WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

LYON
FRANCE

ANNUAL REPORT 1970

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LYON
1971

PRINTED IN SWITZERLAND

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INTRODUCTION

The Director of the International Agency for Research on Cancer (IARC) presents the annual report of the Agency for the year 1970. The previous reports [1,2] cover the origins of the Agency and the early development of its scientific policies and programmes. In 1969 the Governing Council of IARC established a firm budget for the period 1971-75, thus enabling the staff to plan long-term programmes with greater certainty and avoid the problems and dangers involved in the assessment on a short-term basis of the risks presented by carcinogens in the environment. Details of the programmes are given in the pages that follow. In general they represent an expansion of those of 1969, in which the main emphasis was on the identification of environmental factors in human cancer.

A study [3] of the part that international research organizations might play in the field of environmental biology, with particular reference to preliminary experience with IARC, was published during the year.

Admission of Belgium

In 1970, the Government of Belgium made an application to the Director-General of the World Health Organization to become an active participant in the work of the Agency. At the meeting of the Governing Council on 19-20 October 1970, Belgium was admitted to the Agency, in conformity with Articles III and XII of the Agency's Statute. The representative of Belgium then joined in the deliberations of the Council.

Feasibility of an environmental monitoring system for cancer

Both governments and scientists have shown increasing concern about the chemical pollution of the environment and its role in causing human disease. Perhaps the most feared long-term effect of such pollution is cancer, and so, in November 1970, the Director established a working group within the Agency to explore the feasibility of establishing a surveillance system at an international level to detect the presence of new carcinogenic factors in the environment by following changes in cancer patterns.

The Agency was equipped to undertake a study of this nature, since it has continued to collect cancer morbidity statistics in collaboration with the World Health Organization and the International Association of Cancer Registries.

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[1] International Agency for Research on Cancer (1969) *Annual report, 1968*, Lyon.
[2] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon.
[3] Higginson, J. (1970) *Science*, **170**, 935.

Preliminary investigation by the Unit of Epidemiology and Biostatistics and the Unit of Environmental Carcinogens has shown that the establishment of a surveillance system will involve a number of problems:

(*a*) In contrast to the situation with congenital malformations, in which the period between exposure and development of the lesion is very short, present-day cancer patterns in adults probably reflect factors that have been present in the environment for between 20 and 40 years. A shorter latency period may, however, be anticipated in children's cancers.

(*b*) In a retrospective study, it is probable that more than one carcinogenic factor will be involved. It will be very difficult to measure exposure to the various stimuli and ascertain their influence on present cancer patterns. Specific stimuli can be identified at high concentration, as for example in cases of occupational exposure or other exposure to a known radiation hazard.

(*c*) The Unit of Environmental Carcinogens has found not only that the present methods of analysis for many carcinogens are unsatisfactory, even under laboratory conditions, but that no methods suitable for field investigations on a large scale are as yet available. The unit is therefore faced with the task of developing standardized techniques for quantitating environmental carcinogens.

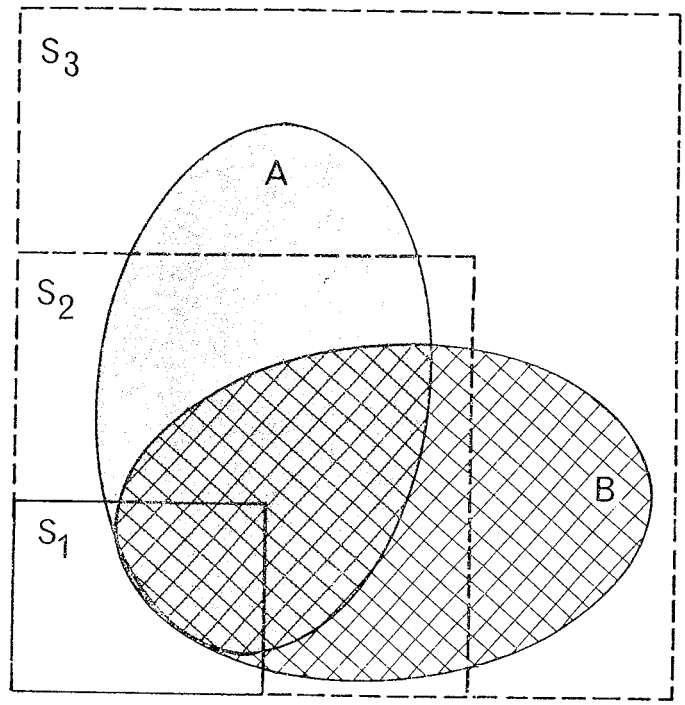
It is probable that, except where a marker of exposure can persist in the human organism for long periods, as is the case with the chlorinated hydrocarbons and asbestos, studies of this type are more likely to be successful when based on a prospective survey rather than on past exposure.

(*d*) Published material from cancer registries that have been in existence for some time show very marked variations in incidence from year to year. Thus, the detection of the presence of a new carcinogenic factor in the environment depends on the magnitude of the resultant variation. For certain rare cancers, however, changes might be recognized from the appearance of a small number of new cases; an example is mesothelioma due to asbestos. In the case of already common cancers, much greater changes in incidence would be necessary.

(*e*) A particularly difficult problem in an industrial society is the separation of risk factors. This can be tackled by extending etiological surveys to several geographical areas on the ground that the risks will be of different intensity in each area.

This is illustrated diagrammatically in Fig. 1, in which the two risk factors A and B, superimposed in area S_1, are separate in area S_3. A surveillance system covering populations living under a variety of environmental conditions permits such a separation of risks and provides the justification for making etiological surveys in less developed areas.

FIG. 1. SEPARATION OF RISK FACTORS



Computer techniques can deal with analyses of risk factors and changes in cancer incidence but the feasibility of a surveillance system will obviously depend on the availability of adequate and accurate data.

In the light of present knowledge, it has been concluded that the most appropriate situations for a monitoring system would be:

(1) the massive exposure of a large population group to an agent of short duration (e.g., nuclear explosion);

(2) the occurrence of cancer after an unusually short incubation period (childhood cancers);

(3) the intense exposure of selected groups, such as industrial workers, to an unusual agent (exposure of workers to β–naphthylamine in the rubber and dye industries);

(4) massive and prolonged, but less intense, exposure to a new agent, involving changes in social behaviour and habits.

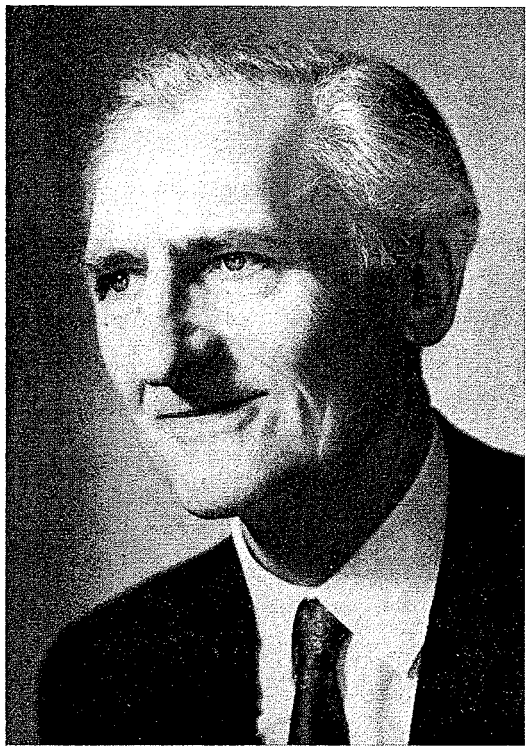
The absence of significant changes or effects may be valuable as an indication that the risk presented by the presence of a given carcinogen in the environment may be ignored under present conditions.

It is felt that the Agency should continue this feasibility study in order to make the most of its past work in this area. It is hoped that some preliminary conclusions will be available by the end of 1971.

