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INTRODUCTION

The Annual Report covers the period July 1980 to June 1981. As the last report for which the present Director is responsible, some general comments as to past scientific activities of the Agency and future research and developments may be appropriate. The detailed account of the work for the year is given in the reports from the Divisions.

General comments on scientific policy

In the mid-sixties, the Director-General of WHO, Dr M. G. Candau, proposed that the World Health Assembly should establish a number of bodies to carry out academic biomedical research to complement the regulatory and public health aspects of WHO's programme. Although the general project was not approved, following the initiative of certain French intellectuals and the declaration of General de Gaulle, the Agency was established by the World Health Assembly in 1965, and has attempted to fulfill some of the intentions so cogently expressed by Dr Candau. Dr Candau ensured that the Agency, during its early formative years, should meet and accept the criteria of an academic institution.

The historical background leading to the founding of the Agency and the developments of its scientific programme were summarized in previous reports[1, 2]. As pointed out at that time, the direction of the programmes, to a great extent, represented logical developments arising out of the direction of cancer research in the late 1960's. At that time, not only was environmental carcinogenesis inadequately developed, but the area was most suitable for development and study through international collaboration. It is probable that the direction of the programme during the forthcoming decade will again reflect the changes and advances that have occurred over the last several years. The interpretation given by me of these developments should in no way be regarded as necessarily reflecting the views of the Scientific or Governing Councils, nor of my successor.

It has long been the general view that the Agency should not replicate the activities of a national laboratory, and that it should be sensitive to changes in the direction of research, and attempt to stimulate efforts in more avant-garde areas which are inadequately developed at the national level. It would appear desirable, therefore, that the Agency should continue to provide an ambience in which multidisciplinary studies can be developed and also stimulated through research agreements with national laboratories or national field programmes, both directed to establishing a more solid foundation of biological data on human cancer. At all costs, the Agency should avoid being locked into systematic programmes only directed to public health data collection and analysis, without obvious originality. It must maintain its reputation as a source of

[1] International Agency for Research on Cancer (1976) *Annual Report 1976*, Lyon p. 9.
[2] Idem (1977) *Annual Report 1977*, ibid, p. 15.

Fig. 1 New members of the Scientific Council

Dr T. Hirayama
1981–1984

Dr Nigel Gray
1981–1984

objective, well-founded scientific judgement in the field of environmental carcinogenesis, through its publications and reports, which are now widely used by many governments, scientists and health and environmental authorities. If the Agency has been able to establish such a reputation, it is in large measure due to the early acceptance by the Governing Council that scientists in the Agency should operate under the same conditions prevalent in national research institutions and universities, remaining free from many of the bureaucratic restraints that exist in inter-governmental bodies.

Recruitment of personnel

Following the decision to recruit a multidisciplinary group to develop the Agency's programmes, there was considerable discussion as to whether the Agency should have its own laboratories. However, it became clear that this would be desirable for a number of reasons. Firstly, the importance of improving collaboration between laboratory research workers and epidemiologists to develop common programmes indicated the necessity for close proximity.

Secondly, recruitment of staff of suitably high quality would be facilitated if the possibility existed for them to remain active within their discipline. Lastly, as the Agency was considered as a potentially important centre for manpower training, the necessity to have a multidisciplinary group with laboratories was obvious. Laboratories were established and the multidisciplinary approach was developed with epidemiologists and laboratory scientists actively involved in joint programmes of research. This has continued up to the present day.

The importance of environmental carcinogenesis

Prior to 1950 the proportion of cancers for which defined etiological factors could be identified was small. However, rapid developments followed in the early 1950's which confirmed the important role in human cancer of certain cultural habits, notably cigarette smoking, betel chewing and alcohol ingestion. This was also the period in which bladder cancer risk in the chemical and rubber industries was identified with exposure to 2-naphthylamine, and when the marked increase in mesothelioma was demonstrated to be the result of industrial exposures to asbestos fibres. In addition, the role of such lifestyle factors, as diet and behavioural habits in many cancers, began to receive serious consideration. Much of this progress depended on increased sophistication of epidemiology and geographical pathology, which became established as serious disciplines within oncology, and provided effective techniques for evaluating and investigating environmental risks in man. During the same period developments in molecular biology and laboratory research have led to a better understanding of carcinogenic mechanisms and have increasingly influenced the direction of scientific research on human cancer.

It is desirable to pay tribute to the role of the International Union Against Cancer and its Committee on Geographical Pathology at that time. This Committee, under the chairmanship of Dr Harold Stewart, was a potent force in stimulating studies on cancer biology in man and emphasizing the importance of integrated multidisciplinary studies. Nonetheless, there was still a general tendency to concentrate on the possible role, in many human cancers, of hereditary factors, and endogenous viruses, as many experimental tumours were shown to be of viral origin. Further, carcinogenic viruses proved to be effective tools in molecular biology. Unfortunately, there was for a time, an intellectual gap between the understanding of cancer causation, as observed by the laboratory scientists, who believed that only a complete study of mechanisms would permit adequate cancer control, and the more pragmatic views of epidemiologists and geographical pathologists, who believed that cancer prevention should be possible on the basis of currently available knowledge. Fortunately, this artificial division between scientists of differing disciplines has largely disappeared.

The decision to establish the Agency in 1965 coincided with this rather uncertain period in cancer research. The stated objective of the Agency was "to promote international collaboration in cancer research. The Agency shall serve as a means through which Participating States and the World Health Organization, in liaison with the International Union Against Cancer and other interested international organizations, may co-operate in the stimulation and support of all phases of research related to the problem of cancer"[3].

To carry out this programme, the Agency was required, in its Statute, to execute a programme of permanent activities which included "the collection and dissemination of information on epidemiology of cancer, on cancer research and on the causation and prevention of cancer throughout the world"[3].

Furthermore, it was decided from the outset, that the direction of the Agency's activities should be determined by scientific criteria, and such studies could be carried out irrespective of whether the location concerned lay within a Participating State or not.

Obviously, in view of its limited resources, the Agency could not develop as wide a programme as envisaged in the Statute. Initial programmes tended to be directed towards rather narrower objectives, which called heavily upon the experience of the Geographical Pathology Committee of the International Union Against Cancer. The work of this Committee, which

[3] Statute, Rules and Regulations of the International Agency for Research on Cancer, March 1966, p. 6.

later became the Commission of Cancer Epidemiology and Prevention, demonstrated that a multidisciplinary research approach involving laboratory workers, pathologists and epidemiologists could effectively attack the problem of cancer causation and its biology in man. Further, from the beginning, there was also mutual agreement that many activities of the Commission could be more effectively carried out by the new international body which possessed greater financial and manpower resources. Thus, the Agency's initial programmes were largely directed to evaluating and developing activities in geographical pathology and epidemiology, which, from its international position, it could study in a number of different environments.

When the Agency was founded, Ruth Carson's book "The Silent Spring" had only recently been published and its impact was beginning to receive wide attention. This coincided with renewed recognition that the greater part of human cancer was influenced by environmental factors, a view that had gradually gained conviction since mid-century and was reflected by reports arising out of the activities of the International Union Against Cancer first put forward in 1950[4]. Further, epidemiological studies in developing countries indicated the importance of studying cancer under a series of different environments but strongly suggested that much of differences between countries of high and low frequency, represented the effect of the environment and not ethnic or hereditary factors[5, 6].

Recognition that the carcinogenic process was highly complex and that simple models were not likely to provide a suitable base for extrapolation of experimental results to man, has resulted in increasing attention being paid to the study of the wide variety of factors that may modulate the development of human cancer. In experimental animal studies such modulating factors have been demonstrated, which are also possibly involved in cancer in man. Accordingly, in recent years, the role of carcinogenic risk factors has come to be better understood, for example in relation to cancers of the gastrointestinal tract, breast, and uterus. There has also been increasing emphasis on the possible role of interactions between the host and his environment which might also modify the carcinogenic process. These aspects were developed at an Agency symposium in 1972, and resulted in a publication[7] which summarized the situation at that time. However, activities have remained relatively modest in this area, and it is only comparatively recently that significant expansion has begun in multifactorial carcinogenesis in man and animals, notably with the activities of Dr E. Wynder and his group at the Americal Health Foundation. It should be noted, however, that the Agency had in fact proposed the creation of a unit of metabolic epidemiology in 1967 as worthy of priority, but this programme was never implemented due to lack of funds.

The Agency's task

Despite pessimistic public misconceptions of progress in cancer research, today the etiology has been recognized of nearly 50% of cancers in males and approximately 20% of cancers in females, in the industrialized countries. These advances are often ignored, and there is a wide gap between the public's conception of cancer causation and what is actually known. The fact that

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[4] Clemmesen, J., ed. (1950) *Symposium on Geographical Pathology and Demography of Cancer*, Paris, Council for the Coordination of International Congresses of Medical Sciences.

[5] Higginson, J. & Oettlé, A.G. (1960) *J. natl. Cancer Inst.*, **24**, 589–671.

[6] Higginson, J. (1960) *Acta Unio Int. contra Cancrum*, **XVI**, 1667–1670.

[7] Doll, R. & Vodopija, I., eds (1973) *Host Environment Interactions in the Etiology of Cancer in Man (IARC Scientific Publications No. 7)*, Lyon, International Agency for Research on Cancer.

cigarette smoking and other aspects of lifestyle are involved, has held back effective preventive actions, since both governments and individuals appear unwilling to control pleasurable habits. Instead, there is often a tendency to distort public health priorities in the cancer field to the less important problems, leaving the major problems with less attention because of difficulties which are both scientific and political. In this context, the Agency has played, and should continue to play, a major role in providing objective data on different carcinogenic hazards, permitting the evaluation of their relative importance as risk factors in man. The scientific independence of the Agency, therefore, remains of major significance in the environmental field, and this independence derives in large measure from the fact that the Agency's programmes are mainly supported by the statutory contributions of the Participating States. This has permitted the Scientific Council to recommend, and the Governing Council to approve, the support of long-term programmes, many of which may have proved negative, but which were essential in evaluating environmental factors and stimuli. Furthermore, it shelters the Agency staff from the necessity to give undue emphasis to short-term projects, which give quickly publishable results, and can be, perhaps, more justifiably carried out and developed within national universities and research organizations. This freedom should be retained, as a study of human cancer does not often lend itself to the rapidly completed, short-term investigation.

This approach has been maintained, although over the years, there have been a number of attempts by exerternal bodies to involve the Agency actively in the establishment of public health standards and legislation. Up to date, the Agency has avoided involvement in such activities, which are more appropriately the role of national regulatory bodies or WHO, ILO and FAO. The division between, on the one hand, the generation and evaluation of scientific data, and, on the other, the application of those data to the framing of regulations, is one that, I believe, should be retained, as much confrontation and confusion in the regulatory field have arisen as a result of mixing the two activities, which should be regarded as essentially independent of each other.

General conclusions

The last fifteen years have seen the Agency establish itself as an international scientific body in the cancer field, with its own laboratories and field programmes, an active member of the world's scientific community. Although its programmes were originally limited to the field of environmental carcinogenesis because of limitations of resources, this has in fact proven a fruitful field for investigation by an international organization and, with recent developments in sophisticated technology and in the concepts of multistage carcinogenesis, should continue to offer an exciting intellectual challenge for the eighties.

It would be unwise to forecast the direction of future research. However, there are a number of recent developments which indicate that the Agency will continue to play an active part in the fight against cancer. In view of the lack of progress in primary prevention of cancers related to lifestyle, it is important to ensure that the future research efforts of the Agency be based on a careful and objective scientific analysis of the prospects for prevention, whilst avoiding excessive promises or claims.

J. HIGGINSON

Funding

During 1981 the income of the Agency totalled US$ 10 243 000. Of this, US$ 7 694 000 represented contributions from the Participating States, the remaining US$ 2 549 000 coming from grants and contracts. The details are given in Table 1.

Personnel

In June 1981, the Agency's staff of 150 consisted of 38 scientists, 55 technicians and 57 administrative and secretarial staff. In September 1980 Dr J. F. Duplan, who had been Scientific Programme Coordinator, returned to his home institute in Bordeaux, France. Dr A. Levin also left the Agency, in December 1980. Eleven visiting scientists, consultants and Fellows contributed to the research programme of the Agency during the year.

Mr T. Mirza, Budget and Finance Officer of the Agency since 1972, was promoted to a new post in headquarters, WHO; his place has been taken by Mr R. M. Scott, who came to the Agency from the Food and Agricultural Organization, Rome.

The staff learned with sadness of the death of Miss Colette Bordet, Division of Environmental Carcinogenesis, in November 1980.

Table 1. Income and expenditure for 1981[a]

	Amount (US$)	Percentage of total
Income		
Statutory budget	7 694 000	75.11
Extra-budgetary	2 549 000	24.89
	10 243 000	100.—
Expenditure		
Intramural		
Headquarters scientific staff	3 591 000	35.06
Administrative staff and office services	1 462 000	14.27
Laboratory research (staff and supplies)	1 249 000	12.19
Building management	860 000	8.40
Publication and information programme	736 000	7.19
Other (data processing, library, organizational and scientific meetings)	740 000	7.22
Total	8 638 000	84.33
Extramural		
Contractual and collaborative research	10.09	
Fellowships and specialized courses	329 000	3.21
Duty travel	243 000	2.37
Total	1 605 000	15.67
Grand total	10 243 000	100.—

[a] All figures are estimates. Statutory budget income and expenditure details are those contained in the approved budget (GC/18/3) as amended, whereas the extra budgetary figure is based on information available in October.

Fig. 2 The late Professor S. Halter, Secretary General, Ministry of Public Health and the Family, Brussels

Obituary

The Director and staff of the Agency learned with great regret of the sudden death of Professor S. Halter, Secretary-General, Ministry of Public Health and the Family, Belgium on 13 July 1981. Professor Halter had been a distinguished member of the Governing Council since 1970, when Belgium became a Participating State of the Agency, and was for two years Chairman of the Governing Council from 1975—76. With his experience and wisdom, his contributions to the work of the Council were always greatly appreciated. His support of the work of the Agency continued outside the Council, for on three occasions, Agency meetings and courses in Belgium received special support from his Ministry.

The Agency has lost a most valued friend.

DIVISION OF EPIDEMIOLOGY AND BIOSTATISTICS

Dr C. A. LINSELL (Director)

1. INTRODUCTION

Over the last 15 years the approach of the Agency's programme of epidemiology, as was necessary in a new venture, has been as broad as possible, ranging from the stimulation and analysis of the descriptive efforts of cancer registries and offices of vital statistics to analytical field studies focussed on the individual cancers or risk factors. The Agency was a response to a desire for new opportunities in international cancer research, with an avowed emphasis on epidemiology. Thus efforts were, of necessity, to a certain extent experimental in the sense of research management.

Field programmes have been undertaken using different approaches: by establishing overseas semi-permanent IARC Centres with their own or collaborating national laboratories, or by repeated visits by Lyon-based teams of Agency staff and consultants to projects which were mainly the responsibility of national scientists. With a number of these field studies drawing to a close, and to deal with the financial problems raised by a global increase in operating costs, it would appear timely to evaluate the range, the direction and the specifics of the Agency's epidemiological programme.

Over the years the publication of *Cancer Incidence in Five Continents* and the *Directory of On-Going Research in Cancer Epidemiology,* together with the activities of the International Association of Cancer Registries (IACR), for which the Agency provides a secretariat, have become permanent features of the programme and they may remain so, but there has been, over the past decade, a definite desire to design programmes to use, rather than merely accumulate, cancer registry data. One of the aims of the SEARCH programme is the routine collection of a body of environmental data to parallel the cancer registry data. The International Radiation Study to evaluate the risks of radiation exposure in cervical cancer patients is using data from a number of cancer registries and clinics in Europe and North America. Both these studies may, apart from their intrinsic value, give rise to a series of future studies which can use the collaboration established between such registries. New techniques of data processing and computer management must be enlisted to enable these studies to be carried out rapidly and routinely using these widely dispersed sources of information. Cancer registries frequently have funding problems which can be dispelled by demonstrating fruitful uses of such routine collection of data. The network of confidence which has been built up, particularly through the IACR and individual studies, must be developed into a major research priority of the Agency. The central costs at the Agency, once the mechanisms are established, should not be an undue strain on the budget, particularly as *ad hoc* problems may attract outside funding, nevertheless leaving the Agency in an unchallenged position as a focus of such efforts. The treatment of this material, and many problems of analytical epidemiology, lend themselves to the application of those biostatistical techniques which have come into prominence over the last few years. The establishment of a series of monographs on statistical methods for use

in epidemiological studies is a new activity of the Division. The monograph on the analysis of case-control studies in an outstanding contribution to this series, and is to be followed shortly by one on the statistical analysis of long-term carcinogenicity experiments, and a further one on the analysis of cohort studies.

A number of field programmes on specific sites—oesophagus, liver, larynx, mesothelioma and Burkitt's lymphoma—have been successful in indicating areas for primary prevention. The Iran and China oesophageal cancer programmes have sought to take advantage of the clinico-pathological studies of "precancerous" lesions which would give rise to programmes of primary intervention if the precancerous nature of the lesions can be confirmed and specific etiological agents identified. It is considered that these two criteria have been met and monitoring of specific intervention is planned with the national authorities. The programme in Swaziland which has been jointly undertaken with WHO and FAO, and partly financed by UNEP, to monitor the effects of the improvement of agricultural practices and the status of hepatitis on the incidence of liver cell cancer, is another example.

The evaluation of cancer screening programmes using well-established centres associated with cancer registration in Finland, Iceland, Norway, Sweden and the United Kingdom will be able to define the protection provided by having regular Papanicolaou tests to screen against the development of clinically apparent invasive cancer of the cervix. The consequences of a given strategy of screening in a population in terms of subsequent morbidity and mortality in that population will also be clarified. The question of who should be screened, at what age, and how often, is very important when so much effort and money is being devoted to such programmes, not only in the industrialized countries, but in the developing countries where the cost-benefit evaluation is of even greater economic importance.

Decisions must soon be taken, as a matter of policy, as to how far the Agency should pursue the phase of intervention. It may be that this phase should be left to other international bodies—the World Health Organization, the United Nations Environment Programme and national governments—and that the Agency's resources involved in these studies should be realigned. The evaluation of the efficacy of such intervention programmes is an area where the Agency can, however, offer expertise and unbiased advice.

Preliminary studies and an evaluation of the problems associated with research on cancers of the digestive tract, and prostate indicate that a concentration of interest on these cancers might be useful. A detailed study of these cancers requires, however, considerable input from nutritionists and, above all, from specialised laboratories. Although cancer epidemiology is now more frequently being linked with laboratory resources at the national level, the Agency as an international research organization is unusual and fortunate in having its own laboratory division and every effort must be made to use these resources in the field of research which has been designated as 'metabolic' epidemiology. An ambitious programme in this branch of epidemiology might be beyond the Agency's current financial resources, so every effort must be made to marshall collaborative national interest and resources. The studies carried out in Scandinavia on risk factors for large bowel cancer have shown promising results and meetings will be sponsored to assess an expansion of this programme in Australasia and the Pacific region.

Information and educational services have concentrated on the production of directories and reference sources, and on basic courses aimed at all who could be attracted to active work on the cancer problem. Courses, with the assistance of Regional Offices have been held in all Regions of WHO and a corps of junior researchers interested in cancer epidemiology has been slowly built up throughout the world.

The Agency has also established effective liaison with the Regional Offices to promote collaborative field epidemiological studies; the study on the hazards of pesticides in Colombia effected through the Pan-American Health Organization, which administers the project using external funding of the Environmental Protection Agency of the United States, with IARC providing epidemiological advice, supervision, and the final statistical analysis, is an example. An expansion of this collaborative mechanism is envisaged.

The cancer hazards which may be present in industry form an important area of research, not only because there is a steady demand, in a rapidly industrializing world, to make the workplace as safe as possible, but because the level of exposures to the hazards may be higher there than in the general environment, and thus more readily incriminated. This will clearly remain an important priority of the epidemiological programme as the evaluation of information derived from the monograph series (see p. 58) may not be directed solely to individual chemicals, but to the complex environment of specific industrial processes or whole industries.

Thus, this Division of the Agency has a long-standing programme of descriptive epidemiology, expansion of which was approved recently by the Scientific and Governing Councils. From this descriptive starting point analytical projects have and will be developed. With the conclusion in the near future of a number of other interdependent analytical studies, and with the background of research management acquired over the last 15 years, a more sytematic approach to current etiological problems, particularly related to prevention, will be sought, making integrated use of cancer registries, laboratory resources, and modern biostatistical techniques and computer technology.

2. DESCRIPTIVE EPIDEMIOLOGY (Dr C. S. Muir)

The aim of the programme of descriptive epidemiology is to map the occurrence of cancer throughout the world and improve the comparability of incidence data. The existence of differences in cancer risk in different populations facilitates the formulation and testing of etiological hypotheses by the Agency and other bodies.

2.1 *Expanded Programme*

The initial phases of the expanded programme in descriptive epidemiology covering all available sources of cancer morbidity and mortality data have been implemented.

Data management (Mr M. Smans)

With the acquisition of a computer at the Agency it has become possible to store at IARC, rather than elsewhere, the large body of cancer occurrence data currently and potentially available. A system has been designed to permit rapid conversational access to that data taking account of the problems posed by changes in rubric title, content, and numbering resulting from successive revisions of the International Classification of Diseases (ICD) and inter-registry variations in grouping and presentation.

The content of the first three volumes of *Cancer Incidence in Five Continents* has now been stored and cancer mortality data kindly provided by the WHO data bank (Dr H. Hansluwka) will

follow. This will permit comparison of incidence and mortality by site by time period for several regions, and their correlation with environmental variables.

Graphical presentation of data (Mr M. Smans)

As an aid to hypothesis building it is very helpful to present data graphically. Programmes have been written to permit virtually instant access to any part of the cancer occurrence data base with rapid presentation of appropriate graphs and diagrams such as age-specific incidence curves and frequency histograms. Work proceeds, *inter alia,* on the cartographical presentation of material with a view to producing atlases showing the geographical distribution of cancer.

2.2 *Cancer Registries*

(*a*) *International Association of Cancer Registries (IACR)* (Dr C. S. Muir and Ms S. Whelan) (RA/73/016)

The Agency continued to act as the secretariat for the Association. The membership increased to 129 in 1981 with the admission of 15 new voting members (the cancer registries of Buenos Aires; Rhode Island and Los Angeles, USA; Hong Kong; Denmark; Doubs and Bas-Rhin, France; Cluj, Romania; Neuchâtel and Vaud, Switzerland; Stockholm-Gotland, Lund, Umea and Uppsala, Sweden; and South Australia). The Liberian Cancer Registry (Dr A. O. Sobo) was affiliated as a non-voting member, as were three non-voting members interested in cancer registration (Professor A. Yaker, Centre Hospitalo-Universitaire Mustapha, Algeria; Professor T. Shigematsu, Fukuoka University, Japan and Professor P. Siegenthaler, Swiss League Against Cancer). Further applications are under consideration.

A preliminary programme has been organized for a two-day scientific meeting of the Association, to be held on 6—8 September 1982 in Seattle, WA, USA—on the occasion of the 13th International Cancer Congress. The programme will centre on the theme of data collection systems, and proffered papers relevant to cancer registration will also be presented.

The IACR and the Agency are collaborating in the production of Volume IV of *Cancer Incidence in Five Continents* (see 2.5), on a revision of the monograph *Cancer Registration and its Techniques*[1] and the production of a companion volume—*The Use of the Computer in the Cancer Registry* (see p. 24) and in studies on malignant melanoma, confidentiality and registry publications. Members of the Association also collaborate with the secretariat in producing the regular Newsletter which includes news about registries and registration throughout the world and details of registry publications.

Registries supported by Agency programmes

(*b*) *Caspian Cancer Registry* (Mr P. Ghadirian, University of Teheran, Mrs A. Arslan and Dr N. E. Day)

Corrected and coded data from the years 1974–78 have been sent to the Agency, combined with the 1968–74 data, and transferrred to the IARC computer prior to analysis.

[1] 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.

(*c*) *Singapore Cancer Registry* (Professor K. Shanmugaratnam, Dr H. P. Lee, Mrs A. Arslan and Dr N. E. Day)

The results of the first ten years of cancer registration in Singapore (1968–77) have been analysed, examining differences in incidence between ethnic groups (Chinese, Malay, Indian and others), between the major Chinese dialect groups (Hokkien, Teochew, Cantonese, Hainanese and Hakka), and by place of birth, either in Singapore or outside Singapore. Time trends were examined over the ten year period, and the results for selected sites are given in Tables 1 and 2. The analyses will be published in a new series of Agency monographs on descriptive epidemiology.

Table 1. Singapore Cancer Registry 1968–77
Cumulative rates (per cent) for age 0 to 74
Sex: MALE

Site	Total	Chinese			Malays	Indians	% change in incidence per year	
		Total	Born in Singapore[1]	Elsewhere[1]			Total population	Chinese
Mouth	0.28	0.21	0.33	0.17	0.23	1.02	− 5.2	− 6.9
Nasopharynx	1.53	1.96	2.15	1.62	0.61	0.13	+ 0.4	+ 0.5
Oesophagus	1.97	2.37	0.99	2.58	0.12	0.81	− 3.4***	− 3.4*
Stomach	4.75	5.61	4.62	5.53	1.17	2.39	− 2.5***	− 2.3*
Colon	1.40	1.61	1.88	1.33	0.42	0.76	+ 2.5	+ 2.6
Rectum	1.36	1.53	1.61	1.33	0.65	0.85	+ 5.2***	+ 6.0***
Liver	3.48	4.00	4.12	3.96	2.15	1.45	− 1.9*	− 2.3**
Larynx	0.87	0.99	1.00	0.83	0.35	0.59	− 1.7	− 2.3
Lung	7.07	8.36	7.10	8.33	2.61	1.91	+ 2.7***	+ 2.2***
Bladder	0.71	0.80	1.06	0.67	0.44	0.35	+ 0.6	+ 1.3

[1] Those with birthplace unknown are omitted.
* Significant at the 5% level.
** Significant at the 1% level.
*** Significant at the 0.1% level.

Table 2. Singapore Cancer Registry 1968–77
Cumulative rates (per cent) for age 0 to 74
Sex: FEMALE

Site	Total	Chinese			Malays	Indians	% change in incidence per year	
		Total	Born in Singapore[1]	Elsewhere[1]			Total population	Chinese
Mouth	0.10	0.07	0.07	0.04	0.08	1.03	− 1.3	+ 4.3
Nasopharynx	0.62	0.73	0.64	0.64	0.11	0.00	+ 1.2	+ 1.1
Oesophagus	0.65	0.67	0.32	0.74	0.38	0.92	− 10.5***	− 11.0***
Stomach	2.03	2.16	2.70	1.87	0.94	1.55	− 1.2	− 0.3
Colon	1.25	1.36	1.74	1.02	0.41	0.92	+ 4.6***	+ 5.2***
Rectum	0.89	0.92	0.89	0.85	0.54	0.51	+ 2.9	+ 2.3
Liver	0.93	0.96	1.20	0.89	0.57	0.72	− 1.8	− 1.3
Lung	2.25	2.41	2.12	2.40	0.94	0.93	+ 1.7	+ 1.9
Breast	2.29	2.29	2.78	1.69	1.71	3.23	+ 1.6	+ 2.3
Cervix	1.96	2.04	2.44	1.46	1.03	3.17	− 0.7	− 0.4
Ovary	0.64	0.62	0.71	0.44	0.84	0.81	− 0.1	− 1.2

[1] Those with birthplace unknown are omitted.
* Significant at the 5% level.
** Significant at the 1% level.
*** Significant at the 0.1% level.

(*d*) *Cancer registration in 'Latin-speaking' countries* (Dr A. J. Tuyns and Mrs J. Nectoux)

The group, studying the epidemiology and registration of cancer in Latin-speaking countries, held its sixth meeting on 28–29 May 1981 in Besançon (France) where Professor S. Schraub runs a Cancer Registry covering the Department of Doubs.

The inaugural lecture "35 years of cancer registration in Denmark" was given by Dr O. M. Jensen, Director of the Danish Cancer Registry, Copenhagen.

A total of 25 papers were presented on the following topics: Incidence and causes of death; Methodology (coordinator: Dr R. Flamant, Gustave Roussy Institute, Villejuif, France); Differential incidence patterns (coordinator: Dr. E. Limbert, Institute of Oncology, Palhava, Lisbon); Colo-rectal cancers (coordinator: Dr J. Faivre, Cancer Registry of Dijon, France); The role of a registry in the evaluation of screening (coordinator: Dr H. Sancho-Garnier, Gustave Roussy Institute, Villejuif, France); Present situation and development of registration in Latin-speaking countries (coordinator: Professor E. Anglesio, Cancer Registry of Turin, Italy).

The proceedings of the previous meeting of the Group, held in 1980 at Viano do Castello, Portugal, have been published with the assistance of the IARC.

(*e*) *Advice to cancer registries and other bodies*

The publication of the monograph *Cancer Registration and its Techniques*[1] has enabled many queries about cancer registration to be answered more expeditiously.

France: The Morbidity and Mortality Service for Cancer in France has now been established permanently in the National Institute for Health and Medical Research (INSERM), Paris, under the direction of Professor R. Flamant. Its purpose is to coordinate the collection of mortality and morbidity cancer data for France, including the work of the regional cancer registries already in existence. Those covering the Departments of Bas-Rhin (Dr. P. Schaffer), Doubs (Professor S. Schraub) and Côte d'Or (Dr J. Faivre) have been in operation for several years; two other registries were created recently in the Department of Isère (Dr F. Ménégoz) and Calvados (Dr J. Robillard) and have now prepared their first sets of incidence figures. A new registry is to be established in the Tarn (Dr M. Carton)

Switzerland: The Swiss Association of Cancer Registries coordinates six population registries operating in the Cantons of Geneva, Vaud, Neuchâtel, Basel (Basel-Stadt and Basel-Land), St-Gall and Appenzell, and Zurich. Dr A. J. Tuyns is concerned with analyses designed to reconcile differing registration practices.

(*f*) *Use of the computer in the cancer registry* (Dr C. S. Muir, Dr J. Estève, Mr M. Smans, Ms S. Whelan, in collaboration with Ms L. Glockler-Ries and Dr C. Zippin, USA; Dr N. W. Choi, Canada; Dr P. Crosignani, Italy; and Dr E. Schifflers, Belgium)

The computer can relieve cancer registration of much of its drudgery and improve data quality by performing validity checks and matches very difficult to undertake manually. Yet, little guidance exists for cancer registries now being created in developed countries who wish to use a computer from the beginning, or for those long-established registries faced with the problem of placing largely manual records on the computer.

A meeting was held in September 1980 at which the outline of a publication proposing solutions to these problems was decided and potential contributors identified. A questionnaire on the present and forecast use of the computer in existing hospital- and population-based cancer

registries has been formulated and sent to registries. The draft chapter will be discussed in the light of the replies in order to make the monograph as directly applicable as possible to cancer registry needs.

The book will complement the monograph *Cancer Registration and its Techniques*, and will propose methods whereby the computer can assist in each aspect of the registration process. Use of such a monograph would foster uniformity of methods in cancer registries throughout the world and improve data comparability.

(*g*) *Relative frequency* (in collaboration with Dr E. P. van der Esch, The Netherlands Cancer Institute, Amsterdam)

As part of the Agency's expanded descriptive epidemiology programme, relative frequency data will be sought systematically from those parts of the world in which neither cancer incidence nor mortality data are likely to be available for some time.

2.3 *Multiple tumours* (Mrs J. Nectoux)

The coding of multiple tumours, synchronous or metachronous, poses many problems to cancer registries. With increased survival and the possibility of developing further neoplasms following treatment by radiation (see p. 51) and by chemotherapeutic agents with carcinogenic potential, this problem is becoming of greater importance. Further, differences in coding practice could result in artefactual differences in incidence rates of perhaps as much as 10% for some sites. A preliminary survey of cancer registries contributing to Vol. IV of *Cancer Incidence in Five Continents* showed that 90% of registries would count each independent primary tumour separately, if the tumours occurred in different organs. 60% of registries would count independent primary tumours in the same organ, such as the colon, as separate tumours, and 60% would consider tumours arising, for example, in each breast, as independent primary tumours. A working party has now been set up to examine these problems and suggest coding rules for international use (Dr C. R. Kay, Albuquerque, USA; Dr F. Levi, Lausanne, Switzerland; Dr P. Prior, Birmingham, UK; Mr L. Raymond, Geneva, Switzerland and Dr P. Schaffer, Strasbourg, France).

2.4 *Time trends in cancer*

Following a general assessment of the role of time trends in the determination of cancer etiology[2] and of time trends for a series of sites, the implication of time trends in cancer mortality was examined[3].

In view of conflicting opinions as to the reality of the increase in cancer incidence observed in several countries, opinions which range from prediction of a "cancer epidemic" in the next two years to denial of any increase, a series of investigations into this question is being conducted.

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[2] Muir, C. S. & Nectoux, J. (1981) In: Magnus, K., ed., *Time Trends in Cancer*, New York, Hemisphere, pp. 365–385.

[3] Muir, C. S., Choi, N. W. & Schifflers, E. (1981) In: Boström, H. & Ljungstedt, N., eds, *Medical Aspects of Mortality Statistics*, Stockholm, Almqvist & Wicksell International, pp. 269–309.

Dr J. A. H. Waterhouse, Birmingham Regional Cancer Registry, UK, has been engaged as a consultant to write a critical monograph describing observed trends, assessing the reality of any changes recorded and attempting to take into account the effect of changes in population age structure and in patterns of other competing causes of death. The reality of the observed increase in cutaneous malignant melanoma is being examined (see 2.7); so too, is the extent to which changes in breast and gastric cancer mortality can be explained on the basis of year-of-birth effect, age effects or time-related factors such as change in diagnostic methods (Professor E. Schifflers, University of Namur, Belgium). Computer programmes to convert cross-sectional age-specific incidence and mortality data into an age-specific year-of-birth presentation are being developed (Mr M. Smans).

An analysis of time-trends in France for oesophagus and stomach cancer mortality over the last 25 years has been carried out[4]. As in other countries, gastric cancer has considerably decreased, being more marked for females than for males. The trend is reversed for oesophageal cancer, which was increasing in males up to 1966, but has since then remained stable. A similar trend was observed for cirrhosis mortality and has perhaps coincided with a stabilization of the level of alcohol consumption in the country.

2.5 *Cancer Incidence in Five Continents, Volume IV* (Dr C. S. Muir and Miss S. Whelan, in collaboration with Dr J. A. H. Waterhouse, Miss J. Powell and Mr D. Peacham, Birmingham Cancer Registry, UK, RA/78/019; and Professor K. Shanmugaratnam, Singapore Cancer Registry)

Data for Volume IV of *Cancer Incidence in Five Continents*, to be published in December 1981, were received from 91 registries, covering 116 ethnic groups. Incoming data were processed at the Birmingham and West Midlands Regional Cancer Registry, UK, where computer programs had been designed to translate the material received, after a series of verifications, into the age-specific and age-standardized incidence rate tables given for each population by site in the volume. Editorial tables giving various indices of reliability including the change in standardized rate from Volume III by site and sex for registries appearing in that volume, were produced for each registry to assist the editorial board in its evaluation of the data.

Innovations in Volume IV include increased use of the cumulative rate, an analysis of incidence rates for the urban and rural populations covered by 13 of the cancer registries, a greater emphasis on the reliability of population denominators and further tabulations by broad age-group for such indices of reliability as the proportion of registrations with histological verification of diagnosis, the proportion of registrations based on a death certificate only, and the relationship between incidence and mortality in the registration area in the time period covered.

Dr L. Sobin (Cancer Unit, WHO/HQ) has collaborated in the analysis of a comprehensive survey of coding practices in a chapter which analyses international and within-country differences and assesses the extent to which these may effect comparability of data. Registries were asked how they coded some 50 diagnostic terms. It was found that a significant proportion of the registries did not follow indexing instructions for certain tumours.

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[4] Audigier, J. C. & Tuyns, A. J. (1981) *Gastroenterol. Clin. Biol*, **5**, 243–250.

These deviations from coding rules have probably resulted from a desire not to "lose" data considered important in the understanding and management of neoplastic disease. Nevertheless, the inquiry showed that the inclusion of certain lesions in cancer incidence data at both national and regional levels is far from uniform and while many of the departures could be considered to be trivial, they could have significant repercussions on epidemiological studies.

Professor K. Shanmugaratnam (Singapore Cancer Registry), who represents the International Association of Cancer Registries on the editorial board, is coordinating a study on the distribution of specific histological types of cancer of the urinary bladder, thyroid and Hodgkin's disease, in which 38 registries have participated.

2.6 *Constraints on epidemiological research*

At a time when there is increasing public interest in the detection of environmental hazards, notably those relating to exposures at work, the detection of such risks by linking of exposed cohorts to cancer registries and death certificates is becoming increasingly difficult in many countries. Constraints and restrictions in many areas are such that a decline in the use of epidemiological methods as investigative tools has been forecast[5]. The concern of the Governing Council of the Agency was expressed in a resolution (GC/20/R9) passed at their meeting in May 1981, which read:

"The Governing Council

Noting that the tasks of the Agency as defined in Resolution GC/12/R1 lie in the detection of environmental cancer hazards in humans;

Recognizing that to do so in an efficient manner it is necessary for medical research workers, bound by an appropriate code of secrecy, to have access to individual medical and employment records, cancer registry records and death certificates;

Realizing that some of the existing unnecessarily severe restrictions of access to such records might make it impossible to undertake certain research and to detect the presence of specific carcinogenic factors; and

Conscious of the fact that published epidemiological studies do not reveal the identity of the individuals concerned, and that persons given access to such confidential information would in turn be bound by secrecy,

1. URGES Participating States, as far as necessary, to take legal and administrative measures which, while preserving confidentiality of medical and employment records, make them accessible for an effective epidemiological approach to the solution of public health problems;
2. EXPRESSES the wish that this resolution be conveyed to the Director-General of WHO for the information of the World Health Assembly."

In an attempt to gauge the extent of such problems, cancer registries have been asked to provide information on the legal basis for reporting, the precautions taken to preserve patient anonymity in registration, and the barriers to analytical epidemiology resulting from confidentiality considerations. To date 52 cancer registries have replied.

[5] Rothman, K. J. (1981) *New Engl. J. Med.*, **304** (10), 600–602.

2.7 *Malignant melanoma* (Dr C. S. Muir, Mrs J. Nectoux)

The incidence of and mortality from malignant melanoma of skin is increasing at a rate of about 5% per annum in many populations[6] (Fig. 1).

Although frequently considered as a disease of fair-skinned people, a largely similar rate of increase has been observed in Japan, for example, although the absolute incidence is still much lower than in the Nordic countries, Australia or New Zealand (Fig. 1). In deeply pigmented races the incidence is very low, except for malignant melanoma of the foot.

It is proposed to mount a series of descriptive international collaborative studies into all forms of malignant melanoma—cutaneous, visceral and ocular. To date 62 cancer registries have replied, 33 being willing to contribute to retrospective studies and 29 to a prospective enquiry.

