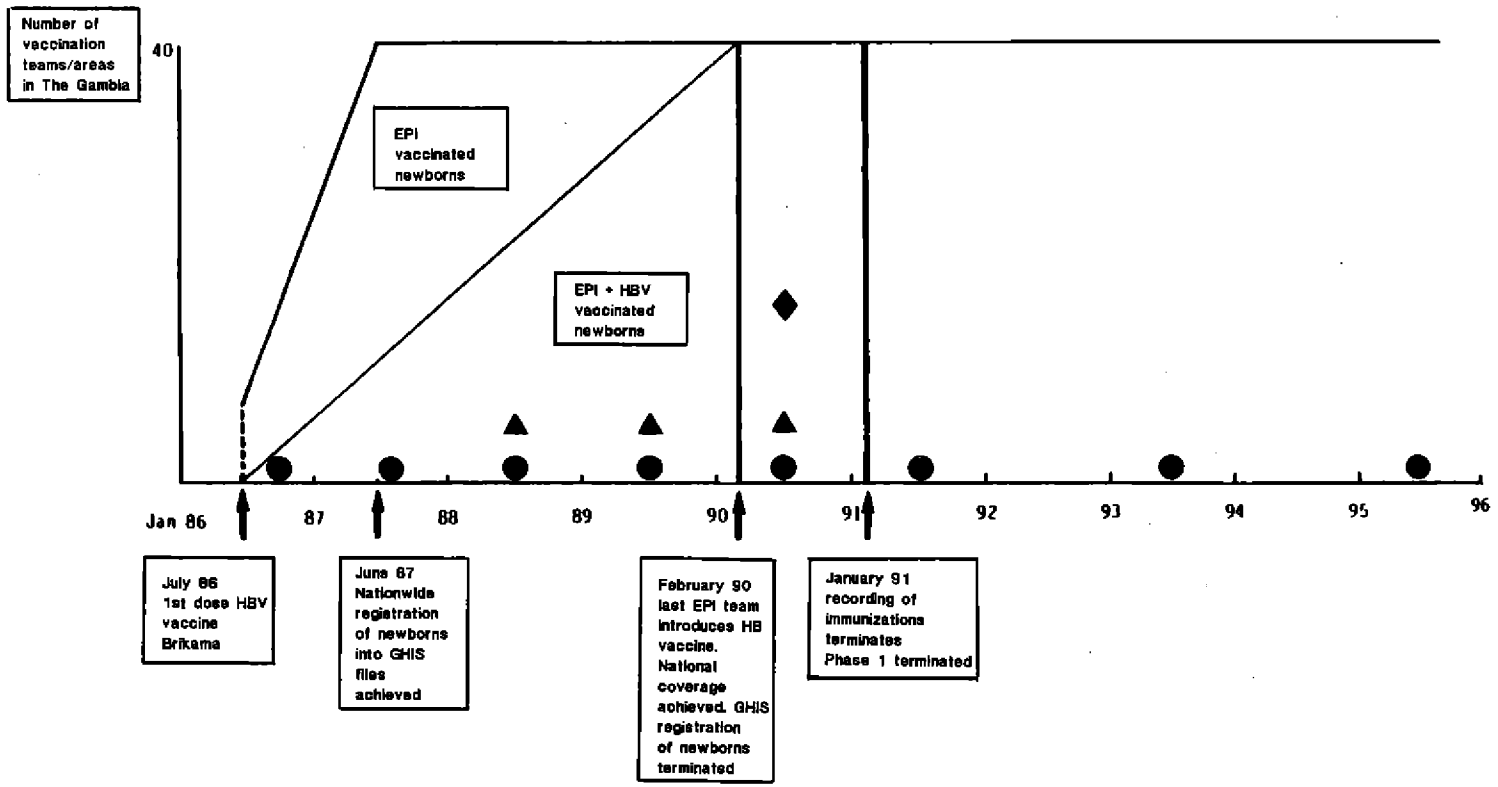

Fig. 14. The GHIS scheme of introduction of hepatitis B vaccine. Timetable for the main activities outlined in the study protocol

final outcome of the project will be assessed by comparing the incidence of liver cancer over the next 35 years between the groups of HB-vaccinated and HB-unvaccinated subjects belonging to the GHIS cohort. The study, funded by the Department of Cooperation and Development of the Italian Ministry for Foreign Affairs, is conducted in collaboration with the Medical Research Council laboratories unit in Fajara, and assists the Government of The Gambia in maintaining a strong immunization programme.

The third meeting of the GHIS Steering Committee took place in Lyon on 13 January 1988, with Dr A.B.H. N'jie as Chairman, and representatives of the Government of The Gambia, Government of Italy, UK Medical Research Council, WHO Representative in Banjul and WHO Regional Office for Africa. The main decisions taken at the meeting were (i) to recruit new staff (Drs Jacques Chotard and Marti Vall Mayans were appointed in March 1988); (ii) to expand the computer configuration in The Gambia; (iii) to adjust the schedule of introduction of HB vaccine to the recruitment rate and the activities of an increased number of vaccination teams and (iv) to prepare a position paper on the need for a booster dose of HB vaccine later in life and its implications.

At a peer review committee on 14 January 1988, the following ancillary studies were approved: the role of endogenous *N*-nitroso compounds in cancer of the liver (see section I.2.*e*.ix); the epidemiology of hepatitis delta virus infection; the natural history of human retro-virus infections; the causes of non-response to HB vaccine; studies on aflatoxin (see section I.2.*g*.iii); randomized trial of trivalent oral polio vaccine; pilot trial of *Haemophilus influenzae* B polysaccharide.

The fourth GHIS Steering Committee meeting took place in The Gambia on 31 January 1989, chaired by Dr N'jie. The main decisions were: (i) to redefine Group 2 as a cross-sectional survey of infants 4 to 5 years old (the survey will take place in 1990); (ii) in the light of the position paper concerning booster of HB vaccine, not to recommend the use of a booster; (iii) to recruit a histopathologist to develop the pathology department at the Royal Victoria Hospital and to give support to the Cancer Registry.

The following projects were approved by the peer review committee, following review by ethical committees in The Gambia and at IARC; evaluation of the cost-effectiveness of the addition of hepatitis B virus vaccination to the Expanded Programme of Immunization in The Gambia; study of environmental and genetic factors in carriage of HBeAg; a study of childhood nephrotic syndrome and hepatitis B infection; a survey of hepatitis B virus infection in Manduar and Keneba; an expansion of the ongoing intervention study on possible HB transmission by arthropods.

HB vaccine was introduced into the Expanded Programme of Immunization in July 1986 in the Brikama district, and coverage has been steadily widened, so that by early 1990, it will be in use throughout The Gambia.

The increase in the number of vaccination teams from 17 in 1985 to 40 in 1986 and the improved mobility of the teams due to better transport has contributed to the improvement in coverage for all antigens. National coverage with BCG (1 dose), DPT (3 doses), polio vaccine (3 doses), yellow fever (1 dose) and measles (1 dose) was evaluated in January 1989. Over 60% of the children aged 12–23 months old had received all the anticipated vaccines, as assessed by review of their Infant Welfare Cards (IWC). For each specific vaccine, the coverage was over 80%.

Three special groups of infants are being monitored to assess the short- and medium-term effects of HB vaccination.

Group 1 consists of 1000 HB-vaccinated infants. Blood samples are being taken every year up to age five years, then every two years until age 10. These will provide information on HB vaccine response rate, antibody titres and duration of protection against HB infection. Surveys of Group 1 were conducted in 1987, 1988 and 1989.

Table 33. Results of the first-year follow-up of Group 1. Child's hepatitis B status by mother's HBsAg status and by number of doses of HB vaccine received

Mother's HBsAg status	No. of doses	Child's status at 1 year					
		Unknown	HBsAb + HBcAb −	HBsAb − HBcAb −	HBsAb + HBcAb +	HBsAb − HBcAb +	Total known status
Negative	1	51	5	0	1	0	6
	2	46	22	1	0	0	23
	3	98	236	3	8	2	249
	4	46	364[a]	6	13	0	383
Positive	1	11	1	0	0	0	1
	2	3	3	0	0	0	3
	3	13	27	1	5	1[a]	34
	4	7	52	0	6	1[a]	59
Unknown		2	6	0	0	0	6
	Total	277[b]	716 (94%)	11 (1%)	33 (4%)	4 (<1%)	1041[c]

[a] Includes 1 child who is HBsAg positive

[b] Includes two children for whom there was insufficient blood to measure HBcAb. Their HBsAb titres were 651 and 90 respectively

[c] Includes the 277 of unknown and 764 of known status

Table 33 shows the number of children who developed an antibody response following HB vaccination in study Group 1 by HBV status of the mother. Table 34 shows the antibody titres in the same group of children. These tables show that 94% of the HB-vaccinated children developed an antibody response and that the HBsAb titres were above the recommended protective level of 10 mIU in 98% of them.

Group 2 consists of 1000 non-HB vaccinated children aged 4 to 5 years. A cross-sectional survey will be conducted in 1990.

Group 3 consists of three cohorts, each of 500 HB-vaccinated children conducted in 1988, 1989 and 1990. The results provide information on the continuing immunogenicity of the vaccine

Table 34. Results of the first year follow-up of Group 1. Child's HBsAb titre response by mother's HBsAg status and number of doses of HB vaccine received

Mother's HBsAg status	No. of doses	Child's HBsAb titre (mIU)				
		<10	10–99	100–999	>1000	Total
Negative	1	0	3	2	1	6
	2	1	1	7	14	23
	3	5	21	81	143	250
	4	6	17	94	266	383
Positive	1	0	2	0	0	2
	2	0	0	1	2	3
	3	2	3	10	19	34
	4	1	1	16	41	59
	Total	15 (2%)	48 (6%)	213 (28%)	490 (64%)	766 (100%)

Table 35. Results of Group 3 for 1988. Immunization coverage of the five areas surveyed.

No. of doses of HB vaccine received	Region					Overall
	Brikama	D/K[a]	B/Y[b]	Essau	Gam	
	[121]	[105]	[129]	[105]	[101]	[561]
1	89	96	98	100	100	96
2	88	96	95	97	100	95
3	79	93	92	90	97	90
4	63	88	60	72	85	73
Fully vaccinated[c]	59	78	50	65	70	62

[a] D/K: Dankunku/Kudang

[b] B/Y: Badjakunda/Yorobawal

[c] BCG, HB 1–4, polio 1–5, DPT 1–3, measles, yellow fever

[], number of children

Results in percentages

lots used and on the coverage achieved in vaccination areas following the introduction of the HB vaccine.

Table 35 shows the results of the coverage achieved by the EPI programme after introduction of HB vaccine, from the GHIS survey of Group 3. Overall, 73% of children scheduled to receive four doses of HB vaccine had done so.

Transfer of data to IARC

The main files of the GHIS are being transferred to IARC in Lyon for permanent storage and future analysis. Information on over 75 000 infants has already been transferred. The foot and palm prints of the infants recruited into GHIS are being locally photographed and negatives will be shipped to IARC for permanent storage.

Cancer registration

Cancer registration had been implemented throughout The Gambia. Table 36 shows some of the results for all sites and for liver cancer for two periods, 1986–87 and 1986–88.

Ancillary projects

In addition to the ancillary projects approved at the third and fourth Steering Committee meetings, the following five projects are being conducted in The Gambia:

(1) Hepatitis B virus infection in the families of neonates receiving hepatitis B vaccine and its influence on the response to vaccination;

(2) A study of twins to determine the genetic contribution to the immune response to vaccine;

(3) An intervention study to evaluate the contribution of arthropods to the transmission of hepatitis B virus between children in The Gambia;

(4) A case–control study to evaluate the etiology of chronic liver disease in The Gambia;

(5) A case–control study to evaluate the protective efficacy of BCG in The Gambia.

Table 36. Cancer incidence in the Gambia for all sites and for primary liver cancer, 1986–87 and 1986–88

	All sites		Liver	
	Male	Female	Male	Female
The Gambia				
(1986–87)	74	55	33	13
(1986–88)	66	47	34	13
excluding skin	63	46		

Figures are rates per 100 000 age-adjusted to the world standard population.

(ii) *Evaluating effectiveness of intervention studies* (Dr D.M. Parkin, Dr J. Kaldor and Dr M.P. Coleman; in collaboration with Professor M. Hakama, University of Tampere, Finland; Dr V. Beral, Centre for Disease Control, Atlanta, GA, USA; and Dr J.W. Cullen, National Cancer Institute, Bethesda, MD, USA)

This project, initiated within the epidemiology programme of the International Union Against Cancer (UICC), has been conducted in collaboration with IARC. It has involved a systematic review of the evidence concerning the effectiveness (or otherwise) of preventive interventions which might have reduced the risk of cancer. Financial support from the Nordic Cancer Union permitted the holding of a workshop in Reykjavik, Iceland, in September 1988[108].

Several interventions in occupational and medical fields, although not designed as preventive trials, unequivocally resulted in reduction or elimination of specific cancers. Much of the interest of the workshop was, however, concerned with reviewing results in relation to interventions in diet and tobacco use. The majority of such studies involved preventive programmes against cardiovascular diseases and these interventions, mainly based on health education on smoking and diet, have not so far resulted in any substantial effect on cancer risk. This does not imply that such efforts were ineffective. The exposure and follow-up have been relatively short and similar changes in behaviour may have been diluted in the control groups.

The edited proceedings of this workshop are to be published as an IARC Scientific Publication[109].

(*b*) Evaluation of early detection programmes

(i) *Screening for cancer of the cervix* (Dr D.M. Parkin; in collaboration with Dr Zhang Z.F. and Professor Yu S.Z., Shanghai Medical University, PR China; Dr D. Esteban, Rizal Medical Center, Manila; and Dr C. Ngelangel, University of the Philippines, Manila)

The results of a population screening programme for cervical cancer in Jing-An county, Jiangxi province, China, have been analysed by a visiting IARC Research Fellow[110]. The screening programme comprised examinations every two years in a population of 22 100 women aged 25

[108] Hakama, M., Beral, V., Cullen, J. & Parkin, M. (1988) *Int. J. Cancer, 43,* 967–969

[109] Hakama, M., Beral, V., Cullen, J.W. & Parkin, D.M. (1989) *Evaluating the Effectiveness of Primary Prevention of Cancer* (IARC Scientific Publications No. 103), Lyon, International Agency for Research on Cancer

[110] Zhang, Z.F., Parkin, D.M., Yu, S.Z., Estève, J., Yang, X.Z. & Day, N.E. (1989) *Cancer Detect. Prevent., 13,* 337–342

years or more. A clear protective effect of screening was demonstrated (relative risk 0.33 for three or more negative tests compared to one or less, and 1.4 for women whose last negative smear was eight or more years previous, compared to two or less). Self-selection for screening by low-risk women did not appear to account for the results.

A pilot study is at present being carried out in the Manila-Rizal area of the Philippines, where a limited screening programme for cervix cancer has been in operation for 15 years. It is proposed to investigate etiological factors for cervix cancer, determinants of screening attendance, and the effectiveness of screening in a larger study in 1990–91.

(ii) *Screening for gastric cancer* (Dr D.M. Parkin, Dr N. Muñoz and Dr M. Khlat; in collaboration with Dr W.E. Oliver and Dr N. Alvarez, Cancer Control Centre, San Cristobal, Venezuela)

A programme of screening for early gastric cancer by photofluoroscopy has been in progress in Tachira State, Venezuela, since 1980, and over 100 000 examinations had been carried out by the end of 1988. A case–control study has been initiated to examine the degree to which screening is associated with a reduction in the risk of death due to gastric cancer. A further study of cases of advanced cancer is planned in conjunction with the investigation of etiological factors (see I.3.*d*.iii).

(iii) *Screening for lung cancer* (D.M. Parkin and Dr M. Khlat; in collaboration with Dr A. Kubik, Research Institute of Tuberculosis and Respiratory Diseases, Prague)

A randomized controlled trial of screening for lung cancer by six-monthly chest X-ray plus sputum cytology was carried out in Czechoslovakia in 1976–79. A total of 6346 middle-aged heavy smokers with no evidence of lung cancer on initial screening were randomized into two groups: (1) an experimental group undergoing semi-annual screening by radiology and sputum cytology study, and (2) a control group which had only one screening test three years after the initial examination. The results immediately after the three-year intervention period have been published[111]. Both groups were followed for an additional three years, and had a chest photofluorogram (but no sputum cytological examination) by the end of the fourth, fifth and sixth year. Lung cancer cases were followed for at least five years from the date of diagnosis, or until death. Further analyses will look at the incidence and mortality of lung cancer in the two groups over the two three-year periods, and at survival in screen-detected and clinically detected cases, up to February 1989.

[111] Kubik, A. & Polak, J. (1986) *Cancer, 57*, 2427–2437

II. STUDIES ON MECHANISMS OF CARCINOGENESIS

A better understanding of the natural history of a disease has always been of importance in the identification of risk factors and the implementation of primary prevention measures. In carcinogenesis, progress in fundamental research in recent years has allowed the detailed examination, in both experimental animals and humans, of the cellular and molecular events that lead to the appearance of cancer. Particularly important has been the recent development of new techniques in biochemistry and molecular biology, as well as the improved understanding of cancer genetics that is making possible a better integration of experimental and epidemiological studies in cancer research. Many of the studies described below aim to assess the role of genetic damage, DNA repair processes, alteration of gene expression and the interaction between viruses and chemical carcinogens in cancer induction and development. In addition, studies are also reported on the role of cell-to-cell communication in the progression of cancer, and on the importance of genetic predisposition in the etiology of some human cancers. These studies are in general limited to situations that appear particularly relevant to public health or in which the integration of laboratory and epidemiological studies appears particularly promising.

1. ROLE OF VIRUSES AND CYTOGENETIC ANOMALIES 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 human cancer and to identify the molecular steps leading to the development of a given cancer. Particular models of cancer being studied are Burkitt's lymphoma (BL), a cancer that shows great geographic variation in its incidence, is associated with the Epstein–Barr virus (EBV) in Africa and carries specific cytogenetic anomalies, and nasopharyngeal carcinoma (NPC), a tumour that is consistently associated with EBV.

Other projects in progress are examining the significance of hepatitis B virus as a cause of liver cancer (see sections I.2.*g*.iii and I.3.*a*), interaction between viral and chemical carcinogenesis (see sections I.2.*g*.vii and I.7.*d*) and the possibility of prevention of liver cancer by vaccination (see section I.7.*a*). The role of human papillomavirus, or of specific subtypes, in causing cervical cancer is being extensively investigated (section I.3.*f*).

(*a*) Collection of biological material related to Epstein–Barr virus and Burkitt's lymphoma

(Dr G. Lenoir, Ms C. Bonnardel, Ms M. Vuillaume and Ms S. Pauly)

As part of various Agency projects, we have constituted a very large collection of sera, human material and cell lines, which are used widely by the scientific community for studies of EBV, BL, NPC and B-cell neoplasia. Sera, biopsies and cell lines (over 120 BL cell lines established in cultures at the Agency, representing one of the largest collections of human tumour cell lines for a given cancer) are shipped free of charge on request to institutions all over the world. During the period under review, 210 lymphoid cell lines were sent to 44 institutions in 12 countries in the form of live cells, frozen cells or DNA, as well as various other materials, such as sera, biopsies and probes.

(*b*) **Studies on lymphomas occurring in AIDS patients** (Dr H.-J. Delecluse and Dr G. Lenoir; in collaboration with Dr M. Raphael, C.H.U. Pitié-Salpêtrière, Paris (cooperative programme supported by the Agence Nationale de Recherches sur le Sida, Paris)

Epstein–Barr virus (EBV) can cause lymphoproliferative diseases in individuals with immune dysfunctions. 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 can also occur at relatively high incidence in individuals who are 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. In relation to HIV infection, a similar lymphoma occurs in AIDS patients with severely altered immune parameters. Some HIV-positive individuals also develop true Burkitt-type lymphoma, carrying characteristic chromosomal translocations, but in some cases, no detectable EBV sequences. This suggests that their pathogenesis is not directly related to the Epstein–Barr virus, 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. The correlation of the data with the clinical and pathological data from the cooperative study group may help in the identification of the risk factors for the two types of lymphoma.

(*c*) **EBV genes involved in cell immortalization and transformation** (Dr A. Calender, Mr M. Billaud, Miss M. Cordier and Dr G. Lenoir; in collaboration with Dr G. Bornkamm, Institute for Virology, Freiburg, FR Germany; and Dr T. Tursz, Gustave Roussy Institute, Villejuif, France)

(i) *Infection experiments*

Various attempts have been made to identify the region of the EBV genome involved in the process of cellular immortalization. Transfection of cloned DNA fragments of the EBV genome into primary rat fibroblasts does not lead to the establishment of permanent cell lines such as those obtained with cloned oncogenes such as *c-myc*, SV40 large-T gene and adenovirus E1A gene. We have been focusing on the EBV nuclear antigen-2 (EBNA2) protein. The gene that codes for this molecule is deleted in the non-immortalizing strain of EBV, P3HR1, suggesting that it plays an important role in B-cell immortalization.

We demonstrated recently that a set of B-cell activation markers, the EBV/C3d receptor (CR2, also called CD21), and Blast2 antigen (or CD23)[1] can be turned on by infecting EBV-genome-negative lymphoma cells with the B95-8 immortalizing strain of the virus. The non-immortalizing EBV variant, P3HR1, does not induce expression of these markers. We have now demonstrated that the EBV-mediated up-regulation of these two cellular genes occurs at the transcriptional level (Fig. 15). These results suggest that the immortalizing potential of EBV is correlated with its ability to induce expression of B-cell activation markers, which are suspected to play a major role in the physiological pathway leading to lymphoid cell proliferation. The EBNA2 gene might act as a transactivator of some cellular genes, in a way similar to how the gene of the HTLV1 retrovirus can turn on expression of the I12 receptor in T-lymphoid cells.

The expression of other cellular genes, possibly involved in Burkitt's lymphoma pathogene-

[1] Calender, A., Billaud, M., Aubry, J.-P., Banchereau, J., Vuillaume, M. & Lenoir, G.M. (1987) *Proc. Natl Acad. Sci. USA, 84,* 8060–8064

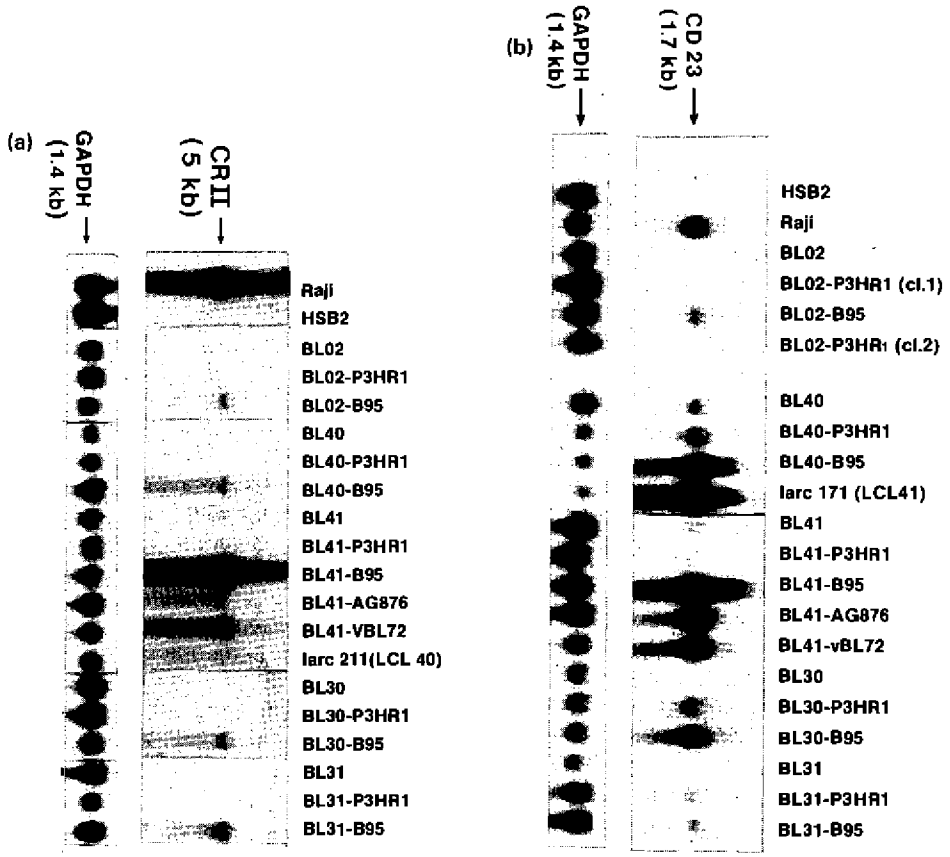

Fig. 15. Phenotypic modification of B-cell activation markers related to EBNA2 expression. Analysis of (a) CR2 and (b) CD23 transcription in various converted cell lines. In both cases, the steady state mRNA is induced in B95 but not in P3HR1 convertants. GAPDH is used as an internal control.

sis, was investigated at the transcriptional level. We have demonstrated that expression of two lymphocyte function-associated molecules, LFA-1 and LFA-3, involved in intercellular adhesion and T cytotoxic pathway, were strongly up-regulated by immortalizing EBV. These results suggest that EBNA2 and/or LMP-mediated deregulation of cellular genes, such as CD21, CD23 as well as LFA-3, could be part of the mechanism of the EBV involvement in B cell immortalization.

(ii) *Transfection experiments*

In order to elucidate the mechanism of activation described above, attempts have been made to introduce EBV latent gene (especially EBNA2) into negative B-cell lines in order to analyse their effect directly. Using electroporation, we have transfected EBNA2 gene cloned in an episomal vector into lymphoma cells containing the P3HR1 viral genome and have obtained cell-clones that stably express the EBNA2 protein. In these clones, EBNA2 expression is associated with increased cell-surface expression of CR2 and with the release of the soluble form of CD23 (sCD23) (Fig. 16).

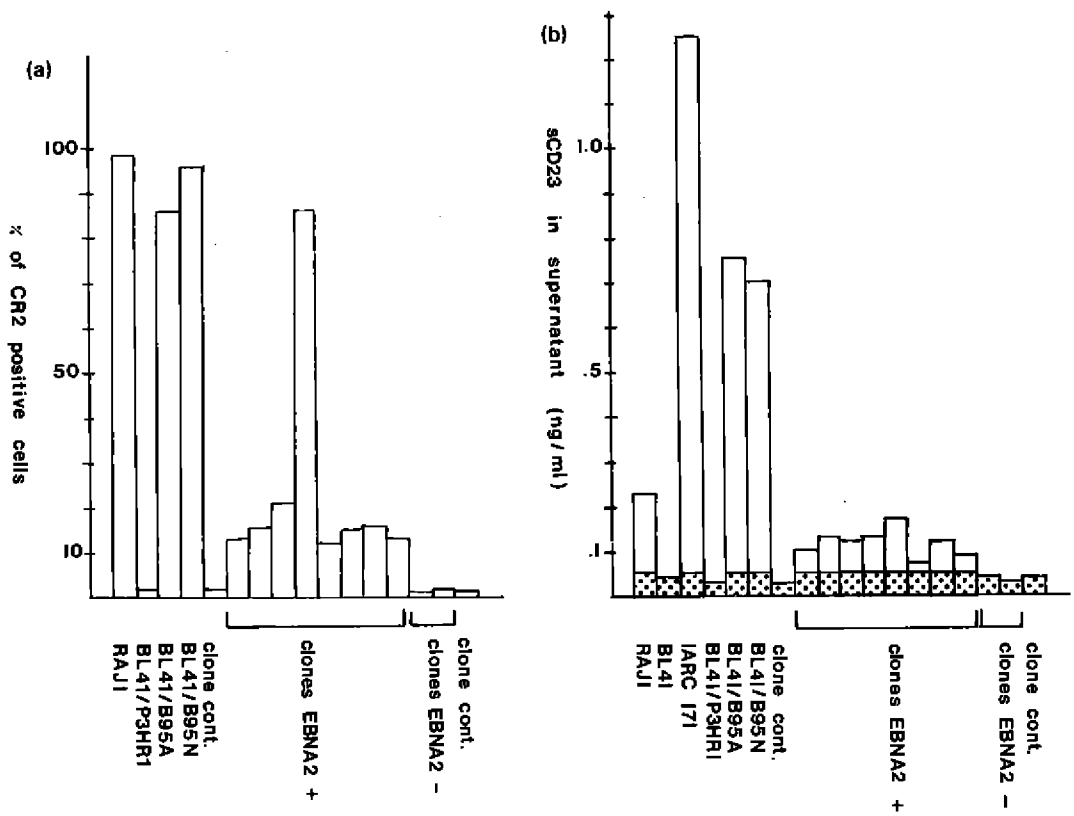

Fig. 16. Increases in (a) cell surface expression of CR2 and (b) release of the soluble form of CD23 (sCD23) related to EBNA2 expression in transfected clones. EBNA2-positive clones express the membrane receptor CR2/CD21 and shed sCD23. CR2/CD21 was analysed using a fluorescence-activated cell sorter, while sCD23 was analysed by immunoassay.

These results demonstrate that EBNA2 gene is able to complement P3HR1 virus latent functions to induce the activation of CR2 and CD23, and emphasize the role of EBNA2 protein in the modulation of cellular genes implicated in B-cell proliferation and thus in EBV-mediated B-cell immortalization.

(iii) *Studies on nasopharyngeal carcinoma*

Anaplastic nasopharyngeal carcinoma (NPC) cells invariably harbour Epstein–Barr virus (EBV) genome, an association that is unique among human virus-associated cancers. Although EBV is able to replicate in epithelial cells, results concerning the expression of the EBV receptor

(complement receptor type 2 (CR2 or CD21)) in normal and malignant epithelial cells are conflicting. We have grown five different EBV-associated NPC tumours in nude mice and using a sensitive transcriptional assay we have been able to detect a very weak transcription signal of the EBV receptor CR2 gene in these cells. This suggests that low levels of EBV receptor may be expressed by malignant epithelial nasopharyngeal cells. The gene coding for Blast2/CD23, a B-cell activation molecule induced by EBV, was transcribed in three of the transplanted NPC tumours. The soluble form of the Blast2/CD23 protein was also detected in media taken from short-term culture of the same NPC cell lines. In contrast to the lymphoid system where Blast2/CD23 expression is associated with EBV nuclear antigen (EBNA2) expression, no EBNA2 protein could be detected in these NPC epithelial cells. Our study represents the first demonstration of Blast2/CD23 expression in epithelial cells[2]. As the soluble form of the Blast2/CD23 protein possesses growth factor activity associated with EBV-induced B-cell immortalization, these results suggest a possible role of this molecule in the pathogenesis of NPC.

***(d)* Immunological response to EBV and EBV-infected cells** (Dr A. Calender, Mr M. Billaud and Dr G. Lenoir; in collaboration with Dr A. Rickinson, Birmingham, UK)

(i) *Expression of latent membrane protein*

We have demonstrated that in Burkitt's cells, EBNA2 may be required for subsequent expression of the EBV-coded latent membrane protein LMP. Both EBNA2 and LMP (but not EBNA1 or EBNA3) may provide target antigens for the EBV-specific T cell response. These data suggest that *in vivo* BL cells may escape the host immune control by down-regulating EBNA2 expression[3].

(ii) *Down-regulation of adhesion molecules*

Lymphocyte function-associated antigen 1 and 3 (LFA-1, LFA-3) and intercellular adhesion molecule 1 (ICAM-1) are cell surface adhesion molecules necessary for immune processes requiring intercellular contacts. It was recently proposed that malignant Burkitt's lymphoma (BL) cells may escape from immunosurveillance through the down-regulation of LFA-1 or both LFA-3 and ICAM-1 molecules[4]. Expression of these three adhesion antigens was investigated in 24 BL lines[5]. LFA-1 or LFA-3 expression was absent or low in 12 out of 15 EBV genome-positive lymphoblastoid cell lines (LCL). Negative or weak expression of LFA-1 and LFA-3 was also observed in eight out of nine EBV genome-negative BL cells. ICAM-1 was expressed on the cell surface of the majority of BL, but with lower density than on LCL. BL lines growing as individual cells did not express LFA-1, whereas clump-forming BL lines expressed this marker which has been demonstrated to be involved in homotypic aggregation of B cells. A transcription analysis revealed that the level of mRNA coding for these adhesion

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[2] Billaud, M., Busson, P., Huang, D., Mueller-Lantzch, N., Rousselet, G., Pavlish, O., Wakasugi, H., Tursz, T. & Lenoir, G.M. (1989) *J. Virol.* (in press)

[3] Murray, R.J., Young, L.S., Calender, A., Gregory, C.D., Rowe, M., Lenoir, G.M. & Rickinson, A.B. (1988) *J. Virol., 62*, 894–901

[4] Billaud, M., Calender, A., Seigneurin, J.M. & Lenoir, G.M. (1987) *Lancet, ii*, 1327–1328

[5] Billaud, M., Rousset, P., Aubry, J.P., Banchereau, J., de Vries, J., Calender, A., Cordier, M., Gurtsevitch, V., Seigneurin, J.M., Springer, T. & Lenoir, G.M. (submitted for publication)

receptors was correlated with protein expression. Consequently, diminished LFA-1 and LFA-3 expression appears to be a characteristic of EBV-positive BL cells as well as EBV-negative ones. This suggests that impairment of interaction with immunocompetent cells could be a central mechanism of malignant progression, not restricted to virus-specific surveillance of EBV-positive BL tumours. We also demonstrated that interleukin 4 (IL4) promotes induction of LFA-1 and LFA-3 on BL cells, suggesting that IL4 could be a valuable tool in immunotherapy[6].

(*e*) **BL tumorigenicity assays** (Dr V. Gurtsevitch)

The metastasizing capacity of BL cells in nude mice has been evaluated by intravenous injection. The animal metastatic model described is easily reproducible and it is suggested that it can be used effectively for identification and analysis of the homing properties of BL cells and their implication in BL pathogenesis. This tumorigenicity/metastatic assay may also be a suitable model for the study of new therapeutic molecules *in vivo* such as IL-4, as recently proposed by Tepper *et al.*[7]

(*f*) **Prevalence of human T-cell leukaemia/lymphoma virus type 1 (HTLV-1) in the population of the far east of the USSR** (Dr V. Gurtsevitch)

The prevalence of HTLV-1 in the population of the far east of the USSR has been studied. Serum samples of 2130 apparently healthy volunteers over 17 years old of both sexes were collected in Khabarovsk and Primorsk territories as well as in Sakhalin province during the summer of 1986. Screening for HTLV-1 antibodies was performed by the passive particle-agglutination (PA) assay. The seropositivity rate for the overall study population was 2.0%. HTLV-1 carriers were more frequently found among ethnic groups native to the region than among subjects originally from the western and central Russian parts of the USSR. Testing of 23 PA-positive samples by Western blot assay resulted in detection of HTLV-1 antibodies for only seven samples. Since the majority were non-reactive in this assay, it appears that viral types may exist which are related to HTLV-1 but different from it. The study clearly documents for the first time the presence of HTLV-1 infection in the far east of the USSR, and indicates the need for further investigation of viral isolates[8].

2. ROLE OF ONCOGENES IN THE DEVELOPMENT OF TUMOURS IN HUMANS AND IN EXPERIMENTAL ANIMALS

Because of their fundamental role in cell proliferation and differentiation, cellular oncogenes are being studied from various viewpoints in IARC laboratories. In this section, studies on analysis of activated oncogenes in tumour samples from humans and experimental animals are reported.

Various cancers related to environmental factors can be attributed to genetic lesions produced by carcinogen exposure, and likely targets of genetic damage leading to cell malignancy are cellular oncogenes that control cell growth and differentiation. A sequence of

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[6] Rousset, F., Billaud, M., Blanchard, D., Figdor, C., Lenoir, G.M., Spits, H. & de Vries, J.E. (1989) *J. Immunology, 143*, 1490–1498

[7] Tepper, R.I., Pattengale, P.K. & Leder, P. (1989) *Cell, 57*, 503–512

[8] Gurtsevitch, V.E., Stepina, V.N., Yakoleva, L.S., Senjuta, N.B., Weber, J., Tosswill, J., Hinuma, Y., Calender, A., Kaldor, J. & Lenoir, G.M. (submitted for publication)

genetic changes involving specific oncogene lesions has been found in a number of experimental or human cancers, notably colon and pancreas carcinomas, where a high proportion of a transforming *ras* oncogene allele, activated by point mutation, was observed[9]. These studies are aimed at investigating in animals and humans the connection between the DNA damage and alterations of gene expression, and to ascertain whether the pattern of oncogene activation resulting from exposure to environmental carcinogens is different in a cancer for which large geographic differences are observed.

Other aspects of oncogene studies are described in sections which deal with mechanisms of tumour promotion and with the role of intercellular communication in carcinogenesis.

(*a*) Transplacental carcinogenesis and H-*ras* mutation induction in mice by 7,12-dimethylbenz[*a*]anthracene (DMBA) (Dr M. Hollstein, Dr A. Loktionov, Dr J.R.P. Cabral, Miss N. Martel, Mrs D. Galendo, Dr H. Yamasaki and Dr L. Tomatis)

Previous results in this programme have shown that skin tumours can be produced by transplacental initiation–postnatal promotion in CD-1 mice and that these tumours contained a specific activating mutation of cellular H-*ras*[10]. Mice exposed *in utero* to DMBA (100 or 10 mg/kg, i.p. to 15-day pregnant mothers) had 4.5-fold greater incidence of lung adenomas than controls. The liver cell tumour incidence in male offspring from DMBA-exposed mothers was 63–65%, compared with 50% in those from non-exposed mothers. A similar increase in lung adenoma incidence was observed after exposure to benzo[*a*]pyrene *in utero*. To further clarify the relationship between DMBA exposure *in utero* and H-*ras* activation in internal organs, 15 mg/kg b.w. of DMBA was injected intraperitoneally into pregnant CD-1 mice. Their offspring and offspring from control mice were then painted dorsally with acetone, 12-*O*-tetradecanoylphorbol 13-acetate (TPA) or benzoyl peroxide. In this experiment, we found an A to T transversion at the 61st codon of H-*ras* in skin papillomas from mice transplacentally exposed and also occasionally in those not exposed to DMBA, suggesting that this mutation could either occur spontaneously or be induced by TPA alone (Table 37). The same mutation was found in 14 out of 26 liver cell tumours that occurred after exposure to DMBA *in utero*, but not in any of nine such tumours from control mice, suggesting that the mutation is DMBA-induced. None of the 26 tested samples of lung adenoma contained the mutation (Table 37). Results from these two experiments suggest that exposure to DMBA *in utero* induces A to T transversion at the 61st codon of fetal H-*ras* and that this mutation is involved in carcinogenesis in some tissues, including skin and liver, but not in others, such as lung. This can be interpreted by at least two different mechanisms: (*a*) DMBA induces the H-*ras* mutation at the 61st codon preferentially in the skin and liver, but not in the lung (possibly due to different DMBA metabolism); (*b*) DMBA induces the mutation in all three organs, but this mutation is not an appropriate signal for the initiation of lung carcinogenesis (K-*ras* mutation may be more important for lung carcinogenesis).

(*b*) Oncogene activation in rat liver epithelial cell lines (Dr K. Enomoto and Dr H. Yamasaki)

In order to examine the relationship between oncogene alteration and tumour progression, cellular oncogenes and transformed phenotypes have been analysed in a series of rat liver epithelial cell lines (termed IAR), which represent different stages of malignancy. DNA and RNA samples purified from IAR cell lines were analysed by blot hybridization using H-*ras*,

[9] Bos, J.L. (1988) *Mutat. Res., 195,* 255–271

[10] Yamasaki, H., Hollstein, M., Martel, N., Cabral, J.R.P., Galendo, D. & Tomatis, L. (1987) *Int. J. Cancer, 40,* 818–822

Table 37. H-*ras* oncogene 61st codon mutation frequency in spontaneous and DMBA-induced tumours of skin, lung, liver and malignant lymphomas of liver in transplacental carcinogenesis experiment in CD-1 mice

Tumour localization	Tissue or tumour type	Treatment		No. of XbaI RLFP-positive tumours[b]/No. of tumours tested
		Transplacental	Postnatal[a]	
Skin	Papilloma	—	TPA	4/7
	Papilloma	DMBA	BZPO	2/3
	Papilloma	DMBA	TPA	7/9
	Papilloma	(DMBA)[c]	TPA	1/4
	Carcinoma	—	TPA	2/3
	Carcinoma	—	BZPO	1/1
	Carcinoma	DMBA	TPA	2/4
Lung	Adenoma & carcinoma	DMBA	—	0/12
	Adenoma & carcinoma	DMBA	TPA	0/13
	Adenoma & carcinoma	DMBA	BZPO	0/6
	Adenoma & carcinoma	DMBA	PB	0/5
Liver	Hist. normal	—	TPA	0/4
	Hist. normal	—	BZPO	0/2
	Hist. normal	—	PB	0/2
	Hist. normal	DMBA	—	0/1
	Adenoma	—	TPA	0/1
	Adenoma	DMBA	—	0/1
	Hepatoma	—	BZPO	0/3
	Hepatoma	—	PB	0/5
	Hepatoma	DMBA	—	4/8
	Hepatoma	DMBA	TPA	4/5
	Hepatoma	DMBA	BZPO	2/3
	Hepatoma	DMBA	PB	4/7
	Mal. lymphoma	—	TPA	0/2
	Mal. lymphoma	—	PB	0/1
	Mal. lymphoma	DMBA	—	0/1
	Mal. lymphoma	DMBA	TPA	0/1
	Mal. lymphoma	(DMBA)[c]	—	0/2
	Mal. lymphoma	(DMBA)[c]	TPA	0/2

[a] 12-*O*-Tetradecanoylphorbol 13-acetate (TPA) and benzoyl peroxide (BZPO) were painted on the skin and phenobarbital (PB) was administered in drinking water.

[b] H-*ras* mutations (A to T transversion) at the 61st codon were detected using RFLP created by XbaI enzyme.

[c] Untreated newborn mice were nursed by DMBA-treated females.

[d] All liver tumours were taken from male mice, whereas all malignant lymphoma material was taken from females.

K-*ras*, *myc* and *raf* genes as probes. Highly transformed IAR 6-1 cells contained an amplified H-*ras*-2 pseudo-gene and rearrangement of the *myc* gene. The moderately transformed cell line IAR 27 exhibited higher levels of H-*ras* and *myc* expression without detectable gene amplification. Non-transformed IAR 20 and weakly transformed IAR 2-28 did not show these oncogene alterations. These results suggest a correlation between cellular oncogene alteration and expression of transformed phenotypes in rat liver cells.

(*c*) Genetic anomalies in human oesophageal tumours with reference to the role of the environment in the mechanisms of oncogene activation

The incidence of oesophageal cancer varies greatly worldwide and even between different regions of certain countries such as France and China. Although this cancer ranks sixth in the world, there have been relatively few investigations at the molecular level on cancers at this site compared to other cancers more prevalent in Western countries such as breast and colon. Such molecular studies at IARC complement the epidemiological research (see section I.3.*b*) and carcinogen exposure investigations (see part 3 below) on oesophageal cancer that are being conducted at the Agency.

The molecular biology programme on DNA lesions associated with human oesophageal cancer is planned as having two stages: (1) identification of oncogene lesions in human squamous cell carcinoma of the oesophagus, and (2) comparisons of nature and frequency of these lesions in various series of tumours from separate geographical regions, each with a high incidence of this cancer but where different etiological environmental factors are thought to be responsible.

(i) ras *activation in oesophageal tumours* (Dr M. Hollstein, Mrs C. Galiana, Miss N. Martel, Dr R. Montesano and Dr H. Yamasaki; in collaboration with Dr J. Bos, University of Leiden; Dr C. Partensky, Edouard Herriot Hospital, Lyon; and Dr A.M. Mandard, François Baclesse Regional Centre, Caen, France)

Although *ras* genes activated by a single point mutation have been identified in approximately 20% of human tumours overall, the frequency of this lesion varies from 0% (stomach carcinomas) to 95% (pancreatic cancer) in different tissue types or organs[9]. In addition, if exposures to environmental carcinogens that cause miscoding DNA adducts are responsible for the high incidence of specific cancers in certain geographical regions, the prevalence of an activating *ras* mutation for a given type of cancer will vary among series of samples from patients residing in different areas.

To complement data on *ras* mutation in cancers at other sites, 25 oesophageal tumours from patients residing in Normandy (a high-incidence area) and Lyon have now been tested for presence of activating mutations in codons 12, 13 and 61 of the H-, K-, and N-*ras* genes, the sites at which mutations can render this gene family transforming. This analysis was performed with the polymerase chain reaction/oligonucleotide hybridization technique, which revealed no mutations in any of the samples tested[11]. Southern analysis of Eco RI-digested tumour DNA did, however, reveal significant amplification of the K-ras gene in two tumours, a less common mechanism of *ras* gene activation seen occasionally in human tumours of other organs. A further 20 samples from Normandy are now being similarly tested and it is planned to continue the project by testing tumours from other high-risk areas of the world.

[11] Hollstein, M.C., Smits, A.M., Galiana, C., Yamasaki, H., Bos, J.L., Mandard, A., Partensky, C. & Montesano, R. (1988) *Cancer Res.*, *48*, 5119–5123

(ii) *Growth factor receptor gene amplification and overexpression* (Dr M. Hollstein, Miss C. Galiana, Miss N. Martel, Dr R. Montesano and Dr H. Yamasaki; in collaboration with Dr J. Bos, University of Leiden; Dr C. Partensky, Edouard Herriot Hospital, Lyon; and Dr A.M. Mandard, François Baclesse Regional Centre, Caen, France)

The proto-oncogenes *c-erb* B and *c-erb* B2 are two closely related sequences coding for growth factor receptors that may play a role in later stages of tumour development. Studies elsewhere on *c-erb* B (EGFR) amplification or overexpression in squamous cell carcinomas and cell lines derived from these tumours have shown that these anomalies occur in some samples[12,13]. There are also reports showing co-amplification in tumours of the oncogenes *hst* (cloned from a stomach tumour[14]) and *int*-2, two genes coding for growth factors which appear to be situated close enough on chromosome 11 at band g13[15,16] to fall within the same replicon. We have tested oesophageal squamous cell carcinomas from patients residing in France for *c-erb* B amplification and overexpression, as well as *c-erb* B2, *hst*, *int*-2 and TGFα amplification (Fig. 17). The alteration frequencies are being compared with results of studies by others on the same cancer in different populations. Amplification or overexpression of genes for certain growth factors or receptors has so far been found consistently in these tumours, and is possibly related to more advanced stages of the disease, perhaps not significantly influenced by environment.

(iii) *New transforming genes in oesophageal squamous cell tumours* (Dr M. Hollstein, Mrs A.-M. Aguelon, Dr Y. Oyamada, Miss C. Galiana and Dr H. Yamasaki)

The NIH 3T3 DNA transfection assay has been used over the last decade as one means of isolating transforming sequences from human tumours. In case aberrant proto-oncogenes contribute to the malignant conversion of squamous cells of the oesophagus that have not yet been cloned and identified, this assay has been used in searching for transforming sequences in such tumours. The DNA from one tumour yielded NIH 3T3 transformants containing human *alu* repeat sequences. Nude mice injected with these transformed cells at 10^6 cells (5 animals) or 10^7 cells (5 animals) per site developed tumours in all cases within one week, whereas no tumours developed in mice injected with 10^7 untransformed NIH 3T3 cells. Eco RI-digested nude mouse tumour DNA contained human *alu* sequences with prominent *alu*-specific bands of approximately 6.5 and 4.5 kb. DNA from a nude mouse tumour was used to perform a second cycle of transfection in NIH 3T3 cells, and transformed foci (0.1 foci/μg) appeared within three weeks. Cells of transformed foci show a consistent pattern of human *alu*-sequence bands by Southern analysis, and one clone of transformed cells was used to prepare a genomic library in the EMBL 3 vector. Recombinants with human *alu* sequences will be characterized and used to search for cDNA library recombinants (constructed from the NIH 3T3 secondary transformant) that could

[12] Hunts, J., Ueda, M., Ozawa, S., Abe, O., Pastan, I. & Shimizu, N. (1985) *Jpn J. Cancer Res., 76,* 663–666

[13] Yamamoto, T., Kamata, N., Kawano, H., Shimizu, S., Kuroki, T., Toyoshima, K., Rikimaru, K., Nomura, N., Ishizaki, R., Pastan, I., Gamou, S. & Shimizu, N. (1986) *Cancer Res., 46,* 414–416

[14] Sakamoto, H., Mori, M., Yoshida, T., Matsukawa, S., Shimizu, K., Sekiguchi, M., Terada, M. & Sugimura, T. (1986) *Proc. Natl Acad. Sci. USA, 83,* 3997–4001

[15] Tsuda, T., Nakatani, H., Matsumura, T., Yoshida, K., Tahana, E., Nishihina, T., Sakamoto, H., Yoshida, T., Terada, M. & Sugimura, T. (1988) *Jpn J. Cancer Res., 79,* 584–588

[16] Tsutsumi, M., Sakamoto, H., Yoshida, T., Kakizoe, T., Koiso, K., Sugimura, T. & Terada, M. (1988) *Jpn J. Cancer Res., 79,* 428–432

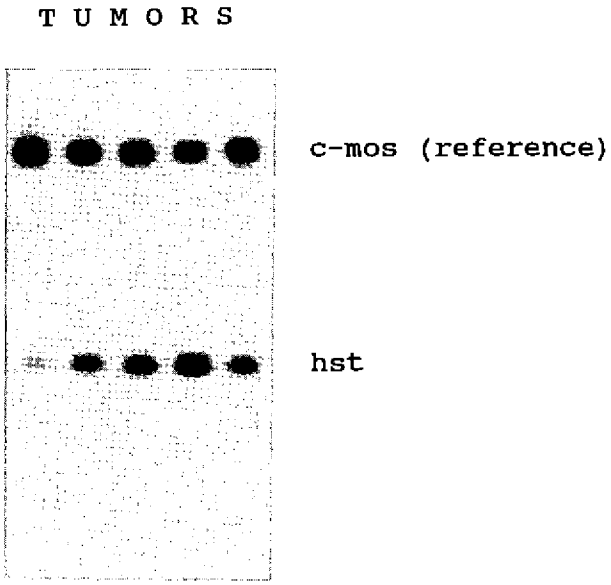

Fig. 17. Southern blot analysis of the *hst* gene in oesophageal carcinomas. Blots were hybridized simultaneously with a radiolabelled *hst* probe and, to provide an internal standard, with *c-mos* sequences detecting the unamplified *mos* locus in each sample

correspond to the transforming sequences in the human tumour. Ten additional human oesophageal carcinoma samples from Normandy and Lyon are being tested for the presence of transforming sequences using the mammalian *in vitro* transfection assay technique.