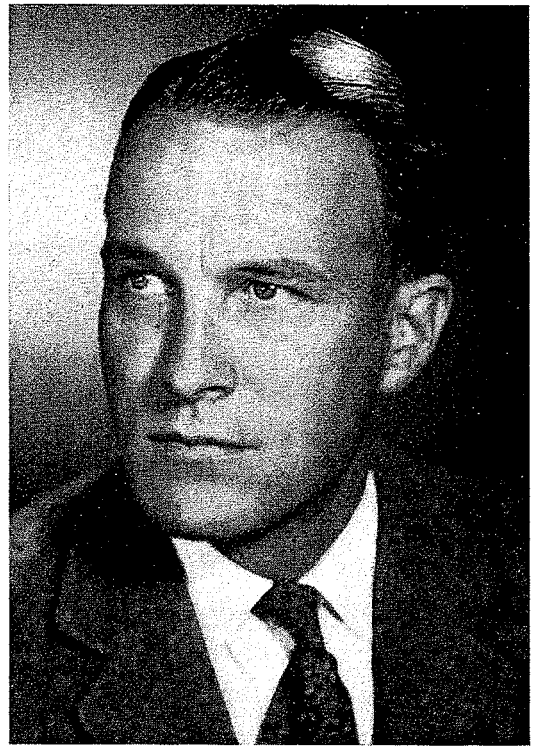
FIG. 2. MEMBERS OF THE SCIENTIFIC COUNCIL OF THE IARC

Professor N. N. Blokhin (1968-70)

Professor P. F. Denoix (1968-70)



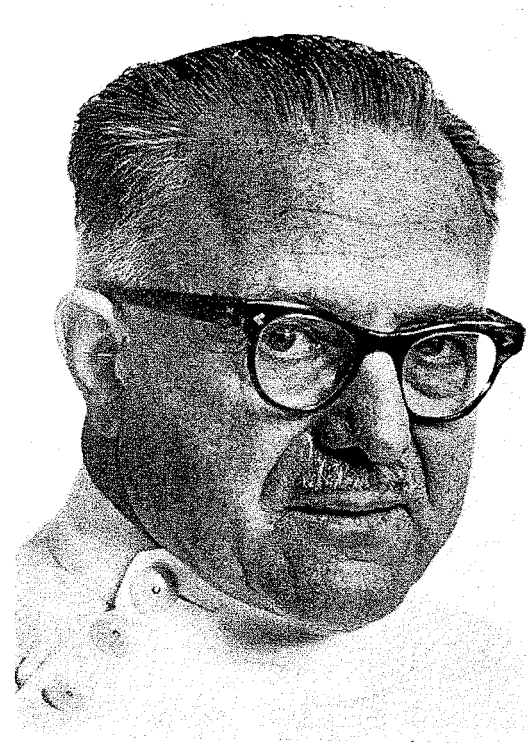
Professor W. R. S. Doll (1968-70)



Professor H. C. Isliker (1968-70)

FIG. 2. MEMBERS OF THE SCIENTIFIC COUNCIL OF THE IARC *(continued)*

Professor B. MacMahon (1969-71)

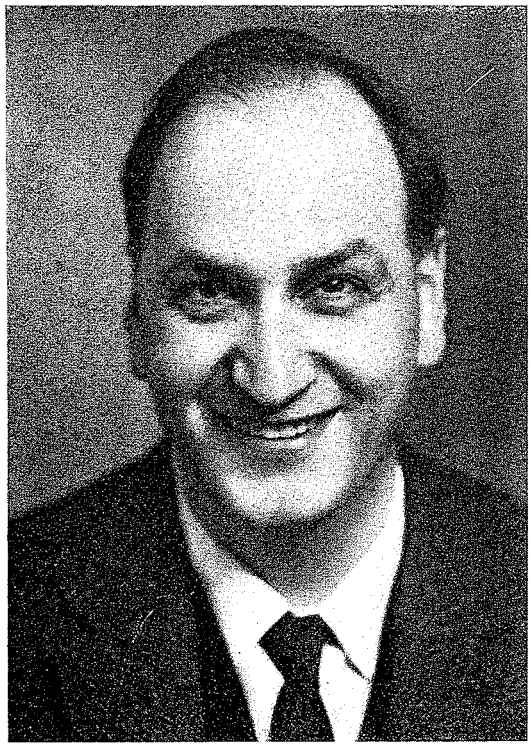


Professor J. H. F. Maisin (1970-72)

Dr G. J. V. Nossal (1970-72)

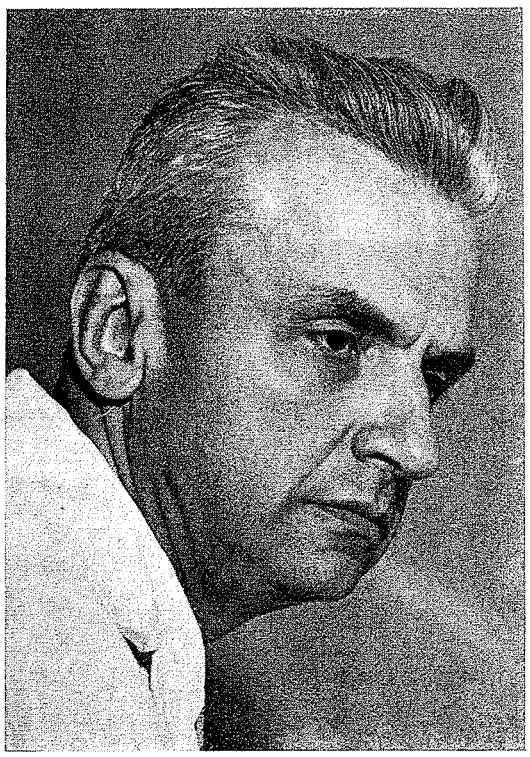
Dr E. Pedersen (1970-72)

FIG. 2. MEMBERS OF THE SCIENTIFIC COUNCIL OF THE IARC *(concluded)*

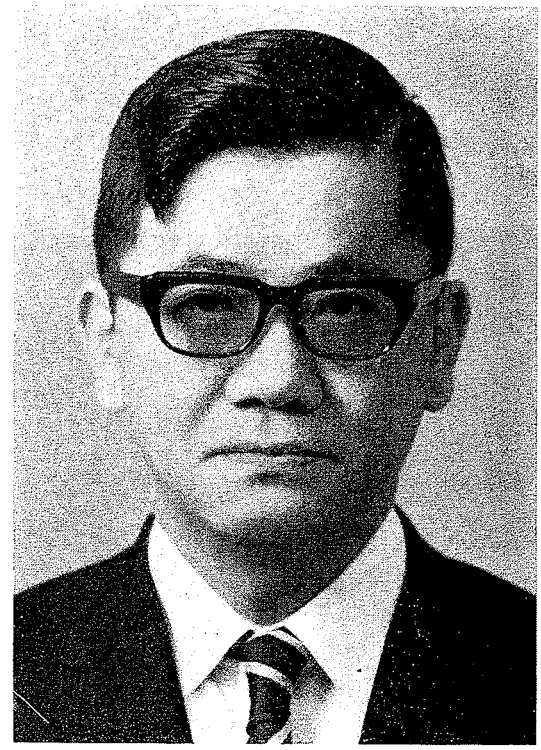


Professor L. Sachs (1969-71)

Professor C. G. Schmidt (1969-71)



Professor L. Severi (1969-71)



Professor T. Sugimura (1970-72)

Development of research programmes

At its meeting in October 1970, the Governing Council invited the Director to explain how the various programmes of the Agency are initiated.

Before recruiting staff, the Director selected a number of programmes on scientific grounds as suitable for immediate implementation with the limited resources available. These programmes were then presented to the Scientific Council for discussion and criticism. As the staff increased, the Director delegated the initiation and planning of new research projects to individual units, provided that these projects fell within the overall objectives and policies of the Agency.

In practice, the unit concerned prepares the preliminary scientific documentation and budgets for the Director. These are discussed with the other units involved, and the following points receive close attention:

(1) the objectives of the project and its relevance to the overall development of the Agency's programme;

(2) whether the programme can be most effectively carried out by a research agreement with a national institute or within the IARC, or by a combination of the two;

(3) whether the budget proposals are reasonable in relation to the objectives, and whether or not the necessary funds are available;

(4) whether the implementation of the programme would be likely to unbalance the overall programmes of the Agency, thus leading to the excessive allocation of limited resources to a single project.