Dr E. van der Esch, Netherlands Cancer Institute, who has been concerned with the European Organization for Research and Treatment of Cancer (EORTC) clinical trials of this cancer is acting in a consultant capacity. Dr C. Leske of the State University of New York (Stony Brook, USA) is collaborating in the study of ocular melanoma.

2.8 *Clearing-House for On-going Research in Cancer Epidemiology* (Dr C. S. Muir, Mrs A. Nagy-Tiborcz and Mrs E. Démaret, in collaboration with Professor G. Wagner, Dr C. O. Köhler and Mr K. Schlaefer, German Cancer Research Centre, Heidelberg, Federal Republic of Germany) (RA/74/003) (Supported by Contract No. NO1-CO-55195 from the National Cancer Institute, USA)

The clearing-house for on-going research in cancer epidemiology was created in 1974 by the Agency and the German Cancer Research Centre, Heidelberg, Federal Republic of Germany and operates with the support of the International Cancer Research Data Bank of the National Cancer Institute (Bethesda, MD, USA).

Five *Directories* have now been published containing respectively 622, 906, 1025, 1092 and 1261 projects. Scientists from 55 countries participated in the first *Directory* (1976); in the latest (1980) the number of countries providing material has risen to 69[7].

Scientists in the United States and the United Kingdom are still by far the largest contributors, followed by Japan, Canada and France. The most frequently studied sites are lung, female breast, cervix uteri and liver, followed by stomach, leukaemia and childhood cancers. There have been no marked changes in the distribution of sites under study since the inception of the clearing-house. The most frequently used technique is the case-control study which has substantially increased during the last two years, with an equivalent fall in studies of case characteristics. Little change was noted in the proportion of cohort studies relating to occupational or other exposures. Cohort studies in which a case-control investigation is carried out on those cohort members who develop cancer, and controls chosen from cohort members, are becoming increasingly frequent. Case-control studies were about twice as frequent in the USA as in the UK, while cohort follow-up had about the same frequency. Statistical studies were comparatively more frequent in areas where analytical studies were uncommon.

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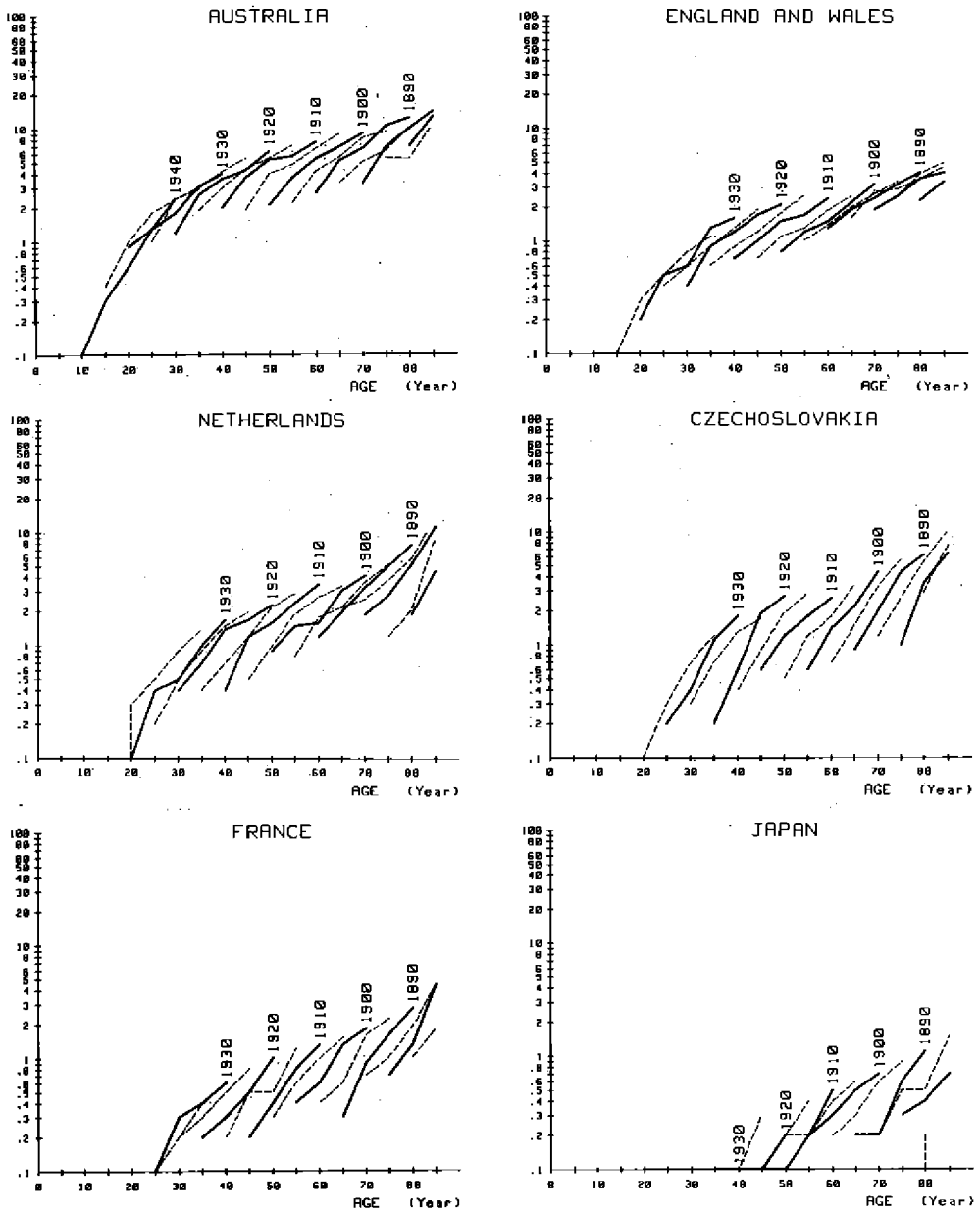
[6] Muir, C. S. & Nectoux, J. (1981) In: K. Magnus, ed., *Trends in Cancer Incidence*, New York, Hemisphere, pp. 365–385.

[7] Muir, C. S. & Wagner, G. (1980) *Directory of On-going Research in Cancer Epidemiology 1980 (IARC Scientific Publications No. 35)*, Lyon, International Agency for Research on Cancer.



DIVISION OF EPIDEMIOLOGY AND BIOSTATISTICS

Fig. 1 Average annual age-specific mortality rates for malignant melanoma per 100,000 population, both sexes combined, for selected countries 1950–1954 to 1970–1974, by year-of-birth cohort. The continuous heavy lines are labelled—thus the 1910 line refers to the persons born between 1910 and 1914 inclusive. Note that although the level of mortality varies very considerably between countries the birth cohort pattern is very similar suggesting a common underlying causation. (Data provided by WHO: diagrams prepared by Dr E. Schifflers and Mr M. Smans of the University of Namur, Belgium.)

An area of increasing interest is human exposure to chemicals and to facilitate identification of such studies, the clearing-house *Directory* provides a separate index of chemicals. In 1980 this contained some 125 individual substances.

Mailing for the 1981 *Directory* began in September 1980 and some 2 500 letters of invitation to participate were sent to research workers in 91 countries. The 1981 *Directory* will contain information on 1 313 studies carried out in 70 countries.

3. ANALYTICAL EPIDEMIOLOGY (Dr A. Linsell)

3.1 *Studies on alcohol and cancer* (Dr A. J. Tuyns and Dr J. Estève)

This is an extensive research programme on the role of alcohol drinking and cancers of the digestive and upper respiratory tract. It has been supported for many years by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the United States. Several reviews of the alcohol-cancer relationship have already been published. Two more contributions on this subject have been prepared[8, 9], as well as a summarizing paper for the use of general practitioners[10].

(*a*) *Oesophageal and other cancers in Normandy* (Dr A. J. Tuyns, in collaboration with Dr G. Péquignot, Nutrition Section of the French National Institute of Health and Medical Research (INSERM) Le Vésinet, France) (RA/75/015)

Oesophageal cancer, a disease which lends itself to prevention and for which attempts of early detection are not encouraging[11], is the most frequent cancer of the digestive tract in Normandy. The mortality data for the two Departments of Calvados and Orne indicate that age-adjusted rates for males are 31.5 and 30.4 per 100 000 inhabitants respectively[12]. In an area which includes the upper cantons of Ille-et-Vilaine rates are above 50 per 100 000. This has been described previously[13].

The collection of data for the case-control study carried out in Calvados has terminated and a preliminary analysis has been undertaken on the 1,976 population controls who were interviewed on their dietary, alcohol consumption and smoking habits[14]. They represent 76% of a sample of the total population of the Department and 5.4‰ of that population, thus providing essential information on the habits of the population.

In this population, cigarette smoking, which is a risk factor for oesophageal cancer (particularly the upper-third of the oesophagus[15]) has been practiced at some time by 80% of males and 20% of females, but the proportion of present smokers is less: 54% of males and 14% of females.

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[8] Tuyns, A. J. (1981) *Cancer Epidemiology and Prevention*, Philadelphia, W. B. Saunders Co. (in press).

[9] Tuyns, A. J. (1981) In: Pfeiffer, C. J., ed., *Cancer of the Esophagus*, Boca Raton, Florida, CRC Press, Inc. (in press).

[10] Tuyns, A. J. (1981) *Concours méd.* (in press).

[11] Tuyns, A. J. (1980) *Symposium International sur le Dépistage en Cancérologie, Caen, 6–8 avril 1979*, Ouest Médical, pp. 261–263.

[12] Tuyns, A. J. & Vernhes, J. C. (1981) *Gastroenterol. Clin. Biol.*, **5**, 257–265.

[13] Tuyns, A. J. & Massé, G. (1975) *Int. J. Epid.*, **4**, 55–59.

[14] Tuyns A. J. & Hu, M. X. (1981) *Br. J. Addict.* (in press).

[15] Keil, S., Tuyns, A. J. & Lowenfels, A. B. (1980) *N. Y. Med. Q.*, **2** (1), 38–40.

Cigarette smoking is less frequent in young men but is increasing in young women, and while it is still rare in middle-aged and old women, only 3–12%, it has now reached 40% in the youngest group of women examined. Males are tending to start smoking at an earlier age but the number of those giving up smoking increases with age.

Hand-rolled cigarettes are still smoked by a large number of males, mainly in older age groups, more so in rural than in urban areas. This finding is important as the risk of oesophageal cancer is probably greater among hand-rolled cigarette smokers[16].

A similar analysis has been started on drinking alcoholic beverages.

The first results of the laboratory investigations on carcinogens and mutagens in alcoholic beverages were published in 1980[17, 18]. Further results of animal experimentation are now available[19]. Wistar rats were fed with various locally produced apple brandies; controls were given equivalent amounts of diluted ethanol and others only water. As in other previous investigations of the same type, there was no significant excess of cancerous or precancerous lesions among the animals exposed.

(*b*) *Cancer of the gastrointestinal tract in Belgium* (Dr A. J. Tuyns, in collaboration with Mrs L. Ravet-Ramioul, Laboratory of Epidemiology, School of Public Health, Brussels) (RA/78/014)

The analysis of mortality data has shown that more die from gastric and rectal cancer in the Flemish Provinces of Belgium than in the southern Walloon provinces. This has been confirmed by a study using more recent data covering both the Netherlands and Belgium. Mortality for gastric cancer in the southern Dutch provinces adjacent to Flemish Belgium is also high.

The case-control study in Flemish and Walloon provinces of Belgium continues (Table 3).

This study is supported by the Belgian National Fund for Scientific Research (FNRS)

Table 3. Number of cases interviewed 1979-1980

	East Flanders		Liège	
Localisation	Males	Females	Males	Females
Oesophagus	25	6	11	6
Stomach	93	58	30	36
Colon	77	97	79	78
Rectum	98	67	75	57

[16] Tuyns, A. J. (1981) *Int. J. Epid.* (in press).

[17] Tuyns, A. J., Castegnaro, M., Toussaint, G., Walker, E. A., Griciute, L. L., Le Talaer, J. Y., Loquet, C., Gerain, J. & Drilleau, J. F. (1980) *Bull. Cancer*, **67**, 15–28.

[18] Tuyns, A. J. & Griciute, L. L. (1980) *Advances in Tumour Prevention, Detection and Characterization*, Vol. 5: *Human Cancer. Its Characterization and Treatment*, Amsterdam, Excerpta Medica, pp. 130–135.

[19] Mandard, A. M., Marnay, J., Hélie, H., Tuyns, A. J. & Le Talaer, J. Y. (1981) *Bull. Cancer*, **68** (1), 49–58.

(*c*) *Cancer of the larynx in southern Europe* (Dr A. J. Tuyns, Dr J. Estève, in collaboration with Dr A. Zubiri, Cancer Registry of Zaragoza, Spain (RA/78/015); Dr A. del Moral Aldaz, Health Department of Navarra, Pamplona, Sapin (RA/78/016); Dr B. Terracini, Institute of Pathology, University of Turin, Italy (RA/78/017) and Dr F. Berrino, National Cancer Institute, Milan, Italy (RA/78/018).

The study involves six research centres located in Italy, Spain, Switzerland and France and investigates the role of diet, tobacco and alcohol in relation to laryngeal cancer, Occupational histories are also examined.

The principal investigators met in Geneva in October 1980 and in Besançon in May 1981 to discuss problems of comparability raised by differing dietary patterns.

A review of the recent time-trends of laryingeal cancer was presented at the Symposium on Time-Trends in Cancer held in Oslo in 1980[20].

3.2 *Liver cancer*

(*a*) *Swaziland* (Dr F. G. Peers and Dr N. Muñoz)

The primary objective of this study is to assess the impact of measures to decrease aflatoxin contamination of food on liver cancer in Swaziland. The natural history of hepatitis B in this population will also be determined.

The laboratory which has been constructed by the Swaziland Government in Malkerns is now in full operation, having been equipped under the UNEP/IARC contract (FP/0107.78.03(1391). Over 1 000 specimens have been analysed for mycotoxins and further countrywide specimens have been collected in an Agricultural Sample Survey carried out by the FAO Prevention of Food Losses Project. This collection will be expanded to include dietary samples which will be comparable with those collected by the Agency in 1968. The Agency's project is working in close collaboration with the FAO team, the technical staff of which will grade and examine all specimens for evidence of insect or rodent damage. The appointment of a mycotoxin analyst by the Netherlands Government as an Associate Expert for FAO has been arranged.

The previous survey of hepatitis B markers in blood donors carried out in 1973 is being repeated on 1 500 samples being stored routinely in the blood bank at the Central Public Health Laboratory in Manzini. Arrangements have been concluded to examine the hepatitis B markers by radioimmunoassay techniques. In an attempt to ascertain the status of hepatitis B virus in the general population, serum collected on a sample basis throughout the country for a water-borne diseases project will be examined. Urine, also collected during this survey, will be analysed by radioimmunoassay for aflatoxin (Dr P. Sizaret).

Cancer registration at hospitals throughout the country continues, but as there is no pathologist available in Swaziland, the number of cases histologically confirmed remains low. Diagnosis of liver cancer, however, can be confirmed by alpha-fetoprotein tests carried out at the Agency's laboratory in Malkerns. The Statistical Health Services of the Ministry of Health, Swaziland, are introducing computerized data bank discharge diagnoses of all patients attending medical facilities, and where possible this will be used to augment cancer registration.

To compensate for initial delays in the establishment of this project, arrangements have been made with the United Nations Environment Programme (UNEP) which provides partial support for this study, to extend the period of the study through 1982.

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[20] Tuyns, A. J. (1981) *Time Trends in Cancer*, New York, Hemisphere (in press).

(*b*) *Cohort study on hepatitis B virus and liver cancer* (Dr N. Muñoz, in collaboration with Professor Phoon Wai-On, Dr Goh Ewe-Hock and Miss Hii Hoi-Chin, Department of Social Medicine and Public Health, University of Singapore, Singapore; Dr Ong Yong-Wan, Director of the Blood Bank, Singapore; Dr Oon Chong-Jin and Professor Chan Soh-Ha, University of Singapore, Singapore) (RA/79/021)

The risk of developing primary liver cancer among Singapore Chinese carriers of hepatitis B surface antigen is being studied by prospective follow-up. Table 4 summarizes the cohort members so far identified from various sources and their prevalence rates of hepatitis B surface antigen.

Table 4. Cohort study on hepatitis B virus and liver cancer

Source	No. tested	Positive HBsAg	
		No.	%
Blood transfusion service	468	16	3.4
SATA	214	21	9.8
Private Practitioners	198	18	9.1
SAGE	47	10	21.3
Others	2	0	–
Total	929	65	7.0

SATA: Singapore Anti-Tuberculosis Association
SAGE: Singapore Action Group for the Elderly

(*c*) *Perinatal studies on hepatitis B virus and liver cancer* (Dr N. Muñoz, in collaboration with Dr E. Domingo and Dr A. Lingao, Department of Internal Medicine, Philippines General Hospital, Manila, and the WHO Regional Office for the Western Pacific, Manila)

(i) *Perinatal transmission of hepatitis B virus*

The aim of this study is to determine the rate of perinatal transmission of hepatitis B virus and subsequent development of a carrier state among Filipino children born to carrier mothers, as compared to non-carrier mothers. A total of 1 000 pairs of blood specimens from the mother and the umbilical cord of the infant have been collected. In 140 pairs, a second blood specimen has been obtained after the first month of life. Follow-up of 500 mother/infant pairs up to the first year of life will be completed.

(ii) *Case-control study of parents of patients with liver cell cancer and of control patients* (RA/81/011)

The hepatitis B serological profile of parents and siblings of patients with hepatocellular carcinoma is being compared with that of parents and siblings of control patients. Blood specimens have so far been collected from both parents of 3 patients with hepatocellular carcinoma, from the mothers of 15 patients and from 53 siblings. The study will proceed until blood specimens from both parents and siblings of 50 patients with liver cell cancer and of 50 control patients have been collected.

3.3 *Oesophageal cancer* (Dr N. Muñoz)

(*a*) *Precancerous lesions of the oesophagus* (in collaboration with Dr. O. Torres, Dr R. H. Castelletto and Dr R. Drut, National University of La Plata, Argentina; and Dr A. M. Mandard, François Baclesse Regional Centre, Caen, France)

Collection of the oesophagi of patients who had died from diseases other than cancer of the oesophagus continues in areas of varying incidence. As there are few opportunities to obtain material sufficiently soon after death, collection has been slow, but this criterion must be met, as histological evaluation is not possible in the presence of autolytic change.

Post-mortem specimens from 257 subjects have been received, but only 174 were suitable for inclusion in the study, and these have been circulated among the participating pathologists, and histopathological evaluation of the lesions using a standard protocol has been completed. The specimens from subjects for whom clinical and demographic data were available were put in three groups according to the rates for oesophageal cancer of the areas of origin; low risk—8 specimens from Seventh Day Adventists from the US; intermediate risk—67 specimens from Argentina, France and Teheran; and high risk—20 specimens from South Africa and Gombad (Iran). There were no significant differences in the prevalence of chronic oesophagitis alone or accompanied by acanthosis, but a higher prevalence of chronic oesophagitis accompanied by atrophy, glandular alterations and dysplasia was observed in the high risk group than in the intermediate and low risk groups.

(*b*) *Precancerous lesions of the oesophagus in a low risk and a high risk population of the People's Republic of China* (in collaboration with Dr Li Ping Wu, Dr Chang Yu Hui, Dr Wang Kao Ching, Dr Su Fang Zheng, Dr Lu Shin Hsin, Dr Liu Fu Sheng, Beijing Cancer Institute, Beijing; Dr Yang Wen Hsien, Professor Shen Chum, Dr Si Je Qiao, Dr Yang Kwan Re, Honan Medical College and Honan Cancer Institute, Honan, People's Republic of China; and Professor M. Crespi and Dr A. Grassi, Regina Elena Institute, Rome)

(i) *High risk population*

A total of 527 individuals from Chang Guan commune of Linxian, with a male age-adjusted rate for oesophageal cancer of over 100 per 100 000 were included in the 1980 survey. The endoscopical and histological findings are summarized in Tables 5 and 6. Endoscopically, the prevalence of oesophagitis was 88.4% in males and 70.2% in females as compared with 87.3% and 87.7% in Iran. Histologically it was 65.0% in males and 63.5% in females, as compared with 83.1% and 76.2% in Iran. As in northern Iran, the high prevalence of oesophagitis was present even in the younger age-groups and it involved mainly the middle and lower thirds of the oesophagus. Histologically, the oesophagitis was accompanied by atrophy of the epithelium in 11.6% of the males and 9.8% of the females; the corresponding figures for Iran were 12.7% and 8.3%, while the prevalence of dysplasia was higher in Linxian (7.9% for males and 8.1% for females) than in Iran (4.7% for males and 2.9% for females). Three squamous cell carcinomas of the oesophagus and seven adenocarcinomas of the cardia were diagnosed in Linxian as compared with 11 squamous cell carcinomas in Iran. The very high prevalence of chronic oesophagitis in both these populations with high risk for oesophageal cancer, though with different lifestyles, suggests that this chronic

Table 5. Endoscopical Findings – Linxian 1980

Age Group	No. of subjects examined	Normal %	Oesophagitis %				Varices %		Incontinent cardia %	Hiatus hernia %	Cancer %
			Mild	Moderate	Severe	TOTAL	Single	Multiple			
MEN											
25-34	21	14.3	57.1	28.6	–	85.7	–	–	19.0	–	–
35-44	77	20.8	40.3	31.2	7.8	79.3	9.1	–	6.5	2.6	2.6
45-54	84	4.8	51.2	36.9	6.0	94.1	7.1	3.6	11.9	–	–
⩾ 55	110	9.1	30.9	46.4	13.6	90.9	1.8	2.7	7.3	–	4.5
Total	292	11.3	41.1	38.4	8.9	88.4	5.1	2.1	9.2	0.7	2.4
WOMEN											
15-24	2	100.0	–	–	–	–	–	–	50.0	–	–
25-34	19	26.3	63.2	10.5	–	73.7	–	5.3	31.6	–	–
35-44	63	25.4	60.3	11.1	3.2	74.6	7.9	3.2	9.5	–	–
45-54	102	33.3	52.9	13.7	–	66.6	3.9	3.9	8.8	–	–
⩾ 55	49	26.5	44.9	24.5	4.1	73.5	6.1	6.1	2.0	–	8.2
Total	235	29.8	53.6	14.9	1.7	70.2	5.1	4.3	9.8	–	1.7

Table 6. Histological Findings – Linxian 1980

Age Group	No. of subjects examined	Normal %	Oesophagitis %				Acanthosis %	Atrophy. %	Dysplasia %	Adenocarcinoma		Squamous cell ca. of oesoph. %	Unknown %
			Mild	Moderate	Severe	TOTAL				cardia %	stomach %		
MEN													
25-34	21	19.0	61.9	9.5	–	71.4	81.0	14.3	4.8	–	–	–	9.5
35-44	77	19.5	49.4	10.4	1.3	61.1	83.2	10.4	7.8	–	–	1.3	19.5
45-54	84	17.9	61.9	2.4	2.4	66.7	76.2	10.7	6.0	–	–	–	15.5
⩾ 55	110	14.5	54.5	9.1	1.8	65.4	82.7	12.7	10.0	2.8	1.8	0.9	18.2
Total	292	17.1	55.8	7.5	1.7	65.0	80.8	11.6	7.9	1.0	0.7	0.7	17.1
WOMEN													
15-24	2	–	100.0	–	–	100.0	100.0	–	–	–	–	–	–
25-34	19	21.1	68.5	–	–	68.5	78.4	10.5	–	–	–	–	10.5
35-44	63	14.3	52.3	11.1	1.6	65.0	73.1	11.1	6.4	–	–	–	20.6
45-54	102	17.6	52.9	5.9	1.0	59.8	66.7	7.9	5.9	1.0	–	1.0	20.6
⩾ 55	49	18.4	61.2	4.1	–	65.3	79.6	12.2	18.3	6.3	2.0	–	14.3
Total	235	17.0	56.2	6.4	0.9	63.5	72.4	9.8	8.1	1.8	0.4	0.4	18.3

oesophagitis is a precursor lesion of oesophageal cancer. In both populations, nutritional studies suggest that deficiency of riboflavin and vitamin A are associated with oesophagitis. To test this association, intervention studies are being planned in Linxian.

(ii) *Low risk population*

A random sample of 251 subjects was selected from seven production brigades in Jiaoxian, a low risk population for oesophageal cancer (male age-adjusted death rate 8 per 100 000) and intermediate rates for gastric cancer (20 per 100 000). A questionnaire containing basic demographic data, information on smoking, alcohol, dietary habits, family history and symptomatology was completed for each subject in May 1981. This was followed by physical and endoscopic examinations of the oesophagus and of the stomach with guided cytology and biopsies. Specimens of hair were collected from most individuals for zinc analysis and blood specimens were collected from 120 subjects for analysis of riboflavin, vitamin A and zinc. Gastric juice and 24 hour specimens of urine were collected from 50 subjects for the assessment of endogenous formation of *N*-nitroso compounds, Table 7 summarizes the endoscopical findings. Endoscopic oesophagitis was present in 47.6% of the males and 29.0% of the females and gastritis was diagnosed endoscopically in 80% of the subjects examined. The histological evaluation of these lesions is in progress. The low prevalence of oesophagitis observed in this low risk population as compared with that observed in the high risk populations of northern Iran and Linxian supports the idea that this lesion is a precursor for oesophageal cancer. The biochemical analyses are under way.

3.4 *Stomach cancer and* N-*nitroso compounds* (Dr N. Muñoz, Dr H. Bartsch and Dr H. Ohshima, in collaboration with Professor M. Crespi, Regina Elena Institute, Rome (RA/79/016); and Dr C. Walters, British Food Manufacturing Industry Research Association, Kent, UK)

Gastric juice and urine specimens from 61 subjects with chronic atrophic gastritis and from 27 subjects with a normal gastric mucosa or with superficial gastritis (control group) have been analysed for volatile nitrosamines. The mean value of volatile nitrosamines in the fasting gastric juice of the 27 control subjects was 0.4 ppb, for the 29 subjects with mild chronic atrophic gastritis it was 1.3 ppb and for the 32 subjects with moderate or severe chronic atrophic gastritis, 2.8 ppb.

Preliminary results of this pilot study have been published[21] and a final evaluation is being completed. There were two major limitations to this study. Firstly, exposure to non-volatile nitrosamines had not been assessed, and, secondly, the current methods of ensuring stability before analysis were only suitable for some of the *N*-nitroso compounds. To overcome these difficulties, the method of measuring *N*-nitrosoproline in urine specimens will be used (see p. 109). In addition, total *N*-nitroso compounds will be measured in the fasting gastric juice of the same subjects.

[21] Walker, E. A., Castegnaro, M., Pignatelli, B., Crespi, M. & Mūnoz, N. (1980) In: Walker, E. A., Castegnaro, M., Griciute, L. & Börzsönyi, M., eds. *N-Nitroso Compounds: Analysis, Formation and Occurrence (IARC Scientific Publications No. 31)*, Lyon, International Agency for Research on Cancer, pp. 633–641.

Table 7. Preliminary results of endoscopic survey – Jiaoxian 1981

Age Group	OESOPHAGUS						STOMACH							
	No. of subjects examined	Normal %	Oesophagitis %				No. of subjects examined	Normal %	Gastritis %				Ulcer %	Cancer or suspect %
			Mild	Moderate	Severe	Total			Antrum patchy	Fundus Atroph.	Antrum patchy & fundic atrophy	Total		
MEN														
15-24	4	75.0	–	25.0	–	25.0	4	–	50.0	–	50.0	100.0	–	–
25-34	31	67.6	29.0	3.3	–	32.3	31	19.3	29.0	12.9	38.7	80.6	–	–
35-44	54	55.5	29.6	14.8	–	44.4	54	16.7	27.8	9.2	42.6	79.6	3.7	–
45-54	43	48.8	34.9	16.3	–	51.2	42	9.1	25.0	11.4	47.7	84.1	–	2.3
⩾ 55	19	21.0	26.3	42.1	10.5	78.9	17	23.5	23.5	5.9	35.2	62.3	5.9	5.9
Total	151	52.3	29.8	16.5	1.3	47.6	148	15.5	27.7	10.1	43.2	81.0	2.0	1.3
WOMEN														
15-24	2	100.0	–	–	–	–	2	50.0	50.0	–	–	50.0	–	–
25-34	10	80.0	10.0	10.0	–	20.0	10	40.0	30.0	10.0	20.0	60.0	–	–
35-44	36	88.9	11.1	–	–	11.1	36	19.4	38.9	5.5	36.1	80.5	–	–
45-54	33	57.6	27.3	9.1	–	36.4	32	12.5	18.7	15.6	50.0	84.3	3.1	–
⩾ 55	19	42.1	21.0	36.8	–	57.8	20	5.0	5.0	30.0	50.0	85.0	5.0	5.0
Total	100	69.0	18.0	11.0	–	29.0	100	17.0	25.0	14.0	41.0	80.0	2.0	1.0

3.5 *Long-term effects of pesticides on human health in Colombia* (Dr N. Muñoz, Dr N. Day and Dr L. Tomatis, in collaboration with Dr E. Guerrero and Dr M. Restrepo, National Institute of Health, Bogota (RA/79/012); Dr J. Ospina, National Cancer Institute, Bogota; Dr J. Davies, Department of Epidemiology and Public Health, University of Miami, Miami, USA; and Dr J. Litvak, WHO Regional Office for the Americas, Washington, DC) (This study is financed by the Environmental Protection Agency of the United States through the WHO Regional Office)

Within the framework of a study on the long-term effects of pesticides, including carcinogenesis, an investigation on possible teratogenic effects of pesticides is being implemented in three phases. In the first phase, a prevalence survey of children with congenital malformations either born to women working in floriculture for more than six months or born to the wives of men working in floriculture for six months or more, is being completed. A total of 9 000 floriculture workers have been interviewed. The questionnaire included basic demographic information, a complete reproductive history of the female workers and the wives of male workers, and general details of occupational exposure to pesticides. The data is being analysed.

During the second phase, a case-control study will be implemented. The cases will be approximately 100 children with congenital malformations identified during the prevalence survey. Two controls will be selected for each case, matched by age of the parents and by birth order. The male and female workers and wives of male workers will be interviewed. The questionnaire will contain basic demographic information, detailed reproductive history and detailed history of occupational exposure to pesticides and other recognized or suspected causes of malformations such as certain infectious diseases, drugs, and other occupational exposures.

The third phase will be a prospective case-control study. All pregnancies occurring in the cohort of 9 000 floriculture workers will be monitored during a two-year period. At the end of the two-year follow-up period, the number of children born with congenital malformations will be identified, and two control children will be selected as in the retrospective case-control study. Parents of cases and controls will be interviewed, using a questionnaire similar to the one used in the retrospective case-control study, and blood and urine specimens of the same parents will be analysed for selected pesticides or their metabolites. The expected number of children with major congenital malformations during the two-year follow-up period is 90. The pesticide exposure, estimated by personal interview and review of company records, will be validated by measuring the relevant pesticides and their metabolites in the samples of urine and blood of the women, collected at the moment of diagnosing pregnancy. The level of pesticides in the air of the greenhouses will also be measured.

The chemical analysis for pesticides and their metabolites will be complex, as there are at least 44 companies cultivating 11 types of flowers and using at least 95 different pesticides in the Bogota plateau. It was therefore decided initially to limit this study to three major crops (carnations, roses and chrysanthemums) and to concentrate on the 22 pesticides used in excess of 1 000 kilos annually (Table 8).

Four fungicides represent over half of the total usage on a weight basis. Approximately 23 550 kg of captan, 10 760 kg of mancozeb, 8 670 kg of sodium metham and 8 490 kg of propineb are used in Colombian floriculture each year. Captan, which represents about 25% of the total usage, is a confirmed rodent teratogen. Its major metabolite, tetrahydrophthalimide, is structurally similar to the major metabolite of thalidomide, a known human tetratogen. Mancozeb and the

other *bis*-thiocarbamates are being carefully studied since they yield carbon disulfide, a known neurotoxic agent, and most of them yield either the rodent carcinogen, ethylenethiourea (ETU) or one of its analogues.

Among the 22 most commonly used pesticides are some common organophosphorus compounds, a few carbamates and some pesticides which do not fit readily into any broad category. Because many samples will be collected, the number of individual analytical procedures run in the laboratory will be initially limited to 11. It is considered that serum analysis for organochlorine pesticides and metabolites will be a useful index of pesticide exposure in general.

Table 8. Pesticides used in floriculture in Colombia in excess of 1 000 Kg/Year

Rank	Name(s)	Usage (Kg/Yr)
1	Captan	23 550
2	Mancozeb (Manzate 200)	10 760
3	Sodium Metham	8.670
4	Propineb (Mezineb, Antracol)	8 490
5	Chlorothalonil (Daconil)	4 800
6	Endosulfan (Thiodan)	3 830
7	Tetradifon (Tedion)	3 570
8	Aldicarb (Temik)	2 840
9	Zineb	2 840
10	Quintozene (PCNB)	2 670
11	Benomyl (Benlate)	2 670
12	Dicofol (Kelthane)	2 300
13	Malathion	2 230
14	Methyl oxydemeton (Metasystemox)	1 600
15	Carbaryl (Sevin)	1 460
16	Methomyl	1 440
17	Diazinon	1 430
18	Maneb	1 360
19	Ometeato (Folimat)	1 140
20	Ethoprop (Mocap)	1 080
21	Phosphamidon (Dimecron)	1 050
22	Dibrom (Naled)	1 040

The following analyses will be made on blood samples: plasma cholinesterase; RBC cholinesterase; organochlorine pesticides and metabolites; and intact organo-phosphorous pesticides.

Urine will be analysed for: creatinine; alkyl phosphates; MCA and DCA from malathion; carbon disulfide; ethylenethiourea and its analogues; tetrahydrophthalimide; and α-naphthol and/or other phenolic compounds.

The analyses will be carried out in the laboratories of the National Institute of Health, Bogota, and of the University of Miami, USA. Not all 11 analyses will be required for all samples. Different pesticides are used on different crops, and background information on each sample will greatly assist the chemists in deciding which analyses should be performed. Environmental assessment by air sampling of the three major crops will also aid in making these decisions.

Cytogenic and cytokinetic effects of 22 floricultural pesticides on the human lymphoid cell line LAZ-007 will also be studied. These tests will include sister chromatid exchange frequency, chromosomal replication, chromosomal structure and cell cycle traverse.

The second study on possible carcinogenic effects of pesticides will be based in a cohort of workers from the anti-malaria campaign and from plants formulating pesticides. A pilot study to determine the feasibility of retrospective follow-up will be implemented during the first phase of this study.

The Agency is advising and supervising the epidemiological aspects of these studies and the WHO Regional Office for the Americas is in charge of the coordinating and administrative aspects.

3.6 *Case-control study of lung cancer in Cubans* (Dr O. Joly and Dr N. Muñoz, in collaboration with Dr M. Caraballoso, Institute of Oncology and Radiobiology, Havana) (RA/77/016) (This study is financed by the National Cancer Institute, Bethesda, MD, USA)

Interviews have been completed and analysis of data is being carried out.

(*a*) *Case-control study in women*

A total of 731 suspected cases of lung cancer were interviewed during the study period (December 1977–December 1980) in 15 hospitals of the city of Havana. In 219 cases, the diagnosis was confirmed by histology or cytology, and 19 were considered 'highly suspicious'. For 207 subjects, the diagnosis was based on clinical or X-ray evidence only. The remaining 286 cases were excluded because of a final diagnosis other than lung cancer. Preliminary analysis of the 219 confirmed cases is given in Table 9. The relative risk of developing lung cancer in Cuban women who smoke was 5.5 when compared to the hospital controls, and 10.9 when compared to the neighbourhood controls. The risk increased with the intensity of smoking, i.e., the number of cigarettes consumed daily and the frequency and depth of inhalation. The association of smoking with lung cancer was present for squamous cell cancer, undifferentiated carcinoma and poorly differentiated carcinoma, but not for adenocarcinoma. No differences between cases and controls were observed in relation to socio-demographic or environmental factors, nor to reproductive history.

Table 9. Analysis of 219 female Cuban lung cancer patients and controls

	Cases	Hospital controls	Neighbourhood controls
Median age (years)	61.5	60.0	60.1
Percentage of regular smokers	76.3	33.3	31.8
Percentage of smokers smoking dark tobacco	89.8	84.3	78.3

(*b*) *Case-control study in men*

A total of 1316 suspect cases of lung cancer were interviewed from December 1978 to December 1980 in 14 hospitals in the city of Havana. In 607 cases the diagnosis was confirmed histologically or cytologically, and 55 were classified as "highly suspicious". In 373, the diagnosis was clinical or radiological, and 281 were excluded with diagnoses other than lung cancer. A preliminary analysis of the 607 confirmed cases is given in Table 10.

The relative risk of developing lung cancer in Cuban men who smoke was 16.4 when cases were compared to the hospital controls and 10.7 when cases were compared to the neighbourhood controls. As in females, the risk of developing lung cancer increased with the intensity of smoking, but, contrary to the females, in males this increased risk existed for all histological types of lung cancer including adenocarcinoma.

Table 10. Analysis of 607 male Cuban lung cancer patients and controls

	Cases	Hospital controls	Neighbourhood controls
Median age (years)	64.5	65.5	66.5
Percentage of regular smokers	98.0	80.2	80.0
Percentage of smokers smoking dark tobacco	96.2	96.6	96.0

3.7 *Etiological studies of Burkitt's lymphoma* (Dr A. Geser)

(*a*) *Prospective study of Burkitt's lymphoma in the West Nile District, Uganda*
Virus Research Institute, Entebbe, Uganda

(i) *Burkitt's lymphoma case detection*

The project was formally terminated in January 1981. Its main contribution was to show that antibodies to the viral capsid antigen (VCA) of Epstein Barr virus (EBV) are already elevated in children years before the appearance of Burkitt's lymphoma (BL). This finding, which is compatible with the hypothesis that the EBV plays an etiological role in BL, was statistically significant but was based on only 14 pre-bled BL cases, and BL detection was therefore continued in the West Nile District beyond 1978 in an attempt to increase the volume of data. The extended search for cases yielded two additional pre-bled BL cases[22], and sera from these two cases—together with sera from suitable controls—have now been tested for EBV antibodies both at the Agency and at Dr W. Henle's laboratory in Philadelphia. The results showed that EBV/VCA titres in the pre-BL sera were about 2 dilutions higher than in the controls and thus accord with the earlier findings, Based now on a total of 16 cases, the relative risk for BL associated with the raised EBV/VCA titre levels found in the pre-BL sera from early childhood is of the order of 25, a very considerable increase.

(*b*) *Malaria suppression trial and Burkitt's lymphoma (BL) incidence, Mara Region, Tanzania*
Tanzania Shirati Mission Hospital, Musoma, Tanzania
Principal investigator: Dr G. Brubaker

During 1981, the search continued actively for BL, both in North and South Mara, together with the attempt to suppress malaria through distribution of chloroquine tablets in North Mara.

(i) *BL detection*

As reported earlier[22] BL incidence in North Mara has been declining since 1974. During 1980 only one new case was confirmed in North Mara and it seems that the downward trend continues.

[22] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 37.