3. DNA DAMAGE AND REPAIR IN HUMAN AND RODENT CELLS

The induction of cancer by chemicals is closely linked to the occurrence of DNA damage and the efficacy of DNA repair processes. Studies on nitrosamines and aflatoxins, chemicals of great public health concern in various parts of the world, have permitted identification of the DNA lesions that appear relevant to processes of carcinogenesis. The main aim of these studies is to analyse DNA and/or protein adducts in human tissues and to assess their relevance as markers of exposure and their biological importance. Other parallel studies are examining the repair of DNA alkylation in humans and in experimental systems and the interaction of hepatitis B virus infection and aflatoxin B_1 in the etiology of liver cancer (see section I.2.*g*).

(*a*) **Recovery of O^6-alkylguanine-DNA-alkyltransferase (AT) following DNA damage by alkylating agents in rat and hamster cells *in vivo* and *in vitro*** (Dr J. Hall, Dr M. Serres, Miss H. Brésil, Miss C. Pezet and Mrs G. Martel-Planche)

The mutagenic and carcinogenic response to alkylating agents is highly dependent not only upon the background level of the DNA repair enzyme, AT, present in given tissues or cells but also on the rate of reconstitution of the pool of repair enzyme. This recovery capacity could be even more important than the background level of AT during chronic exposure to carcinogenic alkylating nitrosamines. Comparison of the levels of AT in liver protein extracts of rats or

hamsters after carcinogen treatment revealed that the inactivation and subsequent rate of recovery was significantly different in these two species. In the hamster, after treatment with a high dose of *N*-nitrosodimethylamine (NDMA) (25 mg/kg), no active enzyme (<0.01 units/mg protein) was detected in liver extracts up to 168 h after treatment, whereas in the rat liver extracts active enzyme was detectable from 24 h and by 96 h an increase in enzyme levels compared to control values was observed. This depletion and time course of resynthesis of AT (Fig. 18) suggest that the different susceptibilities to cancer in hamster (high) and rat (low) liver after a single dose of NDMA may be due more to the reconstitution of this enzyme than to its background levels. No such difference was observed for another DNA glycosylase which repairs 3-methyladenine and 7-methylguanine. These studies also suggest that O^4-MeT is repaired by a

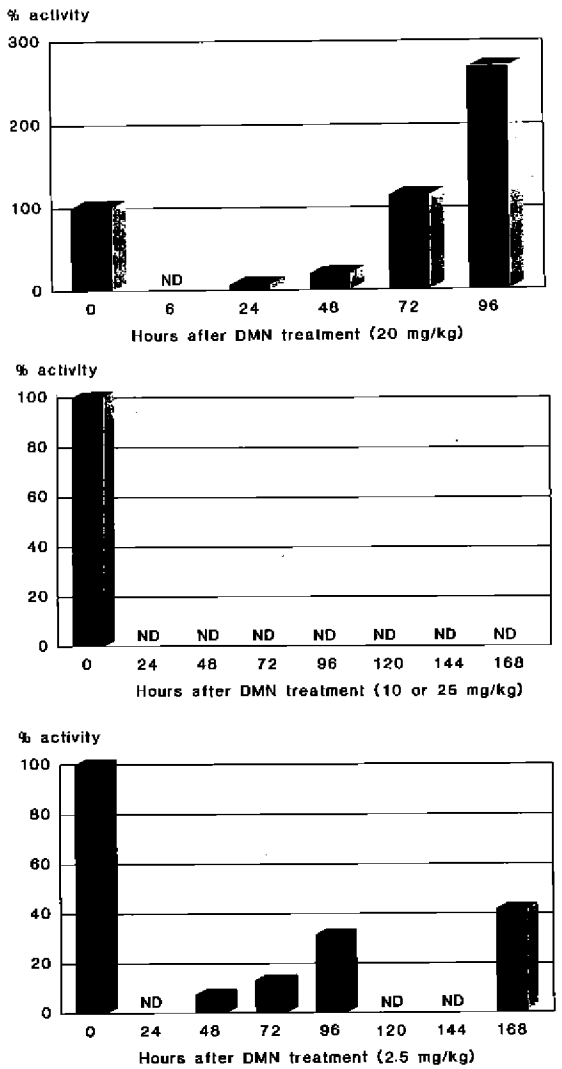

Fig. 18. Recovery of *O*-alkylguanine-DNA-alkyltransferase activity in hamster and rat liver

protein other than AT, since the pattern of disappearance of O^4-MeT does not parallel the AT activity. In order to further investigate these DNA repair mechanisms, tissue culture cell lines resistant to MNNG-induced cytotoxicity have been isolated from Chinese hamster cell lines. These cells are able to 'tolerate' the potentially lethal O^6-methylguanine lesions in DNA, whilst expressing no AT activity.

(*b*) Modulation of DNA repair enzyme levels by alcohol (Dr J. Hall, Miss C. Pezet and Miss H. Brésil; in collaboration with Dr P. Beaune, Biochimie Pharmacologique et Métabolique, Faculté de Médecine, Enfants Malades, INSERM U 75, Paris, France; and Dr B. Holmberg, National Institute of Occupational Health, Solna, Sweden)

Studies have been initiated to measure the modulation by alcohol of O^6-methylguanine DNA methyltransferase (AT), methylpurine- and uracil-DNA glycosylases in human and rodent tissues. Animals were chronically exposed to 1% or 3% ethanol over a period of two years, after which the levels of AT were measured in liver protein extracts. No significant differences in AT activity were found between treated and control animals at the end of the treatment period nor up to three months after the end of treatment.

(*c*) Oligonucleotide assay for O^6-alkylguanine-DNA-alkyltransferase (Dr N.M. Mironov, Dr C.P. Wild, Mrs G. Martel-Planche and Dr R. Montesano)

In view of the implied importance of O^6-alkylguanine-DNA-alkyltransferase (AT) in human susceptibility to cancer induced by alkylating agents, it would be valuable to have a rapid, sensitive assay to measure this activity in small samples, such as biopsies or peripheral blood lymphocytes. These methods could be used in epidemiological studies aimed at assessing the role of alkylating agents in human cancer and also in clinical studies to assess the suitability of alkylating agent chemotherapy.

We have developed a sensitive and rapid procedure for measurement of AT repair activity using oligodeoxynucleotides substrates followed by immunoprecipitation[17]. ^{32}P-labelled dodecadeoxynucleotides containing O^6-methylguanine or O^4-methylthymine provided by Dr P. Swann (University College, London, UK) were used as substrates for ATs and the reaction products of methylated or demethylated substrates were separated by precipitation with highly specific antibodies.

The oligodeoxynucleotide assay of AT gave the same results as the conventional method with ^{3}H-methylated DNA as substrate but was more sensitive, requiring using 10–100-fold less protein and detecting lower levels of AT activity. The immunoprecipitation technique has resulted in a ten-fold faster analysis of samples compared to HPLC separation of methylated and demethylated oligodeoxynucleotides. Thus, the combination of [^{32}P]oligodeoxynucleotides and immunoprecipitation provided a rapid and highly sensitive method for measuring AT activity which may be applied in molecular epidemiological studies. This approach may also have wider application in the assay *in vitro* of other DNA repair enzymes.

(*d*) Repair of alkylated bases in human tissues (Dr J. Hall, Miss H. Brésil, Miss C. Pezet, Mrs G. Martel-Planche, Dr N. Mironov and Dr R. Montesano)

To complement the studies on the detection of alkylated DNA bases in human tissues[18] (see below), measurement of various DNA repair enzymes is being carried out on a variety of human tissues and cell types.

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[17] Mironov, N.M., Wild, C.P., Martel-Planche, G., Swann P.F. & Montesano, R. (1989) *Analyt. Biochem.* (in press)

[18] Hall, J., Bresil, H., Martel-Planche, G., Serres, M., Wild, C.P. & Montesano, R. (1989) In: Lambert, M.W., *et al.*, eds, *DNA Repair Mechanisms and their Biological Implications in Mammalian Cells*, New York, Plenum Press (in press)

Table 38. O^6-Alkylguanine-DNA-alkyltransferase (AT), 3-methyladenine and 7-methylguanine glycosylase activities in human and animal tissues

Tissue[a]	AT[b]	Glycosylases[b]	
		3-MeA	7-MeG
Human liver	1.44 ± 0.2	1.19 ± 0.16	0.02 ± 0.01
Human oesophagus	0.40 ± 0.03	N.T.	N.T.
Rat liver	0.13 ± 0.01	0.54 ± 0.097	0.037 ± 0.003
Hamster liver	0.191 ± 0.022	0.61 ± 0.148	0.059 ± 0.03

[a] For each tissue, more than three samples were tested.
[b] pmol/mg protein
N.T., not tested

The data show that liver has higher AT activity than oesophagus and that glycosylase activity towards 7-methylguanine is low (Table 38). These data are of importance to assess if elevated levels of DNA alkylation adducts detected in human tissues (see section I.2.*g*) are attributable to environmental exposure or to a deficiency in DNA repair.

(*e*) **Correlation between DNA alkylation adducts in peripheral blood cells and internal organs** (Dr P. Degan, Dr C.P. Wild, Miss H. Brésil, Mrs D. Galendo, Mrs M.-P. Cros and Dr R. Montesano)

The relationship between the levels of alkylation adducts in DNA from peripheral blood cells and those in internal organs is unknown. Initial experiments compared adduct levels in rat liver and lymphocyte DNA after a single dose of nitrosodimethylamine (NDMA). The results have shown that the level of DNA adducts in lymphocytes is similar to that seen in liver, the target organ for tumour induction by chronic NDMA exposure[19]. Furthermore upon repeated daily exposure to 1 mg/kg NDMA (five days per week) over three weeks, 7-MedG levels were again similar in lymphocytes and liver (Fig. 19). These studies are now being expanded to explore (*a*) the liver/lymphocyte relationship with much lower chronic NDMA doses (around 100 μg/kg) and (*b*) the relationship between lymphocyte adduct levels and the levels in other internal organs when carcinogens with different target organs are used, such as the tobacco-specific nitrosamine, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and the chemotherapeutic agent procarbazine.

(*f*) **Development of an assay for 7-methyldeoxyguanosine (7-MedG) in DNA from human cells** (Dr C.P. Wild and A. Munnia; in collaboration with Dr J.M. Boyle and Dr D.P. Cooper, Christie Hospital and Holt Radium Institute, Manchester, UK)

7-MedG should be a useful marker of exposure to environmental methylating agents due to its formation at high levels (70–80% of total methylation) compared to O^6-MedG (less than 10%) and slow repair (see section *c*). However, 7-methylguanosine (7-MerG) is a normal component of tRNA at high levels (one 7-MerG present in 350 bases) and would be recognized by the specific antibodies for 7-MedG. Thus careful purification of DNA from RNA is required before analysis for 7-MedG. This has been achieved by extensive treatment of DNA with

[19] Degan, P., Montesano, R. & Wild, C.P. (1988) *Cancer Res., 48,* 5065–5070

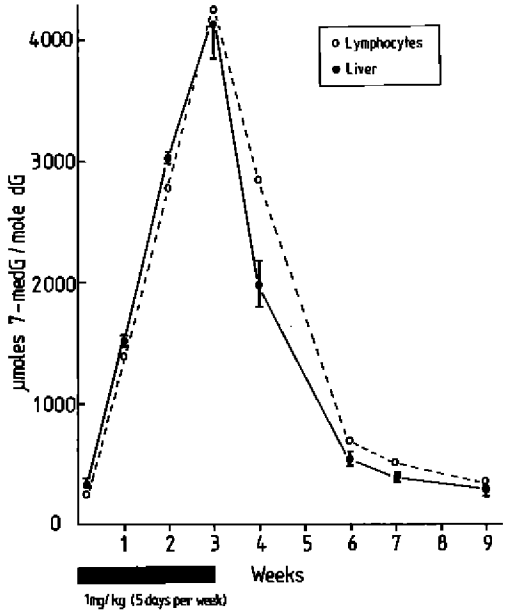

Fig. 19. Levels of 7-MedG following repeated exposure to nitrosodimethylamine

RNases and the use of a boronate affinity column which binds specifically ribonucleosides and not deoxyribonucleosides. These techniques, in conjunction with two chromatography steps and an ELISA, have allowed analysis of 7-MedG in human DNA (see section *g*).

In parallel, monoclonal antibodies to the 7-MedG imidazole ring-open form have been developed and are being used to make affinity columns to purify the 7-MedG adducts before chromatography. Such an approach has been established for O^6-MedG and is now being applied to hydrolysed DNA samples.

(g) Immunocytochemical localization of DNA adducts (Dr V. Krutovskikh and Dr C.P. Wild)

The antibodies to O^6-MedG and 7-MedG have previously been shown to be capable of visualizing, with immunoperoxidase staining, these adducts in tissue sections from rats treated with various methylating agents[20]. This approach is now being used to examine cellular heterogeneity in adduct formation and removal in a dimethylhydrazine-induced colon carcinogenesis model in strains of mice (AKR, DBA/2 and SWR) with different sensitivities to induction of this tumour. Such methods will be used to evaluate this approach for use in assessing carcinogen exposure in human tissues.

[20] Van Benthen, J., Wild, C.P., Vermeulen, E., Winterwerp, H.H.K., Den Engelse, L. & Scherer, E. (1988) In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 102–106

(*h*) Application of immunoassays to the detection of methylated bases in human cells (Dr C.P. Wild, Miss A. Munnia and Dr R. Montesano)

The level of DNA adducts at a given time is an integrated value related to a number of variables that include actual exposure, absorption and body distribution, tissue-specific activation, chemical stability of the metabolites and DNA adducts, efficacy of DNA repair enzymes and DNA replication. These variables can be affected by genetic and environmental factors and, in the case of nitrosamines, by factors that could enhance or inhibit the *in vivo* formation of these carcinogens. The fact that the formation of these DNA adducts is at the end of such a complex chain of events makes this approach particularly informative in assessing differences in levels among different individuals or populations. The main objectives of these studies are (*a*) to determine whether these abnormal DNA alkylation adducts were present in human tissues and at what levels; (*b*) to ascertain if the levels found were attributable to known or suspected environmental exposure(s); (*c*) to examine if variation in DNA adducts could be observed among individuals from geographic areas at different risks of a given cancer; and (*d*) to provide information on the degree of variability that may exist in the level of these adducts at an individual level. The results obtained so far on the presence of O^6-MedG in human tissues are summarized in Fig. 20, that includes also, for comparison, results from other laboratories[21,22].

(i) *Oral mucosal cells from cigarette smokers and non-smokers* (in collaboration with Dr H. Stich, British Columbia Cancer Research Centre, Vancouver, Canada)

DNA in oral mucosal cells of smokers and non-smokers has been examined for the presence of methylated bases[23]. The male smokers had an average age of 43.2 ± 11.2 years, used 30.0 ± 13.6 non-filtered cigarettes per day, and had smoked for 26.7 ± 12.6 years. The smokers had not drunk any alcoholic beverages for one to three months before the sampling of the oral mucosal cells. The non-smokers and non-drinkers had an average age of 39.8 ± 10.6 years. The oral mucosa of each smoker and non-smoker was swabbed 12 to 14 times at four-day intervals to collect the exfoliated cells. A total of 27 DNA samples (40–350 μg DNA per sample) from 20 smokers and seven non-smokers have been examined to date: no O^6-MedG adducts were detected in non-smokers, whereas in smokers, 4 out of 20 samples showed positive levels of O^6-MedG (2.2, 5.4, 5.9 and 7.0 μmol/mol dG). In contrast, 7-MedG was present in almost all samples from smokers and non-smokers at levels up to 100 times higher than that of O^6-MedG. The levels of 7-MedG in non-smokers appear to be too high to be explained by dietary exposure. It is probable that this DNA was contaminated by bacterial DNA and further investigations are being performed to determine whether 7-MedG is a normal constituent of bacterial DNA.

(ii) *Peripheral blood cell DNA from smokers* (in collaboration with Dr A. Likhachev, N.N. Petrov Research Institute of Oncology, Leningrad, USSR)

DNA samples were obtained from the peripheral blood cells of 11 blood donors who were smokers and were analysed for 7-MedG and O^6-MedG. In contrast to the oral mucosa cell DNA, no O^6-MedG was detected and 7-MedG was found in only three samples. In addition, the level of 7-MedG was much lower (9–37 μmol 7-MedG/mol dT) than in the oral cells. These studies are being expanded to compare the results with data on DNA from non-smokers, but already

[21] Saffhill, R., Badawi, A.F. & Hall, C.N. (1988) In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 301–305.

[22] Foiles, P.G., Miglietta, L.M., Akerkar, S.A., Everson, R.B. & Hecht, S.S. (1988) *Cancer Res., 48,* 4184–4188

[23] Wild, C.P., Stich, H.F. & Montesano, R. (1989) *Proc. Am. Assoc. Cancer Res., 30,* 318

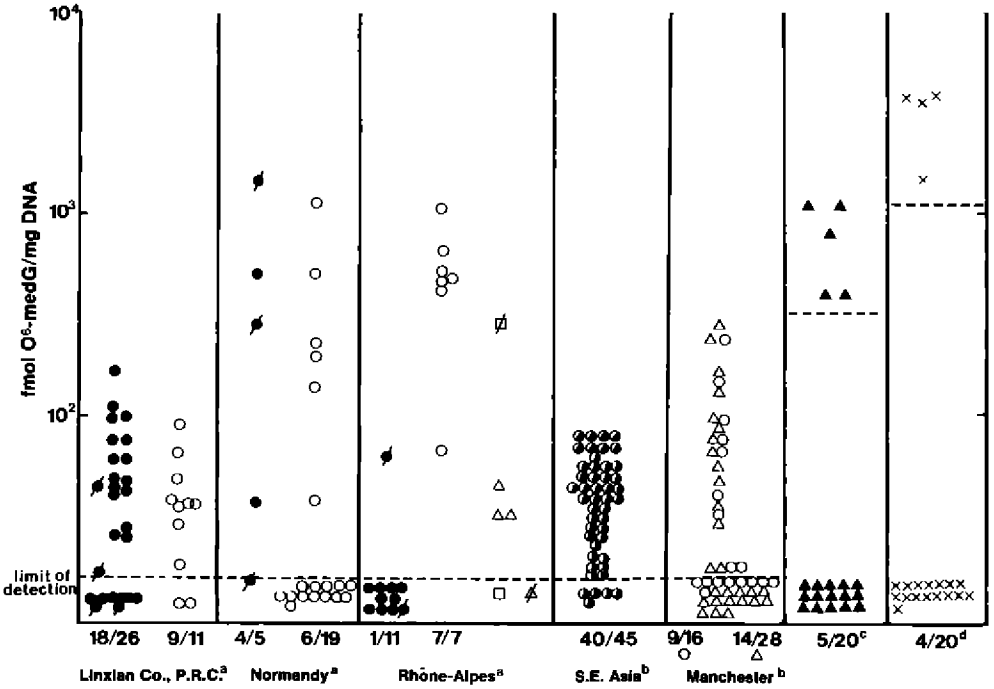

Fig. 20. Level and prevalence of positive samples of O^6-methyldeoxyguanosine in human tissues. ●, oesophagus; ○, stomach; ▲, placenta; △, colon; □, liver; ×, oral mucosa. Symbols with a bar represent tumour samples

illustrate the possibility of using blood cell DNA for this type of study. In parallel, measurements of various repair enzymes in the same blood samples have been made.

(iii) *Lung tissue* (in collaboration with Dr J. Pontén, Department of Pathology, University of Uppsala, Sweden; Dr C.C. Harris and Dr A. Weston, Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD, USA)

Two studies are in progress to examine the levels of methylation adducts in surgical lung tissue samples from smokers and non-smokers.

In the first study, human peripheral lung tissue samples were obtained at autopsy from trauma victims of known smoking and occupational history. The DNA was analysed for adducts of benzo[*a*]pyrene and 4-aminobiphenyl, in addition to O^6-MedG and O^6-ethyldeoxyguanosine. O^6-MedG was analysed by radioimmunoassay and ^{32}P-postlabelling, the latter technique being more sensitive than radioimmunoassay when small amounts of DNA (<100 μg) are available. O^6-MedG and O^6-EtdG were detected by ^{32}P-postlabelling in all samples at levels of 0.1 to 5.2 μmol adduct/mol dG. No correlation was seen, however, with either an estimate of smoking pack years or with the presence of the other DNA adducts measured. These studies are being continued with the additional analysis of 7-MedG.

In the second study, surgical tissue from peripheral and bronchial lung has been collected from individuals with lung cancer. In the first five samples analysed, two contained detectable 7-MedG (6 and 17 μmol/mol dT). Thus in these preliminary studies the levels of alkylation in

lung are of a similar range to those seen in peripheral blood cells and differ from the high levels seen in oral cells.

(*i*) Detection of methylated bases in individuals treated with chemotherapeutic agents (Dr C.P. Wild, Miss A. Munnia, Dr M. Klaude and Dr R. Montesano)

Long-term studies are in progress to examine the biological relevance of various parameters in cancer patients who are at risk of developing a second cancer as a result of treatment with chemotherapeutic drugs (see section I.2.*d*). In a pilot study on cancer patients, we have been examining lymphocytes and total white blood cells for the presence of methylated DNA bases following chemotherapy with procarbazine, dacarbazine and *N*-nitroso-*N*-methylurea. These analyses indicate the biological effective dose at an individual level, which could be related to other changes at the molecular and cellular levels, thus providing new insights into the natural history of the disease. In addition, the DNA adduct level and the DNA repair capacity of an individual may be relevant to assess the efficacy of the therapy. Studies in experimental animals are also in progress to validate these approaches.

(i) *Procarbazine* (in collaboration with Dr J. Kaldor)

In an initial series of ten patients, lymphocytes were analysed before MOPP therapy (including procarbazine) and after treatment. No O^6-MedG was detected either before or after treatment, except in one patient after therapy where a level of 2.3 μmol O^6-MedG per mol dG was measured. This was the only patient from whom total white blood cells were collected and assay sensitivity was therefore 2–10-fold greater than when only lymphocytes were available. A further series of patients are now being analysed with (*a*) collection of total white blood cells and (*b*) 7-MedG analysis to increase sensitivity.

(ii) *N-Nitroso-N-methylurea* (in collaboration with Dr A. Likhachev and Dr M. Gershanovitch, N.N. Petrov Research Institute of Oncology, Leningrad, USSR)

N-Nitroso-*N*-methylurea (NMU) is a more potent methylating agent than procarbazine, and unlike that drug does not require metabolism in order to damage DNA. Thus the possibility of detecting methylated adducts in peripheral blood is much better.

Peripheral blood cell DNA from cancer patients treated with 300 or 600 mg NMU intravenously was collected. 7-MedG and O^6-MedG were detected in all patients with a consistent relationship between treatment dose and alkylation levels. An O^6-MedG:7-MedG ratio of 0.049–0.120 was observed in patients receiving a single dose and levels of 7-MedG were 150–1150 μmol adduct per mole dG[24].

4. MECHANISMS AND SYSTEMS FOR ASSAY OF TUMOUR PROMOTION

(*a*) Control of cellular oncogene expression during differentiation of Friend erythroleukaemia cells and its inhibition by tumour-promoting agents (Miss L. Giroldi, Dr M. Hollstein, Dr H. Nakazawa and Dr H. Yamasaki)

A common feature of phorbol ester tumour promoters and some oncogene products is their ability to modulate various programmes of cell differentiation. In previous studies of molecular

[24] Wild, C.P., Degan, P., Bresil, H., Serres, M., Montesano, R., Gershanovitch, M. & Likhachev, A. (1988) *Proc. Am. Assoc. Cancer Res., 29*, 260

correlates of differentiation induced by hexamethylene bisacetamide (HMBA) and TPA inhibition of differentiation in Friend erythroleukaemia cells (FELC), the nuclear oncogenes *c-fos*, *c-myc* and *c-myb* were found to be expressed during tumour-promoting inhibition of FELC differentiation[25]; none of these oncogenes was critically associated with tumour promoter action. In order to identify critical genes in this system, the following studies have been carried out using cells committed to differentiation (HTC12, permanently grown in the presence of HMBA and TPA) and non-committed cells.

c-vav (*onc-F*) is a new putative nuclear oncogene expressed ubiquitously in haematopoietic cells; its expression may be involved in the maintenance of the proliferation of haematopoietic tissue[26]. Throughout FELC differentiation, *c-vav* expression was stable and was not modulated by TPA. This is unlike the expression of other nuclear oncogenes. There was no detectable expression of *c-vav* in committed cells (HTC12), suggesting a possible association of *c-vav* and FELC commitment to differentiation.

spi-1 1. Increased expression of this gene correlates with rearrangement due to Friend virus integration, and the gene therefore possibly functions to block differentiation[27]. Our results show that TPA does not modulate this gene expression in Friend cells. Thus it is likely that *spi*-1 is not involved in TPA-mediated inhibition of FELC.

(*b*) Control of β-globin expression in Friend erythroleukaemia cells and modulation by TPA (Miss L. Giroldi, Dr M. Hollstein and Dr H. Yamasaki)

High levels of 5-methylcytosine in DNA are often associated with decreased gene expression. β-Globin is a major transcriptional product in FELC differentiation and hypomethylation of its gene has been observed in committed cells (HTCl2) compared with non-committed cells. We reasoned that hypomethylation of the β-globin gene region in these cells corresponds to a primed state; in other words, due to commitment, the β-globin gene would be ready to be transcribed at high rates. However, we detected no β-globin transcripts in the cytoplasm of committed cells. This suggested that TPA blocks β-globin gene expression after initiation of transcription.

In order to test this hypothesis, we carried out experiments to observe β-globin transcription in isolated nuclei from committed cells. We could not detect β-globin expression in such nuclei (Fig. 21). The results thus suggest that the block of β-globin expression in committed cells occurs even before the transcriptional initiation.

(*c*) Search for growth factors which modulate cell transformation (Mr J.-L. Klein and Dr H. Yamasaki; in collaboration with Dr J.-L. Tayot, IMEDEX, Lyon, France)

With the aim of characterizing endogenous tumour-promoting and inhibitory factors, we are using human placenta as source material, since the placenta should contain growth factors important in controlling embryogenesis and fetal development, and such factors may be commonly involved in carcinogenesis[28,29].

Firstly, a placenta extract has been analysed for tumour-promoting activity, using a two-stage BALB/c 3T3 1–1 cell transformation system. After 3-methylcholanthrene (MC) initiation (1 μg/ml) of BALB/c 3T3 1–1 cells, exposure to a placenta extract (30 μg/ml protein) during

[25] Giroldi, L., Hollstein, M. & Yamasaki, H. (1988) *Carcinogenesis, 9,* 817–821
[26] Katsav, S., Martin-Zanca, D. & Barbacid, M. (1989) (submitted for publication)
[27] Moreau-Gachelin, F., Tavitian, A. & Tambourin, P. (1988) *Nature, 331,* 277–280
[28] Hamel, E., Martel, N., Tayot, J.L. & Yamasaki, H. (1984) *Carcinogenesis, 5,* 15–21
[29] Hamel, E., Tayot, J.L. & Yamasaki, H. (1988) *Biochim. Biophys. Acta, 970,* 172–176

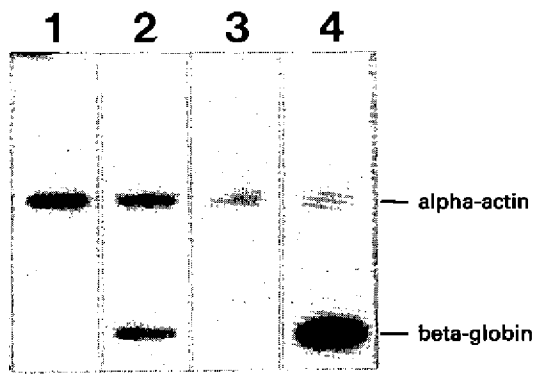

Fig. 21. Gene transcription in nuclei isolated from Friend cells at different stages of differentiation. 1: Human HL60 cells (non-erythroid). 2: Proliferating Friend cells (TS 19-101). 3: Proliferating committed Friend cells ($HTCl_2$). 4: Differentiated Friend cells (TS-19-101)

four weeks enhanced the number of transformed foci 4–5-fold in comparison with cells exposed to MC alone. No significant number of transformed foci was observed when uninitiated cells were cultured with the placenta extract alone. Purification of the placenta extract by affinity chromatography indicated that several factors in placenta could be responsible for this promoting activity. Also, the extract induced the growth of non-tumorigenic cells in soft agar (BPNi and NRK cell lines) and was mitogenic to BALB/c 3T3 1–1 cells.

Secondly, we observed that this same placental extract possesses strong growth-inhibitory activity for transformed cell lines in soft agar (50% inhibition with 10 μg/ml protein). The cell lines tested were BALB/c 3T3 1–1 cells transformed by EJ-*ras* oncogene and a human lung squamous carcinoma cell line A2182, as representative transformed fibroblasts and transformed epithelial cells, respectively. However, the placental extract when added to the monolayer culture of either cell type was not cytotoxic, but rather a slight mitogenic effect was seen. The non-toxicity has been confirmed in plating efficiency assays.

These results suggest that human placental fractions obtained by acid and alcohol extraction contain both tumour-promoting and tumour-inhibitory activities. Further purification of these factors and the study of their relationship to known growth factors such as TGF-β, FGF, etc., are being pursued.

***(d)* Blocked intercellular communication as a possible end-point of a short-term screening test for tumour-promoting activity of environmental chemicals** (Dr D.J. Fitzgerald, Dr S.H.H. Swierenga, Mrs C. Piccoli, Mr F. Katoh and Dr H. Yamasaki; in collaboration with Dr H. Fujiki and Dr T. Sugimura, National Cancer Centre, Tokyo; Dr K. Linnainmaa, Institute of Occupational Health, Helsinki; Dr L.W. Robertson, University of Kentucky, Lexington, KY, USA; and Dr J. DiGiovanni, University of Texas M.D. Anderson Cancer Center, Smithville, TX, USA)

We are continuing to examine the hypothesis that inhibition of gap-junctional intercellular communication (GJIC) is a feature common to many tumour promoters[30]. The fluorescent dye

[30] Zeilmaker, M.J. & Yamasaki, H. (1986) *Cancer Res.*, *46*, 6180–6186

Table 39. Compounds tested at IARC in 1988–89 for effects on gap-junctional intercellular communication (GJIC) as studied by microinjection with the dye Lucifer Yellow

Compound	Promotion *in vivo*	Cell types used in GJIC assay[a]	Inhibition of communication
TPA	+	NHEK, HLE, HMC	+
Phenobarbital	+	V79	+
		HLE-normal	–
		HLE-SV40 trans.	+
		Rat Hep (in 3T3 co-culture)	+
		3T3 (in Rat Hep co-culture)	–
		RLE	–
Anthraline	+	V79	–
		NMEK	+
Elevated pH	+	3T3	+
Ascorbate	+	3T3	–
Uracil	+	3T3	–
Okadaic acid	+	NMEK, NHEK	–
Chrysotile asbestos[b]			
Amosite asbestos[b]		HMC, RLE	–
Glass fibres[b]			
3,3',4,4'-PCB	+	HLE, V79, NHEK	–
2,2',4,4',5,5'-PCB	+	HLE, V79, NHEK	+
2,3,4,4',5-PCB	+	HLE, V79, NHEK	+
2,2',5,5'-PCB	–	HLE	±
		NHEK	+

[a] V79, Chinese hamster V79 fibroblasts; HLE, human liver (biliary) epithelial cells; Rat Hep, primary rat hepatocytes; 3T3, BALB/c 3T3 fibroblasts; NMEK, normal mouse epidermal keratinocytes; NHEK, normal human epidermal keratinocytes; HMC, human mesothelial cells; RLE, rat liver (biliary) epithelial cells.

[b] Carcinogenic to humans.

transfer assay of GJIC can be used with any cell type and we are examining cells that are known targets for various promoters. Table 39 lists compounds and their effects on GJIC in various cell types that we have studied recently. Tissue specificity can be observed for some compounds. For example, the rat liver tumour promoter phenobarbital inhibits communication in target hepatocytes but not in liver epithelial (biliary) cells or 3T3 cells. Anthralin, a mouse skin tumour promoter, does not inhibit communication in V79 fibroblasts but does so in mouse primary keratinocytes, although with kinetics of inhibition different to those of TPA. Nonetheless, the lack of a perfect correlation between promoting activity of chemicals *in vivo* and activity in the GJIC assay could be due to: (i) use of cells that are not normally targets (for example, polychlorinated biphenyls should be tested with human or rat primary hepatocytes); (ii) poor simulation of the *in vivo* environment (for example, the rat urinary bladder tumour promoter uracil probably operates by inducing formation of bladder stones which then have a physical promoting action; this could not be simulated *in vitro*); (iii) the fact that different promoters probably operate by different mechanisms. Further testing with this assay will provide a broader data-base to be used in evaluating the assay's value as a short-term test for tumour promoters.

(*e*) **Target proteins of protein kinase C in mouse skin carcinogenesis** (Dr T. Kuroki, Institute of Medical Science, University of Tokyo)

In order to study the mechanisms of skin tumour promotion *in vivo*, we have examined activation of protein kinase C and the resulting phosphorylation of epidermal proteins by topical application of 12-*O*-tetradecanoylphorbol 13-acetate (TPA) to mouse skin. In untreated skin, about 75% of the protein kinase C activity was found in the cytosol fraction, the rest being associated with the membrane fraction. After treatment with TPA, the activity of the cytosol fraction decreased within 15 min to about 50% of the control level, with a concurrent increase in the activity of the membrane fraction.

Phosphorylation of the epidermal proteins was examined by clamping the dorsal skin of mice with ring-shaped tongue forceps and injection of [^{32}P]phosphate into the clamped area, followed by treatment with TPA. As shown in Fig. 22, treatment with TPA *in vivo* resulted in about two-fold increases in the phosphorylation of epidermal proteins with M_r of 34 000 and 40 000 and isoelectric points of 4.7–5.1 and 5.2–6.2 (p34 and p40, respectively). The phosphorylation of these proteins was also stimulated by teleocidin B. Inhibitors of protein kinase C, such as chlorpromazine, quercetin and staurosporine, inhibited these increases in phosphorylation of p34 and p40 on TPA treatment. Furthermore, p34 and p40 were phosphorylated by purified protein kinase C in a cell-free system. However, they were not found in TPA-treated cultured fibroblast cell lines, suggesting the tissue-specific substrates of protein kinase C.

We have now purified and sequenced these p34 and p40 proteins, and their nature and roles in tumour promotion are under investigation.

5. ROLE OF INTERCELLULAR COMMUNICATION IN CARCINOGENESIS

The role of gap junctional intercellular communication (GJIC) in carcinogenesis has previously been studied in the IARC laboratories using only cell culture models and the dye microinjection and transfer assay as a method to measure the communication. With molecular

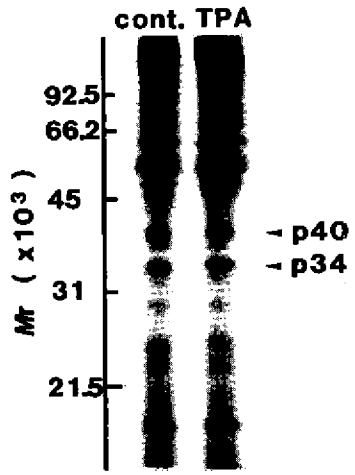

Fig. 22. Autoradiographs of ^{32}P-labelled epidermal proteins isolated from skin treated with acetone (left lane) or 5 µg TPA (right lane)

probes that are now available, we can use cDNA to measure the expression of genes for specific gap-junction proteins, and can use specific antibodies to localize the proteins at tissue and cellular levels[31]. This allows the study of gene expression and localization of gap junctions not only in cultures but also in tissue samples directly removed from experimental animals or human subjects.

(*a*) Tissue-specific decrease in levels of gap junction mRNA by the liver tumour promoter phenobarbital (Dr M. Mesnil, Dr D. J. Fitzgerald and Dr H. Yamasaki)

In the light of strong evidence that inhibited GJIC is mechanistically involved in cell transformation and tumour promotion, we examined the effect of an *in vivo* rat liver tumour promoter, phenobarbital, on the expression of the gene for the gap junction protein connexin 32. Phenobarbital was systematically administered to rats in drinking water and organ samples were taken at various times. Using a cDNA probe for the gap-junction protein gene and northern analysis, we found that expression of this gene was markedly and specifically reduced in liver at 4 and 11 weeks of exposure[32]. This suggests that phenobarbital may affect GJIC by perturbing specific gene expression relating to gap-junction protein synthesis. These studies are now being extended to include other known rat liver tumour promoters.

(*b*) Gap-junction mRNA level in rat liver tumours (Dr D.J. Fitzgerald, Dr M. Oyamada, Dr M. Mesnil and Dr H. Yamasaki; in collaboration with Dr H. Tsuda and Dr N. Ito, Nagoya City University, Nagoya, Japan)

In samples of preneoplastic nodules, adenocarcinomas and hepatocellular carcinomas induced in rat liver by the nitrosamine carcinogens nitrosodiethylamine and nitrosoethylhydroxyethylamine, expression of the gene for gap-junction protein was invariably reduced, often to nearly undetectable levels (Fig. 23)[33]. This may explain the lowered GJIC capacity of the preneoplastic and tumour liver cells. Thus, for rat liver, such decreased gene expression appears to be a feature both of promotion and of the transformed phenotype.

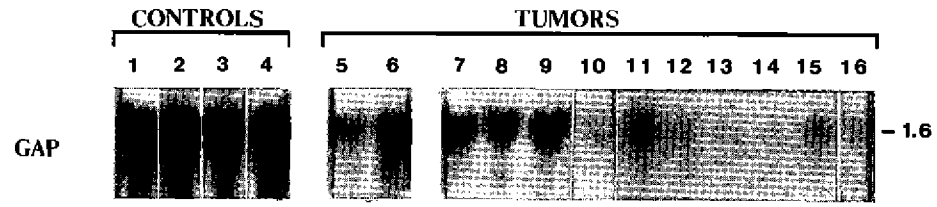

Fig. 23. Autoradiograph showing levels of gap junction proteins (connexin 32) mRNA in normal and neoplastic rat liver. Animals were initiated with NDEA and then exposed to 2-acetylaminofluorene and carbon tetrachloride. Lanes: 1, liver of untreated rat; 2, normal-looking liver 3 months after NDEA treatment; 3 and 4, normal-looking tissue surrounding large hyperplastic nodules (see lanes 8 and 15); 5, from pool of nodules diam. 3–6 nm; 6; from pool of nodules diam. 8–11 mm; 7, 8, 13–16; nodules diam. 1.5–2.0 cm; 9, adenocarcinoma; 10, hepatocellular carcinoma; 11, nodule diam. 2 cm; 12, nodule with some features of carcinoma

[31] Hertzberg, E. & Johnson, R.G., eds (1988) *Gap Junctions*, New York, Alan R. Liss
[32] Mesnil, M., Fitzgerald, D.J. & Yamasaki, H. (1988) *Mol. Carcinog. 1*, 79–81
[33] Fitzgerald, D.J., Mesnil, M., Oyamada, M., Tsuda, H., Ito, N. & Yamasaki, H. (1989) *J. Cell Biochem.* (in press)

(*c*) **Analysis of gap-junction proteins and mRNA in human liver tumours** (Dr M. Oyamada, Dr V. Krutovskikh and Dr H. Yamasaki; in collaboration with Dr C. Partensky, Edouard Herriot Hospital, Lyon)

In human hepatocellular carcinomas and normal surrounding liver tissue, there was no difference in expression of the gene for gap-junction protein. However, immunohistochemical analysis using specific antibody for the 32 kDa gap junction protein revealed that antigenic sites were somewhat fewer and redistributed in the tumours. Thus, for human liver tumours, disturbed GJIC may be manifest at the protein level. These studies are continuing and will involve analysis of gene expression and protein distribution for other gap-junction proteins and other human tumours.

(*d*) **Homologous and heterologous gap-junctional intercellular communication and expression of transformed phenotypes in rat liver epithelial cell lines** (Dr M. Mesnil and Dr H. Yamasaki)

To investigate whether selective intercellular communication exists between transformed epithelial cells and their normal counterparts, the homologous and heterologous communication capacities of four rat liver epithelial cell lines were examined. There was an inverse relationship between homologous communication capacity and expression of transformed phenotypes. In heterologous co-culture, the non-transformed cell line IAR 20 did not communicate with the transformed cell lines IAR 6–1 or IAR 27 F. These latter two cell lines were highly transformed in terms of cell morphology, growth in soft agar and expression of γ-glutamyltranspeptidase activity. Another cell line, IAR 27 E, showed the least degree of transformation and it communicated with IAR 20 cells. Thus, it appears that there is an inverse correlation between the extent of expression of transformed phenotypes by rat liver epithelial cells and their ability to communicate homologously and with non-transformed counterparts. There was no heterologous intercellular communication between any combination of IAR 27 E, IAR 27 F and IAR 6–1 cell lines. Unlike hepatocytes, these cells expressed connexin 43 gene but not connexin 32 gene, supporting the hypothesis that these cells were derived from biliary duct.

(*e*) **Role of gap-junctional intercellular communication during multi-stage skin carcinogenesis** (Dr D.J. Fitzgerald, Mrs C. Piccoli, Dr W.F.M. Jongen and Dr H. Yamasaki; in collaboration with Dr R. C. Klann and Dr T.J. Slaga, University of Texas M.D. Anderson Cancer Centre, Smithville, TX, USA; Dr N.E. Fusenig, German Cancer Research Centre, Heidelberg, FR Germany; and Dr A. Kinsella, Paterson Institute for Cancer Research, Manchester, UK)

In studying the role of GJIC multi-stage carcinogenesis, we have shown that, for a range of adult mouse epidermal cell lines maintained in a medium of low calcium concentration, there was a progressive decline in GJIC with advancing stage of malignancy (Fig. 24)[34]. Among various gap-junction proteins, expression of the gene for the 32 kDa protein is not detected in these lines, while the gene for the 43 kDa protein is poorly expressed in carcinoma cells, highly expressed in a papilloma cell line, and moderately expressed in the initiated cells. Gene expression of the cell adhesion molecule E-cadherin was uniformly high in all lines except one papilloma cell line. Using an Olympus Injectoscope for our microinjection dye-transfer assay, we have found that GJIC in the tumour lines is elevated to that of the non-tumour cells in the presence of calcium levels above 0.3 mM. Similar improvement in GJIC capacity at higher

[34] Klann, R.C., Fitzgerald, D.J., Piccoli, C., Slaga, T.J. & Yamasaki, H. (1989) *Cancer Res.*, *49*, 699–705

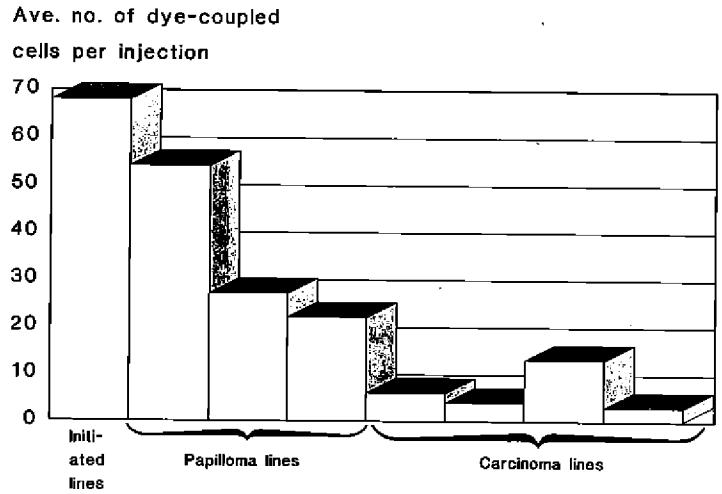

Fig. 24. Gap junctional intercellular communication characteristics (measured by Lucifer yellow microinjection dye-coupling assay) of epidermal cell lines derived from progressive stages of mouse skin carcinogenesis

calcium concentrations was found in all other mouse epidermal cell lines tested, including normal and transformed newborn mouse cells and a range of lines which had been 'initiated' *in vitro* with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and selected with a high-calcium medium.

For a range of human tumorigenic epidermal cell lines, GJIC was only 15% of the level seen in a quasi-normal spontaneously transformed human epidermal cell line (HaCaT). Weak or no expression of genes for the 32 kDa and 43 kDa GJ proteins was observed in all lines studied, while E-cadherin gene expression was uniformly low. These results indicate that epidermal tumour cells have reduced GJIC capacity, which is probably not controlled at the level of gene expression of E-cadherin or the major GJ proteins, but, at least for the mouse tumour lines, is controlled by the calcium concentration of the medium.

Studies of 'initiated cells' should help to clarify how these cells are forced by tumour promoters to grow differently compared with normal cells. One mutagenic lesion often induced by the carcinogen DMBA that is commonly found in mouse epidermal 'initiated' cells that are resistant to calcium-induced terminal differentiation and tumours is an A to T transversion at the 61st codon of the H-*ras* proto-oncogene[35]. We have taken mouse epidermal cell lines obtained from DMBA/TPA-induced papillomas and carcinomas (*ras* activated) and a line initiated *in vitro* with DMBA (no *ras* activation) and examined sensitivity to TPA inhibition of GJIC (cells cultured in a low-calcium medium). This was also done for a range of newborn mouse epidermal cell lines containing either no such mutation, DMBA-induced *ras* mutation, or exogenous *ras* mutation in the form of infected H-*ras* or N-*ras*. For cells cultured in a low-calcium medium, endogenous or exogenous *ras* activation seems to confer enhanced TPA sensitivity, but this pattern does not hold at high calcium levels, at least for the newborn mouse lines. We are studying further the relationship between calcium concentration, *ras* mutation, GJIC and sensitivity to TPA effects on GJIC.

[35] Yamasaki, H., Hollstein, M., Martel, N., Cabral, J.R.P., Galendo, D. & Tomatis, L. (1987) *Int. J. Cancer, 40*, 818–822

(f) Characterization of gap-junctional intercellular communication in transformed tumorigenic and non-transformed human liver and mesothelial cells (Dr D.J. Fitzgerald, Dr S.H.H. Swierenga, Mrs C. Piccoli and Dr H. Yamasaki; in collaboration with Dr K. Linnainmaa, Institute of Occupational Health, Helsinki)

Cell lines of mouse and human epidermal carcinomas generally show poor GJIC capacity. To extend these studies on GJIC tumour cell lines, we have examined two human non-transformed liver cell lines and their SV40 (large T)-transfected counterparts, and a range of human mesothelioma cell lines together with primary pleural mesothelial isolates (Table 40). For the liver cell lines, transfected cells displayed a markedly reduced GJIC capacity, in agreement with other reports that certain oncogenes can act to reduce GJIC. For the mesothelioma lines, GJIC was low compared with the normal mesothelial cells, except with the M20 line. The latter was a pleural fluid-derived line from the same patient from whom the solid tumour line M14K was obtained; the tumour biopsy was taken before chemotherapy, while M20 was established after heavy chemotherapy. Thus, some normalization of GJIC is apparent. We are now analysing the expression of genes for gap-junction proteins in these lines. Overall, these results suggest a good correlation between reduced GJIC and malignancy of human tumours.

(g) Role of selective intercellular communication in expression of oncogene-mediated transformation phenotypes (Dr H. Yamasaki and Mr F. Katoh; in collaboration with Dr M. Bignami, National Institute of Health, Rome; and Dr F. Tato, La Sapienza University, Rome)

In order to investigate the possible role of GJIC in the regulation of oncogene expression, we prepared various v-*onc*-containing NIH 3T3 cell clones, the oncogenes being *ras, src, myc, fos,*

Table 40. GJIC capacity of transformed tumorigenic and non-transformed human liver and mesothelial cell lines

Cell line	Derivation/characteristics	GJIC (average no. of dye-coupled cells per injection)
Liver		
FAH	Adult liver; exhibits bile duct and hepatocyte properties	44.8 ± 5.2
SV-FAH	FAH transfected with large T-oncogene of SV40 virus	8.5 ± 1.1
CFH	Liver of 7 yr-old	17.2 ± 1.7
SV-CFH	CFH transfected with large T-oncogene of SV40 virus	6.6 ± 1.4
Mesothelium		
PL-37	Primary mesothelial cells from pleural fluid obtained from patients devoid of pleural cancers	27.0 ± 2.4
PL-68		17.6 ± 1.5
PL-66		31.5 ± 3.4
PL-74		37.8 ± 2.4
M10K	From biopsies of mesotheliomas that were probably induced by asbestos	1.8 ± 0.3
M14K		6.0 ± 0.9
M09K		7.8 ± 1.1
M38K		2.2 ± 0.5
M20	From pleural fluid of M14K patient after chemotherapy	18.2 ± 1.8

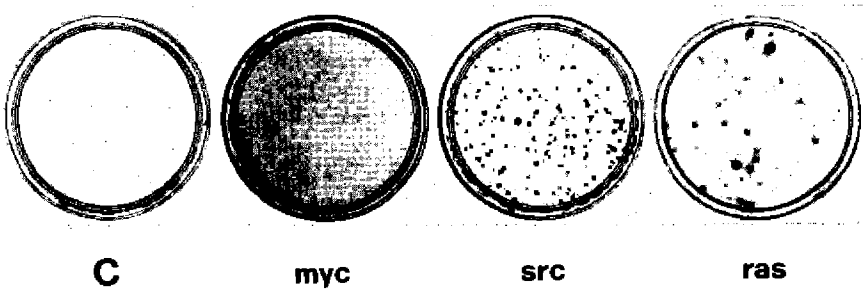

Fig. 25. Focal outgrowth of oncogene transformed NIH 3T3 onto BALB/c 3T3. Confluent cultures of BALB/c 3T3 either alone (C) or with *myc*-1 NIH 3T3 (*myc*), *src* Al-1 NIH 3T3 (*src*), *ras*-6 NIH 3T3 (*ras*)

polyoma large T and polyoma middle T. Transfection of these oncogenes into NIH 3T3 cells did not significantly change the homologous GJIC capacity of these cells. However, when they were mixed with normal BALB/c 3T3 cells, some clones showed a heterologous communication capacity while others did not. Cells containing *myc* or *fos* did communicate with surrounding normal cells, and, moreover, these clones did not form distinct foci on the monolayer of normal cells (Fig. 25). Conversely, *ras*- or *src*-containing cells did form distinct foci over monolayers of normal cells and did not show heterologous communication with surrounding normal cells. When clones containing polyoma middle T and polyoma large T genes were analysed, the polyoma middle T-transfected cells did form a certain number of distinct foci on normal cell monolayers and only low heterologous communication was observed, whereas polyoma large T-transfected cells communicated well with surrounding normal cells and did not form distinct foci (Fig. 26). These results clearly suggest a relationship between heterologous GJIC and oncogene-mediated expression of transformed phenotypes[36].