Once a programme is approved, it is implemented as rapidly as possible. Naturally the Governing Council has the last word, and in this matter it has always acted with the maximum dispatch.

When research projects are carried out in outside laboratories under a research agreement, a unit of the Agency is responsible for each project and its review. The unit is responsible not only for controlling the budgetary aspects but also for the close scientific examination of all operations. This is particularly indicated in the case of programmes with a high epidemiological content, in which quality control in the field is essential. In general, it has been a basic principle that, when collaborative programmes are established with organizations outside the Agency, the organizations contribute to the project by providing staff, finance, or both.

While this control of projects and close contact with collaborating laboratories has necessitated considerable travelling by staff-members, it has certainly proved worth while as an operational method. On the one hand, scientific co-operation has been strengthened and, on the other, the best use of the Agency's budget has been ensured.

1. UNIT OF EPIDEMIOLOGY AND BIOSTATISTICS

Staff: Dr C. S. Muir (Chief)
Dr N. E. Day
Mr D. K. Jain
Dr J. Kmet
Dr Ulrike de Jong
Dr H. Tulinius
Dr A. J. Tuyns
Dr L. Leblanc (Dakar)
Dr F. Berrino (Abidjan)

Supporting staff: 11 (one temporary)

1. INTRODUCTION

In the field of descriptive epidemiology, work continues on the collection of morbidity and relative frequency data on cancer and arrangements have been made to produce future volumes of the monograph *Cancer Incidence in Five Continents* under IARC auspices.

The feasibility of using cancer registry data to give early warning of the appearance of new carcinogens in the environment is under study. The first meeting to formulate IARC recommendations for the cancer section of the Ninth Revision of the International Classification of Diseases has been held.

The link between cigar smoking and cancers of the larynx and hypopharynx in northern Thailand is being examined.

The search for etiological factors in cancer of the oesophagus continues in Iran (where this type of cancer has approximately the same incidence in both sexes) and in France, Jamaica, and Singapore, where this cancer is much commoner in males and has been associated with the consumption of alcoholic drinks.

A study of the relationship between intestinal metaplasia of the gastric mucosa and gastric cancer has shown that the fall in the incidence of gastric cancer observed in certain countries over the past thirty years is probably due to a diminution in the frequency of the "intestinal" form of this cancer.

Studies to evaluate the α_1–fetoprotein test, as a method for screening populations for primary liver cancer, continue in West Africa. These are closely linked to surveys of aflatoxin consumption and of the presence of Australia antigen.

In collaboration with the International Union against Cancer (UICC), the distribution of the various types of cancer of the reticulo-endothelial system is under review in several countries.

As a result of the active collaboration of the Biostatistics section in the programmes of other units, mathematical models to describe the behaviour of a complex antibody-antigen system, and to characterize certain theoretical problems in epidemiological studies, are being developed. Studies of factor analysis are in progress, and methods of age-standardization less arbitrary than those commonly used are being worked out. Data-processing and computing facilities have been provided.

2. DESCRIPTIVE EPIDEMIOLOGY

Data collection continues in several areas of the world, generally with the aim of obtaining background information on cancer patterns in areas where IARC studies are in progress or projected.

2.1 *Morbidity data*

The second volume of the monograph *Cancer Incidence in Five Continents*[1] was published in 1970. It contains cancer morbidity data for 58 populations at risk in 24 countries and presents, for the first time, population-based incidence rates, by histological type, for cancers of the ovary, testis, thyroid, and bladder and for leukaemia. Much of the editorial work was undertaken by the unit.

As the UICC Committee on Cancer Incidence, under whose aegis the volume was produced, has now been disbanded, IARC will continue the work. The International Association of Cancer Registries will nominate a member to the Editorial Board for the third volume, planned to appear in 1975.

2.2 *Comparison of published international mortality and morbidity series*

Mortality data are collected on an international basis both by WHO and by Segi & Kurihara,[2] who publish their results separately. Similarly, international morbidity statistics collected by WHO and by the UICC Committee on Cancer Incidence (see section 2.1) appear in separate publications.

The three sources differ somewhat in coverage. There are wide variations in the methods of presenting the data, WHO tending to give figures without comment or age-standardization. The format of the other publications, which are more interpretative, makes comparison between series relatively easy. The main advantages and disadvantages are summarized in IARC Internal Technical Report No. 70/006.

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[1] Doll, R., Muir, C. & Waterhouse, J., ed. (1970) *Cancer incidence in five continents*, Geneva, UICC, vol. II.

[2] Segi, M. & Kurihara, M. (1966) *Cancer Mortality for selected sites in 24 countries*, No. 4 (1962-1963), Sendai, Department of Public Health, Tohoku University School of Medicine.

2.3 *Study of the epidemiological value of detailed cancer incidence data — Israel Cancer Registry, Ministry of Health, Jerusalem* (RA/67/022)

Principal investigator: Dr Ruth Steinitz

Dr Steinitz reported that during 1970 the coding of cancers of the lung, stomach, and ovary and of leukaemia was completed. Some of the deficiencies noted in the 1969 Annual Report concerning the breast cancer material have now been corrected. All the cards have been transferred to magnetic tape for analysis. The projected tabulations include incidence and "reported mortality", by anatomical sub-site, stage of disease, sex, age, and continent of origin.

2.4 *The cancer registry as a means of environmental monitoring*

There is considerable interest at present in the correlation of data on the level of environmental pollutants (often alleged to be carcinogenic) and cancer incidence.

It is possible, by monitoring congenital malformations, to detect the appearance of a new teratogen in the environment.[1,2] This is relatively easy as the latent period and the critical time of exposure are short.

To monitor the environment for pollutants and correlate the findings with an eventual increase in cancer is more complex as:

(*a*) the induction period for a chemically induced cancer appearing in adult life is likely to be 10–40 years and hence there will be no abrupt increase in cancer soon after the introduction of the carcinogen;

(*b*) time-trends are influenced by improvements in diagnosis and many other factors;[3]

(*c*) even for a single anatomical site, cancer is not one disease, e.g., lung neoplasms include adenocarcinoma (relatively stable, squamous cell carcinoma), which has increased rapidly, and pleural mesothelioma, which has increased dramatically in certain occupational groups exposed to asbestos.

Examination of the feasibility of such correlation studies has begun, using the published time-series. Year-to-year fluctuation has been examined prior to forming an estimate of the magnitude of increase that should be considered significant. The problem is being discussed with certain members of the International Association of Cancer Registries.

2.5 *Advice on cancer registries*

Technical advice was given in connexion with the population-based cancer registries at Geneva (Professor G. Riotton), Saragossa (Dr A. Zubiri), Pamplona (Dr J. Viñes), and Zagreb (Professor Z. Kulcăr).

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[1] Kallén, B. & Winberg, J. (1968) *Pediatrics*, **41**, 765.

[2] Kallén, B. & Winberg, J. (1969) *Pediatrics*, **44**, 410.

[3] Lilienfeld, A. M., Pedersen, E. & Dowd, J. E. (1967) *Cancer epidemiology: methods of study*, Baltimore, The Johns Hopkins Press.

3. COMPARABILITY OF CANCER STATISTICS

3.1 *International Association of Cancer Registries*

The Chief of the unit is a member of the International Association of Cancer Registries, which has decided to create a series of corresponding committees to examine current registration practices and establish a series of recommended registration procedures (see also section 2.1).

3.2 *Differences in cancer mortality as reported by a central bureau of statistics and a cancer register*

(Dr Ruth Steinitz—RA/70/022)

Cancer mortality statistics are based on the cause of death given on the death certificate. A cancer registry often has much more accurate information concerning the same individual in the form of clinical records, biopsy reports, post-mortem information, etc.

The results of a study investigating the differences between the official statistics and the "corrected" data will be presented at a symposium on cancer in migrants in February 1971 (see also section 6.2).