The reason for this is not known; it is certainly not a result of the anti-malarial efforts, as they have failed to reduce malaria parasitaemia in the area (see below).

During the first 5 months of 1981, six new BL suspects were found in South Mara. If most of these cases should be confirmed as BL by the consultant pathologist (Professor D. Wright, Southampton, UK), this would indicate a recrudescence of BL in the area.

(ii) *Malaria suppression*

Various attempts to intensify the chloroquine distribution in North Mara during 1980 did not lead to the desired reduction in malaria parasitaemia in the target child population. In order to reach a decision about the future of the malaria suppression scheme, a meeting was called (London, 20 February 1981) with participation of malariologists from the London School of Hygiene and Tropical Medicine, and from WHO Headquarters, Geneva. The meeting considered results of recent chloroquine sensitivity testing carried out by Dr C. C. Draper in Shirati. *In vivo* testing in North Mara showed that nearly 80% of children who take the prescribed dose of chloroquine (10 mg/kg), actually cleared their malaria parasites within a week. It was therefore concluded that the failure of the project to reduce parasitaemia must be due to a large proportion of the eligible children not getting the chloroquine tablets regularly in spite of the elaborate distribution machinery, that has been established all over North Mara. It was therefore recommended that the community-wide chloroquine distribution should be terminated by the end of 1981 and that chloroquine tablets should continue to be made available in all villages in the area for the benefit of symptomatic cases of malaria. At the same time, continued BL detection was strongly recommended to find out the true time trend of the tumour.

3.8 *Large bowel cancer* (Dr D. G. Zaridze)

The role of diet and related factors have been investigated in large bowel carcinogenesis, both by correlation and case-control studies focused on the assessment of actual dietary intake, and by metabolic studies of faeces and urine. Standardized techniques of measurement have been developed for assessment of individual dietary components.

(*a*) *International study of diet and faecal characteristics in relation to colorectal and other cancer* (Dr O. M. Jensen (present affiliation: Danish Cancer Registry, Copenhagen), Dr J. Wahrendorf and Dr D. Zaridze, in collaboration with Dr P. Helms and Dr A. M. Jorgensen, University of Aarhus, Aarhus, Denmark; Dr R. Seppänen, Dr R. Burton and Dr R. Strand, Research Institute of Social Security, Helsinki; Dr. J. Mosbech, Dr L. Bjerrum and Dr A. Paerregaard, Copenhagen County Hospital, Sr. Elisabeth, Copenhagen; Dr W. P. T. James, Dr S. Bingham, Dr J. Cummings, Dr H. Englyst, Dr R. Williams and Dr H. Wiggins, Dunn Clinical Nutrition Centre, Cambridge, UK; Dr M. J. Hill, Dr M. Thompson and Dr A. Taylor, Bacterial Metabolism Research Laboratory, Central Public Health Laboratory, London; Dr G. Laurell and Dr A. Schwan, Institute of Clinical Bacteriology, University of Uppsala, Sweden; and Dr T. D. Wilkins, Anaerobe Laboratory, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA)

In Copenhagen, rural Denmark, Helsinki and rural Finland, areas which exhibit a three-fold gradient in the incidence of colorectal cancer, some 30 randomly selected men, aged 50–59, were investigated in respect to diet, gut transmit time, faecal bulk, faecal bacteriology, bile acid concentration and volatile phenol production. Dietary information was obtained by the four-day weighing method, and by chemical analysis of a one-day duplicate food portion, of which the mutagenic activity was also assessed.

Average daily fat intake was high in all four areas. Non-starch polysaccharide (dietary fibre), carbohydrate and protein intake was higher in the low incidence area of rural Finland than in Copenhagen where incidence is high. The bile acid concentration in the faeces was greater in the high incidence than in the low incidence area, with the two other areas taking intermediate values. Faecal bulk showed an inverse association with colorectal cancer incidence. No differences were observed with regard to faecal phenol production, bacteriology, and mutagenic activity of the foods.

The present study to a large measure confirms our previous study[23] and supports the hypothesis of a complex interaction of various dietary components in determining colon cancer risk. It is suggested that dietary fat, and possibly protein, promote large bowel cancer by increasing the bile acid output. Dietary fibre modifies risk by influencing faecal bulk and, at a given level of bile acid output, dietary fibre may thus determine the concentrations of carcinogens or co-carcinogens which reach the bowel mucosa.

(*b*) *Case-control study of adenomatous polyps of the large bowel* (Dr D. Zaridze, in collaboration with Professor M. Crespi, Regina Elena Institute, Rome)

Evidence from animal and human studies suggests that cancer of the large bowel develops through the stages of local hyperplasia, adenomatous polyp and non-invasive carcinoma. The factors responsible for the development of adenomas *per se* could, therefore, be different from those influencing the progression to malignant neoplasm, or, alternatively, the lack of some protective factor may favour the development of cancer.

A case-control study has been designed to explore the differences in diet and related factors between patients with adenoma with high-grade (advanced) dysplasia, including non-invasive carcinoma, those with adenoma with low-grade (early) dysplasia, and a group of adenoma-free persons. The study has the advantage that it enables investigation of the suspect etiological chain of events at different, histologically-defined stages of the natural history of the tumour.

(*c*) *Large bowel pathology in autopsy series* (Dr D. G. Zaridze and Dr J. Estève, in collaboration with Dr O. Jensen, Danish Cancer Registry, Copenhagen; Dr N. M. Gibbs, St. Luke's Hospital, Guildford, Surrey, UK; Dr J. Simpson, Dr S. Ewen and Dr J. Clark, Department of Pathology, University of Aberdeen, Scotland; Dr H. Staslberg and Dr J. Eide, Institute of Medical Biology, University of Tromsö, Norway; and Dr G. Koskela and Dr Y. Collan, Department of Pathology, University of Kuopio, Finland)

The study was conducted to compare the distribution and histological types of various lesions of the colon and rectum in populations in Europe with contrasting incidence of large bowel cancer.

[23] IARC Intestinal Microecology Group (1977), *Lancet*, ii, 207–211.

Autopsy material was collected during the period of 1976–79 from consecutive autopsies, 25 accessions being made in each sex- and age-group. The total number of autopsies collected in each centre was 200. Particular attention was given to the macroscopic and microscopic features of the different types of polyps observed, and to cancer, melanosis coli, diverticular and inflammatory disease. The data were submitted to the Agency for analysis. In addition, a "blind" histological evaluation of a random sample of slides of large bowel polyps was carried out.

At the meeting of the working group held at the Agency (26–27 March 1981), the reports from the individual centres and the results of the comparative analysis of the material were discussed. It was shown that the frequency of single and multiple polyps was higher in males than in females, and increased with age in both sexes. The prevalence of polypoid lesions was higher in areas of high incidence of large bowel cancer. There was no difference in distribution of polypoid lesions by size between males and females, but size did increase with age. Polyps tended to be larger in areas of higher incidence.

Considerable inter-observer variation in assessment of histological criteria was demonstrated and further circulation of randomized material was required, before conclusions could be reached on the degree and nature of any differences in the material from areas of contrasting large bowel cancer incidence.

3.9 *Prostatic cancer*

Dutch-Japanese case-control study of prostatic cancer (Dr D. G. Zaridze, in collaboration with Professor P. H. Schröder, Dr F. J. W. ten Kate, Dr F. H. de Jong, Erasmus University, Rotterdam, the Netherlands; Dr R. Hayes, Study Centre of Social Oncology, Dutch Cancer Foundation, Rotterdam, the Netherlands; Professor O. Yoshida, Professor K. Okada, Dr K. Oishi, Dr H. Yamabe, Kyoto University, Kyoto, Japan; and Dr Y. Ohno, Nagoya University, Nagoya, Japan)

The purpose of this study is to identify factors associated with the development of prostatic cancer. Similarities and differences will be observed between two countries, one with a low and the other with a high incidence of this disease.

Evidence suggests that the approximately 30-fold international variation in incidence of prostate cancer may be associated with factors related to tumour development beyond the stage of non-invasive cancer (small latent cancer)[24] and that these factors may operate late in life.

By means of a study of cases and controls in the Netherlands and Japan, it is proposed to explore four groups: (1) patients with clinical prostatic cancer, (2) patients with latent (focal) prostatic cancer diagnosed histologically in glands removed for benign prostatic hyperplasia (BPH), (3) patients with BPH without histological evidence of latent carcinoma and (4) hospital controls. Diet, sexual history, occupational history, blood levels of selected hormones, blood levels of retinol and β-carotene will be investigated, with the main emphasis being directed towards assessing differences in exposure to risk factors between patients with latent and clinical prostatic cancer, that is to the factors believed to be related to the later stages of carcinogenesis.

[24] Breslow, N., *et al.* (1977) *Int. J. Cancer*, **20**, 680–688.

3.10 *Studies in the industrial environment* (Dr R. Saracci and Dr L. Simonato)

(*a*) *Health risks of mineral fibres*

(i) *Man-made mineral fibre production* (Dr R. Saracci, Dr L. Simonato, Dr A. Geser, Dr J. Estève and Miss B. Charnay, in collaboration with Professor E. D. Acheson, School of Medicine, Southampton, UK (RA/78/021); Dr O. M. Jensen, Danish Cancer Registry, Copenhagen (RA/78/020); Dr P. Westerholm, Landsorganisation i Sverige, Stockholm; Dr A. Andersen, Norwegian Cancer Registry, Oslo (RA/78/022); and Dr P. A. Bertazzi, Work Clinic, Milan, Italy (RA/80/002))

The historical follow-up study of the health risks associated with mineral fibre production has reached its final phase. The collection of the data, which started in the second half of 1978, has been completed in each of the 13 factories located in the 7 countries included in the study (Table 11).

Table 11. Factories included in the man-made mineral fibre study

Country	Number of factories	Total workforce registered
Denmark	1	5 369
Germany	1	2 139
Finland	1	941
Italy	1	2 650
Norway	4	2 653
Sweden	3	5 070
UK	2	7 074
Total	13	25 896

Similarly, the results of the environmental surveys carried out by the Institute of Occupational Medicine, Edinburgh, at all the factories included in the study have been sent to the Agency in order to allow quantitative estimation of the exposure to airborne fibres for individual work stations.

Mortality and cancer occurrence will be compared in workers exposed to mineral fibres in the production facilities and in the general population of the areas where the factories are located. Groups of workers with different degrees and lengths of exposure will also be compared. Results will be presented at a meeting jointly organized by the WHO Regional Office for Europe and IARC in Copenhagen, April 1982.

(ii) *Man-made mineral fibre users* (Dr R. Saracci, Dr A. Geser, Dr N. Day and Dr L. Simonato, in collaboration with Dr A. Englund and Mr G. Engholm, 'Bygghälsan', the Swedish Foundation for Occupational Safety and Health in the Construction Industry, Stockholm)

Workers engaged in occupations such as the building construction and demolition industries are likely to be exposed to higher concentrations of fibres than in the production industry, and so 'Bygghälsan' and the Swedish Environment Fund provided funds for a case-control study on 179 lung cancer deaths which occured up to 1978 within a cohort of employees in the building industry surveyed in the period 1971–74. Information on past occupational exposure and smoking habits was available. A preliminary analysis did not show any consistent excess risk in relation to exposure, but the follow-up period for these workers is likely to be too short to reveal such an effect. In addition, in this group of workers, the excess risk due to cigarette smoking exposure appeared to be small.

A further follow-up and analysis will be performed at the end of 1981.

(iii) *Mesothelioma in central Turkey* (Dr R. Saracci and Dr L. Simonato, in collaboration with Dr Y.I. Baris, Department of Chest Diseases, Hacettepe University, Ankara (RA/78/012), and Mr J. Skidmore, MRC Pneumoconiosis Unit, Llandough Hospital, Penarth, Wales)

The results of the survey carried out in collaboration with Dr Baris and the MRC Pneumoconiosis Unit to investigate in two small villages, Karain and Karlik, of central Anatolia (Turkey) the relationship between occurrence of mesothelioma and possible exposure to naturally occurring zeolite fibres, have been analysed and published[25]. An excess adult mortality, shortening of life expectancy and an excess of radiological abnormalities of the pleura were found in Karain, thus supporting the earlier report[26] of an endemic of pleural mesothelioma in the village. Concentrations of airborne respirable fibres were uniformly low in Karlik but higher in some of the samples from Karain. The fibres were similar to those of erionite, a mineral of the zeolite family and the major component of the dust in Karain. Although this is compatible with the hypothesis of a causal association between endemic mesothelioma and inhalation of erionite fibres, the fibre concentrations in all samples are too low to allow a definite assessment.

The analysis of the data collected in a third village, Sarahidir, located in the same area, is underway. This information will provide additional insight into the relationship between occurrence of zeolite or other natural mineral fibres and prevalence of mesothelioma in the area under study.

A case-control approach has been used to ascertain the frequency of the presence of zeolite deposits in the houses of cases who died of mesothelioma in the village of Karain in the period January 1979–January 1981, compared to the houses of controls not affected by mesothelioma, matched by sex and age. The analysis of the rock samples collected is currently being performed blindly at the MRC Pneumoconiosis Unit.

[25] Baris, Y.I., Saracci, R., Simonato, L., Skidmore, J.W. & Artvinli, M. (1981), *Lancet*, 1 (8227), 981–987.
[26] Baris, Y.I., Sahin, A.A., Ozesmi, M., Kerse, I., Ozen, E., Kolacan, B., Altinors, M. & Goktepeli, A. (1978) *Thorax*, 33, 181–192.

(b) Laboratory studies relevant to lung cancer (for a more detailed presentation see p. 94)

(i) In conjunction with Dr C. Giuntini of the Italian National Research Council (University of Pisa), the Agency is evaluating lung function tests capable of early recognition of the effects of inhaled particles. An analysis of 18 such tests, on 60 asymptomatic smokers and 60 non-smokers, to identify the tests which best discriminate between the two groups has been made and a paper presenting the results and methodology of this study has been submitted for publication[27].

(ii) It is proposed to develop the use of data from these lung function tests to study lung function and the activity of pulmonary aryl hydrocarbon hydroxylase (AHH) in surgical lung specimens.

(iii) The determination of the pulmonary microsomal mono-oxygenase levels of 105 cancer patients has been completed, and the results published[28].

(c) IARC Monographs on the Evalutation of the Carcinogenic Risk of Chemicals to Humans (Dr R. Saracci and Dr L. Simonato)

The carcinogenic risk resulting from exposure to miscellaneous chemicals in the working environment of the rubber industry and industrial chemicals and dye-stuffs has been evaluated in the three Working Groups in 1981, which resulted in Volumes 26-28 of the *Monographs* series. Dr Saracci and Dr Simonato acted as secretariat for the epidemiological component of this programme (see p. 58).

(d) Silicosis and lung cancer (Dr L. Simonato and Dr R. Saracci, in collaboration with the Centre for the Study of Environmental Carcinogenesis, University of Padua, Italy)

Silica dust is one of the major contaminants in the occupational environment and its health effects, particularly on the respiratory system, have been known for a long time. The hypothesis that silica dust could also increase the risk of lung cancer has been investigated with conflicting results. Cigarette smoking as a confounding factor, and non-neoplastic respiratory diseases as competing causes of death, seem to be the main obstacles to a definitive evaluation of the problem.

A cohort of about 1000 patients with silicosis diagnosed in the period 1959–63 in the Venice Region (Italy), has been followed-up to the end of 1980. Death certificates for this period have been studied, and mortality data within the cohort will be analysed, in collaboration with the Agency. Information on past silica exposure and smoking habits is available for most of the members of this cohort.

(e) Occupational Cancer Review (Dr L. Simonato, Dr R. Saracci and Miss J. Hawken)

A systematic collection of published studies investigating the carcinogenic risk in the occupational environment has been analysed, and an initial summary prepared as a contribution to the new version of the volume Occupational Health and Safety published by the International Labour Office in Geneva.

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[27] Giuntini *et al.*, (1981) *European Bulletin of Respiratory Physiopathology* (submitted for publication).

[28] Sabadie, N., Richter-Reichhelm, H.B., Saracci, R., Mohr, U. & Bartsch, H. (1981) *Int. J. Cancer*, **27**, 417–425.

3.11 *International radiation study of cervical cancer* (Dr J. Estève and Dr A. Geser) (see also section 5.1 p. 51)

(*a*) *Additional case-control studies*

It is planned to expand the case-control aspect of the cancer registry component of the study to a range of additional sites, in order to define with greater precision the relationship between dose and risk. A detailed study protocol is being drawn up for consideration at the meeting in January 1982.

(*b*) *Follow-up of women in the initial clinical series*

Reactivation of this component of the study has been postponed.

4. SURVEILLANCE OF ENVIRONMENTAL ASPECTS RELATED TO CANCER IN HUMANS (SEARCH) (Dr C. Agthe)

In April 1981 the Governing Council adopted a Resolution extending the period for the use of the funds allocated for SEARCH by the Governing Council Special Fund until the end of 1982.

4.1 *Acquisition of international environmental data for studies with cancer occurrence data*

Considerable efforts were made to collect international data for possible correlation with cancer occurrence data of different countries. In view of the importance of diet in cancer of the digestive tract, and since past food consumption patterns are difficult to assess by interviews, emphasis has been laid on collection of international food consumption data. It appears, however, that although food consumption surveys by the FAO have been undertaken in many countries, the data are not comparable. On the other hand, food supply data (production plus import minus export and losses) elaborated by FAO are comparable. These figures are available from 1962 for as many as 162 countries. They are available on computer tapes, a copy of which is now available at the Agency. These tapes also contain figures on *per capita* supply of total protein, carbohydrate, fat, vitamins, calcium and others. A correlation study with the latter figures and national cancer occurrence data is under way.

Wherever the data permit, trends in the food supply will be compared with trends in cancer incidence.

4.2 *Collection of national inventories of environmental data*

Contacts have been made with the International Referral System for Sources of Environmental Information (INFOTERRA) in the UNEP Programme.

This programme operates through national focal points and has produced an international Directory of Sources of Environmental Information. The information contained therein could be of use for epidemiological studies in which environmental data for various countries are required. Upon request of UNEP, the Agency agreed to become a sectoral focal point of INFOTERRA. As such, the Agency has agreed to answer any queries addressed to it concerning cancer epidemiology and environmental carcinogens. In exchange, the Directory of Sources of Environmental Information in printed form (5 volumes) and the data in computerized form will be available to IARC.

During negotiations with UNEP, visits have been made to Denmark, Germany, Sweden and the United Kingdom to inquire about the availability of environmental information and their sources in these countries.

The study has shown that there is a very large amount of environmental data available, but that their diverse nature will make it difficult to use them in correlation studies.

4.3 *Elaboration of a questionnaire for an intensive SEARCH programme*

A questionnaire has been elaborated for the case-control study of the SEARCH programme. It is designed to assess the long-lasting features of life and how these have changed throughout the lifespan. Most of the parameters are to be assessed in quantitative terms as well as duration of exposure. The questionnaire was tested successfully. The interview lasted about 1 ¼ hours and it is thus expected that it will have to be undertaken in two sessions in order not to tire the patient unduly. Based on observations during the testing of the questionnaire, some sections are being revised.

4.4 *Negotiations with areas of possible participation in SEARCH*

A detailed description of the SEARCH programme has been published[29]. In 1981 efforts have been made to identify three pilot areas for admission to the study. Once experience has been gained, other areas will be asked to join to achieve better geographical distribution. Contacts have been made with Canada, Germany, the Netherlands, Sweden, Switzerland and USA. The main criteria for participation by an area are a population in the order of 1–1.5 million inhabitants in rural and urban regions, and a possibility of interviewing 80% of those cancer patients selected for the study. Furthermore, the government of the country should be prepared to finance the activity in the study area, and to contribute to a fund to finance the study in an area in a developing country. The study in developing countries will, therefore, be started with about one year's delay.

So far, the Netherlands has agreed to participate in SEARCH and the necessary funds have been made available for the study in an area in the Netherlands. The government has also agreed to supervise and finance the study in the Netherlands Antilles.

[29] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, pp. 46–47.

5. BIOSTATISTICS (Dr N. E. Day)

5.1 *International radiation study of cervical cancer* (Dr J. Estève and Miss D. Magnin) (see also section 3.11, p. 49)

An overall description of this study has been published[30]. Progress in the past year has concentrated on the cohort studies in the cancer registries and on a case-control study of leukaemia within these cohorts. Two meetings of the cancer registry participants in the study were held at the Agency (7–8 December 1980 and 7–8 July 1981).

(*a*) *Cohort studies in cancer registries*

The fifteen registries participating at present are those of: Denmark, Finland, Norway, Sweden, Birmingham (UK), South Thames (UK), Slovenia (Yugoslavia), Connecticut (USA), and Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario and Saskatchewan (Canada).

The number of cases enrolled in the study, nearly 180 000, are shown by registry in Table 12. It is of interest to compare this number with the approximately 25 000 individuals in the Japanese atomic bomb series assessed to have received more than 10 rads[31], or the 15 000 individuals in the ankylosing spondylitis series[32].

Table 12. International Radiation Study of Cervical Cancer
Number of cases enrolled by the different cancer registries

	Total no. of cases	Total no. of cases of invasive cancer
Canada		
Alberta	2 507	2 507
British Columbia	3 056	3 050
Manitoba	7 422	2 441
New Brunswick	1 449	1 449
Nova Scotia	779	779
Ontario	8 039	8 039
Saskatchewan	1 509	1 509
Denmark	41 090	25 622
Finland	10 290	7 044
Norway	8 136	6 006
Sweden	58 731	14 760
United Kingdom		
Birmingham	4 569	2 146
South Thames	11 199	7 327
United States		
Connecticut	14 387	7 127
Yugoslavia		
Slovenia	5 474	4 332
Total	178 637	94 138

[30] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 49.
[31] Beebe, G. W., Kato, H. & Land, C.E. (1978) *Radiat. Res.*, **75**, 138–201.
[32] Court Brown, W.M. & Doll, R. (1965) *Br. Med. J.*, **2**, 1327–1332.

Each registry has provided tabulations of the number of second primary tumours observed in their cohort, by site and by time since the initial diagnosis of cancer of the cervix, together with the respective expected numbers. These tabulations are given separately for invasive cervical cancer cases who received radiotherapy, those who did not receive radiotherapy, and for *in situ* lesions.

In addition, registries have provided similar tabulations of the observed and expected numbers of breast cancer cases, further broken down by age at diagnosis of the primary cervical cancer. Corresponding analyses have now been requested for a variety of other sites.

The results from this component of the study were considered of sufficient interest to merit separate, detailed publication, and it has been proposed to publish them as an IARC *Monograph*. A final draft will be reviewed at the next meeting of the cancer registry participants, planned for January 1982.

(*b*) *Case-control study of leukaemia within the cancer registry cohorts*

The analysis of the cohort results, in which the observed number of cases of leukaemia was compared to expected, indicated a possible excess of leukaemia (other than chronic lymphocytic leukaemia) in the 9-year period after irradiation. Most of the participating cancer registries have now abstracted treatment details for the leukaemia cases and for controls matched for age, date of diagnosis of the primary cervical tumour and survival at the time the corresponding leukaemia was diagnosed. The diagnosis of leukaemia, and of the cell type is being reviewed by Dr W. C. Moloney (Brigham and Women's Hospital, Boston, MA, USA). It is hoped to have the full results and an interpretative analysis completed by January 1982, although the latter depends on further work on the distribution of radiation dose to the active bone marrow.

5.2 *Evaluation of cervical cancer screening programmes* (Dr N. E. Day, Mr X. Nguyen-Dinh and Mrs A. Arslan)

The origins and overall aims of this programme have been described[30]. In the present phase of this programme, the aim is to estimate the incidence of invasive cervical cancer among women who have had a previous negative smear, in terms of the time elapsed since the last negative smear and the number of such smears. These data should provide a basis for evaluating the relative protection afforded by different screening strategies. A detailed protocol was developed at a meeting at the WHO Regional Office for Europe in December 1979, and initial results and modification to the protocol were discussed at a further meeting in Oslo in August 1980. The screening programmes which are collaborating in this study are from Aberdeen (N.E. Scotland), Finland, Maribo Amt (Denmark), Iceland, Østfold County (Norway) and the Stockholm region (Sweden). In addition, data from Toronto, Canada, which derive from a case-control study rather than an organized screening programme, have been put in a comparable form and will be included in the final evaluation.

Since the populations covered by the six screening programmes are all covered by cancer registration, identification of the invasive cases arising in the screened group is simple. The major difficulty in some areas is the reconstruction of the screening histories of the entire population screened. The abstraction of the screening records should be completed by the end of 1981, and all the necessary data will be available in computer-readable form.

The Norwegian Cancer Society has generously provided funds for a meeting to be held in Oslo (Spring, 1982), at which the final results of this phase of the study will be presented and reviewed.

To complement the work in progress, the purpose of which is to provide an empirical description of the effect of screening, attention is being given to the development of simple, realistic models of the screening process. The aim is to describe the large array of incidence rates conditional on different screening histories, in terms of the underlying parameters of sensitivity, specificity and of the distribution of the time spent in the detectable pre-clinical state. These models have been applied initially to published data on breast cancer screening, and the results are being prepared for publication. When the data become available, the models will be applied to screening for cervical cancer. They could be used to predict the changes in morbidity and mortality, that would be expected in a population, after the introduction of a particular intensity of screening. Retrospective data from the collaborating programmes will be used to assess the value and precision of these predictions.

5.3 *HLA antigens and nasopharyngeal carcinoma (NPC)* (Dr N. E. Day and Dr J. Wahrendorf, in collaboration with Professor S. H. Chan, University of Singapore, Singapore)

The study has been completed. Chinese cases and Chinese controls have been typed for HLA Loci A and B antigens. The significant results are shown in Table 13.

There is a suggestion that survival among NPC patients is related to HLA phenotype, the presence of A2 in the absence of B17 or BW46 being associated with better survival.

Table 13. Relations of HLA antigens to risk for nasopharyngeal carcinoma

	TOTAL	A2	B17	BW46
Cantonese:				
Normal	134	75	15	34
NPC negative	55	32	11	15
Total non-NPC	189	107	26	49
NPC positive	105	64	25	45
Teochew:				
Normal	62	35	10	17
NPC negative	40	17	10	5
Total non-NPC	102	52	20	22
NPC positive	72	52	19	23
Hokkien:				
Normal	134	69	21	28
NPC negative	72	30	15	15
Total non-NPC	206	99	36	43
NPC positive	136	81	40	44
Relative risk		1.58	2.22	1.91
X^2 on l.d.f.		9.46	11.5	15.9
P value		~ 0.002	< 0.001	< 0.001

5.4 *Oesophageal cancer in Iran* (Dr N. E. Day and Mrs A. Arslan, in collaboration with Dr A. Nadim, Institute of Public Health Research, Teheran)

(*a*) *Field studies*

The material available for analysis from the 1978 field study has been described[33]. Most of the laboratory assays have been performed, and a combined statistical analysis is planned for the second half of 1981.

(i) *Morphine metabolites in urine* (Dr C. Gorodetzky, National Institute of Drug Abuse, Lexington, KY, USA)

Six hundred samples have so far been tested and the remaining 1 300 are currently being assayed. The preliminary results confirm a high prevalence of opium metabolites in urine among the Turkoman population of both sexes, the prevalence increasing with age. Approximately 50% of those over age 35 had morphine metabolites in the urine.

(ii) *Antipyrine half-life determination* (Professor M. Roberfroid, Free University of Brussels, Louvain, Belgium)

Sequential saliva samples (4, 12 and 24 hours after administration of antipyrine) were assayed in 184 individuals of both sexes, all age groups and regions of high and low incidence of oesophageal cancer. The results will be analysed in conjunction with the urinary morphine results when these become available (see p. 112).

(iii) *Mutagenicity testing of urine* (see section 109)

5.5 *The analysis of time trends in cancer incidence and mortality data* (Dr N. E. Day, Dr J. Estève and Miss B. Charnay, in collaboration with Dr P. Boyle, West of Scotland Cancer Surveillance Unit, Glasgow, Scotland, and Dr K. Magnus, Norwegian Cancer Registry, Oslo)

When a particular cancer increases in incidence, it is often found that this increase operates on a cohort basis, as seen for lung cancer or malignant melanoma. Some changes, however, are more closely associated with the year of diagnosis, indicating perhaps a change in diagnostic practices or, possibly, new exposure to a rapidly acting factor, such as replacement oestrogens in relation to cancer of the endometrium. Methods for the analytical description of time trends are being developed in which the influences of both effects are assessed. A paper summarising some initial results using data from Finland and Slovenia (Yugoslavia) was presented at the Oslo symposium on time trends[34] and the Norwegian melanoma data (Dr P. Boyle, Dr K. Magnus) have been further examined. It is planned to develop a systematic analysis of the first four volumes of *Cancer Incidence in Five Continents* along these lines, in collaboration with the programme of descriptive epidemiology.

[33] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 33.
[34] Day, N.E. & Charnay, B. (1980) In: Magnus, K., ed., *Trends in Cancer Incidence*, New York, Hemisphere, pp. 51–66.

5.6 *Monographs on statistical methodology*

The first of these monographs has been published on the analysis of case-control studies[35]. It has been used as the basic teaching material at an IARC course on statistical methods in cancer epidemiology (Lyon, 29 June–3 July 1981), as well as at courses outside the Agency (see p. 116).

A second monograph is in preparation on the statistical analysis of long-term carcinogenicity experiments, intended as a complement to the simple guidelines already published[36]. A meeting was held in February 1981 of the editorial group: Dr N. E. Breslow (University of Washington, Seattle, USA), Dr D. Krewski (Health and Welfare, Ottawa, Canada), Mr P. Lee (London), and Dr R. Tarone (National Cancer Institute, Bethesda, MD, USA), together with Dr J. Wahrendorf and Dr N. Day. The structure of the book was agreed, and the individual chapters allocated. An initial manuscript should be drafted by early 1982.

The third volume planned is on the analysis of cohort studies.

5.7 *Statistical evaluation of carcinogenicity experiments*

To supplement the "Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments"[37], a simple transferable computer programme has been developed to carry out these analyses, and is available on demand.

5.8 *Analysis of more complex carcinogenesis experiments* (Dr J. Wahrendorf, Dr R. Montesano and Mrs B. Dodet)

In long-term animal experiments, in addition to the question of whether certain exposures are carcinogenic or not, further questions may be posed on different aspects of the carcinogenic process. Experiments may then include in their design such alternatives as limited duration or fractionated exposure, or the serial sacrifice of animals, and these situations demand special statistical analysis. Statistical models have been proposed, which estimate both tumour prevalence and lethality, taking into account the multistage nature of the carcinogenic process. In this context, previous experiments with exposure to DDT of limited duration were reviewed to examine the extent to which the tumour yield is reduced by cessation of treatment.

5.9 *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (Dr J. Wahrendorf)

The evaluation of many of the chemicals considered in the *Monographs* programme (see p. 58) requires assessment by a variety of statistical techniques, and Dr J. Wahrendorf participates in the secretariat for the preparation of the *Monographs*.

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[35] Breslow, N. E. & Day, N. E. (1980) *Statistical Methods in Cancer Research*, Vol. 1 *The Analysis of Case-Control Studies*, Lyon, International Agency for Research on Cancer *(IARC Scientific Publications No. 32.)*.

[36] Peto, R., Pike, M. C., Day, N.E., Gray, R. G., Lee, P.N., Parish, S., Peto, J., Richards, S. & Wahrendorf, J. (1980) In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement No. 2, *Long-term and short-term screening assays for carcinogens: a critical appraisal*, Lyon, International Agency for research on Cancer, pp. 311–426.

5.10 *Interactive effects* (Dr J. Wahrendorf)

The appropriate statistical treatment of the effect of joint exposure to two or more agents is a much discussed issue in the experimental as well as epidemiological context. Special attention has to be given to the fact that statistical methods should reflect knowledge of the biology of the problem and possibly of the public health aspects. Attempts have to be made to consider more than just whether a multiplicative or additive model for the effects of the joint exposure is appropriate[37, 38]. Methods have been developed for the experimental context, and an extension to the epidemiological situation is under way[39].

5.11 *Statistical and computing assistance to other programmes* (Dr J. Estève and Miss B. Charnay)

To improve the speed of response and efficiency of statistical and computing assistance, efforts have been made in two directions. Firstly, a standard approach to data management has been established, and secondly, interactive 'easy to use' software has been developed so that those with no formal training in programming can use the computer facilities.

Several studies not mentioned in earlier sections of this report are now in the stage of data management and/or analysis. They represent an important part of the biostatistics programme:

(*a*) *Man-made mineral fibres study.*(Dr R. Saracci and Miss B. Charnay) (see section 3.10 *(a)*)

The data base of 26 000 workers from the various factories is regularly updated, various controls and consistency checks are performed as well as error corrections. The first statistical analysis of the cohort should be completed by the end of 1981.

(*b*) *Alcohol and cancer* (Dr A. J. Tuyns) (see section 3.1)

The data from Clavados are now ready for statistical evaluation. Some preliminary tabulations have been prepared and the full analysis of the case-control studies is under way, in collaboration with the principal investigators. The data of the Spanish component of the larynx case-control study are still in the preliminary stages of data management.

(*c*) *Large bowel autopsies study* (Dr D. Zaridze and Miss D. Magnin) (see section 3.8 *(c)*)

Various statistical analyses were prepared for the meeting held in Lyon (26–27 March 1981). Further work is foreseen when the second reading of the slides is completed.

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[37] Wahrendorf, J. & Brown, C.C. (1980) *Biometrics*, **36**, 653–657.
[38] Wahrendorf, J., Zentgraf, R. & Brown, C.C. (1980) *Biometrics*, **37**, 45–54.
[39] Wahrendorf, J. (1981) In: *Proceedings of the First European Symposium on Medical Statistics, Rome, 25–27 September 1980*, London, Academic Press (in press).

(*d*) *Precancerous lesions of the oesophagus in China* (Dr N. Muñoz and Mrs A. Arslan) (see section 3.3 *(b)*)

The data are now in computer-readable form and statistical analysis is under way.

5.12 *Miscellaneous*

A paper was given on the methodology of time trend evaluation in Besançon (France) at the meeting of the cancer registries from Latin-speaking countries. A presentation of the regression method in case-control studies was given in Nancy (France) at the French Biometrics Society.

DIVISION OF ENVIRONMENTAL CARCINOGENESIS

Dr L. TOMATIS (Director)

1. INTRODUCTION

To achieve its objectives, the Division, on the one hand, coordinates and carries out research programmes which generate primary information of use in integrated epidemiological studies for the identification of human cancer risk factors, the development of laboratory methods which might be applied to such studies and which might provide the possibility of distinguishing individuals or groups within the human population that are at different risks of developing cancer. On the other hand, the Division collects and critically analyses secondary information derived from the published literature on the carcinogenicity of individual chemicals or complex mixtures and evaluates this information with the help of international experts. These evaluations provide the basis for assessing the existence of a possible risk of cancer to humans.

Within the limited laboratory facilities of the Division, priority has been given to investigations which either respond to the needs of epidemiological studies, or are aimed at generating hypotheses that can be tested by epidemiological surveys. Studies in the Agency also serve the purpose of catalysing research carried out by national laboratories, and of co-ordinating the results.

2. RETRIEVAL AND COORDINATION OF CARCINOGENICITY DATA[1]

2.1 *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (Dr L. Tomatis, Mr J. Wilbourn, Miss L. Haroun and Mrs C. Partensky)

The aim of the *IARC Monographs* programme is to identify potential carcinogenic risks to humans due to exposures to chemicals or complex mixtures, which occur in the environment, and to assemble and evaluate existing knowledge on chemicals known to be, or considered potentially, carcinogenic for humans.

Implementation of the programme involves three steps: i) collection of all published data relevant to the assessment of the carcinogenic risk (including data on chemical production, occurrence, experimental carcinogenesis, toxicology, mutagenicity and epidemiology) for the selected chemicals or complex mixtures; ii) critical evaluation of these data by international working groups of experts in epidemiology and chemical carcinogenesis and related disciplines; and iii) publication and dissemination of the summarized data and evaluations as *IARC Monographs.*

[1] The IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans and the IARC Information Bulletins on the Survey of Chemicals Being Tested for Carcinogenicity are supported in part by the US National Cancer Institute under Contract No. N01 CP 15751.

The critical evaluations of the data are intended to assist national public and occupational health authorities in formulating decisions relating to preventive measures through the control of exposures. They are available to the international organizations responsible for making recommendations in this field. By pin-pointing gaps in the existing knowledge, the *Monographs* may also help define areas where further research efforts are needed.

During the past year, three Working Groups were convened in Lyon; the deliberations and conclusions of these Working Groups resulted in Volumes 26, 27 and 28 of the *IARC Monographs*[2, 3, 4].

Volume 26 contains 18 monographs on antineoplastic and immunosuppressive agents. The compounds include alkylating agents, antimetabolites, mitotic inhibitors and/or immunosuppressants. In experimental systems the alkylating agents were generally found to be carcinogenic and mutagenic and to produce neoplasms at multiple sites. For several of the drugs no epidemiological study was available which compared the observed number of secondary cancers in patients who had received the drug in question with the expected number of cancers. For the majority of drugs, only case reports of secondary cancers occurring after treatment with the drug, or combinations of drugs, were available.

The Working Group concluded that there was *sufficient evidence* of carcinogenicity in humans for the following compounds: azathioprine, cyclophosphamide, intensive regimes that include alkylating agents, vinca alkaloids, procarbazine hydrochloride and prednisone, and treosulphan. There was *limited evidence* for the carcinogenicity of chlorambucil in humans. For several compounds, bischloroethyl nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), dacarbazine, procarbazine hydrochloride, the data in humans was inadequate for evaluation, but there was *sufficient evidence* of their carcinogenicity in experimental animals.

No evaluation could be made for 5-azacytidine, bleomycins, cisplatin, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, vinblastine sulphate and vincristine sulphate.

Volume 27 contains 18 monographs on some aromatic amines, anthraquinones and nitroso compounds, and inorganic fluorides used in drinking water and dental preparations. Occupational exposure to fluoride compounds and exposures in the general population due to contamination of the environment were not evaluated and may be considered at a future date.

The Working Group concluded that there was *sufficient evidence* for the carcinogenicity of the following compounds in experimental animals: *ortho*-anisidine, 4-chloro-*ortho*-phenylenediamine, *para*-cresidine, 2,4-diaminoanisole sulphate, 4,4'-thiodianiline, *ortho*-toluidine hydrochloride. For the remaining compounds, the evidence of carcinogenicity in experimental animals was either *limited* or the data were inadequate for evaluation.

In the case of fluorides used in drinking water and dental preparations the Working Group concluded that there was no evidence of carcinogenic risk associated with the fluoridation of drinking water.

The Working Groups considered that in the absence of adequate data in humans, compounds for which there is *sufficient evidence* for carcinogenicity in animals should be regarded for practical purposes, as though they presented a carcinogenic risk to humans.

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[2] International Agency for Research on Cancer (1981) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, 26: *Some Antineoplastic and Immunosuppressive Agents*, Lyon.

[3] International Agency for Research on Cancer (1981) Ibid, 27: *Some Aromatic Amines, Anthraquinones, Nitroso Compounds and Inorganic Fluorides Used in Drinking Water and Dental Preparations*, Lyon.