A further interesting pattern observed is that the absence of heterologous GJIC and concomitant foci formation are associated with cytoplasmic/membrane oncogenes (*ras*, *src*, polyoma middle T), while the presence of heterologous GJIC and subsequent lack of foci formation are associated with nuclear oncogenes (*myc*, *fos*, polyoma large T). More studies are required to determine whether this relationship represents a general phenomenon.

6. *IN VITRO* MUTAGENESIS AND CARCINOGENESIS

(*a*) Simultaneous assay of cytotoxicity, mutagenicity and cell transformation by environmental chemicals in BALB/c 3T3 cells (Dr H. Yamasaki, Mrs C. Piccoli and Dr D.J. Fitzgerald)

We have employed BALB/c 3T3 cells in a simultaneous cell transformation and mutation assay protocol to see whether both genotoxic and non-genotoxic carcinogens can be identified. Three known mutagenic animal carcinogens showed positive transforming activity: nitrosodimethylamine, 3-methylcholanthrene and nitrosomethylurea. In addition, we tested three non-mutagenic compounds—two human carcinogens, benzene and diethylstilbestrol, and the possible human carcinogen dichlorodiphenyltrichloroethane (DDT); all three displayed

[36] Bignami, M., Rosa, S., Falcone, G., Tato, F., Katoh, F. & Yamasaki, H. (1988) *Mol. Carcinog.*, *1*, 67–75

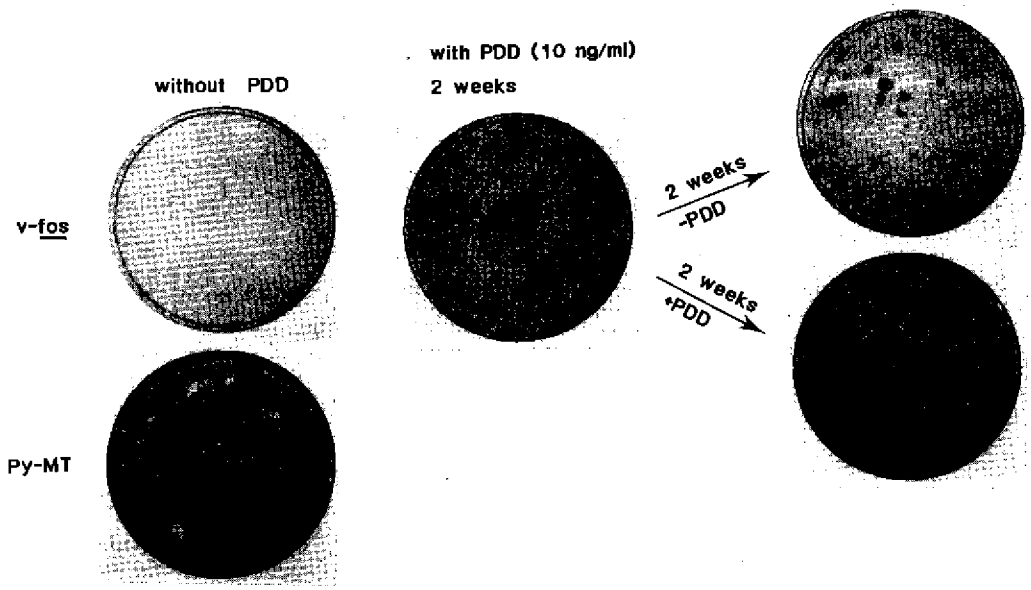

Fig. 26. Induction of foci by v-*onc* cells in co-culture with normal BALB/c 3T3 cells. Co-culture of v-*onc* (500 cells) and normal BALB/c 3T3 cells (10^6 cells) in the absence or presence (10 ng/ml) of phorbol 12,13-didecanoate (PDD). Co-cultures of V-*fos* and normal cells kept in PDD for two weeks were divided into two groups, for continuous presence or removal of PDD

transforming activity. These results add to an existing data bank which supports the validity of the BALB/c 3T3 cell transformation system as a reliable short-term *in vitro* test for carcinogens in general, and for non-genotoxic carcinogens in particular.

(*b*) Development of human hair-follicle epidermal culture system for studying mutation and transformation *in vitro* (Dr S.H.H. Swierenga, Dr M. Goldberg and Dr D.J. Fitzgerald)

Methods have been developed for studying intercellular communication in primary culture of human hair follicle cells. Cultures can be grown from single plucked hairs. Preliminary studies involving TPA treatment showed that the cultures were well suited for GJIC analysis. This system appears highly suitable for studying human skin carcinogens and toxic agents; it consists of metabolically competent, easily accessible human tissue. Testing of inter-individual variation in carcinogen metabolism and response is possible (see section I.6.*c*).

(*c*) Enhancement of BALB/c 3T3 cell transformation by okadaic acid, a non-TPA-type tumour promoter (Dr H. Yamasaki and Mr F. Katoh; in collaboration with Dr H. Fujiki and Dr T. Sugimura, National Cancer Centre, Tokyo)

Okadaic acid, present in sponges and certain shellfish such as mussels or scallops, is a human poison. Recently, okadaic acid and its derivatives were shown to have tumour-promoting activity

on mouse skin[37]. However, unlike TPA, it did not activate protein kinase C. In order to study the mechanisms of action of this new tumour-promoting agent, we examined its effect on cell transformation, cell differentiation and gap-junctional intercellular communication.

At non-toxic doses, okadaic acid did not inhibit induced differentiation of Friend erythroleukaemia cells nor inhibit gap-junctional communication of human and mouse keratinocytes or BALB/c 3T3 cells. TPA inhibits both differentiation and communication of these cells. However, it enhanced cell transformation of BALB/c 3T3 cells initiated with 3-methylcholanthrene. Thus, okadaic acid's tumour-promoting effect in BALB/c 3T3 cell is similar to that of TPA, although other related effects are not shared by these two compounds.

We also observed that okadaic acid exerts a strong cytotoxic effect only when cells are at confluence; during growing phase, it has little cytotoxic effect. This appears to be a cell contact-mediated cytotoxicity and its underlying mechanism is now being studied.

(*d*) Development of an assay to measure spontaneous and induced mutation frequency of H-*ras* gene using polymerase chain reaction (Dr H. Nakazawa, Dr M. Hollstein, Mrs A.M. Aguelon and Dr H. Yamasaki)

Classical mutation assays are based on expression of mutated phenotypes by selective markers, such as thioguanine resistance, ouabain resistance, etc. Thus, the target genes that can be studied are limited and so far mutation of genes that are related to carcinogenesis has been detected only in cells which are already tumorigenic. There is a need for an assay that will measure mutation frequency of cellular oncogenes, for studying mechanisms of carcinogenesis and for assessing the biological consequences of exposure to carcinogens.

This approach appears to be possible, since a single cell mutation in 10^4–10^5 cells has been detected using a polymerase chain reaction[38]. We have started to apply this technique to the detection of H-*ras* mutations in rodent and human tissues exposed to environmental chemicals. Preliminary results suggest that it is possible to detect one cell which has an A to T transversion at the 61st codon of H-*ras* gene in 10^3–10^4 cells, using polymerase chain reaction. We are now developing this technique with the aim of detecting a mutation frequency of one in 10^5–10^6 cells.

(*e*) Cellular and biochemical markers of neoplastic transformation of epithelial cells in culture (Dr J. Vasiliev, All-Union Cancer Research Centre, Moscow)

Reorganizations of cytoskeleton essential for alterations of cell shape and, especially, for the extension of cytoplasmic processes have been studied. 12-*O*-Tetradecanoylphorbol 13-acetate (TPA) induced two types of morphological change in cultured fibroblasts and epitheliocytes: (*a*) extension of motile lamellae, and (*b*) transformation of these lamellae into immobile narrow processes. The lamella–stalk transformation seems to be due to membrane-induced alterations in the interactions of the actin system with microtubules and, possibly, with intermediate filaments.

New monoclonal antibodies have been characterized to a large heparan sulfate proteoglycan that has been found by immunoelectron microscopy to be a ubiquitous component of human basement membranes[39].

A novel phenomenon of substratum-mediated extracellular matrix assembly in epithelial cells was observed in cultures of IAR 2 and IAR 2–31 cells. On fibronectin and laminin substrata, the cells assembled numerous short fibrils of alternative proteins which were not seen on ordinary

[37] Suganuma, M., Fujiki, H., Suguri, H., Yoshizawa, S., Hirota, M., Nakayasu, M., Ojika, M., Wakamatasu, K., Yamada, K. & Sugimura, T. (1988) *Proc. Natl Acad. Sci. USA, 85,* 1768–1771

[38] Kumar, R. & Barbacid, M. (1988) *Oncogene, 3,* 647–651

[39] Horiguchi, Y., Couchman, J., Ljubimov, A., Yamasaki, H. & Fine, J.-D. (1989) *J. Histochem. Cytochem.* (in press)

plastic. This was prevented by cycloheximide, monensin and cytochalasin D, suggesting a cellular origin of the fibrils and the involvement of the actin system in the assembly. Fibrils of fibronectin co-distributed with focal contacts, while fibrils of laminin did not. The mechanisms of this phenomenon are under investigation.

(f) **Role of differential cell proliferation in the development of spontaneous hepatocellular carcinomas in LEC rats** (Dr K. Enomoto, Dr H. Takahashi, Dr N. Sawada and Dr M. Mori, Department of Pathology, Sapporo Medical College, Japan)

The LEC (Long–Evans with a cinnamon-like coat colour) rat is a new mutant strain which show a sudden onset of spontaneous hepatitis around four months after birth[40]. Genetic analysis revealed that an autosomal recessive gene is responsible for the appearance of the hepatitis[41]. We found that hepatocellular carcinomas (HCC) developed spontaneously at a high incidence in LEC rats that survived for more than one year[42].

In order to elucidate the role of cell proliferation in the process of spontaneous HCC development in LEC rats, we examined the growth potential of cultured hepatocytes isolated from LEC rats before and after the onset of hepatitis, and compared this with hepatocytes from LEA (Long-Evans with an agouti coat colour). Hepatocytes isolated after collagenase perfusion were plated onto collagen-coated dishes under serum-free conditions. Two hours after plating, the culture medium was changed to DMEM/Ham's F-12 containing epidermal growth factor (20 ng/ml) to stimulate DNA synthesis. To determine the number of hepatocytes that entered the S phase of the cell cycle during the culture period, BrdU was added to the culture medium at 36 h after plating, and the cells were fixed in ice-cold 90% ethanol 36 h later. Incorporation of BrdU into the nuclei was immunohistochemically demonstrated using an antibody against BrdU (cell proliferation kit, Amersham).

As shown in Fig. 27, about 35% of cultured hepatocytes isolated from eight-week-old LEA and LEC rats incorporated BrdU into the nuclei. On the other hand, at the 20th week after birth, only 15% of the cells from LEC rats had entered S phase, compared with 30% of those from LEA rats, suggesting significant reduction in the growth potential of hepatocytes from LEC rats that had suffered from hepatitis. These data suggest the hypothesis that the initiated hepatocyte fraction undergoes selective proliferation in response to the growth stimuli produced by the continuous loss of hepatocytes associated with hepatitis.

7. PERINATAL CARCINOGENESIS

(a) **Multigeneration effects of carcinogens after exposure of males** (Dr J.R.P. Cabral, Dr V.S. Turosov, Mrs D. Galendo, Mrs M.P. Cros, Miss M. Laval, Mrs N. Lyandrat, Dr H. Yamasaki and Dr L. Tomatis; in collaboration with Professor N.P. Napalkov, N.N. Petrov Research Institute of Oncology, Leningrad, USSR; and Dr B.N. Hemsworth, Life Sciences Laboratory, Teeside Polytechnic, Cleveland, UK)

The susceptibility of different strains of mice to two-stage carcinogenesis in skin and internal organs has been studied using transplacental initiation and postnatal promotion. Results to date indicate that CD-1 mice are more sensitive than C57BL/6. TPA did not appear to promote

[40] Yoshida, M.C., Masuda, R., Sasaki, M., Takeichi, N., Kobayashi, H., Dempo, K. & Mori, M. (1987) *J. Heredity, 78,* 361–365

[41] Masuda, R., Yoshida, M.C., Sasaki, M., Dempo, K. & Mori, M. (1988) *Lab. Anim., 22,* 166–169

[42] Masuda, R., Yoshida, M.C., Sasaki, M., Dempo, K. & Mori, M. (1988) *Jap. J. Cancer Res., 79,* 828–835

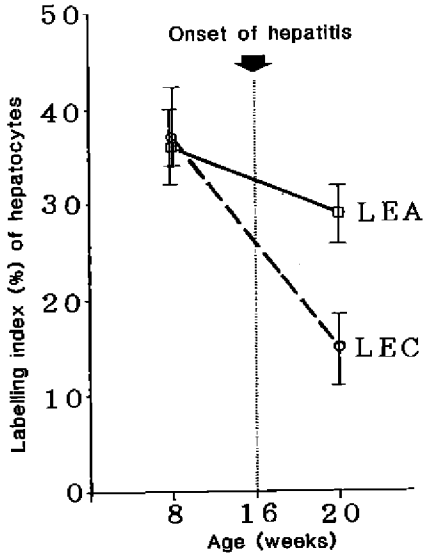

Fig. 27. Change of labelling index of cultured hepatocytes before and after onset of hepatitis in Long-Evans rats with either cinnamon-like (LEC) or agouti (LEA) coat colour

internal tumours in either strain. A further study is under way to assess the incidence of TPA-induced tumours in control BALB/c mice and in F_1 and F_2 offspring of nitrosoethylurea-treated fathers. Oncogene analysis of tumours derived from these studies has been carried out as described in section II.2.*a*.

Tumour incidence in the offspring (F_1, F_2 and F_3) of male Swiss mice treated with nitrosoethylurea or nitrosomethylurea and subsequently mated is being examined.

Studies on the role of various promoting agents (phenobarbital, butylated hydroxytoluene or X-ray irradiation) on carcinogenesis in the offspring of mice exposed to nitrosoethylurea before mating are currently under way.

Studies on the role of griseofulvin and analogues in the induction of liver porphyria and carcinogenesis in newborn mice have been started.

(*b*) International symposium on perinatal and multigeneration carcinogenesis

In collaboration with the N.N. Petrov Research Institute of Oncology, Leningrad, USSR, an international symposium was organized to discuss models, mechanisms and etiology of perinatal and multigeneration carcinogenesis. Some 60 scientists from Europe, USSR, USA, India and Japan discussed recent advances in understanding the molecular mechanisms of perinatal carcinogenesis. While there is clear evidence of perinatal human carcinogenesis, participants recognized the difficulty in identifying etiological factors and their mechanisms. The proceedings of this symposium are being published in the IARC Scientific Publication series[43].

[43] Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds (1989) *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96), Lyon, International Agency for Research on Cancer

III. DATA COLLECTION AND RESEARCH METHODS

1. SUPPORT FOR CANCER REGISTRIES

(*a*) Advice and support to registries (Dr D.M. Parkin, Dr M.P. Coleman, Mrs J. Nectoux, Ms S. Whelan and Mr A. Bieber)

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.

Registries are encouraged to send copies of any reports published to the Agency. An abstract of all such reports 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 common verification checks, 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 I.1.*h*).

Treatment, analysis and publication of the results for the data collected within the small area of Ardèche du Nord, covering a population of around 50 000 persons, are carried out within the Agency.

In collaboration with the International Union Against Cancer (UICC) and the Pan-American Health Organization (PAHO), a workshop on cancer registration in Latin America was held in Barquisimeto, Venezuela, on 3–7 October 1988. The purpose was to stimulate cancer registration activities and cancer research associated with registries in the countries of Latin America.

The Unit of Descriptive Epidemiology also provides more direct support and encouragement for cancer registration activities in Africa, Asia, Oceania and Central and South America.

Fiji (Principal investigator, Dr L.M. Seruvatu, Ministry of Health, Suva). A collaborative research agreement with the Ministry of Health has been renewed, and visits were made in 1988 and 1989 to advise on updating and coordination of registration activities. Data collected by the registry for a 10-year period (1979–88) have been transferred to IARC for analysis.

South Pacific. Visits were made to cancer registries in Nouméa, New Caledonia (Dr M. Huerre, Institut Pasteur) and Papeete, Tahiti, French Polynesia (Dr F. Laudon, Direction de la Santé Publique) to discuss collaboration and to install the CANREG system (see section *c* below). The South Pacific Commission in Nouméa (Dr F. Bach), which operates a cancer registry combining data from several South Pacific territories, was also visited and CANREG installed there, to enable more efficient compilation of incidence data for the region.

Mali (Principal investigator, Professor S. Bayo, National Institute of Public Health, Bamako). Financial support to enhance the activities of the recently founded registry, which covers the population resident in the capital, Bamako, has been given via a collaborative

research agreement. This has permitted more exhaustive data collection, and results for the first two years have been analysed and published (see section I.1.*e*.ii).

Gabon (Principal investigator, Dr P. Walter, University Omar Bongo, Libreville). The histopathology-based registry in Gabon has been used as a demonstration project for the microcomputer system 'CANREG' (see section *c* below) under a collaborative research agreement. Data from this registry are now available for a 10-year period, and will be analysed in 1989–90.

Zimbabwe (Principal investigator, Professor C. Chetsanga, Zimbabwe Cancer Registry, Harare). A collaborative research agreement was established with the newly founded registry in Harare. A visit in June 1989 has permitted a review of registration procedures and the use of the CANREG software, installed in 1986.

Rwanda (Principal investigator, Dr P. Ngendahayo, University of Rwanda, Butare). A collaborative research agreement has allowed the employment of a full-time registrar, and data have been collected for a period of two years from the prefecture of Butare. Various logistic problems have meant that case-finding has been incomplete, but there appear to be unusually high frequencies of stomach cancer and of Kaposi's sarcoma.

Thailand (Principal investigator, Miss S. Sontipong, National Cancer Institute, Bangkok). Support to the national cancer registry in Bangkok has included advice on automation of the registry, and on the analysis of geographic variations in the frequency of different cancers. A workshop was held in the National Cancer Institute, Bangkok, in January 1988 to discuss methods of population-based registration in the principal provincial centres. Support for the development of registration activities has been provided for Chiang Mai (Dr N. Martin) and Khon Kaen (Dr V. Vatanasapt).

Philippines (Principal investigators, Dr A.V. Laudico, University of the Philippines, Manila, and Dr D. Esteban, Rizal Medical Center, Manila). Consultant support was provided for the computerization of the Central Tumour Registry in Manila. This registry covers four municipalities of the greater Manila area, the remainder and other surrounding districts being covered by the Rizal Tumour Registry. The data from both registries, for a three-year period, have been analysed and published as an IARC Technical Report (see section I.1.*e*.iii). Advice on methodology and computerization was provided for a new registry in the city of Cebu (Dr N. Alsay, Eduardo J. Aboitiz Cancer Center).

Vietnam (Principal investigator, Dr Pham Hoang Anh, Cancer Institute, Hanoi). A population-based cancer registry has been created in the city of Hanoi, and assistance provided with methodology, training of personnel and computerization. Analysis of data for the first year of operation shows that the most frequent cancers in males are those of the lung (19.2%), stomach (15.6%) and liver (11.4%), and in females cancers of the breast (18.0%) and stomach (12.7%).

Uganda (Principal investigator, Professor R. Owor, Makerere University, Kampala). Following a visit in February 1989, plans were made to re-start the Kampala cancer registry, which was first founded in 1951. A collaborative research agreement has provided funds to employ a tumour registrar, and to train registry personnel.

Algeria, Algiers (Principal investigator, Dr L. Abid, Secteur Sanitaire Universitaire de Bologhine). Consultant advice was provided to the Digestive Tract Tumour Registry for the *Wilaya* (administrative district) of Algiers. The registry has been included as a collaborating centre in the EEC study of chronic gastritis and stomach cancer (EUROGAST; see section I.3.*d*.v). Assistance is being provided in the preparation of plans for one or more general population-based cancer registries in Algeria, to be submitted to the National Cancer Control Committee.

Algeria, Sétif (Principal investigator, Dr M. Hamdi Cherif, CHU de Sétif). Following a visit in

February 1989, planning for a general population-based cancer registry in the *Wilaya* of Sétif has been initiated and a retrospective study of cancer incidence in the one million population of the *Wilaya* planned. The latter will act as a pilot study for the prospective collection of data, planned from 1 January 1990, and as a preliminary assessment of the descriptive epidemiology of cancer in Algeria.

Tanzania (Principal investigator, Dr J. Kitinya, University of Dar es Salaam). Following a visit in September 1988, a collaborative research agreement was established with the Department of Histopathology, Muhimbili Medical Centre, to extend data collection by the Cancer Registry of Tanzania to all laboratory and clinical disciplines, and to permit the transfer of registry operations to a microcomputer.

Benin (Principal investigator, Dr T. Zohoun, National University of Benin, Cotonou). A pilot study to investigate the feasibility of different methods of data collection, with a view to establishing a cancer registry, was funded via a collaborative research agreement.

Paraguay (Principal investigator, Dr P.A. Rolón, National University, Asunción). A cancer registry utilizing histopathology reports and data from death certificates, and covering the city of Asuncion and environs, previously published data for the years 1975–77[1]. The registry was re-established from January 1988, with more comprehensive data collection, and using a computerized system.

Bolivia (Principal investigator, Dr J. Rios Dalenz, La Paz Cancer Registry). The interesting cancer pattern in Bolivia was revealed via data from a histopathology-based registry[2]. Support to recommence registration, using an extended data collection system, from 1 January 1988, has been provided. The first year's results are available, and confirm the previously noted elevated incidence of gallbladder and cervix cancer.

(*b*) International Association of Cancer Registries (Dr C.S. Muir and Ms S. Whelan; in collaboration with Professor K. Shanmugaratnam, Singapore Cancer Registry; and Dr D.B. Thomas, Seattle, WA, USA)

The Agreement whereby the Agency provides a secretariat for the Association was renewed for two years in 1988. Membership continues to increase rapidly, and now comprises over 320 cancer registries and affiliated organizations.

Members of the Association have collaborated with the Agency in many of the epidemiological studies described in Part I of this report. They have been active in advising the Agency in the preparation of the neoplasms section of the International Classification of Diseases (section III.2.*b*).

Some 130 members participated in the 1987 scientific meeting of the Association, which was held in Copenhagen, Denmark. The theme of the programme was 'The Cancer Registry and Environmental Cancer', and studies on diet, radiation and occupation, as well as registration methodology, mapping and descriptive epidemiology were included.

The 1988 meeting, held in Melbourne, Australia, was attended by some 70 participants representing 45 registries from 23 countries. The scientific programme featured presentations with the themes of cancer in migrants and on research into dietary risk factors.

The Association continues to collaborate with WHO in its capacity as a non-governmental organization in official relations; this collaboration was favourably reviewed in the triennial

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[1] Rolon, P.A. (1986) In: Parkin, D.M., ed., *Cancer Occurrence in Developing Countries* (IARC Scientific Publications No. 75), Lyon, International Agency for Research on Cancer, pp. 179–184

[2] Rios Dalenz, J.L. (1986) In: Parkin, D.M., ed., *Cancer Occurrence in Developing Countries* (IARC Scientific Publications No. 75), Lyon, International Agency for Research on Cancer, pp. 147–150

assessment carried out by WHO in 1988. Many members of the Association participate in WHO meetings and act as advisers to national and regional health programmes.

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 and with WHO, scientific meetings and relevant literature, including abstracts of all registry publications.

(c) Computer software for cancer registries (Mr C.A. Bieber, Dr D.M. Parkin and Dr M.P. Coleman)

The 'CANREG' project concerns the development, maintenance and installation in cancer registries of a set of computer programs designed for use on a microcomputer[3]. It is aimed specifically at cancer registries in developing countries, since it is suitable for use on relatively simple equipment, by personnel with no formal training in computing. It provides facilities for entering, altering, removal and display of up to 45 items of information on cases of cancer, with built-in checks on validity of the data items. In addition to these functions, there are programs for analysing the data which have been collected, as listings, tables and simple statistics. The CANREG system can be easily modified to meet the needs of different registries (suitable data items to collect, local coding schemes) and versions are available in English, French and Spanish. Registry personnel with no experience can be taught to use the system within a few days.

The CANREG system has been installed in several centres in developing countries: in Africa in Algeria, Burundi, Gabon, Mali and Zimbabwe; in Asia in China (Shanghai), Pakistan, Malaysia, Philippines (two centres), Thailand (two centres), Singapore and Vietnam; in the Americas in Bermuda and Costa Rica; and in Oceania in Fiji, French Polynesia and New Caledonia. In most of these centres it now provides the standard method of recording and analysing cancer incidence data.

In addition to its use in developing countries, the system has been supplied to several smaller cancer registries in Europe, notably in France, Italy and Spain.

The project has been funded by a grant from the Governing Council Special Fund, and it is hoped that an external source of finance can be found to allow it to continue. This would permit improvements and enhancements to the system to continue to be made, particularly in relation to data verification and data analysis options. Further installations of the CANREG system have been requested from South America and Africa.

(d) Survey of cancer registries in the European Economic Community (Dr M.P. Coleman and Mrs E. Démaret)

An EEC-funded survey of cancer registration in the EEC was carried out in 1987–88 and the results have been published[4,5]. A total of 89 registries were identified in ten of the 12 EEC member states, and a 92% response was achieved. In three states (Denmark, Netherlands, UK), general cancer registration covers the entire population, while in seven others, the proportions covered range from 2 to 19%, and in two member states there is no population-based cancer registry. About 350 000 new tumours are registered each year from the 32% of the EEC population covered by registration, and it is estimated that 988 000 new cancers (excluding

[3] Bieber, C.A., Coleman, M.P. & Parkin, D.M. (1989) *CANREG: Cancer Registration Software for Microcomputers* (IARC International Report No. 89/001), Lyon, International Agency for Research on Cancer

[4] Coleman, MP. & Démaret, E. (1988) *Cancer Registration in the European Economic Community* (IARC Technical Report No. 3), Lyon, International Agency for Research on Cancer

[5] Coleman, M.P. & Démaret, E. (1988) *Int. J. Cancer, 42,* 339–345

non-melanoma skin cancer) occur in the EEC each year. The quality and completeness of cancer registration varies considerably, however, and this could be improved by allowing cancer registries to obtain confidential access to death certificates where this is not yet available, and by the regular use of simple methods to assess completeness of registration.

(*e*) **Cancer registration and cancer epidemiology in Latin countries** (Dr J. Estève, Mrs A. Rivoire and Dr A.J. Tuyns; in collaboration with Mr L. Raymond, Geneva Tumour Registry, Switzerland, and R. Zanetti, Piedmont Tumour Registry, Turin, Italy)

IARC provides administrative support to the 'Groupe pour l'épidémiologie et l'enregistrement du cancer dans les pays de langue latine', in particular for the organization of annual meetings.

The 1988 meeting of the group was held in Pamplona (Spain) at the invitation of Dr N. Ascunce and Dr A. Del Moral, and the 1989 meeting in Vevey (Switzerland) at the invitation of the group of Swiss registries. Results from cancer registries and from epidemiological studes presented at these meetings are available from IARC. 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 1989, a two-day seminar on the analysis of survival data was organized before the Vevey meeting.

(*f*) ***Cancer Registration: Principles and Methods*** (Dr D.M. Parkin and Dr C.S. Muir; in collaboration with Dr O.M. Jensen, Danish Cancer Registry, Copenhagen; Dr R. MacLennan, Queensland Institute of Medical Research, Brisbane, Australia; and Mr R. Skeet, Thames Cancer Registry, Sutton, UK)

The first volume on *Cancer Registration and its Techniques*[6] was published in 1978, and has become the standard work of reference in this field. With increasing automation in cancer registries, it was agreed that a replacement should be published, which would assume that the principal registration processes would be carried out by computer (retaining, nevertheless, a description of manual card-filing methods). The new volume[7] will contain chapters on the Purpose of registration, Planning a registry, Data items collected, Sources of data, Classification and coding, Quality control, Reporting of results, Statistical methods for registries, Registries in developing countries, The hospital registry, and Confidentiality and legal aspects. In addition, the methods used in several very different registries will be presented as a series of appendices.

It is expected that publication will take place in early 1990.

(*g*) **Confidentiality in cancer registries** (Dr M.P. Coleman, Mrs E. Démaret and Dr C.S. Muir)

The Agency was represented on a subcommittee of the EEC Committee of Cancer Experts, which met in Brussels in October 1988 to discuss confidentiality issues linked to cancer registration. The subcommittee recommended the creation of a legal framework in those EEC states where it was required, in order to enable effective operation of cancer registries, whilst ensuring protection of data from unauthorized access. The recommendation was accompanied by a set of guidelines on confidentiality in cancer registration, prepared by the Agency, capable of adaptation as the basis for local rules governing confidentiality in cancer registration. The

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[6] MacLennan, R., Muir, C.S., Steinitz, R. & Winkler, A., eds (1978) *Cancer Registration and Its Techniques* (IARC Scientific Publications No. 21), Lyon, International Agency for Research on Cancer

[7] Jensen, O.M., Parkin, D.M., MacLennan, R., Muir, C.S. & Skeet, R., eds (1990) *Cancer Registration: Principles and Methods* (IARC Scientific Publications No. 95), Lyon, International Agency for Research on Cancer (in press)

subcommittee's recomendation was presented at the meeting of EEC cancer experts in London in May 1989.

(*h*) **Training manual for cancer registry staff in developing countries** (Dr D.M. Parkin; in collaboration with Dr D. Esteban, Rizal Medical Center, Manila; and Dr A.V. Laudico, University of the Philippines, Manila)

At the present, the only formal courses for cancer registry personnel are held in the United States, and the training materials available are oriented towards the health care system of that country. Tumour registry staff in developing countries are faced with very different problems in tracing cases of cancer, and recording details about them. An instruction manual more appropriate to their needs is being developed, in collaboration with the Cancer Registry of Rizal Province, Philippines. It provides information on basics of anatomy, pathology, diagnosis and treatment of cancer, as well as on registration methods, for staff who will be responsible for finding, abstracting and recording data on cancer cases.

2. DISSEMINATION OF INFORMATION

(*a*) ***Directory of On-going Research in Cancer Epidemiology*** (Dr M.P. Coleman, Mrs E. Démaret, Ms S. Whelan, Mrs A.-M. Beh and Mrs A. Nagy-Tiborcz; in collaboration with Professor J. Wahrendorf, Mr K. Schlaefer and Mr H.-J. Baur, German Cancer Research Centre, Heidelberg, FR 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 an annual compilation of research abstracts in the field of cancer epidemiology, and has been published annually since 1976, in collaboration with the German Research Centre in Heidelberg. The 1988 edition contained abstracts of 1237 projects being carried out in 84 countries, and the next edition, to be published in late 1989, will contain abstracts of some 1300 projects being carried out in 86 countries.

Continued effort has been made to obtain abstracts for projects in the field of mutation epidemiology, but with only limited success, and the future inclusion of such projects is under review. Systematic attempts have also been made to improve the quality of the abstracts, and many have been excluded for lack of clarity or informativeness. Indexing has also been reviewed, and ambiguous or rarely-used terms excluded; in particular, the index of study types has been completely revised to conform with conventional practice.

There are two major changes in the next issue. A new index of projects by cancer registry will be provided: some 240 population-based cancer registries are indexed, and each project in which they are collaborating is identified. The extent of cancer registry involvement in epidemiological research around the world is thus being revealed for the first time. The index continues to provide a comprehensive list of registry directors and their addresses. The second change is the provision of all the indexes on diskette for IBM-compatible microcomputers. The PROSE (PROject SEarch) system will enable projects to be identified using several of the indexes at once; for example case–control studies of bladder cancer involving sweeteners and being carried out in the USA or Canada can be rapidly identified in a single operation. Further developments in electronic publishing, including provision of the entire Directory on CDROM (compact disk, read-only memory), are being explored.

(*b*) Revisions of the International Classification of Diseases

(i) *Tenth revision of the International Classification of Diseases* (*ICD*-10) (Dr C.S. Muir and Ms S. Whelan; in collaboration with Professor J.W. Berg, University of Colorado Health Sciences Center, Denver, CO, USA; Dr P. Maguin, INSERM, Le Vésinet, France; Dr N.P. Napalkov, Petrov Research Institute of Oncology, Leningrad, USSR; Dr G.T. O'Conor, Loyola University Medical Center, Maywood, IL, USA; Mrs C. Percy and Ms V. Van Holten, National Cancer Institute, Bethesda, MD, USA; Professor F. Rilke, National Institute for the Study and Treatment of Tumours, Milan, Italy; Dr L.H. Sobin, Armed Forces Institute of Pathology, Washington, DC, USA; and Dr D.H. Wright, Southampton General Hospital, UK)

The Agency has undertaken the revision of the neoplasms chapter of the 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD-10). Expert advisers have attended a series of working parties. As the proposed 10th revision is substantially different from the 9th (the alphanumeric structure in effect virtually doubling the number of three-digit rubrics available), 150 three-character rubrics (COO–C99 and DOO–49) are now available for neoplasms. Many of the new rubrics were previously fourth digit sub-categories in the 9th revision of the ICD, e.g. ovary, previously 183.0, will be C56. There are, however, fundamental differences in the section on non-Hodgkin lymphomas which accommodate recent concepts of classification and in the grouping of connective tissue tumours, with separate categories for mesothelioma and Kaposi's sarcoma.

The final draft of this neoplasms chapter was presented and accepted at the meeting of the Heads of WHO Collaborating Centres for the Classification of Diseases, held in Paris on 28 February to 7 March 1989. At the same time proposed rules for coding cancer mortality, formulated by Mrs C. Percy (US National Cancer Institute) were reviewed and amended. The content of ICD-10 will be finalized during the WHO Revision Conference to be held in Geneva on 26 September to 2 October 1989. Among the new rubrics to be considered are several for human immunodeficiency virus (HIV) infection in the presence of or complicated by a variety of diseases. One of these rubrics is entitled 'HIV disease with malignant neoplasm'. Extensive consultation with cancer registries has revealed virtually universal opposition to this proposal, which would result in the location of the same neoplasm in two different sections of the classification, and which further opens the door to the dispersal of neoplasms elsewhere throughout the classification.

(ii) *The International Classification of Diseases for Oncology* (Dr C.S. Muir; in collaboration with Mrs C. Percy, National Cancer Institute, Bethesda, MD, USA)

The final field trial version of the revised ICD-O (1988) has been extensively field-tested. Permission was given at the meeting of WHO collaborating centres held in Paris on 28 February to 7 March 1989 to publish the revised morphology codes with the topography codes of ICD-10 in 1990. Great care has been taken to ensure that the revision of ICD-O is compatible with the proposed ICD-10. The College of American Pathologists has agreed, as previously, to incorporate the neoplasms rubrics in the third edition of the systematized nomenclature of medicine (SNOMED), due to be published in 1991, thus ensuring comparability of diagnostic coding for the morphology of neoplasms in these widely used classifications.

(iii) *International comparability of cancer mortality data* (Dr C.S. Muir; in collaboration with Mrs C. Percy, National Cancer Institute, Bethesda, MD, USA)

A collaborative two-part study[8] was undertaken with Mrs C. Percy on the international comparability of coding of death certificates mentioning cancer by the 9th revision of ICD, to see whether there has been an improvement since the 8th revision. In the first part, during 1987, nine countries coded the same 1234 United States death certificates mentioning cancer. The proportion of disagreements in coding the underlying cause of death by ICD-9 fell by about 35%, compared to coding the same certificates by ICD-8, a reduction probably due to the more detailed rules for coding cancer death certificates given in the 9th revision. To meet criticism of the possible bias associated with using United States death certificates only, in the second part of the study each of seven countries submitted about 100 certificates—translated into English—which had posed problems in coding. Discrepancies in assigning the underlying cause were found in 54% of these problem certificates and mainly arose when multiple cancer sites were mentioned on the death certificates or when a choice had to be made between the selection of heart disease or cancer as the underlying cause of death.

(*c*) **The mapping of cancer** (Mr M. Smans, Dr P. Boyle, Dr C.S. Muir and Dr J. Estève; in collaboration with Mr A. Doneux, National Institute of Statistics, Brussels; Dr H. Bille, National Board of Health, Copenhagen; Dr M.H. Pejovic and Dr A. Rezvani, Gustave-Roussy Institute, Villejuif, France; Dr K. Kern, Federal Statistics Bureau, Wiesbaden, FR Germany; Mr J. Stephens, Central Statistics Office, Dublin; Dr P. Morganti, Central Statistical Institute, Rome; Mr P. Henckes, Health Statistics Service, Luxembourg; Dr J.K.S. van Ginneken, Netherlands Central Bureau of Statistics, Voorburg, Netherlands; Mr L.H. Anderson, Office of Population Censuses and Surveys, London; Mr D. Salmond, General Register Office for Scotland, Edinburgh, UK; Dr W. Hunter, European Economic Community, Luxembourg; Dr Z. Péter, National Institute of Oncology, Budapest; Dr C. Cislaghi, Institute of Biometrics and Medical Statistics, Milan, Italy; Dr W.H. Mehnert, National Cancer Registry, Berlin-Johannisthal; Dr D. Cicovic, Savezni Zarod za Statistika, Belgrade; Dr I. Plesko, Cancer Research Institute of the Slovakian Academy of Sciences, Bratislava, Czechoslovakia; and Dr W. Zatonski, Institute of Oncology, Warsaw)

The cancer mortality maps for nine countries of the EEC were completed in 1987; they have already been used by several scientists and some have been published in several reports. The publication of the atlas itself has, however, been delayed in order to try to include data from the three countries of the European Community which were not participating in the project when it started.

The design of the atlas of cancer incidence in the German Democratic Republic has been slightly changed to include more recent data and in particular to match the data published in the fifth volume of *Cancer Incidence in Five Continents*. The data analysis and the maps have been completed, taking into account this new design. A new bilingual volume co-published by the Agency and the 'Zentralinstitut für Krebsforschung der DDR' will appear during 1990.

A series of maps were prepared for use by the European Economic Community for public information in support of the Europe Against Cancer programme. Mortality data by appropriate administrative area have now been obtained from Spain and it is hoped that similar data can be provided for Portugal and Greece. Consideration is now being given to the preparation of a mortality atlas covering all European countries. Sweden and Switzerland have already expressed their interest. A meeting was held in Warsaw in October 1988, at which representatives of several central European countries expressed their desire to participate.

[8] Percy, C. & Muir, C. (1989) *Am. J. Epidemiol., 129,* 934–946

(*d*) IARC survey of chemicals being tested for carcinogenicity (Mrs M.J. Ghess, Mr J. Wilbourn and Dr A. Aitio)

The survey project was initiated in 1973 in collaboration with the National Cancer Institute of the USA. The 13th Survey questionnaire was sent out in September 1987 to the institutes reporting in Bulletin No. 12 as well as to 25 additional institutes asking them to provide information on their long-term carcinogenicity tests in progress, completed or published, as well as on their recently started or planned studies. Information Bulletin No. 13, published in June 1988, gives information on 983 chemicals or complex mixtures being tested for carcinogenicity in 88 institutes in 20 countries; a total of 264 published reports on 237 agents are listed.

Each bulletin lists chemicals under investigation, animal species and strain, purity of substance, route of exposure, dose levels, stage of experiment, and principal investigator.

A special section giving cross-references to epidemiological studies reported in the *Directory of On-going Research in Cancer Epidemiology* is also included in order to link the data on chemicals in the bulletin with epidemiological information on cancer risk obtained in human populations possibly exposed to some of these chemicals.

Of the 983 chemicals listed in Bulletin No. 13, 17 have already been evaluated in the first 46 volumes of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans as '*carcinogenic to humans*', 18 as '*probably carcinogenic to humans*' and 67 as having '*sufficient evidence of carcinogenicity in experimental animals*'. Several recent published studies were used in making IARC evaluations. For the remaining chemicals which have not yet been evaluated by IARC Working Groups, the Survey will be a valuable guide for the selection of chemicals for future monographs.

3. STATISTICAL METHODOLOGY

(*a*) Development of statistical methodology (Dr J. Estève, Dr J. Kaldor, Dr E. Cardis, Mr P. Damiecki and Mr M. Smans; in collaboration with Dr D. Clayton, University of Leicester, UK; Dr C. Portier, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; Dr E. Schifflers, Department of Mathematics, Faculty of Science, Namur, Belgium; Dr E. Benhamou, Gustave-Roussy Institute, Villejuif, France; Mr L. Raymond, Geneva Tumour Registry, Switzerland; and Mr M. Croasdale, Central Electricity Generating Board, London)

(i) *Measurement error in cancer epidemiology*

Research on the problem of measurement error in epidemiology is continuing. Following earlier work on methods for analysing studies in which categorical variables are misclassified[9], methods have been proposed for accounting for measurement error in studies of diet[10] and papillomavirus infection[11]. Current work is directed at design issues related to measurement error, in particular the optimal sample size for accurate and inaccurate measurements, under different assumptions about the cost of making the measurement.

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[9] Kaldor, J.M. & Clayton, D.G. (1985) *Stat. Med.*, *4*, 327–335

[10] Kaldor, J. (1989) In: Muñoz, N., Bosch, F.X. & Jensen, O.M., eds, *Human Papillomavirus and Cervical Cancer* (IARC Scientific Publications No. 94), pp. 125–133

[11] Kaldor, J. (1988) In: Riboli, E. & Saracci, R., eds, *Diet, Hormones and Cancer: Methodological Issues for Prospective Studies* (IARC Technical Report No. 4), Lyon, International Agency for Research on Cancer

(ii) *Methodological issues in the quantification of cancer risk*

Methodological problems arising in the quantification of cancer risk have been explored in various areas. The epidemiological and experimental results on anticancer drugs have been used as a model data-base for this purpose[12]. Statistical methods which take into account temporal factors in the estimation of risk have been presented for studying second cancer risks[13]. The methods could be equally well applied to studies of occupational carcinogens. The role of multistage mathematical models in the study of liver cancer risk factors has been investigated[14]. Statistical problems arising in the design and analysis of multigeneration carcinogenesis experiments have been discussed, with particular reference to differences in the sensitivity related to species or whether the father or mother was exposed[15].

(iii) *Migrant populations*

The statistical analysis of cancer risk in migrant populations raises some problems similar to those of estimating risk due to age, period and cohort; other difficulties are due to the lack of appropriate denominator populations. These issues and relevant statistical methods have been discussed with particular reference to a study of the migrants to Israel[16] (see section I.1.*g*.i).

(iv) *Interactive effects—the case of alcohol and tobacco*

Several contradictory statements have been made regarding the interaction of alcohol drinking and tobacco smoking as a risk factor for cancer of the upper aerodigestive tract. The uncertainty came partly from the weak power of the statistical tests used to detect such an interaction. Several data sets related to case–control studies of the upper aerodigestive tract have been reviewed and it was possible to demonstrate, using a one degree of freedom test designed by Breslow and Storer[17], that the multiplicative model gives the best description in all cases, and it was possible to reject the additive model on statistical grounds[18]. Oesophageal cancer is the site for which a sub-multiplicative effect seems most likely; this could be explained by the high risk of oesophageal cancer for alcohol drinking among light smokers. For other sites, the joint effect observed is not compatible with the relatively large risk at low doses that would be implied by an additive or strongly sub-multiplicative model.

(v) *Methods for measuring relative survival*

The methods which are used for calculating survival, corrected for independent causes of death, are subject to various biases when the cohort for which the survival is evaluated is heterogeneous for life expectancy. A maximum likelihood method, which avoids these problems, has been designed. It also permits control for covariates in the framework of a proportional hazard model[19]. It is therefore a natural extension to relative survival of the tools which are now

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[12] Kaldor, J. (1989) Carcinogenic drugs: A model data-base for human risk quantification. Paper prepared for the SIMS Conference, Alta, USA, 17–22 June 1989

[13] Kaldor, J.M. & Day, N.E. (1989) *Stat. med.* (in press)

[14] Kaldor, J.M. & Bosch, F.X. (1989) *Bull. Cancer* (in press)

[15] Turusov, V. & Cardis, E. (1989) In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96), Lyon, International Agency for Research on Cancer, pp. 105–120

[16] Kaldor, J., Khlat, M., Parkin, D.M., Shiboski, S. & Steinitz, R. (1989) *Int. J. Epidemiol.* (in press)

[17] Breslow, N.E. & Storer, B.E. (1985) *Am. J. Epidemiol., 122,* 149–162

[18] Estève, J.E. & Tuyns, A.T. (1988) In: *Chemical Carcinogenesis* (Proceedings of the Fourth Sardinian International Meeting, 23–27 October 1987)

[19] Estève, J., Benhamou, E., Croasdale, M. & Raymond, L. (1989) *Stat. Med.* (in press)

used regularly by cancer registries for studying survival of cancer patients. A computer program, which can be obtained from the Agency, has been written for performing the calculation.

(*b*) Application of statistical methods in cancer research

The existing monographs on statistical methods in cancer research have been widely distributed and are regularly quoted in the scientific literature as a source of methodological information. A monograph on statistical methods in descriptive epidemiology is being completed.

The dissemination of statistical expertise is also undertaken through courses (see section V.2) and by direct collaboration with various research institutes in different countries[20,21,22]; the pooling of existing data and the statistical analysis in collaboration with the investigators is also undertaken as a means of improving the quality of epidemiological information through the use of more advanced statistical approaches. Examples of such collaboration are described below.

(i) *Large-bowel cancer and polyps* (Dr J. Estève; in collaboration with Dr J. Faivre and Dr M.C. Boutron, Burgundian Register of Digestive Tumours, Dijon, France, and the Large Bowel Study Group of the European Organization for Cooperation in Cancer Prevention Studies)

A European case–control study on diet and polyps in relation to colorectal cancer is almost completed and an intervention study to test the efficacy of oral calcium supplementation and oral dietary fibre supplementation in preventing neoplastic polyps of the large bowel is being planned. Active participation in this study group will permit the best statistical methodology to be used in the design and analysis of these studies.

(ii) *Cohort study of workers in the nylon and tergal industry* (Dr E. Cardis; in collaboration with Dr M. Hours and Professor J. Fabry, Faculty of Medicine, Lyon, France)

The analysis of the follow-up, until 1986, of a cohort of workers in the synthetic fibres industry in Lyon has been completed. A slightly increased risk of cancers, in particular of the lung (SMR = 140 based on 44 cases), marginally related to exposure category yet not significantly related to length of exposure, was found. The excess of skin cancers noted previously[23] has disappeared, while an excess of bladder cancer cases (based on seven cases, five of which had worked in nylon production) was observed. The cohort is still young (87% of the subjects are still alive); follow-up is continuing since it may yield important information about potential hazards associated with the nylon and tergal industry. A study of the cigarette-smoking habits of the workers, based on information available in the medical records of the plant, is in progress.

(iii) *Case–control study of bladder cancer in relation to occupational exposure* (Dr E. Cardis and Mr R. Chiflet; in collaboration with Dr M. Hours and Dr J. Fabry, Faculty of Medicine, Lyon, France)

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[20] Negri, E., Piolatto, G., Pira, E., Decarli, A., Kaldor, J. & LaVecchia, C. (1989) *Br. J. Ind. Med.* (in press)

[21] Paci, E., Buiatto, E., Constantini, A., Miligi, N., Scarpelli, A., Petrioli, G., Simonato, L., Winkelmann, R. & Kaldor, J. (1989) (submitted for publication)

[22] Hours, M., Cardis, E., Marciniak, A., Quelin, P. & Fabry, J. (1989) *Br. J. Ind. Med., 46,* 665–670

[23] Hours, M., Bertholon, J., Estève, J., Cardis, E., Freyssinet, C.L., Quelin, P. & Fabry, J. (1986) *Scand. J. Work. Environ. Health, 12,* 455–460

A case–control study was carried out in the urological services of five public hospitals in Lyon between 1984 and 1987. 120 bladder cancer cases and 240 hospital controls matched for age and sex were interviewed using a detailed employment history questionnaire. A panel of chemists and industrial hygienists estimated the level of exposure to 320 compounds for each individual in the study; the statistical analysis is being carried out at IARC.

(iv) *Melanoma and naevi* (Dr J. Kaldor; in collaboration with Dr A.J. Swerdlow, London School of Hygiene and Tropical Medicine, London; Dr R. Gallagher, Cancer Control Agency, Vancouver, BC, Canada; and Dr D. English, Research Unit in Epidemiology and Preventive Medicine, NHMRC, Nedlands, WA, Australia)

A meeting was held in June 1989 to discuss combined analyses of melanoma case–control studies, and possible cooperation in naevus prevalence surveys. Representatives from most major completed case–control studies of melanoma were present, and proposals were made for combining the studies to carry out analyses of the risk associated with a broad range of variables, including naevi, other constitutional factors such as hair, eye and skin colour, sunlight exposure, family history and use of hormones. The main goal of the combined analysis would be to examine these risk factors in subgroups defined by age, sex, melanoma subtype and body site. It was agreed that such analyses would be of considerable value and that the proposals should be further refined by a subgroup of the meeting. Several ongoing naevus prevalence surveys were also described and participants expressed interest in further cooperation, possibly including combined analysis of studies to examine geographical correlations between naevi, melanoma incidence and latitude, and the establishment of common criteria for counting and evaluating naevi.

(v) *Breast cancer in Argentina* (Dr J. Kaldor; in collaboration with Dr J. Iscovich, Israel Cancer Registry, Jerusalem, Israel; and Professor G. Howe, National Cancer Institute of Canada Epidemiology Unit, Toronto, Canada)

The data collected in the case–control study in Argentina have been analysed at IARC[24]. The most striking observation from the study was a far higher intake of calories among cases than among controls. Egg consumption was associated with an increased risk, and whole milk products and green leaf vegetables were protective. In analyses by nutrient adjusting for total calories, fibre and β-carotene were associated with reduced risk.