4. IARC-SUPPORTED CANCER REGISTRIES AND RATIO STUDIES

The Agency supports studies of the relative frequency of cancer in areas where reliable incidence data are unlikely to be obtained for some time. Such studies are generally undertaken in areas where the Agency has, or is likely to have, other programmes.

4.1 *Regional Centres*

The cancer registries at the Regional Centres at Nairobi (Dr M. Rogoff: RA/67/001) and Singapore (Professor K. Shanmugaratnam: RA/67/009), at Blantyre, Malawi (Dr J. A. A. Borgstein: RA/68/003), and at Dar-es-Salaam (Dr C. Anderson: RA/68/005) are described in the reports of the Regional Centres (pages 84-95). The cancer registry at Khartoum (RA/69/004) is described in the report of the Regional Centre, Nairobi (page 85).

4.2 *West Africa* (Dr A. J. Tuyns)

(*a*) *Cameroon*

The ratio study (Dr P. Ravisse: RA/70/010) continued in 1970. Nearly 500 cases were recorded in 1969, and as many are expected in 1970. The material for 1968 is now under review; if suitable, it will be included in the proposed 3–year survey.

(*b*) *Ivory Coast*

The collection of histologically proven cancer cases[1] continues (Professor R. Loubière: RA/68/017). In addition, the files of the medical departments in the hospitals of Abidjan have been reviewed in order to determine the cancer pattern more precisely. From November 1966 to June 1970, 375 cases of cancer were diagnosed and only 149 of them were histologically confirmed. The proportion of cases pathologically confirmed varies from site to site; for liver cancer, the most frequent tumour in both sexes, it is 82/151 (54 %).

The age distribution of cases seems to indicate that liver cancer occurs earlier in life among people from the north of the country; the higher relative frequency of liver cancer in the north as compared with the south was referred to in the 1969 Annual Report.

(*c*) *Senegal*

An analysis of the material for the years 1967-69 (Professor C. Quenum: RA/68/015) was prepared for presentation at a meeting in Dakar in January 1971.

In males, the liver was the most frequent site (24.2 %), closely followed by the skin (20.8 %); in females, the breast (16.3 %) and skin (16.2 %) came first, being followed by the cervix uteri (14.7 %).

A more detailed analysis of the skin cancers (Professor P. Camain, Dr H. Sarrat, Dr I. Faye, and Dr A. J. Tuyns) showed that squamous cell carcinoma was the most frequent histological variety (83 %), basal cell carcinoma being very rare (3 %). Most of the squamous cell carcinomas and malignant melanomas were found on the legs (80 %). Kaposi's sarcoma formed 7 % of the skin cancers in males.

These features are typical of an African, as opposed to an Asian or a European, pattern of skin cancer.

The very high frequency of liver cancer confirms the suitability of Dakar as a centre for the extensive study of this neoplasm (see also 9.1).

4.3 *Barbados and Curaçao*

The work of the Barbados (RA/70/006) and Curaçao (RA/68/004) registries is described on pages 96-97.

4.4 *Peru*

Principal investigator: Dr J. Gálvez-Brandon (RA/69/003)

The data for 1968 published in the 1969 Annual Report have now been reworked to include late registrations. The rank order remains substantially the same: cancers of the stomach, lung, and prostate were the most common in males, cancers of the cervix uteri, breast, and stomach the most frequent in females.

Incidence rates will be published when the results of the 1971 census become available.

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[1] Duvernet-Battesti, F. (1970) *Le cancer en Côte d'Ivoire*, Abidjan (Thesis).

4.5 *Thailand*

The ratio study is now completed and the results have been accepted for publication.[1]

The registration of clinically diagnosed cases of cancer (RA/68/009) has now ended, but analysis has been deferred until the results of the 1970 census become available.

A retrospective case-control study (principal investigators: Dr Sanan Simarak and Dr Kobkiat Ruckphaopunt) to determine whether the very high frequency of cancer of the laryngeal/hypopharyngeal region is associated with the consumption of "keeyo" (a cigar containing home-grown, sun-dried, uncured tobacco and the bark of the "koi" tree (*Streblus asper*) in approximately equal proportions) is under way. One of the principal difficulties in the study has been to obtain interviewers proficient in Northern Thai. Dr Nibondh Sasidhorn, Dean of the Faculty of Social Science, University of Chiengmai, has arranged for the interviewing of community controls.

4.6 *Poland*

The study on the relationship between mortality and incidence data for Warsaw, Cracow, Katowice, and four rural areas in Poland is progressing well.

The principal investigator, Dr J. Staszewski (RA/69/007), has compared the Polish material with cancer mortality data from 24 countries and, whenever possible, with the mortality experience of Polish migrants in the United States of America and Australia. Urban-rural differentials have been examined. Attention is concentrated on those sites which are most likely to yield information of etiological importance. The analysis, although incomplete, strengthens earlier impressions of an unusual profile of cancer risks: the incidence of gastric cancer is higher than in most countries, but is just beginning to decline; a low risk is evident for cancer of the large bowel and female breast.

It is proposed to publish the findings in the form of monographs in Polish and English.

5. INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)

The working parties [2] established by IARC to make recommendations to WHO concerning the cancer section of the Ninth Revision of the International Classification of Diseases (due to appear in 1975) held their first meetings in November. To assist them they had available detailed critiques from over 70 of the 200 national statistical offices, cancer registries, and interested individuals canvassed in 1969.

The working parties noted that the cancer section of the Eighth Revision [3] was used much more frequently for morbidity and clinical statistics than for mortality statistics. They

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[1] Menakanit, W., Muir, C. S. & Jain, D. K. (1971) *Brit. J. Cancer* (in press).

[2] Working Party on Rubric Content: Dr C. S. Muir, Mr H. Page, Dr E. Pedersen, Dr A. Winkler. Working Party on Histology Code: Dr H. Tulinius, Professor E. Saxén, Dr L. Sobin, Professor G. Wagner.

[3] World Health Organization (1967) *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, Eighth Revision 1965,* Geneva, vol. 1, p. 85.

felt most strongly that, unless an attempt was made to make the section more flexible, registries and clinicians would turn elsewhere and devise schemes of their own, undermining the basis of international comparability.

For several sites there is a need to be able to code with greater anatomical precision and to code information on morphology (histology) in parallel at two levels: (1) by broad histological type (such as tumour of epithelium, tumour of connective tissue, tumour of lymphatic tissue, etc.), and (2) according to a much more detailed histological description. Many respondents have suggested that if possible there should be only one primary coding axis for the cancer section, that it should be possible to denote carcinoma-in-situ for organs other than the cervix uteri, and that in view of the growing interest in the long-term behaviour of benign neoplasms there is a need for greater anatomical specificity in the coding of these lesions.

Close contact has been maintained with the Division of Health Statistics at WHO Headquarters. Dr Madeleine Guidevaux, of the WHO Centre for the Classification of Diseases, Paris, has proved most helpful.

6. MIGRANT STUDIES

The study of changes in cancer risk in population groups after their migration to a new environment can provide useful etiological indicators. The unit has previously reviewed such studies [1] and compiled a list of migrant populations of suitable size.[2] Unfortunately, much of the pertinent information collected by census and vital statistics bureaux is not readily available and its publication would be costly.

6.1 *Migrants to Canada and the United Kingdom*

The Dominion Bureau of Statistics in Canada has been requested to make available its detailed tabulations on migrants to Canada which would be most useful to workers in this field. In the United Kingdom, the Birmingham Cancer Registry is now exploring the possibility of obtaining similar information for recent migrants to the Birmingham area from the West Indies and Pakistan. Data on the West Indian immigrants could usefully be compared with the rates published by the Kingston and St Andrew Cancer Registry, Jamaica.