[4] International Agency for Research on Cancer (1982), Ibid, 28: *The Rubber Manufacturing Industry*, Lyon (in press).

Volume 28 of the *Monographs* evaluated the carcinogenic risks of occupational exposures in the rubber manufacturing industry. This is the second example in the *Monographs* series in which complex exposures to mixtures of chemicals are considered. The *Monograph* covers the tyre manufacturing and repair sector, the cable-making sector and the manufacture of other rubber products (e.g., hoses, belting, rubberized fabrics and latex products). Only those exposures subsequent to the mixing of elastomers with chemicals and their subsequent conversion into finished products were considered. The manufacture of monomers and synthetic elastomers was not considered, although exposures to low levels of monomers such as acrylonitrile, chloroprene and styrene may however occur in the rubber industry. Many of the monomers used have already been evaluated[5].

An appendix of chemicals used or produced as by-products in the rubber industry was included. For the chemicals used, data on synonyms and trade names, production volumes and recommended standards were given. Similar data (where available) were given for the by-products formed.

To evaluate the carcinogenic risks within the rubber industry, the Working Group examined both the evidence from epidemiological data relating to the extent and distribution of cancer within the rubber industry, and that from relevant industrial hygiene and toxicological information. The evaluation was made in terms of the three degrees of evidence prescribed for this *Monograph* series—sufficient, limited, inadequate.

Primary consideration was given to the quality of the epidemiological research, and to the strength and consistency of the reported cancer associations within the industry. In further evaluating the likelihood of an occupational causation for any observed excess incidence of cancer, judgements were made about the types of exposures experienced by groups of workers, and the evidence that such exposures have carcinogenic effects.

The assessments are given in Table 1.

In the first 28 volumes of the *Monographs* evaluations or re-evaluations were made for a total of 572 chemicals, groups of chemicals, industrial processes or occupational exposures. For 43 of these a positive association or a strong suspicion of an association with human cancer was found (Table 2). The list reflects the conclusions of an *ad hoc* Working Group that met in Lyon in January 1979 to consider chemicals evaluated in Volumes 1–20 of the *Monographs* for which some data on carcinogenicity in humans were available[6], together with evaluations given in Volumes 21-28 of the *Monographs*.

For the remaining 529 chemicals, industrial processes or occupational exposures, epidemiological data were either inadequate or unavailable to evaluate the carcinogenicity to humans, except for fluorides used in drinking water and dental preparations where no evidence of a carcinogenic effect was found. However, 523 chemicals or groups of chemicals have been tested in experimental animals and there is *sufficient evidence* that 141 of these are carcinogenic in animals. There is *limited evidence* of carcinogenicity in experimental animals for a further 153 of these chemicals. The data were inadequate to evaluate the presence or absence of a carcinogenic effect for the remaining 229 chemicals.

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[5] International Agency for Research on Cancer (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, 19: *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon.

[6] International Agency for Research on Cancer (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement No. 1, *Chemicals and Industrial Processes Associated with Cancer in Humans*, Lyon.

Table 1. Strength of Past and Currently Available Evidence for any Observed Excess Incidence of Cancer in the Rubber Industry[1]

Strength of evidence	Type of cancer	Presumed agent or job category
Sufficient for excess occurence in rubber workers and for causal association with occupational exposures	Bladder	Aromatic amines
	Leukaemia	Solvents
Sufficient for excess occurrence in rubber workers; and *limited* for causal association with occupational exposures	Stomach	Compounding, mixing and and milling
	Lung	Various
Limited for excess occurrence in rubber workers and for causal association with occupational exposures	Skin	Tyre building
Limited for excess occurrence in rubber workers; and *inadequate* for causal association with occupational exposures	Colon	
	Prostate	
	Lymphoma	
Inadequate for excess occurrence in rubber workers and for causal association with occupational exposures	Brain	
	Thyroid	
	Pancreas	
	Oesophagus	

[1] Listing does not imply that the cancer hazard is universal in all rubber factories in all countries, nor that the degree of evidence applies to all situations.

2.2 *Survey of Chemicals Being Tested for Carcinogenicity* (Mrs M.-J. Ghess, Dr H. Bartsch, Mr J. Wilbourn and Dr L. Tomatis)

Due to the long duration and high costs of carcinogenicity testing, the IARC, together with the US National Cancer Institute, initiated in 1973 an international survey of institutes involved in long-term testing of chemicals for carcinogenicity. Nine *Information Bulletins* have been published to date, in which survey results are arranged alphabetically by country, and within each country by city, and within each city by institute. For each institute, the chemicals being tested are listed in alphabetical order.

(*a*) *Information Bulletin* No. 9

In July 1980 questionnaires were sent to participating laboratories and newly identified investigators/institutes. The information received was compiled into *Information Bulletin* No. 9[7], and includes data from 99 institutes in 18 countries on a total of 970 chemicals. Data that appeared in *Information Bulletin* No. 8[8] were updated, adding a use category section. Special attention was

[7] Ghess, M.-J., Wilbourn, J., Bartsch, H. & Tomatis, L., eds (1981) Information Bulletin on the *Survey of Chemicals Being Tested for Carcinogenicity*, No. 9, Lyon.

[8] Ghess, M.-J., Bartsch, M. & Tomatis, L., eds (1979) *Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity*, No. 8, Lyon.

paid to studies that have been completed, to publication of results and to verifying that studies mentioned previously had not been discontinued.

Of the 1261 projects from 69 countries listed in the *IARC Directory of On-going Research in Cancer Epidemiology* 1980[9], 285 are wholly or partly concerned with 62 chemicals or chemical substances listed in *Information Bulletin* No. 9, which has been fully cross-indexed.

Table 2. Chemicals, groups of chemicals, industrial processes and occupational exposures associated with (or strongly suspected to be associated with) the induction of cancer in humans (compiled from Volumes 1-28 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*)[a]

I. Chemicals, groups of chemicals, industrial processes and occupational exposures that are carcinogenic for humans

1. 4-Aminobiphenyl
2. Arsenic and arsenic compounds
3. Asbestos
4. Auramine (manufacture of)
5. Benzene
6. Benzidine
7. *N, N*-Bis (2-chloroethyl)-2-naphthylamine
8. Bis (chloromethyl) ether and technical grade chloromethyl methyl ether
9. Boot and shoe manufacture and repair (certain occupations)[b]
10. Chromium and certain chromium compounds
11. Conjugated oestrogens[b]
12. Cyclophosphamide[b]
13. Diethylstilboestrol
14. The furniture and cabinet-making industry (certain occupations)[b]
15. Haematite mining (radon ?)
16. Isopropyl alcohol (manufacture of, using the strong acid process)
17. Melphalan
18. MOPP[bc]
19. Mustard gas
20. 2-Naphthylamine
21. Nickel refining
22. Rubber manufacturing industry (certain occupations)[b]
23. Soots, tars and oils[d]
24. Vinyl chloride

II. Chemicals or groups of chemicals that are probably carcinogenic for humans

SUBGROUP A – HIGHER DEGREE OF HUMAN EVIDENCE

1. Aflatoxins
2. Azathioprine[b]
3. Cadmium and certain cadmium compounds
4. Chlorambucil
5. Nickel and certain nickel compounds
6. Tris (1-aziridinyl) phosphine sulphide (thiotepa)
7. Treosulphan[b]

SUBGROUP B – LOWER DEGREE OF HUMAN EVIDENCE

1. Acrylonitrile
2. Amitrole
3. Auramine
4. Beryllium and certain beryllium compounds
5. Carbon tetrachloride
6. Dimethyl carbamoyl chloride
7. Dimethyl sulphate
8. Ethylene oxide
9. Iron dextran complex
10. Oxymetholone
11. Phenacetin
12. Polychlorinated biphenyls

[a] This table does not include known human carcinogens such as tobacco smoke, betel quid and alcoholic beverages since they have not yet been included within the *Monographs* programme.

[b] Added by the secretariat subsequent to the *ad hoc* IARC Working Group held in January 1979.

[c] Nitrogen mustard, vincristine, prednisone and procarbazine.

[d] Mineral oils may differ in their composition particularly in relation to the content of carcinogenic polycyclic aromatic hydrocarbons.

[9] Muir, C. S. & Wagner, G., eds (1980) *Directory of On-going Research in Cancer Epidemiology* 1980 *(IARC Scientific Publications No. 35)*, Lyon, International Agency for Research on Cancer.

(*b*) *Future plans*

The survey questionnaire for *Information Bulletin* No. 10 will be distributed in January 1982 to all previous participants, and to newly identified investigators/institutes undertaking long-term chemical carcinogenicity testing. The data will be compiled into *Information Bulletin* No. 10, which will be published in 1982.

3. PROGRAMME OF MECHANISMS OF CARCINOGENESIS (Dr R. Montesano)

3.1 *Introduction*

The process of carcinogenesis is multifactorial in its etiology and multistep in its development, and thus diversified approaches are necessarily required for the elucidation of the mechanisms of carcinogenesis. An attempt has been made to contribute to the understanding of the main steps of carcinogenesis, namely initiation, promotion and progression, and to the development of methods of testing, which could identify chemicals with carcinogenic activity.

A network of national laboratories that collaborate in the carcinogenicity testing of environmental chemicals has continued its activity, testing chemicals that had been selected, taking into account the outcome of the IARC *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* and the various national programmes of toxicology testing. There is a limited testing facility in the Agency, the bulk of the carcinogenicity testing and test development being performed in 12 laboratories in 9 countries; the Agency's role is one of coordination. Thirteen compounds or combinations have been under test during the year, in experimental animals. A limited project on testing of chemicals for mutagenicity in mammalian cells is also underway. Recently, attempts have been made to develop an *in vitro* screening assay to detect chemicals with tumour promoting activity, based on the capacity of some promoting agents to cause suspended cells in culture to adhere to the glass walls of the culture vessel. At least within the group of plant diterpenes, there was a good correlation between the *in vivo* tumour promoting activity of a compound and its ability to cause adhesion of cells in culture. When the test was applied to tumour promoters and co-carcinogens that were not in the group of diterpenes, no correlation was observed.

A major problem that still remains is the extrapolation to human beings of the data obtained both in long-term carcinogenicity tests and in the various, more rapid screening tests. The studies on the mechanisms of carcinogenesis that have been carried out, aim to provide scientific data as a basis for such an extrapolation. Particular model compounds and experimental systems have been selected for study of the process of initiation and promotion.

Metabolism of carcinogens, and DNA damage and repair processes have been shown to be critical determinants in the initiation of the carcinogenic process by chemical carcinogens. The nitrosamines are a group of environmental carcinogens with high degree of organ and species specificity in their carcinogenic effect, and studies were aimed at determining the biological relevance of the variety of DNA damage produced by them, and at assessing how the efficiency of

repair of the DNA lesions they produce are related to the probability that nitrosamine-treated tissue and/or cells might develop into a tumour. Comparative *in vitro* studies on the capacity of human and rodent tissue extracts to recover from DNA miscoding lesions, like O^6-alkylguanine, could contribute to the development of better criteria on which to base an extrapolation of experimental animal data to human beings. Dose-response in carcinogenesis and mutagenesis could also be better understood by examining at cellular and molecular levels, the modulation of DNA repair processes during continuous exposure to carcinogens.

Since the majority of human cancers are of epithelial origin, considerable efforts have been devoted to examining whether the process of neoplastic transformation of epithelial cells *in vitro* shows any similarity to that observed in mesenchymal cells. Morphological changes and alterations in the cytoskeletal structure, which are related to the ability of the cells to spread on a substratum and form cell-cell contacts, were examined in a series of tumorigenic and non-tumorigenic rat liver epithelial cells. In other studies, the comparative metabolism of benzo(*a*)pyrene was studied in epidermal keratinocytes and dermal fibroblasts derived from humans and from mice. Striking differrences were observed between the behaviour of the cells of human origin, and of those from rodents.

Studies on the mechanisms of tumour promotion have continued with emphasis being placed on the effects of tumour promoters in the modulation of cell differentiation and gene expression.

In the past, extensive studies have been carried out by the Agency on the etiopathogenesis of Burkitt's lymphoma (BL). More recently, these studies have concentrated mainly on the characterization of the lymphoma that occurs in Europe (an area non-endemic for BL), with histopathological features similar to those reported for BL. Preliminary results, based on a study of these Burkitt-type lymphomas collected in the Lyon area (France) indicated that they represented 30–50% of the cases of childhood non-Hodgkin's lymphomas. However, only 10–20% of the cases were associated with the presence of the Epstein-Barr virus (EBV) compared with African BL, where 95% of the cases are EBV-associated.

Cytogenetic studies have also been conducted on various lymphomatous cell lines derived from both BL and Burkitt-type lymphomas collected in the framework of these investigations. It appears that Burkitt's lymphoma, independent of its geographic origin or EBV-association, is characterised by a non-random cytogenetic change involving the long arm of chromosome 8. With the availability of these cell lines and their variants, it may be possible to study the role of chromosomal stability, and the interaction between viral and cellular genome, in the process of neoplastic transformation.

Recently, studies have been initiated in the preparation and characterization of specific antibodies against carcinogenic compounds and cellular macromolecular adducts. One of the possible practical applications of such antibodies would be the detection in human body fluids and/or human tissues, of antigens related to carcinogen exposure. A meeting will be held towards the end of the year at which epidemiologists and experimentalists will discuss the applicability of such immunological assays to the identification of specific risk factors.

In summary, the programme of mechanisms of carcinogenesis is aimed at identifying potential human carcinogens by means of experimental studies; increasing the feasibility of extrapolating from animal data to humans; studying the role of tumour promoters, compared with tumour initiators; developing techniques for the identification of point exposures of carcinogens; and at clarifying the possible role of the interaction between viral and cellular genomes in the origin of Burkitt's and Burkitt-type lymphomas.

3.2 *International network of carcinogenicity testing*

This project is based, to a limited extent, on intramural activities carried out in the Agency laboratories and to a much larger extent on extramural activities. The latter comprise mainly the coordinated carcinogenicity tests carried out in a number of collaborating national laboratories, involving long- and short-term testing of chemicals for their possible carcinogenicity and/or mutagenicity.

The carcinogenicity tests in experimental animals are carried out following the guidelines described in an IARC publication[10] in an effort to improve and standardize testing procedures. The national laboratories involved and the various tests carried out within the international network of carcinogenicity testing are given below; in addition, the carcinogenicity tests carried out in the Agency laboratories also are listed.

A working group was convened in December 1980 to suggest priority lists of chemicals and/or complex mixtures to be submitted for carcinogenicity tests[11]. The selection was made taking into account the degree of evidence of carcinogenicity (see section 2.1) and national programmes of toxicology testing.

(*a*) *Carcinogenicity studies*[a]

(i) *Maleic hydrazide* (Dr R. Cabral, in collaboration with Dr G. J. van Esch, National Institute of Public Health, Bilthoven, The Netherlands)

Maleic hydrazide (99% pure) containing 0.6 mg/kg of hydrazine impurity was given to groups of C57 BL mice either subcutaneously on days 1, 7, 14 and 21 after birth at a total dose of 55 mg, or orally at a weekly body weight dose of 510 mg/kg for life to adult mice. The incidence in treated groups was not significantly increased when compared with the respective solvent controls[12].

A study on Wistar rats was conducted using the same sample of maleic hydrazide. The animals were fed for their life-span on diets containing 1% and 2% maleic hydrazide. There was no indication of a carcinogenic effect in this study[13].

(ii) *Styrene oxide* (Dr R. Cabral)

Female BDIV rats were treated orally with a single dose of 200 mg/kg body weight of styrene oxide on the 17th day of gestation. Starting from weaning, the resulting offspring were given oral doses of 100 mg/kg body weight styrene oxide, weekly for 100 weeks. All survivors were killed at 120 weeks. In the progeny of the styrene oxide-treated group an increased incidence of preneoplastic lesions of the forestomach was noted in both sexes[14].

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[a] All the histology preparations of the carcinogenicity studies carried out at the IARC were done by Miss M. Laval and Mrs L. Lyandrat, and the technical assistance was provided by Mrs D. Galendo.

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[10] International Agency for Research on Cancer (1980) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement No. 2, *Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal*, Lyon.

[11] *IARC Internal Technical Report, No. 81/001* (1981): *Selection of Chemicals and Complex Mixtures for Carcinogenicity Testing*, Lyon, International Agency for Research on Cancer.

[12] Cabral, J. R. P., Ponomarkov, V. & Tomatis, L. (1982) Society of Toxicology, 21st Annual Meeting, Boston, MA, USA.

[13] Van der Heijden, C. A., Den Tonkelaar, E. M., Garbis-Berkvens, J. M. & van Esch, G. J. (1981) *Toxicology*, **19**, 139–150.

[14] Ponomarkov, V., Cabral, J. P. R. & Tomatis, L. (1981) (submitted for publication).

(iii)

5-Bromodeoxyuridine (BUdR) (Dr R. Cabral, Dr A. Likhatchev)

BUdR was given intraperitoneally to female BDVI rats on the 21st day of gestation at a single dose of 10 mg per animal. BUdR was also administered intraperitoneally to 50 female BDVI rats on the 21st day of gestation at a dose level of 20 mg per animal, and, starting from birth (days 1, 3, 5 and 7), the offspring of the treated mothers received a dose of 0.01 mg/g body weight. Since previous experiments had shown that BUdR induced kidney lesions, and ethyl methanesulphonate (EMS) produced kidney tumours, the continued and combined administration of BUdR with EMS was tested. Groups of newborn BDVI rats were given subcutaneously BUdR 0.1-0.3 mg/g body weight on days 1, 3 and 5 after birth. Other groups of newborn BDVI rats received subcutaneously BUdR 0.3 mg/g body weight on day 1 after birth followed by administration of EMS 50 mg/kg body weight on day 10. Groups of newborn rats were also treated with EMS alone, with solvent alone and untreated controls were also kept. All these experiments are scheduled to be terminated in October 1981.

(iv) *Deltamethrin* (Dr R. Cabral, in collaboration with Dr H. Hollinger and Ms. M. Sonnier, INSERM, Experimental Toxicology Unit 26, Paris)

Groups of C57 BL mice received daily for life, orally in arachis oil 0-8 mg/kg body weight of the pesticide, deltamethrin. The experiments are in progress.

Studies are also underway to estimate the amount of deltamethrin or its metabolites in different tissues of mice and rats following acute and subacute oral administration. The potential mutagenicity of deltamethrin and related compounds is being tested (see p. 98).

(v) *Shale oil fly ash*
Institute of Experimental and Clinical Medicine, Tallinn, Estonian SSR (RA 81/008)
Principal investigator: Dr A. Kung-Vösamäe

Samples of fly ash generated during combustion of shale oil have been chemically analysed and the mutagenic and carcinogenic activities determined. The carcinogenicity of shale oil fly ash was studied by intratracheal administration to rats and mice.

(vi) *Chloramphenicol and Diazepam*
Scientific Institute for the Study and Treatment of Tumours, Genoa, Italy (RA/80/013)
Principal investigator: Dr L. Rossi

Groups of 50 male and 50 female C57 BL/6N and BALB/C mice, 5 weeks old, received chloramphenicol in drinking water at the concentrations of 0.05% and 0.2% daily for life. These experiments are in progress.

Preliminary dose range-finding studies with diazepam are in progress.

(vii) *Spironolactone*
Institute of Oncology, Medical Academy, Sofia (RA/80/012)
Principal investigator: Dr I. Chernozemsky

Spironolactone is under test in mice and rats.

(viii) *Studies on the co-carcinogenic action of oil shale phenols on the lung carcinogenicity of asbestos dust*

Laboratory of Morphology, Institute of Experimental and Clinical Medicine, Tallinn, Estonian SSR (RA/79/004)

Principal investigator: Dr A. Kung-Vösamäe

The studies undertaken to determine the possible co-carcinogenic action of phenol extracted from Estonian oil shale generator tar on the carcinogenicity of asbestos and benzo(*a*)pyrene (B[*a*]P) in rat lung have been terminated, and although the phenols potentiated the action of intratracheally-instilled B[a]P, they did not exert any substantial modifying action on asbestos-induced lung carcinogenesis. When B[*a*]P, and chrysotile asbestos dust were administered intratracheally, similar results were obtained, but with fewer lung tumours. The incidence of lung tumours was highest in rats exposed to a combination of all three test substances; lung tumours developed in 56 rats out of 71 effective animals (78.9%) and in most cases (57.7%) they were epidermoid carcinomas.

(ix) *Investigation on the combined action of several chemical carcinogens* (in collaboration with Dr L. Griciute, Institute of Epidemiology, Microbiology and Hygiene, Vilnius, Lithuanian SSR; Dr V. Turusov, Oncological Research Centre, Moscow; Dr B. Teichmann, Central Institute for Cancer Research, Berlin-Buch; Dr I. Chernozemsky, Institute of Oncology, Sofia, and Dr A. Telycenas, Oncological Institute of Lithuanian SSR, Vilnius) (RA/77/024)

A collaborative study in five laboratories on the combined action of several carcinogens has been continued. Mice of different strains and hamsters are treated with three environmental carcinogens: benzo(*a*) pyrene (B[*a*]P), aflatoxin B_1 (AFB_1) and *N*-nitrosodiethylamine (NDEA). The part of the study carried out at the Agency has been completed and showed that the combined administration of the three carcinogens shortened the life span of the mice and increased the incidence of lymphomas when compared with groups treated with the single compounds and untreated controls.

In the other experiments carried out in mice (Dr Turusov and Dr Teichman) and in hamsters (Dr Chernozemsky) an overall increased tumour incidence was noted in the groups treated with the combination of the 3 carcinogens. The experiments in DBA mice carried out by Dr Telycenas are still in progress.

(x) N-*Nitrosonornicotine and alcohol* (Dr L. Griciute, Dr R. Cabral and Mr C. Béréziat)

Groups of young BDVI rats received intragastric instillations of *N*-nitrosonornicotine in a 40% alcoholic solution twice a week for 78 weeks. Adequate control groups were also available. After 78 weeks, a marked increase in the mortality rate was noted in the groups treated with a high dose of *N*-nitrosonornicotine (3 mg/rat) in ethanol or water vehicles.

(xi) *Study on the effects of combined exposure to radiation and to chemical carcinogens*

German Cancer Research Centre, Institute for Toxicology and Chemotherapy, Heidelberg, Federal Republic of Germany

Principal investigator: Professor D. Schmähl

Groups of 20-30 C57BL mice of both sexes were irradiated once with fast neutrons (165-305 rad) and treated thereafter with carbon tetrachloride or chloroform. These experiments are due to be terminated in December 1981.

(xii) *Pesticides and drugs*

National Institute of Public Health, Budapest (RA/75/014)

Principal investigator: Dr M. Börzsönyi

In vitro studies have shown that the pesticide Tribunil and the drug Cimetidine can be nitrosated and the derivatives are mutagenic for *Salmonella typhimurium.*

Studies on the transplacental carcinogenic effect of the pesticides Trimorphamide and Tribunil administered to mice with or without sodium nitrite are continuing. Preliminary results indicate that the combined administration of Trimorphamide and sodium nitrite resulted in an increase of lung adenomas in the offspring. Other studies show that the antioxidant, bis-2,2-dimethyl-4-methanesulfonic acid sodium salt-1,2-dihydroquinoline-6-6 methane (MTDQ-DA) inhibits the nitrosation and the induction of lung adenomas in mice treated with morpholine and sodium nitrite.

(xiii) *Drug and food samples*

The Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan (RA/80/001)

Principal investigator: Dr S. Riazuddin

"Naswar" is a local product obtained by mixing leaves of various plants and available in various types of blends, which are used as a narcotic or as a medicine. Extracts from four blends of green, grey and red "Naswar" were tested for mutagenicity in various strains of *S. typhimurium;* the results indicated a slight mutagenic activity with green "Naswar" from Peshawar. Studies on the identification of the active mutagenic agent(s) present in this sample are under way.

(b) *Prenatal carcinogenesis*

(i) (Dr R. Cabral, Dr A. Likhachev and Dr L. Tomatis)

Experiments designed to study the possibility that exposure of female BDVI rats to *N*-nitroso-*N*-ethylurea (ENU) during pregnancy results in an increased cancer risk for successive generations (up to 4) have now been completed[15].

A preliminary study designed to investigate the effects on the progeny of male BDVI rats treated with ENU before mating is now completed[16]. An expanded study has been started, in which BDVI male rats were given a single dose of 80 mg/kg body weight of ENU and mated 1, 2, 3 and 4 weeks later with groups of virgin, untreated females.

(ii) *N. N. Petrov Research Institute of Oncology, Leningrad, USSR* (RA/77/022)

Principal investigator: Professor N. P. Napalkov

Investigations are being carried out to study the effect of oestrous function shifts, inhibition or stimulation of thyroid function, and application of tumour promoters on carcinogenesis in rats and mice of two successive generations, by transplacental administration of methyl- and ethylnitrosourea (MNU and ENU), dimethylbenzanthracene (DMBA) and benzo(*a*)pyrene (B[*a*]P).

In the first series of experiments, mice, transplacentally-treated with ENU and DMBA, are under observation.

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[15] Tomatis, L., Cabral, J. R. P., Likhachev, A. J., Ponomarkov, V., Euzeby, B. (1981) (submitted for publication).

[16] Tomatis, L., Cabral, J. R. P., Likhachev, A. J., Ponomarkov, V. (1981) Int. J. Cancer, **28**, 475–478.

In the second series, where the effect of prenatal administration of MNU and subsequent thyroidectomy or methylthiouracil treatment in rats was studied, tumours had developed in 88 out of 159 autopsied animals of the first generation and 15 out of 60 animals of the second generation.

In the third series, where the effect on tumour incidence of prenatal administration of DMBA or MNU and postnatally-induced persistent oestrous in rats was studied, 35 out of 90 autopsied animals of both generations had developed different tumours.

(*c*) *Relationship between karyotypic pattern of cancer cells and etiological factors* (Department of Clinical Genetics, University Hospital of Lund, Sweden) (RA/78/013)
Principal investigator: Dr F. Mitelman

Results from experimental cytogenetic studies indicate a relationship between the etiologic factor(s) and the karyotypic pattern of tumour cells. Unfortunately, it is at present almost impossible to test directly in humans whether specific chromosome aberrations may be caused by specific inducing agents. Human tumours associated with known environmental carcinogens are uncommon, and so far none has been subjected to chromosome analysis. However, detailed analysis of the karyotipic pattern of malignant cells in patients occupationally exposed to potentially mutagenic/carcinogenic agents may offer an opportunity to test this relationship in man.

In a collaborative study comprising 162 patients with acute nonlymphocytic leukemia (ANLL) treated at Lund (Sweden), and Rome, the chromosome banding pattern of bone marrow cells, cell morphology, and clinical findings were compared in two groups of adult patients: 52 patients occupationally exposed to chemical solvents, insecticides, or petrol products, and 110 patients with no history of occupational exposure to potential mutagenic/carcinogenic agents. Striking differences were found between the two groups: 1) clonal chromosomal aberrations were present in 75% of exposed patients compared with only 32% in the non-exposed group. 2) 92% of patients exposed to solvents and insecticides had abnormal chromosomes, whereas only 29% of patients exposed to petrol products showed abnormalities. 3) The relationship between chromosomal abnormality and exposure was evident in both females and males. However, only 29% of women with an abnormal karyotype were exposed, whereas 70% of males with an abnormal karyotype were exposed. 4) The incidence of certain characteristic karyotypic abnormalities, i.e.–5/5 q, –7/7 q, + 8, + 21, t(8;21) and t(9;22), were decidedly more common in exposed than in non-exposed patients. At least one of these changes was present in 92% of exposed patients with aberrations.

The present data on exposure to chemical solvents, insecticides and petrol products are no doubt incomplete as regards environmental hazards. However, the relationship between chromosomal deviations to such exposure, although only indirect evidence, suggest that such correlations may exist. Work is continued to elucidate further the interaction between exposure to potentially mutagenic/carcinogenic agents and various characteristics of the leukaemic cells.

(*d*) *Sister chromatid exchange* (First Institute of Pathology, Medical University, Budapest) (RA/80/007)
Principal investigator: Professor K. Lapis

Human embryo fibroblast cells in culture and treated with mytomycin C and methylcholanthrene show an increased frequency of sister chromatid exchange (SCE). Studies are in progress to test the differential sensitivity of fibroblasts from normal individuals or from *xeroderma pigmentosum* patients to the induction of SCE by various agents.

(*e*) In vivo *two-stage carcinogenesis* (Dr H. Yamasaki, Dr R. Cabral, Dr L. Tomatis)

A standard, classical two-stage skin carcinogenesis study and a modified two-stage internal organ carcinogenesis study have been set up, using C57BL mice. Preliminary results show that C57BL mouse skin is susceptible to a standard protocol of "initiation" (benzo(*a*)pyrene) and "promotion" (TPA).

Experiments with transplacental initiation (B[*a*]P) and 200 weeks of promotion (TPA) of internal organs are planned to be terminated at the end of 1981.

3.3 *Studies on DNA repair and metabolism of carcinogens*

Metabolism of carcinogens, DNA damage and subsequent DNA repair processes have been shown to be critical determinants in the initiation of the carcinogenic process of various chemical carcinogens. In this project the biological relevance of specific DNA damage and repair processes have been investigated in particular with *N*-nitroso compounds[17]. This group of chemical carcinogens induces various DNA modifications and the studies so far carried out in collaboration with various national laboratories have been centred on the role of DNA repair processes in organ-specific carcinogenic effects and in the carcinogenic dose response induced by these carcinogens. Studies have been also carried out to examine the capacity of liver extract from various rodents as well as from human beings to repair specific DNA adducts like O^6-alkylguanine, which appear biologically more critical than other adducts in the carcinogenicity of *N*-nitroso compounds. The possible difference in DNA alkylation and repair has been examined in rats of different ages treated with a methylating agent.

(*a*) *Modulation of repair of alkylated DNA in liver of rats treated chronically with* N-*nitrosodimethylamine (NDMA)* (Dr R. Montesano, Miss H. Brésil, Mrs G. Planche-Martel, in collaboration with Dr G. P. Margison, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK; Dr A. E. Pegg, The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA, USA)

Repeated administration to rats of low doses of NDMA results in a greater removal of O^6-methylguanine from liver DNA than in rats treated with a single dose[18]. This effect appears to be specific for O^6-methylguanine, since it was not observed for other DNA adducts, such as 7-methylguanine or 3-methyladenine. The effect is mediated by an induced enzymic process, since liver extracts from prepared rats specifically remove O^6-methylguanine from DNA alkylated *in vitro*, faster than do liver extracts from control rats[19]. This increased removal of O^6-methylguanine was dependent on the dose with which the animals were pretreated; the effect occurred within 2-3 weeks of daily pretreatment with 2 mg/kg body weight of NDMA.

Under these experimental conditions it was also found[20, 21] that the increased removal could be detected 10 min after administration of the challenging dose (2 mg/kg body weight) of

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[17] Montesano, R. In: Cerutti, P. & Harris, C., eds, *Mechanisms in Chemical Carcinogenesis*, New York, Alan R. Liss Publ. (in press).

[18] Montesano, R., Brésil, H. & Margison, G. P. (1979) *Cancer Res.*, **39**, 1798–1802.

[19] Montesano, R., Brésil, H., Planche-Martel, G., Margison, G. P. & Pegg, A. E. (1980) *Cancer Res.*, **40**, 452–458.

[20] Montesano, R., Brésil, H., Planche-Martel, G. & Margison, G. P. (1980) *Proc. Am. Assoc. Cancer Res./Am. Soc. Clin. Oncol.*, **21**, 2.

[21] Montesano, R. & Margison, G. P. (1980) In: Pullman, B., Ts'o, P.O.P. & Gelboin, H., eds, *Carcinogenesis: Fundamental Mechanisms and Environmental Effects*, Dordrecht, Reidel, pp. 441–451.

^{14}C-NDMA, after which the liver again has a limited capacity to remove O^6-methylguanine. Following the rapid removal, the rate of loss of this DNA adduct did not appear to be significantly different in pretreated and control rats and may indicate the presence of two processes for the removal of this DNA adduct.

These results are in marked contrast to the finding that inhibition of O^6-methylguanine removal is produced by large single doses of alkylating agents[22].

Long-term carcinogenicity studies (R. Peto, personal communication) with a wide range of doses of NDMA indicate that, with doses of NDMA above a certain level, the risk for liver cancer in rats increases rapidly, resulting in a more than 1000-fold increase in tumour incidence with a 10-fold increase in daily dose rate. This type of response is consistent with the kinetics of repair of O^6-methylguanine in liver DNA during continuous treatment with various doses of NDMA. The repair process(es) may thus be activated by exposure to low levels of alkylating agents, but high doses of such agents may overtax the capacity of the constitutive and even of the induced DNA repair process(es), thus substantially increasing the risk of cancer in animals that receive large doses.

As a continuation of these studies, a series of experiments were carried out to examine the persistence with time of the increased removal of O^6-methylguanine from the liver DNA of rats pretreated with 2 mg/kg during a period of three weeks. The results shown in Fig. 1 indicate that within a week from the end of the pretreatment, the capacity of the liver to remove O^6-methylguanine returned to control values.

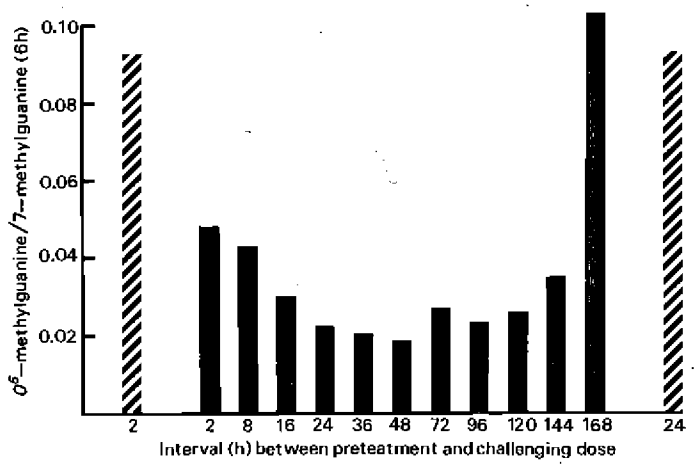

Fig. 1 O^6-methylguanine/7-methylguanine ratios in liver of BDIV rats 6 h after a dose of 2 mg/kg ^{14}C-NDMA administered at various time intervals after a pretreatment of 2 mg/kg for a period of three weeks.

control non-pretreated

pretreated rats

[22] Pegg, A. E. & Hui, G. (1978) *Biochem. J.*, **173**, 739–748.

(*b*) *Formation and loss of alkylated DNA adducts from chromatin fractions of liver of rats treated with* N-*nitrosodimethylamine (NDMA)* (Dr R. Montesano and Miss H. Brésil, in collaboration with Dr P. Cerutti, Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland)

Preliminary data are available on the formation and removal of 7-methylguanine, O^6-methylguanine and 3-methyladenine formed by NDMA in purified nucleosomal core DNA and in total nuclear DNA of liver of rats receiving a single dose or multiple doses of the nitrosamine. Results indicated that the formation of these DNA adducts was equally distributed within the chromatin fractions and no substantial differences existed in their rates of removal from the DNA.

(*c*) *Removal from DNA of* O^6-*methylguanine by human liver extracts* (Dr R. Montesano, Dr A. Likhachev, Miss H. Brésil, Miss O. Deblock, in collaboration with Dr M. Roberfroid, Unit of Biochemical Toxicology and Cancerology, University of Louvain, Belgium, and Dr O. Von Bahr, Karolinska Institute, Laboratory of Clinical Pharmacology, Hugginge, Sweden (RA/81/025) and Dr A. E. Pegg, the Milton S. Hershey Medical Center, Hershey, PA, USA)

An *in vitro* assay has been used to demonstrate that human liver extracts are able to catalyse the removal of O^6-methylguanine from DNA. The activity in the two specimens so far examined is at least 6-10 times greater than with comparable rat liver extracts (see Table 3).

Table 3. Loss of O^6-methylguanine from DNA upon incubation with human or rat liver extracts

Amount of protein added (mg)	pmol O^6-methylguanine removed from DNA in 60 min.		
	Human liver I	Human liver II	Rat liver
0.78	0.69 (57%)	0.75 (62%)	0.05
1.56	0.96 (79%)	0.99 (82%)	0.08 (7%)
3.12	1.03 (85%)	1.08 (89%)	0.24 (20%)
6.25	1.11 (92%)	1.13 (93%)	0.46 (38%)
12.50	1.15 (95%)	1.15 (95%)	0.81 (67%)
18.75	1.15 (95%)	1.15 (95%)	0.89 (74%)
25.00	1.16 (96%)	1.15 (95%)	0.95 (79%)

(*d*) *Effect of age on DNA alkylation and repair in rats* (Dr A. Likhachev, Miss O. Deblock and Dr R. Montesano, in collaboration with Dr V. Anisimov, Dr A. Ovsyannikov and Dr S. Revskoy, N.N. Petrov Research Institute of Oncology, Leningrad, USSR)

In these experiments, which were undertaken as a part of a study on the carcinogenic susceptibility of young and old rats, the effect of age of rats on the metabolism, as well as on formation and loss, of DNA methylated purines formed by *N*-nitroso acetoxymethylmethylamine (NDMA-OAC), was examined.

Decomposition of NDMA-OAC adminstered intraperitoneally was much faster in 3 month-old than in 14 month-old rats. The highest level of methylation in both younger and older rats was found in the DNA of ileum, liver, uterus, and colon. Liver of older rats had a higher capacity for

excision of O^6-methylguanine from DNA, whereas in the DNA of the ileum and colon, this DNA adduct was excised more efficiently in younger animals. Except for brain and uterus, all tissues of younger rats revealed a higher rate of DNA synthesis.

After intravenous administration of NDMA-OAC to rats, a non-uniform pattern of metabolism was observed, and DNA adducts persisted in various organs of both young and old rats.

(*e*) *Effect of intestinal chalones on methylation of DNA in rats after intraperitoneal administration of NDMA–OAC* (Dr A. Likhachev, Miss O. Deblock, in collaboration with Dr V. Okulov, Dr V. Anisimov and Dr A. Ovsyannikov, N. N. Petrov Research Institute of Oncology, Leningrad, USSR)

Chalones are known to act as reversible biological inhibitors of DNA synthesis, and the effect of rabbit intestinal chalones on the rate of DNA synthesis and formation of methylated purines in rats treated intraperitoneally with NDMA-OAC was studied.

G_1 and G_2 chalone-containing fractions isolated from mucous of rabbit ileum, decreased two-fold compared with the level of DNA methylation in the ileum, and increased two-fold compared to the level of DNA methylation in the colon. When the chalone-containing fraction was administered 1.5h before treatment with NDMA-OAC, no marked effect was observed on DNA methylation in either the liver or kidneys. The effect of the chalone-containing fraction was non-specific. When it was injected into rats 4.5h before they were treated with NDMA-OAC, the inhibition of DNA methylation, compared with the levels observed in rats treated with NDMA alone, was 32–34% in the ileum, colon and kidney, and 8% in the liver. O^6-Methylguanine/7-methylguanine ratio was independent, both of the tissue and treatment schedule.