4. METHODS FOR DETECTING CARCINOGENS

(*a*) International network of carcinogenicity testing (Mr J. Wilbourn, Dr A. Aitio, Dr J.R.P. Cabral and Dr R. Montesano)

The Agency, in collaboration with the International Programme on Chemical Safety (IPCS) of WHO, continues to coordinate a network of laboratories involved in the long-term testing of chemicals for carcinogenicity in rodents, the development and validation of new tests *in vitro*, and studies of transplacental carcinogenesis. Recently a study on atrazine in rats has been prepared for publication and a long-term study in rats given ethanol in isocalorific diets has been terminated. A study on simazine has been started as well as a study on the skin tumour-

[24] Iscovich, J.M., Iscovich, R.B., Howe, G., Shiboski, S. & Kaldor, J.M. (1989) *Int. J. Cancer* (in press)

promoting effects in mice of alternating magnetic fields and on the liver foci-promoting effect of such fields in rats. IARC support is given through research agreements which are renewed periodically.

(*b*) Development of methods for biological monitoring of vinyl chloride exposure (Dr A. Barbin and Mrs F. Ciroussel; in collaboration with Professor C. Trépo and Dr M.-J. Marion, INSERM U271, Lyon, France; Professor M.F. Rajewsky and Dr G. Eberle, Institute of Cell Biology, University of Essen, FR Germany; Professor M. Gérin, Department of Occupational and Environmental Medicine, University of Montreal, Quebec, Canada; Dr J. Swenberg, Chemical Industry Institute of Toxicology, Research Triangle Park, NC, USA; Professor A.T. Natarajan, Sylvius Laboratories, University of Leiden, The Netherlands; and Dr H.V. Gelboin, National Cancer Institute, Bethesda, MD, USA)

Since the finding that occupational exposure to vinyl chloride (VC) is associated with the development of a rare human tumour (hepatic angiosarcoma), levels of atmospheric VC have been drastically reduced in working places. However, workers who were heavily exposed to VC before 1975 are still at risk of developing this tumour. The aims of this project are to develop methods for biological monitoring of humans exposed to VC and to elucidate the molecular biology of angiosarcoma development.

Several potential markers of exposure to VC have been investigated. Attempts to measure *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, a VC-derived thioether in urine samples from workers exposed to VC (8-h average concentration in the range of 0.05 to 0.9 ppm) by HPLC and spectrofluorometry after derivatization, gave negative results. This metabolite is therefore unsuitable for biological monitoring at the present occupational VC exposure limits.

The formation and repair of two VC–DNA adducts have been investigated *in vivo* and *in vitro*. A sensitive method based on a combination of HPLC and competitive radioimmunoassay has been developed to measure 1,N^6-ethenodeoxyadenosine (εAdR) and 3,N^4-ethenodeoxycytidine (εCdR) in DNA hydrolysates, and has been used to show the presence of εAdR and εCdR in the liver and lung from young Sprague–Dawley rats exposed to VC[25]. The same adducts have been measured in several organs from BDVI rats following two weeks' exposure to VC (Table 41). εAdR and εCdR were found in the liver, lung and brain, but not in the kidney of young animals. In liver DNA, levels of both ethenonucleosides were about six times lower in adult rats than in young animals. Comparison with published carcinogenicity data suggests that the levels of etheno-adducts in DNA may be indicative of the organs which are at risk for tumour development following exposure to VC[26,27].

The persistence of εAdR and εCdR has been measured in liver DNA from young CD rats exposed to VC for five days and killed at day 3, 7 or 14 following the end of exposure. Preliminary data indicate that these adducts are stable or poorly repaired *in vivo*. The repair of εAdR and εCdR has also been studied *in vitro*, by incubating chloroethylene oxide-modified DNA in the presence of tissue homogenates from rat or human liver. No release of ethenobases was observed, although under similar conditions, the same extracts released 3-methyladenine

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[25] Eberle, G., Barbin, A., Laib, R.J., Ciroussel, F., Thomale, J., Bartsch, H. & Rajewsky, M.F. (1989) *Carcinogenesis, 10*, 209–212

[26] Barbin, A., Ciroussel, F. & Bartsch, H. (1989) In: Lambert, M.W., Lambert, C. & Laval, J., eds, *DNA Repair Mechanisms and their Biological Implications in Mammalian Cells*, Plenum Press, New York (in press)

[27] Ciroussel, F., Barbin, A., Eberle, G. & Bartsch, H. (1989) *Biochem. Pharmacol.* (in press)

Table 41. DNA adducts in BDVI rats exposed to vinyl chloride

Organ	Molar ratio ($\times 10^7$) of	
	εAdR/AdR[a]	εCdR/CdR[b]
Liver	1.31[c]	4.80[c]
	0.19[d]	0.80[d]
Lung	0.97[c]	2.34[c]
Brain	0.61[c]	2.06[c]

[a] εAdR/AdR: 1,N^6-ethenodeoxyadenosine/deoxyadenosine.

[b] εCdR/CdR: 3,N^4-ethenodeoxycytidine/deoxycytidine.

[c] 7-day old rats exposed to 500 ppm VC in air for two weeks, 7 h per day; sacrifice at 12 h following end of exposure.

[d] 28-day old rats exposed to 500 ppm VC in air for two weeks, 5 days per week, 7 h per day; sacrifice immediately following end of exposure.

from methylated DNA. Therefore, in contrast to a previous report[28], our study failed to show *N*-glycosylase activity towards ethenonucleosides in DNA in mammalian cells. εAdR and εCdR have been considered as potential promutagenic lesions[29]. Their stability in DNA *in vivo* and *in vitro* suggests that they could be involved in the initiation of VC-induced carcinogenesis.

Two pilot studies are evaluating potential markers of early biological effects associated with VC exposure. (1) To detect circulating antibodies directed against VC-modified epitopes of serum albumin, sera or plasma from humans and rodents exposed to VC are being analysed, using an ELISA methodology and chloroethylene oxide-treated human serum albumin as the antigen. (2) Somatic mutations are being measured in blood cells from retired workers who were heavily exposed to VC in their employment. Two endpoints are under investigation: (*a*) mutations at the hypoxanthine phosphoribosyltransferase locus in peripheral lymphocytes; (*b*) haemoglobin variants in erythrocytes.

Human liver angiosarcoma cases are generally of poor prognosis and are usually diagnosed only a few months before a fatal outcome. One of the objectives of the VC project is to measure tumour markers in blood or urine so as to allow earlier diagnosis of liver angiosarcoma and give a better chance of successful treatment. We are evaluating the factor VIII-related antigen, a known marker for endothelial cells. Using an ELISA technique, this antigen is measured in the serum from VC-exposed workers, including a few patients with VC-associated liver tumours. In parallel, it is measured in plasma from rats exposed to VC and kept alive until liver tumours appear.

Earlier experiments using human liver microsomal fractions revealed a wide interindividual variation in the ability to activate VC into mutagenic metabolites[30]. To get further insight into

[28] Oesch, F., Adler, S., Rettelbach, R. & Doerjer, G. (1986) In: Singer, B. & Bartsch, H., eds, *The Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis* (IARC Scientific Publications No. 70), Lyon, International Agency for Research on Cancer, pp. 373–379

[29] Barbin, A. & Bartsch, H. (1986) In: Singer, B. & Bartsch, H., eds, *The Role of Cyclic Nucleic Acid Adducts in Carcinogenesis and Mutagenesis* (IARC Scientific Publications No. 70), Lyon, International Agency for Research on Cancer, pp. 345–358

[30] Sabadie, N., Malaveille, C., Camus, A.-M. & Bartsch, H. (1980) *Cancer Res.*, *40*, 119–126

these interindividual variations, we are investigating the induction of various cytochrome P450 isozymes by VC. Newborn BDVI rats were exposed to VC for two weeks and cryostat sections from the liver were stained by immunohistochemistry, using the specific monoclonal antibodies developed by H.V. Gelboin. Preliminary data suggest that VC induces more specifically the cytochrome P450j isozyme. Rats from two other strains (Sprague–Dawley and CD) are now being exposed to VC and their hepatic cytochrome P450s will be analysed by Western blotting, in addition to immunohistochemistry.

The role of oncogene activation in the genesis of VC-associated hepatic angiosarcoma is under investigation in both humans and rodents. A group of 48 newborn male and female Sprague–Dawley rats has been exposed to 500 ppm VC for six weeks (8 h/day, 6 days/week). Animals are kept under observation until the appearance of liver tumours. Blood and urine samples are collected for analysis of tumour markers and markers of early biological effects.

(*c*) Development and use of microencapsulated trapping agents for carcinogens in the gastrointestinal tract (Dr I.K. O'Neill and Mrs A. Ellul; with support from the US National Cancer Institute; Grant No. RO1 CA 39417-01)

Semi-permeable magnetic microcapsules containing polymeric nucleophiles to simulate DNA for trapping carcinogen metabolites[31,32,33] have been developed further for use in the gastrointestinal tract, with particular attention to correlating such trapping with DNA damage, seeking modulation of trapping by variation of human diets in levels of substances believed to be associated with colorectal cancer risk, and adapting the microcapsules to permit identification of captured electrophilic compounds. Cross-linking by as-yet unidentified agents *in vivo* on polyethyleneimine (PEI) has been confirmed, and three studies have been conducted to show that the microcapsules pose no risk for human use.

(i) *Interrelationships between microcapsule trapping, dietary intake, mucosal DNA damage, enterohepatic circulation and gut transit of an orally ingested carcinogen* (with Dr A. Povey, Dr M. Klaude, Ms F. El-Ghissassi and Ms B. Inçaurgarat; in collaboration with Dr S. Bingham, MRC, Cambridge, UK; and Dr D. Phillips, Institute of Cancer Research, London)

A series of experiments was undertaken to elucidate the complex interrelationships that affect both microcapsule trapping and presumably some part of dietary modulation of carcinogenesis. Male F344 rats were first adapted to a series of isocaloric human diets. PEI microcapsules were then administered in gavages at −2, +22 and +46 h with [^{14}C]benzo[*a*]pyrene at 0 h. Microcapsules were recovered magnetically from faeces and the distribution of metabolites measured between microcapsules and the solid/liquid phases of faecal material. The results show marked effects of dietary fibre, of reduced calorific and mass intake, and of a Chinese diet on microcapsule binding and of benzo[*a*]pyrene (BP) excretion. After seven days, animals were sacrificed and colon mucosal DNA is being assayed by ^{32}P-postlabelling for BP adducts that persisted in spite of the rapid turnover of epithelial cells.

In another experiment, the time-dependence was studied of the movement of [^{14}C]BP through the rat GI tract and consequent effects on DNA adducts (Table 42) and microcapsule binding. With these factors clarified, an experiment was undertaken to investigate the

[31] Povey, A.C., Brouet, I., Nixon, J.R. & O'Neill, I.K. (1987) *J. Pharm. Sci., 76,* 201–207
[32] Povey, A.C., Bartsch, H. & O'Neill, I.K. (1987) *Cancer Letters, 36,* 45–53
[33] O'Neill, I.K., Castegnaro, M., Brouet, I. & Povey, A. (1987) *Carcinogenesis, 8,* 1469–1474

Table 42. Evolution of [^{14}C]benzo[*a*]pyrene adducts in mucosa of F344 rats after gavage.

	Adduct level (dpm/mg DNA) per 5×10^7 dpm BP dose			
	1.5 h	6 h	16 h	24 h
Stomach	95	24	0	0
Jejunum	387	2795	248	235
Ileum	871	730	130	113
Caecum	23	71	50	27
Colon	25	59	33	37

long-standing question of whether mucosal DNA is attacked by carcinogen electrophiles principally from the bloodstream or from the GI cavity.

Since most BP given by gavage is not absorbed from the rodent GI tract[34], and dietary and microflora factors affect microcapsule binding[35], it is clear that intra-luminal events dominate the DNA-damaging potential of this carcinogen.

(ii) *Gastrointestinal enzymes involved in carcinogen metabolism* (in collaboration with Dr C. Malaveille, Dr A. Povey and Mrs G. Brun)

Fischer 344 rats were adapted to a set of four human diets used to test microcapsule trapping (or chow for comparison), either with or without Aroclor treatment for enzyme induction. After sacrifice, the liver, small intestine (proximal and distal) and colon were removed for assay of ethoxyresorufin *O*-decthylase (EROD), pentoxyresorufin *O*-depentylase, NADPH–cytochrome C reductase and DT diaphorase. Compared to the liver, enzyme patterns in the GI tract were very different, with almost no EROD and much lower and higher amounts of NADPH–cytochrome C reductase and DT diaphorase, respectively, and a marked decrease and increase, respectively, in proceeding from proximal small intestine to colon. In the colon, high DT diaphorase activity could arise from continuous endogenous quinone exposure. The principal metabolites, within the colon, of BP[36] and IQ are quinoid compounds, probably presented as quinone and reactive semi-quinone radicals. Statistical analysis of the results is in progress to examine whether the activities of the enzymes measured could be related to the colon cancer risk associated with the human diets tested.

(iii) *Correlation of diet-modulated levels of colonic nuclear aberrations and microcapsule binding* (in collaboration with Dr M. Klaude and Ms B. Inçaurgarat, IARC, and Dr M. Goldberg, University of Guelph, Ontario, Canada)

Male C57/B6 mice were adapted for three weeks to human diets and treated by gavage with PEI microcapsules (−2 h) and ^{14}C-labelled BP (200 mg/kg) at 0 h, before sacrifice at 24 h. These conditions have been previously established as providing an optimum level of nuclear aberrations. Compared to a diet containing low fat, low dietary fibre and low beef, three-fold increased levels respectively of either fat, fibre or beef gave 0, 48 and 36% decrease in nuclear

[34] Chipman, J.K., Hirom, P.C., Frost, G.S. & Millburn, P. (1981) *Biochem. Pharmacol., 30,* 937–944
[35] O'Neill, I.K., Povey, A.C., Bingham, S. & Cardis, E. (unpublished)
[36] Adrian, J., Billaud, C. & Rabache, M. (1985) *Int. J. Vit. Nutr. Res., 55,* 119–124

aberrations. These data demonstrate not only that previously-found modulations of microcapsule binding by diet[37] are reflected in alterations to DNA damage, but also that modest variations in real human diets can produce significant biological alterations experimentally. Examination of microcapsule-trapped metabolites is in progress.

(iv) *Endogenous cross-linking agents*

During GI transit PEI microcapsules undergo alterations consistent with extensive attack by endogenous cross-linking agents[37], and this can be reproduced *in vitro* by chemical cross-linking agents. The effect seems to be diet- and microflora-dependent[37], and since many cross-linking agents are known to be carcinogens and many carcinogens (e.g. industrial chemicals, chemotherapeutic agents, ionizing radiation) cause DNA cross-linking, studies are in progress to evaluate the significance of those observations. Administration of microcapsules to F344 rats and removal of the GI tract at a series of intervals allowed microcapsules to be recovered from different parts of the GI tract. Both acid-hydrolysed and acid-resistant cross-links were formed in the stomach and caecum/colon, respectively. Aldehydes seem not to be responsible (the effect was not enhanced by $NaBH_4$ reduction), but three DNA-damaging substances (faecapentaenes, the lipid peroxidation product 4-hydroxynonenal and semiquinone radicals) could be candidates.

(v) *Microcapsule modification to permit identification of endogenous DNA-damaging agents* (with Ms B. Inçaurgarat and Dr M. Ashwell; in collaboration with Dr B. Golding, University of Newcastle, UK; and Dr P. Farmer, MRC, Carshalton, UK)

In order to attempt to identify endogenous DNA-damaging agents and their sources, subsequently-cleavable targets are being inserted in suitable microcapsules. Microcapsules have been prepared using poly(vinyl alcohol) with attached guanine residues (see Fig. 28). This structure is potentially capable of being selectively cleaved by periodate, forming stable N7 adducts with DNA-alkylating agents, and amenable to mass spectrometry.

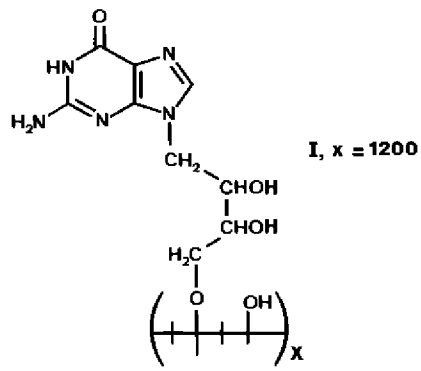

Fig. 28. Structure of poly(vinyl alcohol) with attached guanine residues for use in microcapsules

[37] O'Neill, I.K., Povey, A., Bingham, S., Brouet, I., Béréziat, J.C. & Ellul, A. (1988) In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 107–112

(vi) *Potential safety of microcapsules* (Dr A. Povey, Dr J.R.P. Cabral and Mrs M.P. Cros; in collaboration with Mrs D. Godeneche, INSERM, Clermont-Ferrand)

Three experiments have been performed on different aspects of possible hazard.

(1) Microcapsules (total five doses per animal) were administered to 30 male F344 rats at age 8 and 9 weeks. Compared to controls[38], no differences were seen in body-weight gain, morbidity or mortality up to age 120 weeks.

(2) Radio-labelled microcapsules were administered to male DBA 2 mice and the time-course of disposition was followed in two ways. Animals were sacrificed at intervals up to 72 hours and sagittal sections were applied to autoradiographic films. Other animals were maintained in gas-tight metabolic cages and the total radioactivity in faeces, urine, exhaled breath, blood and ten principal organs assessed. No localized spots of radioactivity were found outside the gastrointestinal tract, and 98.7% of dose was excreted in faeces during 22 h, with no significant radioactivity retained in GI lymph nodes or Peyer's patches[39].

(3) Large quantities of microcapsules (mean diameter 30 μm) were administered to F344 rats (up to 25 doses containing total 50 million for each animal). After sacrifice, no microcapsules were found in tissues removed or within lymph nodes or Peyer's patches. Rats given latex particles retained a very small number, as expected due to the smaller diameter (2 μm).

(*d*) Analysis of environmental carcinogens

(i) *International mycotoxin check sample programme* (Dr M. Friesen, Mrs L. Garren and Mrs E. Bayle; supported in part 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 a graph (Fig. 29) showing the distribution of the results of all participants and with which they can compare their own results. In 1987, 204 laboratories in 50 countries participated in the analysis of aflatoxins B and G in maize and peanuts, 125 laboratories in 38 countries in the analysis of aflatoxin M_1 in milk and 91 laboratories in 39 countries in the analysis of ochratoxin A in wheat flour.

(ii) *International* N-*nitrosamine check sample programme* (Dr M. Castegnaro and Mrs Z. Schneider)

An evaluation of methods for determination of *N*-nitrosodiethanolamine (NDELA) in cosmetic products has been initiated. Four samples (two unspiked and two spiked with NDELA) have been circulated together with the standard spiking solution.

Results have been received from 16 laboratories. Statistical parameters for those laboratories that used the method of Sommer *et al.* (1988)[40] and for those that used other methods indicated that the laboratories experienced in using the Sommer *et al.* method obtained the best inter-laboratory reproducibility.

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[38] Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A. & McConnel, E.E. (1985) *J. Natl. Cancer Inst.*, *75*, 975–984

[39] Povey, A.C., Godeneche, D. & O'Neill, I.K. (1988) *J. Pharm. Pharmacol.*, *40*, 431–433

[40] Sommer, H., Loefller, H.P. & Eisenbrand, G. (1988) *J. Soc. Cosmet. Chem.*, *39*, 133–137

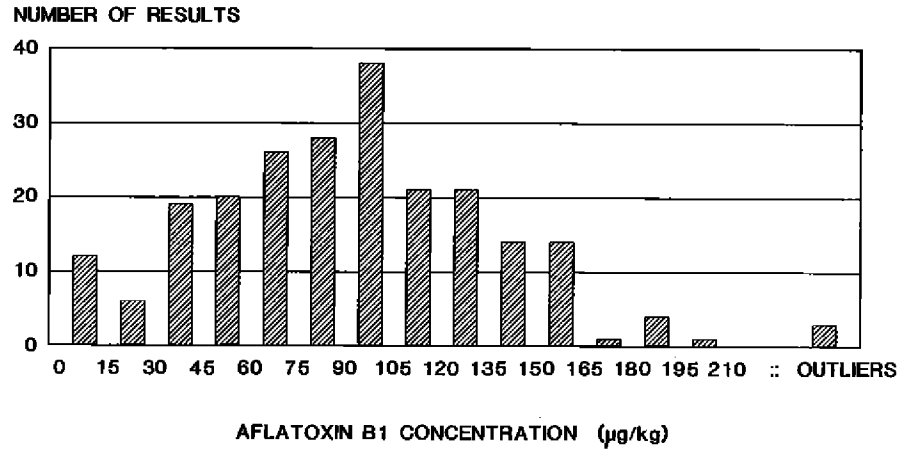

Fig. 29. Distribution of the results from 204 laboratories for the analysis of aflatoxin-B_1 in a sample of maize meal

(iii) *Determination of total* N-*nitroso compounds in environmental samples* (M. Castegnaro; in collaboration with Dr R. Massey, Ministry of Agriculture, Fisheries and Food, Norwich, UK; and Dr G. Ellen, National Institute of Public Health, Bilthoven, The Netherlands)

A method has been developed at IARC for determination of total *N*-nitroso compounds in aqueous media containing nitrate and nitrite (see section I.2.*e*.xiv)[41]. A small study involving the Agency and the two collaborating laboratories has been organized to test the method. After evaluation of the results, the method description will be revised, if necessary, and will be subjected to full collaborative testing.

(iv) *Collaborative study of methods of analysis of volatile nitrosamines in rubber nipples and pacifiers* (Dr M. Castegnaro; in collaboration with Dr L. Rossi, Commission of the European Communities, Brussels; Dr J.R.A. Pollock, Pollock and Pool Ltd, Reading, UK; and the IUPAC Commission of Food Chemistry)

At the request of the Commission of the European Communities, a collaborative study to determine levels of NOC in rubber nipples and pacifiers has been initiated. Twelve samples and a standard solution for quantification have been circulated to 21 laboratories. The samples had to be tested by two methods: that described by Havery and Fazio[42] and that of Spiegelhalder[43].

Results received from 14 laboratories have been fully evaluated. In looking at the raw data, a striking difference was noted between the quoted detection limits, which, for the same *N*-nitrosamine in the sample varied by as much as a factor of 60. This could explain the number of non-detected values especially in the low concentration range for both methods.

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[41] Pignatelli, B., Chen, C.S., Thuillier, P. & Bartsch, H. (1989) Group-selective determination of total *N*-nitroso compounds (NOC) in nitrate-containing human urine samples. *Analyst* (in press)

[42] Havery, D.C. & Fazio, T. (1982) *Food Chem. Toxicol., 20,* 939–944

[43] Spiegelhalder, B. (1983) In: Preussman, R., O'Neill, I.K., Eisenbrand, G., Spiegelhalder, B. & Bartsch, H., eds, *Environmental Carcinogens: Selected Methods of Analysis,* Vol. 6 (IARC Scientific Publications No. 45), Lyon, International Agency for Research on Cancer, pp. 265–273

At a comparable level of detection, both methods have similar statistical parameters for *N*-nitrosamine detection. In most cases, particularly in the 1 mg/kg range, median values are far from the mean values, probably reflecting an exaggerated number of 'non-detected values' quoted because of high limits of detection.

At mean levels, around 1 mg/kg, coefficients of variation for *N*-nitrosodimethylamine were respectively 108.18 and 104.50 by the US method and 116.11, 114.79 and 106.50 by the German method. Similar results were seen for *N*-nitrosodibutylamine.

At higher average levels (5–20 mg/kg), coefficients of variation were slightly better when using Spiegelhalder's artificial saliva method. This probably reflects the fact that this method contains less critical steps with regard to variability of recovery than the US method.

These data were discussed by the CEC partners at a meeting in October 1987, and it was decided, despite some poor performances, to recommend the adoption of the artificial saliva method as the official CEC method for the analysis of nitrosamines in baby nipples and pacifiers.

(v) *Environmental Carcinogens: Methods of Analysis and Exposure Measurement* (Dr I.K. O'Neill and Mrs B. Dodet; in collaboration with Dr L. Fishbein, Environmental Corporation, Washington DC, USA; and Dr A. Mackenzie-Peers, St-Alvère, France; partly supported by the Netherlands Ministry of the Environment and the French Ministry of the Environment)

This series of volumes is produced with the aim of improving assessment and measurement of exposure to known or suspected carcinogens in the environment. Following a programme developed in previous years and approved by an Editorial Board meeting in 1986, the following activities have been undertaken:

(1) Publication of volume 9 on passive smoking (IARC Scientific Publications No. 81);

(2) Publication of volume 10 on benzene and alkylated benzenes (IARC Scientific Publication No. 85);

(3) Continued preparation of volume 11 on dioxins, polychlorinated dibenzofurans and biphenyls;

(4) Continued preparation of volume 12 on indoor air contaminants;

(5) Preliminary work for the next volume, on substances related to synthetic polymers and plastics.

Volume 9 was published because of the continuing difficulties found by researchers in measuring exposure to environmental tobacco smoke, and volume 12 is being prepared in response to the recent awareness that indoor air is a source of other carcinogens and mutagens of diverse nature, e.g. radon, combustion products from wood and coal, formaldehyde from construction materials, and numerous emissions from household products. The importance of benzene and dioxins and substances related to them is partly due to their ubiquity in the environment.

Measurement of polychlorinated dioxins and dibenzofurans is difficult, requiring highly detailed procedures for which the volume in preparation will be the first to cover the full range of accepted methods. The Review Board was convened in August 1988 (Co-Chairmen: Prof. C. Rappe, Umeå, Sweden, and Dr R. Buser, Zurich, Switzerland) to monitor progress. Editing meetings were also held (Chairman: Dr B. Seifert, West Berlin) for the volume on indoor air. It is expected to convene a Review Board in late 1989 to preparation of a volume on substances related to synthetic polymers and plastics.

5. DESTRUCTION OF CARCINOGENIC WASTES

This programme, initiated in 1979, has produced eight publications on degradation techniques and one on safe handling. The substantial demand for these volumes and the request

for new destruction procedures has led to further work in this area. In addition, because of frequent requests by health authorities, courses on safe handling have been held on various occasions.

(*a*) **Destruction of some alkylating agents** (Dr M. Castegnaro; in collaboration with Dr G. Dumenil and Dr M. De Méo, Faculty of Pharmacy, Marseille, France)

A project for the degradation of dimethyl sulfate (DMS), diethyl sulfate (DES), methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS) has been established. A high-pressure liquid chromatography method for the analysis of DMS, using derivatization of *p*-nitrophenol into *p*-nitroanisole has been set up and adapted to evaluate the kinetics of degradation of both methylating and ethylating compounds using 1 molar sodium carbonate, sodium hydroxide, ammonia or sodium thiosulfate. The mutagenic activity of the destruction products was evaluated by the Ames test using four *Salmonella* tester strains. The kinetics of destruction of alkylating agents followed an equation of the type $C = C_0 e^{-at}$, where a is a constant depending on the compound to be degraded. Solutions of 1 M $Na_2S_2O_3$ were the most effective in destroying the four alkylating agents, the half-lives of DMS, DES, MMS and EMS being 0.14 min, 1.26 min, 0.6 min and 5.26 min respectively. Following complete destruction in 1 M $Na_2S_2O_3$, no mutagenic activity was detected in the residues[44].

(*b*) **Destruction of some mycotoxins and some polycyclic heterocyclic compounds** (Dr M. Castegnaro; with the support of the French Ministry of the Environment and of the Office of Safety of the US National Institutes of Health)

A programme has been undertaken to investigate methods of degradation of two new series of compounds: some mycotoxins (citrinin, ochratoxin A, patulin and sterigmatocystin) and some polycyclic heterocyclic compounds (dibenzacridines and dibenzocarbazoles). Implementation of such a programme involves:

(1) Collection and evaluation of published information on the degradation techniques and the chemistry of the carcinogenic substances considered;

(2) Laboratory evaluation and development of the proposed methods;

(3) Collaborative studies to ascertain the efficiency of the methods;

(4) Finalization of the description of the method by a meeting of experts, for publication as an IARC Scientific Publication.

(i) *Chemical degradation of mycotoxins* (Dr M. Castegnaro and Miss J. Michelon; in collaboration with Dr J.-M. Fremy, Ministry of Agriculture, Paris; and Dr M. De Méo, Faculty of Pharmacy, Marseille, France)

Following evaluation of published literature, four methods have been evaluated for the decomposition of ochratoxin A. Oxidation by potassium permanganate in the presence of sulfuric acid and by sodium hypochlorite resulted in complete degradation. The two methods suggested in the literature (heat treatment alone or ammonia treatment, either at room temperature or at 100°C) resulted in poor and non-reproducible degradation.

The three methods tested for the decomposition of citrinin (oxidation by sodium hypochlorite or potassium permanganate in presence of sulfuric acid and treatment by 10% ammonia) led to better than 99% degradation of this compound.

[44] De Méo, M., Laget, M., Castegnaro, M. & Duménil, G. (1989) *Am. Ind. Hyg. Assoc. J.* (in press)

Three methods for the degradation of sterigmatocystin (oxidation by sodium hypochlorite or potassium permanganate in presence of sulfuric acid and treatment with 6N sulfuric acid) all gave acceptable levels of destruction.

Samples of the residues have been prepared for mutagenicity testing in four *Salmonella typhimurium* strains.

(ii) *Chemical degradation of polycyclic heterocyclic compounds* (Dr M. Castegnaro; in collaboration with Dr J. Barek, Charles University, Prague)

The two oxidation techniques which gave satisfactory results for the degradation of polycyclic aromatic hydrocarbons, oxidation by potassium permanganate alone and in presence of sulfuric acid, also gave good levels of degradation for acridine compounds. The sensitivity of the polarographic method used to test the degradation of carbazole compounds did not allow testing at better than 95%; a more sensitive HPLC technique is being set up.

(iii) *Initiation of collaborative studies* (M. Castegnaro)

Networks of laboratories which will participate in both studies have been established. Six laboratories from Czechoslovakia, France, Italy, the Netherlands, the United Kingdom and the USA, have agreed to take part in the mycotoxin study, and six laboratories in France, Germany, Czechoslovakia, the UK, the USA and the USSR in the study on polycyclic heterocyclic compounds.

(c) Safe handling of genotoxic substances (Dr M. Castegnaro and Dr A. Sasco; with the support of the French Ministry of Health Working Groups)

Following the occurrence of several cancer cases in the Pasteur Institute and the Orsay University, the French Ministry of Health organized a working party to evaluate present knowledge and propose recommendations for safe handling of genotoxic substances. Four working groups were created to examine laboratory work, cytostatic drug industry, handling of cytostatic drugs by nurses, and training in handling genotoxic substances.

IARC staff participated in the first, second and fourth of these groups. From group 1, six documents are being published by the Institut National de Recherche et de Securité (INRS)[45,46,47] and specialized scientific journals[48,49,50] and a poster has been prepared for use in laboratories handling these compounds. Reports from groups 2 and 3 were submitted to the Ministry and have been accepted. In group 4, numerous documents which could be used for training have been evaluated, a report[51] has been issued, and it was decided that IARC and INRS will jointly organize training sessions for laboratory workers and nurses who might be exposed to genotoxic agents.

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[45] Dayan, J., Pleven, C. & Castegnaro, M. (1989) *Manuel sur la prévention et la securité lors de la manipulation des substances génotoxiques utilisées au laboratoire* (in press)

[46] Picot, A., Zadjela, F. & Castegnaro, M. (1989) *Liste des produits génotoxiques utilisés au laboratoire* (in press)

[47] Castegnaro, M. (1989) *Cancérogenes chimiques: traitement des dechéts avant rejet* (in press)

[48] Sasco, A.J. (1989) *Medicine et Science* (in press)

[49] Picot, A. & Castegnaro, M. (1989) *L'Actualité Chimique*, Jan./Feb., pp. 12–27

[50] Picot, A. & Castegnaro, M. (1989) *L'Actualité Chimique* (in press)

[51] Castegnaro, M. (1989) In: *Documentation pour les médecins du travail*, No. 37(1), Paris, Institut National de Recherche et de Sécurité, pp. 39–41

IV. TECHNICAL SUPPORT

1. COMPUTING AND BIOSTATISTICAL SUPPORT (Mr M. Smans, Mrs B. Charnay, Mr P. Damiecki, Mr X. Nguyen-Dinh, Mrs A. Arslan, Mrs H. Renard, Miss D. Magnin, Mrs B. Kajo, Dr E. Cardis, Dr J. Kaldor and Dr J. Estève)

After replacing the VAX 11/780 in 1986, the VAX 8300 became the main component of the scientific computing hardware at the Agency. Twice as powerful as the old machine, and equipped with a larger central memory and more disk space, this system made it possible to take up the ever-increasing load. However, the number and especially the size of the epidemiological studies undertaken by the Agency necessitated the addition of a disk unit of 622 Mb to the computer configuration in June 1989. The connection of the different work stations through terminal servers allowed increased productivity (it is no longer rare to have one user carrying out two or three sessions in parallel), but it also contributed to accelerating the saturation of the central processor. In the near future, it will be necessary to consider the replacement of the VAX 8300 by a more powerful machine to absorb this continuous increase in the demand for computing resources.

During the last two years, word processing had been undertaken by two compatible systems: the first generation of Digital Equipment word processors (now obsolete) and the WPS+ software on a MicroVax II. The latter system, capable of supporting 16 concurrent users, had become clearly insufficient to face the increasing demand; it was therefore decided to replace it by a MicroVax 3300 in March 1989. This machine was installed in June 1989 and will meet the total demand for word-processing resources at the Agency. At the same time, investigations were made in conjunction with the publications programme to find a desktop publishing system compatible with the word-processing equipment.

In September 1987, recognizing the value and importance of the work performed by the Agency, Digital Equipment offered a Microvax II equipped with 5 Mb main memory and 71 Mb disk space. This machine, integrated into the existing network, is used mainly for the research programme on geographic variations. It is also used to temporarily relieve the main system from any particularly heavy task.

During these two years, an increasing interest in personal computers has emerged. A few machines have been acquired by units which benefited from the wide variety of software available for these computers. Central support is provided in choice of adequate configurations, particularly when communication with the central system is needed. Furthermore, the most efficient and economical way to integrate personal computers into the main network is being investigated.

It has been decided to link the main computer to the Packet Switching Data (TRANSPAC) to allow Agency staff to establish connections with distant computers in collaborating centres, as well as with various on-line services. Thanks to TRANSPAC, our computer is now linked to a machine at the IN2P3 in Lyon (Institut de Physique Nucléaire), which is a node of the BITNET/EARN electronic mail system; all scientists in the Agency can have access to this system.

The computer resources implemented in the Agency have been considerably expanded and diversified and the informatics support staff have been deeply involved in teaching continuously

advancing techniques. These developments and the trend towards a full integration of the computing resources in a local network enhance the effectiveness of the traditional activity of this programme by enabling the provision of biostatistical consultation to be done at a higher level, the routine statistical work being performed through better use of existing software.

The consulting activity in data-base management has continued, both for scientific data management and for other activities such as bibliographic references, biological samples data bank, fellowships programme and the data-bases of on-going epidemiological and animal experimental studies. However, the limited number of staff made it difficult to respond completely to the increasing demand in this field.

2. BIBLIOGRAPHIC SUPPORT (Mrs A. Nagy-Tiborcz, Miss H. Miido, Mrs L. Ossetian and Mrs M. Coudert)

(*a*) Library services

The library provides active support to all scientific programmes of the Agency, and to the medical and scientific community in Lyon and elsewhere.

Currently, the library receives 212 journals including annuals and reference books and serial subscriptions; the present stock of bound journals is approximately 9200. A total of 8500 books including WHO publications and annual reports are held, many of which were purchased with funds provided by voluntary donors.

The Library Bulletin continues to list papers published by staff members, annual reports received from other organizations and all recent book acquisitions.

(*b*) Computerized bibliographic services

The library has a computer link to SUNIST (Isle d'Abeau, France), giving access to the French National Collection Catalogue which allows journals in other French libraries to be located. Photocopies of articles are ordered directly from any terminal of the Agency computer network and transmitted directly to a suitable supplier, such as the British Lending Library.

The Agency continues to maintain access to on-line search services such as Dialog, Telesystemes, STN and others. Many standard literature searches are routinely run every month, in addition to specific searches that are run on request. The workload of the service has increased considerably over the past two years, as shown in Table 43. In addition, bibliographic searching in relation to the IARC Monographs programme is carried out by Mrs M.J. Ghess, and a total of 316 searches have been performed during the period covered by this report.

The Agency has developed an internal database which will contain references to all the reprint stock held by the staff of the Agency, as well as specialized internal databases.

Table 43. Workload of computerized bibliographic services

	1987–88	1988–89
Searches	725	825
Monthly updating	102	70

3. COMMON LABORATORY SERVICES (Dr J.R.P. Cabral, Dr H. Yamasaki, Miss M. Laval and Mrs 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 and C57BL/6 mice. Facilities for the maintenance of nude mice and rabbits 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.

V. EDUCATION AND TRAINING

1. RESEARCH TRAINING FELLOWSHIPS (Dr R. Montesano, Mrs M. Davis and Mrs E. El Akroud)

(*a*) 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 T. Kakunaga (1988)[1]	Oncogene Research Center, Osaka University, Osaka, Japan
Dr A. Likhachev (1988–89)	N.N. Petrov Research Institute of Oncology, Leningrad, USSR
Dr A.B. Miller (1988–89)	National Cancer Institute of Canada, Epidemiology Unit, Toronto, Ontario, Canada
Dr B. Mansourian (1989)	Office of Research Promotion and Development, WHO, Geneva, Switzerland
Dr J. Pontén (1988–89)	University of Uppsala, Department of Pathology, Uppsala, Sweden
Dr T.J. Slaga (1988)	University of Texas System Cancer Center, Smithsville, TX, USA (UICC representative)
Dr A. Tavitian (1989)	INSERM Unité 248, Faculté de Médecine Lariboisière, Paris, France (UICC representative)
Dr S. Watanabe (1989)	National Cancer Center Research Institute, Division of Epidemiology, Tokyo, Japan

The Agency representatives were Dr R. Montesano (Chairman), Dr H. Bartsch and Dr D.M. Parkin.

In 1988, a total of 13 fellowships were awarded out of 40 applications; and in 1989, 15 out of 52 eligible candidates received fellowships. In the two years, a total of eight of these fellowships were tenable at the IARC.

The distribution of fellowships awarded by discipline is given in Table 44 the list of Fellows is given in Table 45.

The 'Associazione Italiana per la Ricerca sul Cancro' provided US$100 000 in 1988–89 in support of the Fellowships Programme.

(*b*) Visiting Scientist Awards

There was no Visiting Scientist Award in 1988. In 1989, one was made to Dr M. Oyamada (Sapporo Medical College, Sapporo, Japan), to spend a period of one year in the Unit of Mechanisms of Carcinogenesis.

[1] Deceased.

Table 44. Distribution of research training fellowships awarded by discipline

Scientific discipline	No. of fellowships		
	1988	1989	1966–89
Epidemiology and biostatistics	4	4	79
Chemical carcinogenesis	0	4	22
Viral carcinogenesis	3	2	12
Cell biology, cell differentiation and cell genetics	6	1	42
Biochemistry and molecular biology	0	4	54
Others	0	0	152
Total	13	15	361

2. TRAINING COURSES

Ten courses were held during the period under review.

(*a*) **Epidemiology of Cancer** (in Spanish), Asunción, Paraguay, 7–12 August 1987, in collaboration with the Pan American Health Organization and the National Cancer Institute, Asunción (Director: Professor M. Riveros)

The programme was coordinated by Dr P. Correa (Louisiana State University Medical Center) and Dr N. Muñoz (IARC). The other members of the teaching faculty were Dr J.M. Pacheco de Souza, Faculty of Public Health, São Paulo, Brazil; Dr P.A. Rolón, National University Medical School, Asunción; Dr E. de Stefani, Hospital de Clinicas 'Dr Manuel Quintelá', Montevideo; and Dr C. Victora, Federal University of Pelotas, Brazil. The course, which was organized in conjunction with the Latin-American Cancer Congress, brought together 43 participants from five countries.

(*b*) **Role of Viruses in Human Cancer**, IARC, Lyon, 15–18 September 1987, in collaboration with the European School of Oncology

This was the second course in which the European School of Oncology had collaborated. Professor G. Klein, Karolinska Institute, Stockholm, and Professor R. Weiss, Chester Beatty Laboratories, London, were the programme co-ordinators and other lecturers included Dr M. Alizon, Pasteur Institute, Paris; Professor A. Burny, University of Brussels; Dr G.B. de-Thé, 'Alexis Carrel' Medical Faculty, Lyon, France; Dr P. Mortimer, Public Health Laboratory Service, London; Professor C.M. Scully, University of Bristol, UK; Professor P. Tiollais, Pasteur Institute, Paris; Dr C. Trépo, INSERM, Lyon, France; Professor D. Trichopoulos, University of Athens; Dr V. Vonka, Institute of Sera and Vaccines, Prague; and Professor H. zur Hausen, German Cancer Research Centre, Heidelberg, FR Germany; and from the Agency, Dr F.X. Bosch, Dr P. Boyle, Dr. G. Lenoir, Dr N. Muñoz and Dr R. Saracci. There were 44 participants from 17 countries in Europe, Africa, Asia and the Americas.

(*c*) **Epidemiology of Cancer** (in Spanish), Pamplona, Spain, 28 September–9 October 1987

The course was organized with the framework of a one-year course for a Masters of Public Health offered by the Institute of Public Health (Director: Dr J.-I. Eliorreta), of the

Table 45. Fellowships awarded in 1988 and 1989

Name	Institute of origin	Host institute
1988		
BIZIK, J.	Cancer Research Institute, Department of Viral Oncogenesis, Bratislava, Czechoslovakia	New York University Medical Center, Department of Cell Biology, New York, NY, USA
CHARACIEJUS, D.	Research Institute of Oncology, Ministry of Health of the Lithuanian SSR, Vilnius, Lithuania, USSR	Utrecht University, Department of Experimental Pathology, Utrecht, The Netherlands
FENECH, M.	Flinders Medical Centre, Department of Haematology, Bedford Park, S.A., Australia	University of Sussex, MRC Cell Mutation Unit, Brighton, Sussex, UK
KHAZAIE, K.	European Molecular Biology Laboratory, Differentiation Programme, Heidelberg, FR Germany	Université Claude Bernard Faculté de Médecine Alexis Carrel, Laboratoire d'Epidémiologie et Immunovirologie des Tumeurs, Lyon, France
KRAMAROVA, E.	Institute of Experimental Oncology, Department of Epidemiology, Bratislava, Czechoslovakia	London School of Hygiene and Tropical Medicine, Department of Medical Statistics, London, UK
L'ABBE, K.	University of Toronto, Department of Preventive Medicine and Biostatistics, Toronto, Ontario, Canada	Unit of Analytical Epidemiology, IARC, Lyon, France
LITVINOV, S.	All-Union Cancer Research Center, USSR Academy of Medical Sciences, Moscow, USSR	The Netherlands Cancer Institute, Division of Tumour Biology, Amsterdam, The Netherlands
NAROD, S.	Hospital for Sick Children, Department of Medical Genetics, Toronto, Ontario, Canada	Unit of Biostatistics Research and Informatics and Unit of Mechanisms of Carcinogenesis, IARC, Lyon, France
NWANKWO, J.	University of Ibadan, College of Medicine, Department of Biochemistry, Ibadan, Nigeria	University of Southern California, Comprehensive Cancer Center, Departments of Microbiology & Pathology, Los Angeles, CA, USA
OYAMADA, Y.	National Cancer Center Research Institute, Carcinogenesis Division, Tokyo, Japan	Unit of Mechanisms of Carcinogenesis, IARC, Lyon, France
SAULE, S.	Institut Pasteur de Lille, Unité d'Oncologie Moléculaire, Lille, France	University of California, San Francisco, Cancer Research Institute, San Francisco, CA, USA
SERRAINO, D.	Centro di Riferimento Oncologico, Unit of Epidemiology, Aviano, Italy	London School of Hygiene and Tropical Medicine Department of Epidemiology, London, UK

Table 45. Continued

Name	Institute of origin	Host institute
TONG, S.-P.	Shanghai Medical University, School of Basic Medical Sciences, Department of Microbiology, Shanghai, PR China	University of Freiburg, Department of Medicine, Hepatitis Research Unit B5, Freiburg, FR Germany
1989		
ALLDAY, M.	Royal Postgraduate Medical School, Department of Virology, London, UK	Tufts University, Department of Pathology, Boston, MA, USA
APPLEGATE, L.A.	M.D. Anderson Cancer Center, Department of Immunology, Houston, TX, USA	Swiss Institute for Experimental Cancer Research, Epalinges/Lausanne, Switzerland
BICHARA, M.	Institut de Biologie Moléculaire et Cellulaire du CNRS, Groupe de Cancérogénèse et de Mutagénèse Moléculaire et Structurale, Strasbourg, France	Harvard University, Department of Biochemistry and Molecular Biology, Cambridge, MA, USA
BOUCHARDY, C.	Registre Genevois des Tumeurs, Geneva, Switzerland	Unit of Descriptive Epidemiology, IARC, Lyon, France
BUSSON, P.	Institut Gustave Roussy, Laboratoire d'Immunobiologie des Tumeurs, Villejuif, France	Lineberger Cancer Research Center, Laboratory of Tumor Virology, Chapel Hill, NC, USA
CHAMBARD, J.-C.	Centre de Biochimie du CNRS, Nice, France	University of California, San Diego, Department of Pharmacology M-036, La Jolla, CA, USA
COX, B.	University of Otago Medical School, Department of Preventive and Social Medicine, Dunedin, New Zealand	Unit of Analytical Epidemiology, IARC, Lyon, France
GAJALAKSHMI, C.	Cancer Institute, Madras, India	University of Toronto, Department of Preventive Medicine and Biostatistics, Toronto, Ontario, Canada
LIU, Q.	Sun Yat-sen University of Medical Sciences, Department of Medical Statistics and Community Medicine, Guangzhou, PR China	Unit of Analytical Epidemiology, IARC, Lyon, France
LU, F.-X.	Cancer Institute, Chinese Academy of Medical Sciences, Beijing, PR China	Institute of Cancer Research, Division of Environmental Science, Department of Pharmacology, Columbia University, New York, NY, USA

Table 45. Continued

Name	Institute of origin	Host institute
MIELE, M.	National Institute for Research on Cancer, Laboratory of Mutagenesis, Genoa, Italy	Unit of Mechanisms of Carcinogenesis, IARC, Lyon, France
MIKHEEV, A.	N.N. Petrov Research Institute of Oncology, Leningrad, USSR	Unit of Mechanisms of Carcinogenesis, IARC, Lyon, France
POGNONEC, P.	Institut Pasteur de Lille, Unité d'Oncologie Moléculaire Lille, France	Rockefeller University, Laboratory of Biochemistry and Molecular Biology, New York, NY, USA
REISMAN, D.	Weizmann Institute of Science, Department of Cell Biology, Rehovot, Israel	University of Colorado, Department of Chemistry and Biochemistry, Boulder, CO, USA
SATOH, M.	University of Tokyo, Institute of Medical Science, Tokyo, Japan	Imperial Cancer Research Fund, Clare Hall Laboratories, Potters Bar, Herts, UK

Government of Navarra, Spain, and planned by the Fundación Miguel Servet (Director: R. Tortajada). The programme co-ordinators were Drs N. Muñoz and F.X. Bosch (IARC). The faculty included Dr N. Ascunce, Institute of Public Health, Pamplona, Spain; Professor P. Correa, Louisiana State University, New Orleans, USA; Dr H. Sancho-Garnier, Gustave-Roussy Institute, Villejuif, France; and Dr C. Victora, Federal University of Pelotas, Brazil. In addition, invited lectures were presented by Dr E. Benito, Dr J. Borras, Dr L. Cayolla da Motta, Dr F. Garcia Beñavides, Dr C. Gonzales, Dra I. Izarzugaza, Dr G. Lopez-Abente, Dra C. Navarro, Dr R. Peris-Bonet, Dr A. Segura and Dr P. Viladiu. Of the 50 participants, most came from all the main centres in Spain, but there were also two from Portugal, three from Brazil and one each from Colombia and Chile. Many of the Spanish participants were already involved in collaborative research projects with the Agency.

(*d*) International Course on Cancer Epidemiology, Moscow, 11–21 May 1988

At the invitation of the All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR (Director: Academician N.N. Trapeznikov), a course was organized in the Institute of Carcinogenesis (Director: Dr D. Zaridze) of the All-Union Cancer Research Centre, coordinated by Professor J.M. Elwood, University of Nottingham, UK. The other faculty members were Professor S. Grufferman, University of Pittsburgh School of Medicine, USA; Dr R. Gurevicius, Lithuanian Institute for Cancer Research, Vilnius, USSR; Dr T. Hakulinen, Finnish Cancer Registry, Helsinki; Dr F. Merletti, University of Turin, Italy; Dr J. Osborn, London School of Hygiene and Tropical Medicine; Dr D. Zaridze, All-Union Cancer Research Centre, Moscow; and Dr P. Boyle and Dr W. Davis from the Agency. There were 47 participants, of whom 16 came from the different republics of the USSR, the remainder coming from 14 countries of Europe, Asia and Australasia.

(e) European Educational Programme in Epidemiology—First Residential Summer Course, Florence, Italy, 28 June–15 July 1988

The European Educational Programme in Epidemiology, which started on the initiative of the Panel for Epidemiology and Social Medicine in the European Community (Chairman: Professor W. Holland) requested the Agency's collaboration and sponsorship in organizing a summer school at the CISL Study Centre in Florence. Dr R. Saracci and Dr W. Davis were respectively nominated as course director and course secretary. The other members of the faculty included: Dr G. Bréart, INSERM Unit for Epidemiological Research on Mother and Child, Paris; Dr D.G. Clayton, University of Leicester, UK; Dr N.E. Day, MRC Biostatistics Unit, Cambridge, UK; Dr C. Hill, Gustave Roussy Institute, Villejuif, France; Professor U. Keil, Ruhr University, Bochum, FR Germany; Dr F. Merletti, University of Turin, Italy; Professor J. Olsen, University of Aarhus, Denmark; Dr P. Pietinen, National Public Health Institute, Helsinki and Professor D. Trichopoulos, University of Athens. 50 students coming from 14 different countries participated in the course which was generously supported by the WHO Regional Office for Europe and the Regional Government of Tuscany.