6.2 *Cancer and other diseases in migrants to Israel*

The Agency is co-sponsoring a symposium on cancer and other chronic diseases in migrants to Israel (February 1971) (Dr J. Silberstein: RA/70/027). At this meeting the

[1] Kmet, J. (1970) *J. chron. Dis.*, **23**, 305.
[2] Staszewski, J. et al. (1970) *J. chron. Dis.*, **23**, 351.

available population-at-risk data for Jews of diverse geographical origins will be critically reviewed, and the numerator information in registers of cancer, congenital malformations, and other diseases will be examined.

7. ETIOLOGICAL FACTORS IN OESOPHAGEAL CANCER

Cancer of the oesophagus, in those areas where it is found predominantly in males, has been generally linked with excessive consumption of strong alcoholic drinks, tobacco having a synergistic role. In a few regions, nearly all with very high incidence, this cancer is as common in women as in men, and there is no clue to its etiology. Both types of situation are being studied.

7.1 *Iran* (Dr J. Kmet)

The study team, composed of Dr E. Mahboubi, Dr J. Kmet, Miss P. Cook, and Dr N. E. Day, has collected further information on the incidence of oesophageal cancer along the Caspian littoral and in neighbouring areas of Iran, and on the physical, biological, and cultural characteristics of the ecologically diverse regions of these areas (see also page 37).

(*a*) *Incidence rates* (RA/69/008, RA/70/024)

In June 1970, two years of cancer registration were completed in the province of Mazandaran and one year in the province of Gilan. Table 1 shows the age-standardized incidence rates for males and females by district. For the two districts of highest frequency, Gorgan and Gonbad, incidence is also given for the northern and southern parts (Fig. 3). To permit international comparisons, incidence rates have been calculated both for the age group 35–64 years and for all age groups.

The age-standardized incidence rates confirm previous observations based on crude rates. The outstanding features are:

(i) The incidence in northern Gonbad is among the highest recorded anywhere in the world.

(ii) Incidence is higher in women than in men in northern Gonbad.

(iii) Incidence is lower in southern Gorgan and Gonbad than in the northern parts of these districts, with a concomitant change in sex ratio, so that in the southern parts there is a slightly higher proportion of cancers in men.

(iv) On moving west, there is a steady decline of incidence and an increase in the preponderance of male cases. The difference in incidence between northern Gonbad and Gilan is 32–fold for women and 6–fold for men.

The accuracy of registration was checked by examining the frequency of visits to each doctor by the technicians who collect the cancer forms, and by analysing the regional distribution of doctors, specialist surgeons, and radiologists per head of population and the

TABLE 1. INCIDENCE OF CANCER OF THE OESOPHAGUS ALONG THE CASPIAN LITTORAL, IRAN

District	Males			Females			Sex ratio of age-standardized rates	Truncated rate [b] for age group 35-64 years	
	No. of cases [a]	Incidence [b]		No. of cases [c]	Incidence [b]			Males	Females
Mazandaran Province [d]									
Northern Gonbad	83	110.0		106	184.0		0.6	272.1	412.6
Northern Gorgan	44	90.4		36	75.1		1.2	194.0	139.8
Southern Gonbad	61	82.9		45	61.9		1.3	135.4	134.5
Southern Gorgan	51	58.5		18	25.2		2.3	95.9	59.4
Behshahr	11	17.8		12	16.8				
Sari	20	17.0		18	16.0				
Shahi	30	27.0		29	24.0				
Babol	33	24.3	25.9	9	5.2	17.0	1.5	50.4	34.7
Amol	36	44.5		28	25.0				
Nur	6	22.4		4	12.8				
Shahsavar	14	18.9		6	8.0				
Nowshahr	12	18.5	19.6	3	4.4	6.4	3.1	51.2	19.2
Gilan Province [e]									
Rudsar	11	26.7		3	7.4				
Langarud	4	23.9		1	5.0				
Lahijan	11	17.9		6	7.3				
Rasht	17	18.2		4	2.7				
Bandar Pahlavi	3	19.5	18.8	4	20.3	5.8	3.3	33.3	11.4
Sowma-Eshara	2	8.5		1	3.7				
Fowman	3	7.8		0	0.0				
Tavalesh	6	19.1		2	5.3				
Astara	2	21.4		1	15.1				

[a] Excluding 12 cases of unknown age.

[b] Rates per 100 000 per annum, age-standardized to world population structure (Segi, M. (1960) *Cancer mortality for selected sites in 24 countries (1950-1957)*. Sendai, Department of Public Health, Tohoku University School of Medicine).

[c] Excluding 20 cases of unknown age.

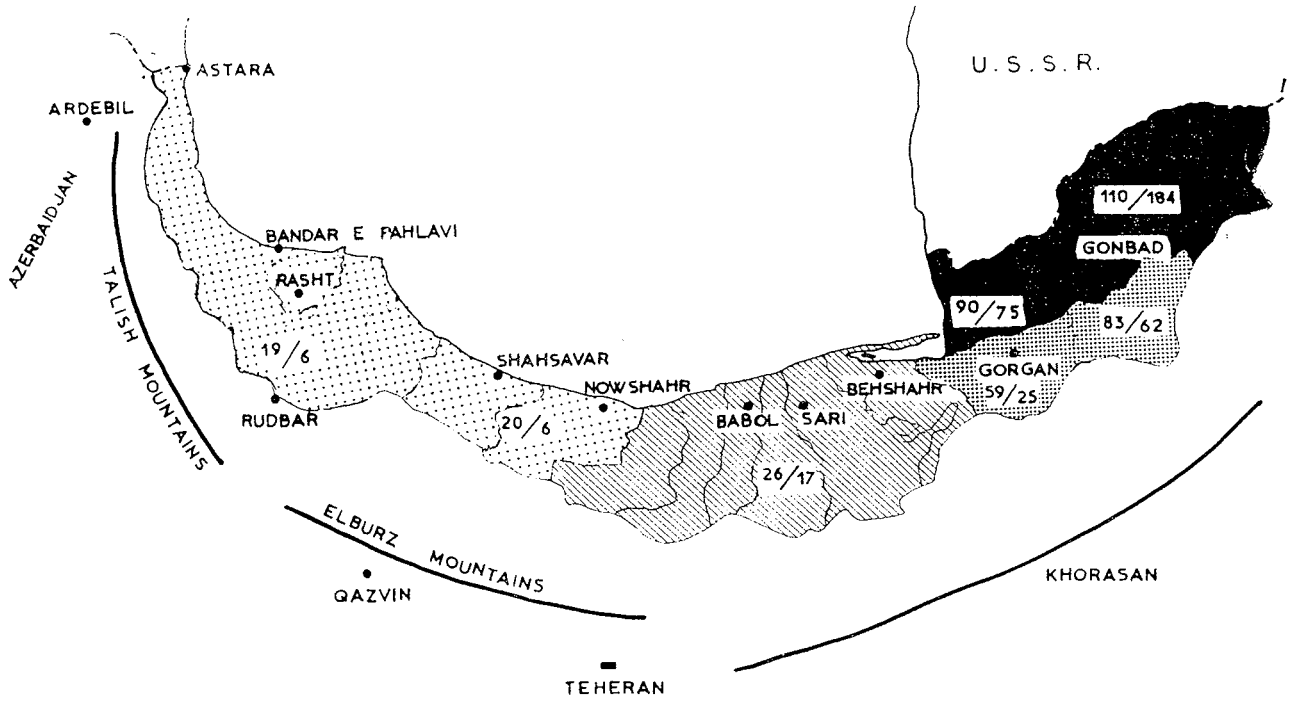
[d] July 1968-June 1970.

[e] July 1964-June 1970.

incidence of tumours of sites other than the oesophagus. There is no evidence of a bias towards over-reporting or under-reporting of oesophageal cancer cases in any region.