(*f*) *Effect of administration of some* N-*nitroso compounds to pregnant animals on carcinogenesis, DNA methylation and repair, in fetal and maternal tissues* (Dr A. Likhachev, Miss O. Deblock and Dr H. Ohshima, in collaboration with Dr V. Alexandrov, Dr V. Anisimov, Dr A. Ovsyannikov and Dr M. Korsakov, N. N. Petrov Research Institute of Oncology, Leningrad, USSR)

Administration of NDMA-OAC to rats towards the end of pregnancy did not result in an increased tumour incidence in the descendants. Parallel studies showed that the level of DNA methylation in embryonal tissues was very low, compared with the level in the maternal tissues. The capacity of NDMA-OAC to cross the placenta, and the level of esterases in maternal and fetal tissues are being studied.

Comparative studies of DNA alkylation in fetal and maternal tissues of rats treated with *N*-nitroso-*N*-methylurea (MNU) are in progress.

(*g*) *Study of persistence of 5-bromo-2'-deoxyuridine (BUdR) in DNA of different tissues in newborn rats* (Dr A. Likhachev, Miss O. Deblock, Dr L. Tomatis, in collaboration with Dr G. P. Margison, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK)

Although BUdR is incorporated into DNA of different tissues, it shows no evidence of carcinogenicity[23].

[23] Margison, G. P., Likhachev, A. J. & Tomatis, L. (1980) *Chem. Biol. Interact.*, **30**, 297–303.

It was found that BUdR, when administered to newborn rats, was incorporated into DNA and persisted over 3 weeks. There was no evidence of any excision from DNA in all the tissues studied. In spite of this, there was no indication of an initiation of carcinogenesis.

(*h*) *Effect of ring substitution in dimethylphenyltriazenes on their metabolism and DNA methylation in rats* (Dr A. Likhachev, Miss O. Deblock, in collaboration with Dr G. Kolar, German Cancer Research Centre, Heidelberg, Federal Republic of Germany, and Dr G. P. Margison, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK)

A previous study[24] supported the hypothesis that dimethylphenyltriazene (DMPT) exerted its methylating effect by means of conversion into monomethylphenyltriazene (MMPT).

The preliminary results suggested that ring-substituted DMPT derivatives, 4-chloro-DMPT, and Cl_3-DMPT, which are relatively poor carcinogens and powerfully cytostatic, are stable in *in vivo* conditions and possess a low ability to methylate rat DNA, in comparison with DMPT and MMPT. These features of ring-substituted DMPT derivatives could indicate potential utility as anti-cancer preparations.

3.4 *Chemical carcinogenesis and mutagenesis in cultured cells*

The studies on the process of neoplastic transformation of epithelial cells *in vivo* have continued in collaboration with various laboratories.

A series of the newly developed pesticides, pyrethroids, were tested for mutagenicity in mammalian V79 cells.

Studies on the effect of multiple treatment with alkylating agents on mutation frequency are also being continued.

(*a*) *Cellular and biochemical markers of neoplastic transformation of epithelial cells in culture*
Cancer Research Centre, Academy of Medical Sciences of the USSR, Moscow (RA/79/101)
Principal investigator: Dr Y. M. Vasiliev

Morphological changes associated with neoplastic transformation of epithelial cells were studied in a series of IAR cell lines derived from rat liver. The series included three independently obtained, nontumorigenic lines and five derived tumorigenic lines, and the results of the study are being published[25].

The morphology of cell surfaces was observed by scanning electron microscopy; the distribution of actin, tubulin and fibronectin was determined by indirect immunofluorescence. Various degrees of disorganization of monolayered cell sheets were observed in tumorigenic cultures, accompanied by an altered distribution of microfilament bundles.

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[24] Margison, G. P., Likhachev, A. J. & Kolar, G. F. (1979) *Chem. Biol. Interact.*, **29**, 345–353.
[25] Bannikov, G. A., Guelstein, V. I., Montesano, R., Tint, I. S., Tomatis, L., Troyanovsky, S. M. & Vasiliev, J. M. (1981) *J. Cell Sci.*, (in press).

It was concluded that alterations in the ability to spread on the substratum and to form cell-cell contacts were common features of morphologically transformed fibroblastic and epithelial cultures. However, the actual changes in the cytoskeletal structures which accompanied these alterations were different in transformed cultures of various tissue types.

(b) *Pathology of tumours originating from IAR rat liver epithelial cells* (Dr R. Montesano, Dr L. Tomatis, in collaboration with Dr V. Turusov, Oncological Research Centre, Moscow)

Various IAR-cell lines, established in the Agency laboratory, underwent neoplastic transformation either spontaneously or after treatment with chemical carcinogens. These cell lines, once injected into syngeneic newborn rats, gave rise to tumours, many of them being well-differentiated carcinomas. Others were more anaplastic. Systemic pathological descriptions of all the tumours obtained with the various IAR cells have been undertaken to correlate them with the *in vitro* morphological and biological properties of the various cell lines.

(c) *Location of the human fibronectin gene on chromosome two*
Scientific Institute for the Study and Treatment of Tumours, Genoa, Italy (RA/80/006)
Principal investigator: Dr L. Zardi

Fibronectin, which seems to play an important role in the mechanism that anchors cells to the extra-cellular matrix, is absent or greatly reduced on the surface of malignantly-transformed cultured cells. This may be responsible for the expression of the malignant phenotype. The chromosomal localization of the gene directing the synthesis of human fibronectin has been studied by several laboratories, but with discordant results, that might result from the difficulties of producing really species-specific antibodies to use as probes for the synthesis of human fibronectin. In the present studies, somatic cell hybrids releasing monoclonal antibodies to human fibronectin that do not cross-react with calf, hamster nor mouse fibronectin, have been produced. Using these antibodies, it was found that in human-murine and human-hamster somatic cell hybrids, the production of human fibronectin is in complete concordance (34/34) with the presence of human chromosome two and with isocitrate dehydrogenase (IDH1), an enzymatic marker for human chromosome two. This suggests that the gene for human fibronectin is localized on chromosome two.

(d) *Metabolism of benzo(a)pyrene in cultured epidermal and dermal cells of humans and mice*
Institute of Medical Science, University of Tokyo, Tokyo (RA/79/006)
Principal investigator: Dr T. Kuroki

Variation in cancer induction is found between different tissues within a single individual and between different cell types within a single tissue. Such variation may exist in every phase of the chemical carcinogenic process—metabolic activation of carcinogens, binding to DNA, repair of damaged DNA and promotion of initiated cells.

Use of human materials is certainly valuable in investigating this variation, and, particularly, in providing a link between experimental studies in animal and human cancers. For this purpose,

the metabolism of benzo(*a*)pyrene (B[*a*]P) in epidermal keratinocytes and dermal fibroblasts was studied in humans and mice. Human epidermal and dermal cells were isolated from the skin of normal subjects.

In confirmation of previous studies[26, 27], metabolic activity of human epidermal cells on B[*a*]P was consistently demonstrated by cell-mediated assay, in which V79 Chinese hamster cells were plated on top of sheets of epidermal cells and treated with B[*a*]P for 48h. Mutation of the V79 cells, measured as ouabain resistance, was induced in dose-related fashion, although the extent of induced mutation varied from 5 to 22 ouabain-resistant colonies per 10^5 survivors per 10 μM B[*a*]P in cultures derived from different individuals (Fig. 2).

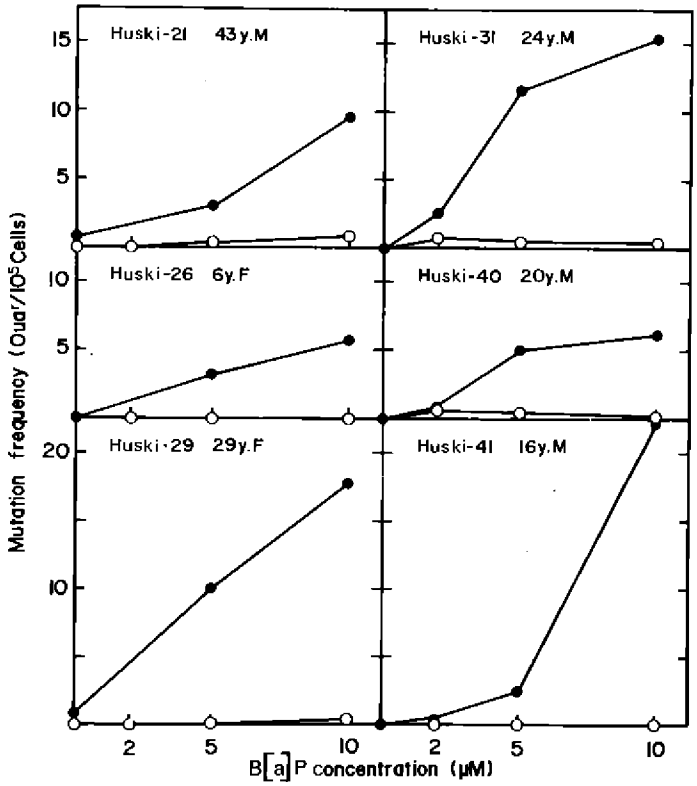

Fig. 2 Induction of mutations in co-cultured V79 cells when B[*a*]P was activated by pairs of human epidermal (●) and dermal (○) cells isolated from six individuals. Among these, only the donor of HUSKI-31 culture smoked. The V79 cells were plated on the top of confluent cultures of human epidermal or dermal cells and treated with B[*a*]P at concentrations of 2.5 and 10 μM for 48 h. The V79 cells were then cultured in fresh medium for 2-4 days for expression of the induced mutation. They were replated in medium containing 1 mM ouabain for determination of induced mutations, which were expressed as numbers of resistant colonies per 10^5 survivors, taking into account the number of cells plated and the plating efficiency.

[26] Kuroki, T., Nemoto, N. & Kitano, Y. (1980) *Carcinogenesis*, **1**, 559–565.

[27] Kuroki, T., Nemoto, N. & Kitano, Y. (1980) In: Pullman, B., Ts'o, P. O. P. & Gelboin, H. V., eds, *Carcinogenesis: Fundamental Mechanisms and Environmental Effects*, Dordrecht, Reidel, pp. 417–426.

More striking was the observation that human dermal fibroblasts did not activate B[*a*]P to a form that was mutagenic to co-cultured V79 cells. This was observed without exception in nine cultures of dermal fibroblasts and the one culture of embryo fibroblasts (IMR-90) tested (Fig. 2). Analysis by high pressure liquid chromatography indicated that human epidermal and dermal cells both metabolized B[*a*]P, producing almost the whole series of its known metabolites. The amount of 7,8-dihydrodiol B[*a*]P, a proximate metabolite, produced by human dermal cells varied from 0.2—2.7% of the total B[*a*]P added, and seemed to be enough to induce mutation. Furthermore, human dermal cells, were not able to convert 7,8-dihydrodiol B[*a*]P as such to a form, which was mutagenic to V79 cells. These observations suggest that further metabolism of 7,8-dihydrodiol B[*a*]P is partly or entirely blocked in by human fibroblasts. In contrast to human fibroblasts, mouse fibroblasts isolated from the dermis of embryos did activate B[*a*]P and induced mutation in co-cultured V79 cells to a higher extent than did mouse epidermal cells, indicating interspecies variation (Table 4).

Table 4. Interspecies variation of metabolic activation of B[*a*]P between epidermal keratinocytes and dermal and embryonal fibroblasts in cell-mediated assay

Cell type	Species	
	Rodent	Human
Epidermal keratinocytes	+[a]	+
Dermal fibroblasts	+	−
Embryonal fibroblasts	+	−

[a] (+) presence or (−) absence of induced mutation in co-cultured V79 cells with the indicated cells used as a layer for activating B[*a*]P

(*e*) *Mutagenicity testing of environmental chemicals in mammalian cells* (Miss C. Drevon, Dr R. Montesano, Miss A. M. Aguelon, Mrs C. Piccoli, Mr M. Pluijmen)

In parallel with *in vivo* experiments (see section 3.2) and mutagenicity tests on bacteria (see section 4.3), the mutagenic properties of some pyrethroid pesticides have been tested in V79 Chinese hamster cells, using 6-thioguanine resistance and ouabain resistance as genetic indicators, in the presence of freshly-isolated rat hepatocytes as the metabolic activation systems. NDMA and methylnitrosourea (MNU) were used as positive controls. Preliminary results indicate that, in the absence of hepatocytes, decamethrine, permethrine, cismethrine, resmethrine, and bioresmethrine were toxic to V79 cells in a dose-related fashion. When primary hepatocytes were included in the assay system, the cytotoxicity was no longer seen. Decamethrine and bioresmethrine were not mutagenic to V79 cells. Confirmatory studies on all these pyrethroid pesticides are under way.

(*f*) *Mutagenic activity of MNU on IAR 27 liver cells following single or multiple exposures* (Miss C. Drevon, Dr R. Montesano, Mrs C. Piccoli)

Studies[28] in *E. coli* showed that pretreatment with low doses of *N*-methyl-*N*-nitroguanine (MNNG) resulted in the development of a resistance to the mutagenic effect of MNNG. This effect has been associated with the induction of a DNA error-free repair by low dose of alkylating agents. Although *in vivo* studies in rat liver (section 3.3) showed similar phenomena, comparable experiments on mutagenicity in mammalian cells are limited. Using an IAR liver-cell line as the target for a mutagenicity assay, and 6-thioguanine resistance as the genetic marker, the mutagenic effect of a challenging dose of MNU was tested in cells previously exposed to low non-toxic, non-mutagenic doses of MNU. Preliminary results showed a 20–40% reduction in toxicity and 50%, in mutagenicity in the cells pretreated with low doses of MNU, compared with cells not receiving such pretreatment.

3.5 *An attempt to establish a short-term screening test for the detection of tumour promoters* (Dr H. Yamasaki, Miss N. Martel, in collaboration with Dr I. B. Weinstein, Columbia University, New York, USA & Dr B. L. Van Duuren, New York University, New York, USA)

Various types of mutagenicity tests are being used as screening methods for environmental chemicals that may be carcinogenic as a result of their interaction with cellular DNA. However, the carcinogenic process is multistep and is influenced by a number of agents, e.g. tumour promoters, hormonal factors, nutritional and other co-factors[29, 30]. In contrast to classical chemical carcinogens, tumour promoters do not appear to bind covalently to DNA and are not mutagenic in conventional assay systems[30]. It is imperative, therefore, to develop an *in vitro* screening assay which detects chemicals with a tumour-promoting activity.

The present study was undertaken to validate a Friend erythroleukaemia cell (FELC) system as a simple and rapid *in vitro* model system to study structure-activity relationship of certain classes of tumour promoters, and possibly as a pre-screening test for them. The assay was based on the recent finding that, whereas 12-*O*-tetradecanylphorbol-13-acetate (TPA)-sensitive clones of FELC normally grow in suspension culture, when exposed to TPA and related compounds, they rapidly adhere to the culture dish[31].

When 20 plant diterpenes were tested in this adhesion assay, and compared with their *in vivo* tumour promoting activity, there was, generally, a good correlation between these two biological activities[32]. There was an even better correlation, when the adhesion assay was compared with the inflammatory activity of these compounds on mouse ear (Fig. 3). The adhesion assay may prove to be a useful short-term screening test for a plant diterpene tumour promoter, since the assay requires only two days to test 10–20 compounds[32]. Studies on the structure-activity relationship of other plant diterpenes using this adhesion assay is being continued, in collaboration with Professor E. Hecker (Heidelberg).

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[28] Samson, L. & Cairns, J. (1977) *Nature*, **267**, 281.

[29] Slaga, T. J., Sivak, A. & Boutwell, R. K., eds, (1978) *Carcinogenesis Vol. 2. Mechanisms of Tumour Promotion and Cocarcinogenesis*, New York, Raven Press.

[30] Weinstein, I. B., Yamasaki, H., Wigler, M., Lee, L. S., Fisher, P. B., Jeffrey, A. M. & Grunberg, D. (1979) In: Griffin, A. C. & Shaw, C. R., eds, *Carcinogens: identification and mechanisms of action*, New York, Raven Press, pp. 399–418.

[31] Yamasaki, H., Weinstein, I. B., Fibach, E., Rifkind, R. A. & Marks, P. A. (1979) *Cancer Res.*, **39**, 1989–1994.

[32] Yamasaki, H., Weinstein, I. B. & Van Duuren, B. L. (1981) *Carcinogenesis*, **2**, 537–543.

It should be stressed, however, that other chemical classes of known tumour promoters and co-carcinogens did not induce adhesion of FELC (Table 5). This may reflect the fact that the tumour-promoting activity of these compounds is less than one-thousandth of that of the plant diterpenes, or that their mechanism of action is different from plant diterpenes, or it may be due to tissue specificity. Many of these compounds also failed to induce plasminogen activator in chick embryo fibroblasts, to inhibit FELC differentiation, or to affect EGF-receptor binding of HeLa cells. Thus, it appears that the FELC-adhesion screening method is valid only for the detection of plant diterpene and related tumour promoters[33].

Table 5. Failure of certain non-diterpene tumour promoters and cocarcinogens to induce FELC adhesion [32]

Compouds	ME^{50} for FELC adhesion (mg/ml)	Tumour-promoting activity [33]	Cocarcinogenic activity [33]
Iodoacetate	> 1	+	
Anthralin	> 0.1	+	+
Limonene	> 1	+	−
Tween 60	> 0.3	+	
Undecane	> 1		+
Catechol	> 1	−	+
Pyrogallol	> 1	−	+
Fluoranthene	> 0.1	±	+
Oleic acid	> 10	+	−
Phenobarbital	> 1	+	−
Saccharin	> 1	+	

3.6 *Mechanism of action of tumour promoters* (Dr H. Yamasaki, Miss C. Drevon, Miss N. Martel, in collaboration with Dr W. Ostertag, Beatson Institute for Cancer Research, Glasgow, UK; Dr Y. Kanno, Dr Y. Shiba and Dr T. Enomoto, University of Hiroshima, Hiroshima, Japan; Dr R. Ouasana and Dr J. Brun, University of Lyon I, Lyon, France; Dr K. Owada and Dr K. Molling, Max-Planck Institute for Molecular Genetics, Berlin; Dr H. Eisen, Pasteur Institute, Paris; Dr T. Kakunaga, National Cancer Institute, Bethesda, MD, USA)

The molecular mechanism of tumour promoter-mediated inhibition of cell differentiation[34-36] has been studied using a continuous cell line of FELC in which the terminal differentiation

[33] For the definition of *tumour promoting activity* and *cocarcinogenic activity*, see Van Duuren, B. L., Witz, G. & Goldschmidt, B. M. (1978) In: Slaga, T. J., Sivak, A. & Boutwell, R. K., eds, *Carcinogenesis: Mechanism of Tumor Promotion and Cocarcinogenesis*, New York, Raven Press, pp. 491–507.

[34] Diamond, L., O'Brien, T. G. & Rovera, G. (1978) *Life Sci.*, **23**, 1979–1988.

[35] Yamasaki, H. (1980) In: Montesano, R., Tomatis, L. & Bartsch, H., eds, *Molecular and Cellular Aspects of Carcinogen Screening Tests (IARC Scientific Publications No. 27)*, Lyon, International Agency for Research on Cancer, pp. 91–111.

[36] Weinstein, I. B., Lee, L. S., Fisher, P. B., Mufson, A. & Yamasaki, H. (1979) *J. Supramol. Struct.*, **12**, 195–208.

is suppressed in the presence of a tumour promoter, TPA[37]. In these cells, there was almost no globin mRNA present, but its rapid accumulation was observed upon the release of the cells from the TPA block (with Dr W. Ostertag, Glasgow, Scotland). Other gene expressions related to erythroid differentiation, such as spectrin and IP_{25} synthesis are now being investigated in this continuous cell line, in collaboration with Dr H. Eisen (Paris)

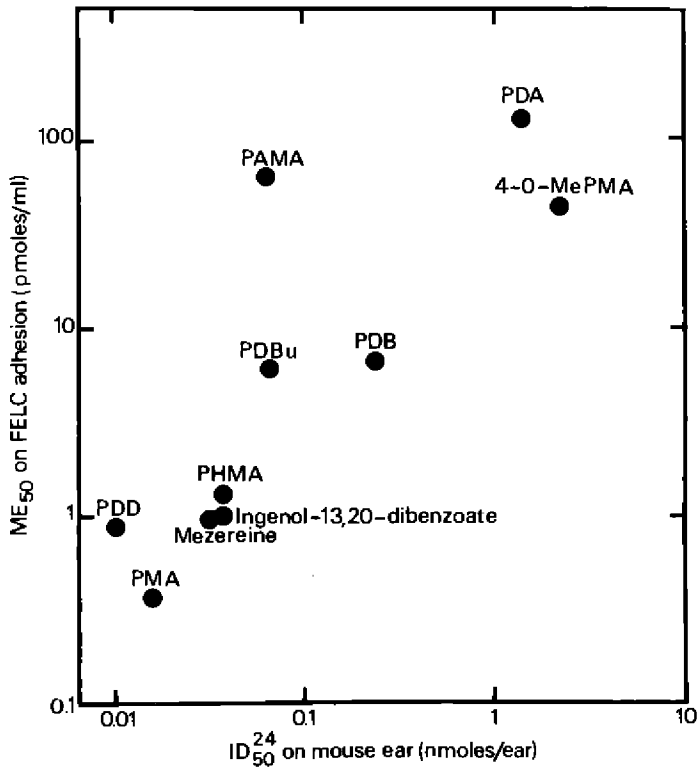

Fig. 3 Correlation of FELC-adhesion assay results with mouse ear-irritating activities of phorbol esters and related compounds.[a]

ME_{50} = concentration of compound in pmol/ml which gave 50% of maximal effect
ID_{50}^{24} = concentration of compound in nmoles which gave irritating activity in 50% of tested mouse ears
PAMA = phorbol-9-myristate-9a-acetate-3-aldehyde
PDA = phorbol-9,9a-diacetate
PDB = phorbol-9,9a-dibenzoate
PDBu = phorbol-9,9a-dibutyrate
PDD = phorbol-9,9a-didecanoate
PHMA = phorbolol-9-myristate-9a-acetate
PMA = phorbol-9-myristate-9a-acetate (also called 12-*O*-tetra-decanoylphorbol-13-acetate, TPA)
4-*O*-MePMA = 4a-*O*-methyl-phorbol-9-myristate-9a-acetate

[a] Yamasaki, H., *et al.* (1981) *Carcinogenesis*, **2**, 537–543.

[37] Yamasaki, H., Saint-Vincent, L. & Martel, N. (1980) *Cancer Res.*, **40**, 3780–3785.

Since phorbol ester tumour promoters modulate a variety of programmes of cell differentiation, in which different gene expressions are involved, it was predicted that there should be a common mechanism underlying such modulation[35]. It has long been postulated that cell-cell communication is one of the important factors which regulate cell differentiation and proliferation[38]. Earlier studies have shown that phorbol esters exert a number of effects through the perturbation of the cell surface membrane[36, 30]. Therefore, the effect of phorbol ester tumour promoters on gap-junctional cell-cell communication in culture has been examined.

In collaboration with Dr Y. Kanno's group at Hiroshima University, it has been demonstrated, by means of an electrophysiological method, that tumour-promoting phorbol esters reversibly inhibited the formation and maintenance of gap-junctional cell-cell communication of human amniotic membrane epithelial cells (FL). There was no change in membrane potential, membrane resistance, or cell growth in the presence of these tumour promoters, indicating a rather specific effect on gap-junctional cell-cell communication[39, 40]. These findings may explain partially the mechanism by which phorbol esters modulate metabolic cooperation, cell differentiation and cell proliferation.

Specific binding sites for phorbol esters have been demonstrated in a variety of cells[41, 42]. Employing the method of Blumberg[41], the presence of similar receptors in a nematode, *C. elegans,* has been demonstrated, with Dr R. Ouazana and Dr J. Brun Lyon, France), and in hydra *(hydra Japonica),* with Dr Y. Shiba (Hiroshima, Japan). Since the development of these lower animals is also inhibited by phrobol esters, these animals might be useful as models to study the mechanism of action of the tumour promoters on cell differentiation and development, and such studies are now being undertaken.

The study, at biochemical levels, of the mechanism of the modulation of ASV gene expression by tumour promoters is being continued (with Dr K. Owada and Dr K. Molling, Berlin).

In an attempt to study the mechanism of tumour promotion at cellular level, two-stage transformation of Balb 3T3 cells[43] has been initiated in collaboration with Dr T. Kakunaga Bethesda, MD, USA). The system may also provide a screening test for chemical carcinogens, tumour promoters and other modifiers.

3.7 *Specific antibodies against carcinogens and DNA adducts of carcinogens*

Progress has been made in the development and characterization of antibodies against aflatoxin B_1 and in the reliability and sensitivity of radioimmunoassay methods in the detection of DNA modifications induced by nitrosamines, compared with classical radiochemical methods.

The characterization of antibodies for monitoring individual human exposure to various carcinogenic agents is actively pursued in national laboratories, and a meeting is scheduled towards the end of the year to discuss the developments in this field.

[38] Loewenstein, W. R. (1979) *Biochem. Biophys. Acta,* **560,** 1–65.
[39] Yamasaki, H., Enomoto, T., Sasaki, Y., Shiba, Y. & Kanno, Y. (1981) *Proc. Am. Assoc. Cancer Res.,* **22,** 133.
[40] Enomoto, T., Sasaki, Y., Shiba, Y., Kanno, Y. & Yamasaki, H. (1981) *Proc. natl. Acad. Sci. USA,* **78,** 5628–5632.
[41] Driedger, P. E. & Blumberg, P. A. (1980) *Proc. natl. Acad. Sci. USA,* **77,** 567–571.
[42] Shoyab, M. & Todaro, G. J. (1980) *Nature,* **288,** 451–455.
[43] Kakunaga, T. (1973) *Int. J. Cancer,* **12,** 463–473.

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(*a*) *Characterization of antibodies against aflatoxin* B_1 (Dr P. Sizaret, Miss A. M. Aguelon)

Aflatoxin B_1 (AFB_1) has been coupled at the C^1- and C^8-positions with bovine serum albumin and corresponding antisera have been raised in rabbits by multiple injections of the immunogens. In a competitive radioimmunoassay, using ^3H-AFB_1 as a tracer, and anti-C^8-aflatoxin conjugate antiserum, 0.9 pmol of AFB_1 inhibited tracer-antibody binding by 50%. The amounts of aflatoxin G_1 (AFG_1) and sterigmatocystin required to give the same degree of inhibition were respectively about 33 and 4 000 times greater. These data are indicative of the specificity and sensitivity of the assay (Fig. 4).

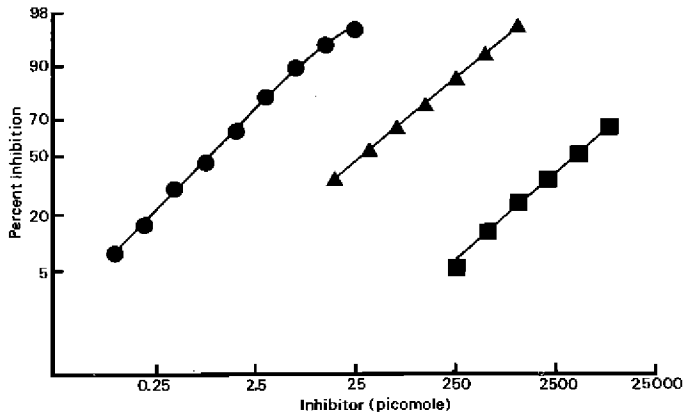

Fig. 4 Dose response curves of three mycotoxins assayed against a rabbit antiserum raised against a conjugate in which AFB_1 was coupled to bovine serum albumin through C^8-position

AFB_1 ●

AFG_1 ▲

Sterigmatocystin ■

Using this radioimmunoassay, the excretion of AFB_1 and/or its metabolites have been monitored over a period of four weeks in the urine of rats treated either with a single oral dose of 270 or 90 µg of AFB_1. Figure 5 shows that the pattern of excretion is related to the doses administered and some AFB_1 metabolites can still be detected after four weeks. Studies are in progress to increase the sensitivity of this technique of detection and to apply it to human urine samples.

In parallel with these studies, it was found[44] that the mutagenicity of AFB_1 for *S. typhimurium* could be inhibited by anti-AFB_1 antisera, which also points to the high specificity of the antibodies.

[44] Sizaret, P., Malaveille, C., Brun, G., Aguelon, A. M. & Toussaint, G. (1981) *J. oncodev. Biol. Medic.* (in press).

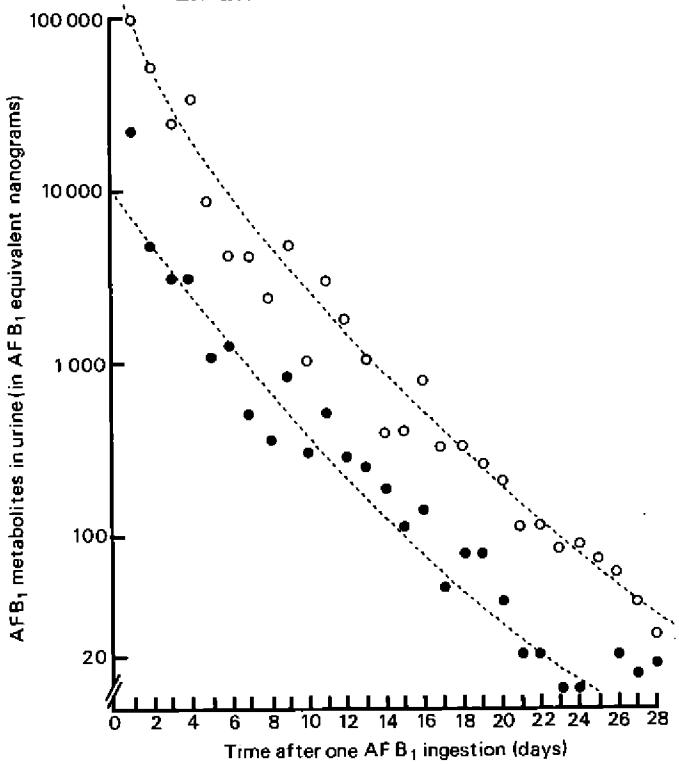

Fig. 5 Kinetics of excretion of AFB_1 metabolites in BDIV adult male rats after a single intragastric intubation of 270 µg (○) and 90 µg (●) of AFB_1.

(*b*) *Detection of O^6-methylguanine in DNA by specific antibodies* (Miss C. Bordet, Miss H. Brésil)

Following previous studies on the development of a radioimmunoassay for the detection of O^6-methylguanine in tissue DNA[45], a comparison has been made between this method of detection and the classical radiochemical method. Table 6 shows that similar amounts of O^6-methylguanine were detected by the two methods in liver DNA of rats treated with various doses of DMN.

(*c*) *Detection of DNA adducts produced by nitrosamines in human tissues* (in collaboration with Dr M. F. Rajewsky, Institute for Cell Biology, Tumour Research, University of Essen, Federal Republic of Germany (RA/81/003) and Dr S. H. Lu, Cancer Institute, Chinese Academy of Medical Sciences, Beijing (RA/81/002))

Antibodies against DNA modifications induced by various nitrosamines are now available[46] and attempts are being made to use them to detect human exposure to nitrosamines. Some samples of oesophageal tissues have been obtained from people at high risk of developing tumours at this site, and studies are in progress to detect DNA modifications related to nitrosamine exposure using a panel of high affinity antibodies.

[45] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 94.

[46] Rajewsky, M. F., Muller, R., Adamkiewicz, J. & Drosdziok, W. (1980) In: Pullman, B., Ts'o, P. O. P. & Gelboin, H., eds, *Carcinogenesis: Fundamental Mechanisms and Environmental Effects*, Dordrecht, Reidel, pp. 207–218.

(*d*) *Working Group on the "Development and possible use of immunological techniques to detect individual exposure to carcinogens"*, Essen, Federal Republic of Germany, November 30–December 1, 1981

The purpose of this Working Group is to discuss among experimentalists and epidemiologists the advantages and disadvantages of these immunological techniques compared with other analytical methods of detecting the presence of carcinogenic agents in human body fluids and/or tissues. A second topic of discussion will be the contribution that such immunological assays could make to epidemiological studies by identifying specific risk factors.

Table 6. Amount of O^6-methylguanine in liver DNA of rats treated with *N*-nitrosodimethylamine (NDMA)

Dose of NDMA	Mol of O^6-methylguanine/10^6 mol of guanine		
	Radioimmunoassay [a]	Liquid chromatography + radioimmunoassay [a]	Radiochemical method [b]
20 mg/kg	520	611	651
2 mg/kg	37.5	41	45
0.2 mg/kg	not detectable	2	5.9

[a] O^6-Methyl-2'-deoxyguanosine (O^6-MedGuo) content (pmol) in DNA (µg) is obtained by plotting the percentage of inhibition of tracer-antibody binding against the amount of DNA, and by referring to a standard curve established with different concentrations of O^6-MedGuo as inhibitor. Results are expressed in mol of O^6-MedGuo/10^6 mol of dGuo, taking a content of 23 % of guanine in rat liver DNA. Control values obtained with DNA from nontreated rat liver are subtracted. The radioimmunoassay was carried out using the intact DNA or the fractions containing O^6-methylguanosine obtained by separation in Sephadex G-10 of the hydrolysed DNA.

[b] Method described in Margison *et al.* (1977), *Biochem. J.*, **165**, 463–468.

3.8 *Role of viruses and cytogenetic changes in the etiology of human cancer*

Particular emphasis has been put on the characterization of Burkitt-type lymphomas in non-endemic areas, like France, and in the examination of their virological and cytogenetic characteristics, compared with Burkitt's lymphoma (BL) occurring in endemic areas. Laboratory activities have been directed towards *in vitro* studies aimed at understanding the role of Epstein-Barr virus (EBV) and/or cytogenetic changes in the oncogenic process. Two approaches are being attempted: 1) biochemically, to investigate the role of EBV or cellular gene products in the transforming processes; and 2) biologically, to study transformation of human lymphocytes in tissue culture.

Serological tests have been carried out for the presence of EBV, to complete the immunogenetic studies in Singapore (see p. 53) and in Morocco. In parallel to these activities, considerable effort has been devoted to the collection, storage and redistribution of biological material among collaborating laboratories.

(*a*) *Laboratory activities related to field programmes* (Dr G. Lenoir, Miss C. Bonnardel, Mrs M. F. Lavoué, and Ms S. Pauly)

(i) *Studies on African Burkitt's lymphoma* (in collaboration with Dr G. Bornkamm, Institute for Virology, Health Centre, Freiburg, Federal Republic of Germany; Dr G. Klein, Karolinska Institute, Stockholm, and Dr D. Wright, University of Southampton, UK)

Most of the virological testing related to this project has been completed.

The prospective study of BL conducted in the West Nile district of Uganda indicated that children who will develop BL were infected by EBV long before tumour manifestation[47]. An extension of these studies indicated that elevated anti-EBV antibody titres occur up to 6 years prior to tumour development, supporting the hypothesis that initiation of BL may occur very early in life, and bringing additional epidemiological evidence for a strong association between EBV and BL[48].

Some rare cases of BL occurring in endemic African areas were not associated with EBV, as indicated by the absence of viral markers within tumour cells. In order to estimate better the proportion of such cases, 54 biopsy samples collected in the framework of Agency programmes in Uganda were analyzed by molecular hybridization and 52 were found to contain the EBV genome. These observations are consistent with the finding reported in other studies (Table 7).

Table 7. EBV-DNA in African Burkitt's lymphoma

Reference	No. of cases studied	No. EBV-positive	Percentage of EBV-positive cases	Mean No. of EBV genome equival./cell
Zur Hausen *et al.* *Nature* (1970)	10	10	100	–
Nonoyama *et al.* *Proc. nat. Acad. Sci.* (1973)	20	19	95	40.4
Lindahl *et al.* *Int. J. Cancer* (1974)	27	26	96	39.1
Olweny *et al.* *J. natl. Cancer Inst.* (1977)	15	14	93	38.8
Present study	54	52	96	34.7
Total	126	121	96	38.2

(ii) *Studies on non-endemic Burkitt type-lymphoma*

Lymphomas with histopathological features similar to those described for BL have been reported to occur in a sporadic manner outside Africa. In order to characterize the frequency of these lymphomas, their association with EBV and their cytogenetic characteristics, a survey is

[47] De Thé, G., Geser, A., Day, N. E., Tukei, P. M., Williams, E. H., Beri, D. P., Smith, P. G., Dean, A. G., Bornkamm, G. W., Feorino, P. & Henle, W. (1978) *Nature*, 274, 756–761.

[48] Geser, A., de Thé, G., Lenoir, G., Day, N. E. & Williams, E. W. (1981) (submitted for publication).

being implemented in Europe, and in France in particular. Preliminary results[49] obtained from cases collected in the Lyon area indicate that: 1) Burkitt-type lymphomas may represent as much as 30–50% of the cases of childhood non-Hodgkin's lymphomas; 2) only 10–20% of the cases are found to be EBV-associated; 3) clinically, these lymphomas are very similar to lymphomas described in Africans, in particular with regard to the sensitivity to chemotherapy. The majority, however, present an abdominal form primarily; and 4) contrary to previous reports, the distribution by age is similar to that observed in Africa (Fig. 6).

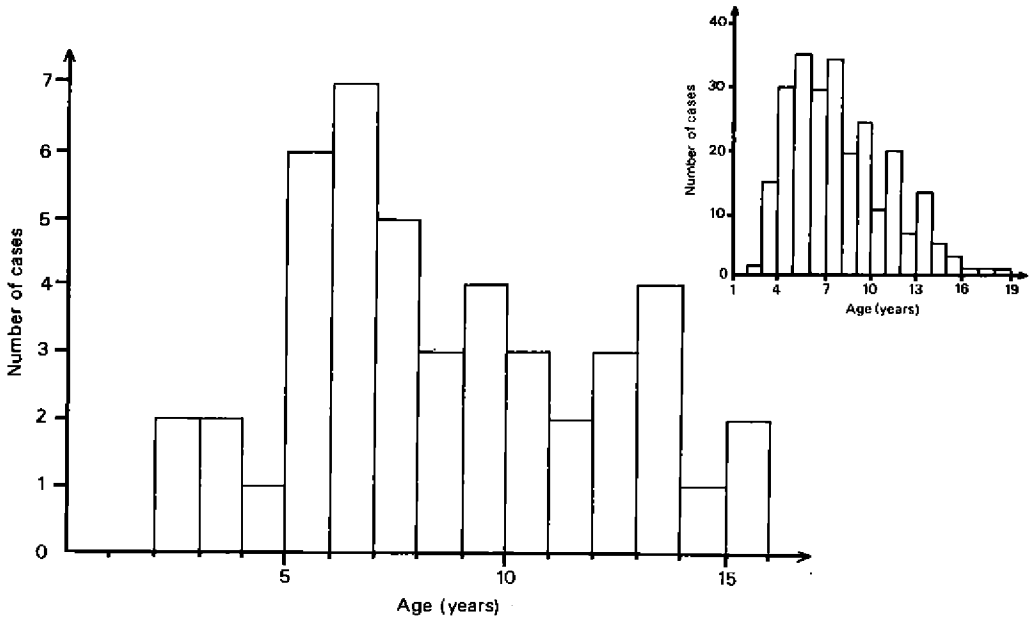

Fig. 6 Age distribution of 47 French Burkitt-type lymphomas. In the upper right, age distribution of African Burkitt's lymphoma. (From Olweny *et al.*, (1980) *Int. J. Cancer*, **26**, 261.)