(f) International Course on Molecular Biology for Cancer Epidemiologists, Oslo, 2–12 August 1988

At the suggestion of Professor O. Iversen, Chairman, Institute of Pathology, Oslo, the Agency held its second course on molecular biology for cancer epidemiologists at the Soria Moria Conference Centre, in Oslo. Professor J. Cairns, Harvard School of Public Health, Boston, acted as programme coordinator together with Professor Iversen. The rest of the faculty were Dr J. Mullins, Harvard School of Public Health, Boston; Dr B. Ponder, Haddow Laboratories, Sutton, UK; Professor J. Pontén, Uppsala University, Sweden; Professor M. Rajewsky, Institute of Cell Biology, University of Essen, FR Germany; Professor N. Teich, Imperial Cancer Research Fund Laboratories, London; Dr R. Montesano and Dr G. Lenoir, from the Agency. The 25 participants came from 13 different countries.

(g) International Course on Epidemiology and Cancer Control (in Spanish), Medellín, Colombia, 10–22 October 1988

In collaboration with the Pan American Health Organization, the Agency sponsored a course on the epidemiology and cancer control which was held at the University of Antioquia, in Medellín. Dr N. Muñoz from the Agency and Professor P. Correa, from the Louisiana State University, New Orleans, LA, USA, acted as co-directors for the course programme. The other members of the faculty were Professor N. Breslow, the University of Washington at Seattle; Dr A. Muñoz, Johns Hopkins University, Baltimore, MD; Dr H. Restrepo, PAHO; Drs R. Guerrero, C. Cuello and N. Ariztizabal, University del Valle, Cali. Dr K. Colimón, of the University of Antioquia, Medellín, acted as local organizer and was assisted in teaching by a number of colleagues from the University. Dr J.-M. Pacheco de Souza from the Faculty of Public Health of São Paulo also participated in the teaching. 22 participants came from 8 different countries in Latin America and one came from Spain.

The course was followed by a one-week seminar (24–28 October 1988) on advances in epidemiological methods.

(h) Course on Statistical Methods in the Design and Analysis of Long-term Animal Experiments, IARC, Lyon, 12–16 December 1988

At the suggestion of Dr C. Portier, from the Division of Biometry and Risk Assessment of the National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA,

and with their collaboration and support, the Agency organized a course on statistical methods in the design and analysis of long-term experiments. Dr Portier acted as programme coordinator and teacher. The other members of the team were Dr R. Kodell, National Center for Toxicological Research, Jefferson, AR, USA; Dr E. McConnell, National Institute of Environmental Health Sciences, Research Triangle Park, NC; Dr B. McKnight, University of Washington at Seattle; Professor J. Wahrendorf, Institute of Epidemiology and Biometry, Heidelberg, FR Germany and Drs E. Cardis and J. Kaldor, IARC. 53 participants coming from 22 different countries attended the course.

(*i*) **International Course on the Detection of Health Hazards in Human Populations Exposed to Chemical Mutagens and Carcinogens,** Mexico City, 16–27 January 1989

Organized in collaboration with the International Programme on Chemical Safety and the International Association of Environmental Mutagens Societies, the course, directed by Professor H. Vainio, from the Institute of Occupational Health, Helsinki, was held at the Institute of Biomedical Research in Mexico City, with the collaboration and local support of Dr C. Cortinas de Nava. The local teachers included Dr J. Espinosa, Dr I. Jimenez, Dr R. Montero, Dr P. Ostrosky, Dr A. Hernandez, Dr O. Mutchinik, Dr T.D. Ellison and Dr M. Cebrián. The foreign members of the faculty were Dr G. Becking from IPCS, Research Triangle Park, NC; Dr N. Bianchi, from IMBICE, La Plata; Dr M. Legator, University of Texas Medical Branch, Galveston, TX; Dr M. Sorsa, Secretary, IAEMS, Institute of Occupational Health, Helsinki; Professor B. Weinstein, College of Physicians and Surgeons, Columbia University, New York, NY and Dr N. Muñoz, IARC. 37 participants came from 7 different countries.

(*j*) **European Educational Programme in Epidemiology—Second Residential Summer Course,** Florence, Italy, 19 June–7 July 1989

As a follow-up to the first successful experience of the course held in 1988, the European Educational Programme in Epidemiology held its second residential summer school in the same premises, at the CISL Study Centre, in Florence. The WHO Regional Office for Europe, the Regional Government of Tuscany and the Commune of Florence generously contributed to the course. Dr R. Saracci from the Agency acted again as course director and was assisted in his task by Drs E. Buiatti and D. Palli, Centre for Study and Prevention of Cancer, Florence; Dr D. Clayton, University of Leicester, UK; Drs M. Hills and J. Osborn, London School of Hygiene and Tropical Medicine; Professor A. Hofman, Erasmus University, Rotterdam, Netherlands; Professor M. Marmot, University College London; Dr F. Merletti, University of Turin, Italy; Professor J. Olsen, University of Aarhus, Denmark and Professor D. Trichopoulos, University of Athens. 42 students from 16 different countries participated in the course.

3. PUBLICATIONS (Dr W. Davis (until 31 December 1987), Dr J. Cheney (from 1 January 1988), Mrs M. Coudert (until 1 August 1988), Mrs M.-M. Courcier, Mrs E. El Akroud, Mrs A. Romanoff and Mrs J. Thévenoux)

The Advisory Committee on Publications, under the chairmanship of the Deputy Director, continues to critically review all proposals for new IARC publications to ensure their suitability for inclusion in the programme and to verify that appropriate procedures for guaranteeing scientific quality of the manuscripts will operate.

A new series of Technical Reports was launched during 1988, which contain substantial but specialized results of Agency research. These are produced in limited quantity by economical methods for free distribution or sale through WHO sales agents. To avoid confusion, the Agency's series of 'Internal Technical Reports' was renamed IARC Internal Reports.

Table 46. Distribution and sales of IARC publications up to 30 June 1989

No.	Official distribution	Sales	No.	Official distribution	Sales
Scientific Publications					
1	799	872	41	1256	467
2	882	1280	42	1374	735
3	1042	964	43	1589	512
4	1009	871	44	1149	460
5	1200	1766	45	1012	448
6	1057	1425	46	983	278
7	1152	753	47	931	252
8	1134	1124	48	957	333
9	1076	847	49	1531	428
10	1111	1058	50	890	280
11	1181	677	51	1105	410
12	1364	1098	52	454	189
13	1067	887	53	720	438
14	1059	752	54	1641	420
15	1105	1098	55	1633	395
16	1179	830	56	663	367
17	1058	448	57	705	403
18	1096	643	58	641	195
19	1218	606	59	1118	413
20	1006	470	60	729	406
21	1483	1034	61	658	302
22	1047	507	62	457	341
23	1149	1105	63	702	273
24	947	478	64	845	318
25	1200	629	65	674	507
26	1216	415	66	746	373
27	1173	708	67	590	299
28	1017	344	68	601	326
29	1029	596	69	847	310
30	1269	740	70	702	275
31	1128	611	71	824	365
32	2303	4883	72	850	361
33	1435	1609	73	1502	318
34	990	674	74	595	427
35	673	448	75	738	368
36	998	421	76	664	311
37	1834	504	77	664	297
38	949	393	78	600	257
39	1297	444	79	663	674
40	1454	170	80	563	194

Table 46. Continued

No.	Official distribution	Sales	No.	Official distribution	Sales
81	719	405	88	835	452
82	911	2330	89	905	309
83	717	328	90	744	156
84	920	296	91	3565	204
85	618	214	92	698	372
86	677	271	93	774	283
87	732	397	94	60	123
Monograph series					
1	2638	2099	27	2441	1275
2	2084	2439	28	2583	1229
3	2165	2389	29	2522	1395
4	2079	2389	30	2508	1018
5	1874	2009	31	2417	1094
6	2054	2024	32	2431	1361
7	2272	1850	33	2486	1176
8	2271	1845	34	2431	1222
9	2277	1681	35	2126	1248
10	2245	1832	36	1650	1048
11	2392	1530	37	1825	956
12	2303	1708	38	2130	1317
13	2297	1532	39	2172	1070
14	2485	2213	40	2131	904
15	2372	1727	41	2104	1033
16	2362	1642	42	2058	1429
17	2504	1569	43	2003	985
18	2444	1584	44	2011	913
19	2393	1582	Suppl. 1	2470	1440
20	2321	1583	Suppl. 2	2671	1888
21	2401	1215	Suppl. 3	2195	918
22	2383	1282	Suppl. 4	2874	2076
23	2516	1454	Suppl. 5	1310	558
24	2554	1264	Suppl. 6	1959	853
25	2383	1244	Suppl. 7	2225	1914
26	2443	1114			
Information Bulletin on the Survey of Chemicals being Tested for Carcinogenicity, No. 13				464	195

Major features of the Scientific Publications series were the completion of Volume II of *Statistical Methods in Cancer Research*, by Breslow & Day and of Volume V of *Cancer Incidence in Five Continents*. Volume I of *Statistical Methods in Cancer Research* continues to be widely bought and used, and both Volumes I and II had to be reprinted in early 1989 to keep up with demand.

Towards the end of the period under review, the decision was taken to purchase a modern desktop publishing system in order to reduce publication times and increase the capacity and flexibility of the publishing section of the Agency.

The numbers of copies of IARC publications distributed free of charge and of those sold as of 30 June 1989 are detailed in Table 46.

(*a*) New titles

During the period covered by this Biennial Report, the following publications have appeared:

Environmental Carcinogens: Methods of Analysis and Exposure Measurement. Vol. 9, *Passive Smoking* (IARC Scientific Publications No. 81)

Statistical Methods in Cancer Research, Vol. II, *The Design and Analysis of Cohort Studies* (IARC Scientific Publications No. 82)

The Relevance of N-Nitroso Compounds to Human Cancer: Exposures and Mechanisms (IARC Scientific Publications No. 84)

Environmental Carcinogens: Methods of Analysis and Exposure Measurement. Vol. 10, *Benzene and Alkylated Benzenes* (IARC Scientific Publications No. 85)

Directory of On-going Research in Cancer Epidemiology 1987 (IARC Scientific Publications No. 86)

International Incidence of Childhood Cancer (IARC Scientific Publications No. 87)

Cancer Incidence in Five Continents, Vol. V (IARC Scientific Publications No. 88)

Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention (IARC Scientific Publications No. 89)

Non-Occupational Exposure to Mineral Fibres (IARC Scientific Publications No. 90)

Trends in Cancer Incidence in Singapore 1968–1982 (IARC Scientific Publications No. 91)

Cell Differentiation, Genes and Cancer (IARC Scientific Publications No. 92)

Directory of On-going Research in Cancer Epidemiology 1988 (IARC Scientific Publications No. 93)

Human Papillomavirus and Cervical Cancer (IARC Scientific Publications No. 94)

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 42, *Silica and some Silicates*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 43, *Man-made Mineral Fibres and Radon*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 44, *Alcohol Drinking*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 45, *Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 6, *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1–42*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1–42*

Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 13

Cancer in Costa Rica (IARC Technical Report No. 1)

Cancer Registration in the EEC (IARC Technical Report No. 3)

Diet and Cancer Study Methodology (IARC Technical Report No. 4)

Cancer in the Philippines (IARC Technical Report No. 5)

(*b*) Publications in preparation

The following titles are being prepared for publication or are in press:

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, Volume 1, *Tumours of the Rat*, 2nd Edition (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)

Atlas of Cancer Incidence in the German Democratic Republic (IARC Scientific Publications No. 106)

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*

SEARCH Users' Guide (IARC Technical Report No. 2)

(c) Scientific illustrations (Mr J. Déchaux and Mr G. Mollon)

Illustrations for IARC publications and for journal articles, lectures and poster presentations of 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 has been installed to enhance the capacity of the service and the quality of output for both slides and printed illustrations.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE TWENTY-NINTH SESSION OF THE IARC GOVERNING COUNCIL 28–29 April 1988

Australia

Dr D. De Souza
Deputy Secretary and Chief
Commonwealth Medical Officer
Department of Health, Canberra, ACT

Dr W. Langsford
Medical Director, Australian Embassy
Paris

Belgium

Dr J. François
Director-General
Ministry of Public Health and the Family
Brussels

Canada

Dr E. Somers (*Chairman*)
Director-General
Drugs Directorate
Department of National Health and
Welfare
Ottawa

Dr P. Bois
President
Canadian Council for Medical Research
Ottawa

Finland

Dr M. Hakama
Director-General
National Board of Health
Helsinki

Professor J. Rantanen
Director-General
Institute of Occupational Health
Helsinki

France

Dr J. Marchal
Directorate-General for Health
Ministry of Health and the Family
Paris

Mr R. Leclerc
Budget Directorate
Ministry of Economy and Finance
Paris

Federal Republic of Germany

Mr M. Debrus
International Health Relations
Federal Ministry for Youth,
Family Affairs, Women and Health
Bonn

Italy

Professor G.B. Rossi
Chairman, Laboratory of Virology
National Institute of Health
Rome

Professor V. Garofalo
International Relations Office
Ministry of Health
Rome

Japan

Dr K. FURUICHI
Director-General
Statistics and Information Department
Ministry of Health and Welfare
Tokyo

Dr M. MUGITANI
Deputy Director
International Affairs Division
Ministry of Health and Welfare
Tokyo

The Netherlands

Dr R. KROES
Director
National Institute of Public Health and Environmental Protection
Bilthoven

Mr F.H. DE MAN
Deputy Head
International Health Affairs
Ministry of Welfare, Health and Cultural Affairs
Rijswijk

Sweden

Professor H. DANIELSSON (*Vice-Chairman*)
Secretary-General
Swedish Medical Research Council
Stockholm

Union of Soviet Socialist Republics

Professor N.P. NAPALKOV
Director, N.N. Petrov Research Institute of Oncology
Leningrad

Dr A. PAVLOV
Senior Medical Officer
External Relations Board
Ministry of Health of the USSR
Moscow

United Kingdom

Sir Donald ACHESON
Chief Medical Officer
Department of Health and Social Security
London

Dr D.C. EVERED
Second Secretary
Medical Research Council
London

United States of America

Dr I.J. MASNYK
Office of 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 HU CHING-LI
Assistant Director-General

Mr A. IMBRUGLIA
Director, Budget and Finance

Dr J. STJERNSWARD
Chief, Cancer Unit

Dr C.-H. VIGNES
Legal Counsel

Observers

Professor R. MONIER
Incoming Chairman
Scientific Council

Mr C. Press
External Audit, WHO

Professor R. Simard
Outgoing Chairman
Scientific Council

Mr N. Treen
External Audit, WHO

Brazil

Dr A.F. Montoro
President, Fundaçao Oncocentro
São Paulo

PARTICIPATING STATES AND REPRESENTATIVES AT THE THIRTIETH SESSION OF THE IARC GOVERNING COUNCIL
4–5 May 1989

Australia

Dr D. De Souza
Minister of Health
Australian High Commission
Australia House
London

Belgium

Dr J. François
Director-General
Social Medicine Administration
Brussels

Canada

Dr E. Somers
Director-General
Drugs Directorate
Department of National Health and Welfare
Ottawa

Professor R. Simard
Vice-Rector
Montreal University
Montreal

Finland

Dr M. Ruokola (*Vice-Chairman*)
Director-General
National Board of Health
Helsinki

Professor J.K. Huttunen
Director-General
National Public Health Institute
Helsinki

France

Professor M.R. Tubiana
Honorary Director
Gustave Roussy Institute
Villejuif

Mrs A. Cukierman
Budget and Foreign Affairs
Vice-Directorate
Ministry of Foreign Affairs
Paris

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Mr H. Voigtländer
Director
International Health Relations
Federal Ministry for Youth, Family Affairs, Women and Health
Bonn

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Ministerial Councillor
International Relations Office
Ministry of Health
Rome

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Director, Laboratory of Cellular Biology
National Institute of Health
Rome

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Director, Institute of Oncology
Genoa

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Statistics and Information Department
Ministry of Health and Welfare
Tokyo

Dr Y. AMINO
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 Department
Ministry of Welfare, Health and
Cultural Affairs
Rijswijk

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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

Union of Soviet Socialist Republics

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Director, Cancer Research Centre
Academy of Medical Sciences
Moscow

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Ministry of Health of the USSR
Moscow

United Kingdom

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Second Secretary
Medical Research Council
London

Dr M.F. CUTHBERT
Medical Assessor, UK Advisory
Committee on NHS Drugs
Department of Health
London

Mr T. VITTERY
Finance Officer
Medical Research Council
London

United States of America

Dr F. WELSH
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 C.M. CHOLLAT-TRAQUET
Tobacco or Health Programme

Dr J. STJERNSWARD
Chief, Cancer Unit

Mr E.E. UHDE
Director, Division of Budget and Finance

Dr C.-H. VIGNES
Legal Counsel

Observers

Mr S. LOIBORG
Ministry of Health
Copenhagen

Professor R. MONIER
Outgoing Chairman
Scientific Council

Professor E.J. SAKSELA
Incoming Chairman
Scientific Council

Mr A.J. TURNBULL
Acting Executive Director
UICC

Annex 2

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS TWENTY-FOURTH SESSION 18–21 JANUARY 1988

Professor R. SIMARD (*Chairman*)
Vice-Rector
Montreal University
Montreal, Quebec
Canada

Professor R. MONIER (*Vice-Chairman*)
Director, Laboratory of Molecular Oncology
Gustave Roussy Institute
Villejuif
France

Dr P.G. SMITH (*Rapporteur*)
Head, Tropical Epidemiology Unit
London School of Hygiene and Tropical Medicine
London

Professor B.K. ARMSTRONG
University Department of Medicine
Queen Elizabeth II Medical Centre
Nedlands, WA
Australia

Professor L. CHIECO-BIANCHI
Director, Institute of Oncology
University of Padua
Italy

Professor F. DE WAARD
Head, Department of Epidemiology
National Institute of Public Health and Environmental Protection
Bilthoven
The Netherlands

Professor S. GRAHAM
Department of Social and Preventive Medicine
University of Buffalo
Faculty of Health Sciences
Buffalo, NY
USA

Professor L. GRICIUTE
Director
Oncological Research Institute
Vilnius
USSR

Professor O.H. IVERSEN
Institute of Pathology
University of Oslo
Norway

Professor T. MATSUSHIMA
Department of Molecular Oncology
Institute of Medical Science
University of Tokyo
Japan

Professor U. PETTERSSON
Department of Medical Genetics
Biomedical Centre
Uppsala
Sweden

Professor E.J. SAKSELA
Department of Pathology
University of Helsinki
Finland

Professor A. WAMBERSIE
Unit of Radiobiology and Radioprotection
Catholic University of Louvain
Faculty of Medicine
Brussels

Professor H. ZUR HAUSEN
Director
German Cancer Research Centre
Heidelberg
Federal Republic of Germany

World Health Organization

Dr K. STANLEY
Cancer Unit

Advisers

Dr A.L. BROWN
Dean, School of Medicine
University of Wisconsin
Madison, WI, USA

Professor H. J. EVANS
Clinical and Population Cytogenetics Unit
Medical Research Council
Western General Hospital
Edinburgh
United Kingdom

MEMBERS OF THE IARC SCIENTIFIC COUNCIL AT ITS TWENTY-FIFTH SESSION 9–12 JANUARY 1989

Professor R. MONIER (*Chairman*)
Director, Laboratory of Molecular Oncology
Gustave Roussy Institute
Villejuif
France

Professor L. GRICIUTE (*Vice-Chairman*)
Director
Oncological Research Institute
Vilnius
USSR

Professor E.J. SAKSELA (*Rapporteur*)
Department of Pathology
University of Helsinki
Finland

Professor L. CHIECO-BIANCHI*
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University of Padua
Italy

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School of Medicine
Buffalo, NY
USA

Professor O.H. IVERSEN
Institute of Pathology
University of Oslo
Norway

Professor J. KLASTERSKY
Free University of Brussels
Jules Bordet Institute
Brussels

* Unable to attend

A.J. McMICHAEL
Department of Community Medicine
University of Adelaide
Australia

Professor U. PETTERSSON
Department of Medical Genetics
Biomedical Centre
Uppsala
Sweden

Professor R. SIMARD
Vice-Rector
Montreal University
Montreal, Quebec
Canada

Dr P.G. SMITH
Head, Tropical Epidemiology Unit
London School of Hygiene and
Tropical Medicine
London

Dr S. TAKAYAMA
Director
National Cancer Center Research Institute
Tokyo

Professor H. ZUR HAUSEN
Director
German Cancer Research Centre
Heidelberg
Federal Republic of Germany

World Health Organization

Dr V. KOROLTCHOUK
Cancer Unit

International Union Against Cancer

Dr F. CLETON
Oegstgeest
The Netherlands

Adviser

Professor K.J. NETTER
Department of Pharmacology and
Toxicology
Philipps University
Marburg
Federal Republic of Germany

Annex 3

STAFF AT IARC
1 July 1987 – 30 June 1989

Office of the Director

Director, IARC	Dr L. TOMATIS
Deputy Director	Dr C.S. MUIR
Adviser (Scientist)	Dr G. MARTIN-BOUYER (until 30 Nov. 88)
Scientist	Dr V.S. TURUSOV (until 31 Dec. 88)
Administrative Assistants	Mr C. AUGROS Mrs M. DAVIS Mrs A. GESER Mrs E. RIVIERE
Secretaries	Miss S. ANTHONY (until 27 May 88) Mrs C. DECHAUX Miss A. DUFOURNET (from 1 Dec. 88) Mrs W. FEVRE-HLAHOLUK

Gambia Hepatitis Intervention Study

Project Leader/Epidemiologist	Dr A.J. HALL
Medical Officers	Dr J. CHOTARD (from 16 Mar. 88) Dr F. LOIK (until 29 Nov. 87) Dr M. VALL MAYANS (from 1 Feb. 89)
Associate Professional Officer/Laboratory Officer	Dr C. ALTAVILLA (until 15 Oct. 88)
Statistician/Programmer	Dr H.M. INSKIP
Secretary	Miss S. COTTERELL (from 20 Jul. 87)

Editorial, Translation and Publication Services

Head, Editorial & Publications Services/Editor	Dr J. CHENEY (from 4 Jan. 88)
Translator	Miss M.-C. GRAN (until 13 May 88)
Laboratory Technician (Photography)	Mr G. MOLLON
Secretaries	Mrs J. BAILLY (until 31 Aug. 87) Mrs E. EL AKROUD Mrs A.-C. MORET (from 1 Sep. 87)
Clerks	Mrs M.-M. COURCIER (until 31 Oct. 88) Mr J. DECHAUX Mrs A. ROMANOFF 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 A. Nagy-Tiborcz (until 30 Apr. 88) Miss H. Miido (from 1 Jun. 89)
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. Boyle Dr E. Johnson (until 8 Jul. 87) Dr E. Kogevinas (from 15 Jan. 89) Dr E. Riboli Dr L. Simonato (until 31 Dec. 88) Dr A. J. Sasco (on secondment from INSERM)
Assistants (Statistics)	Ms G. Burnod (half-time) Mrs M. Charrel (from 4 Jan. 88 — half-time) Mr P. Maisonneuve (from 1 Sep. 87) Miss R. Winkelmann
Secretaries	Miss A. Shannon Mrs S. Somerville (from 1 Oct. 88) Mrs S. Stallard Mrs A. Zitouni
Unit of Biostatistics Research and Informatics	
Chief	Dr J. Esteve
Scientists	Dr J.M. Kaldor Dr E. Cardis (from 1 Jul. 88)
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 (from 9 Jan. 89)
Secretaries	Miss J. Nyairo (from 17 Apr. 89) Mrs A. Rivoire

Clerks (Computer Operators)	Mr M. JABOULIN (until 25 Jan. 88) Mrs B. KAJO (from 1 Apr. 88)
Unit of Field and Intervention Studies	
Chief	Dr N. MUÑOZ
Scientist	Dr F. X. BOSCH
Assistant (Statistics)	Miss S. TEUCHMANN (from 1 Mar. 89)
Secretaries	Mrs H. BIEHE (from 3 Jan. 89) Mrs K. ZOUHAIR (until 27 Nov. 87)
Unit of Descriptive Epidemiology	
Chief	Dr D.M. PARKIN
Scientists	Dr M.P. COLEMAN (from 1 Jul. 87) Dr M. KHLAT (from 29 Sep. 87)
Assistants (Statistics)	Mr C.A. BIEBER (until 3 Feb. 89) Miss F. CASSET (until 26 Aug. 88) Mr J. FERLAY (from 1 May 89)
Technical Assistants	Mrs E. DEMARET Mrs J. NECTOUX Miss S. WHELAN
Secretaries	Miss O. BOUVY Miss M. GEESINK (from 14 Sep. 87)
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 M. AHOTUPA (until 31 Jul. 87) Dr A. BARBIN Dr M. CASTEGNARO Dr M. FRIESEN Dr E. HIETANEN (from 19 Oct. 87) Dr C. MALAVEILLE Dr I.K. O'NEILL Dr H. OHSHIMA Dr B. PIGNATELLI Dr D. SHUKER (from 1 Mar. 89)
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 (from 1 Nov. 88) Mrs A. HAUTEFEUILLE Miss J. MICHELON Miss I. RICHARD

Secretaries	Mrs E. Bayle (from 1 May 88) Miss Y. Granjard (half-time) Mrs L. Neyret (from 1 Oct. 88) 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 Dr K. Enomoto (until 16 Jun. 88) Dr D.J. Fitzgerald Dr V. Gurtsevitch (until 21 Jun. 88) Dr J. Hall (from 4 Jan. 88) Dr M. Hollstein Dr V. Krutovskikh (from 2 Nov. 88) Dr G.M. Lenoir (Head, Programme on Viral & Hereditary Factors in Carcinogenesis) Dr A. Loktionov (from 15 Jan. 89) Dr N. Mironov Dr H. Nakazawa (from 13 Sep. 88) Dr B. Sylla Dr C. P. Wild Dr H. Yamasaki (Head, Programme on 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 (from 1 Aug. 88) Mrs S. Pauly
Secretaries	Mrs P. Collard-Bianchi Mrs C. Fuchez Mrs E. Perez (half-time) Mrs A. Trochard (from 1 Jun. 88)

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 (on leave without pay)
Scientist/Officer in Charge	Dr A. Aitio (from 5 Jul. 87)
Scientists	Mrs L. Haroun (half-time — until 31 Aug. 87) Dr T. Kauppinen (until 1 Apr. 89) Dr L. Shuker Dr A. Tossavainen (until 31 Aug. 87) 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
Secretaries	Mrs M. Mainaud (half-time) Miss S. Reynaud
Clerk	Mrs M. Lezere

Division of Administration and Finance

Director	Mr E. Westenberger (until 31 Mar. 89)
Administrative Assistant	Mrs J. Martinez

Personnel

Personnel Officer	Mrs A. Escoffier
Clerk-stenographer	Mrs A.-M. Maillol

Budget and Finance

Budget and Finance Officer	Mr M. 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 — from 4 Jan. 88)

Administrative Services	
Administrative Services Officer	Mr B. Borgstrøm
Administrative Assistant	Mrs R. Sextier
Switchboard Operator	Mrs R. Kibrisliyan
Driver	Mr J.-F. Durand-Gratian
Usher (Messenger)	Mr D. Lagarde
Assistant (Building Maintenance)	Mr E. Cathy
Maintenance Technicians	Mr M. Barbieux Mr P. Bazin Mr J.-P. Bonnefond Mr G. Tholly
Assistant (Registry)	Mrs M.-H. Charrier
Clerks	Mrs M. Greenland (half-time) Mrs L. Vigier
Assistant (Supplies)	Mrs J. Popoff
Clerks	Mrs M. Filippi (from 1 Nov. 88) Mrs L. Gravier (half-time)
Storekeeper	Mr M. Prat
Equipment Operators (Reproduction)	Mr D. Graizely Mr M. Javin
Documents and Stenographic Pool	
Assistant	Mrs J. Borgstrøm
Clerk	Mrs M.-B. D'Arcy (from 1 Sep. 88)
Clerk-stenographers	Miss A. Cousseau (from 1 Dec. 87) Miss S. Haver (from 20 Jun. 88) Miss W. Kinuthia (from 1 Jun. 88)

SHORT-TERM EMPLOYMENTS (CONSULTANTS AND TEMPORARY STAFF) 1 July 1987 – 30 June 1989

Office of the Director

Consultants	Mr P. DUNDERDALE Professor R. SOHIER* Dr V. TURUSOV
Social Adviser	Mrs P. MALINDINE* (part-time)
Clerk-stenographer	Mrs A.-C. MORET (half-time)
Gambia Hepatitis Intervention Study	
Consultant	Dr M. VALL-MAYANS
Editorial, Translation and Publication Services, Education and Training	
Consultants	Dr W. DAVIS* Mrs A. NAGY-TIBORCZ (half-time)
Translator	Ms L. EYDOUX*

Division of Scientific Activities

Unit of Analytical Epidemiology	
Consultant	Mr G. MACFARLANE
Technical Officers	Mr R. KAAKS* Dr R. MCGINN* Ms H. SCHUNK
Assistant (Statistics)	Mrs M. CHARREL (half-time)
Technical clerk	Miss V. KLIEBSCH
Clerks (Statistics)	Mr G. FERRO* Mr P. MAISONNEUVE
Clerk	Mrs M. LEPETIT*
Unit of Biostatistics Research and Informatics	
Consultants	Dr E. CARDIS Professor E. SCHIFFLERS
Unit of Field and Intervention Studies	
Consultants	Mr M. CASAS-CORDERO Professor P. CORREA
Technical Clerks	Miss S. TEUCHMANN Miss A. STIGGELBOUT

* Still on short-term employment on 30 June 1989.

Unit of Descriptive Epidemiology

Consultant	Mr A. Bieber*
Clerk (Statistics)	Mr P. Maisonneuve
Technical clerks	Miss B. Fischer*
	Mr E. Masuyer*

Unit of Environmental Carcinogens and Host Factors

Consultant	Dr M. Ashwell*
Scientist	Mr A. Povey
Technical Officer (Bibliographic Research)	Mrs B. Dodet* (part-time)
Laboratory Technicians	Miss F. El Ghissassi*
	Mrs A. Ellul (half-time)
	Mr P. Thuillier*

Unit of Mechanisms of Carcinogenesis

Scientist	Dr T. Shirai*
Laboratory Technicians	Miss B. Chambe*
	Miss F. Daguet
	Mrs Y. Delzoppo
	Miss C. Pezet*
Laboratory Aides	Miss L. Fraissinet-Tachet
	Mr S. Sebaoui*

Unit of Carcinogen Identification and Evaluation

Consultant	Dr F. Sunderman
Technical Officer (Bibliographic Research)	Mrs B. Dodet* (part-time)
Secretary	Mrs J. Atherton* (half-time)
Clerks	Mr J. Cereda* (part-time)
	Mrs M. Lepetit (half-time)

Division of Administration and Finance

Budget and Finance

Consultant	Mr A. Imbruglia
Clerk	Miss A. Milone (half-time)

Administrative Services

Consultant	Dr A. Geser

Supplies

Clerk	Mrs M. Filippi

* Still on short-term employment on 30 June 1989.

Documents and Stenographic Pool

Clerk-stenographers	Mrs E. BAYLE
	Miss A. COUSSEAU
	Miss C. DOUCELIN
	Miss A. DUFOURNET
	Miss B. GEOFFRE*
	Miss J. GIBERT*
	Miss S. HAVER
	Miss W. KINUTHIA

* Still on short-term employment on 30 June 1989.

Annex 4

VISITING SCIENTISTS, FELLOWS AND TRAINEES

Scientists and fellows

Dr F. Alexander, Unit of Analytical Epidemiology (18–27 March 1988)

Dr K. Alexandrov, Unit of Environmental Carcinogens and Host Factors (from 2 November 1988)

Dr C. Amos, Unit of Biostatistics Research and Informatics (3 January–10 February 1989)

Dr P. Arvela, Unit of Environmental Carcinogens and Host Factors, Fellowship from the Centre National de Recherche Scientifique (1–30 June 1988)

Dr P. Baghurst, Unit of Analytical Epidemiology (29 March–7 April 1989)

Mrs D. Balzi, Unit of Descriptive Epidemiology (24 October–9 December 1988 and 6–10 March 1989)

Professor S. Bayo, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (March 1988)

Dr E. Benito, Unit of Field and Intervention Studies (18–27 February 1989 and 24–30 June 1989)

Dr F. Berrino, Unit of Analytical Epidemiology (31 May–8 June 1988)

Dr W. Blot, Unit of Analytical Epidemiology (28 November–3 December 1988)

Dr H. Borba, Unit Environmental Carcinogens and Host Factors (2–20 November 1987)

Dr J. Borras, Unit of Field and Intervention Studies (10–17 June 1989)

Mr G. Bouvier, Unit of Environmental Carcinogens and Host Factors, Fellowship from the Ligue Nationale Française contre le Cancer (from 1 October 1988)

Dr D. Burch, Unit of Analytical Epidemiology (5–16 June 1989)

Professor J. Cairns, Office of the Director (1 February–31 July 1988)

Dr R. Cartwright, Unit of Analytical Epidemiology (9–13 November 1987 and 12–23 September 1988)

Dr C.S. Chen, Unit of Environmental Carcinogens and Host Factors, Fellowship from Association pour la Recherche sur le Cancer (12 April 1988–30 June 1989)

Dr Virasadki Chongsuvivatwong, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (March 1988)

Dr J.W. Coebergh, Unit of Descriptive Epidemiology (6–15 June 1988)

Mrs J. Cogan, Unit of Field and Intervention Studies (2 May–30 November 1988)

Mr M. Croasdale, Unit of Biostatistics Research and Informatics (18 July–24 September 1988)

Dr P. Degan, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellowship (until October 1987)

Mr M. Dumont, Unit of Analytical Epidemiology (5–9 October 1987)

Dr A.M. El Bendary, Office of the Director, Fellowship from the International Atomic Energy Agency (2–6 May 1988)

Dr D. Esteban, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (July 1987)

Mr N. Fairhurst, Unit of Environmental Carcinogens and Host Factors, Fellowship from the European Science Foundation (16 February–23 March 1989)

Dr A. Fletcher, Unit of Analytical Epidemiology (16 May–3 June 1988)

Dr S. Franceschi, Unit of Analytical Epidemiology (20–26 June 1989)

Dr Gao Yu Tang, Unit of Descriptive Epidemiology and Office of the Director (16 May–9 June 1989)

Dr J. Galceran, Unit of Field and Intervention Studies (10–17 June 1989)

Dr J.P. Garne, Unit of Analytical Epidemiology (13–18 February 1989)

Dr M. Gerin, Unit of Analytical Epidemiology (16–20 May 1988)

Dr P. Ghadirian, Unit of Analytical Epidemiology (10–17 March 1989)

Dr M. Goldberg, Unit of Environmental Carcinogens and Host Factors (10 July 1988–30 June 1989)

Dr S. Gonzalez, Unit of Analytical Epidemiology (23 January–3 February 1989)

Dr C. Gray, Unit of Analytical Epidemiology (16–20 May 1988)

Dr R. Gurevicius, Unit of Analytical Epidemiology (6 June–7 July 1989)

Dr S.C. Hadler, Unit of Field and Intervention Studies, 23 January–2 February 1989)

Dr N.J. Haley, Unit of Analytical Epidemiology (16–23 February 1989)

Dr M. Hamdi Cherif, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (March 1989)

Mr K.U. Henss, Unit of Environmental Carcinogens and Host Factors (18 October–15 December 1988)

Professor G. R. Howe, Unit of Analytical Epidemiology (28 February–11 March 1989)

Dr C.-C. Hsieh, Unit of Analytical Epidemiology (February 1988–March 1989)

Dr A.M. Idris, Unit of Biostatistics Research and Informatics, Fellowship from the International Cancer Research Technology Transfer Programme (3–23 October 1988)

Miss D. Jeannel, Unit of Descriptive Epidemiology (2–15 November 1987)

Dr Y.-Z. Jiang, Unit of Mechanisms of Carcinogenesis, Fellowship from the Association pour la Recherche sur le Cancer (from 12 April 1988)

Dr W.M.F. Jongen, Unit of Mechanisms of Carcinogenesis, Fellowship from the EEC (from 1 January 1989)

Mr S. Kané, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (April 1989)

Dr K. Katsouyanni, Unit of Analytical Epidemiology (29 February–11 March 1988)

Dr M. Klaude, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellowship (October 1987–October 1988)

Dr A. Kubik, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (June 1989)

Dr K. L'Abbé, Unit of Analytical Epidemiology, IARC Research Training Fellowship (15 October 1988–15 October 1989)

Dr E. Lau, Unit of Biostatistics Research and Informatics, Fellowship from the International Cancer Research Technology Transfer Programme (21 September–2 October 1987)

Dr A. Likhachev, Unit of Education and Training and Unit of Mechanisms of Carcinogenesis (26 April–18 May 1989)

Dr D. Lin, Unit of Environmental Carcinogens and Host Factors, Fellowship from the Chinese Government (from 2 May 1989)

Dr M.S. Linet, Unit of Analytical Epidemiology (1–11 November 1987 and 6–16 September 1988)

Dr K. Linnainmaa, Unit of Mechanisms of Carcinogenesis (20 April–5 May 1989)

Dr J. Little, Unit of Analytical Epidemiology (30 January–4 February 1989)

Dr S.H. Lu, Unit of Mechanisms of Carcinogenesis and Unit of Environmental Carcinogens and Host Factors, Fellowship from the International Cancer Research Technology Transfer Programme (July–August 1988)

Dr J.R. Marshall, Unit of Analytical Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (10–26 September 1987 and 6–18 March 1988)

Dr J. Martin-Moreno, Unit of Analytical Epidemiology (5–16 December 1988)

Dr G. Maru, Unit of Environmental Carcinogens and Host Factors (1 March 1987–31 January 1989)

Dr M. McCredie, Unit of Analytical Epidemiology (30 January–3 February 1989)

Dr R. Mehrotra, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (25 October–22 November 1987 and 8 June–6 July 1988)

Dr J. Mierzwinska, Unit of Biostatistics Research and Informatics, Fellowship from the International Cancer Research Technology Transfer Programme (25 January–28 February 1988)

Dr M. Mori, Unit of Mechanisms of Carcinogenesis (21–25 October 1987)

Dr U. Nair, Unit of Environmental Carcinogens and Host Factors (from 16 January 1989)

Dr S.A. Narod, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellowship (from July 1988)

Dr E. Negri, Unit of Analytical Epidemiology (16–26 January 1989)

Professor S. Niu, Unit of Analytical Epidemiology (23 May–12 June 1988)

Dr C.B. Nyathi, Unit of Mechanisms of Carcinogenesis, Fellowship from the International Cancer Research Technology Transfer Programme (January 1989)

Dr A. Obrador, Unit of Field and Intervention Studies (18–27 February 1989)

Dr H. Ohgaki, Unit of Environmental Carcinogens and Host Factors (4–22 April 1988)

Dr A. Osterlind, Unit of Analytical Epidemiology (26–30 June 1989)

Dr M. Oyamada, Unit of Mechanisms of Carcinogenesis (from 16 August 1988)

Dr Y. Oyamada, Unit of Mechanisms of Carcinogenesis, IARC Research Training Fellowship (from 16 August 1988)

Dr E. Paci, Unit of Analytical Epidemiology (20 July–2 August 1987)

Dr M. Peluso, Unit of Environmental Carcinogens and Host Factors (from 16 May 1989)

Dr B. Pettersson, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (June 1988)

Miss S. Poirier, Unit of Environmental Carcinogens and Host Factors, Fellowship from the Ligue Nationale Française contre le Cancer (to August 1988)

Dr S. Preston-Martin, Unit of Analytical Epidemiology, 12–18 February 1989

Dr J. Rifa, Unit of Field and Intervention Studies (24–30 June 1989)

Dr C. Robertson, Unit of Analytical Epidemiology (27 June–8 July 1988)

Dr M. Rojas-Moreno, Unit of Environmental Carcinogens and Host Factors (from 2 November 1988)

Professor P.A. Rolón, Unit of Descriptive Epidemiology and Unit of Field and Intervention Studies (2–6 November 1987)

Professor E. Schifflers, Unit of Descriptive Epidemiology (several one- to three-week visits)

Dr D. Shuker, Unit of Environmental Carcinogens and Host Factors (May 1986–November 1988)

Dr Yu Shun-Zhang, Unit of Descriptive Epidemiology, Yamagiwa–Yoshida Memorial International Cancer Study Grant (15 September–15 December 1987)

Dr R. Sierra, Unit of Field and Intervention Studies, Fellowship from the International Cancer Research Technology Transfer Programme (14 November–9 December 1988)

Miss S. Sontipong, Unit of Descriptive Epidemiology (17 April–5 May 1989)

Dr P. Srivatanakul, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (April–May 1989)

Dr E. de Stefani, Unit of Field and Intervention Studies and Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (14 November–16 December 1988)

Mr C.A. Stiller, Unit of Descriptive Epidemiology (26–30 September 1988)

Dr H.H. Storm, Unit of Analytical Epidemiology (16–20 October 1988)

Dr F.W. Sunderman, Unit of Carcinogen Identification and Evaluation (30 May–12 June 1988)

Dr S.H.H. Swierenga, Unit of Mechanisms of Carcinogenesis, Fellowship under the INSERM/MRC agreement between France and Canada (September 1988–May 1989)

Dr P.O. Uyanwah, Unit of Analytical Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (18 September–8 October 1987)

Dr P. Viladiu, Unit of Field and Intervention Studies, Fellowship from the International Cancer Research Technology Transfer Programme (3–28 April 1989)

Professor F. de Waard, Unit of Analytical Epidemiology (19–30 June 1988 and 6–16 March 1989)

Dr H.R. Wabinga, Unit of Descriptive Epidemiology, Fellowship from the International Cancer Research Technology Transfer Programme (June 1989)

Dr A.M. Walker, Unit of Analytical Epidemiology (4–15 July 1988 and 23–27 January 1989)

Dr Q. Wang, Unit of Mechanisms of Carcinogenesis, Fellowship from the Fondation Marcel Mérieux and from the Association pour la Recherche sur le Cancer

Dr P. Wutzler, Unit of Mechanisms of Carcinogenesis (26 October–4 November 1987)

Dr D.G. Zaridze, Unit of Analytical Epidemiology (3–10 April 1988 and 7–21 December 1988)

Dr W. Zatonski, Unit of Analytical Epidemiology (4–15 September 1988)

Dr Zhang Zuo-Feng, Unit of Descriptive Epidemiology, IARC Research Training Fellowship (from 15 September 1987)

Dr S.-Y. Zhao, Unit of Analytical Epidemiology, Fellowship from the Association pour la Recherche sur le Cancer (from 1 September 1988)

Trainees

Dr M.-L. Aitio, Unit of Environmental Carcinogens and Host Factors (4 January 1988–30 June 1989)

Dr D. Assouline, Unit of Mechanisms of Carcinogenesis (from 1 November 1988)

Ms D. Battistuta, Unit of Biostatistics Research and Informatics (16 May–13 July 1989)

Mr D. Benyamine, Unit of Analytical Epidemiology (2 November 1987–1 May 1988)

Mr O. Bertrand, Unit of Mechanisms of Carcinogenesis (from 10 October 1988)

Mr M. Billaud, Unit of Mechanisms of Carcinogenesis (supported by Association pour la Recherche sur le Cancer and Fondation Marcel Mérieux)

Dr R. Black, Unit of Analytical Epidemiology (13 March–12 May 1989)

Ms H. Brune, Unit of Analytical Epidemiology (from 1 June 1989)

Mr A. Calender, Unit of Mechanisms of Carcinogenesis (Special Training Award from 1 June 1985)

Dr S. Calmels-Rouffet, Unit of Environmental Carcinogens and Host Factors (supported by the Ligue Nationale Française contre le Cancer to 30 June 1988 and Special Training Award from 1 July 1988)

Dr A. Chalkias, Unit of Field and Intervention Studies (1 February 1988–15 February 1989)

Dr M.O. Charbaut-Lagarde, Unit of Analytical Epidemiology (2 November 1987–20 June 1988)

Mrs F. Ciroussel, Unit of Environmental Carcinogens and Host Factors (Special Training Award from 1 November 1988)

Miss B. Colson, Unit of Biostatistics Research and Informatics (16 May–12 August 1988)

Miss M. Cordier, Unit of Mechanisms of Carcinogenesis (supported by the Ligue Nationale Française contre le Cancer and Fellowship from the Association pour la Recherche sur le Cancer)

Mr P. Crooks, Unit of Biostatistics Research and Informatics (16 May–14 August 1989)

Miss S. Daniel, Unit of Mechanisms of Carcinogenesis (1 March–30 June 1988)

Ms P.C.M. de Jong, Unit of Analytical Epidemiology (1 January–1 November 1988)

Dr H.J. Délécluse, Unit of Mechanisms of Carcinogenesis (from June 1988)

Ms M. Delgado, Unit of Mechanisms of Carcinogenesis (30 May–30 June 1988)

Miss B. Fischer, Unit of Descriptive Epidemiology (Special Training Award, September–December 1987, April 1988–March 1989)

Miss C. Galiana, Unit of Mechanisms of Carcinogenesis (Special Training Award from 1 September 1987)

Dr D. Gardiman, Unit of Analytical Epidemiology (23 January–21 April 1989)

Ms E. Gendre, Unit of Analytical Epidemiology (from 12 June 1989)

Miss S. Giraud, Unit of Mechanisms of Carcinogenesis (3 April–5 May 1989)

Miss L. Giroldi, Unit of Mechanisms of Carcinogenesis (supported by the Association pour la Recherche sur le Cancer, 1 July 1988–30 June 1989)

Mrs E. Hamel, Unit of Mechanisms of Carcinogenesis (supported by Institut Mérieux until December 1987, then IARC Special Training Award until 30 June 1988)

Dr M. Hertog, Unit of Analytical Epidemiology (1 February–31 May 1989)

Dr I.I. Huon, Unit of Mechanisms of Carcinogenesis (20 March–21 April 1989)

Ms B. Inçaurgarat, Unit of Environmental Carcinogens and Host Factors (Special Training Award from 5 September 1988)

Ms B. Jamot, Unit of Mechanisms of Carcinogenesis (from June 1989)

Mr R. Kaaks, Unit of Analytical Epidemiology (1 October 1988–31 March 1989)

Miss M. Klaude, Unit of Environmental Carcinogens and Host Factors (Special Training Award from 14 February 1989)

Mr J.L. Klein, Unit of Mechanisms of Carcinogenesis (supported by Fondation Marcel Mérieux (GERP) from 1 October 1988)

Miss U. Kliebsch, Unit of Analytical Epidemiology (1 March–31 July 1988)

Miss A. Lacroix, Unit of Analytical Epidemiology (14–18 March 1988)

Dr C. Lasset, Unit of Biostatistics Research and Informatics (2 October 1988–12 May 1989)

Miss V. Levy, Unit of Biostatistics Research and Informatics (18 May–18 August 1987)

Dr M. Maillet-Vioud, Unit of Mechanisms of Carcinogenesis (from 1 November 1988)

Mrs V. Maru, Unit of Environmental Carcinogens and Host Factors (Special Training Award to 31 August 1988)

Mr C. McConkey, Unit of Biostatistics Research and Informatics (21–29 September 1987)

Mr M. Mesnil, Unit of Mechanisms of Carcinogenesis (supported by the Association pour la Recherche sur le Cancer)

Miss A. Munnia, Unit of Mechanisms of Carcinogenesis (28 March–22 April 1988)

Miss C. Nabet, Unit of Mechanisms of Carcinogenesis (10–28 August 1987)

Dr M. Peluso, Unit of Environmental Carcinogens and Host Factors (Special Training Award, 1 February 1988–31 January 1989)

Mr C. Pépin, Unit of Descriptive Epidemiology (Special Training Award, March–May 1989)

Ms V. Prévost, Unit of Environmental Carcinogens and Host Factors (Special Training Award, 5 January–31 December 1988)

Mr J. Ricketts, Unit of Biostatistics Research and Informatics (21–29 September 1987)

Miss A. Salvetti, Unit of Mechanisms of Carcinogenesis (1 July–30 August 1988)

Dr S. de Sanjosé Llongueras, Unit of Field and Intervention Studies (from 16 January 1989)

Ms I. Schuffenecker, Unit of Mechanisms of Carcinogenesis (from June 1988)

Miss H. Schunk, Unit of Environmental Carcinogens and Host Factors (Special Training Award from 2 May 1989)

Ms N. Slimani, Unit of Analytical Epidemiology (from 13 March 1989)

Dr H. Sobol, Unit of Mechanisms of Carcinogenesis

Miss A. Stiggelbout, Unit of Analytical Epidemiology (1 October 1987–31 January 1988), and Unit of Field and Intervention Studies (from January 1988)

Miss A. Stolwyk, Unit of Analytical Epidemiology (4 May–15 September 1988)

Miss S. Teuchmann, Unit of Field and Intervention Studies (until 31 August 1987)

Miss A. Thiollier, Unit of Mechanisms of Carcinogenesis (14–18 March 1988)

Dr A. Vannieuwenhuyze, Unit of Mechanisms of Carcinogenesis (14–25 November 1988)

Ms J. Zeihsel, Unit of Biostatistics Research and Informatics (16 August–28 October 1988)

Annex 5

RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS
1 July 1987–30 June 1989

Cancer registries

DEB/73/16	International Association of Cancer Registries (Provision of a secretariat and other supporting services)
DEB/85/09	Osaka Cancer Registry, Department of Field Research, Center for Adult Diseases, Osaka, Japan (Improvement of Death Certificate Only (DCO) and Histologically Verified (HV) indices in Japan)
DEB/85/32	Ministry of Health, Harare (Cancer Registry of Harare)
DEB/85/41	Department of Anatomo-pathology, Faculty of Medicine, University of Rwanda, Butare (Establishment of a cancer registry)
DEB/85/42	Ministry of Health, Suva (Provision of a cancer registry service for the Fiji Islands)
DEP/87/02	National Institute of Public Health, Bamako (Cancer Registry of Mali)
DEP/87/01	Hanoi Cancer Institute, Hanoi (Establishment of a cancer registry for the Hanoi area)
DEP/87/04	Srinagarind Hospital, Faculty of Medicine, Khon Kaen, Thailand (Population-based cancer registry of Khon Kaen Province)
DEP/87/06	National Cancer Institue, Bangkok (Development of population-based cancer registration in Thailand)
DEP/87/07	College of Medicine, University of the Philippines, Manila (Preparation of training manuals for registry personnel in developing countries)
DEP/87/09	La Paz Cancer Registry, Oncological Society of Bolivia, La Paz (La Paz Cancer Registry)
DEP/88/02	Chiang Mai Cancer Registry, Faculty of Medicine, Chiang Mai, Thailand (Chiang Mai Cancer Registry)
DEP/88/04	Faculty of Health Sciences, Cotonou (Pilot study with a view to creating a cancer registry for Benin)