The northern and southern parts of the Gorgan and Gonbad districts show striking differences in the physical environment and, to a lesser extent, in the ethnic composition of the population. The northern part of each district is sparsely populated semi-desert with predominantly saline soils and is inhabited by central Asian Turkomans. The southern parts are in the Elburz piedmont, form a densely populated agricultural zone with non-saline soils and more abundant rainfall, and are inhabited principally by Iranians of Indo-European origin. In the lowest incidence area of Gilan the rainfall is over 10 times that of northern Gorgan and Gonbad. The continued westward decline of frequency within the Caspian area and reports (as yet unconfirmed by systematic registration) of a high incidence among populations of Indo-European origin on the Iranian plateau strongly suggest

FIG. 3. INCIDENCE OF CANCER OF THE OESOPHAGUS ALONG THE CASPIAN LITTORAL, IRAN
Rates per 100 000 per annum *
(Males/Females)



* Age-standardized to world population structure (Segi, M. (1960) *Cancer mortality for selected sites in 24 countries (1950-1957)*, Sendai, Department of Public Health, Tohoku University School of Medicine).

that the variation observed along the Caspian littoral reflects environmental rather than ethnic differences. As reported in 1969, there is evidence that alcohol is not implicated in the development of cancer of the oesophagus in the areas of highest frequency.

(*b*) *Environmental studies*

During the past two years, the available environmental data have been analysed to see whether any features show distribution patterns similar to that of cancer of the oesophagus.

There is reasonable coverage in broad outline of the features of the physical environment such as geology, climate, soil, and natural vegetation. The maps of natural regions prepared by the Soil Institute in Teheran for its land evaluation study are particularly useful.

The 1966 census and the village gazetteers prepared from the census returns by the Central Statistical Office in Teheran give a great deal of valuable data on the age and sex structure of the population, migration patterns, occupation and employment status, educational standards, availability of medical facilities, sources of water, types of fuel used, and crops. To supplement the published district volumes, additional census tabulations have been purchased for the smaller subdivisions of the high-frequency districts of Gorgan and Gonbad.

Sample survey data on agricultural practices, household economy, the health and genetic constitution of the people, and the adequacy of dietary intake give some indication of the situation throughout the Caspian littoral, but the sampling, planned for other purposes, does not adequately examine the regional variations on the scale needed for the studies.

(*c*) *The study plan*

The environmental data collected so far are being used to define some 10 or 12 regions within the Caspian littoral that are geographically and sociologically relatively homogeneous and cover the whole range of oesophageal cancer incidence. These will be used to sample the population for information that is not routinely available. The households of oesophageal cancer patients will be submitted to the same investigations as the selected households in the population samples.

The major gaps in the existing data on the pattern of regional variation are:

(i) figures for the ethnic composition of the population;

(ii) details of dietary customs and methods of preparing food, as well as the chemical composition of food and drinking water, including known carcinogens (see page 47) (Dr H. Hedayat: RA/70/033);

(iii) information on the habits of the population with regard to smoking, chewing, drinking, and the taking of opium;

(iv) data on the health of the population, including the occurrence of conditions such as iron, zinc, and vitamin deficiencies that may be related to oesophageal cancer etiology.

The experience of different national and university institutes in Iran in carrying out population surveys provides an immensely valuable body of knowledge on which to build this study.

Following this broad environmental approach, it should be possible to eliminate from the study the obviously non-related variables and concentrate on those that show significant correlation and are biologically meaningful.

7.2 *Brittany* (Dr A. J. Tuyns)

(*a*) *Mortality studies* (Professor L. Massé: RA/69/015)

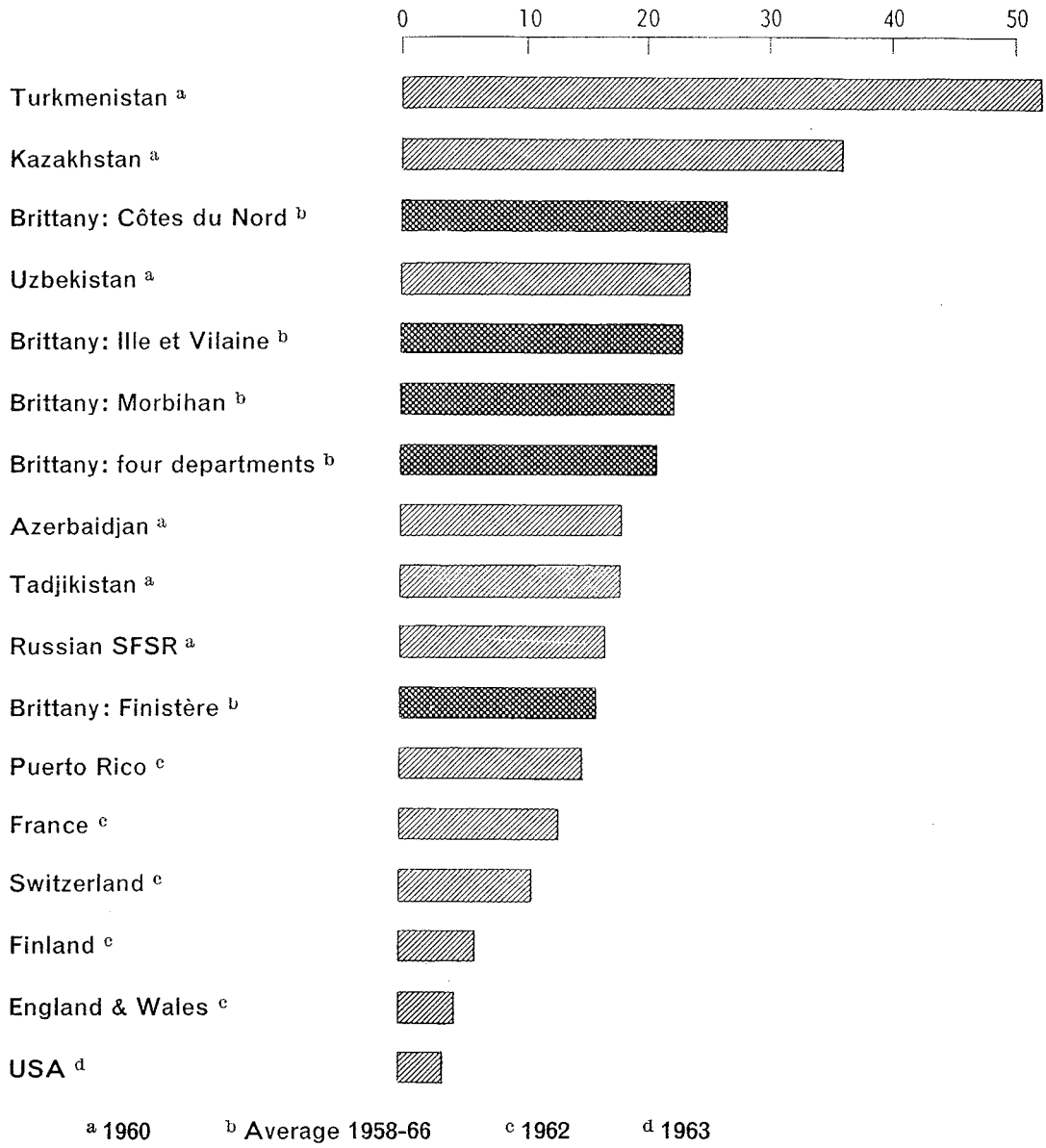
Brittany and Normandy experience the highest mortality rates in France for cancer of the oesophagus, alcoholism, and liver cirrhosis.[1,2]

Age-specific oesophageal cancer rates have been calculated for each of the four departments of Côtes-du-Nord, Finistère, Ille-et-Vilaine, and Morbihan. The age-standardized *mortality* rates for males (Fig. 4) are the highest published in the world with the exception

[1] Lasserre, C. (1963) *Thesis*, Paris.
[2] Tuyns, A. J. (1970) *Int. J. Cancer*, **5**, 152.