(iii) *Immunogenetic studies on nasopharyngeal carcinoma in Morocco* (Professor R. Sohier, consultant, in collaboration with Dr H. Bétuel, Lyon Blood Transfusion Centre, Beynost, France, and Professor S. Nejmi, Director, National Virus Centre, Mohamed V Hospital, Rabat, Morocco)

In order to determine whether NPC risk in intermediate risk areas is associated with a particular HLA profile, a pilot study was conducted in Morocco. Sera and biopsies from 139 suspected NPC cases were collected and sent to Lyon for histopathological and virological analysis. The first part of the study was aimed at better characterizing NPC in Morocco, in particular with regard to its association with EBV. The second part, HLA typing, carried out collaboratively between Professor S. Nejmi (Rabat) and Dr H. Bétuel (Beynost, France) is in progress.

[49] Philip, T., Lenoir, G. M., Brunat-Mentigny, M., Bertrand, S., Gentilhomme, O., Souillet, G. & Philippe, N. (1980) *Pédiatrie*, 35 (8), 659–676.

(*b*) *Laboratory investigations*

(i) *EBV serological activities* (Dr G. Lenoir, Mrs M.-F. Lavoué, Mrs S. Pauly)

EBV-primary infection is usually clinically silent in the general population, and a very good immune control of the viral infection occurs, with no recurrence. However, in rare individuals with primary or secondary immunodeficiency, viral infection may be ill-controlled, and it has been proposed that, among these individuals, EBV infection may be the cause of polyclonal lymphoproliferative disorders. Serological methods are being used to study the possible role of EBV in their etiology by testing for indications of EBV infection in individuals suffering from various immunodeficiencies, as well as on patients having various B-cell type lymphomas, other than Burkitt-type lymphoma. In a recent study[50] it was reported that angioimmunoblastic lymphadenopathy may be associated with a poor control of EBV infection.

(ii) *Tissue culture studies* (Dr G. Lenoir, Mrs M. Vuillaume, Mrs S. Pauly, Mrs I. Philip)

The majority of Burkitt-type lymphomas may be cultivated *in vitro* as lymphomatous continuous cell lines independent of the presence of the EBV-genome. Moreover, normal "non malignant" human B lymphocytes can also be cultivated *in vitro* continuously, once they have been "immortalized" by EBV. Taking advantage of these two facts, transformation of human lymphocytes is being studied. More than 20 new lymphomatous lines derived from non-endemic Burkitt-type lymphomas have been established, seven from EBV-free lymphomas. These cell lines are being used in collaborative studies on the phenotype of the Burkitt cell, and, especially, its cytogenic characteristics (see below).

Furthermore, in parallel, lymphoblastoid lines have been established from individuals at high risk of developing lymphomas, and their characteristics are under investigation.

(iii) *Cytogenetic studies* (In collaboration with Dr R. Berger, Institute for Research on Blood Disorders, Paris; Dr J. Fraisse, Blood Transfusion Centre, St-Etienne, France, and Dr G. Manolov, Institute of Oncology, Sofia)

Cytogenetic studies are being performed in collaboration with the three institutes mentioned above, using both the biopsy material collected from BL (endemic and non-endemic) cases, and the continuous lymphoma lines established from this collection. The results can be summarized as follows:

1. The t(8;14) translocation, considered as characteristic of the African BL tumours, has also been found in the majority of non-endemic BL cases studied.
2. Other translocations designated as 'variant' have also been found in the non-endemic BL, such as: t(8;22) and t(2;8)[51, 52].

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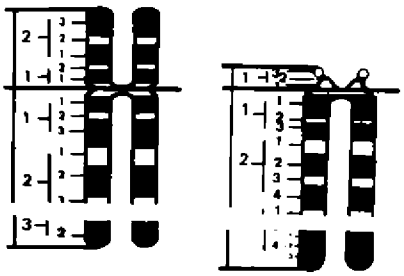
[50] Seigneurin, J. M., Mingat, J., Lenoir, G. M., Couderc, P. & Micoud, M. (1981) *Brit. Med. J.*, **282**, 1574–1575.

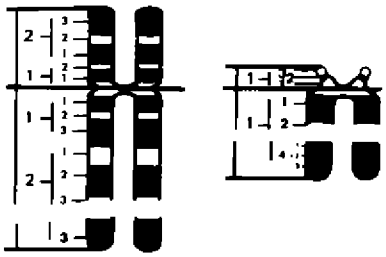
[51] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 102.

[52] Bertrand, S., Berger, R., Philip, T., Bernheim, A., Bryon, P. A., Bertoglio, J., Doré, J. F., Brunat-Mentigny, M. & Lenoir, G. M. (1981) *Europ. J. Cancer*, 17(5), 577–584.

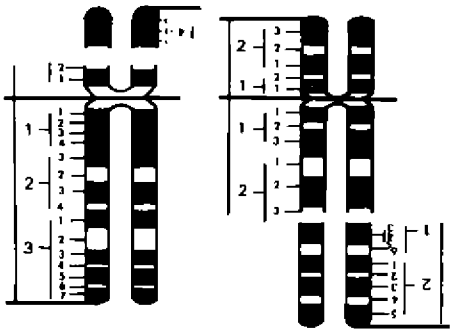
3. A study done retrospectively on 10 cell lines established from African BL in the early 70's clearly showed that the variant translocations are also found in African BL and are, therefore, independent of the endemicity of the lymphoma[53-56] (Table 8). This suggests that Burkitt's lymphoma, independent of its geographic origin or EBV-association, is characterized by a non-random cytogenetic change involving the long arm of chromosome 8 (in 8q23-24) (Fig. 7), and not chromosome 14, as previously thought. The significance of these consistent cytogenic changes remains to be determined. Studies on the specific break-point on chromosome 8 are being carried out using high resolution cytogenetic techniques (Dr G. Manolov).



t(8;14) (q 2 3; q 3 2)



t (8; 22)(q23;q12)



t (2; 8) (p12; q23)

Fig. 7 Schematic diagram of the 3 types of translocations observed in Burkitt's lymphoma.

[53] Berger, R., Bernheim, A., Bertrand, S., Fraisse, J., Frocrain, C., Tanzer, J. & Lenoir, G. (1981) *Nouv. Rev. Fr. Hematol.*, 23, 39–41.

[54] Fraisse, J., Lenoir, G., Vasselon, C., Jaubert, J. & Brizard, C. P. (1981) *Cancer Genet. Cytogenet.*, 3, 149–153.

[55] Bernheim, A., Berger, R. & Lenoir, G. (1981) *Cancer Genet. Cytogenet.*, 3, 307–315.

[56] Philip, T., Lenoir, G. M., Fraisse, J., Philip, I., Bertoglio, J., Ladjaj, S., Bertrand, S. & Brunat-Mentigny, M. (1981) *Int. J. Cancer* (in press).

Table 8. Translocations observed in 10 African BL lines

Identification	Geographical origin	Sex	Tumour site	Date of reception at IARC	Date of culture establishment	EBV genome (presence)	Translocation
LY 46	Nairobi (Kenya)	F	ovary	2/26/1970	5/13/1970	+	t(8;14)
LY 74	Kampala (Uganda)	M	abdomen; kidney	11/12/1971	2/01/1972	+	t(8;14)
LY 81	Nairobi (Kenya)	F	maxillary	11/26/1971	2/29/1972	+	t(8;14)
Silfere		F		sent from Karolinska Institute		+	t(8;14)
Seraphina	Nairobi (Kenya)	F	ovary	sent from Karolinska Institute		+	t(8;14)
LY 65	Shirati (Tanzania)	F	ovary	7/09/1971	8/18/1971	+	8q-
LY 66	Nairobi (Kenya)	M	maxillary; lymph node	4/09/1971	8/25/1971	+	t(2;8)
LY 91	Uganda	F	ovary	11/08/1972	12/21/1972	+	t(2;8)
LY 47	Kampala (Uganda)	M		May 1970	10/25/1970	+	t(8;22)
LY 67	Nairobi (Kenya)	M	recurrence	6/04/1971	8/25/1971	+	t(8;22)

A study is being done on lymphoblastoid cell lines derived from patients with ataxia-telangiectasia, to correlate cytogenetic changes with increase in cell growth capability, and already a cellular clone showing rearrangement of chromosome 14 (14q+) has been isolated. This chromosome change is frequently associated with lymphoma development.

(iv) *Biochemical studies on EBV* (In collaboration with Professor J. Daillie, and Dr A. Calender, Claude Bernard University, Lyon, France)

The study has been continued, of EBV early gene products, which may possibly play a role in cell transformation, including the function of EB nuclear antigen[57] and the characterization of EBV-DNA polymerase and deoxythymidine kinase[58]. New techniques for nucleic acid analysis are being developed to study the control of transcription of EBV viral DNA.

(*c*) *Reference and banking related activities* (Professor R. Sohier, Consultant)

Anti-EBV working sera have been prepared, which are used to ensure comparability of EBV serological data obtained from different laboratories. The sera are available in lyophilized form, and are sent on request.

Sera collected during the EBV sero-epidemiological studies, and lymphoid cell lines have also been provided regularly to national laboratories.

3.9 *Tumour associated antigens* (Dr P. Sizaret)

(*a*) *Provision of reference material*

IARC has continued to deliver reference materials for the assay of α-fetoprotein and for β1 specific pregnancy glycoprotein (SP1).

(*b*) *Problems of standardization of immunoassays* (Dr P. Sizaret and Dr J. Estève, in collaboration with Dr P. Schultz-Larsen, Copenhagen, and Dr B. Teisner, Sydney, N.S.W., Australia)

A collaborative study has shown that, even when identical reference preparations are used, results may differ depending on the technique of assay of mixtures of the α and β components of the SP1. When methods such as radial immunodiffusion or Rockett immunoelectrophoresis are used, where antibody is present in excess, the relative affinities of these two components seem to be identical. However, when the competitive radioimmune assay is used, in which the amount of antibody is limited, the affinity of the β component, which has a smaller molecular weight, seems to be greater. This results in the systematic underestimation of the α component when a radioimmune assay is used to analyse SP1 preparations, in which the α component is predominant.

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[57] Hentzen, D., Lenoir, G. M., Berthelon, M. C. & Daillie, J. (1980) *Biochem. Biophys. Res. Commun.*, **96** (1), 425–432.

[58] Ooka, T. & Calender, A. (1980) *Virology*, **104**, 219–223.

(*c*) *Clinical usefulness of assays of immune complexes in breast cancer patients* (In collaboration with Dr R. Herberman, Bethesda, MD, USA, Dr M. Bordes, Dijon, France; Dr P. H. Lambert, Geneva, Switzerland; Dr H. S. Luthra, Rochester, NY, USA; Dr R. A. Robins, Nottingham, UK, and Dr A. Theofilopoulos, La Jolla, CA, USA)

Immune complexes in a limited number of coded sera (breast carcinoma, 30; benign breast diseases, 30; and blood donors, 30) were assayed by four laboratories using four techniques: ^{125}I Ciq binding assay; conglutinin binding assay; Raji assay; and monoclonal rheumatoid factor assay. Contrary to earlier reports, the results indicated that such assays were of no value in the diagnosis of breast carcinoma. When carcinoembryonic antigen was assayed, a good discrimination was found between normal blood donors and patients with breast carcinoma. The assay was not able, however, to discriminate between cancer patients and those with benign breast diseases.

3.10 *Visiting fellows*

Dr A. E. Pegg, from the Milton S. Hershey Medical Center, Hershey, PA, USA (with the support of the ICRETT award), Dr G. P. Margison, from the Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, UK, and Dr V. Turusov, from the All-Union Cancer Research Center, the USSR Academy of Medical Sciences, Moscow, visited the laboratory for periods of 3–4 weeks, working on various collaborative research projects.

4. PROGRAMME OF ENVIRONMENTAL CARCINOGENS AND HOST FACTORS (Dr H. Bartsch)

4.1 *Introduction*

During the past year, more emphasis has been given to developing, or refining, analytical and biochemical methods which could be applied either for monitoring carcinogen exposure of human subjects, or for identifying possible host-risk factors involved in human carcinogenesis.

Approaches to monitoring carcinogen exposure involve the improvement and application of short-term tests for screening for the presence of suspected carcinogens of chemicals and complex environmental mixtures to which man is exposed. Chemical analysis of body fluids of subjects living in high-risk areas for certain types of cancer have also been carried out. These include, for example, cancer of the urinary tract associated with endemic Balkan nephropathy in Bulgaria and cancer of the oesophagus in Linxian, northern China. Similarly, patients have been investigated for a possible increase in formation of endogenous carcinogens, *N*-nitroso compounds, following, for example, surgery or drug treatment which are among the factors suspected of increasing endogenous nitrosation. For a better assessment of exposure to such *N*-nitroso compounds, a new monitoring method has been developed in experimental animals and tested in pilot population studies.

In studies related to metabolic factors involved in human cancer, estimations of carcinogen-metabolizing enzymes have been carried out in tissues that are targets for tobacco-smoke carci-

nogens. The activities of various enzymes, capable of activating or detoxifying foreign compounds, have been measured in peripheral lung tissue and bronchial epithelium, taken from both healthy individuals and lung cancer patients. Another related study measured actual exposure of individuals to cigarette-smoke constituents, and assessed their genetically-determined responsiveness to cigarette smoke by analysing aryl hydrocarbon hydroxylase (AHH) inducibility in cord blood and in maternal lymphocytes and comparing it with that of placental AHH activity in smoking mothers. Studies to measure true exposure to cigarette smoke by using serum or urine thiocyanate levels and urinary thioether excretion are in progress.

Compounds which are non-toxic but which are metabolized by the same enzyme system as carcinogens may be used to predict reaction to carcinogens. Antipyrine is such a predictor drug and its half-life has been compared with the metabolism of a set of chemical carcinogens in two mice strains. The responsiveness to polycyclic aromatic hydrocarbon-induced carcinogenesis of these strains appears to be determined to a large extent by the genetic make-up at the Ah-locus. Thus, by comparing the oxidative metabolism of the predictor drug with several carcinogens, it should be possible to ascertain whether the metabolism of the drug and the carcinogen are under similar genetic control, and thus, whether or not activation pathways of a given carcinogen can be predicted by antipyrine half-life determination.

Individual susceptibility to chemical carcinogens is also being investigated by studying biochemical and cytogenetic markers of carcinogen-induced damage, measured during administration of a carcinogen, *N*-nitrosodiethylamine, to a group of outbred rats. These animals are genetically heterogeneous and such a study may simulate the situation in a human population.

Also of relevance to the human situation are the investigations on DNA adducts formed by vinyl chloride (VC), which produces the same type of liver tumour in man and in rats. The formation of miscoding VC-DNA adducts is being linked to the induction of DNA damage and repair in rats exposed to VC, which is correlated with the induction of liver angiosarcomas and hepatomas in the rat.

Precise measurement of environmental carcinogens is an essential part of many epidemiological studies of cancer etiology, so that the dissemination of information related to methods of analysis for environmental carcinogens is of considerable importance. Three volumes on selected methods of analysis of nitrosamines, vinyl chloride and polycyclic aromatic hydrocarbons have been published[59-61] and volumes on aromatic amines, metals and mycotoxins are in preparation. A working conference on N-*Nitroso Compounds: Occurrence and Biological Effects*, will be held in Tokyo in October 1981. A large proportion of the selected presentations deal with the biological effects of *N*-nitroso compounds, indicating an increasing interest in the underlying biological mechanisms of carcinogenesis.

Problems related to the safe handling of carcinogens and mutagens in chemical laboratories is of concern to the Agency, which has, with the support of the Division of Safety, National Institutes of Health, Bethesda, MD, USA, undertaken a special programme to develop, validate and publish methods for the destruction and disposal of laboratory waste containing carcinogens. A mono-

[59] Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds (1978) *Environmental Carcinogens — Selected Methods of Analysis*, Volume 1: *Analysis of Volatile Nitrosamines in Food (IARC Scientific Publications No. 18)*, Lyon.

[60] Squirrell, D. C. M. & Thain, W, (1978) ibid, Volume 2: *Vinyl Chloride (IARC Scientific Publications No. 22)*, Lyon.

[61] Castegnaro, M., Bogovski, P., Kunte, H. & Walker, E. A., eds (1979) ibid, Volume 3: *Polycylic Aromatic Hydrocarbons (IARC Scientific Publications No. 29)*, Lyon.

graph on aflatoxins, the first in that series, has appeared[62] and future volumes will report methods of destruction for nitrosamines, polycyclic aromatic hydrocarbons, alkylating agents, aromatic amines and hydrazines. An important feature of this special programme is to establish a base of information from which appropriate methods can be developed and validated. Individual scientists and laboratories are encouraged to participate in this endeavour by contributing suggested methods and participating in collaborative studies. The programme should serve as a catalyst, stimulating research and collaboration in this area.

The International Mycotoxin Check Sample Survey Programme has provided analytical quality assurance to 123 laboratories in 31 countries. It is coordinated by the Agency and supported by the Food and Drug Administration, USA. The programme was expanded this year to include the analysis of aflatoxin M_1 in cow's milk, and ochratoxin A in animal feed.

In summary, therefore, the goal of the programme of environmental carcinogens and host factors is to identify carcinogenic chemicals that occur in the human environment or are generated *in vivo,* and to develop sensitive and reliable methods for assessing such exposures in the human population in conjunction with epidemiological studies. In parallel, attempts are being made to predict the level of genotoxic risk posed by chemicals or complex mixtures to man.

4.2 *Carcinogen-metabolizing enzymes, DNA adduct formation and susceptibility to chemical carcinogenesis*

Inherent variations in the activity of metabolizing enzymes, mainly inducible mono-oxygenases, may be associated with individual variations in susceptibility in human populations exposed to genotoxic agents. Data from studies in inbred mouse strains show that the carcinogenic effect of the polycyclic aromatic hydrocarbons, for example, is, to a great extent, determined by the genetically controled inducible mono-oxygenases. In genetically heterogeneous human populations, individuals may similarly display differing susceptibilities. There is evidence of genetically controlled variation in the levels of the enzymes that are involved in the metabolism of certain drugs. Lastly, irrespective of which assay system is used, there has been a consistent observation that measures of the activity of the carcinogen-metabolizing enzymes and the resulting formation of carcinogen-DNA adducts, show interindividual variations, which are 100-fold or more.

Experimental approaches for studying carcinogen metabolism in man are limited by ethical considerations, and therefore studies have been carried out *in vitro,* using human tissue homogenates or cultured lymphocytes. An alternative is to study the metabolism *in vivo* of drugs that are metabolized by the same enzymes as carcinogens. Although such predictor drugs have not yet been explored in population studies, Idle *et al.*[63], using debrisoquine as probe, found that among patients in Nigeria with carcinoma of the liver, colon and rectum, individuals who were fast oxidisers of this drug were more frequent than among controls, suggesting that the level of oxidising activity may influence responsiveness to environmental carcinogens. Usefulness of such predictor drugs is being investigated in inbred mouse strains.

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[62] Castegnaro, M. *et al.*, eds (1980) *Laboratory Decontamination and Destruction of Aflatoxins B_1, B_2, G_1, G_2 in Laboratory Wastes (IARC Scientific Publications No. 37),* Lyon.

[63] Idle, J. (1981) In: Armstrong, B. & Bartsch, H., eds, *Host Factors in Human Carcinogenesis (IARC Scientific Publications No. 39)* (in preparation).

Investigations are in progress to develop monoclonal antibodies for the sensitive detection of DNA adducts formed by carcinogens *in vivo*. The synthesis of model compounds and reactive metabolites required for these studies is achieved through collaborative research agreements.

In summary, the objective is to determine whether the metabolic factors of the host, which control the level and type of carcinogen-DNA adducts formed, determine individual susceptibility to chemically-induced cancer, and whether early markers of cytogenetic damage in rodents may be used as indicators of individual cancer risk.

(*a*) *Benzo(a)pyrene metabolism in surgical lung tissue and mucosa specimens from lung cancer and cancer-free patients* (Dr A. Aitio, Miss A. M. Camus, Dr R. Saracci, in collaboration with Professor C. Giuntini, National Research Council, University of Pisa, Italy)

The aim of this study is to elucidate the activities of various mono-oxygenases, epoxide hydrolase(s), glutathione S-transferase(s) and UDP-glucuronosyltransferase(s) in human lung tissue, both from healthy individuals and patients with lung cancer. Surgical samples are collected, in the same individual, from peripheral lung tissue, and from the bronchial epithelium. The data collected in this study will be related to anamnestic data on pulmonary function tests, and on the disease status of the lungs.

(*b*) *Benzo(a)pyrene-hydroxylase (AHH) inducibility and individual susceptibility to toxic effects of cigarette smoke* (Department of Pharmacology, University of Oulu, Finland) (RA/79/002)

Principal investigator: Dr O. Pelkonen

Cigarette smoking is a major determinant in many human diseases, including cancer, and a considerable proportion of the population is exposed to smoke already in their mother's womb. The purposes of the present project are to find procedures which would allow: 1) the actual exposure of an individual to cigarette-smoke constituents to be measured, and 2) an individual's genetically determined responsiveness to constituents of cigarette smoke to be assessed.

In a study on smoking mothers[64], AHH inducibility in cord blood and in maternal lymphocytes was compared with placental AHH activity. Placental AHH activity showed a statistically significant correlation with cord blood lymphocyte AHH inducibility ($r = 0.75$, $p < 0.01$, $n = 15$). The correlation between maternal lymphocyte AHH inducibility and placental AHH activity was poor ($p = 0.04$). These findings suggest that AHH induction in man may be "systematically" controlled and that the genetic background will determine the extent of induction at a given level on exposure to polycyclic hydrocarbons. On the other hand, in hospital patients, correlations between lymphocyte AHH induction, hepatic mono-oxygenase activities and antipyrine elimination were rather poor, even in groups with no indications of liver injury[65].

In another study on psoriatic and control patients, it was demonstrated that cigarette smoking has an effect on lymphocyte AHH activities and AHH inducibility[66]. The nature of this effect, which is present after 3-day culturing of lymphocytes, is not known and is being studied.

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[64] Pelkonen, O., Karki, N. T. & Tuimala, R. (1981) *Cancer Lett.*, **13**, 103–110.
[65] Pelkonen, O., Karki, N. T. & Sotaniemi, E. (1981) (in preparation).
[66] Karki, N. T., Karvonen, J. & Pelkonen, O. (1981) (in preparation).

Studies are being made to measure the true exposure to cigarette smoke by using serum and urine thiocyanate levels, urinary nicotine and cotinine and urinary thioether excretion.

(c) *Interrelationships of antipyrine half-life, liver mixed function oxidases activities and liver S9-mediated mutagenicity of aflatoxin B_1 (AFB_1)* N-*nitrosomorpholine (NOM), benzo(a)pyrene (B[a]P) and 2-acetylaminofluorene (AAF)* (Mr C. Malaveille, Mrs A. Hautefeuille and Mrs G. Brun, in collaboration with Dr R. Roberfroid, Laboratory of Biotoxicology, Catholic University of Louvain, Brussels)

The use of predictor drugs, which are by definition non-toxic but which are metabolized by the same enzyme systems as environmental carcinogens, has been proposed for estimating carcinogen metabolism in human subjects[67]. It has been shown that the rates of hydroxylation of B[*a*]P (the carcinogen) and of antipyrine (the predictor drug) were parallel in human liver specimens. A recent study[68] showed a relationship between the rate of B[*a*]P hydroxylation (AHH) in human liver biopsies and antipyrine half-life *in vivo*.

In order to evaluate the relevance of antipyrine half-life as a parameter for estimating the metabolic activation of different classes of carcinogens *in vivo*, groups of C57BL/6 and DBA/2 mice were either treated with mono-oxygenase inducers (phenobarbital; pregnenolone 16 α-carbonitrile; 5,6-benzoflavone; 3-methylcholanthrene) or mono-oxygenase inhibitors (7,8-benzoflavone; disulfiram). Groups of mice were also given ethanol (3% in drinking water) for 12 days. Antipyrine half-life in mouse serum was measured by radioimmunoassay[a] according to Chang *et al.*[69]. This metabolic parameter was compared with *in vitro* activity of either hepatic microsomal B[*a*]P hydroxylase (AHH), determined by spectrofluorimetric assay[70], or with arylamide *N*-hydroxylase (N-HYD), assayed by the gas-liquid chromatographic method[71] and with the liver microsome-mediated mutagenicity of AFB_1, B[*a*]P-7,8-dihydrodiol, NOM and AAF in the *Salmonella*/microsome liquid incubation assay[72].

The results showed:

1) statistically significant negative correlation between antipyrine half-life and hepatic AHH activity;
2) statistically significant positive correlations for a) AHH activity *versus* AFB_1 mutagenicity; b) N-HYD activity *versus* B[*a*]P-7,8-dihydrodiol mutagenicity and c) N-HYD activity *versus* AAF mutagenicity;
3) no correlation between antipyrine half-life and neither N-HYD activity nor liver microsome mediated mutagenicity of the carcinogens tested.

Such data suggest that in mice, half-life of antipyrine *in vivo* is not a good indicator of the individual capacity to convert the carcinogens into reactive intermediates that are mutagenic *in vitro*.

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[67] Kapiltunik, J., Poppers, P. J. & Conney, A. H. (1977) *Clin. Pharmacol. Ther.*, **21**, 166–176.

[68] Kalamegham, M., Krishnaswamy, K., Krishnamurthy, S. & Bhargava, R. N. K. (1979) *Clin. Parmacol. Ther.*, **25**, 67–73.

[a] antibody against antipyrine, kindly provided by Dr A. Wood, Hoffmann-La Roche Institute for Molecular Biology, Nutley, NJ, USA.

[69] Chang, R. L., Wood, A. W., Dixon, W. R., Conney, A. H., Anderson, K. E., Eiseman, J. & Alvares, A. P. (1976) *Clin. Pharmacol. Ther.*, **20**, 219–226.

[70] Dehnen, W., Tomingas, R. & Roos, J. (1973) *Anal. Biochem.*, **53**, 373–383.

[71] Razzouk, D., Lhoest, G., Roberfroid, M. & Mercier, M. (1977) *Biochem. J.*, **83**, 194–203.

[72] Robertfroid, M., Malaveille, C. & Bartsch, H. (1980) In: *Proceedings of the 7th European Workshop on Drug Metabolism, Zurich, 5–10 October 1980.*

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(*d*) *Differential excretion of mutagenic benzo*(a)*pyrene (B[a]P) metabolites in the urine of mouse strains, with genetically determined susceptibility to PAH-induced carcinogenesis* (Miss A. M. Camus, Mrs N. Sabadie, Dr A. Aitio and Dr J. Wahrendorf)

Mouse strains with inducible B[*a*]P-hydroxylase (AHH) ('responsive') show a very pronounced susceptibility to carcinogenesis by subcutaneous and dermal application of polycyclic aromatic hydrocarbons (PAH), as compared to strains without inducible AHH activity ('non-responsive'). The purpose of this study was to elucidate the mechanisms underlying this difference, by studying the overall metabolism of B[*a*]P in responsive (C57BL/6) and non-responsive (DBA/2) mouse strains after a single administration. Mutagenicity was monitored in the urine, and the mutagenic B[*a*]P metabolites were identified, and quantified by high-performance liquid chromatography. In addition, to obtain an overall view of the metabolism of B[*a*]P in these mice, the faecal excretion of total ^{14}C-radiolabelled B[*a*]P-metabolites was followed. For the most part, the mutagenicity in urine was attributable to conjugates of 3-hydroxy B[*a*]P in both mouse strains. The amount of B[*a*]P excreted as 7,8-dihydroxy-7,8-dihydro-B[*a*]P was smaller in the susceptible mouse strain. The susceptible mouse strain showed a more rapid total excretion of B[*a*]P derivatives in the faeces. It thus appears that differences of the overall metabolism of B[*a*] in the body cannot explain the differential susceptibility of these mouse strains.

(*e*) *Biochemical and cytogenetic markers of individual susceptibility to* N*-nitroso compound-induced cancer in rodents* (Dr A. Aitio and Miss A. M. Camus, in collaboration with Dr K. Husgafvel-Pursiainen, Institute of Occupational Health, Helsinki)

In this study, metabolic parameters possibly determining differences in individual susceptibility of rodents to chemically-induced cancer are being investigated. In parallel, early markers of genetic damage will be examined to establish whether they can serve as an indicator for predicting individual cancer risk. The activities of drug and carcinogen metabolizing enzymes were determined *in vitro* using liver samples obtained by partial hepatectomy, and *in vivo* by following the metabolism of predictor drugs like antipyrine and disopyramide. The rats—outbred to simulate better the human situation of genetic dispersion—were thereafter dosed with *N*-nitrosodiethylamine, a hepatocarcinogen which requires metabolic activation by liver mono-oxygenases. During carcinogen administration, some reaction products of the carcinogen with DNA and proteins, i.e., *N*-7-ethylguanine as well as ethylcysteine and ethylacetylcysteine were monitored in the urine; cytogenetic damage was investigated in circulating blood lymphocytes using the sister chromatid exchange assay. Individual susceptibility to the carcinogen (absence or presence of tumours and latency period) will be correlated with the biochemical and cytogenetic markers measured during the period of carcinogen administration.

(*f*) *Biological consequences of DNA adducts formed by vinyl chloride metabolites and their detection by monoclonal antibodies* (Mr A. Barbin, Mr J.-C. Béréziat and Dr R. Laib, in collaboration with Professor M. F. Rajewsky, Institute for Cell Biology, University of Essen, Federal Republic of Germany, and Miss M. H. Perrard, Laboratory of Microbial Biochemistry, Claude-Bernard University, Lyon, France)

Vinyl chloride (VC) is a human and animal carcinogen producing the same type of tumour in both species. Its target organs are the liver, brain, lung and haemo-lymphopoietic system[73]. It is

[73] International Agency for Research on Cancer (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers and Acrolein*, Lyon, pp. 377–458.

thought to exert its adverse biological effects through its metabolic conversion to chloroethylene oxide (CEO) and chloroacetaldehyde (CAA). CEO and CAA are both mutagens and form adducts with cellular macromolecules. CEO but not CAA was shown to be carcinogenic in mice[74]. 1,N^6-Ethenoadenine (εA) and 3,N^4-ethenocytosine (εC) are produced *in vitro* by reaction of CEO, CAA or metabolically-activated VC with nucleosides or nucleic acids. They have been found in the DNA of rat liver following a two-year exposure to VC. In a collaborative study, it has been recently demonstrated that εA and εC miscode for *E. coli* DNA polymerase I when they are introduced into synthetic templates[75]. In close analogy to the alkylation of oxygen atoms of DNA bases, which is thought to be involved in the induction of carcinogenesis by monofunctional alkylating agents, the miscoding lesions εA and εC may represent a critical step in VC- or CEO-induced carcinogenesis. However, the formation of εA and εC in DNA *in vivo* has been questioned because only 7-*N*-(2-oxoethyl)guanine was detected in DNA of rats exposed for 5 hours to VC[76]. Furthermore, this adduct was probably in equilibrium with a cyclic hemiacetal form involving the O^6-position; the latter form, by analogy to O^6-alkylguanine, would be expected to cause faulty base pairing during DNA replication.

With a view to a better understanding of the role of miscoding DNA lesions in VC-induced tumorigenesis, the nature of the VC-DNA adducts formed *in vivo* is being reinvestigated using specific antibodies. Monoclonal antibodies against εA, εC and 7-*N*-(2-oxoethyl)guanine ribonucleosides are being prepared (in collaboration with Professor M. F. Rajewsky). Radioimmunoassays will be developed to measure adducts in DNA hydrolysates from the liver of VC-treated rats. The miscoding properties of VC-DNA adducts are being further explored. CEO- or CAA-treated poly(dG-dC) templates will be analysed for their content in 7-*N*-(2-oxoethyl)guanine or other possible modified bases, and replicated with *E. coli* DNA polymerase I in the presence of complementary and non-complementary nucleotides. The types of base-pair substitutions induced by CEO and CAA will be investigated in selected *E. coli* strains auxotrophic for tryptophan.

(*g*) *Synthesis of model compounds and putative intermediates used in experimental carcinogenesis*
Curie Institute, Orsay, France (RA/80/018)
Principal investigator: Dr A. Croisy

In order to study the nature of reactive intermediates formed from *N*-nitrodialkylamines, the following compounds were synthesized: *N*-nitro-monomethylamine, *N*-nitro-(hydroxymethyl)methylamine and *N*-nitro(acetoxymethyl)methylamine. To investigate the formation of mutagenic metabolites from phenacetin in rodents[77], the following compounds were synthesized and spectroanalytically characterized: *N*-hydroxy-*p*-phenetidine, *p*-nitrosophenetol, *p*-azoxyphenetol, *N*-hydroxyphenacetin, *N*-acetoxyphenacetin, 2-hydroxyphenacetin and 2-acetoxyphenacetin.

[74] Zajdela, F., Croisy, A., Barbin, A., Malaveille, C., Tomatis, L. & Bartsch, H. (1980) *Cancer Res.*, **40**, 352–356.
[75] Barbin, A., Bartsch, H., Leconte, P. & Radman, M. (1981) *Nucleic Acids Res.*, **9**, 375–387.
[76] Laib, R. J., Gwinner, L. M. & Bolt, H. M. (1981) *Chem. biol. Interact.*, **37**, 219–231.
[77] Camus, A. M., Friesen, M., Croisy, A. & Bartsch, H. (1981) (submitted for publication).

4.3 *Short-term tests for the detection of carcinogens*

(*a*) *Routine testing of chemicals in the* Salmonella/*microsome plate and preincubation assay* (Mr C. Malaveille, Mrs A. Hautefeuille, Mrs G. Brun, Miss A. M. Camus, Mr J.-C. Bérézíat)

Mutagenicity data on compounds tested in 1981 are presented in Table 9.

Table 9. Mutagenicity data on chemicals tested in *Salmonella typhimurium*/microsome assays in 1981

Compound/mixture	Occurence/use	Type of assay[a]	Mutagenic response in strain			
			TA 1530	TA 1535	TA 100	TA 98
Cypermethrine	insecticide	P, PI			–	–
Permethrine	insecticide	P, PI			–	–
Decamethrine	insecticide	P, PI			–	–
Bioresmethrine	insecticide	P, PI			–	–
Resmethrine	insecticide	P, PI			–	–
Cismethrine	insecticide	P, PI			–	–
Nitroso alanylalanine	*in vitro* nitrosated peptides	PI	–	+	+	
6-chloro-6-deoxyglucose	antifertility compound	PI			–	–
Diphenylhydantoine	drug	P			–	–
Reserpine	drug	P, PI			–	–
Organic extract of *Bacillus thuringiensis israelensis*	larvacidal powder	P			–	–

[a] Mutagenicity assays were carried out with or without Aroclor-treated rat liver S-9 and an NADPH generating system
P = plate assay; PI = preincubation assay

(*b*) *Testing of selected chemicals in multiple short-term tests for the detection of carcinogens/mutagens* (Mr C. Malaveille, in collaboration with Dr A. Davis, WHO Parasitic Diseases Programme, Geneva; Dr E. Vogel, Laboratory of Radiation, Genetics and Chemical Mutagenesis, University of Leiden, The Netherlands; Dr T. Kuroki, Institute of Medical Science, University of Tokyo; Dr C. A. van der Heijden, Laboratory for Carcinogenesis and Mutagenesis, National Institute of Public Health, Bilthoven, The Netherlands; Professor N. Loprieno, Genetics Laboratory, University of Pisa, Italy and Dr D. Neubert, Institute of Toxicology and Embryonal Pharmacology, Free University of Berlin, Federal Republic of Germany)

(i) *Bis (tri-n-butyltin) oxide (TBTO)*

To evaluate possible toxic effects of a molluscicide already in use, bis (tri-*n*-butyltin) oxide (TBTO) a multicentre trial has been initiated (financially supported by the Parasitic Diseases Programme, WHO) on the mutagenic/genotoxic potential of TBTO using the following assays:

1) Mutagenesis in *S. typhimurium* strains using cell-free and cellular activation system (IARC).
2. Mutagenesis in V79 Chinese hamster keratinocyte (Dr T. Kuroki).
3) Assays in yeast for the induction of mutations and gene conversions or 'petite' mutations (Professor Loprieno).
4) Induction of DNA-repair synthesis and of sister chromatid exchanges in cultured mammalian cells (Professor Loprieno).
5) Tests for the induction of recessive lethal mutations in *Drosophila melanogaster* (Dr Vogel).
6) Tests for *in vitro* and *in vivo* teratogenic effects (Dr Neubert).
7) Chronic toxicology and carcinogenicity studies in rats (Dr van der Heijden).

(ii) *Metabolic activation studies with yeasts* (Professor N. Loprieno) (RA/78/006)

Cyclophosphamide and different enzyme inducers have been used for the evaluation of some parameters relevant to the metabolic conversion of cyclophosphamide. The substances were tested using two yeast species, *S. pombe*—forward-mutation system—and *S. cervisiae*—gene-conversion system. When cyclophosphamide was tested *in vitro* it appeared more mutagenic than when tested *in vivo* in the host-mediated assay (intrasanguineous test). These results were the contrary of those obtained for *N*-nitrosodimethylamine, and the two methods are now being compared[78].

(iii) *Metabolic fate of epichlorohydrin (ECH)* (Professor N. Loprieno) (RA/78/006)

In vitro mutagenicity studies, using *S. pombe* (forward-mutation system), have demonstrated that glutathione-transferases and the epoxide hydrolase were responsible for the decrease of the mutagenic effects of ECH. Different liver microsomal preparations—S-9 microsomal, and cytosolic fractions—from untreated and phenobarbital pretreated mice were used in these *in vitro* experiments. Studies *in vivo* showed that ECH and its diol-derivative were not detectable in the blood of mice administered intraperitoneally with 200 mg/kg body weight within a few minutes of treatment[79].

(iv) *Methodological studies on monitoring exposed individuals for chromosome aberrations* (Professor N. Loprieno) (RA/78/006)

Factors which might affect the cytogenetic changes observed in workers exposed to chromium, were studied in a group of 50 individuals. The influence of smoking habits, alcohol consumption, drug therapy, diagnostic irradiation, and age were all being evaluated[80].

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[78] Barale, R., Rusciano, D., Loprieno, N., Stretti, G., Monaco, M. & Mossesso, P. (submitted for publication).
[79] Migliore, L., Rossi, A. M., Lascialfari, D., Loprieno, N., Tortoreto, M., Pantarotto, C. (submitted for publication).
[80] Lascialfari, D., Sbrana, I., Bosco, C., Lari, T., Marchi, M., Rossi, G., Loprieno, N. (submitted for publication).

(*c*) *Detection of carcinogens in the* Salmonella*/hepatocyte assay (SHA)* (Mr C. Malaveille and Mrs G. Brun)

The mutagenic activity of procarbazine and 1,2-dimethylhydrazine has been studied in *S. typhimurium his*$^-$ strains in the presence or absence of freshly isolated rat hepatocytes.