DEP/88/05	Cancer Registry of Tanzania, Pathology Department, Muhimbili Medical Centre, University of Dar-es-Salaam (Cancer Registry of Tanzania)
DEP/89/02	Cancer Registry, Department of Pathology, National University, Asuncion (Cancer Registry of Asuncion)
DEP/89/03	National Cancer Registry of Cuba, National Cancer Institute, Havana (National Cancer Registry of Cuba)
DEP/89/04	Kampala Cancer Registry, Department of Pathology, Makerere University Medical School, Kampala, Uganda (Kampala Cancer Registry)

Collaborating centres

DEB/74/03	Institute for Documentation, Information and Statistics, German Cancer Research Centre, Heidelberg, FR Germany (Clearing-house for on-going research in cancer epidemiology)
AEP/87/01	Royal Free Hospital, School of Medicine, University of London, London (Controlled therapeutic trials in cancer)
AEP/87/05	Research Group in Morbid Anatomy, University of Trieste, Italy (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 (To explore the feasibility of conducting case-control studies in Beijing, within the SEARCH programme of the IARC)

Incidence studies

DEB/85/37	All-Union Cancer Research Centre of the USSR, Academy of Medical Sciences, Moscow (Descriptive epidemiology of cancer in the USSR)
DEP/87/03	Honorary Commission against Tuberculosis, Ministry of Public Health, Montevideo (Cancer risk in migrants to Uruguay)
DEP/87/05	Israel Center for Registration of Cancer and Allied Diseases, Jerusalem, Israel (Cancer risk in second generation migrants to Israel)
DEP/87/10	Cancer Registry of São Paulo, Institute of Public Health, University of São Paulo, Brazil (Cancer risk in European migrants to the State of São Paulo)
DEP/88/03	Foundation Doctor Pedro Belou, Faculty of Medical Sciences, National University, La Plata, Argentina (Cancer risk in migrants to Buenos Aires Province)

DEP/89/07	New South Wales Central Cancer Registry, Macquarie Hospital, North Ryde, Australia (Study on Italian migrants)

Second cancers and DNA damage following chemotherapy

DEB/85/35	Department of Epidemiology, London School of Hygiene and Tropical Medicine, London (Case-control studies of second malignancies in relation to cytotoxic therapy)
BRI/87/02	Department of Radiation Physics, University of Texas Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, TX, USA (Radiation dosimetry for cases and controls enrolled in the IARC international study of second malignancies in relation to cytotoxic therapy)
BRI/87/03	Cancer Institute of the Netherlands, Amsterdam (Case-control study of second leukaemia and myelodysplasia after Hodgkin's disease)
BRI/87/04	Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada (Case-control studies of second malignancies in relation to cytotoxicity therapy)
BRI/87/05	Gustave Roussy Institute, Villejuif, France (Case-control study of second leukaemia and lung cancer after Hodgkin's disease)
BRI/89/01	Academic Hospital, Groeningen, The Netherlands (Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients)
BRI/89/02	Antoni Van Leeuwenhoek Institute, Amsterdam (Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients)
BRI/89/03	Rotterdam Cancer Institute, Rotterdam, The Netherlands (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 (Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients)
BRI/89/05	Gartnavel General Hospital, Glasgow, United Kingdom (Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients)
BRI/89/06	Cookridge Hospital, Leeds, United Kingdom (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 (Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients)

Studies on breast cancer

DEB/86/10	Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, USA (Breast cancer and hormonal profile in Chinese and Chinese-American women)
DEB/86/11	Department of Medical Statistics and Epidemiology, Sun Yat Sen University of Medical Sciences, Guangzhou, PR China (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 (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)
AEP/88/03	Institute of Pathology, University of Trieste, Italy (Collaborative study to investigate the fatty acid composition of subcutaneous adipose tissue of the breast in cases of breast cancer, in benign breast tumours, and in controls)

Studies on cervical cancer

DEB/85/14	Hospital Santa Caterina, Gerona, Spain (Pilot study on risk factors for cervical cancer)
DEB/85/15	Cancer Registry of Zaragoza, Zaragoza, Spain (Pilot study on risk factors for cervical cancer)
DEB/85/16	Department of Preventive and Social Medicine, University of Seville, Spain (Pilot study on risk factors for cervical cancer)
DEB/85/17	Foundation for Higher Education, Cali, Colombia (Pilot study on risk factors for cervical cancer)
DEB/86/06	Department of Health and Social Security, Vitoria, Spain (Case-control study on risk factors for cervical cancer)
DEB/86/07	Cancer Registry of Murcia, Regional Health Authority, Murcia, Spain (Case-control study on risk factors for cervical cancer)
DEB/86/08	Cancer Registry of Pamplona, Institute of Public Health, Pamplona, Spain (Case-control study on risk factors for cervical cancer)
DEB/86/09	Department of Epidemiology, Institute of Social Welfare, Salamanca, Spain (Case-control study on risk factors for cervical cancer)

FIS/87/02	Department of Pathology, University of Aberdeen, Scotland, United Kingdom (Human papilloma virus (HPV) and cervical cancer studies: in-situ hybridization test)
FIS/87/06	Danish Cancer Registry, Institute of Cancer Epidemiology, Copenhagen (Evidence of human papilloma virus infection in the etiology of cancer of the cervix uteri)
FIS/88/01	Department of Immunology and Infectious Diseases, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA (Human papilloma virus (HPV) and cervical cancer: analysis of specimens for HPV–DNA)
DEB/89/06	College of Medicine, University of the Philippines, Manila (Pilot case-control study on cervix cancer in Rizal Province)
FIS/89/01	Laboratory of Immunology and Bacteriology, University Hospital, Amiens, France (Detection of antibodies to chlamydia for the study of cervical cancer in Colombia and Spain)
FIS/89/02	Department of Social Medicine, Faculty of Medicine, Federal University of Pelotas, Brazil (International biological study on cervical cancer)
FIS/89/03	Cancer Registry, Department of Pathology, National University, Asuncion, Paraguay (International biological study on cervical cancer)
FIS/89/04	Department of Pathology, School of Medicine, University of Athens (International biological study on cervical cancer)
FIS/89/05	Faculty of Health Sciences, Cotonou, Benin (International biological study on cervical cancer)
FIS/89/06	National Institute of Public Health, Bamako, Mali (International biological study on cervical cancer)
FIS/89/07	Department of Oncology, Regional Hospital, Ministry of Health, Conception, Chile (International biological study on cervical cancer)
FIS/89/08	National Cancer Institute, Havana, Cuba (International biological study on cervical cancer)

Studies on cancers linked with herpesviruses

DEC/83/09	Laboratoire de Cytogénétique, Centre de Transfusion Sanguine, St Etienne, France (Characterization of cytogenetic anomalies observed in Burkitt-type lymphoma cells)

MCA/87/01	Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow (Prevalence of anti-HTLV-I antibodies in the population of the USSR from different geographic areas)

Studies on cancers of the larynx and hypopharynx

DEP/87/11	Cancer Registry of São Paulo, Institute of Public Health, University of São Paulo, Brazil (Collaborative study of the descriptive epidemiology of the subsite distribution of cancers of the larynx and hypopharynx)
DEP/87/13	Birmingham and West Midlands Regional Cancer Registry, Queen Elizabeth Medical Centre, Birmingham, United Kingdom (Collaborative study of the descriptive epidemiology of the subsite distribution of cancers of the larynx and hypopharynx)
DEP/88/01	Bombay Cancer Registry, Indian Cancer Society, Bombay, India (Collaborative study of the descriptive epidemiology of the subsite distribution of cancers of the larynx and hypopharynx)

Studies on liver cancer

DEB/86/12	National Cancer Institute, Bangkok (Study of etiological factors for liver cancer in Thailand)
DIR/86/01	Medical Research Council, London (Gambia Hepatitis Intervention Study)
FIS/87/01	National Cancer Institute, Bangkok (Cohort study of HBsAg carriers in Bangkok)
FIS/88/02	Institute of Oncology, University of Padua, Italy (Natural history of human retrovirus infections in the Gambia)
FIS/88/03	Division of Gastroenterology, Hospital San Giovanni Battista, Turin, Italy (Causes of non-response to hepatitis B vaccine)
FIS/88/04	Department of Clinical Immunology, University of Rome, Rome (Causes of non-response to hepatitis B vaccine)
FIS/88/05	Department of Social Medicine and Public Health, University of Singapore, Singapore (Cohort study on hepatitis B carriers and liver cancer)
FIS/89/09	Mount Holyoke College, South Hadley, Massachusetts, USA (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 (Aflatoxin exposure and its interaction with other associated factors in the etiology of liver cancer in Zimbabwe)
MCA/89/03	Institut für Toxikologie, Universität Würzburg, FR Germany (Development, validation and evaluation of methods to detect aflatoxin-protein adducts for monitoring human exposure to aflatoxins)

Studies on malignant melanoma

DEP/87/08	Cancer Registry, Department of Pathology, National University, Asuncion (Case-control study of etiological factors of plantar melanoma in Paraguay)

Studies on nutrition and on cancer of the gastrointestinal tract

DEB/84/01	Singapore Cancer Registry, Department of Pathology, University of Singapore, Singapore (Development of methodology for the conduct of diet-directed case-control studies in Singapore)
DEB/85/05	Department of Clinical Chemistry, University Hospital, University of Lund, Sweden (Chemical stability of nutrients in body fluids)
DEB/85/36	Medical Clinic for Gastroenterology, University Clinical Centre, Ljubljana, Yugoslavia (Precancerous lesions of the stomach in Slovenia)
DEB/85/44	Department of Pathology, Faculty of Medicine, National University, Montevideo (Case-control study of oesophageal cancer in Uruguay)
DEB/85/45	Faculty of Medicine, National University, La Plata, Argentina (Case-control study on oesophageal cancer in La Plata, Argentina)
DEB/86/13	Study Group on Colorectal Cancer, Academy of Medical Sciences of Catalonia and Baleares, Majorca, Spain (Case-control study of colorectal cancer in Majorca)
ECH/87/02	Institut Pasteur, Lyon, France (Analysis of gastric bacterial flora in patients with precancerous lesions of the stomach)
ECH/87/03	M. Curie–Sklodowska Institute of Oncology, Warsaw, Poland (Study on the nutritional status and urinary excretion of *N*-nitroso compounds and alkylpurines in high- and low-risk subjects for stomach cancer in Poland)
ECH/87/08	Institute of Virology, Chinese Academy of Preventive Medicine, Beijing, PR China (Study on urinary excretion of *N*-nitoso compounds and alkylpurines in high- and low-risk subjects for nasopharyngeal carcinoma in China)
ECH/88/03	Nagoya City University Medical School, Nagoya, Japan (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)
FIS/87/03	University of Costa Rica, Costa Rica (Stomach cancer in Costa Rica)

FIS/87/04	Department of Social Medicine, Faculty of Medicine, Federal University of Pelotas, Brazil (Validation of the information on the temperature of maté drinking)
FIS/87/05	Cancer Registry, Department of Pathology, National University, Asuncion (Case-control study on oesophageal cancer in Paraguay)
BRI/87/06	Digestive Tract Tumour Registry of the 'Côte-d'Or', Dijon, France (Case-control study of polyps and cancer of the large bowel)
AEP/88/02	Department of Epidemiology and Statistics, Hospital San Jaume i Santa Magdalena, Mataro, Spain (Case-control study on stomach cancer and diet)
AEP/89/01	Rowett Research Institute, Aberdeen, United Kingdom (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 (Planning phase of a project on prospective studies on diet and cancer)
AEP/89/03	Unit of Epidemiology, National Institute for the Study and Treatment of Cancer, Milan, Italy (Planning phase of a project on prospective studies on diet and cancer)
AEP/89/04	Gustave Roussy Institute, Villejuif, France (Planning phase of a project on prospective studies on diet and cancer)
AEP/89/05	Institute of Anatomy, University of Turin, Italy (Planning phase of a project on prospective studies on diet and cancer)
DEP/89/05	Cancer Control Centre, San Cristobal, Venezuela (Case-control study to investigate the effect of screening by X-ray examination in preventing death from gastric cancer)
ECH/89/02	Beijing Institute for Cancer Research, PR China (Interrelationships between total *N*-nitroso compounds in gastric juice, genotoxicity and severity of precancerous lesions of the stomach)
ECH/89/04	Institute of Medical Science, University of Tokyo, Japan (Study on evaluation of vicine/divicine as a possible glandular stomach carcinogen in short-term *in vivo* assays)

Studies on occupational cancer

DEB/85/50	National Cancer Registry, Central Institute for Cancer Research, Berlin (Epidemiological study of silica-exposed state quarry workers in the German Democratic Republic)

DIR/87/02	Department of Biomedical Science and Human Oncology, University of Turin, Italy (Study on early lesions produced by low environmental exposures [passive smoking and pollution] and by low levels of occupational exposures)
AEP/89/06	Wellington School of Medicine, Wellington Hospital, University of Otago, Wellington, New Zealand (International register of persons exposed to phenoxy acid herbicides and contaminants)

Studies on the effects of passive smoking

AEP/87/02	Department of Epidemiology and Statistics, Hospital San Jaume 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 (International collaborative study on lung cancer in non-smokers)
AEP/87/04	Maria Sklodowska-Curie Memorial Centre, Institute of Oncology, Warsaw (International collaborative study on lung cancer in non-smokers)
AEP/88/04	Red Cross Blood Bank Foundation, Eindhoven, The Netherlands (Collaborative study to evaluate the validity of self-reported past exposure to passive smoking)

Studies on chemical carcinogenesis

DEC/79/06	Institute of Medical Sciences, University of Tokyo (Mutagenesis and neoplastic transformation *in vitro* of cultured cells by environmental chemicals)
DEC/79/10	Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow (Investigation on 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 (Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines)
DEC/81/03	Institute for Cell Biology, University of Essen, FR Germany (Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines)
DEC/81/08	Institute of Experimental and Clinical Medicine, Tallinn, Estonian SSR, USSR (Studies in the mutagenic and carcinogenic activities of fly ashes originating from the combustion of shale-oil)
DEC/81/09	Oncological Institute of the Ministry of Health, Ministry of Health of Lithuanian SSR, Vilnius, Lithuanian SSR, USSR (Long-term carcinogenicity testing of environmental chemicals)

DEC/81/35	National Institute of Hygiene, Budapest (Long-term carcinogenicity testing of environmental chemicals)
DEC/82/01	Life Science Laboratory, Teesside Polytechnic, Cleveland, United Kingdom (Study on carcinogenic effects in the offspring of male Swiss mice treated with MNU or ENU before mating)
DEC/82/06	School of Pharmacy, Catholic University of Louvain, Brussels (Study on the promoting activity of diazepam and related compounds)
DEC/82/22	Joint Mass Spectrometry Centre, Claude Bernard University, Lyon, France (Study on the development of methods of analysis of carcinogens by combined high-performance liquid chromatography-mass spectrometry)
DEC/83/01	Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, United Kingdom (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/83/03	Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, United Kingdom (Studies on analgesic-associated renal pelvic and ureteral/urothelial hyperplasia and carcinoma)
DEC/83/10	Cancer Research Unit, University of York, United Kingdom (Detection of aflatoxin B_1 and metabolites by immunoassay in human biological materials)
DEC/83/11	Institute of Oncology, Medical Academy, Sofia (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/84/04	Institute of Pathology, Semmelweis Medical University, Budapest (Study of the capacity of UV light to induce DNA repair processes in human cells)
DEC/84/05	Laboratory of Pathology, N.N. Petrov Research Institute of Oncology, Leningrad, USSR (Early alterations in the kinetics of cell populations in the mucosa of rat intestine following administration of 1,2-dimethylhydrazine)
DEC/85/02	Department of Pathology, Nagoya City University Medical School, Nagoya, Japan (Testing of environmental chemicals in the rat-liver two-stage model)
DEC/85/06	N.N. Petrov Research Institute of Oncology, Leningrad, USSR (Study on O^6-alkylguanine-DNA methyltransferase activities in human tissues)

DEC/85/07	N.N. Petrov Research Institue of Oncology, Leningrad, USSR (Study on tumour promotion in offspring of carcinogen-treated male mice)
DEC/86/04	Hazleton IFT, Les Oncins, St Germain sur l'Arbresle, France (Microcapsule trapping in primates of carcinogens from human food metabolites)
DEC/86/05	Rijks Instituut voor de Volksgezondhert, Bilthoven, The Netherlands (Long-term carcinogenicity testing of environmental chemicals)
DEC/86/06	Faculty of Medicine, Chinese University of Hong Kong, Hong Kong (Detection of transforming genes in human oesophageal cancer cells growing in nude mice)
CIE/86/07	Laboratory of Carcinogenic Substances, Oncological Research Centre, Moscow (Role of prezygotic events in increasing cancer risk in subsequent generations)
ECH/87/01	Département de Médecine du Travail et d'Hygiène du Milieu, Université de Montréal, Montréal, Québec, Canada (Study on thioethers as indicators of exposure to mutagenic and carcinogenic products)
ECH/89/04	Cancer Research Institute, Tata Memorial Centre, Bombay, India (Study on DNA-damage as marker of exposure to betel quid/tobacco)
ECH/87/05	Department of Pharmacology, University of Oulu, Finland (Evaluation of warfarin/carcinogen metabolism in man)
ECH/87/06	Laboratoire de Microbiologie, Faculté de Pharmacie, Marseille, France (Studies of methods for degradation of chemical carcinogens)
ECH/87/07	MRC Toxicology Unit, Carshalton, United Kingdom (Characterization and analysis of alkylpurines in urine by mass spectrometry)
ECH/88/02	Institute of Occupational Health, Helsinki (Cigarette smoking and asbestos exposure as determinants of individual susceptibility to lung cancer)
ECH/88/04	Department of Organic Chemistry, University of Newcastle-upon-Tyne, United Kingdom (Nucleotide modifications in recoverable microcapsules)
ECH/89/01	N.N. Petrov Institute of Oncology, Leningrad, USSR (Urinary excretion of 3-methyladenine in NMU-treated patients: correlations with DNA methylation)
ECH/89/03	MRC Toxicology Unit, Carshalton, United Kingdom (Characterization and analysis of alkylpurines in urine by mass spectrometry)

ECH/89/05	School of Dentistry, University of Khartoum, Sudan (Identification of carcinogenic agents in tomback in the Sudan)
MCA/87/02	Hepatitis Laboratory, INSERM U 271, Lyon, France (Interactions between chronic infection by duck hepatitis B virus and consumption of aflatoxins in the etiology of hepatocarcinoma)
MCA/88/01	Department of Pathology, Sapporo Medical College, Sapporo, Japan (Molecular and cellular mechanisms of cultured liver cell transformation)
MCA/88/02	Human Molecular Genetics Laboratory, Imperial Cancer Research Fund Laboratories, London (Study of the human X-chromosome by the irradiation and fusion gene transfer method)
MCA/89/01	Institute of Pathology and Experimental Cancer Research, Semmelweis Medical University, Budapest (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 Manuel Quintala', Montevideo, Uruguay (Molecular epidemiology of oesophageal cancer — detection of *ras* oncogene mutations)
MCA/89/05	Life Science Laboratory, Teeside Polytechnic, Cleveland, United Kingdom (Carcinogenic effects in the offspring of male Swiss mice treated with NMU or ENU before mating)

Annex 6

MEETINGS AND WORKSHOPS ORGANIZED BY IARC
July 1987–June 1989

Meeting of the International Association of Cancer Registries	Copenhagen, 5–7 August 1987
Course on cancer epidemiology (in collaboration with PAHO and the National Cancer Institute, Asunción)	Asunción, Paraguay 7–12 August 1987
Review Board for the Manual on Environmental Carcinogens — Selected Methods of Analysis: Biological Monitoring	Helsinki, 1 September 1987
International conference on detection methods for DNA-damaging agents in man: applications in cancer epidemiology and prevention	Espoo, Finland 2–4 September 1987
International symposium on mineral fibres in the non-occupational environment (in collaboration with the French Ministry of the Environment, the Commission of the European Communities, the International Programme on Chemical Safety and the World Health Organization Regional Office for Europe)	Lyon, 8–10 September 1987
Postgraduate course on the role of viruses in human cancer: epidemiology and basic mechanisms (in conjunction with the European School of Oncology, Milan, Italy)	Lyon, 15–18 September 1987
Course on cancer epidemiology (in collaboration with the Institute of Public Health, Navarra)	Pamplona, Spain 28 September–9 October 1987
IARC Monographs Working Group on alcohol and alcoholic beverages	Lyon, 13–20 October 1987
Meeting on lung cancer in non-smokers	Lyon, 29–30 October 1987
Second meeting of the IARC collaborative group on the European vinyl chloride multicentric cohort study	Lyon, 6 November 1987
Family breast cancer meeting	Lyon, 9–10 November 1987
DNA damage and second cancer risk following chemotherapy	Lyon, 7–8 December 1987
Meeting of collaborators in the SEARCH study on breast and colorectal cancer	Lyon, 11 December 1987
Editorial Board meeting for *Cancer Registration and its Techniques: Principles and Methods*	Lyon, 16–17 December 1987

3rd Steering Committee & Peer Review Meetings. The Gambia Hepatitis Intervention Study	Lyon, 13–14 January 1988
IARC Scientific Council	Lyon, 19–21 January 1988
EBV meeting	Lyon, 22–23 February 1988
Workshop on human papilloma virus infection in the etiology of cancer of the cervix uteri (in collaboration with the Danish Cancer Registry)	Copenhagen, 1–3 March 1988
IARC Monograph Working Group on occupational exposures in petroleum refining, crude oil and major petroleum fuels	Lyon, 1–8 March 1988
SEARCH Working Group on epidemiological analysis of nutritional data	Lyon, 7–9 March 1988
Working Group on potential carcinogenic risk from exposure to styrene	Lyon, 10–11 March 1988
Childhood leukaemia in Europe following the Chernobyl accident	Cambridge, UK 28 March 1988
Chemotherapy collective group meeting	Cambridge, UK 29–31 March 1988
Working Group on the historical cohort study of welders in Europe	Lyon, 14–15 April 1988
IARC Governing Council	Lyon, 28–29 April 1988
Meeting on electromagnetic fields and cancer risks	Lyon, 2–3 May 1988
IARC Fellowships Selection Committee	Lyon, 3–4 May 1988
Working Group on larynx cancer	Pamplona, Spain 11 May 1988
Course on cancer epidemiology (in collaboration with the WHO Regional Office for Europe and the All-Union Cancer Research Centre, Moscow)	Moscow, 11–21 May 1988
International symposium on perinatal and multigeneration carcinogenesis	Leningrad, USSR 31 May–June 1988
Cancer risk among workers in the nuclear industry	Lyon, 7–10 June 1988
IARC Monographs Working Group on engine exhausts and some nitroarenes	Lyon, 14–21 June 1988
European Educational Programme in Epidemiology: Residential summer course	Florence, Italy 27 June–15 July 1988
Meeting on the Israel migrants study	Lyon, 4–7 July 1988
Course on molecular biology for epidemiologists	Oslo, 2–12 August 1988
Workshop on evaluation of primary prevention programmes (in collaboration with UICC)	Reykjavik, 21–23 September 1988
Meeting on cancer risk in children infected by HIV through maternal transmission	Lyon, 27 September 1988
Meeting of collaborators in the international study on lung cancer in nonsmokers	Lyon, 4–6 October 1988

Course on epidemiology	Medellin, Colombia 10–22 October 1988
IARC Monograph Working Group on some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting	Lyon, 18–25 October 1988
Meeting on the case-control studies of second cancers	Padua, Italy 21–22 October 1988
Working Group on welding fumes	Lyon, 7–8 November 1988
Meeting of Spanish collaborators in cervical cancer case-control study	San Sebastian, Spain 7–8 November 1988
Meeting of the International Association of Cancer Registries	Melbourne, Australia 15–17 November 1988
Protocol Sub-committee meeting for cancer risk among nuclear workers	Toronto, Canada 16–17 November 1988
Programme Committee meeting for the tenth international meeting on *N*-nitroso compounds, mycotoxins and tobacco smoke: relevance to human cancer	Lyon, 21–22 November 1988
IARC *ad-hoc* Working Group on the evaluation of the carcinogenicity of mixtures and groups of chemicals	Lyon, 29 November– 1 December 1988
Meeting of collaborators in the SEARCH study of malignant melanoma	Lyon, 2 December 1988
Working Group on vinyl chloride	Lyon, 12–13 December 1988
Course on design and analysis of long-term animal experiments	Lyon, 12–16 December 1988
Meeting to discuss planning for a prospective study on diet and cancer in Italy and Spain	Lyon, 13–14 December 1988
Meeting of collaborators in the SEARCH study on cancers of the breast and colorectum in the European Community	Lyon, 14–16 December 1988
IARC Scientific Council	Lyon, 9–12 January 1989
Meeting on the international study of cancer risk in biology research laboratory workers	Lyon, 16–17 January 1989
Course on detection of health hazards in human populations exposed to chemical mutagens and carcinogens	Mexico City 16–27 January 1989
4th Steering Committee & Peer Review Meetings. The Gambia Hepatitis Intervention Study	Fajara, The Gambia 30–31 January 1989
Meeting of collaborators in the SEARCH studies on brain tumours in children and on brain tumours in adults	Lyon, 31 January–3 February 1989

Working Group of collaborators in the IARC international study on man-made mineral fibres	Lyon, 20 February 1989
IARC Monograph Working Group on some flame retardants and textile chemicals, and exposures in the textile manufacturing industry	Lyon, 21–28 February 1989
Meeting of collaborators in the multicentric case-control study of male breast cancer	Lyon, 2–3 March 1989
Editorial Board meeting for the evaluation of primary prevention programmes	Lyon, 7–8 March 1989
Meeting to discuss plans for prospective studies on diet and cancer in Europe	Lyon, 20–22 March 1989
Working Group on styrene	Lyon, 30–31 March 1989
Meeting of collaborators in the SEARCH study on nasal cancer	Ottawa, 30–31 March 1989
Meeting of collaborators in the SEARCH study on cancers of pancreas, gallbladder and bile duct	Lyon, 4–7 April 1989
IARC *ad-hoc* Working Group to review priorities for IARC Monographs	Lyon, 4–6 April 1989
Dosimetry Sub-committee meeting for cancer risk among nuclear workers	Lyon, 24–25 April 1989
Meeting on survival	Vevey, Switzerland 3 May 1989
IARC Governing Council	Lyon, 4–5 May 1989
Working Group on evaluation of job exposure matrices for the vinyl chloride study	Lyon, 11 May 1989
Workshop on experimental and epidemiological applications to risk assessment of complex mixtures	Espoo, Finland 14–17 May 1989
Advisory Group on the use of cancer registry data for surveillance of HIV-related cancers	Lyon, 17 May 1989
Editorial Board meeting for *Cancer Incidence in Five Continents Vol. VI*	Lyon, 18–19 May 1989
Working Group to discuss dietary methods for prospective studies on diet and cancer in Europe	Lyon, 22–23 May 1989
International symposium on the role of autopsy in epidemiology, medical research and clinical practice	Trieste, Italy 1–3 June 1989
IARC Monograph Working Group on chromium, nickel and welding	Lyon, 6–13 June 1989
Working Group to prepare a protocol on sexually transmitted diseases and CIN in prostitutes	Lyon, 22–23 June 1989
Genetic effects in the offspring of cancer patients treated with radiation or chemotherapy	Lyon, 9–10 May 1989
Meeting on the epidemiology of melanoma and naevi	Lyon, 27–28 June 1989
Meeting of collaborators in the SEARCH study on malignant melanoma	Lyon, 29–30 June 1989

Annex 7

VISITORS TO IARC
1 July 1987–30 June 1989

A total of 1074 persons from 56 countries visited the Agency during the period under review. The following gave lectures:

Dr S. Aaronson, National Cancer Institute, Bethesda, MD, USA
Oncogenes, growth factors and human cancer

Dr B. Ames, University of California at Berkeley, USA
Ranking possible carcinogenic hazards

Professor J.M. Andrieu, Laennec Hospital, Paris
Tumeurs hématologiques en relation avec le virus HIV — premières données recueillies grâce au Registre français

Dr P. Band, Cancer Control Agency of British Columbia, Vancouver, Canada
The occupational studies at the Cancer Control Agency of British Columbia

Dr P. Beaune, Necker Hospital, Paris
Human liver cytochromes P450: isoenzymes and genes

Dr R.J. Biggar, Danish Cancer Registry, Copenhagen
Epidemiology of cancer related to AIDS

Dr W.J. Blot, National Cancer Institue, Bethesda, MD, USA
Field studies of cancer in China

Dr K.W. Bock, Institute of Toxicology, University of Tübingen, FR Germany
Toxicology in Tübingen — recent advances in drug metabolism and carcinogenesis

Dr D. Burkitt, Bussage, Stroud, UK
Potential prevention of some common cancers

Professor J. Cairns, Harvard University, Boston, MA, USA
The history of mortality

Dr J. Chen, Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine, Beijing, PR China
Diet and cancer mortality in China

Dr J.W. Coebergh, Childhood Leukaemia Study Group, Erasmus University, Rotterdam, The Netherlands
Future explorations of cancer control in The Netherlands, 1985–2000

Dr P. Correa, Louisiana State University Medical Center, New Orleans, LA, USA
Gastric cancer etiology revisited

Dr E. de la Peña de Torres, Council for Scientific Research, Madrid
Mutagenicity of pesticides: *Salmonella typhimurium* and sperm abnormalities

Dr C.A.M.J.L. De Meester, Université Catholique de Louvain, Belgium
Risk assessment of heterocyclic amines in heat-processed food as possible human carcinogens

Dr G. Dirheimer, Institut de Biologie Moléculaire et Cellulaire, Strasbourg, France
Mécanisme d'action de l'ochratoxine A

Dr S. Duffy, MRC Biostatistics Unit, Cambridge, UK
Reproductive factors and breast cancer in Scandinavia

Dr G. Eberle, Institute of Cell Biology, University of Essen, FR Germany
Development and application of monoclonal antibodies highly specific for carcinogen-induced alkylated DNA adducts

Dr F. Fagnani, Centre d'Etudes Nucléaires, Fontenay-aux-Roses, France
Relations dose-effet pour les faibles doses de radiation ionisante

Professor R. Flamant, Director, Institut Gustave Roussy, Villejuif, France
L'Institut Gustave Roussy, centre pilote contre le cancer

Dr H. Greenfield, University of New South Wales, Kensington, Australia
Methodological issues in the preparation and use of food composition tables

Dr C. Harris, National Cancer Institute, Bethesda, MD, USA
Molecular mechanisms of human lung carcinogenesis

Dr A. Haugen, National Institute of Occupational Health, Oslo
Genotoxic exposure and human health: biomonitoring of aluminium and coke oven workers

Professor C.F. Hollander, Merck, Sharp & Dohme–Chibret Laboratories, Riom, France
Safety assessment of drugs under development

Professor G.R. Howe, National Cancer Institute of Canada, Toronto, Canada
The use of record linkage techniques in cohort studies of nutrition and cancer

Dr E. Huberman, Argonne National Laboratory, Argonne, IL, USA
The role of protein kinase C and topoisomerase II in the induction of human HL-60 leukaemia cell differentiation

Dr B. Jordan, Centre d'Immunologie de Marseille-Lumigny, France
Cartographie physique du chromosome X par électrophorèse en champ pulsé

Dr F. Kadlubar, National Center for Toxicological Research, Jefferson, AR, USA
Assessment of exposure and individual susceptibility to aromatic amine carcinogens; and Metabolic phenotyping of human subjects for acetyltransferase and cytochrome P450: implications for bladder cancer risk following aromatic amine exposure

Dr T. Kakunaga, Research Institute for Microbial Diseases, Osaka, Japan
Molecular mechanisms of malignant cell transformation

Dr P. Karran, Imperial Cancer Research Fund, Potters Bar, Herts, UK
Epigenetic control of resistance to alkylating agents

Dr H. Kato, Radiation Effects Research Foundation, Hiroshima, Japan
Risk of cancer among A-bomb survivors and those exposed *in utero*

Dr K. Khazaie, European Molecular Biology Laboratory, Heidelberg
Transforming potential of the human EGF receptor

Dr V. Kobljakov, Cancer Research Centre, Moscow, USSR
Cytochrome P-450 in tumours

Dr M. Kogevinas, University College and Middlesex School of Medicine, London
Socio-economic status and cancer survival

Dr M. Krawczak, Institute for Human Genetics, Göttingen, FR Germany
The mapping of C–F gene

Dr E. Kriek, Netherlands Cancer Institute, Amsterdam
Polycyclic aromatic hydrocarbons in ambient air, benzo[*a*]pyrene-DNA adducts in lymphocytes and 1-hydroxypyrene in the urine of coke-oven workers. A combined study performed in The Netherlands during 1986–88

Dr T. Kuroki, Institute of Medical Sciences, Tokyo
Pleiotropic actions of a hormonally active form of vitamin D3 on cell differentiation, tumour promotion and gene expression

Dr J. Lafuma, Institut de Protection et de Sûreté Nucléaire, Centre d'Etudes Nucléaires de Fontenay-aux-Roses, France
Le risque nucléaire: épidémiologie, expérimentation, prévention

Dr R. Laib, University of Dortmund, FR Germany
Species difference in butadiene-induced carcinogenesis: inhalation pharmacokinetics and DNA adduct pattern in rats and mice

Professor R. Latarjet, Fondation Curie, Paris
Réflexions sur l'accident de Tchernobyl et ses conséquences

Dr M.S. Linet, National Cancer Institute, Bethesda, MD, USA
Benzene-induced leukaemia

Dr R.N. Loeppky, University of Missouri, Columbia, MO, USA
Bioactivation of β-oxidized nitrosamines — chemical and biochemical model

Dr D.G. Longfellow, National Cancer Institute, Bethesda, MD, USA
The Chemical and Physical Carcinogenesis Extramural Program, NCI

Professor R. MacLennan, Queensland Institute of Medical Research, Brisbane, Australia
Oral cancer in Papua New Guinea

Dr N. Marceau, Centre de Recherche en Cancérologie, Hôtel-Dieu de Québec, Québec, Canada
Bipotential features of fetal liver epithelial cells as assayed in primary culture

Dr K. McPherson, Oxford University, UK
Oral contraceptives and breast cancer

Dr C.A. Meanwell, Hoffman-La Roche, Basel, Switzerland
Longitudinal study of early cervical neoplasia and human papillomavirus

Dr B. Mechler, Institute of Genetics, Mainz, FR Germany
Neuroblastoma genes in *Drosophila:* hereditary suppression of tumour development by gene transfer

Dr F. Ménégoz, Registre du Cancer de l'Isère, Grenoble, France
L'Atlas du Cancer du Département de l'Isère: résultats pour 25 topographies; analyses par zone géographique

Professor L. Montagnier, Pasteur Institute, Paris
Rétrovirus et physiopathologie du SIDA

Dr M.A. Moore, Nagoya City University Medical School, Japan
Experimental investigations of interactions between liver fluke and carcinogenesis in the Syrian golden hamster

Dr M. Mori, Sapporo Medical School, Sapporo, Japan
Application of genetically mosaic animals to the study of hepatocarcinogenesis

Professor N.E. Morton, Cancer Research Campaign Research Group in Genetic Epidemiology, University of Southampton, UK
Genetic epidemiology in cancer

Dr O. Møller-Jensen, Danish Cancer Registry, Copenhagen
Recent results regarding the epidemiology of malignant melanoma from the Danish Cancer Registry

Dr L. Mullenders, State University of Leiden, The Netherlands
Heterogeneity of UV-induced repair in mammalian cells

Dr A.T. Natarajan, University of Leiden, The Netherlands
Techniques for population monitoring of exposure to mutagenic agents

Dr P. Ngendahayo, University of Rwanda, Butare, Rwanda
Preponderance of centroblastic lymphomas among Ugandan cases of non-Hodgkin's-non-Burkitt's lymphomas — sequelae of tropical malaria?

Dr S. Niu, Director, Institute of Environmental Health, Beijing, PR China
Indoor air pollution and lung cancer in China

Dr H. Ohgaki, National Cancer Center Research Institute, Tokyo
Differential proliferative response during MNNG-induced gastric carcinogenesis in rats with contrasting susceptibilities

Dr A.E. Pegg, Pennsylvania State University, Philadelphia, PA, USA
Recent studies on the regulation and specificity of mammalian O^6-alkyl-guanine-DNA-alkyltransferase

Dr R. Peto, Radcliffe Infirmary, Oxford, UK
Avoidance of premature death

Dr L. Philipson, European Molecular Biology Laboratory, Heidelberg, FR Germany
The negative regulation of cell growth

Dr L.A. Poirier, National Center for Toxicological Research, Jefferson, AR, USA
Physiological methyl donors in carcinogenesis

Dr M. Radman, Institut Jacques Monod, Paris
DNA mismatch repair in mutagenesis recombination and carcinogenesis

Dr F. Rippmann, German Cancer Research Centre, Heidelberg, FR Germany
Evidence for threshold doses for tumour promotion by quantitative dose-time-response relationships

Dr L. Rossi, National Cancer Institute, Genoa, Italy
Carcinogenic activity of murine sarcoma viruses in rodent embryos

Dr R.H.C. San, Vancouver, BC, Canada
Antigenotoxic activity of retinol and β-carotene

Dr R. Schmauz, University of Lübeck, FR Germany
Multiple infections in cases of cervical cancer from a high incidence area

Dr M. Schwab, German Cancer Research Centre, Heidelberg, FR Germany
Oncogene amplification in tumour progression

Dr Y. Shimizu, Radiation Effects Research Foundation, Hiroshima, Japan
Change in cancer risk coefficient with revised dose (DS–86) among A-bomb survivors

Dr Yu Shun Zhang, Shanghai Medical University, Shanghai, PR China
The cancer control programme in the People's Republic of China

Dr G.J. Smith, University of New South Wales, Kensington, NSW, Australia
Cell lines from normal mouse lung and urethane-induced lung adenoma: a model for molecular study of spontaneous and chemical transformation to malignancy

Dr T.F. Smith, Molecular Biology Computer Research Resource, DFCI, Boston, MA, USA
Estimating the 'age' of HIV

Dr C. Stiller, Childhood Cancer Research Group, Oxford, UK
Childhood cancer survival: variation by treatment centre

Dr P.D. Stolley, University of Pennsylvania, Philadelphia, PA, USA
Exogenous female hormones and human cancer: a summary of the epidemiologic evidence

Professor J. Sugar, National Institute of Oncology, Budapest
Studies on pathobiologic features of breast and gastrointestinal tumours

Dr T. Sugimura, National Cancer Center, Tokyo
Topics from collaborative studies between the Hospital and the National Cancer Center Institute

Professor F.W. Sunderman, University of Connecticut, Farmington, CT, USA
Metal binding to finger loop domain in proteins that regulate gene expression

Dr P. Tambourin, Centre Hospitalier Universitaire Cochin-Port Royal, Paris
Identification d'oncogènes par l'étude des leucémies expérimentales

Dr A. Tavitian, INSERM U.248, Paris
Genes, oncogenes and anti-oncogenes of the *ras*-super family

Dr D.C. Thomas, University of Southern California, Los Angeles, CA, USA
Models for predicting radiation risks in the BEIR V Report

Dr J. Torrado, Nuestra Señora de Aranzazu Hospital, San Sebastian, Spain
Blood group-related antigens in gastric cancer

Dr K. Toyoshima, Institute of Medical Sciences, University of Tokyo, Tokyo
Proto-oncogenes of the *src*-family in the protein-kinase superfamily

Dr L. Van't Veer, University Hospital, Leiden, The Netherlands
The role of oncogenes in human melanomas and ovarian cancer

Dr E.W. Vogel, University of Leiden, The Netherlands
Nucleophilic selectivity of carcinogens as a determinant of mutational response in excision repair defective strains in *Drosophila*

Professor I.B. Weinstein, Columbia University, New York, NY, USA
Molecular mechanisms of multistage carcinogenesis: implications with respect to cancer prevention and treatment

Dr A. Weston, National Cancer Institute, Bethesda, MD, USA
The development of new techniques for the determination of human cancer risk factors

Dr C.R. Wolf, Imperial Cancer Research Fund, Edinburgh, UK
Molecular genetic and functional analysis of the cytochrome P450 system

Dr C. Yang, University of New Jersey, Piscataway, NJ, USA
Cytochrome P450 IIE1: regulation and roles in nitrosamine metabolism

Annex 8

INTERNAL REPORTS

The series title was modified from 'Internal Technical Reports' to the shorter 'Internal Reports' in 1989.

IARC Internal Technical Report 88/001	Report of the Meeting on Cancer Risk Among Nuclear Industry Workers; Lyon June 9–10, 1988
IARC Internal Technical Report 88/002	Report of an IARC Working Group to review the approaches and processes used to evaluate the carcinogenicity of mixtures and groups of chemicals; Lyon, 29 Nov.–1 Dec. 1988
IARC Internal Report 89/001	CANREG — Cancer Registration Software for Microcomputers
IARC Internal Report 89/002	European Childhood Leukemia Incidence Study — Protocol
IARC Internal Report 89/003	Report of a Mortality and Cancer Incidence follow-up of an Historical Cohort of European Welders
IARC Internal Report 89/004	Chemicals, Groups of Chemicals, Mixtures and Exposure Circumstances to be evaluated in future *IARC Monographs* — Report of an ad hoc Working Group; Lyon, 4–7 April 1989
IARC Internal Report 89/005	Protocol — Combined Analysis of Cancer Mortality among Nuclear Industry Workers

Annex 9

PAPERS PUBLISHED BY IARC STAFF AND FELLOWS

Adolph, S., Hameister, H., Henglein, B., Lipp, M., Hartl, P., Baas, F., Lenoir, G.M. & Bornkamm, G.W. (1989) t(2;8) variant translocation in Burkitt's lymphoma: mapping of chromosomal breakpoints by in situ hybridization. *Int. J. Cancer* (in press)

Ahotupa, M., Bérériat, J.-C., Bussacchini, V., Camus, A.-M., Hietanen, E. & Bartsch, H. (1987) Studies on the role of lipid peroxidation in experimental carcinogenesis. In: Lapis, K. & Eckhardt, S., eds, *Carcinogenesis and Tumour Progression* (Lectures and Symposia, 14th Int. Cancer Congr., Budapest 1986), Budapest, Akademiai Kiado, Vol. 4, pp. 3–8

Ahotupa, M., Bussacchini-Griot, V., Bérériat, J.-C., Camus, A.-M. & Bartsch, H. (1987). Rapid oxidative stress induced by *N*-nitrosamines. *Biochem. Biophys. Res. Commun., 146,* 1047–1054

Ahotupa, M., Camus, A.M., Giuntini, C., Aitio, A., Hietanen, E., Petruzzelli, S., Carrozzi, L., Ghelarducci, L., Rindi, M., Menconi, G.F., Angeletti, C.A., Saracci, R. & Bartsch, H. (1987) Pulmonary drug-metabolizing enzyme activities in patients with lung cancer or a non-neoplastic lung disease; effect of cigarette smoking. In: Sotaniemi, E. and Pelkonen, R. O., eds, *Enzyme Induction in Man,* London, New York, Taylor & Francis, pp. 165–176

Aitio, A., Cabral, J.R.P., Camus, A.-M., Galendo, D., Bartsch, H., Aitio, M.-L., Norppa, H., Salomaa, S., Sorsa, M., Husgafvel-Pursiainen, K.H. & Nurminen, M. (1988) Evaluation of sister chromatid exchange as an indicator of sensitivity to *N*-ethyl-*N*-nitrosourea-induced carcinogenesis in rats. *Teratog. Carcinog. Mutag., 8,* 273–286

Alexandrov, K., Sala, M. & Rojas, M. (1988) Differences in the DNA adducts formed in cultured rabbit and rat dermal fibroblasts by benzo[*a*]pyrene and (−)benzo[*a*]pyrene-7,8-diol. *Cancer Res., 48,* 7132–7139

Armstrong, B., Jensen, O.M., Muñoz, N. & Bosch, F.X. (1988) Human papillomavirus and cervical cancer. *Lancet, i,* 756–758

Athanasiou, K., Arzimanoglou, I., Piccoli, C. & Yamasaki, H. (1987) Mutagenicity, clastogenicity and in-vitro transforming ability of particulates from Athens air. *Cell Biol. Toxicol., 3,* 251–261

Barbin, A. & Bartsch, H. (1989) Nucleophilic selectivity as a determinant of carcinogenic potency (TD_{50}) in rodents: a comparison of mono- and bifunctional alkylating agents and vinyl chloride metabolites. *Mutat. Res.* (in press)

Barbin, A., Bérériat, J.-C., Croisy, A., O'Neill, I.K. & Bartsch, H. (1989) Nucleophilic selectivity and reaction kinetics of chloroethylene oxide assessed by the 4-(*p*-nitrobenzyl)pyridine assay and proton nuclear magnetic resonance spectroscopy. *Chem.-Biol. Interactions* (in press)

Barbin, A., Ciroussel, F. & Bartsch, H. (1989) Formation of 1,N^6-ethenodeoxyadenosine and 3,N^6-ethenodeoxycytidine in DNA from several organs of rats exposed to vinyl chloride. In: Lambert, M.V., Lambert, C. & Laval, J., eds, *DNA Repair Mechanisms and their Biological Implications in Mammalian Cells,* New York, Plenum Press (in press)

Barek, J., Castegnaro, M., Malaveille, C., Brouet, I. & Zima, J. (1987) A method for the efficient degradation of melphalan into nonmutagenic products. *Microchem. J., 36,* 192–197

Baris, I., Simonato, L., Artvinli, M., Pooley, F., Saracci, R., Skidmore, J. & Wagner, J.C. (1987) Epidemiological and environmental evidence of the health effects of exposure to erionite fibres. *Resp. Dis. Digest, 5,* 17–18

Barley, G.C., Graf, U., Higham, C.A., Jarrah, M.Y., Jones, E.R.H., O'Neill, I., Tachikawa, R., Thaller, V., Turner, J.L. & Hodge, A.V. (1987) Natural acetylenes. Part 61. Fungal polyacetylenes and the Crepenynate Pathway: the biosynthesis of some C_9-C_{25} polyacetylenes in fungal cultures. *J. Chem. Res.* (*S*), 232–233

Bartsch, H. & Malaveille, C. (1987) The Ames test. *IST Atlas of Science: Pharmacology, 1* (1), 1–85

Bartsch, H. & Malaveille, C. (1989) Prevalence of genotoxic chemicals among animal and human carcinogens evaluated in the *IARC Monograph* series. *Cell Biol. Toxicol., 5,* 115–127

Bartsch, H. & Malaveille, C. (1989) The role of short-term tests (STT) in the identification of potential human carcinogens: an analysis of agents evaluated in the IARC Monographs, vol. 1–42. *Rev. Toxicol., 5,* 7–13

Bartsch, H. & O'Neill, I.K. (1988) Meeting Report: Ninth International Meeting on *N*-Nitroso Compounds: Exposures, Mechanisms and Relevance to Human Cancer. *Cancer Res., 48,* 4711–4714

Bartsch, H., Hietanen, E. & Malaveille, C. (1989) Carcinogenic nitrosamines: Free radical aspects of their action. *Free Radical Biol. Med.* (in press)

Bartsch, H., Hietanen, E., Ahotupa, M., Camus, A.-M. & Béréziat, J.-C. (1988) Modulation by polyunsaturated lipid diets of nitrosamine-induced cancers in rats: Effects of prooxidant state and drug metabolism. In: Feo, F., Pani, P., Columbano, A. & Garcea, R., eds, *Chemical Carcinogenesis. Models and Mechanisms*, New York, Plenum Press, pp. 609–617

Bartsch, H., Ohshima, H. & Pignatelli, B. (1988) Inhibitors of endogenous nitrosation. Mechanisms and implications in human cancer prevention. *Mutat. Res., 202,* 307–324

Bartsch, H., Ohshima, H., Muñoz, N., Calmels, S., Crespi, M., Cassale, V., Ramazzotti, V., Vincent, P., Leclerc, H. & Kamiyama, S. (1987) Nitrosamines and gastric cancer: a research protocol for the characterization of individuals and areas of high risk. In: Crespi, M. *et al.*, eds., *Epidemiology, Prevention and Early Detection of Gastric Cancer.* CIC Edizioni Internazionali, Rome, pp. 91–102

Bartsch, H., Ohshima, H., Pignatelli, B. & Calmels, S. (1989) Human exposure to endogenous *N*-nitroso compounds: Quantitative estimates in subjects at high risk for cancer of the oral cavity, esophagus, stomach and urinary bladder. *Cancer Surveys, 8,* No. 2 (in press)

Bartsch, H., Ohshima, H., Pignatelli, B., Shuker, D. & Calmels, S. (1989) Identification of high risk subjects for cancers possibly associated with increased endogenous nitrosamine synthesis. *Rev. Lat. Amer. Genet.* (in press)

Bartsch, H., Ohshima, H., Shuker, D.E.G., Pignatelli, B. & Calmels, S. (1989) Exposure of humans to endogenous *N*-nitroso compounds: implications in cancer etiology. *Mutat. Res.* (in press)

Bartsch, H., Ohshima, H., Shuker, D.E.G., Pignatelli, B. & Calmels, S. (1989) Human exposure to endogenous *N*-nitroso compounds: mechanisms of formation and implications in cancer etiology. In: *The Cellular and Molecular Biology of Human Carcinogenesis*, London, Academic Press (in press)

Bartsch, H., Préat, V., Aitio, A., Cabral, J.R.P. & Roberfroid, M. (1988) Partial hepatectomy of rats ten weeks before carcinogen administration can enhance liver carcinogenesis: preliminary observations. *Carcinogenesis, 9,* 2315–2317

Bayo, S. & Parkin, D.M. (1988) *Le Cancer au Mali 1986–1987,* Lyon, International Agency for Research on Cancer

Benito, E., Obrador, A. & Bosch, F.X. (1988) Epidemiologia del càncer de budell gros. In: Grup d'estudi del cáncer colo-rectal. *El càncer colorectal a Mallorca (1982–1986)* (Monografies Mèdiques 32), Barcelona, Acadèmia de Ciències Mèdiques de Catalunya i de Balears, pp. 19–43