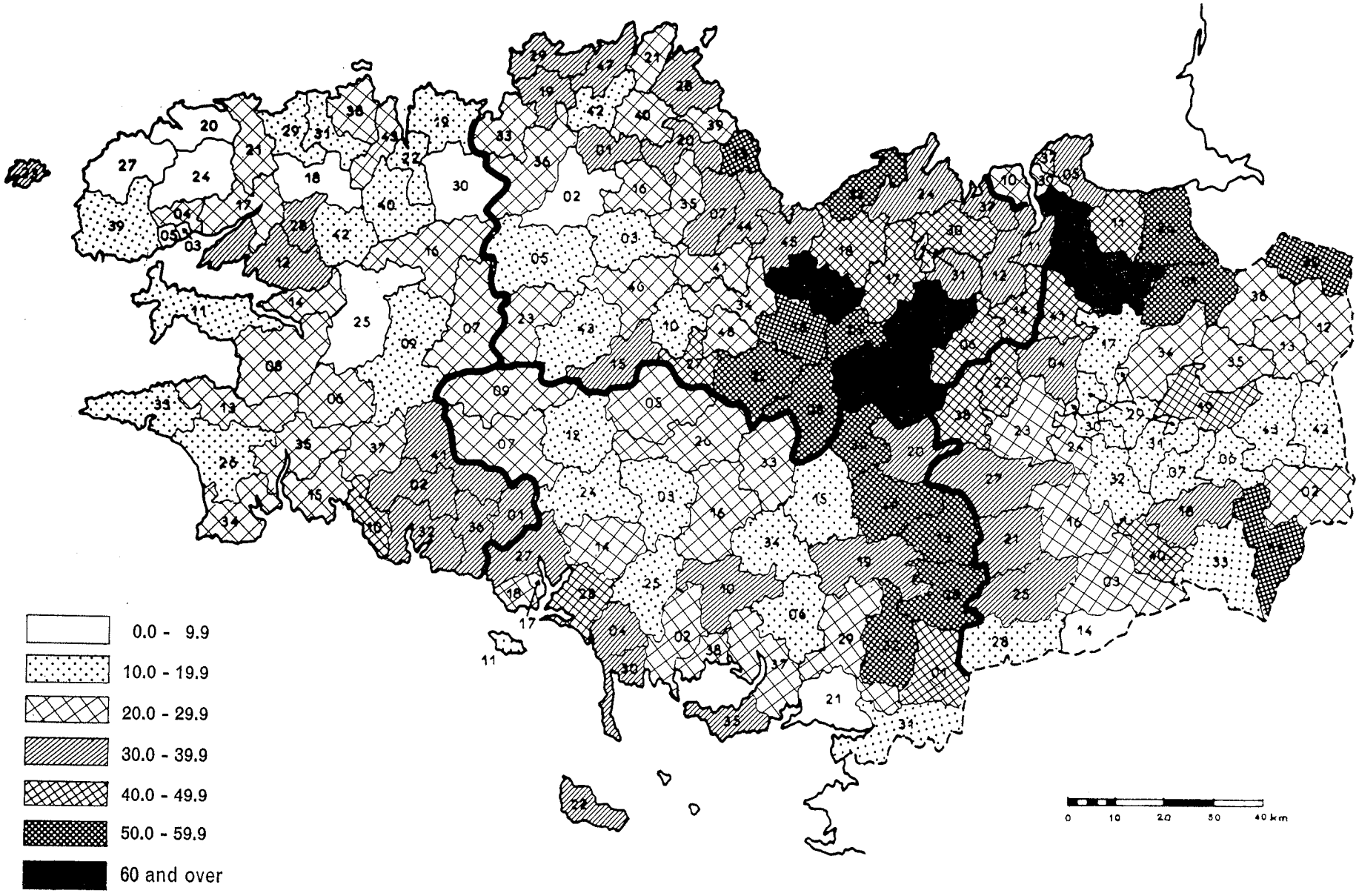
of the rates from Turkmenistan, Kazakhstan, and Uzbekistan in the USSR. The sex ratio of 10 : 1 is the highest known.

FIG. 4. CANCER OF THE OESOPHAGUS: AGE-STANDARDIZED MORTALITY RATES PER 100 000 POPULATION, MALES



Over the nine years 1958-66 there was a tendency for these rates to increase for males, but not for females. Crude mortality rates by canton (Fig. 5) indicate the pattern of distribution within the province. Recent analyses show that, after indirect standardization for age, the pattern of the map remains the same. The distribution of other causes of death, namely alcoholism, liver cirrhosis, and cardiovascular diseases, has been examined; the geographical patterns of these diseases were quite different from that of oesophageal cancer and confirm the latter's specificity.

FIG. 5. CANCER OF THE OESOPHAGUS: AVERAGE CRUDE ANNUAL MORTALITY RATES PER 100 000 POPULATION, BY CANTON, BRITTANY, 1958-66



(*b*) *Morbidity data*

Morbidity data from various sources have been collated and compared. The register of cases that has been compiled shows clearly the need to use all the sources of information in order to obtain complete medical histories. A methodological study on this aspect of the investigation is under way.

A first analysis of histopathological material has indicated that almost all cases are of the squamous cell type; the middle third of the oesophagus is involved in 50 % of the cases, the lower third in 33 %, and the upper third in only 17 %.

(*c*) *Case-control study*

A case-control study designed to test the role of alcoholic beverages and smoking is in preparation. It will involve the participation of at least three anti-cancer centres in western France (Dr J. P. Jardel: RA/70/032).

(*d*) *Co-ordination Committee*

The Co-ordination Committee for the studies in Brittany met three times in 1970. At these meetings, papers were presented on several aspects of these studies [1,2,3] that have led to the development of new techniques and methods now integrated in the teaching and research programmes of the École nationale de la Santé publique.

7.3 *Jamaica* (Dr Ulrike de Jong)

See p. 97.

7.4 *Singapore* (Dr Ulrike de Jong)

See p. 93.

7.5 *Intra-oesophageal temperature* (Dr Ulrike de Jong)

A high frequency of oesophageal cancer has been linked, in both China and Iran, to the consumption of very hot food and drinks. To examine the physiological basis for this old hypothesis, the relationship between the temperature at the lower end of the oesophagus and the temperature and volume of ingested hot beverages is being investigated at the Hôpital Edouard Herriot, Lyon (by kind permission of Dr P. Mounier-Kuhn). Preliminary results indicate that the cooling mechanisms can cope with volumes of 5 ml or less up to 65°C but are unable to deal with volumes of 20 ml or more at lower temperatures.

While further work is necessary to demonstrate that the temperature of swallowed fluid is important, the individual who takes large gulps appears to be at greater risk than the person who takes small sips, even though these are at a much higher temperature.

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[1] Meynier, A. (1970) *Bull. trim. Ec. nat. Santé publ.*, **2**, 165.
[2] Massé, L., Maufoy, J. J. & Sourty, M. J. (1970) *Bull. trim. Ec. nat. Santé publ.*, **2**, 173.
[3] Massé, L., Sourty, M. J. & Tuyns, A. J. (1970) *Cah. Social. Démogr. méd.*, **10**, 142.

8. GASTRIC CANCER AND INTESTINAL METAPLASIA

Two main histological types of gastric cancer have been described: the "intestinal" type or well-differentiated adenocarcinoma, and the "diffuse" type or undifferentiated carcinoma. Studies in Finland, Colombia, Mexico, and the United States of America have shown that these two types differ not only in morphology but also in their clinical and epidemiological features. Compared to the diffuse type, intestinal cancer has a better prognosis, a higher sex ratio, and is more frequent in older age groups and in areas of high gastric cancer incidence.

8.1 *Norway and Israel* (Dr Nubia Muñoz)

To extend these observations, studies have been carried out in Norway (Dr J. Asvall) and in Israel (Professor B. Gellei, Dr E. Liban, Dr Ruth Steinitz, Professor H. Ungar, and Professor M. Wolman).

In Norway, the time-trend of these two types of gastric cancer was studied. Stratified samples by sex and age of the histologically confirmed gastric cancer cases were drawn for three different periods: 1940-44, 1952-53, and 1964-66. From the 339 cases studied, it was found that the decline in gastric cancer rates reported during these periods was primarily due to a fall in the incidence of the intestinal type. This decline was more marked in persons under 50 years of age.

In Israel, the distribution of the two types of gastric cancer was studied in 278 cases from different migrant groups. The intestinal type was more frequent among migrants from high-risk areas for gastric cancer, such as Eastern Europe and the USSR, than among migrants from low-risk areas, such as Iraq and Iran, or subjects born in Israel.