Hepatocytes were isolated from male rats following the collagenase perfusion technique adapted from Seglen[81]. The viability of the hepatocytes (80–90%) was examined by trypan blue exclusion. For incubation with bacteria, the hepatocytes were suspended in buffered Hanks BSS medium. Each assay consisted of 2 ml of medium containing a varying number of cells, 2×10^8–8×10^8 bacteria, and the test compound, either in buffered saline or in dimethyl sulphoxide. After not more than 3 h of incubation at 37°C, 1 ml of the incubation medium was plated in duplicate on to minimal glucose agar.

Under these conditions, procarbazine, which does not exhibit mutagenic activity in the microsome mediated assay, was shown to be directly mutagenic in *S. typhimurium* TA 1530 strain. At 15 mM, the number of *his*$^+$ revertants per plate was almost 10 times the spontaneous level. It was also metabolized by rat hepatocytes into derivatives that were mutagenic in the same strain. At 5 mM, in the presence of 8×10^6 hepatocytes, the mutagenic activity was 7 times higher than in the absence of hepatocytes. When lysed hepatocytes were used in the assay, the mutagenic activity of procarbazine was more or less the same as that found with no hepatocytes at all.

1,2-Dimethylhydrazine was shown to be directly mutagenic in *S. typhimurium* TA 1530 using Hanks BSS as incubation medium. At 1 mM, the number of revertants was about 200 times higher than in the absence of substrate. It was not mutagenic, however, when Williams E or Hanks BSS medium containing appropriate concentrations of non-essential amino-acids were used. This may be explained by the trapping of any mutagenic derivatives of 1,2-dimethylhydrazine by the nucleophilic amino-acids.

The mutagenic activity of 1,2-dimethylhydrazine when incubated with rat hepatocytes, was related to the number of hepatocytes used in assay, and was dependent on the incubation medium used. At 0.25 mM, in the presence of 8×10^6 hepatocytes, and using Hanks BSS medium containing an appropriate concentration of amino-acid, the cell-mediated mutagenicity was about 60 times higher than the spontaneous mutation rate.

When Williams E medium was used, however, only weak mutagenicity was observed, probably due to the different concentrations of nucleophiles present on the two media.

In these assays the generation of mutagenic metabolites of aflatoxin B_1 and benzo(*a*)pyrene increased with incubation time during the first 3 hours. With procarbazine and 1,2-dimethylhydrazine, however, mutagenic effects were only observed after 3 hours of incubation. These data illustrate the importance of incubation time in the *Salmonella*/hepatocyte assay, and also the necessity of using intact mammalian cells as the complementary source for activation of test compounds.

(*d*) *The alkaline elution assay as a short-term test for the detection of DNA damage* in vivo (Mr A. Barbin and Mr J.-C. Béréziat)

DNA damage induced by mutagens/carcinogens can be monitored by an alkaline elution assay, in which the rate of DNA elution from filters, at alkaline pH is measured. The rate is directly

[81] Seglen, P. O. (1976) In Prescott, D. M., ed., *Methods in Cell Biology*, Vol. 13, New York, Academic Press, pp. 29–59.

dependent on the dose of the DNA-damaging agent administered. This assay has been used successfully to study the organ specificity of carcinogens[82, 83]. Fluorimetry is used to measure the DNA, thus avoiding *in vivo* radioisotope labelling. The method is being used to measure DNA damage induced by nitrosamines in rodent organs such as the liver, kidney, lung, nasal cavity, oesophagus and trachea.

(*e*) *Screening for environmental mutagens/carcinogens and isolation of biologically active compounds from opium dross (sukhteh) and pyrolysis products of opium or opium alkaloids* (Dr M. Friesen, Mrs L. Garren, Miss A. M. Camus, Mrs A. Hautefeuille, Mr C. Malaveille, Dr J. Cabral and Dr N. Day, in collaboration with Dr I. Chouroulinkov, Institute for Scientific Research on Cancer, Villejuif, France; Dr H. F. Evans, Medical Research Council, Edinburgh, UK; Dr G. Grimmer, Biochemical Institute for Environmental Carcinogens, Ahrensburg, Federal Republic of Germany; Professor U. Mohr and Dr H. B. Richter-Reichhelm, School of Medicine, Hanover, Federal Republic of Germany; Professor M. R. Roberfroid, Laboratory of Biotoxicology, Catholic University of Louvain, Brussels; Dr K. Szendrei, Department of Pharmacognosy, University Medical School, Szeged, Hungary and Dr V. Turusov, Oncological Research Centre, Moscow; supported in part by NCI Contract No. NOI-CP 43342)

Work has continued to characterize possible etiological agents associated with an increased risk of oesophageal cancer in areas around the world where opium is smoked or its pyrolysis products are ingested. Field studies carried out in the Caspian littoral in North-eastern Iran have revealed that chewing opium dross (sukhteh) is a common habit in both females and males in this region.

Microsome-mediated bacterial mutagenicity tests of opium dross samples have indicated the presence of potent mutagens. Crude opium itself is not mutagenic, but its pyrolysates or those of certain opium alkaloids such as morphine, are highly mutagenic, being many times more active than tobacco-smoke condensate.

Large amounts of pyrolysis products have been prepared from crude opium and morphine, and a large sample of opium dross has been collected in Iran. Organic solvent extracts of these three complex mixtures are at present undergoing a series of short- and long-term tests to investigate their genotoxic activity. These include: further tests for mutagenicity in *S. typhimurium* in the presence of either rodent liver cells or S-9 fractions; assessment of DNA damage and repair in hepatocytes or *in vivo*; detection of sister chromatid exchange and chromosomal aberration in Chinese hamster ovary (CHO) cells or lymphocytes; detection of morphological changes after treatment of rodent tracheal tissue in organ cultures; and the effect of the mixtures on the induction of drug-metabolizing enzymes in mice and rats.

The mixtures are also being tested for carcinogenicity in rodents, by transplacental administration in rats, and subcutaneous injection in mice. Their initiating and/or promoting effects are being tested on mouse skin and by intratracheal instillation in hamsters.

Efforts to isolate and identify biologically active compounds in the mixtures have concentrated on the highly mutagenic pyrolysis products of morphine, of which the mutagenic activity

[82] Parodi, S., Taningher, M., Santi, L., Cavanna, M., Sciaba, L., Maura, A. A. & Brambilla, G. (1978) *Mutat. Res.*, **54**, 39–46.

[83] Petzold, G. L. & Swenberg, J. A. (1978) *Cancer Res.*, **38**, 1589–1594.

was shown to vary with its nitrogen content. Mass spectrometric data were also consistent with the presence of aromatic nitrogen-containing compounds. Cycloartenol (Fig. 8, I) and a sterol mixture containing β-sitosterol, campesterol and stigmasterol were isolated from opium and poppy straw and were submitted for pyrolysis and mutagenicity tests.

The same sterol-type compounds were detected in opium dross in much smaller quantities, indicating their possible decomposition during combustion.

As a possible alternative source for mutagenic pyrolytic products, the compounds derived by oxidative decomposition of morphinane-type alkaloids were studied. The initial decomposition product was strongly fluorescent, and was characterized as being 10-oxomorphine (Fig. 8, II). It was also detected in small amounts in both crude opium and opium dross. The compound will be submitted for mutagenicity tests when sufficient quantities become available.

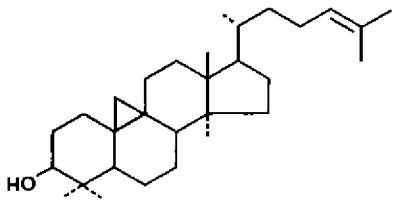

Fig. 8.I The structure of cycloartenol.

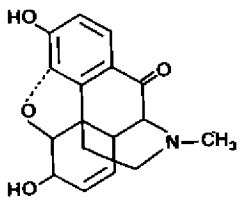

Fig. 8.II The structure of 10-oxomorphine.

4.4 *Analysis of environmental carcinogens, evaluation and development of methods*

The overall objectives of this programme are two-fold. First, the elaboration, perfection and standardization of analytical methods for the detection of known carcinogens, and, second, the determination of the relation between human cancer incidence and exposure to endogenously-formed or exogenous carcinogens. Approaches towards those goals include the collection of data on the occurrence of chemical carcinogens in the human environment and in human body fluids of subjects living in areas with differing cancer incidence.

(*a*) *Analysis of environmental samples*

(i) *International mycotoxin check sample programme* (Dr M. Friesen, Mrs L. Garren and Miss Y. Granjard) (Supported in part by the Food and Drug Administration, USA, under Contract No. NO1 CP 55630 with the National Cancer Institute, USA, and, in part, by the Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme)

It is important for laboratories carrying out routine analysis of contaminants in foodstuffs to control periodically the quality of their analytical results, and for aflatoxins such a service has been made available through the International Mycotoxin Check Sample Survey Programme[84]. Any

[84] Friesen, M. D., Walker, E. A. & Castegnaro, M. (1980) *J. Assoc. off. anal. Chem.*, 63, 1057–1066.

laboratory wishing to compare its analytical results with those of a large group of laboratories using the same or different methodology may participate without charge. Individual results are not released to other participants. Apart from quality control of results, their statistical analyses assist in the comparison of different methods or analytical techniques.

In the current series, 123 laboratories in 31 countries participated in the analysis of samples of raw peanut meal, deoiled peanut meal, and yellow corn meal (maize) for aflatoxins B_1, B_2, G_1 and G_2; 80 laboratories in 30 countries analysed lyophilized milk for aflatoxin M_1; and 40 laboratories in 21 countries, animal feed (barley) for ochratoxin A. The frequency distribution of results for the analysis of aflatoxin M_1 in milk, a new programme this year, is shown in Fig. 9.

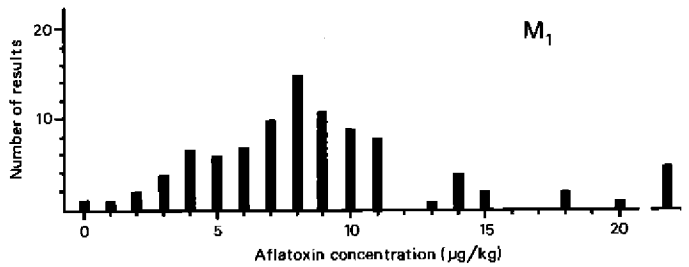

Fig. 9 Frequency distribution of results for analysis of aflatoxin M_1 in lyophilized milk.

A sub-group of laboratories also participated as a part of the UNEP sponsored Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme to help verify the quality of results generated by the programme's collaborating centres around the world.

(ii) *Volatile nitrosamines in environmental samples* (Dr M. Castegnaro and Miss M.-C. Bourgade, in collaboration with Dr R. Scriban, National College of the Agricultural and Food Industries (ENSIA), Douai, France; the Association of Official Analytical Chemists (AOAC); and Mr L. Charpenet, Science Faculty, St-Cyr-l'Ecole, France)

Phase II of the collaborative study (Dr R. Scriban) to determine nitrosamines in malt samples using the technique of extraction from wort has been completed. Each laboratory received 5 samples (two duplicates and one blank for calibration). Statistical evaluation of the results showed large variations (about 40% at the 6.5 µg/kg level and 25% at the 23 µg/kg level), indicating a lack of sensitivity, especially when applied to malt samples with low levels of nitrosamines.

AOAC has organized a collaborative study of a method for detection of trace levels of volatile nitrosamines in beer. The Agency was involved in this programme, the results of which will be published in the near future. The Agency was also asked to participate in the AOAC board for organizing further studies on other foodstuffs.

Regular analyses for the presences of volatile nitrosamines and aflatoxin B have been performed four times during the year on animal feed received at the Agency. The concentration of carcinogens that were detected ranged from 1.5 to 4 µg/kg for nitrosodimethylamine. No aflatoxins were detected.

A pilot study (Mr L. Charpenet) is in progress to determine suitable sampling conditions for volatile nitrosamines which avoid artefact formation, in exhaust gas from diesel engines.

(iii) *Polycyclic aromatic hydrocarbons (PAH)* (Dr I. K. O'Neill, Dr M. Castegnaro and Mrs L. Garren, in collaboration with Dr P. Grover, Chester Beatty Research Institute, London)

PAH has long been associated with human occupational cancer, but studies to assess PAH exposure of humans, and its storage in fat tissues in the general population have not been carried out. Breast tissue samples were obtained from several healthy women undergoing cosmetic size-reduction of over-large breasts. Extraction and analysis for PAH is now in progress.

(*b*) *Development of methods for quantitative estimation of* N-*nitrosation* in vivo

(i) *Monitoring* N-*nitrosamino acids excreted in the urine and faeces of rats as an index for endogenous nitrosation* (Mr H. Ohshima, Mr J.-C. Bérézíat and Miss M.-C. Bourgade)

Although formation of *N*-nitroso compounds has been studied under *in vitro* conditions, the lack of a suitable method for estimating endogenous *N*-nitrosation has hindered attempts to investigate this reaction under *in vivo* conditions. A simple and sensitive procedure has been developed for quantitative estimation of *N*-nitrosation *in vivo* in rats. The procedure is based on the findings that *N*-nitrosamino acids [*N*-nitrosoproline (NPRO), *N*-nitrosohydroxyproline (NHPRO), and *N*-nitrososarcosine (NSAR)] administered orally to rats are excreted unchanged almost quantitatively in the urine and faeces. Sequential administration to rats of aqueous solutions of a nitrosatable amino acid and sodium nitrite, was followed by determination of the nitrosamino acid that had been formed *in vivo* and excreted in the urine and faeces. The kinetics of this endogenous *N*-nitrosation has been studied, and the amounts of NPRO excreted in the urine of rats receiving trace amounts of proline and nitrite was shown to be proportional to the amount of proline administered and to the square of the amount of nitrite. Ascorbic acid or α-tocopherol, given together with the precursors, significantly reduced the urinary levels of NPRO, which increased when thiocyanate was administered. Thus the amounts of *N*-nitrosamino acids excreted in the urine and faeces appeared to reflect well *in vivo N*- nitrosation: similarly the results obtained from *in vivo* experiments in rats were all in good agreement with those of the *in vitro* experiments, proving that the nitrosation reaction in animals occurred in a similar manner to that of *in vitro* reaction. The newly developed method is currently being used to study the endogenous formation of *N*-nitroso compounds in rats related to various physiological and environmental conditions such as the pH of gastric juice, transnitrosation *in vivo* and role of bacteria.

(ii) *The influence of catalysts/inhibitors on the formation of* N-*nitroso compounds* in vivo *and* in vitro (Dr B. Pignatelli, Dr I. K. O'Neill and Mr J.-C. Bérézíat, in collaboration with Professor G. Descotes, Claude-Bernard University and the College for Industrial Chemistry, Lyon, France; and Professor R. Scriban, National College of the Agricultural and Food Industries (ENSIA), Douai, France; supported by the Directorate-General for Research, Science and Technology, France)

Phenolic compounds, which can potentially form *C*-nitroso derivatives by reaction with nitrite, can act as catalysts in the formation of *N*-nitrosodiethylamine (NDEA); by contrast, those which are readily oxidized by nitrous acid can act as nitrite scavengers, inhibiting NDEA forma-

tion[85]. As many naturally-occurring polyphenols are widely distributed in commonly consumed food and beverages, a study has been undertaken to determine whether phenolic compounds could catalyse or inhibit *in vivo* formation of *N*-nitroso compounds.

The effect of resorcinol, catechin, and chlorogenic acid on the formation of NPRO were measured in both *in vitro* and *in vivo* experiments. The variation with pH of the amount of NPRO formed *in vitro* was measured under normal conditions, and also in the presence of these phenolic compounds. Resorcinol and catechin both acted as catalysts over the range of pH 2.2–5; chlorogenic acid acted as an inhibitor. Both uncatalyzed and catalyzed reactions were strongly pH dependent. In all cases, the optimum pH for *N*-nitrosation was about pH 2.5 although the most potent catalytic effect was exerted at pH 4. The inhibition of NPRO formation by chlorogenic acid was most marked at pH < 4.

The effect of concentration of resorcinol and catechin on the catalytic effect was also studied *in vitro*. It was found that there was an optimum ratio of the concentration of nitrite to the concentration of the catalyst, being 4 for resorcinol, and 5 for catechin.

The two precursors (aqueous proline followed by aqueous nitrite) were then administered to rats with or without phenolic compounds included in the proline solution. The solutions of precursors were buffered to pH 4. The mean enhancement of yield of NPRO in the presence of resorcinol reached 18.7-fold and with catechin 7.7-fold. In the presence of chlorogenic acid the yield of NPRO was reduced by 50%. These preliminary results indicated that commonly-occurring polyphenolic compounds might have a significant effect on *in vivo* exposure to endogenously formed *N*-nitroso compounds.

(*c*) *Destruction of carcinogenic wastes from laboratories* (Dr M. Castegnaro)

The project includes five stages:

i) Collection of the bibliography related to methods of degradation and chemical reactivity of the compounds. ii) Evaluation of this bibliography and preparation of intermediate documents which include suggested methods. iii) Laboratory assay of the methods suggested in the literature and, where necessary, elaboration of new methods. iv) Finalization of the intermediate documents and organization of collaborative studies to ascertain the efficiency of the proposed methods. v) Critical review of the document in a meeting of experts and submission for final publication as an IARC Scientific Publication.

i) *Bibliographical research* (in collaboration with Mr H. Baxter, London)

The bibliography on the following compounds has been kept up-to-date: Polycyclic aromatic hydrocarbons, nitrosamines, nitrosamides, chloroethers, amino-fluorene derivatives, polychlorinated biphenyls and vinyl chloride.

A bibliographic collection is being established on aromatic amines, ozonisation techniques and aziridines.

ii) *Evaluation of the bibliography and preparation of individual monographs* (in collaboration with Mr E. A. Walker, London)

Intermediate documents on the decontamination of wastes contaminated by nitrosamines and by polycyclic aromatic hydrocarbons have been prepared. Another on hydrazines is in preparation.

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[85] Pignatelli, B., Friesen, M. D. & Walker, E. A. (1980) In: Walker, E. A. *et al.*, eds, *N-Nitroso Compounds: Analysis, Formation and Occurrence (IARC Scientific Publications No. 31)*, Lyon, pp. 95–106.

iii) *Assays and development of methods*

a) Aflatoxins (Dr M. Castegnaro, Miss J. Michelon, Mr C. Malaveille and Mrs I. Brouet)

A method for aflatoxin wate destruction using treatment with sodium hypochlorite followed by dilution and addition of acetone [62] has been tested. Complete degradation of aflatoxin M_1 was obtained. Mutagenicity assays have confirmed a complete inactivation after treatment of aflatoxins B_1, B_2, G_1, and G_2, and their products.

b) Nitrosamines (Dr M. Castegnaro, Miss J. Michelon, Mr C. Malaveille, Mrs I. Brouet, in collaboration with Dr E. Sansone, Frederick Cancer Research Center, Frederick, MD, USA)

Four methods have been tested for inactivation of various wastes contaminated by nitrosodimethylamine, nitrosodiethylamine, nitrosodipropylamine, nitrosodibutylamine, nitrosopiperidine, nitrosopyrrolidine, nitrosomorpholine and dinitrosopiperazine. These are: treatment with 3% hydrobromic acid in acetic acid; oxidation with potassium permanganate in sulfuric acid; rinsing with dichloromethane; and formation of salt with triethyloxonium tetrafluoroborate and further treatment with caustic soda.

Residues after treatment by the last method of *N*-nitrosodibutylamine have been tested in a mutagenicity assay, which was negative both for the dichloromethane extract and the neutralized residue.

Two other methods are being tested (Dr E. Sansone): reduction with a nickel: aluminium alloy in alkaline medium; and with copper(I) chloride in hydrochloric acid solution.

c) Polycyclic aromatic hydrocarbons (Dr M. Castegnaro and Miss J. Michelon)

The degradation of benzo(*a*)anthracene has been attempted by the following methods: action of saturated potassium permanganate solution; treatment with concentrated sulfuric acid; treatment with potassium permanganate in acid solution. Their effectiveness is being tested by mutagenicity assays.

d) Evaluation of catalytic pyrolysis as a degradation technique (Dr M. Castegnaro and Miss J. Michelon)

Catalytic pyrolysis has been tested as a method of decontaminating organic and aqueous effluents containing aflatoxins, but is not yet considered feasible as a routine technique.

e) Evaluation of the use of ozonisation as a decontamination technique (Dr M. Castegnaro, in collaboration with Dr P. Chambon, Faculty of Pharmacy, Lyon, France and Mr M. Legeron, "Trailigaz" General Ozone Co., Garges-les-Gonesse, France)

Ozonisation is being tested for its appicability to wastes contaminated with polycyclic aromatic hydrocarbons, aromatic amines, aflatoxins and polychlorinated biphenyls.

f) Nitrosamides (in collaboration with Dr C. L. Walters, British Food Manufacturers Industries Research Association, Leatherhead, UK)

Ammoniation and treatment with hydrobromic acid is being tested for the destruction of nitrosamides. The efficiency of destruction is being checked, by using hydrobromic acid to split any residual nitrosamines prior to TEA analysis.

g) Aromatic amines (in collaboration with the National Institute of Research and Safety (INRS), Paris)

The evaluation of published methods has started, and method development will be undertaken.

iv) *Initiation of collaborative studies* (in collaboration with Dr E. Sansone, Frederick Cancer Research Center, Frederick, MD, USA)

A collaborative study to validate methods of decontamination of nitrosamine-contaminated wastes is in progress. The study involves 8 laboratories in the Federal Republic of Germany, France, the Netherlands, UK and the USA.

v) *Final evaluation of document and publication*

The document on destruction of aflatoxin-contaminated wastes was revised by a review board (Lyon, October 1980) and has since been published[62].

(*d*) *Safe handling of aflatoxins and their solutions* (Dr M. Castegnaro, Miss J. Michelon, in collaboration with Dr P. L. Schuller and Dr H. P. Van Egmond, National Institute of Public Health, Bilthoven, the Netherlands)

The protective efficiency of latex gloves (wall thickness 0.1–0.14 mm and 0.6–0.8 mm) and vinyl gloves (0.8–1 mm) have been tested against aflatoxins in chloroform or dimethylsulfoxide (DMSO) solution. Both thick and thin latex gloves afforded good protection against permeation of aflatoxins in DMSO, but none of the types tested was entirely effective against the chloroform solution, and immediate change of gloves after such contamination would appear expedient.

(*e*) *Manual of selected methods of analysis of environmental carcinogens* (Dr I. K. O'Neill, Dr M. Castegnaro, in collaboration with Professor H. Egan, Laboratory of the Government Chemist, London) (Supported in part by UNEP Contract No. FP/0107-79-02 (2070))

Three review boards were convened (Table 10) by the editorial board to review methods for the analysis of mycotoxins, mineral fibres and metals. The sixth editorial board (Lyon, 9-10 October 1980) considered that high priority should be given to preparing manuals of analytical methods for: low molecular-weight halogenated compounds (such as solvents), chlorinated dioxins and pesticides, synthetic estrogens, benzene, and polycyclic aromatic hydrocarbons and their heterocyclic analogues. The last topic would be a revised edition of volume 3 in the series[86].

[86] Castegnaro, M., Bogovski, P., Kunte, H. & Walker, E. A., eds (1979) *Environmental Carcinogens—Selected Methods of Analysis*, Vol. 3, *Polycyclic Aromatic Hydrocarbons (IARC Scientific Publications No. 29)*, Lyon.

Table 10. Participants of the sixth editorial board and review boards for the manual of selected methods of analysis of environmental carcinogens

Sixth editorial board (9-10 October 1980)	
Prof. H. Egan (Chairman)	Prof. R. Preussmann
Prof. P. Bogovski	Prof. C. Rappe
Prof. E. Boyland	Dr. P.L. Schuller
Dr N. Crosby	Dr P. Scott
Dr L. Fishbein	Mr L. Stoloff
Dr M. Jemmali	Mr E.A. Walker
Review Boards	
Mycotoxins (8 October 1980)	
Mr L. Stoloff (Chairman)	Prof. C. Rappe
Dr N. Crosby	Dr P. Scott
Dr M. Jemmali	
Mineral Fibres (16 June 1981)	
Dr A. Critchlow (Chairman)	Dr P. Elmes
Mr N. Crawford	Dr A. Hodgson
Dr J.M. Dement	Dr P. Meyer
Some Elements and Their Compounds (17 June 1981)	
Dr P.L. Schuller (Chairman)	Dr L.E. Coles
Dr K. Boyer	Prof. H. Egan
Dr R. Coleman	Dr F.W. Sunderman, Jr.

The following volumes are being prepared:

i) *Aromatic amines* (Chariman of review board: Dr L. Fishbein, National Center of Toxicological Research, Jefferson, AR, USA)

ii) N-*Nitrosamines* (Chairman of review board: Professor R. Preussmann, German Cancer Research Center, Heidelberg, Federal Republic of Germany) This is a revised edition of volume 1 in the series[87].

iii) *Mycotoxins* (Chairman of review board: Mr L. Stoloff, Food and Drug Administration, Washington, D.C., USA)

iv) *Mineral fibres* (Chairman of review board: Dr A. Critchlow, Health and Safety Executive, Sheffield, UK)

v) *Some elements and their compounds* (Chairman of review board: Dr P. L. Schuller, National Institute for Public Health, Bilthoven, The Netherlands)
This volume will include methods of analysis for arsenic, chromium and nickel—all associated with the induction of human cancer—and for a group of suspected carcinogens or substances considered to modify the effect of carcinogens, including beryllium, cadmium, lead, selenium, zinc and molybdenum.

[87] Preussmann, R., Walker, E. A., Wasserman, A. E. & Castegnaro, M., eds (1978) *Environmental Carcinogens—Selected Methods of Analysis*, Vol. I, *Analysis of Volatile Nitrosamines in Food (IARC Scientific Publications No. 18)*, Lyon.

(*f*) *Seventh International Working Conference on* N-*nitroso Compounds: Occurrence and Biological Effects, Tokyo, 28 September–1 October 1981* (Dr I. K. O'Neill and Dr M. Castegnaro, in collaboration with Dr M. Okada, Chairman of the Japanese Organizing Committee) (Co-sponsored by the Japanese Cancer Society)

The proceedings of the 6th International Conference held in Budapest in October 1979 have now been published[88]. The next conference of the series (28 September–1 October 1981, in Tokyo) is being organized in collaboration with the Japanese Cancer Society and Dr M. Okada, Chairman of the Organizing Committee.

Seventy two papers were accepted by the selection committee held in Lyon (18–19 March 1981) for presentation at the meeting.

4.5 *Monitoring of human subjects for endogenous carcinogen formation and exposure*

The *in vivo* formation of *N*-nitroso compounds has been associated with an increased risk for cancer of the stomach, oesophagus and bladder, but in spite of the fact that compounds are recognized carcinogens for very many animal species, no convincing epidemiological evidence of the etiological role of these compounds in any human cancer has been presented. One of the reasons is the lack of simple, reliable methods to estimate the extent of the *in vivo* formation of *N*-nitroso compounds. Now, however, the recently developed method of measuring the levels of *N*-nitrosoproline formation and excretion after ingestion of known amounts of precursors, may make this possible.

The endogenous formation of *N*-nitroso compounds will be measured in patients with precursor lesions of gastric and oesophageal cancer, and in healthy controls, living in areas with high and low incidences for these cancers.

Analyses are being performed for the presence of mycotoxins in urine specimens of patients in Vratza district, Bulgaria, affected by Balkan nephropathy and at risk for urinary tract cancer.

Urine samples collected from men and women in northern Iran who had ingested opium pyrolysates, are being tested for the presence of mutagenic morphine metabolites.

(*a*) *Quantitative estimation of endogenous nitrosation in man by monitoring* N-*nitrosoproline excreted in the urine* (Mr H. Ohshima and Miss M.-C. Bourgade)

Using a sensitive and selective chemiluminescence detection method, the urinary levels of *N*-nitrosoproline (NPRO) were monitored as an index for *N*-nitrosation *in vivo* (see p. 37) in man, after ingestion of a standard diet consisting of vegetable juice as a source of nitrate and an amino acid, proline. NPRO has been reported not to be carcinogenic or mutagenic[89, 90] and to be excreted unchanged in the urine almost quantitatively after its oral administration to rats (see p. 104). This procedure is being applied to assess human exposure to endogenously formed *N*-nitroso compounds in high risk populations or human subjects.

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[88] Walker, E. A., Castegnaro, M., Griciute, L. & Börzsönyi, M., eds (1980) N-*Nitroso Compounds: Analysis, Formation and Occurrence (IARC Scientific Publications No. 31)*, Lyon.

[89] International Agency for Research on Cancer (1978) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 17: *Some* N-*Nitroso Compounds*, Lyon.

[90] Mirvish, S. S., Bulay, O., Runge, R. G. & Patil, K. (1980) *J. natl Cancer Inst.*, **64**, 1435–1440.

(i) *Endogenous formation of* N-*nitroso compounds in patients with precursor lesions of stomach cancer*—

—*in Finland* (Mr H. Ohshima, Miss M.-C. Bourgade and Dr A. Aitio, in collaboration with Dr S. Viikari, Dr M. Inberg and Dr A. Lehtonen, Clinics of Surgery and Medicine, University of Turku, Finland) (RA/81/006)

Gastric achlorhydria has been associated with an increased risk of stomach cancer. In particular the increased frequency has been observed in patients with pernicious anaemia[91] or in patients who have undergone gastric surgery such as Billroth-II gastrectomy and gastroenterostomy[92]. It has been postulated that achlorhydric stomach found in such patients may provide a suitable milieu for intragastric formation of *N*-nitroso compounds by virtue of its high concentration of nitrite and the presence of large numbers of bacteria[93, 94].

However, the conversion of nitrate to nitrite and subsequent nitrosation in the colonized stomach have not yet been unequivocally demonstrated. In collaboration with Turku University Hospital, *N*-nitrosation capacity *in vivo* in such high risk patients is now being assessed by using the new procedure. Patients with pernicious anaemia, with gastric ulcer, and with duodenal ulcer are being given vegetable juice as a source of nitrate and then amino acid, proline. The 24-hour urine samples are being analysed for *N*-nitrosoproline and the results will be correlated with gastric pH, concentrations of nitrate and nitrite and bacteria count.

—*in Italy* (Mr H. Ohshima, Miss M.-C. Bourgade and Dr N. Muñoz, in collaboration with Dr M. Crespi, Regina Elena Institute, Rome)

It has been suggested that chronic atrophic gastritis (CAG) is a precursor lesion for the intestinal type of stomach cancer and that formation of *N*-nitroso compounds in achlorhydric stomach may play an important role in gastric carcinogenesis[93]. Biological evidence for intragastric *N*-nitrosation in these patients is being sought, using the NPRO procedure. Results will be compared with those of control subjects without any atrophic changes in the mucosa.

(ii) *Evaluation of human exposure to* N-*nitroso compounds and nitrate in high risk areas of oesophageal cancer in the People's Republic of China* (Mr H. Ohshima, Miss M.-C. Bourgade and Dr N. Muñoz, in collaboration with Dr Li Ping and Dr Lu Shih Hsin, Cancer Institute, Chinese Academy of Medical Sciences, Beijing)

In order to study a possible association between ingestion or *in vivo* formation of *N*-nitroso compounds and oesophageal cancer in northern China, 24-hour samples of urine were collected in the high and low incidence areas of the cancer (see p. 37), and analysed for nitrate/nitrite and *N*-nitroso compounds. The results obtained will be correlated with the presence or absence of precancerous lesions of the oesophagus.

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[91] Blackburn, E. K., Callender, S. T., Dacie, J. V., Doll, R., Girdwood, R. H., Mollin, D. L., Saracci, R., Stafford, J. L., Thomson, R. B., Varadi, S. & Wetherley-Mein, G. (1968) *Int. J. Cancer*, 3, 163–170.

[92] Stalsberg, H. & Taksdal, S. (1971) *Lancet, ii*, 1175–1177.

[93] Correa, P., Haenszel, W., Cuello, C., Tannenbaum, S. & Archer, M. (1975) *Lancet, ii*, 58–59.

[94] Ruddel, W. S. J., Bone, E. S., Hill, M. J., Blendis, L. M. & Walters, C. L. (1976) *Lancet, ii*, 1037–1039.

(iii) *Endogenous formation of* N-*nitroso compounds in patients or healthy volunteers after oral administration of large amounts of nitrate* (Mr H. Ohshima and Miss M.-C. Bourgade, in collaboration with Dr P. L. Schuller and Dr G. Ellen, National Institute of Public Health, Bilthoven, The Netherlands)

Persons who tend to develop calcium phosphate renal stones can be protected by daily administration of gram amounts of ammonium nitrate (NH_4NO_3). These high loads of nitrate may lead to *in vivo* formation of *N*-nitroso compounds, and so 24-hour samples of urine are being collected from these patients and from healthy volunteers who are given orally 5–10 g of NH_4NO_3 at a time, or 5–10 g of $NaNO_3$ intravenously in about 30 min., followed by an aqueous solution of 100–500 mg proline. Urinary excretion of NPRO is being monitored as an index for endogenous *N*-nitrosation.

(*b*) N-*Nitrosamines in gastric juice, blood and urine in relation to stomach cancer and precancerous lesions* (Dr M. Castegnaro, Dr B. Pignatelli, Mr H. Ohshima, Miss M.-C. Bourgade, and Dr N. Muñoz, in collaboration with Dr M. Crespi, Regina Elena Institute, Rome, and Dr C. L. Walters, British Food Manufacturing Industries Research Association (BFMIRA), Leatherhead, UK)

Specimens of gastric juice, blood, and urine were collected from 62 patients with CAG and from 22 patients with a normal gastric mucosa or with superficial gastritis, and volatile nitrosamines and nitrite in the specimens have been determined. Higher levels of volatile nitrosamines were found more often in the gastric juice of patients with CAG than in control subjects[95]. Because of the possible artefact formation of volatile nitrosamines, the study will be repeated, using a different, more reliable method.

(*c*) *Nitrosamines and mycotoxins in urine in relation to nephropathy and bladder cancer* (Dr M. Castegnaro and Miss M.-C. Bourgade, in collaboration with Dr I. N. Chernozemsky, National Institute of Oncology, Sofia)

Consumption of ochratoxin A has been associated with nephropathy and renal cancer in some strains of animals. In view of the geographical correlation between the occurrence of endemic nephropathy and urinary tract tumours in Vratza district in Bulgaria, a pilot study is being undertaken to look for ochratoxin A in food, and for its metabolites in the urine of subjects living in this area.

[95] Walker, E. A., Castegnaro, M., Pignatelli, B., Muñoz, N. & Crespi, M. (1980) In: Walker, E. A., Castegnaro, M., Griciute, L. & Börzsönyi, M., eds, N-*Nitroso Compounds: Analysis, Formation and Occurrence (IARC Scientific Publications No. 31)*, Lyon, International Agency for Research on Cancer, pp. 633–641.

(*d*) *Mutagens and morphine metabolites in the urine of human subjects ingesting opium pyrolysates in Iran, and their drug metabolizing capacity* (Dr H. Bartsch and Dr N. Day, in collaboration with Dr C. Gorodetzky, National Institute on Drug Abuse, Lexington, KY, USA; Professor M. R. Roberfroid, Laboratory of Biotoxicology, Catholic University of Louvain, Brussels) (Supported in part by Contract No. 01–CP–77048 of the National Cancer Institute, Bethesda, MD, USA)

The activity of hepatic mixed function oxidases, which play a role in activating or detoxifying chemical carcinogens and mutagens which are ingested, have been determined in samples of saliva collected in areas of high and low incidence of oesophageal cancer in Iran.

The half-life of antipyrine in the saliva was measured in 212 samples collected 4, 12 and 24 hours after a single dose of antipyrine had been given orally to young and adult residents of either the high or low incidence areas. The antipyrine concentration in the saliva was measured by the radioimmunoassay developed by Chang[69] (the antibodies against antipyrine were kindly supplied by Dr A. Wood, Hoffmann-La Roche Institute for Molecular Biology, Nutley, NJ, USA)

One hundred and twenty four (58.5%) of the 212 samples gave interpretable results which could be used to estimate antipyrine half-life.

Literature data indicate that the average value of antipyrine half-life is 9–16 h in human saliva or serum. In the present study, 34% were less than 9 h; 45%, 9–16 h, and 21% higher than 16 h, reaching values as high as 25 h. These data indicate that half the population tested had normal levels of mixed function oxidase activity, one third were fast metabolizers, and one fifth, slow.

4.6 *Research training and visiting fellows*

Technical advice and training on methods in mutagenicity testing was given to nine visiting scientists from national laboratories.

PROGRAMME OF RESEARCH TRAINING AND LIAISON

Dr W. Davis (Head)

1. INTRODUCTION

The training role of the Agency, one of its designated "permanent activities", is now closely focussed on the task of stimulating an interest and developing expertise in those aspects of cancer research, which make up the Agency's own programmes. Four epidemiologically-orientated courses and one on chemical carcinogenesis in the last year, have imposed a heavy teaching load on the scientific staff of the Agency, in spite of the major contribution made to the planning and execution of the courses, by scientists from outside the Agency. Nevertheless, the successful development of the plans to continue educational activity in all the Regions of WHO, with special emphasis on aspects of the epidemiology of cancer, will depend first and foremost on the readiness of the scientific staff of the two Divisions to devote time and thought to the preparation of the programme of specialized courses.

At the outset of the fellowships programme, in 1966, it was envisaged that when the possibility presented itself, when the Agency's own research activities got underway, fellows should be encouraged to seek their research training in the Agency itself. Now that the fellowships programme is restricted to awards only in the fields of environmental carcinogenesis, and epidemiology and biostatistics, the demand for research training places in the laboratories and epidemiological offices of the Agency has increased sharply, and some pre-selection has been essential to advise applicants whether to maintain their request to study in Lyon, or whether to seek host laboratories outside of the Agency. This year two research training fellows worked in the Division of Epidemiology and Biostatistics, and next year, out of 13 awards, there will be one fellow in the Programme of Descriptive Epidemiology, and four in the Division of Environmental Carcinogenesis. Three applicants this year, for whom no laboratory space could be made available in Lyon, were successfully placed in laboratories that collaborate closely with the Agency's research activity.

Travel costs and cost-of-living-linked stipends have increased between 1966 and 1981, so that the cost of a person-year of fellowship has more than tripled over the period. Although the budget allocation for fellowships has increased steadily, the number of awards is now half of what it was in 1966. The sharp increase in bench and course fees in a number of countries has placed an additional charge on the fellowships' budget.

2. RESEARCH TRAINING FELLOWSHIPS

2.1 *The Fellowships Selection Committee*

The Fellowships Selection Committee met in Lyon, 13–14 April 1981, to review applications for Research Training Fellowships. The members of the committee were:

Dr T. Kuroki	Department of Pathobiochemical Cell Research, University of Tokyo, Tokyo *(chemical carcinogenesis)*
Dr R. Kroes	Director, TNO Division for Nutrition and Food Research, Zeist, The Netherlands *(chemical carcinogenesis)*
Dr V. B. Okulov	N. N. Petrov Research Institute of Oncology, Leningrad, USSR *(immunology)*
Dr T. J. Slaga	Cancer & Toxicology Program, Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, USA (Representative of the UICC Programme on Fellowships & Personnel Exchange) *(chemical carcinogenesis)*

Dr Slaga was attending for the first time, and Dr B. G. Mansourian, Office of Research Promotion and Development, WHO, Geneva, again participated in the work of the meeting.