Benito, E., Obrador, A., Stiggelbout, A., Bosch, F.X., Mulet, M., Muñoz, N. & Kaldor, J.M. (1989) Diet and colorectal cancer: a population based case-control study in Majorca. *Int. J. Cancer* (in press)

Berrino, F., Merletti, F., Zubiri, A., Del Moral, A., Raymond, L., Estève, J. & Tuyns, A.J. (1988) A comparative study of smoking, drinking and dietary habits in population samples in France, Italy, Spain and Switzerland. II. Tobacco smoking. *Rev. Santé Publ. Epidémiol.* (in press)

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

Bignami, M., Dogliotti, E., Aquilina, G., Zijno, A., Wild, C.P. & Montesano, R. (1989) O^6-Methyltransferase-deficient and -proficient CHO cells differ in their responses to ethyl- and methyl nitrosourea-induced DNA alkylation. *Carcinogenesis, 10,* 1329–1332

Bignami, M., Rosa, S., Falcone, G., Tato, F., Katoh, F. & Yamasaki, H. (1988) Specific viral oncogenes cause differential effects on cell-to-cell communication, relevant to the suppression of the transformed phenotype by normal cells. *Mol. Carcinog., 1,* 67–75

Billaud, M., Busson, P., Huang, D., Mueller-Lantzch, N., Rousselet, G., Pavlish, O., Wakasugi, H., Tursz, T., Seigneurin, J.M. & Lenoir, G.M. (1989) Epstein-Barr virus (EBV) containing nasopharyngeal carcinoma cells express the B-cell activation antigen Blast2/CD23 but not the EBV/receptor/CR2. *J. Virol.* (in press)

Billaud, M., Calender, A., Seigneurin, J.M. & Lenoir, G.M. (1987) LFA-1, LFA-3, and ICAM-1 expression in Burkitt's lymphoma. *Lancet, ii,* 1327–1328

Blanche, S., Le Diest, F., Veber, F., Lenoir, G.M., Fischer, J., Brochier, J., Boucheix, C., Dalaage, M., Griscelli, C. & Fischer, A. (1988) Treatment of severe Epstein-Barr virus-induced polyclonal B-lymphocyte proliferation by anti-B-cell monoclonal antibodies. *Ann. Intern. Med., 108,* 199–203

Boice, J.D. Jr, Blettner, M., Kleinerman, R.A., Engholm, G., Stovall, M., Lisco, H., Austin, D.F., Bosch, A., Harlan, L., Krementz, E.T., Latourette, H.B., Merrill, J.A., Peters, L.J., Schulz, M.D., Wactawski, J., Storm, H.H., Björkholm, E., Pettersson, F., Bell, C.M.J., Coleman, M.P., Fraser, P., Neal, F.E., Prior, P., Choi, N.W., Hislop, T.G., Koch, M., Kreiger, N., Robb, D., Robson, D., Thomson, D.H., Lochmüller, H., von Fournier, D., Frischkorn, R., Kjørstad, K.E., Rimpela, A., Pejovic, M.-H., Pompe Kirn, V., Stanuksova, H., Pisani, P., Sigurdsson, K., Hutchison, G.B. & MacMahon, B. (1989) Radiation dose and breast cancer risk in patients treated for cancer of the cervix. *Int. J. Cancer* (in press)

Boice, J.D. Jr, Engholm, G., Kleinerman, R.A., Blettner, M., Stovall, M., Lisco, H., Moloney, W.C., Austin, D.F., Bosch, A., Cookfair, D.L., Krementz, E.T., Latourette, H.B., Merrill, J.A., Peters, L.J., Schulz, M.D., Storm, H.H., Björkholm, E., Pettersson, F., Bell, C.M.J., Coleman, M.P., Fraser, P., Neal, F.E., Prior, P., Choi, N.W., Hislop, T.G., Koch, M., Kreiger, N., Robb, D., Robson, D., Thomson, D.H., Lochmüller, H., von Fournier, D., Frischkorn, R., Kjørstad, K.E., Rimpela, A., Pejovic, M.-H., Pompe Kirn, V., Stankusova, H., Berrino, F., Sigurdsson, K., Hutchison, G.B. & MacMahon, B. (1988) Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiation Res., 116,* 3–55

Boice, J.D., Blettner, M., Kleinerman, R.A., Stovall, M., Moloney, W.C., Engholm, G., Austin, D.F., Bosch, A., Cookfair, D.L., Krementz, E.T., Latourette, H.B., Peters, L.-J., Schulz, M.D., Lundell, M., Pettersson, F., Storm, H.H., Bell, C.M.J., Coleman, M.P., Fraser, P., Palmer, M., Prior, P., Choi, N.W., Hislop, T.G., Koch, M., Robb, D., Robson, D., Spengler, R.F., von Fournier, D., Frischkorn, R., Lochmüller, H., Pompe-Kirn, V., Rimpela, A., Kjørstad, K., Pejovic, M.H., Sigurdsson, K., Pisani, P., Kucera, H. & Hutchison, G.B. (1987) Radiation dose and leukaemia risk in patients treated for cancer of the cervix. *J. Natl Cancer Inst., 79,* 1295–1311

Borrás, J., Galceran, J., Anglada, Ll., Moreno, V., Creus, J., Bosch, F.X., Viladiu, P., Calbet, J., Lafuerza, A., Campillo, M., Arias, A. & Martin, M. (1988) *El Cáncer en Tarragona 1980–1985: Estudio Epidemiológico Descriptivo* (RCT Monografia No. 2), Tarragona, Registre de Cáncer

Bosch, F.X. (1989) Cancer epidemiology: updating opportunities for prevention [in Catalan]. *Salut Catalunya* (in press)

Bosch, F.X. (1989) Registro de Tumores del Principado de Asturias. In: Echeverría Rodríguez, M., García Tardón, A., Alonso de la Torre López, R. & Arrones Noval, L., eds, *Incidencia del cancer en Asturias 1982–1984.* Principado de Asturias, Consejeria de Sanidad y Servicios Sociales, Registro de Tumores, p. 7

Bosch, F.X. & Benito, E. (1989) Epidemiology of cancer of the colon and rectum [in Spanish] (in press)

Bosch, F.X. & Muñoz, N. (1988) Perspectives en els estudis epidemiològics. In: Grup d'estudi del càncer colo-rectal. *El càncer colo-rectal a Mallorca (1982–1986)* (Monografies Mèdiques 32), Barcelona, Acadèmia de Ciències Mèdiques de Catalunya i de Balears, pp. 147–158

Bosch, F.X. & Muñoz, N. (1988) Prospects for epidemiological studies on hepatocellular cancer as a model for assessing viral and chemical interactions. In: Bartsch, H., Hemminki, K. & O'Neill, I.K. eds, *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, pp. 427–438

Bosch, F.X. & Muñoz, N. (1989) Etiological factors on cervical cancer. In: Zatonski, W. & Boyle, P., eds, *Cancer. Descriptive Epidemiology through Prevention,* Warsaw, Interpresse (in press)

Bosch, F.X. & Muñoz, N. (1989) Cervical cancer: Current epidemiological evidence and new hypothesis on risk factors [in Spanish]. *Revisiones en Salud Publica y Administracion Sanitaria* (in press)

Bosch, F.X. & Muñoz, N. (1989) Epidemiology of hepatocellular carcinoma. In: Bannasch, P., Keppler, D. & Weber, G., eds, *Liver Cell Carcinoma* (Falk Symposium No. 51), Dordrecht, Kluwer, pp. 3–14

Bosch, F.X. & Muñoz, N. (1989) Human papillomavirus and cervical neoplasia: Critical review of the available epidemiological evidence. In: Muñoz, N., Bosch, F.X. & Jensen, O.M., eds, *Human Papillomavirus and Cervical Cancer* (IARC Scientific Publications No. 94), Lyon, International Agency for Research on Cancer, pp. 135–151

Boutron, M.-C., Faivre, J., Milan, C., Lorcerie, B. & Estève, J. (1989) A comparison of two diet history questionnaires that measure usual food intake. *Nutr. Cancer, 12,* 83–91

Bouvier, G., Polack, A., Traub, B., Bornkamm, G.W., Ohshima, H., Bartsch, H. & de-Thé, G. (1989) Food extracts from high risk areas induce an EBV early promoter. In: *Epstein-Barr Virus and Human Disease,* Vol. II, Clifton, NJ, Humana Press (in press)

Boyle, P. (1988) The epidemiology of breast cancer. In: Veronesi, U., ed., *Baillière's Clinical Oncology, 2,* 1–58

Boyle, P. (1989) Breast cancer—do dietary factors matter? *Hospital Update, 38,* 725–726 and 810

Boyle, P. (1989) Diet and cancer. In: Garrow, J. & James, W.P.T., eds, *Passmore's Textbook of Nutrition,* Edinburgh, Churchill Livingstone (in press)

Boyle, P. (1989) Relative value of incidence and mortality data in cancer research. In: Boyle, P., Muir, C. & Grundmann, E., eds, *Cancer Mapping* (Recent Results in Cancer Research Vol. 114), Berlin, Heidelberg, New York, Springer Verlag, pp. 41–63

Boyle, P. & Robertson, C. (1987) Age-period-cohort modelling of malignant melanoma incidence in Scotland, 1960–1984. *Am. J. Epidemiol., 126,* 766

Boyle, P. & Robertson, C. (1987) Statistical modelling of colon cancer and breast cancer

incidence in Scotland, 1960–1979. *J. Natl Cancer Inst., 79,* 1175–1179

Boyle, P. & Robertson, C. (1988) Re: Statistical modelling of cancer data. *Am. J. Epidemiol, 129,* 225–226

Boyle, P., Hsieh, C.-C., Maisonneuve, P., La Vecchia, C., Macfarlane, G.J., Trichopoulos, D. & Walker, A.M. (1989) The epidemiology of pancreas cancer. *Int. J. Pancreatology* (in press)

Boyle, P., Macfarlane, G.J. & McGinn, R. (1989) The epidemiology of head and neck cancers. In: De Wries N. & Gluckman, J., eds, *Second Primary Cancers in Head and Neck* (in press)

Boyle, P., Macfarlane, G.J., Maisonneuve, P., Scully, P. & Tedesco, B. (1989) Epidemiology of mouth cancer. *J. Roy. Soc. Med.* (in press)

Boyle, P., Maisonneuve, P. & Hsieh, C.-C. (1989) Descriptive epidemiology of breast cancer. In: Zatonski, W. & Boyle, P., eds, *Cancer. Descriptive Epidemiology through Prevention,* Warsaw, Interpresse

Boyle, P., Muir, C.S. & Grundmann, E. (1989) Introduction. In: Boyle, P., Muir, C. & Grundmann, E., eds, *Cancer Mapping* (Recent Results in Cancer Research Vol. 114), Heidelberg, Springer Verlag, pp. i–vii

Boyle, P., Soukop, M., Scully, C., Robertson, A.G., Burns, H.J.G. & Gillis, C.R. (1988) Improving prognosis of Hodgkin's disease in Scotland. *Eur. J. Cancer Clin. Oncol., 24,* 229–234

Brent, T.P., Dolan, M.E., Fraenkel-Conrat, H., Hall, J., Karran, P., Laval, F., Margison, G.P., Montesano, R., Pegg, A.E., Potter, P.M., Singer, B., Swenberg, J.A. & Yarosh, D.B. (1988) Repair of O-alkylpyrimidines in mammalian cells: a present consensus. *Proc. Natl Acad. Sci. USA, 85,* 1759–1762

Bycorez, A.I., Turusov, V.S., Wilbourn, J. & Shuker, L. (1988) Evaluation of carcinogenic hazard of chemicals to man (Report on IARC Working Group Session, 10–18 March 1987) [in Russian]. *Exp. Oncol. (USSR), 10,* 73–74

Cabral, J.R.P. (1987) Carcinogenicity of pesticides. In: Costa, L.G. *et al.* eds, *Toxicology of Pesticides: Experimental, Clinical and Regulatory Aspects* (NATO ASI Series, Vol. H13), Berlin, Heidelberg, New York, Springer-Verlag, pp. 125–145

Cabral, J.R.P. & Galendo, D. (1989) Carcinogenicity study of the pesticide fenvalerate in mice. *Toxicologist, 9,* 211

Cabral, J.R.P. & Neal, G.E. (1987) Modification of aflatoxin B_1 carcinogenesis by the antioxidant ethoxyquin. *Proc. Am. Assoc. Cancer Res., 28,* 135

Cabral, J.R.P. & Wilbourn, J. (1987) An approach to the evaluation of the carcinogenic risk of chemicals—the IARC Monographs Programme. In: *Predictive Value of Carcinogenicity Testing in Drug Evaluation.* (Nordic Workshop on Toxicology. NLN Publication No. 19), Uppsala, Sweden, Nordic Council on Medicines, pp. 147–169

Calender, A., Billaud, M. & Lenoir, G.M. (1988) Cooperation between cellular and Epstein-Barr virus genes in the genesis of Burkitt's lymphoma. In: Kakunaga, T., Sugimura, T., Tomatis, L., & Yamasaki, H., eds, *Cell Differentiation, Genes and Cancer* (IARC Scientific Publications No. 92), Lyon, International Agency for Research on Cancer, pp. 159–164

Calender, A., Billaud, M. & Lenoir, G.M. (1988) Induction of B cell activation markers by Epstein-Barr virus. In: Mani, J.C. & Dornand, J., eds, *Lymphocyte Activation and Differentiation,* Berlin, Walter de Gruyter, pp. 183–189

Calender, A., Billaud, M., Aubry, J.-P., Banchereau, J., Vuillaume, M. & Lenoir, G.M. (1987) Epstein-Barr virus (EBV) induces expression of B-cell activation markers on in-vitro infection of EBV-negative B-lymphoma cells. *Proc. Natl. Acad. Sci. USA, 84,* 8060–8064

Calmels, S., Ohshima, H. & Bartsch, H. (1988) Nitrosamine formation by denitrifying and non-denitrifying bacteria: implication of nitrite reductase and nitrate reductase in nitrosation catalysis. *J. Gen. Microbiol., 134,* 221–226

Calmels, S., Ohshima, H., Crespi, M., Leclerc, H., Cattoen, C. & Bartsch, H. (1987) *N*-Nitrosamine formation by microorganisms isolated from human gastric juice and urine: biochemical studies on bacteria-catalysed nitrosation. In: Bartsch, H., O'Neill, I.K. & Schulte-Hermann, R., eds, *The Relevance of N-Nitroso Compounds to Human Cancer: Exposures & Mechanisms* (IARC Scientific Publications No. 84), Lyon, International Agency for Research on Cancer, pp. 391–395

Cardis, E. & Kaldor, J. (1989) Radiation and cancer: Overview and implication for prevention. In: Heller, T., Davey, B. & Bailey, L., eds, *Reducing the Risk of Cancer,* London, Hodder & Stoughton, pp. 51–57

Carnevale, F., Montesano, R., Partensky, C. & Tomatis, L. (1987) Comparison of regulations on occupational carcinogens in several industrialized countries. *Am. J. Ind. Med., 12,* 453–473

Castegnaro, M. (1988) International *N*-nitrosamine check sample programme: report on the performance in the 1st study dedicated to determination of *N*-nitrosamines in beer and malt. *Food Add. Contam., 5,* 283–288

Castegnaro, M. (1988) Rapport de synthèse du sous-groupe de travail sur la formation à la manipulation des substances génotoxiques. Paris, Institut National de Recherche et de Sécurité (in press)

Castegnaro, M. (1989) Cancérogènes chimiques: traitement des dechéts avant rejet. Paris, Institut National de Recherche et de Sécurité (in press)

Castegnaro, M., Massey, R.C. & Walters, C.L. (1987) The collaborative evaluation of a procedure for the determination of *N*-nitroso compounds as a group. *Food Add. Contam., 4,* 37–43

Castegnaro, M., Bartsch, H., Béréziat, J.C., Arvela, P., Michelon, J. & Broussolle, L. (1989) Polymorphic ochratoxin A hydroxylation in rat strains phenotyped as poor and extensive metabolizers of debrisoquine. *Xenobiotica, 19,* 225–230

Castegnaro, M., Chen, J., Ohshima, H., Yang, H., Li, J., Campbell, T.C., Peto, R. & Bartsch, H. (1987) A correlation study on urinary excretion of *N*-nitroso compounds and cancer mortality in China: interim results. In: Bartsch, H., O'Neill, I.K. & Schulte-Hermann, R., eds, *The Relevance of N-Nitroso Compounds to Human Cancer: Exposures & Mechanisms* (IARC Scientific Publications No. 84), Lyon, International Agency for Research on Cancer, pp. 503–506

Chernozemsky, I. & Bartsch, H. (1987) Meeting Report: Endemic nephropathy and urinary tract tumors in the Balkans. *Cancer Res., 47,* 3608–3609

Chouroulinkov, I., Lasne, C., Lowy, R., Wahrendorf, J., Becher, H., Day, N.E. & Yamasaki, H. (1989) Dose and frequency effect in mouse skin tumor promotion. *Cancer Res., 49,* 1964–1969

Clayton, D.G. & Kaldor, J.M. (1987) Empirical Bayes estimates of age-standardized relative risks for use in disease mapping. *Biometrics, 43,* 671–681

Clayton, D.G. & Kaldor, J.M. (1988) Diagnostic plots for departures from proportional hazards in cohort study data. *J. Chron. Dis.* (in press)

Clofent, G., Klein, B., Commes, T., Vincent, C., Ghanem, N., Lenoir, G.M., Lefranc, M.P. & Bataille, R. (1989) Limiting dilution cloning of B cells from patients with multiple myeloma: emergence of non-malignant B-cell lines. *Int. J. Cancer, 43,* 578–586

Cohen, J.H.M., Fischer, E., Kazatchkine, M.D., Lenoir, G.M., Lefevre-Delvincourt, C. & Revillard, J.P. (1987) Expression of CR1 and CR2 complement receptors following Epstein-Barr virus infection of Burkitt's lymphoma cell lines. *Scand. J. Immunol, 25,* 587–598

Coleman, M.P. & Beral, V. (1988) A review of epidemiological studies of the health effects of living near and working with electricity generation and transmission equipment. *Int. J. Epidemiol., 17,* 1–13

Coleman, M. & Cardis, E. (1989) Extremely low frequency electric and magnetic field and human cancer risk, IARC, Lyon, France, 2–3 May 1988. *Bioelectromagnetics* (in press)

Coleman, M.P. & Démaret, E. (1988) Cancer registration in the European Community. *Int. J. Cancer, 42,* 339–345

Coleman, M.P. & Démaret, E. (1988) *Cancer Registration in the European Economic Community* (IARC Technical Report No. 3), Lyon, International Agency for Research on Cancer

Coleman, M.P. & Law, M. (1989) Prevention of cancer: review of the evidence from intervention trials. In: Hakama, M., Beral, V., Cullen, J. & Parkin, M., eds, *Evaluating Effectiveness of Primary Prevention for Cancer* (IARC Scientific Publications No. 103), Lyon, International Agency for Research on Cancer (in press)

Coleman, M.P. & Wahrendorf, J., eds (1988) *Directory of On-going Research in Cancer Epidemiology 1988* (IARC Scientific Publications No. 93), Lyon, International Agency for Research on Cancer

Coleman, M.P. & Wahrendorf J., eds (1989) *Directory of On-Going Research in Cancer Epidemiology 1989/90* (IARC Scientific Publications No. 101), Lyon, International Agency for Research on Cancer (in press)

Coleman, M.P., Bell, C.M.J., Taylor, H.-L. & Primic-Zakelj, M. (1989) Leukaemia and residence near electricity transmission equipment: a case-control study. *Br. J. Cancer* (in press)

Conference report (1988) Human papillomavirus and cervical cancer. *Lancet, i,* 756–758

Cordioli, G., Guoghi, L., Solari, P.L., Berrino, F., Crosignani, P. & Riboli, E. (1987) Cancer mortality in a cohort of glass workers [in Italian]. *Epidemiologia e Prevenzione, 30,* 16–18

Cuzick, J. & Boyle, P. (1988) Trends in cervix cancer mortality. *Cancer Surveys, 7,* 417–439

Dayan, J., Pleven, C. & Castegnaro, M. (1988) Manuel sur la prévention et la securité lors de la manipulation des substances génotoxiques utilisées au laboratoire. Paris, Institut National de Recherche et de Sécurité (in press)

De Méo, M., Laget, M., Castegnaro, M. & Duménil, G. (1989) Studies of procedures for the destruction of some alkylating agents. In: Proceedings of the Fifth International Conference on Environmental Mutagens, 10–15 July 1989. *Environ. Mol. Mutag., 14* (suppl. 15), 45 (abstract)

De Turenne-Tessier, M., Ooka, T., Calender, A., de Thé, G. & Daille, J. (1989) Relationship between nasopharyngeal carcinoma and high antibody titers to Epstein-Barr virus-specific thymidine kinase. *Int. J. Cancer, 43,* 45–48

DeFlora, S., Hietanen, E., Bartsch, H., Camoirano, A., Izzotti, A., Bagnasco, M. & Millman, I. (1989) Enhanced metabolic activation of chemical hepatocarcinogens in woodchucks infected with hepatitis B virus. *Carcinogenesis, 10,* 1099–1106

Degan, P., Montesano, R. & Wild, C.P. (1988) Antibodies against 7-methyldeoxyguanosine: its detection in rat peripheral blood lymphocyte DNA and potential applications to molecular epidemiology. *Cancer Res., 48,* 5065–5071

Delendi, M., Gardiman, D., Riboli, E. & Sasco, A.J. (1989) Prevalence of latent colorectal cancer

discovered at necropsy (letter to the Editor). Lancet (in press)

Den Engelse, L., Bax, J., Terheggen, P.M.A.B., Van Schooten, F.-J., Van Benthem, J., Wild, C.P. & Scherer, E. (1989) Single cell analysis of DNA modifications induced by chemical carcinogens and cytostatic drugs. *Ann. Ist. Super. Sanità, 25,* 11–20

Den Engelse, L., Ploem, J.S., Wild, C.P. & Scherer, E. (1989) Visualization and computer-assisted quantification of DNA modifications in individual cells. In: Castellani, A., ed., *DNA Damage and Repair* (Proceedings of the First International Congress on DNA Damage and Repair, Rome 1987), New York, Plenum Press, pp. 251–262

Donnan, S.P.B., Wong, F.W.S., Ho, S.C., Lau, E.M.C., Takashi, K. & Estève, J. (1989) Reproductive and sexual risk factors and human papilloma virus infection in cervical cancer among Hong Kong Chinese. *Int. J. Epidemiol.* (in press)

Duperray, C., Klein, B., Durie, B.G.M., Zhang, X., Jourdan, M., Poncelet, P., Favier, F., Vincent, C., Brochier, J., Lenoir, G.M. & Bataille, R. (1989) Phenotypic analysis of human myeloma cell lines. *Blood, 73,* 566–572

Eberle, G., Barbin, A., Laib, R.J., Ciroussel, F., Thomale, J., Bartsch, H. & Rajewsky, M.F. (1989) 1,N^6-Etheno-2′-deoxyadenosine and 3,N^4-deoxycytidine detected by monoclonal antibodies in lung and liver DNA of rats exposed to vinyl chloride. *Carcinogenesis, 10,* 209–212

Elovaara, E., Zitting, A., Nickels, J. & Aitio, A. (1987) *m*-Xylene inhalation destroys cytochrome P-450 in rat lung at low exposure. *Arch. Toxicol., 67,* 21–26

Enomoto, K., Katoh, F., Montesano, R. & Yamasaki, H. (1988) Oncogene alterations and intercellular communication in transformed and non-transformed rat liver epithelial cell lines. *Proc. Am. Assoc. Cancer Res., 29,* 141

Ernst, H., Ohshima, H., Bartsch, H., Mohr, U. & Reichart, P. (1987) Tumorigenicity study in Syrian hamsters fed areca nut together with nitrite. *Carcinogenesis, 8,* 1843–1845

Estève, J. (1987) Evaluation of screening programmes: Methodology. In: Faivre, J. & Hill, M. J., eds, *Colorectal Cancer: Etiology, Causes and Prevention,* Amsterdam, Elsevier, pp. 163–172

Estève, J. & Tuyns, A.J. (1988) Models for combined action of alcohol and tobacco on risk of cancer: What do we really know from epidemiological studies? In: Feo, F., Pani, P., Columbano, A. & Garcea, R., eds, *Chemical Carcinogenesis: Models and Mechanisms,* New York, Plenum Press

Favrot, M.C., Philip, T., Coze, C. & Lenoir, G.M. (1989) Déficit immunitaire et cancer. *Pédiatrie, 44,* 11–18

Ferguson, M.M., Hart, D.McK., Boyle, P. & Lindsay, R. (1988) Influence of oestrogen therapy on climacteric symptoms in oophorectomised women. *Maturitas* (in press)

Ferrer, A. & Cabral, J.R.P. (1987) Critical review of pesticide-related alimentary outbreaks. In: Costa, L.G. *et al.*, eds, *Toxicology of Pesticides: Experimental, Clinical and Regulatory Aspects* (NATO ASI Series, Vol. H13), Berlin, Heidelberg, New York, Springer-Verlag, pp. 273–278

Ferrer, A. & Cabral, J.R.P. (1989) Epidemics of poisoning caused by the contamination of foods with pesticides. *Toxicologist, 9,* 224

Fishbein, L. & Cabral, J.R.P. (1987) Perspectives on toxicity of inert pesticidal ingredients. *Toxicologist, 7,* 14

Fishbein, L. & O'Neill, I.K. (1987) Metals in indoor environments: Sources and aspects of bioavailability. In: Seifert, B., Esdorn, H., Fischer, M., Rüden, H. & Wegner, J., eds, *Indoor Air '87* (Proceedings of the 4th International Conference on Indoor Air Quality and Climate, West Berlin, 17–21 August 1987), Berlin, Institute for Water, Soil and Air Hygiene, Vol. 1, pp. 501–508

Fishbein, L., O'Neill, I.K. & Tossavainen, A. (1987) Past and present exposure determination techniques for benzene, toluene and xylene in work-place and ambient air. In: Fishbein, L. & O'Neill, I.K., eds, *Environmental Carcinogens: Methods of Analysis and Exposure Measurement,* Volume 10: *Benzene and Alkylated Benzenes* (IARC Scientific Publications No. 85), Lyon, International Agency for Research on Cancer, pp. 123–148

Fitzgerald, D.J. & Yamasaki, H. (1989) The role of inhibited gap junction function in carcinogenesis. *Toxicology In Vitro* (in press)

Fitzgerald, D.J. & Yamasaki, H. (1989) Tumor promotion: models and assay systems. *Teratog. Carcinog. Mutag.* (in press)

Fitzgerald, D.J., Mesnil, M., Oyamada, M., Tsuda, H., Ito, N. & Yamasaki, H. (1989) Changes in gap junction protein (connexin 32) gene expression during rat liver carcinogenesis. *J. Cell. Biochem.* (in press)

Fitzgerald, D.J., Piccoli, C. & Yamasaki, H. (1989) Detection of nongenotoxic carcinogens in the BALB/c 3T3 cell transformation/mutation assay system. *Mutagenesis* (in press)

Friesen, M., Cabral, J.R.P., Galendo, D., Garren, L. & Bartsch, H. (1989) Carcinogenicity studies in rodents of morphine pyrolysate (MO) implicated in the aetiology of oesophageal cancer. *Toxicologist, 9,* 213

Friesen, M., Maru, G., Bussacchini, V., Bartsch, H., Nair, U., Nair, J. & Floyd, R.A. (1988) Formation of reactive oxygen species and of 8-hydroxy-2′-deoxyguanosine in DNA *in vitro* with betel-quid ingredients. In: Bartsch, H.,

Hemminki, K. & O'Neill, I.K., eds. *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, pp. 417–421

Frixen, U. & Yamasaki, H. (1987) Enhancement of transformation and continuous inhibition of intercellular communication by 1-oleoyl acetylglycerol in BALB/c 3T3 cells. *Carcinogenesis, 8,* 1101–1104

Galloway, D.J., Jarret, F., Boyle, P., Indran, W., Carr, K. & George, W.D. (1989) Dietary manipulation during experimental colorectal carcinogenesis: an ultrastructural study. *Int. J. Colorectal Dis.* (in press)

Gardner, M.J. & Saracci, R. (1989) Effects on health of non-occupational exposure to airborne mineral fibres. In: Bignon, J., Peto, J. & Saracci, R., eds, *Non-occupational Exposure to Mineral Fibres* (IARC Scientific Publications No. 90), Lyon, International Agency for Research on Cancer, pp. 375–379

Geser, A., Brubaker, G. & Draper, C.C. (1989) Effect of a malaria suppression program on the incidence of African Burkitt's lymphoma. *Am. J. Epidemiol., 120,* 740–752

Gillis, C.R., Hole, D.J. & Boyle, P. (1988) Cigarette smoking and male lung cancer in an area of very high incidence: report of a case-control study in the West of Scotland. *J. Epidem. Commun. Health, 42,* 38–43

Giroldi, L., Hollstein, M. & Yamasaki, H. (1988) Cellular oncogene expression in Friend erythroleukemia cells: relationship to differentiation, commitment, and TPA effects. *Carcinogenesis, 9,* 817–821

Goddard, M.J., Krewski, D. & Boyle, P. (1987) SEARCH—A Programme of IARC. *Chronic Disease in Canada, 9,* 31–34

Gonzales, C.A., Riboli, E. & Lopez-Abente, G. (1988) Bladder cancer among workers in the textile industry. Results of a Spanish case-control study. *Am. J. Ind. Med., 14,* 673–680

Gonzalez, C.A., Lopez-Abente, G., Errezola, M., Escolar, A., Riboli, E., Izarzugaza, I. & Nebot, M. (1989) Occupation and bladder cancer in Spain: A multi-centre case-control study. *Int. J. Epidemiol.* (in press)

Goudie, B.M., Burt, A.D., Macfarlane, G.J., Boyle, P., Gillis, C.R. & Watkinson, G. (1989) Prognostic factors in primary biliary cirrhosis. *Am. J. Gastroentesol., 84,* 713–720

Green, M.H.L., Lowe, J.E., Petit-Frère, C., Karran, P., Hall, J. & Kataoka, H. (1989) Properties of *N*-methyl-*N*-nitrosourea-resistant, Mex$^-$ derivatives of an SV40-immortalized human fibroblast cell line. *Carcinogenesis, 10,* 893–898

Gurtsevitch, V., O'Conor, G.T. & Lenoir, G.M. (1988) Burkitt's lymphoma cell lines reveal different degrees of tumorigenicity in nude mice. *Int. J. Cancer, 41,* 87–95

Hakama, M., Beral, V., Cullen, J. & Parkin, M. (1989) UICC Workshop on evaluating interventions to reduce cancer risk. Meeting held at Reykjavik, Iceland, September 21–24, 1988. *Int. J. Cancer, 43,* 967–969

Hakama, M., Beral, V., Cullen, J. & Parkin, M., eds (1989) *Evaluating Effectiveness of Primary Prevention of Cancer* (IARC Scientific Publications No. 103), Lyon, International Agency for Research on Cancer (in press)

Haley, N.J. & O'Neill, I.K. (1987) Collection of urine for prospective studies in passive smoking. In: O'Neill, I.K., Brunneman, K.D., Dodet, B. & Hoffmann, D., eds, *Environmental Carcinogens—Selected Methods of Analysis and Exposure Measurement,* Volume 9: *Passive Smoking* (IARC Scientific Publications No. 81), Lyon, International Agency for Research on Cancer, pp. 293–297

Hall, A.J., Inskip, H.M., Loik, F., Day, N.E., O'Conor, G., Bosch, X., Muir, C.S., Parkin, D.M., Muñoz, N., Tomatis, L., Greenwood, B., Whittle, H., Ryder, R., Oldfield, F.S.J., Njie, A.B.H., Smith, P.G. & Coursaget, P. (1987) The Gambia Hepatitis Intervention Study. *Cancer Res., 47,* 5782–5787

Hall, A.J., Inskip, H.M., Loik, F., Chotard, J., Jawara, M., Vall Mayans, M., Greenwood, B.M., Whittle, H., Njie, A.B.H., Cham, K., Bosch, F.X. & Muir, C.S. (1989) Hepatitis B vaccine in the Expanded Programme of Immunisation: The Gambian Experience. *Lancet, i,* 1057–1060

Hall, J., Brésil, H., Martel-Planche, G., Serres, M., Wild, C.P., & Montesano, R. (1989) Differential repair of O4-methylthymine and O6-methylguanine in rat and hamster liver. In: Lambert, M.W., Lambert, C. & Laval, J., eds, *DNA Repair Mechanisms and their Biological Implications in Mammalian Cells,* New York, Plenum Press (in press)

Hall, J., Karran, P., Kataoka, H., Macpherson, P. & Stephenson, C. (1989) Mechanisms of alkylating agent induced cytotoxicity in *E. coli* and mammalian cells. In: Castellani, A., ed., *DNA Damage and Repair* (Proceedings of the First International Congress on DNA Damage and Repair, Rome 1987), New York, Plenum Press, pp. 97–106

Hall, J., Kataoka, H., Stephenson, C. & Karran, P. (1988) The contribution of O^6-methylguanine and methylphosphotriesters to the cytotoxicity of alkylating agents in mammalian cells. *Carcinogenesis, 9,* 1587–1593

Hamel, E., Katoh, F., Mueller, G., Birchmeier, W. & Yamasaki, H. (1988) Transforming growth factor beta is a potent promoter in two-stage BALB/c 3T3 cell transformation. *Cancer Res., 48,* 2832–2836

Hamel, E., Tayot, J.-L. & Yamasaki, H. (1988) Modulation of cellular phorbol ester binding and/or protein kinase C activity by human placental fractions. *Biochim. Biophys. Acta, 970,* 172–176

Hanai, A., Benn, T., Fujimoto, I. & Muir, C.S. (1988) Comparison of lung cancer incidence rates by histological type in high and low incidence countries, with reference to the limited role of smoking. *Jpn. J. Cancer Res., 79,* 445–452

Harris, A., Lenoir, G.M. & Lankester, S.A. (1988) X-linked lymphoproliferative disease: linkage studies using DNA probes. *Clin. Genet., 33,* 162–168

Hayoz, D., Lenoir, G.M., Nicole, A., Pugin, P. & Regamey, C. (1988) X-linked lymphoproliferative syndrome: Identification of a large family in Switzerland. *Am. J. Med., 84,* 529–534

Henry, I., Grandjouan, S., Couillin, P., Barichard, F., Huerre-Jeanpierre, C., Glaser, T., Philip, T., Lenoir, G., Chaussain, J.L. & Junien, C. (1989) Tumor-specific loss of 11p15.5 alleles in del11p13 Wilms tumor and in familial adrenocortical carcinoma. *Proc. Natl Acad. Sci. USA, 86,* 3247–3251

Hietanen, E. (1988) Reactive species and other mediators of phototoxic damage. In: Douglas, R., Moan, J. & Dall'acqua, eds, *Light in Biology and Medicine,* Vol. 1, New York, Plenum Press, pp. 273–279

Hietanen, E., Ahotupa, M., Bériziat, J.-C., Park, S.S., Gelboin, H.V. & Bartsch, H. (1987) Monoclonal antibody characterization of hepatic and extrahepatic cytochrome P450 activities in rats treated with phenobarbital or methylcholanthrene and fed various cholesterol diets. *Biochem. Pharmacol., 36,* 3973–3980

Hietanen, E., Bartsch, H., Camus, A.-M., Bériziat, J.-C., DeFlora, S., Park, S.S. & Gelboin, H.V. (1989) Elevated Ah-locus-linked monooxygenases in woodchuck livers as a predisposing factor to carcinogenesis. In: Schuster, I., ed., *Cytochrome P-450: Biochemistry and Biophysics,* London, Taylor & Francis, pp. 511–514

Hietanen, E., Castegnaro, M. & Bartsch, H. (1989) Inhaled carcinogens and DNA adducts. Proceedings of the 2nd Conference on Pneumopathies. Paris, 14–15 March 1989. (*INSERM Publications Series*) (in press)

Hietanen, E., Stählberg, M.R. & Mäki, M. (1989) Development of intestinal drug-metabolizing enzymes in man. *Progr. Pharmacol. Clin. Pharmacol., 7,* 267–274

Higginson, J., Muir, C.S. & Sheriden, M.J. (1989) The role of epidemiology in toxicology. In: Clayton, D.B. & Shubik, P., eds, *Progress in Predictive Toxicology,* Amsterdam, Elsevier (in press)

Hollstein, M. & Yamasaki, H. (1987) Tumor promoter-mediated modulation of cell differentiation and communication: the phorbol ester-oncogene connection. In: Aarbakke, J., Chiang, P.K. & Koeffler, H.P., eds, *Tumor Cell Differentiation,* Clifton, NJ, Humana Press, pp. 317–339

Hollstein, M. & Yamasaki, H. (1989) Understanding multi-stage carcinogenesis at the molecular level: Notes on recent progress. In: Travis, C.C., ed., *Biologically Based Methods for Cancer Risk Assessment,* New York, Plenum Press (in press)

Hollstein, M., Bos, J., Galiana, C., Mandard, A., Yamasaki, H. & Montesano, R. (1988) Mutation and amplification of cellular oncogenes in human esophageal cancer. *Proc. Am. Assoc. Cancer Res., 29,* 260

Hollstein, M.C., Smits, A.M., Galiana, C., Yamasaki, H., Bos, J.L., Mandard, A., Partensky, C. & Montesano, R. (1988) Amplification of EGF receptor gene but no evidence of *ras* mutations in primary human esophageal cancers. *Cancer Res., 48,* 5119–5123

Horiguchi, Y., Couchman, J.R., Ljubimov, A.V., Yamasaki, H. & Fine, J.-D. (1989) Distribution, ultrastructural localization, and ontogeny of the core protein of a heparan sulfate proteoglycan in human skin and other basement membranes. *J. Histochem. Cytochem.* (in press)

Hours, M., Cardis, E., Marciniak, A., Quelin, P. & Fabry, J. (1989) A further follow-up of a cohort for mortality in a polyamide-polyester factory in Lyon. *Br. J. Ind. Med.* (in press)

Iscovich, J., Castelleto, R., Estève, J., Muñoz, N., Colanzi, R., Coronel, A., Deamezola, I., Tassi, V. & Arslan, A. (1987) Tobacco smoking, occupational exposure and bladder cancer in Argentina. *Int. J. Cancer, 40,* 734–740

Iscovich, J.M., Iscovich, R.B., Howe, G., Shiboski, S. & Kaldor, J.M. (1989) Case-control study of diet and breast cancer in Argentina. *Int. J. Cancer* (in press)

Jongen, W., Fitzgerald, D.J. & Yamasaki, H. (1989) Use of cell culture systems to study mechanisms of tumor promotion. *Toxicology In Vitro* (in press)

Kalandidi, A., Trichopoulos, D., Hatzakis, A., Tzannes, S. & Saracci, R. (1987) Passive smoking and chronic obstructive lung disease. *Lancet, ii,* 1325–1326

Kaldor, J.M. (1987) Cross-species comparison of carcinogenic potency: the example of anticancer drugs. *Proceedings of the Course on Quantitative Risk Assessment for Human Health,* Istituto Superiore di Sanita, Rome, May 1987, pp. 199–213

Kaldor, J.M. (1988) The problem of measurement error in cancer epidemiology, with particular reference to cohort studies of diet. In: Riboli, E. & Saracci, R., eds, *Diet and Cancer: Methodological Issues for Prospective Studies* (IARC Technical Report No. 4), Lyon, International Agency for Research on Cancer, pp. 65–70

Kaldor, J.M. (1989) Statistical methods for complex exposure histories in epidemiological studies. In: Dwyer, J.H., ed., *Statistical Models for Longitudinal Studies of Health,* Oxford, Oxford University Press (in press)

Kaldor, J.M. & Bosch, F.X. (1989) Multistage theory of carcinogenesis: The epidemiological evidence for liver cancer. In: Proceedings of symposium on Hepatic Tumour Promotion: Role of Environmental Factors, Paris, 27–28 April 1989. *Bull. Cancer* (in press)

Kaldor, J. & Byar, D.P. (1989) Quantification of the effects of preventive measures. In: Hakama, M., Beral, V., Cullen, J. & Parkin, M., eds, *Evaluating Effectiveness of Primary Prevention for Cancer* (IARC Scientific Publications No. 103), Lyon, International Agency for Research on Cancer (in press)

Kaldor, J.M. & Clayton, D.G. (1988) The role of advanced statistical techniques in cancer mapping. In: Boyle, P., Muir, C. & Grundmann, E., eds, *Cancer Mapping* (Recent Results in Cancer Research Vol. 114), Berlin, Heidelberg, New York, Springer Verlag, pp. 87–98

Kaldor, J.M. & Day, N.E. (1987) Interpretation of epidemiological studies in the context of the multistage model of carcinogenesis. In: Barrett, J.C., ed., *Mechanisms of Environmental Carcinogenesis.* Volume II, *Multistep Models of Carcinogenesis,* Boca Raton, Florida, CRC Press, pp. 21–57

Kaldor, J.M. & Day, N.E. (1988) Epidemiological studies of the relationship between carcinogenicity and DNA damage. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 460–468

Kaldor, J.M. & Day, N.E. (1989) Estimation of temporal effects in drug-induced leukaemia. *Stat. Med.* (in press)

Kaldor, J.M. & Parkin, D.M. (1988) IARC-coordinated study of cancer incidence following the Chernobyl accident. *Proceedings of the OECD Workshop on Epidemiology and Radiation Protection, Paris, October 1987,* Paris, OECD

Kaldor, J.M. & Shuker, D.E.G. (1989) Risk estimation for leukaemogenic drugs. In: Travis, C.C., ed., *Biologically Based Methods for Cancer Risk Assessment* (NATO Advanced Study Institute Series), Berlin, Heidelberg, New York, Springer Verlag, pp. 339–348

Kaldor, J.M. & Tomatis, L. (1988) The use of animal experiments in cancer risk assessment. *Stat. Sci., 3,* 41–43

Kaldor, J.M., Day, N.E. & Hemminki, K. (1988) Quantifying the carcinogenicity of antineoplastic drugs. *Eur. J. Cancer Clin. Oncol., 24,* 703–711

Kaldor, J.M., Schmähl, D. & Bartsch, H. (1987) International Symposium on the carcinogenicity of alkylating cytostatic drugs (meeting report). *Cancer Res., 47,* 2749–2751

Karran, P. & Hall, J. (1989) Repair of cytoxic lesions introduced into DNA by methylating agents. *Ann. Ist. Super. Sanità, 25,* 21–26

Katsouyani, K., Willett, W., Trichopoulos, D., Boyle, P., Trichopoulos, A., Vasilaros, S., Papadiamantis, J. & MacMahon, B. (1988) Risk of breast cancer among Greek women in relation to nutrient intake. *Cancer, 61,* 181–185

Kaye, S.B. & Boyle, P. (1989) The impact of chemotherapy in germ-cell tumours. *Cancer Surveys* (in press)

Khan, S., Martin, M., Bartsch, H. & Rahimtula, A.D. (1989) Perturbation of liver microsomal calcium homeostasis by ochratoxin A. *Biochem. Pharmacol., 38,* 67–72

Klann, R.C., Fitzgerald, D.J., Piccoli, C., Slaga, T.J. & Yamasaki, H. (1989) Characterization of gap-junctional intercellular communication in SENCAR mouse epidermal cell lines. *Cancer Res., 49,* 699–705

Kouzarides, T. & Ziff, E. (1989) The role of the leucone zipper in the fos-jun interaction. *Nature, 336,* 646–651

L'Abbé, K.A., Hoey, J.R., Hanley, J.A., Wacholder, S. & Nantel, A. (1988) Visits to a physician before and after exposure to urea-formaldehyde foam insulation. *Am. J. Public Health, 78,* 1489–1491

La Vecchia, C., Boyle, P., Cislaghi, C., Decarli, A. & Negri, E. (1989) Descriptive epidemiology of Hodgkin's disease in Italy. *Tumori* (in press)

La Vecchia, C., Negri, E. & Boyle, P. (1989) Reproductive factors and breast cancer: An overview. *Med. Soc. Prev., 34,* 101–107

La Vecchia, C., Negri, E., d'Avanzo, B., Ferraroni, M., Gramenzi, A., Savoldelli, R., Hsieh, C.-C., Boyle, P. & Franceschi, S. (1989) Medical history, diet and pancreatic cancer, *Oncology* (in press)

La Vecchia, C., Parazzini, F., Negri, E., Boyle, P., Gentile, A., Decarli, A. & Franceschi, S. (1989) Breast cancer and combined oral contraceptives: an Italian case-control study. *Eur. J. Cancer Clin. Oncol.* (in press)

Laib, R.J., Bolt, H.M., Cartier, R. & Bartsch, H. (1989) Increased alkylation of DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. *Toxicol. Lett., 45,* 231–239

Laitinen, M., Juvonen, R. & Hietanen, E. (1988) The effect of selenium on the hepatic drug metabolism and inducibility in rat. *Int. J. Biochem., 20,* 675–681

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

Laval, G., Souillet, G., Philippe, N. & Tuyns, A.J. (1988) Environmental factors in childhood leukaemia. *Pédiatrie, 43,* 59–65

Lee, H.P., Gourley, L., Duffy, S.W., Estève, J., Lee, J. & Day, N.E. (1989) Colorectal cancer and diet in an Asian population—A case-control study among Singapore Chinese. *Int. J. Cancer* (in press)

Lenoir, G.M. & Délécluse, H.J. (1989) Lymphoma and immunocompromised host. In: Revillard, J.-P. & Wierzbicki, N., eds, *Immune Disorders and Opportunistic Infections, Local Immunity, 5,* Fondation Franco-Allemande, Suresnes, France, pp. 173–183

Levi, F., Maisonneuve, P., Filiberti, R., La Vecchia, C. & Boyle, P. (1989) Cancer incidence and mortality in Europe. *Med. Soc. Prev.* (in press)

Lingao, A.L., Torres, N.T., Nuñoz, N., Lansang, M.A.D., West, S.K., Bosch, F.X. & Domingo, E.O. (1989) Mother to child transmission of hepatitis B virus in the Philippines. *Infection* (in press)

Lunn, G., Castegnaro, M. & Sansone, E.B. (1988) Decontamination and destruction of chemical carcinogens. In: Woo, Y.T., Lai, D.Y., Arcos, J.C. & Argus, M.F., eds, *Chemical Induction of Cancer,* Vol. IIIC, San Diego, Academic Press, pp. 711–740

Macfarlane, G.J., Boyle, P. & Scully, C. (1987) Rising mortality from cancer of the tongue in young Scottish males (letter). *Lancet, ii,* 912

Mack, T., Boyle, P. & Pour, P. (1989) Pancreas cancer: integration of epidemiology and laboratory. *Int. J. Pancreatology* (in press)

Macquart-Moulin, G., Riboli, E., Cornee, J., Kaaks, R. & Berthezene, P. (1987) Colorectal polyps and diet: A case-control study in Marseilles. *Int. J. Cancer, 40,* 179–188

Malaveille, C., Brun, G., Park, S.S., Gelboin, H.V. & Bartsch, H. (1987) A monoclonal antibody against cytochrome P-450 enhances mutagen activation of *N*-nitrosodimethylamine by mouse liver S9: studies on the mode of action. *Carcinogenesis, 8,* 1775–1779

Malaveille, C., Vineis, P., Estève, J., Ohshima, H., Brun, G., Hautefeuille, A., Gallet, P., Ronco, G., Terracini, B. & Bartsch, H. (1989) Levels of mutagens in the urine of smokers of black and blond tobacco correlate with their risk of bladder cancer. *Carcinogenesis, 10,* 577–586

Mark-Vendel, E., Philip, I., Philip, T., Lenoir, G.M., Berger, R. & Mitelman, F. (1988) Cytogenetic evaluation of bone marrow involvement in Burkitt's lymphoma. *Leukemia Res., 12,* 263–265

Mastrangelo, G., Zambon, P., Simonato, L. & Ricci, P. (1988) A case-referent study investigating the relationship between exposure to silica dust and lung cancer. *Int. Arch. Occup. Environ. Health, 60,* 299–302

Masui, T., Fukushima, S., Katoh, F., Yamasaki, H. & Ito, N. (1988) Effects of sodium L-ascorbate, uracil, butylated hydroxyanisole and extracellular pH on junctional intercellular communication of BALB/c 3T3 cells. *Carcinogenesis, 9,* 1143–1146

McCann, J., Gold, L.S., Horn, L., McGill, R., Graedel, T.E. & Kaldor, J. (1988) Statistical analysis of Salmonella test data and comparison to results of animal cancer tests. *Mutat. Res., 205,* 183–195

Mesnil, M. & Yamasaki, H. (1988) Selective gap junctional communication capacity of transformed and nontransformed rat-liver epithelial cell lines. *Carcinogenesis, 9,* 1499–1502

Mesnil, M. & Yamasaki, H. (1989) Role de la communication jonctionnelle intercellulaire lors de la cancérogenèse hépatique chez le rat. *Cancer Bull.* (in press)

Mesnil, M., Fitzgerald, D.J. & Yamasaki, H. (1988) Phenobarbital specifically reduces gap junction protein mRNA level in rat liver. *Mol. Carcinog., 1,* 79–81

Mesnil, M., Fraslin, J.-M., Piccoli, C., Yamasaki, H. & Guguen-Guillouzo, C. (1987) Cell contact but not junctional communication (dye coupling) with biliary epithelial cells is required for hepatocytes to maintain differentiated functions. *Exp. Cell Res., 173,* 524–533

Miller, G., Grogan, E., Rowe, D., Rooney, C., Heston, L., Eastman, R., Andiman, W., Niederman, J., Lenoir, G., Henle, W., Sullivan, J., Schooley, R., Vossen, J., Strauss, S. & Issekutz, T. (1987) Selective lack of antibody to a component of EB nuclear antigen in patients with chronic active Epstein-Barr virus infection. *J. Infect. Dis., 156,* 26–35

Monroe, J.E., Calender, A. & Mulder, C. (1988) Epstein-Barr virus positive and negative B-cell lines can be infected with human immunodeficiency virus types 1 and 2. *J. Virol., 62,* 3497–3500

Montesano, R. & Wild, C.P. (1988) Repair of alkylated DNA in rodent and human tissues. In: Iversen, O.H., ed., *Theories of Carcinogenesis,* Washington, Hemisphere, pp. 99–117