2.2 *Fellowships awarded*

Out of 73 applications received, 35 were ineligible, mostly because the scientific disciplines fell outside the present scope of the programme. The committee recommended 13 awards out of the 38 applications it received. Of these, five were for fellowships tenable at the Agency. The distribution by discipline is given in Table 1.

2.3 *Isabelle Decazes de Noüe prize*

No further prizes have been provided by the Foundation.

Table 1. Distribution of research training fellowships by scientific discipline, 1981

Scientific discipline	No. of fellowships
Cell biology	1
Chemical carcinogenesis	2
Environmental carcinogenesis	2
Epidemiology & biostatistics	2
Experimental carcinogenesis	6

3. SPECIALIZED COURSES

3.1 *Epidemiological Approach to Occupational Cancer, Lyon, 28 July–1 August 1980*

Because of the exceedingly heavy demand for places in the course held in March 1980[1], a similar course was organized in which places were offered to those who were unable to find places in the first course. The programme was co-ordinated by Dr R. Saracci; the external faculty were: Professor P. Cole (Department of Public Health, University of Alabama, Birmingham, AL, USA), Dr M. Gardner (MRC Environmental Epidemiology Unit, University of Southampton, UK), Professor F. D. K. Liddell (Department of Epidemiology and Health, McGill University, Montreal, Canada), Dr R. Murray (consultant in occupational health, London), Mr J. T. Sanderson (Industrial Hygiene Adviser, ESSO Europe Inc., London). Dr N. E. Day, Dr C. S. Muir and Mr J. D. Wilbourn from the Agency's staff were also members of the teaching faculty.

There were 48 participants from 15 countries.

3.2 *Aspects of Chemical Carcinogenesis, Lyon, 3-8 November 1980*

The course, the first to be held for three years on this topic, was co-ordinated by Professor M. F. Rajewsky (Institute for Cell Biology [Tumour Research], University of Essen, Federal Republic of Germany). The teaching faculty included Professor W. Doerfler (Genetics Institute, University of Cologne, Federal Republic of Germany), Professor C. Heidelberger (Kenneth Norris Jr Cancer Research Institute, University of Southern California, Los Angeles, CA, USA), Professor Marian Hicks (School of Pathology, Middlesex Hospital School of Medicine, London), Professor T. Lindahl (Department of Medical Biochemistry, University of Göteborg, Sweden), Dr P. J. O'Connor (Paterson Laboratories, Christrie Hospital and Holt Radium Institute, Manchester, UK), Mr J. Peto (ICRF Cancer Epidemiology and Clinical Trials Unit, University of Oxford, UK), Professor J. Pontén (Wallenberg Laboratory, University of Uppsala, Sweden), Professor H. zur Hausen (Institute of Virology, Albert-Ludwig's University, Freiburg-im-Breisgau, Federal Republic of Germany) and Dr H. Bartsch, Dr M. Friesen, Dr J. Higginson, Dr R. Montesano, Dr C. S. Muir, Dr R. Saracci, Dr L. Tomatis and Dr J. Wahrendorf, from the Agency's scientific staff.

48 scientists from 19 countries participated in the course.

3.3 *Regional Course on Cancer Epidemiology with Special Emphasis on Cancer Registration, Limassol, Cyprus, 17–29 November 1980*

This was the second course organized jointly with the Regional Office for the Eastern Mediterranean. The first joint course was held in Karachi in 1977[2].

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[1] International Agency for Research on Cancer (1980) *Annual Report 1980*, Lyon, p. 148.
[2] International Agency for Research on Cancer (1978) *Annual Report 1978*, Lyon, p. 115.

The teaching faculty included: Professor M. R. Alderson (Division of Epidemiology, Institute of Cancer Research, London), Professor P. Cole (Department of Public Health, University of Alabama, Birmingham, AL, USA), Dr J. Osborn (Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, London), Professor D. Trichopoulos (Department of Hygiene and Epidemiology, University of Athens), and Dr N. Muñoz and Dr W. Davis from the Agency.

There were 20 participants from 15 countries.

3.4 *Regional Course on Epidemiology of Non-Communicable Diseases with Emphasis on Cancer, Ndola, Zambia, 11–29 May 1981*

This was the first occasion on which the Agency has collaborated with the Regional Office for Africa to organize an epidemiology course. This course was destined to the anglophone countries. Two years hence, a similar course is foreseen for the francophone countries of the African Region. The Agency was greatly assisted in the local organization by Dr E. K. Njelesani, Director of the WHO Tropical Diseases Research Centre, Ndola, and his staff, and also by the Principal Tutor, Miss D. McCahon, and the staff of the Ndola School of Nursing, where the course was held.

The teaching faculty included: Dr S. Grufferman (Unit of Epidemiology and Biostatistics, Duke University Medical Center, Durham, NC, USA), Mr S. Lwanga (WHO Tropical Diseases Research Centre, Ndola, Zambia), Dr R. H. Morrow (Parasitic Diseases Programme, WHO, Geneva), Dr C. Olweny (Uganda Cancer Institute, Kampala), Professor R. Owor (Department of Pathology, Makerere University, Kampala), Mr P. Smith (Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, London), Dr F. Wurapa (WHO Tropical Diseases Research Centre, Ndola, Zambia), and Dr C. S. Muir and Dr W. Davis from the Agency).

There were 26 participants from 9 countries in the African Region.

3.5 *Short Course on Statistical Methods in Cancer Epidemiology, Lyon, 29 June–3 July 1981*

This course, which was the first of its kind organized by the Agency, aroused a great deal of interest and more than a hundred applications were received for places in the course. Unfortunately, this meant that a considerable number were disappointed, but it is intended to hold a similar course next year.

The programme was prepared and co-ordinated by Dr N. E. Day. Other members of the teaching faculty included: Professor N. E. Breslow (Department of Biostatistics, University of Washington, Seattle, WA, USA), Dr D. Hémon (Epidemiological and Statistical Research Unit, INSERM, U170, Villejuif, France), Mr. J. Peto (ICRF Cancer Epidemiology and Clinical Trials Unit, University of Oxford, UK), Mr P. Smith (Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, London), and Dr J. Estève, Dr R. Saracci and Dr J. Wahrendorf from the Agency.

47 participants from 25 countries attended the course.

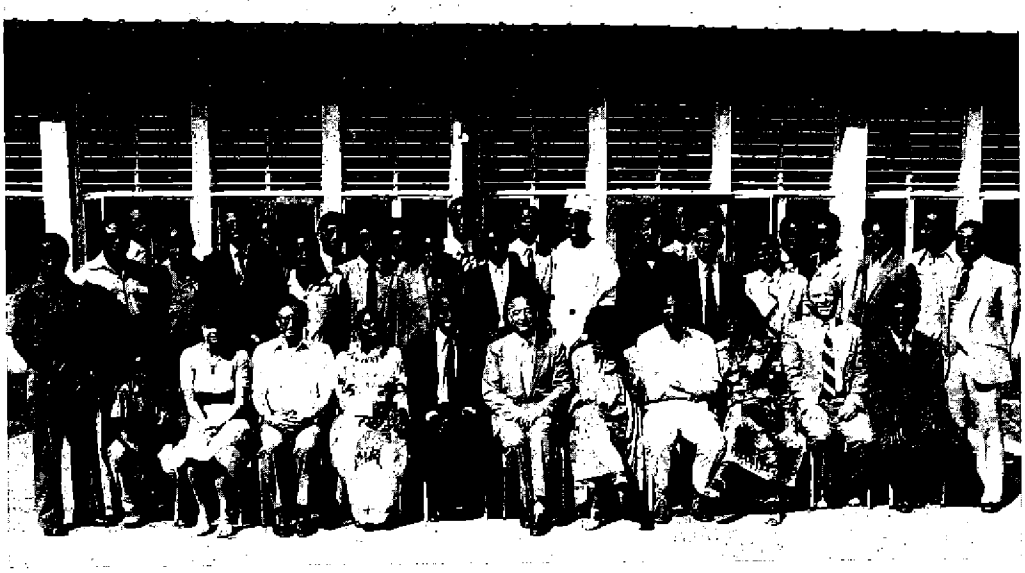

Fig. 1 Teaching faculty and participants of the epidemiology course in Ndola, Zambia, 11–29 May 1981.

3.6 *Future courses*

The courses planned for 1981–1982 include: epidemiology of cancer (in Spanish), Bogotá, 2–13 November 1981; epidemiology of cancer, Bombay, India, 11–30 January 1982; epidemiology of cancer, Warsaw, 21 June–3 July 1982; epidemiology of cancer, Eastern Mediterranean Region, October 1982; epidemiological aspects of occupational cancer, Kitakyushu, Japan, November 1982.

4. SYMPOSIA

4.1 *Host Factors in Human Carcinogenesis, Cape Sounion, Greece, 8–11 June 1981*

With the support of the Ministry of Welfare and Science of Greece, and the Directorate-General for Research, Science and Education of the Commission of European Communities, the Agency held a symposium on host factors in human carcinogenesis, with the participation of just over one hundred scientists. Forty-nine papers were presented during the symposium, and will be published as an IARC Scientific Publication.

5. PUBLICATIONS

The list of new titles appearing in the *IARC Scientific Publications* series this year includes:

N-*Nitroso Compounds: Analysis, Formation and Occurrence* (1980)

Directory of On-going Research in Cancer Epidemiology 1980 (1980)

Biological Effects of Mineral Fibres, Volumes 1 and 2 (1980)

Statistical Methods in Cancer Research, Vol.1 The Analysis of Case-Control Studies (1980)

There are three titles in press:

Pathology of Tumours in Laboratory Animals, Vol. III *Tumours of the Hamster* (1981)

Cancer Mortality by Occupation and Social Class (1851–1971) (1981)

Environmental Carcinogens—Selected Methods of Analysis Vol. IV: *Analysis of Aromatic Amines* (1981)

and in preparation:

Host Factors in Human Carcinogenesis (1981)

N-*nitroso Compounds: Occurrence and Biological Effects* (1982)

Laboratory Decontamination and Destruction of Nitrosamines in Laboratory Wastes (1981)

The complete list of publications is given in Table 2.

The figures for the distribution and sales of scientific publications and monographs is given in Table 3.

6. LIBRARY (Mrs A. Nagy-Tiborcz)

The library provided a service to the scientific staff of the Agency and to the local medical and scientific community. Close liaison is maintained with the library of WHO Headquarters and the library of the Medical Faculty in Lyon.

At present, there are 240 subscriptions to journals and annuals. Thanks to a large anonymous donation, which has been devoted to the purchase of books for the library, the book stock is now approximately 4800.

7. INTERDISCIPLINARY SUPPORT SERVICES

7.1 *Computerized bibliographic service* (Mrs M. Soulat)

The use of the terminal, giving access to the computerized bibliographic files of the National Library of Medicine, USA, has increased. A total of 285 searches were made, taking 94 hours of search-time. There were 105 off-line searches requested and 147 regular monthly up-datings are made.

The use of the terminal is supported by contracts with the National Cancer Institute (Bethesda, MD, USA) to the *Clearing-house for On-going Research in Cancer Epidemiology* and to the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.*

7.2 *Scientific illustrations group*

The photographic and drawing services continue to provide an efficient service for the preparation of illustrations for publications, and slides for lectures; the other aspects of the photographer's work for the laboratories continues.

8. COORDINATING COMMITTEE FOR HUMAN TUMOUR INVESTIGATIONS

The Ninth International Symposium on the Biological Characterization of Human Tumours will be held in Bologna, Italy, from 23–27 September 1981. It has the overall title of "The Control of Tumour Growth and Its Biological Bases", and a total of 85 main lectures and proffered papers have been submitted.

Table 2. List of *IARC Scientific Publications*

No.	*Title*	*Year of Publication*
1	Liver Cancer	1971
2	Oncongenesis and Herpesviruses	1972
3	N-Nitroso Compounds – Analysis and Formation	1972
4	Transplacental Carcinogenesis	1973
5	Pathology of Tumours in Laboratory Animals, Vol. 1: The Rat, Part 1	1973
6	Pathology of Tumours in Laboratory Animals, Vol. 2: The Rat, Part 2	1976
7	Host-Environment Interactions in the Etiology of Cancer in Man	1973
8	Biological Effects of Asbestos	1974
9	N-Nitroso Compounds in the Environment	1974
10	Chemical Carcinogenesis Essays	1974
11	Oncogenesis and Herpesviruses II – Parts 1 and 2	1975
12	Screening Tests in Chemical Carcinogenesis	1976
13	Environmental Pollution and Carcinogenic Risks	1976[a]
14	Environmental N-Nitroso Compounds – Analysis and Formation	1976
15	Cancer Incidence in Five Continents, Vol. III	1976
16	Air Pollution and Cancer in Man	1977
17	Directory of On-going Research in Cancer Epidemiology, 1977	1977[b]
18	Environmental Carcinogens – Selected Methods of Analysis, Vol. I: Nitrosamines	1978
19	Environmental Aspects of N-Nitroso Compounds	1978
20	Nasopharyngeal Carcinoma: Etiology and Control	1978
21	Cancer Registration and its Techniques	1978
22	Environmental Carcinogens – Selected Methods of Analysis Vol. II: Vinyl Chloride	1978

No.	Title	Year of Publication
23	Pathology of Tumours in Laboratory Animals, Vol. 2: The Mouse	1978
24	Oncogenesis and Herpesviruses III – Parts 1 and 2	1978
25	Carcinogenic Risks – Strategies for Intervention	1978[a]
26	Directory of On-going Research in Cancer Epidemiology, 1978	1978[b]
27	Carcinogen Screening Tests – Molecular and Cellular Aspects	1979
28	Directory of On-going Research in Cancer Epidemiology, 1979	1979[b]
29	Environmental Carcinogens – Selected Methods of Analysis, Vol. II: Polycyclic Aromatic Hydrocarbons	1979
30	Biological Effects of Mineral Fibres, Parts 1 and 2	1980[a]
31	N-Nitroso Compounds: Analysis, Formation and Occurrence	1980
32	Statistical Methods for Cancer Epidemiology, Vol. I: The Analysis of Case-Control Studies	1980
33	Handling Chemical Carcinogens in the Laboratory: Problems of Safety	1980
34	Pathology of Tumours in Laboratory Animals, Vol. III: The Hamster	1982[c]
35	Directory of On-going Research in Cancer Epidemiology, 1980	1980[b]
36	Cancer Mortality by Occupation and Social Class (1851-1971)	1981[e]
37	Laboratory Decontamination and Destruction of Aflatoxins B_1, B_2, G_1, G_2 in Laboratory Wastes	1980
38	Directory of On-going Research in Cancer Epidemiology, 1981	1981[b]
39	Host Factors in Human Carcinogenesis	1981[d]
40	Environmental Carcinogens – Selected Methods of Analysis, Vol. IV: Analysis of Aromatic Amines	1981[c]
41	N-Nitroso Compounds: Occurrence and Biological Effects	1982[d]
42	Cancer Incidence in Five Continents, Vol. IV	1981[d]
43	Laboratory Decontamination and Destruction of Nitrosamines in Laboratory Wastes	1981[d]
	Non-Serial Publications	
	Alcool et Cancer	1978
	Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 8	1978
	Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 9	1981
	Cancer Morbidity and Causes of Death Among Danish Brewery Workers	1980

[a] joint publication with INSERM
[b] joint publication with DKFZ
[c] in press
[d] in preparation
[e] joint publication with HMSO

Table 3. Distribution of *IARC Scientific Publications* and *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*

	Official distribution	Sales
Scientific Publications		
No. 1	730	967
2	831	1480
3	992	1050
4	953	996
5	1073	1524
6	941	1266
7	1086	858
8	1077	1129
9	1029	946
10	1060	1073
11 - Part 1	1118	676
11 - Part 2	1123	689
12	1300	1242
13	979	903
14	999	900
15	1008	1062
16	1053	863
17	1025	536
18	991	744
19	1142	660
20	936	523
21	1121	764
22	962	524
23	1062	854
24 - Part 1	885	524
24 - Part 2	886	521
25	1074	675
26	1076	505
27	1123	697
28	989	498
29	936	611
30 - Part 1	1111	583
30 - Part 2	1109	583
31	1050	562
32	1361	938
33	1078	1012
35	628	483
37	1408	530
38	706	405
Information Bulletin No. 9	200	205
Cancer Morbidity and Causes of Death Among Danish Brewery Workers	728	455
Alcool et Cancer	666	158

	Official distribution	Sales
Monograph Series		
No. 1	2638	2099
2	1987	2349
3	2046	2360
4	1807	2226
5	2047	1930
6	1837	1934
7	2126	1717
8	2046	1721
9	2023	1569
10	2090	1739
11	2213	1395
12	2113	1566
13	2061	1400
14	2254	2033
15	2148	1564
16	2109	1476
17	2253	1368
18	2154	1298
19	2107	1328
20	2111	1163
21	2091	768
22	2183	869
23	2094	1000
24	2233	808
25	1928	726
26	1998	686
Supplement No. 1	2375	1349
Supplement No. 2	2327	1189

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE TWENTIETH SESSION OF THE IARC GOVERNING COUNCIL 29–30 April 1981

Australia

Dr D. F. BOOTH
Assistant Director-General
International Health and TB Branch
Department of Health
Woden
Canberra, A.C.T.
Australia

Mr B. FRIEND
Director
Accounting Office
Australian Department of Finance
Australian Consulate
Geneva
Switzerland

Belgium

Dr J. FRANÇOIS
Director-General
Ministry of Public Health and the Family
Brussels

France

Professor E. J. AUJALEU
Honorary Director-General
National Institute of Health and Medical Research
Paris

Federal Republic of Germany

Mr H. VOIGTLÄNDER
International Health Relations Section
Federal Ministry for Youth, Family Affairs and Health
Bonn

Italy

Professor R. VANNUGLI *(Chairman)*
Director
Bureau of International Relations
Ministry of Health
Rome

Professor L. SANTI
Director
Institute of Oncology
University of Genoa
Genoa
Italy

Japan

Dr S. YOSHIZAKI
Director-General
Statistics and Information Department
Ministry of Health and Welfare
Tokyo

Dr (Mrs) N. HATA
Deputy-Director
Division of Health Statistics
Ministry of Health and Welfare
Tokyo

Dr (Mrs) J. IKENOUCHI
Deputy-Director
Division of International Affaires
Minister's Secretariat
Ministry of Health and Welfare
Tokyo

Mr H. ISHIMOTO
First Secretary
Permanent Mission of Japan to the United Nations Office and to the International Organizations at Geneva
Geneva
Switzerland

Netherlands

Dr J. SPAANDER
Late Director-General of the National Institute of Public Health
Bilthoven
Netherlands

Mr W. J. KAKEBEEKE
Deputy-Director for International Affairs
Ministry of Public Health and Environmental Protection
Leidschendam
Netherlands

Sweden

Professor H. DANIELSSON
Secretary-General
Swedish Medical Research Council
Stockholm

Professor L. ENNERBÄCK
Department of Pathology
University of Göteborg
Göteborg
Sweden

Union of Soviet Socialist Republics

Professor N. N. BLOKHIN
President, Academy of Medical Sciences of the USSR
General Director, Cancer Research Center
Moscow

Dr S. K. LITVINOV
Deputy Chief
External Relations Board
Ministry of Public Health of the USSR
Moscow

Dr Y. I. PUCHKOV
Chief, Department of International Scientific Relations
Cancer Research Center
Moscow

United Kingdom

Dr J. L. GOWANS
Secretary, Medical Research Council
London

Dr R. J. WRIGHTON *(Rapporteur)*
Senior Medical Officer
Department of Health and Social Security
London

United States of America

Dr G. T. O'CONOR *(Vice-Chairman)*
Director, Office of International Affairs
National Cancer Institute
Department of Health and Human Services
Bethesda, MD, USA

Mr N. A. BOYER
Director, Health and Narcotics Programs
Bureau of International Organization Affairs
Washington, DC

World Health Organization

Dr Ch'en WEN-CHIEH
Assistant Director-General

Mr A. GROENENDIJK
Director, Division of Budget and Finance

Dr J. STJERNSWÄRD
Chief, Cancer Unit

Dr C.-H. VIGNES
Director, Legal Division

Observers

Professor J. CAIRNS
Incoming Chairman Scientific
Council

Dr J. F. DELAFRESNAYE
Executive Director
International Union Against Cancer
Geneva
Switzerland

Professor M. TUBIANA
Outgoing Chairman Scientific Council

Annex 2

MEMBERS OF THE SCIENTIFIC COUNCIL AT ITS SEVENTEENTH SESSION, 6–8 JANUARY 1981

Professor P. BOGOVSKI *(Vice-Chairman)*
Director
Institute of Experimental and Clinical Medicine
Tallinn, Estonian SSR

Professor J. CAIRNS
Department of Microbiology
Harvard School of Public Health
Boston, MA, USA

Professor G. DELLA PORTA *(Rapporteur)*
Director
Division of Experimental Oncology A
National Institute for the Study and Treatment of Tumours
Milan, Italy

Professor P. EMMELOT
Acting Scientific Director
Department of Biochemistry
The Netherlands Cancer Institute
Slotevaart
Amsterdam

Professor A. GEORGII
Secretary-General, German Cancer Society
Director, Institute of Pathology
Medical School
Hanover, Federal Republic of Germany

Dr N. GRAY
Director
Anticancer Council of Victoria
East Melbourne, Vic., Australia

Professor B. GUSTAFSSON
Professor and Chairman
Department of Germfree Research
Karolinska Institute
Stockholm

Dr T. HIRAYAMA
Chief, Epidemiology Division
National Cancer Center Research Institute
Tokyo

Professor A. R. M. LAFONTAINE
Director
Institute of Hygiene and Epidemiology
Ministry of Public Health and the Family
Brussels

Professor E. R. SAXÉN
Director
Department of Pathology
University of Helsinki
Helsinki

Professor M. TUBIANA *(Chairman)*
Head, Radiation Department
Gustave Roussy Institute
Villejuif, France

Professor I. B. WEINSTEIN
Director
Division of Environmental Sciences
College of Physicians and Surgeons of Columbia University
Cancer Center Institute of Cancer Research
New York, NY, USA

World Health Organization

Dr Ch'en WEN-CHIEH
Assistant Director-General

Dr L. H. SOBIN
Cancer Unit

Dr J. STJERNSWÄRD
Chief, Cancer Unit

Observer

Dr J. F. DELAFRESNAYE
Executive Director
International Union Against Cancer

Annex 3

RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS July 1980–June 1981

Support of IARC Research Centres

RA/68/002	University of Singapore (Contribution to the maintenance of an IARC Research Centre at the University of Singapore)
RA/57/020	University of Nairobi (Contribution to the maintenance of an IARC Research Centre at the University of Nairobi)

References centres/Serum banks

RA/73/029	Institute of Experimental Oncology, University of Genoa, Genoa, Italy (IARC Reference Centre for environmental carcinogenesis)
RA/73/033	Medical College, Hanover, Federal Republic of Germany (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/74/003	Institute for Documentation, Information and Statistics, German Cancer Research Centre, Heidelberg, Federal Republic of Germany (Clearing-house for on-going research in cancer epidemiology)
RA/75/014	National Institute of Hygiene, Budapest (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/76/109	Angel H. Roffo Oncological Institute, Buenos Aires (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/78/002	School of Pharmacy, Catholic University of Louvain, Brussels (Creation of an IARC Reference Centre for the *in vivo* monitoring of drug metabolizing enzymes)
RA/78/006	Laboratory of Genetics, University of Pisa, Pisa, Italy (Creation of an IARC Reference Centre for environmental carcinogenesis)
RA/78/026	Immunology Laboratory, INSERM Unit 80, Lyon, France (Preparation of reference material for standardization of β-2-microglobulin)
RA/79/018	Georges-François Leclerc Centre, Dijon, France (Constitution of a serum bank for the study of biological markers for cancer)

RA/79/019	Immunology and Experimental Medicine Laboratory, Medical Faculty, Dijon, France (Collection of samples of sera for the study of biological markers for tumours)
RA/79/020	University Medical Centre, Dijon, France (Collection of samples of sera for the study of biological markers for tumours)

Cancer registries/Incidence studies

RA/67/009	IARC Research Centre, University of Singapore (Cancer registry at Singapore)
RA/73/016	International Association of Cancer Registries (Provision of a secretariat and other supporting services)
RA/76/008	Joint European Medical Research Board, Liverpool, UK (International epidemiological research programme to examine health effects, particularly as these concern cancer, of exposure to man-made mineral fibres in man)
RA/77/028	National Institute of Health and Medical Research, Nutrition Department, Le Vésinet, France (Study on the relationship between alcohol and ischaemic heart disease in Rouen)
RA/78/014	School of Public Health, Free University of Brussels, Laboratory of Epidemiology and Social Medicine, Brussels (Study of digestive-tract cancer in Belgium)
RA/78/015	Zaragoza Tumour Registry, Zaragoza, Spain (Epidemiological study on cancers of the larynx)
RA/78/016	Health Department of Navarra, Pamplona, Spain (Epidemiological study on cancers of the larynx)
RA/78/017	Institute of Anatomy and Histopathology, University of Turin, Turin, Italy (Epidemiological study on cancers of the larynx)
RA/78/018	National Institute for the Study and Treatment of Tumours, Milan, Italy (Epidemiological study on cancers of the larynx)
RA/78/019	Regional Cancer Registry, Birmingham, Queen Elizabeth Medical Centre, Birmingham, UK (Production of Volume IV of 'Cancer Incidence in Five Continents')
RA/78/020	Danish Cancer Registry, Copenhagen (Study of Man-Made Mineral Fibres (MMMF) — Prospective investigation in the producer industry)
RA/78/022	Norwegian Cancer Registry, Oslo (Study on Man-Made Mineral Fibres (MMMF) — Prospective investigation in the producer industry)
RA/78/025	Mathematics Department, University of Namur, Namur, Belgium (Joint compilation of a commentary on the data contained in the first three volumes of 'Cancer Incidence in Five Continents')

RA/79/001	Swedish National Board of Occupational Safety and Health, Stockholm (Study on Man-Made Mineral Fibres (MMMF) – Prospective investigation in the producer industry)
RA/79/008	Radium Department, Copenhagen (Case-control study of larynx, pharynx and oesophageal cancer among Danish brewery workers)
RA/80/002	Clinic of Occupational Medicine 'Luigi Devoto', University of Milan, Milan, Italy (Study of Man-Made Mineral Fibres (MMMF): Historical mortality follow-up of a cohort of exposed workers previously employed at Balzaretti-Modigliani MMMF producing plant in Besana Brianza, Milan)

Oesophageal cancer studies

RA/75/015	National Institute of Health and Medical Research, Division of Medico-Social Research, Le Vésinet, France (Study of cases of oesophageal cancer and their controls in the Calvados region of France)
RA/79/016	Department of Epidemiology, Environmental Oncology and Protection, Regina Elena Institute, Rome (Feasibility study on the sampling of gastric juice and blood for *N*-nitroso compounds)
RA/80/011	London School of Hygiene and Tropical Medicine, London (Biochemical analyses of blood samples collected during an endoscopical survey in Linxian, People's Republic of China)
RA/80/017	Cancer Epidemiology and Clinical Trials Unit, University of Oxford, Oxford, UK (Monograph on oesophageal cancer in Iran)

Studies on cancers linked with herpesviruses

RA/70/017	Department of Pathology, University of Singapore, Singapore (Studies on the relationship between herpes-type infection and nasopharyngeal carcinoma)
RA/71/007	Shirati Mission Hospital, Tarime District, Tanzania (Study of the epidemiology of Burkitt's lymphoma in the North Mara District, Tanzania)
RA/75/002	Ross Institute, London School of Hygiene and Tropical Medicine, London (Malaria antibody testing to be carried out by the Institute on sera from Burkitt's lymphoma studies in the West Nile District of Uganda and the Mara Region of Tanzania)
RA/77/008	Shirati Mission Hospital, Tarime District, Tanzania (Studies on the effect of partial malaria suppression on incidence of Burkitt's lymphoma in North Mara)

RA/77/015 Department of General and Applied Biology, Claude Bernard University, Villeurbanne, France
(Characterization and purification of viral antigens for the development of serological tests)

RA/79/014 Department of Clinical Genetics, University Hospital, Lund, Sweden
(Cytogenetic study of 8–14 translocation in non-tumoral cells to be carried out by the Department in children from Mara Region of Tanzania)

RA/80/008 Microbiology Laboratory, Mohamed V Hospital, Rabat
(Collaboration with the research programme on nasopharyngeal carcinoma in Morocco)

RA/80/009 Cytogenetics Laboratory, Research Institute on Leukaemias and Blood Diseases, Saint-Louis Hospital, Paris
(Characterization of cytogenetic abnormalities observed in cells of a Burkitt-type lymphoma)

Liver cancer studies

RA/79/021 Department of Social Medicine and Public Health of the University of Singapore, Singapore
(Cohort study on hepatitis B carriers and liver cancer)

Studies on chemical carcinogenesis

RA/76/017 Cancer Research Center, Academy of Medical Sciences of the USSR, Moscow
(Investigation on the effect of prenatal exposure to a chemical on successive untreated generations)

RA/76/027 Institute for Experimental Toxicology and Chemotherapy, German Cancer Research Centre, Heidelberg, Federal Republic of Germany
(Study of elaboration of analytical methods for identification and quantification of *N*-nitroso compounds in various environmental media)

RA/77/022 N. N. Petrov Research Institute of Oncology, Leningrad, USSR
(Multi-generation studies of modifying factors in transplacental carcinogenesis)

RA/77/026 Central Institute for Cancer Research, Academy of Sciences of the German Democratic Republic, Berlin-Buch
(Investigation on the combined action of several chemical carcinogens)

RA/78/004 Laboratory of Biophysics and Radiobiology, Free University of Brussels, Rhode-Saint-Genèse, Belgium
(Investigation of an *in vitro* biochemical assay for somatic mutagenesis by chemical mutagens/carcinogens and the effects of promoters in chemical carcinogenesis)

RA/78/005 Department of Pharmacognosy, Medical School, University of Szeged, Szeged, Hungary
(Study to identify the mutagenic components of crude opium and opium dross)

RA/78/009	National Institute for the Study and Treatment of Tumours, Milan, Italy (Study on the possible role of environmental factors in the origin of human cancer)
RA/79/002	Department of Pharmacology, University of Oulu, Oulu, Finland (Study on the AHH-inducibility and individual susceptibility to toxic effects of cigarette smoke)
RA/79/003	The Oncological Institute of the Lithuanian SSR, Vilnius, Lithuanian SSR (Investigation on the combined action of several chemical carcinogens)
RA/79/004	Institute of Experimental and Clinical Medicine, Tallinn, Estonian SSR (Studies on the co-carcinogenic action of shale phenols on lung carcinogenicity of asbestos dust)
RA/79/006	Institute of Medical Sciences, University of Tokyo, Tokyo (Mutagenesis and neoplastic transformation *in vitro* of cultured cells by environmental chemicals)
RA/79/007	Confederation of the French Malting Industry, Paris (Study of volatile *N*-nitroso compounds in samples of malt or in the treatment process)
RA/79/010	Cancer Research Centre, 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)
RA/79/012	Department of Environmental Health, National Institute of Health of Colombia, Bogotá (Feasibility study on long-term effects of pesticides on human health)
RA/80/001	Nuclear Institute for Agriculture and Biology, Faisalabad, Pakistan (Investigation of mutagenicity testing in bacteria and yeast by environmental chemicals within an international network of carcinogenicity testing)
RA/80/006	Institute of Oncology, University of Genoa, Genoa, Italy (Investigation on the development of cellular and biochemical markers of neoplastic transformation in cultured cells)
RA/80/007	First Institute of Pathology, Medical University, Budapest (Studies on chromosome alterations in fibroblasts of human and rodent origin after treatment with chemical carcinogens)
RA/80/012	Institute of Oncology, Medical Academy, Sofia (Long-term carcinogenicity testing of environmental chemicals)
RA/80/013	Institute of Oncology, University of Genoa, Genoa, Italy (Long-term carcinogenicity testing of environmental chemicals)
RA/80/018	Curie Institute, Biology Section, Faculty of Sciences, Orsay, France (Synthesis of unlabelled and radio-labelled chemicals to be used in experimental studies)

RA/80/019 Biotoxicology Laboratory, School of Pharmacy, Faculty of Medicine, Catholic University of Louvain, Brussels
(Determination of antipyrine half-life in saliva samples from 184 human subjects)

RA/81/002 Cancer Institute, Chinese Academy of Medical Sciences, Beijing
(Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines)

RA/81/003 Institute for Cell Biology (Tumour Research) University of Essen, Essen, Federal Republic of Germany
(Detection in human tissues by specific antibodies of cellular macromolecule modifications induced by nitrosamines)

RA/81/006 Clinics of Surgery and Medicine, University of Turku, Turku, Finland
(Study on endogenous formation of *N*-nitrosamines)

Studies of various other cancer forms

RA/78/013 Department of Clinical Genetics, University Hospital of Lund, Lund, Sweden
(Study on the possibility of correlating karyotypes of cancer cells to specific etiological factors)

RA/80/005 Swedish Cancer Registry, Stockholm
(Cohort study to evaluate the risk of second tumours in patients originally diagnosed for cervical cancer)

RA/80/015 The Ontario Cancer Treatment and Research Foundation, Toronto, Ontario, Canada
(Cohort study to evaluate the risk of second tumours in patients originally diagnosed for cervical cancer)

RA/80/016 Danish Cancer Registry, Finsen Institute, Copenhagen
(Cohort study to evaluate the risk of second tumours in patients originally diagnosed for cervical cancer)

RA/80/020 Cancer Registry of Slovenia, Ljubljana, Yugoslavia
(Cohort study to evaluate the risk of second tumours in patients originally diagnosed for cervical cancer)

Support of meetings

RA/80/004 German Cancer Research Centre, Heidelberg, Federal Republic of Germany
(Support for part cost of symposium on co-carcinogenesis and biological effects of tumour promoters)

RA/80/010 Dr J. Burchenal, Organizing Committee 1980 International Symposium on Cancer, c/o Memorial Sloan-Kettering Cancer Center, New York, NY USA
(Part cost of symposium from 13–18 September 1980)

RA/81/005 Japanese Organizing Committee c/o Dr Masashi Okada (Chairman), Tokyo Biochemical Research Institute, Tokyo
(Regarding Seventh International Meeting on Analysis and Formation of *N*-Nitroso Compounds — for services connected with organization)

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Annex 5

MEETINGS AND WORKSHOPS ORGANIZED BY IARC 1980–1981

Working group on laryngeal cancer study	Geneva, 6–7 October 1980
Meeting of the review board for the manual 'Destruction and disposal of laboratory waste containing nitrosamines'	Lyon, 7–8 October 1980
Meeting of the review board and editorial board for the manual 'Environmental carcinogens—selected methods of analysis'	Lyon, 8–10 October 1980
International symposium on co-carcinogenesis and biological effects of tumor promoters (jointly organized with the German Cancer Research Centre, Heidelberg)	Garmisch-Partenkirchen, Federal Republic of Germany, 13–16 October 1980
Working group on the evalutation of the carcinogenic risk of chemicals to humans: some anticancer drugs and immunosuppressive agents	Lyon, 14–21 October 1980
International course on aspects of chemical carcinogenesis	Lyon, 3–7 November 1980
International course on cancer epidemiology with special reference to cancer registration	Nicosia, 17–29 November 1980
Study group meeting on the international radiation study of cervical cancer	Lyon, 10–11 December 1980
X-ray reading panel on mesothelioma in central Turkey	Lyon, 6–9 February 1981
Editorial board meeting on cancer incidence in five continents	Lyon, 10 February 1981
Working group on the evaluation of the carcinogenic risk of chemicals to humans: some aromatic amines, anthraquinones and nitroso-compounds, formaldehyde and inorganic fluorides	Lyon, 10–17 February 1981
Programme committee meeting for the 7th international symposium on analysis and formation of *N*-nitroso compounds	Lyon, 18–19 March 1981
Working group on large bowel pathology in autopsy series	Lyon, 26–27 March 1981
Working group on the clearing house for on-going research in cancer epidemiology	Lyon, 31 March–2 April 1981
IARC Fellowships Selection Committee	Lyon, 13–14 April 1981
IARC Governing Council	Lyon, 29–30 April 1981

International course on cancer epidemiology	Ndola, Zambia, 11–30 May 1981
International symposium on host factors in human carcinogenesis	Cape Sunion, Greece, 8–11 June 1981
Review board for the manual 'Environmental carcinogens—selected methods of analysis'	London, 16–17 June 1981
Working group on the evaluation of the carcinogenic risk of chemicals to humans: working exposures in the rubber industry	Lyon, 16–23 June 1981
Short course on statistical methods in cancer epidemiology	Lyon, 29 June–3 July 1981

Annex 6

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Annex 7

VISITING LECTURERS TO IARC — JULY 1980 TO JUNE 1981

Professor L. M. Schuman	'The trend of prostate cancer'
Dr T. Kakunaga	'Approaches to identify the cellular macromolecules responsible for the expression of malignant phenotypes'
	'Process of malignant transformation of mammalian cells by chemical carcinogens'
Dr A. E. Pegg	'Role of DNA alkylation and repair in the organ specific carcinogenicity of nitrosamines'
Dr R. D. Bulbrook	'Hormonal models for breast cancer'
Dr N. W. Choi	'A migrant study on cancer among Icelanders'
Dr C. A. Heckman	'Quantitative cytoskeletal changes in oncogenic transformation'
Dr P. A. Cerutti	'Bloom's syndrome: a deficiency in the detoxification of active oxygen species'
Dr W. K. Lutz	'*In vivo* covalent binding to DNA and carcinogenic potency of chemicals: its possible use in risk assessment'
Dr A. Sarasin	'Induction of SOS function in eukaryotic cells treated with carcinogens'
Dr P. Boyle	'Bladder and laryngeal cancer in Western Scotland'
Dr D. Parkin	'Evaluating effectiveness of cervical cytology screening'
Dr M. Okada	'Metabolic aspects in organotropic carcinogenesis by *N*-nitrosamines'
Dr R. J. Laib	'Studies on the mechanisms of haloethylene carcinogenesis with special respect to vinyl chloride'
Dr C. W. Gorodetzky	'Screening methods for the detection of opioids suitable for field studies'
Dr S. D. Walters	'Evaluation of cancer screening programmes'
Dr J. P. Lamelin	'Some controversial findings related to the inheritance of acquired immune tolerance'
Dr O. Lloyd	'Respiratory cancer in a small industrial town in Scotland'

Annex 8

INTERNAL TECHNICAL REPORTS 1981–81

IARC Internal Technical Report No.	
81/001	Selection of chemicals and complex mixtures for carcinogenicity testing

Annex 9

PAPERS PUBLISHED OR SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS

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