Montesano, R., Brésil, H., Degan, P., Martel-Planche, G., Serres, M. & Wild C.P. (1988) Detection in human cells of alkylated macromolecules attributable to nitrosamine exposure. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 75–82

Montesano, R., Cabral, J.R.P. & Wilbourn, J. (1988) Environmental carcinogens: using pesticides and nitrosamines as paradigms. *Ann. N.Y. Acad. Sci., 534,* 67–73

Montesano, R., Parkin, D.M. & Tomatis, L. (1989) Carcinogenesis producida por agentes ambientales. In: Barbacid, M., Mayor, F. & Ochoa, S., eds, *Recientes Progresos en Etiologia del Cancer y Patologia Molecular,* Madrid, Fundacion Ramon Areces, pp. 241–272

Montesano, R., Degan, P., Serres, M. & Wild, C.P. (1989) DNA alkylation adducts in human cells attributable to exposure to alkylating agents. In: Castellani, A., ed., *DNA Damage and Repair* (Proceedings of the First International Congress on DNA Damage and Repair, Rome 1987), New York, Plenum Press, pp. 83–86

Muir, C.S. (1989) Changing international patterns of cancer incidence. In: Rhoads, J.E., ed., *Accomplishments in Cancer Research, 1988,* Philadelphia, Lippincott, pp. 126–144

Muir, C.S. (1989) Geographical patterns of cancer: role of environment. In: Macieira-Coelho, A., ed., *Cancer and Aging,* Boca Raton, FL, CRC Press (in press)

Muir, C.S. (1989) The cancer burden with special reference to Europe and the EEC countries. In: Heller, T., Davey, B. & Bailey, L., *Reducing the Risk of Cancer,* London, Hodder & Stoughton, pp. 38–50

Muir, C.S. & Gran, M.-C. (1989) Cancer epidemiology. In: Veronesi, U., Arnesjo, B., Burn, I., Denis, L. & Mazzio, F., eds, *European Handbook of Surgical Oncology—the Present State of the Art in Europe,* Berlin, Heidelberg, New York, Springer Verlag, pp. 31–43

Muir, C.S. & Staszewski, J. (1989) Oropharyngeal cancer—pointers to aetiology from *Cancer Incidence in Five Continents.* In: Smith, C.J. & Pindborg, J.J., eds, *Oral Cancer in Western Countries, Epidemiology, Etiology and Pathology,* Geneva, Union International Contre le Cancer (in press)

Muir, C.S. & Whelan, S. (1989) International cancer registration. In: Zatonski, W. & Steffen, J., eds, *Proceedings of the Symposium on Cancer Prevention—Vital Statistics to Intervention, Warsaw, October 1988,* Warsaw, Sklodowska-Curie Memorial Cancer Centre

Muir, C.S. & Zaridze, D. (1987) Tobacco-associated non lung cancers. In: *Proceedings of the 14th International Cancer Congress, August 1986,* Budapest, Akademiai Kiado

Muir, C.S. & Zaridze, D.G. (1988) Smokeless tobacco and cancer. In: Eylenbosch, W.J., Van Larebeker, N. & Depoorter, A.M., eds, *Primary Prevention of Cancer* (Monograph Series of the European Organization for Research and Treatment of Cancer, Vol. 19), New York, Raven Press, pp. 93–104

Muir, C.S., Nectoux, J. & Staszewski, J. (1988) L'épidemiologie du cancer de la prostate: repartition géographique et évolution dans le temps. In: Khoury, S., ed., *Cancer de la Prostate,* Paris, Fondation Internationale pour l'Information Scientifique (FIIS)

Muir, C.S., Powell, J., Nectoux, J., Whelan, S. & Malhotra, A. (1988) Cancer registration in Europe: Coordination and role in cancer control. In: Eylenbosch, W.J., Van Larebeker, N. & Depoorter, A.M., eds, *Primary Prevention of Cancer* (Monograph Series of the European Organization for Research and Treatment of Cancer, Vol. 19), New York, Raven Press, pp. 1–36

Muir, C.S., Waterhouse, J., Mack, T., Powell, J. & Whelan, S., eds (1987) *Cancer Incidence in Five Continents,* Vol. V (IARC Scientific Publications No. 88), Lyon, International Agency for Research on Cancer

Muñoz, N. (1988) Descriptive epidemiology of stomach cancer. In: Reed, P.I. & Hill, M.J. eds, *Gastric Carcinogenesis,* Amsterdam, Excerpta Medica, pp. 51–69

Muñoz, N. & Bosch, F.X. (1987) Epidemiology of hepatocarcinoma. In: Okuda, K. & Ishak, K.G., eds, *Neoplasms of the Liver,* Tokyo, Springer, pp. 3–19

Muñoz, N. & Bosch, F.X. (1988) Epidemiological studies implicating human papillomavirus in the causation of carcinoma of the lower genital tract. In: De Palo, G., Rilke, F. & zur Hausen, H., eds, *Herpes and Papilloma Viruses: Their Role in the Carcinogenesis of the Lower Genital Tract,* Vol. II (Serono Symposia Publications, Vol. 46), New York, Raven Press, pp. 97–114

Muñoz, N. & Bosch, F.X. (1989) Epidemiology of cervical cancer. In: Muñoz, N., Bosch, F.X. & Jensen, O.M., eds, *Human Papillomavirus and Cervical Cancer* (IARC Scientific Publications No. 94), Lyon, International Agency for Research on Cancer, pp. 9–39

Muñoz, N., & Bosch, F.X. (1989) Epidémiologie moléculaire des papillomavirus et cancers génitaux. In: *M.S.T.: Hèrpes et papillomavirus* (Proceedings of 'Euromédecine 88', Montpellier (France), 8–12 November 1988), Paris, SN Editel, pp. 212–213

Muñoz, N., Bosch, F.X. & Kaldor, J.M. (1988) Does human papillomavirus cause cervical cancer? The state of the epidemiological evidence. *Br. J. Cancer, 47,* 1–5

Muñoz, N., Bosch, F.X. & Kaldor, J.M. (1989) Does human papillomavirus cause cervical cancer? the state of the epidemiological evidence (abstract). *Ob/Gyn. Digest, 3,* 22–24

Muñoz, N., Hayashi, M., Lu, J.B., Wahrendorf, J., Crespi, M. & Bosch, F.X. (1987) The effect of riboflavin, retinol and zinc on micronuclei of buccal mucosa and of oesophagus: A randomized double-blind intervention study in China. *J. Natl Cancer Inst., 79,* 687–691

Muñoz, N., Wahrendorf, J. & Bosch, F.X. (1987) Intervention studies in cancer research preven-

tion: some methodological issues of randomised intervention studies. In: Faivre, J. & Hill, M.J., eds, *Colorectal Cancer: Etiology, Causes and Prevention*, Amsterdam, Elsevier, pp. 141–153

Muñoz, N., Wahrendorf, J., Lu, B.J., Crespi, M. & Grassi, A. (1988) Vitamin intervention on precancerous lesions of the oesophagus in a high-risk population of China. *Ann. N.Y. Acad. Sci., 534*, 618–619

Murray, R.J., Young, L.S., Calender, A., Gregory, C.D., Rowe, M., Lenoir, G.M. & Rickinson, A.B. (1988) Different patterns of EBV gene expression and of cytotoxic T-cell recognition in B-cell lines infected with transforming (B95.8) or nontransforming (P3HR1) virus strains. *J. Virol., 62*, 894–901

Nair, J., Nair, U.J., Ohshima, H., Bhide, S.V. & Bartsch, H. (1987) Endogenous nitrosation in the oral cavity of chewers while chewing betel quid with or without tobacco. In: Bartsch, H., O'Neill, I.K. & Schulte-Hermann, R., eds, *The Relevance of N-Nitroso Compounds to Human Cancer: Exposures & Mechanisms* (IARC Scientific Publications No. 84), Lyon, International Agency for Research on Cancer, pp. 465–469

Nair, U., Floyd, R.A., Nair, J., Bussacchini, V., Friesen, M. & Bartsch, H. (1987) Formation of reactive oxygen species and of 8-hydroxydeoxyguanosine in DNA *in vitro* with betel quid ingredients. *Chem. Biol. Interactions, 63*, 157–169

Nakamura, Y., Mathew, C.G.P., Sobol, H., Easton, D.F., Telenius, H., Bragg, T., Chin, K., Clark, J., Jones, C., Lenoir, G.M., White, R. & Ponder, B.A.J. (1989) Linked markers flanking the gene for multiple endocrine neoplasia type 2A. *Genomics, 5*, 199–203

Napalkov, N., Loktionov, A., Likhachev, A., Anisimov, V., Zabezhinski, M. & Tomatis, L. (1987) Persistence of carcinogenic effect in intact progeny of mice treated transplacentally with 7,12-dimethylbenz(a)anthracene. *Cancer Lett., 38*, 231–234

Napalkov, N.P., Anisimov, V.N., Likhachev, A.J. & Tomatis, L. (1989) 5-Bromodeoxyuridine-induced carcinogenesis and its modification by persistent estrus syndrome, unilateral nephrectomy, and X-irradiation in rats. *Cancer Res., 49*, 318–323

Narod, S.A., Sobol, H., Nakamura, Y., Calmettes, C., Baulieu, J.L., Bigorgne, J.C., Chabrier, G., Couette, J., de Gennes, J.L., Duprey, J., Gardet, P., Guillausseau, P.J., Guilloteau, D., Houdent, C., Lefebvre, J., Modigliani, E., Parmentier, C., Pugeat, M., Siame, C., Tourniaire, J., Vandroux, J.C., Vinot, J.M. & Lenoir, G.M. (1989) Linkage analysis of hereditary thyroid carcinoma with and without pheochromocytoma. *Hum. Genet.* (in press)

Neal, G.E., Mandel, H.G., Manson, M.M. & Cabral, J.R.P. (1989) The increased formation of altered foci in the livers of aflatoxin B_1 treated partially hepatectomised rats resulting from ethyoxyquin administration. *Toxicologist, 9*, 209

Nectoux, J., Muir, C.S. & Parkin, D.M. (1988) International patterns of cancer. In: Zaridze, D.G., MacMahon, B. & Maclure, K.M., eds, *The Epidemiology of Cancer* [in Russian] (in press)

Negri, E., Piolatto, G., Pira, E., Decarli, A., Kaldor, J. & La Vecchia, C. (1989) Cancer mortality in a Northern Italian cohort of rubber workers. *Br. J. Ind. Med.* (in press)

Ngendahayo, P., Mets, T., Bugingo, G. & Parkin, D.M. (1989) Le sarcome de Kaposi au Rwanda: aspects clinico-pathologiques et épidémiologiques. *Bull. Cancer, 76*, 383–394

O'Neill, I.K., Castegnaro, M., Brouet, I. & Povey, A.C. (1987) Magnetic semipermeable polyethyleneimine microcapsules for monitoring of *N*-nitrosation in the gastrointestinal tract. *Carcinogenesis, 8*, 1469–1474

O'Neill, I.K., Povey, A.C., Bingham, S., Brouet, I. & Béréziat, J.-C. (1988) Recoverable semipermeable microencapsulated DNA surrogates for monitoring the colorectal cavity; *in situ* effects of fibre/meat in human diets on benzo[*a*]pyrene and possible endogenous crosslinking agents. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 107–112

Ohshima, H. & Bartsch, H. (1988) Urinary *N*-nitrosamino acids as an index of exposure to *N*-nitroso compounds. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 83–91

Ohshima, H., Friesen, M. & Bartsch, H. (1989) Identification in rats of *N*-nitrosonipecotic acid as a major urinary metabolite of the areca-nut alkaloid-derived nitrosamines, *N*-nitrosoguvacoline and *N*-nitrosoguvacine. *Cancer Lett., 44*, 211–216

Ohshima, H., Friesen, M., Malaveille, C., Brouet, I., Hauteuille, A. & Bartsch, H. (1989) Formation of direct-acting genotoxic substances in nitrosated smoked fish and meat products: Identification of simple phenolic precursors and phenyldiazonium ions as reactive products. *Food Chem. Toxicol., 27*, 193–203

Ohshima, H., Furihata, C., Matsushima, T. & Bartsch, H. (1989) Evidence of potential tumour-initiating and -promoting activities of hickory smoke condensate when given alone or with nitrite to rats. *Food Chem. Toxicol.* (in press)

Ohshima, H., Pignatelli, B., Malaveille, C., Friesen,

M., Calmels, S., Shuker, D., Muñoz, N. & Bartsch, H. (1988) Markers for intragastric nitrosamine formation and resulting DNA damage. In: Reed, P.I. & Hill, M.J., eds, *Gastric Carcinogenesis,* Amsterdam, Excerpta Medica, pp. 175–185

Olaya, F. & Nectoux, J., eds (1987) *Le Cancer en Ardèche du Nord—Incidence 1983–1986,* Lyon, International Agency for Research on Cancer

Paci, E., Buiatti, E., Constantini, A., Miligi, L., Pucci, N., Scarpelli, A., Petrioli, G., Simonato, L., Winkelmann, R. & Kaldor, J. (1989) Aplastic anaemia, leukaemia and other cancer mortality in a cohort of shoe workers exposed to benzene. *Scand. J. Work Environ. Health* (in press)

Parfenov, Y.D., Nikonova, T.V., Montesano, R., Politova, S.N. & Turusov, V.S. (1987) Influence of duration of 1,2-dimethylhydrazine treatment on its carcinogenic effect. *Exp. Oncol.* (Kiev), *9*, NS, 56–60

Parkin, D.M. (1988) Surveillance of cancer. In: Eylenbosch, W.J. & Noah, N.D., eds, *Surveillance in Health and Disease,* Oxford, Oxford University Press, pp. 143–165

Parkin, D.M. (1989) Cancer detection and screening: High risk groups. In: Veronesi, U., ed., *European Handbook of Surgical Oncology,* Berlin, Heidelberg, New York, Springer-Verlag (in press)

Parkin, D.M. (1989) Trends in lung cancer incidence worldwide. *Chest* (in press)

Parkin, D.M. & Coleman, M.P. (1989) Changes in diet and changes in cancer risk: observational studies. In: Hakama, M., Beral, V., Cullen, J. & Parkin, M., eds, *Evaluating Effectiveness of Primary Prevention of Cancer* (IARC Scientific Publications No. 103), Lyon, International Agency for Research on Cancer (in press)

Parkin, D.M., Läärä, E. & Muir, C.S. (1988) Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int. J. Cancer, 41,* 184–187

Parkin, D.M., Stiller, C..A., Draper, G.J. & Bieber, C.A. (1988) The international incidence of childhood cancer. *Int. J. Cancer, 42,* 511–520

Parkin, D.M., Stiller, C.A., Draper, G.J., Bieber, C.A., Terracini, B. & Young, J.L., eds (1988) *International Incidence of Childhood Cancer* (IARC Scientific Publications No. 87), Lyon, International Agency for Research on Cancer

Parkin, D.M., Nectoux, J., Stiller, C.A. & Draper, G.J. (1989) L'incidence des cancers de l'enfant dans le monde. *Pédiatrie* (in press)

Pavenello, S., Rojas, M., Paleologo, M., Levis, A.G. & Alexandrov, K. (1989) Evidence for substantial formation of *r*-7,*t*-8-dihydroxy-*c*-9,10-oxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenedeoxyguanosine in human lymphocytes treated *in vitro* with benzo[*a*]pyrene. *Carcinogenesis, 10,* 945–947

Percy, C. & Muir, C.S. (1989) The international comparability of cancer mortality data: results of an international death certificate study. *Am. J. Epidemiol., 129,* 934–946

Petkova-Bocharova, T., Chernozemsky, I.N. & Castegnaro, M. (1988) Ochratoxin A in human blood in relation to Balkan endemic nephropathy and urinary system tumours in Bulgaria. *Food Addit. Contam., 5,* 299–301

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) Long-lasting effects of tobacco smoking on pulmonary drug-metabolizing enzymes: A case-control study on lung cancer patients. *Cancer Res., 48,* 4695–4700

Petruzzelli, S., DeFlora, S., Bagnasco, M., Hietanen, E., Camus, A.-M., Saracci, R., Izzotti, A., Bartsch, H. & Giuntini, C. (1989) Carcinogen metabolism studies in human bronchial and lung parenchymal tissues. *Am. Rev. Resp. Dis.* (in press)

Péquignot, G., Crosignani, P., Terracini, B., Ascunce, N., Zubiri, A., Raymond, L., Estève, J. & Tuyns, A.J. (1988) A comparative study of smoking, drinking and dietary habits in population samples in France, Italy, Spain and Switzerland. III. Consumption of alcohol. *Rev. Santé Publ. Epidémiol.* (in press)

Picot, A. & Castegnaro, M. (1989) Sécurité et prévention. II. Risques liés à la manipulation des produits cancérogènes. B. Liste reactualisée des principaux produits génotoxiques utilisés au laboratoire. *L'Actualité Chimique,* janvier-fevrier, 12–27

Picot, A., Zadjela, F. & Castegnaro, M. (1989) Liste des produits génotoxiques utilisés au laboratoire. Paris, Institut National de Recherche et de Sécurité (in press)

Pignatelli, B., Calmels, S., Malaveille, C., Ohshima, H., Muñoz, N. & Bartsch, H. (1989) Bacteries, nitrosation intragastrique et lesions précancéreuses de l'estomac. Proceedings of meeting on *Campylobacter pylori* in Nancy, January 1988 (in press)

Pignatelli, B., Chen, C.-S., Thuillier, P. & Bartsch, H. (1989) An improved method for the analysis of total *N*-nitroso compounds (NOC) in biological matrices including human gastric juice. Proceedings of a symposium 'The significance of *N*-nitrosation of drugs', Titisee, FR Germany, September 1988 (in press)

Pignatelli, B., Chen, C.-S., Thuillier, P. & Bartsch, H. (1989) Group-selective determination of total *N*-nitroso compounds (NOC) in nitrate-containing human urine samples. *Analyst* (in press)

Pignatelli, B., Malaveille, C., Friesen, M., Hautefeuille, A. & Bartsch, H. (1987) Synthesis, structure-activity relationships and a reaction mechanism for mutagenic *N*-nitroso derivatives of glycosylamines and Amadori compounds—model

substances for *N*-nitrosated early Maillard reaction products. *Food Chem. Toxicol., 25,* 669–680

Pignatelli, B., Richard, I., Bourgade, M.-C. & Bartsch, H. (1987) Improved group determination of total *N*-nitroso compounds in human gastric juice by chemical denitrosation and thermal energy analysis. *Analyst, 112,* 945–949

Poirier, S., Hubert, A., De-Thé, G., Ohshima, H., Bourgade, M.-C. & Bartsch, H. (1987) Occurrence of volatile nitrosamines in food samples collected in three high-risk areas for nasopharyngeal carcinoma. 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. 415–422

Povey, A.C. & O'Neill, I.K. (1988) A microencapsulated target system capable of intercepting labile metabolites formed *in situ* within the intestinal lumen. In: *Gnotobiology and its Applications,* Lyon, Edition Fondation Marcel Mérieux, pp. 157–159

Povey, A.C., Bingham, S., Brouet, I., Béréziat, J.-C. & O'Neill, I.K. (1987) The effect of fibre and meat in human diets upon binding of benzo(*a*)pyrene metabolites *in vivo* to magnetic polyethyleneimine (PEI) microcapsules. *Proc. Am. Assoc. Cancer Res., 28,* 110

Povey, A.C., Godeneche, D. & O'Neill, I.K. (1988) time-dependent distribution and excretion of radio-labelled semi-permeable, stable magnetic microcapsules. *J. Pharm. Pharmacol., 40,* 431–433

Povey, A.C., Nixon, J.R. & O'Neill, I.K. (1987) Membrane formation and characterization of semi-permeable polyhexamethyleneterephthalamide microcapsules containing polyethyleneimine (PEI) for trapping carcinogens. *J. Microencaps., 4,* 299–314

Rahimtula, A.D., Béréziat, J.-C., Bussacchini-Griot, V. & Bartsch, H. (1988) Lipid peroxidation as a possible cause of ochratoxin A toxicity. *Biochem. Pharmac., 37,* 4469–4477

Rahimtula, A.D., Castegnaro, M., Béréziat, J.C., Bussacchini-Griot, V., Broussolle, L., Michelon, J. & Bartsch, H. (1989) Lipid peroxidation as a possible cause of ochratoxin A toxicity. In: Bach, P.H. & Lock, E.A., eds, *Nephrotoxicity: Extrapolation from* in vitro *to* in vivo, *and Animals to Man,* New York, Plenum Press, pp. 617–622

Raymond, L., Infante, F., Tuyns, A.J. & Lowenfels, A.B. (1987) Alimentation et cancer du pancréas. *Gastroenterol. Clin. Biol., 11,* 488–492

Riboli, E. (1987) Epidemiology of colorectal cancer and diet. In: Hill, M. & Faivre, J., eds, *Colorectal Cancer: Etiology, Prevention and Early Diagnosis,* Amsterdam, Elsevier, pp. 49–60

Riboli, E. (1987) Questionnaire used in the International Study on Exposure to Other People's Smoke and Urinary Cotinine Levels in Nonsmokers. In: O'Neill, I.K., Brunnemann, K.D., Dodet, B. & Hoffmann, D., eds, *Environmental Carcinogens. Selected Methods of Analysis and Exposure Measurement,* Vol. 9, *Passive Smoking* (IARC Scientific Publications No. 81), Lyon, International Agency for Research on Cancer, pp. 353–372

Riboli, E. (1989) Methodological issues in the investigation of diet and cancer in humans. In: Miller, A.B., ed., *Diet and the Aetiology of Cancer* (ESO Monograph Series), Berlin, Heidelberg, New York, Springer Verlag, pp. 55–63

Riboli, E. & Saracci, R., eds, (1988) *Diet, Hormones and Cancer: Methodological Issues for Prospective Studies* (IARC Technical Report No. 4), Lyon, International Agency for Research on Cancer

Riboli, E., Péquignot, G., Repetto, F., Axerio, M., Raymond, L., Boffetta, P., Zubiri, A., Del Moral, A., Estève, J. & Tuyns, A.J. (1988) A comparative study of smoking, drinking and dietary habits in population samples in Italy, Spain, Switzerland and France: I. Study design and dietary habits. *Rev. Epidemiol. Santé Publ., 36,* 151–165

Riboli, E., Rönnholm, M. & Saracci, R. (1987) Biological markers of diet. *Cancer Surveys, 6,* 685–718

Robertson, J., Boyle, P. & Imrie, C.W. (1988) Patients with ampullary carcinoma are prone to other malignant tumours. *Br. J. Cancer, 58,* 216–218

Rousset, F., Billaud, M., Figdor, C., Blanchard, D., Lenoir, G.M., Spitz, H. & de Vries, J.E. (1989) IL-4 induces LFA-1 and LFA-3 expression on Burkitt's Lymphoma cell lines: Requirement of LFA-1 activation for induction of homotypic cell adhesions. *J. Immunol., 143,* 1490–1498

Saracci, R. (1987) The interactions of tobacco smoking and other agents in cancer etiology. *Epidemiol. Rev., 9,* 175–193

Saracci, R. (1988) Prospective studies on diet and cancer: reasons and opportunities for international collaboration. In: Riboli, E. & Saracci, R., eds, *Diet, Hormones and Cancer: Methodological Issues for Prospective Studies* (IARC Technical Report No. 4), Lyon, International Agency for Research on Cancer, pp. 1–11

Saracci, R. (1989) The health hazards of man-made mineral fibers. In: Mohr, U., ed., *Assessment of Inhalation Hazards,* Berlin, Heidelberg, New York, Springer Verlag (in press)

Saracci, R. & Riboli, E. (1989) Passive smoking and lung cancer: Current evidence and ongoing studies at the International Agency for Research on Cancer. *Mutat. Res., 222,* 117–127

Sasco, A. (1988) Cancer risk in biology laboratory workers. In: *Proceedings* '1988 *European Meeting*

of the Toxicology Forum', Lyon, 1988, pp. 215–222

Sasco, A.J. (1988) Etiologic and prevented fractions in case-control studies for the evaluation of screening (letter to the editor). *J. Clin. Epidemiol., 41,* 809–811

Sasco, A.J. (1988) Lead time and length bias in case-control studies for the evaluation of screening (letter to the editor). *J. Clin. Epidemiol., 41,* 103–104

Sasco, A.J. (1988) Screening for lung cancer. In: Lapis, K. & Eckhardt, S., eds, *Epidemiology, Diagnosis, Prevention. Lectures and Symposia of the 14th International Cancer Congress, Budapest, 1986,* Vol. 6, Budapest, Akademiai Kiado, pp. 177–185

Sasco, A.J. (1989) Risques pour la santé dans les laboratoires de recherche biomédicale. In: Fridman, W.H., ed., *Risques liés à la manipulation des produits mutagènes et génotoxiques* (Bulletin Officiel No. 89, 8 bis), Paris, Ministère de la Solidarité, de la Santé et de la Protection sociale.

Sasco, A.J. (1989) Migrations et cancers. *Rev. Med. Int.* (in press)

Sasco, A.J. (1989) Risques pour la santé dans les laboratoires de recherche biomédicale. Le point sur les connaissances épidémiologiques actuelles. *Médecine/Science* (in press)

Sasco, A.J., Van der Elst, P. & Dalla-Vorgia, P. (1989) *Comparative Study of Anti-smoking Legislation in the Member States of the EEC* (IARC-EEC Technical Report)/*Etude comparative des législations anti-tabac dans les pays de la Communauté Economique Européenne* (Rapport technique CIRC-CEE) (in press)

Saul, C., Crespi, M., Braga, N., Victora, C.G. & Munõz, N. (1987) Peptic lesions of the gastroduodenal mucosa in volunteers submitted to a programme of endoscopic examination [in Portugese]. *Revista Brasiliera de Medicine, 44,* 265–268

Scully, C., Boyle, P. & Prime, S. (1989) Oral cancer (editorial). *Lancet, ii,* 311–312

Seigneurin, J-M., Lavoué, M.-F., Genoulaz, O., Bornkamm, G.W. & Lenoir, G.M. (1987) Antibody response against the Epstein-Barr virus-coded nuclear antigen 2 (EBNA2) in different groups of individuals. *Int. J. Cancer, 40,* 349–353

Shao, Y.M., Poirier, S., Ohshima, H., Malaveille, C., Zeng, Y., de Thé, G. & Bartsch, H. (1988) Epstein-Barr virus activation in Raji cells by extracts of preserved food from high risk areas for nasopharyngeal carcinoma. *Carcinogenesis, 9,* 1455–1457

Shiba, Y., Yamasaki, H. & Kanno, Y. (1987) Tumor-promoting phorbol esters, but not carcinogens, rapidly inhibit bud formation in hydra. *Roux's Arch. Develop. Biol., 196,* 445–449

Shuker, D.E.G. (1987) Determination of urinary alkylated nucleic acid bases by immunoassay. *Br. J. Cancer, 56,* 191–192

Shuker, D.E.G. (1987) Reliable exposure assessment. *Nature, 329,* 582–583

Shuker, D.E.G. (1988) Determination of *N*7-methylguanine by immunoassay. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 296–300

Shuker, D.E.G. (1989) Detection of adducts arising from human exposure to *N*-nitroso compounds. *Cancer Surveys, 8,* No. 2 (in press)

Shuker, D.E.G. (1989) Nucleic acid-carcinogen adducts in human dosimetry. *Arch. Toxicol.* (in press)

Shuker, D.E.G. & Farmer, P.B. (1988) Urinary excretion of 3-methyladenine in humans as a marker of nucleic acid methylation. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 92–96

Siemiatycki, J., Wacholder, S., Dewar, R., Cardis, E. & Greenwood, C. (1988) The degree of confounding bias related to smoking, ethnic group and socioeconomic status in estimates of the associations between occupation and cancer. *J. Occup. Med., 30,* 617–625

Sierra, R., Parkin, D.M. & Muñoz Leiva, G. (1989) Cancer in Costa Rica. *Cancer Res., 49,* 717–724

Sierra, R., Parkin, D.M., Barrantes, R., Bieber, C.A., Muñoz Leiva, G. & Muñoz Calero, N. (1988) *Cancer in Costa Rica* (IARC Technical Report No. 1), Lyon, International Agency for Research on Cancer

Simonato, L., Baris, I., Saracci, R., Skidmore, J. & Winkelmann, R. (1989) Relation of environmental exposure to erionite fibres to the risk of respiratory cancer. In: Bignon, J., Peto, J. & Saracci, R., eds, *Non-occupational Exposure to Mineral Fibres* (IARC Scientific Publications No. 90), Lyon, International Agency for Research on Cancer, pp. 398–405

Simonato, L., Fletcher, A.C., Cherrie, J., Andersen, A., Bertazzi, P., Bolander, A.M., Charnay, N., Claude, J., Estève, J., Frentzel-Beyme, R., Gardner, M.J., Jensen, O., Olsen, J., Saracci, R., Teppo, L., Westerholm, P., Winkelmann, R., Winter, P.D. & Zochetti, C. (1988) Mortality among a cohort of man-made mineral fibres (MMMF) production workers in seven countries: extension of the follow-up until 1982. *Ann. Occup. Hyg., 32,* 725–734

Simonato, L., Vineis, P. & Fletcher, A.C. (1988) Estimates of the proportion of lung cancer

attributable to occupational exposure. *Carcinogenesis, 9,* 1159–1165

Skare, J., Grierson, H.L., Sullivan, J.L., Nussbaum, R.L., Purtilo, D.T., Sylla, B.S., Lenoir, G.M., Reilly, D.S., White, B.N. & Milunsky, A. (1989) Linkage analysis of seven kindreds with the X-linked lymphoproliferative syndrome confirms that the XLP locus is near DXS42 and DXS37. *Hum. Genet., 82,* 354–358

Smans, M., Boyle, P. & Muir, C.S. (1989) Cancer mortality atlas of the European Economic Community. In: Boyle, P., Muir, C. & Grundmann, E., eds, *Cancer Mapping* (Recent Results in Cancer Research Vol. 114), Berlin, Heidelberg, New York, Springer Verlag, pp. 253–268

Smith, A.G., Francis, J.E., Carthew, P., Manson, M.M. & Cabral, J.R.P. (1989) Carcinogenicity of iron with hexachlorobenzene in C57BL/10SCSN mice. *Toxicologist, 9,* 209

Smith, G.A., Dinsdale, D., Cabral, J.R.P. & Wright, A.L. (1987) Goitre and wasting induced in hamsters by hexachlorobenzene. *Arch. Toxicol., 60,* 343–349

Sobol, H., Narod, S.A., Nakamura, Y., Boneu, A., Calmettes, C., Chadenas, D., Charpentier, G., Chatal, J.F., Dupond, J.L., Delepine, N., Delisle, M.J., Gardet, P., Godefroy, H., Guillausseau, P.J., Guillausseau-Scholer, C., Houdent, C., Lalau, J.D., Mace, G., Parmentier, C., Soubrier, F., Tourniaire, J., & Lenoir, G.M. (1989) The screening for multiple endocrine neoplasia type 2A by DNA polymorphism analysis. *New Engl. J. Med., 321,* 996–1001

Sobol, H., Salvetti, A., Bonnardel, C. & Lenoir, G.M. (1988) Screening multiple endocrine neoplasia type 2A families using DNA markers. *Lancet, i,* 62

Srivistanakul, P., Sontipong, S., Chotiwan, P. & Parkin, D.M. (1988) Liver cancer in Thailand. Temporal and geographic variations. *J. Gastroenterol. Hepatol., 3,* 413–420

Stählberg, M.-R., Hietanen, E. & Mäki, M. (1988) Mucosal biotransformation rates in the small intestine of children. *Gut, 29,* 1058–1063

Steinitz, R., Parkin, D.M., Young, J.L., Bieber, C.A. & Katz, L., eds (1989) *Cancer Incidence in Jewish Migrants to Israel, 1961–1981* (IARC Scientific Publications No. 98), Lyon, International Agency for Research on Cancer (in press)

Sundqvist, K., Liu, Y., Nair, J., Bartsch, H., Arvidson, K. & Grafström, R.C. (1989) Cytotoxic and genotoxic effects of areca nut-related compounds in cultured human buccal epithelial cells. *Cancer Res.* (in press)

Sylla, B.S., Wang, Q., Hayoz, D., Lathrop, G.M. & Lenoir, G.M. (1989) Multipoint linkage mapping of the Xq25-q26 region in a family affected by the X-linked lymphoproliferative syndrome. *Clinical Genetics, 36* (in press)

Szajnert, M.F., Saule, S., Bornkamm, G.W., Wajcman, H., Lenoir, G.M. & Kaplan, J.C. (1987) Clustered somatic mutations in and around first exon of non-rearranged c-myc in Burkitt lymphoma with t(8;22) translocation. *Nuc. Acids Res., 15,* 4553–4565

The Gambia Hepatitis Study Group (1989) Hepatitis B vaccine in the expanded programme of immunisation: the Gambian experience. *Lancet, i,* 1057–1060

Thurnham, D.I., Muñoz, N., Lu, J.B., Wahrendorf, J., Zheng, S-F., Hambidge, K.M. & Crespi, M. (1988) Nutritional and haematological status of Chinese farmers: the influence of 13.5 months treatment with riboflavin, retinol and zinc. *Eur. J. Clin. Nutr., 42,* 647–660

Tomatis, L. (1987) An efficient primary prevention of cancer requires an integrated approach: Muhlbock Memorial Lecture. *Eur. J. Cancer Clin. Oncol., 23,* 1571–1575

Tomatis, L. (1987) The identification of cancer risk factors and the possibility for cancer prevention [in Russian]. *Vopr. Oncol.,* XXXIII (12), 3–12

Tomatis, L. (1988) Cancro professionale: rassegna storica e occasione attuali di prevenzione. *Medicine dei Lavoratori, 9,* 135–147

Tomatis, L. (1988) Contro l'epatite in Gambia. *Cooperazione, 76,* 47–48

Tomatis, L. (1988) Environmental cancer risk factors (a review). *Acta Oncologica, 27,* 1–8

Tomatis, L. (1988) Prenatal carcinogenesis. In: Kakunaga, T., Sugimura, T., Tomatis, L. & Yamasaki, H., eds, *Cell Differentiation, Genes and Cancer* (IARC Scientific Publications No. 92), Lyon, International Agency for Research on Cancer, pp. 121–132

Tomatis, L. (1988) The contribution of the IARC Monographs program to the identification of cancer risk factors. In: Maltoni, C. & Selikoff, I.J., eds, *Living in a Chemical World—Occupational and Environmental Significance of Industrial Carcinogens* (Annals of the New York Academy of Sciences, Vol. 534), New York, New York Academy of Sciences, pp. 31–38

Tomatis, L. (1989) Factores de riesgo ambientales en el cáncer. *Revisión Oncología, 5,* 221–230

Tomatis, L. (1989) Overview on perinatal and multigeneration carcinogenesis. In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96), Lyon, International Agency for Research on Cancer, pp. 1–16

Tomatis, L., Aitio, A., Wilbourn, J. & Shuker, L. (1989) Human carcinogens so far identified. *Jpn J. Cancer Res.* (in press)

Tomatis, L., Turusov, V.S., Cardis, E. & Cabral, J.R.P. (1989) Tumour incidence in the progeny of male rats exposed to ethylnitrosourea before mating. *Mutat. Res.* (in press)

Toniolo, P., Riboli, E., Protta, F., Charrel, M. & Cappa, A.P.M. (1989) Calorie-providing nutrients and risk of breast cancer. *J. Natl Cancer Inst., 81,* 278–286

Touraine, J.L., Deteix, P., El Yafi, M., Traeger, J., Dubernard, J.M., LeFrançois, N., Lenoir, G. & de-Thé, G. (1987) Virus-induced lymphomas in transplant patients under immunosuppressive therapy. *Transplantation Proceedings,* Vol. XIX, pp. 4087–4088

Trillet, V., Wang, Q., Moro, D., Mornex, J.F., Brambilla, E., Brambilla, C., Brune, J. & Lenoir, G.M. (1989) Molecular analysis on primary lung cancer biopsies: feasibility of a systematic approach. *Bull. Cancer* (in press)

Turc-Carel, C., Aurias, A., Mugneret, F., Lizard, S., Sidaner, I., Volk, C., Thiery, J-P., Olschwang, S., Philip, I., Berger, M.P., Philip, T., Lenoir, G.M. & Mazabraud, A. (1988) Chromosomes in Ewing's sarcoma. I. An evaluation of 85 cases and remarkable consistency of t(11;22) (q24;q12). *Cancer Genet. Cytogenet., 32,* 229–238

Turusov, V.S. (1988) On the histogenesis of neurinomas induced in rats by ethylnitrosourea [in Russian]. *Vopr. Oncol. (USSR), 34,* 699–704

Turusov, V.S. & Cabral, J.R.P. (1988) Histogenesis of endocardial tumours of rats [in Russian]. *Exp. Oncol. (USSR), 10* (1), 23–27

Turusov, V. & Cardis, E. (1988) Review of experiments on multigeneration carcinogenicity: design, experimental models and analysis. In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96), pp. 105–120

Turusov, V., Tomatis, L., Cabral, R., Cardis, E. & Tiutiunnik, N.F. (1988) Transzygotic carcinogenic effect of nitrosoethylurea in rats. *Exp. Oncol.* (Kiev), *10*(3), 25–28

Turusov, V.S., Cardis, E., Tomatis, L. & Cabral, J.R.P. (1989) Tumour incidence in the progeny of male rats exposed to ethylnitrosourea before mating. *Exp. Oncol.* (Kiev) (in press)

Tuyns, A.J. (1987) Cancer risks derived from alcohol. *Med. Oncol. Tumour Pharmacol., 4,* 241–244

Tuyns, A.J. (1988) Beer consumption and rectal cancer. *Rev. Epidémiol. Santé Publ., 36,* 144–145

Tuyns, A.J. (1988) Drinking sensibly. *Br. J. Addict., 83,* 35–43

Tuyns, A.J. (1988) Prévention des cancers induits par l'alcool et le tabac. *Encycl. Med. Chir.* (Paris), 1–5

Tuyns, A.J. (1988) Salt and gastrointestinal cancer. *Nutr. Cancer, 11,* 229–232

Tuyns, A.J. (1989) Tobacco, alcohol and diet as cancer risk factors, with particular reference to cancer of the upper aero-digestive tract. In: Maskens, A.P., Molimard, R., Preussman, R. & Wilmer, J.W., eds, *Tobacco and Cancer: Perspectives in Preventive Research,* Amsterdam, Elsevier, pp. 131–134

Tuyns, A.J. & Péquignot, G. (1989) Alcohol, cirrhosis and cancer. The dose-response relationship. Practical implications. In: Waahlberg, R.B., ed., *Prevention and Control/Realities and Aspirations,* Vol. IV, Oslo, National Directorate for the Prevention of Alcohol and Drug Problems, pp. 671–673

Tuyns, A.J. & Péquignot, G. (1989) Recent findings on alcohol use in relation to laryngeal cancer in four latin European countries. In: Waahlberg, R.B., ed., *Prevention and Control/Realities and Aspirations,* Vol. IV, Oslo, National Directorate for the Prevention of Alcohol and Drug Problems, pp. 674–683

Tuyns, A.J., Haelterman, M. & Kaaks, R. (1987) Colorectal cancer and the intake of nutrients: Oligosaccharides are a risk factor, fats are not: A case-control study in Belgium. *Nutr. Cancer, 10,* 181–196

Tuyns, A.J., Estève, J., Raymond, L., Berrino, F., Benhamou, E., Boffetta, P., Crosignani, P., Del Moral, A., Lehmann, W., Merletti, F., Péquignot, G., Riboli, E., Sancho-Garnier, H., Terracini, B., Zubiri, A. & Zubiri, L. (1988) Cancer of the larynx/hypopharynx, tobacco and alcohol. *Int. J. Cancer, 41,* 483–491

Tuyns, A.J., Kaaks, R. & Haelterman, M. (1988) Colorectal cancer and the consumption of foods: A case-control study in Belgium. *Nutr. Cancer, 11,* 189–204

Vainio, H. (1987) Occupational cancer prevention. *J. Cancer Res. Clin. Oncol., 113,* 403–412

Vainio, H., Parkin, D.M. & Tomatis, L. (1989) Cancer. In: Lambo, T. & Day, S.B., eds, *Issues in International Health,* New York, Plenum Press (in press)

Van Benthem, J., Wild, C.P., Vermeulen, E., Winterwerp, H.H.K., Den Engelse, L. & Scherer, E. (1988) Immunocytochemical localization of DNA adducts in rat tissues following treatment with *N*-nitrosomethylbenzylamine. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 102–106

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., Philpps, R., Pfau, R.S., Prade, M., Pozharisski, K.M., Rilke, F. & Schafler, K. (1989) Temporal change in diagnostic criteria as a cause of the increase of malignant melanoma over time is unlikely. *Int. J. Cancer* (in press)

Viladiu, P. & Bosch, F.X. (1987) The opportunities

for epidemiological research [in Spanish]. *Medicina Integral, 10,* 84–90

Villard-Mackintosh, L., Coleman, M.P. & Vessey, M.P. (1988) The completeness of cancer registration in England: an assessment from the Oxford-FPA contraceptive study. *Br. J. Cancer, 58,* 507–511

Vineis, P., Fletcher, A. & Simonato, L. (1987) Estimates of the proportion of lung cancer attributable to occupation. *Scand. J. Work Environ. Health, 13,* 158

Wahrendorf, J., Muñoz, N., Lu, J.B., Thurnham, D.I., Crespi, M. & Bosch, F.X. (1988) Blood, retinol and zinc riboflavin status in relation to precancerous lesions of the esophagus: findings from a vitamin intervention trial in the People's Republic of China. *Cancer Res., 48,* 2280–2283

Wallace, L.A. & O'Neill, I.K. (1987) Personal air and biological monitoring of individuals for exposure to environmental tobacco smoke. In: O'Neill, I.K., Brunnemann, K.D., Dodet, B. & Hoffmann, D., eds, *Environmental Carcinogens—Methods of Analysis and Exposure Measurement,* Volume 9, *Passive Smoking* (IARC Scientific Publications No. 81), Lyon, International Agency for Research on Cancer, pp. 87–103

Westin, J.B., Castegnaro, M. & Friesen, M. (1987) *N*-Nitrosamines and nitrosatable amines, potential precursors of *N*-nitramines in children's pacifiers and baby-bottle nipples. *Environ. Res., 43,* 126–134

Wild, C.P., Chapot, B. & Montesano, R. (1988) Highly specific aflatoxin (AF) antibodies recognise antigenic epitopes on human serum albumin obtained from populations exposed to aflatoxin. *Proc. Am. Assoc. Cancer Res., 29,* 259

Wild, C.P., Chapot, B., Scherer, E., Den Engelse, L. & Montesano, R. (1988) Application of antibody methods to the detection of aflatoxin in human body fluids. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *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, pp. 67–74

Wild, C.P., Degan, P., Brésil, H., Serres, M., Montesano, R., Gershanovitch, M. & Likhachev, A. (1988) Quantitation of 7-methyldeoxyguanosine (7-medG) in peripheral blood cell DNA after exposure to methylating agents. *Proc. Am. Assoc. Cancer Res., 29,* 260

Wild, C.P., Jiang, Y.Z., Montesano, R., Parkin, M., Khlat, M. & Srivatanakul, P. (1989) Correlation study of aflatoxin exposure and liver cancer incidence in five geographical regions of Thailand. *Proc. Am. Assoc. Cancer Res., 30,* 317

Wild, C.P., Pionneau, F.A., Montesano, R., Mutiro, C.F. & Chetsanga, C.J. (1987) Aflatoxin detected in human breast milk by immunoassay. *Int. J. Cancer, 40,* 328–333

Wild, C.P., Stich, H.F. & Montesano, R. (1989) Presence of alkylated DNA in oral mucosal cells from cigarette smokers. *Proc. Am. Assoc. Cancer Res., 30,* 318

Wilson, V.L., Weston, A., Manchester, D.K., Trivers, G.E., Roberts, D.W., Kadlubar, F.F., Wild, C.P., Montesano, R., Willey, J.C., Mann, D.L. & Harris, C.C. (1989) Alkyl and aryl carcinogen adducts detected in human peripheral lung. *Carcinogenesis* (in press)

Wilson, V.L., Weston, A., Manchester, D.K., Trivers, G.E., Roberts, D.W., Kadlubar, F.F., Serres, M., Wild, C.P., Montesano, R., Willey, J.C., Mann, D.L. & Harris, C.C. (1988) Alkyl and aryl carcinogen DNA adducts detected in human peripheral lung. *Proc. Am. Assoc. Cancer Res., 29,* 261

Yamasaki, H. (1987) Carcinogenesis taken as the result of disrupted cell society [in Japanese]. *Oncologia, 20,* 57–70

Yamasaki, H. (1987) The role of cell-to-cell communication in tumor promotion. In: Butterworth, B.E. & Slaga, T.J., eds, *Nongenotoxic Mechanisms in Carcinogenesis* (Banbury Report No. 25), Cold Spring Harbor, CSH Press, pp. 297–309

Yamasaki, H. (1988) Multi-stage carcinogenesis: Implications for risk estimation. *Cancer Metastasis Rev., 7,* 5–18

Yamasaki, H. (1988) Role of gap-junctional intercellular communication in malignant cell transformation. In: Hertzberg, E.L. & Johnson, R.G., eds, *Gap Junctions* (Modern Biology Vol. 7), New York, Alan R. Liss, pp. 449–465

Yamasaki, H. (1988) Tumor promotion: from the view point of cell society. In: Iversen, O.H., ed., *Theories of Carcinogenesis,* New York, Hemisphere, pp. 143–157

Yamasaki, H. (1989) Molecular and cellular mechanisms of multistage carcinogenesis: role of oncogenes and intercellular communication. In: Galli, C.L., Marinovich, M. & Hensby, C.N., eds, *Skin Pharmacology and Toxicology,* New York, Plenum Press (in press)

Yamasaki, H. (1989) Role of cell-cell communication in tumour suppression. In: Klein, G., ed., *Tumor Suppression,* New York, Marcel Dekker (in press)

Yamasaki, H. (1989) Short-term assays to detect tumor-promoting activity of environmental chemicals. In: Slaga, T.J., Klein-Szanto, A.J.P., Boutwell, R.K., Stevenson, D.E., Spitzer, H.L. & D'Motto, B., eds, *Skin Carcinogenesis: Mechanisms and Human Relevance* (Progress in Clinical and Biological Research Vol. 298), New York, Alan R. Liss, pp. 265–279

Yamasaki, H. & Fitzgerald, D.J. (1988) The role of selective junctional communication in cell transformation. In: Langenbach, R., Barrett, J.C. & Elmore, E., eds, *Tumor Promoters, Biological*

Approaches for Mechanistic Studies and Assay Systems, New York, Raven Press, pp. 131–147

Yamasaki, H. & Fitzgerald, D.J. (1989) Possible role of selective gap junctional intercellular communication in multistage carcinogenesis. In: Moolgavkar, S. & Thomsen, D., eds., *Scientific Issues in Quantitative Cancer Risk Assessment*, Boston, Birkhauser (in press)

Yamasaki, H. & Katoh, F. (1988) Further evidence for the involvement of gap-junctional intercellular communication in induction and maintenance of transformed foci in BALB/c 3T3 cells. *Cancer Res.*, *48*, 3490–3495

Yamasaki, H. & Katoh, F. (1988) Novel method for selective killing of transformed rodent cells through intercellular communication, with possible therapeutic applications. *Cancer Res.*, *48*, 3203–3207

Yamasaki, H. & Mesnil, M. (1987) Cellular communication in cell transformation. In: Milman, H.A. & Elmore, E., eds., *Biochemical Mechanisms and Regulation of Intercellular Communication in Toxicology*, Princeton, NJ, Princeton Scientific Publishing, pp. 181–207

Yamasaki, H., Hollstein, M., Cabral, J.R.P. & Tomatis, L. (1989) Role of oncogene activation during prenatal (transplacental) initiation and postnatal promotion of mouse skin tumours. In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96), pp. 221–237

Yamasaki, H., Enomoto, K., Fitzgerald, D.J., Mesnil, M., Katoh, F. & Hollstein, M. (1988) Role of intercellular communication in the control of critical gene expression during multistage carcinogenesis. In: Kakunaga, T., Sugimura, T., Tomatis, L. & Yamasaki, H., eds, *Cell Differentiation, Genes and Cancer* (IARC Scientific Publications No. 92), Lyon, International Agency for Research on Cancer, pp. 57–75

Yamasaki, H., Hollstein, M., Cabral, J.R.P., Martel, N., Galendo, D. & Tomatis, L. (1987) Activation of *H-ras* gene in mouse skin tumors produced by transplacental initiation and postnatal promotion. *Proc. Am. Assoc. Cancer Res.*, *28*, 148

Yamasaki, H., Hollstein, M., Hamel, E., Giroldi, L., Rivedal, E., Sanner, T. & Kakunaga, T. (1988) Use of cell variants to study the molecular and cellular determinants of tumor promotion. In: Colburn, N., Moses, H. & Stanbridge, E., eds, *Growth Factors, Tumor Promoters, and Cancer Genes*, New York, Alan R. Liss, pp. 283–293

Yamasaki, H., Hollstein, M., Martel, N., Cabral, J.R.P., Galendo, D. & Tomatis, L. (1987) Transplacental induction of a specific mutation in fetal Ha-*ras* and its critical role in post-natal carcinogenesis. *Int. J. Cancer*, *40*, 818–822

Yamasaki, H., Hollstein, M., Mesnil, M., Martel, N. & Aguelon, A.M. (1987) Selective lack of intercellular communication between transformed and non-transformed cells as a common property for chemical and oncogene transformation of BALB/c 3T3 cells. *Cancer Res.*, *47*, 5658–5664

Zaridze, D.G. & Boyle, P. (1989) Colorectal cancer: descriptive epidemiology. In: Zatonski W. & Boyle P., eds, *Cancer: Descriptive Epidemiology through Prevention*, Warsaw, Interpresse (in press)

Zhang, Z.-F., Parkin, D.M., Yu, S.-Z., Estève, J. & Yang, X.-Z. (1989) Risk factors for cancer of the cervix in a rural Chinese population. *Int. J. Cancer*, *43*, 762–767

Zhang, Z.F., Parkin, D.M., Yu, S.Z., Estève, J., Yang, X.Z. & Day, N.E. (1989) Cervical screening attendance and its effectiveness in a rural population in China. *Cancer Detec. Prev.*, *13*, 337–342

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