8.2 *Yugoslavia* (Dr Nubia Muñoz)

Intestinal metaplasia may be a precancerous lesion for the intestinal type of gastric cancer: firstly, a correlation between the risk for gastric cancer and the prevalence of intestinal metaplasia has been reported for different racial groups, and secondly, a transition from intestinal metaplasia to intestinal-type carcinoma has been reported in man and laboratory animals.

To study this relationship further, a collaborative research agreement (RA/70/015) has been made with Dr I. Matko of the Department of Gastroenterology, University of Ljubljana, Yugoslavia. A total of 807 blind and 437 guided gastric biopsies, taken from 1965 to 1970, were reviewed for the presence of intestinal metaplasia and some 325 cases were found. A retrospective case-control study has been started to determine some of the demographic and clinical characteristics associated with intestinal metaplasia and also to determine the risk of developing gastric cancer among persons with this lesion in comparison with a control group. The results of this inquiry will be confirmed by a prospective study.

9. EPIDEMIOLOGICAL AND SEROLOGICAL SURVEYS OF LIVER CANCER IN AFRICA

These studies, under the general direction of Dr A. J. Tuyns, are closely linked with the liver cancer work undertaken by the Nairobi Regional Centre (see page 86).

9.1 *Dakar* (Dr L. Leblanc)

A study has been designed to provide an estimate of the prevalence and incidence of primary liver cancer and to clarify time relationships between a positive α_1–fetoprotein test and the appearance of clinical symptoms. This study, which is also supported by the Anna Fuller Fund, is now developing satisfactorily after the initial difficulties in 1969. The project involves 9864 male adults, made up of workers in 36 factories (7013 persons) and 11 groups from the Senegalese Army (2851 persons). Five bleeding sessions have taken place at 4–month intervals.

In the course of the study, the investigator was faced with the problem of "losses", and had to decide whether to make every effort to obtain blood each time and run the risk of really "losing" cases, or whether emphasis should rather be placed on obtaining information on health status even without subsequent bleeding. The latter course was chosen and arrangements were made for identity and health controls. As a result, the number of persons actually bled at the most recent session had fallen to 3508, i.e., 37 % of the total, but the number lost to view was reduced to 356, or 4 % of the total.

A total of 22 401 blood samples had been collected and examined by 1 December. The total number of man-years of observation has been estimated at 8062 (corresponding roughly to a year of observation for most of the study population and a little less for a few groups). Six persons with liver cancer were detected: four at the first bleeding and two at second or subsequent examinations. This would suggest an approximate crude prevalence rate in the male adult African population in Dakar of 70 per 100 000 per annum. In connection with this survey, blood samples from the Senegalese soldiers have also been tested for the Australia antigen by Dr A. M. Prince, using electro-osmophoresis; 12 % were found to be positive for the antigen. In a sample of 220 sera from liver cancer patients, 42 % were positive.[1] To follow up this finding, a more systematic study of liver disease is now being planned in collaboration with the Faculty of Medicine of Dakar.

9.2 *Ivory Coast*

The serological survey (Dr F. Sérié: RA/69/011) to detect primary liver cancer by the α_1–fetoprotein test started in January 1970. Representative samples of villages in the north and south of the country, i.e., in the savannah and forest regions respectively, had previously

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[1] Prince, A. M. et al. (1970) *Lancet*, **2**, 717.

been selected. The target population in each zone was 11 000; 7638 were bled in the south (69 %) and 9203 in the north (84 %). The overall participation in the first blood collection was thus 76.6 % (Table 2).

TABLE 2. SEROLOGICAL SURVEY IN IVORY COAST, 1970: RESULTS OF FIRST BLEEDING, BY SECTOR

Randomly selected villages								
Sector	Ethnic group	Target population	Census population	Expected number of adults	Number bled	Percentage of expected number bled	Percentage of target number bled	Date of first bleeding
Abidjan	Lagunaires (6 villages)	3 000	6 253	2 651	1 976	74.5	65.9	20 Jan.-2 Mar.
	Akans (9 villages)	2 000	6 702	2 956	1 666	56.4	83.3	
	Total	5 000	12 955	5 607	3 642	65.0	72.8	
Adzopé	Lagunaires (7 villages)	3 000	8 669	4 130	2 491	60.3	83.0	10 Feb.-24 Mar.
	Akans (7 villages)	3 000	6 319	2 360	1 505	63.8	50.2	
	Total	6 000	14 988	6 490	3 996	61.6	66.6	
Bouaké	Akans (12 villages)	3 000	6 692	3 280	2 506	76.4	83.5	4 Mar.-7 Jun.
	Senoufos (11 villages)	3 000	6 205	2 640	3 702	140.2	123.4	
	Total	6 000	12 897	5 920	6 208	104.9	103.5	
Korhogo	Senoufos (47 villages)	3 000	9 658	4 260	2 402	56.4	80.1	24 Feb.-13 Apr.
	Malinkes (5 villages)	2 000	4 141	1 830	593	32.4	29.7	
	Total	5 000	13 799	6 090	2 995	49.2	59.9	
Grand total		22 000	54 639	24 107	16 841	69.9	76.6	

Two cases were detected, a 55-year-old man who died a few weeks later, and a woman of 30, apparently healthy, whose condition later deteriorated rapidly.

In three sectors out of four, a second blood collection took place in the spring; 8827 sera were collected compared with 10 627 at the first bleeding (a drop of 17 %); these included the sera of 1343 new subjects who were registered but not bled at the first visit (Table 3). One new case was discovered in a village in the north.

TABLE 3. SEROLOGICAL SURVEY, IVORY COAST, 1970: SERUM SPECIMENS COLLECTED AT FIRST AND SECOND BLEEDINGS IN THREE SECTORS

Sector	Ethnic group	Serum specimens collected at first bleeding	Serum specimens collected at second bleeding		
			From the same persons	From persons registered but not bled at first bleeding	Total for second bleeding
Abidjan	Lagunaires	1 976	1 360	273	1 633
	Akans	1 666	926	267	1 193
	Total	3 642	2 286	540	2 826
Adzopé	Lagunaires	2 481	2 001	178	2 179
	Akans	1 509	778	467	1 245
	Total	3 990	2 779	645	3 424
Korhogo	Senoufos	2 402	1 969	158	2 127
	Malinkés	593	450	—	450
	Total	2 995	2 419	158	2 577
Grand total		10 627	7 484	1 343	8 827

The third bleeding (the second in the area of Bouaké) was planned for October-November: in view of the cholera epidemic, however, the teams of the Organisation de Coopération et de Coordination pour la Lutte contre les Grandes Endémies were engaged in an active campaign of vaccination and the collection of sera was postponed until December.

It is planned to examine the sera available further by more sensitive methods (RA/68/014). A first group of 3000 sera has been forwarded to the Gamaleja Institute, Moscow, for this purpose. It is envisaged to extend this examination to more sera in Abidjan itself, if possible. Dr P. Sizaret has been closely associated with this aspect of the work.

In parallel with the serological survey, a food survey has now been started in the same areas. The sampling and analysis techniques are similar to those successfully used in Murang'a (see page 86). The food samples will be dried and lyophilized at the Department of Nutrition of the Institut national de la Santé publique in Abidjan, and then forwarded to the IARC Regional Centre in Nairobi for analysis (Dr F. Sérié: RA/70/012).

10. CLASSIFICATION OF MALIGNANT NEOPLASMS

10.1 *Reticulo-endothelial system malignancy* (Dr H. Tulinius)

The unit is collaborating with the Commission of Epidemiology of the UICC and participates in the Sub-Committee on Geographical Pathology, the main purpose of which is to clarify the epidemiology of reticulo-endothelial malignancies.

There is epidemiological evidence that the diagnostic label "Hodgkin's disease" embraces at least two biological entities.[1] Further, the disease seems to be much commoner in children in South America than would be expected. Lymphatic leukaemia and lymphosarcoma have long been suspected to be of low incidence in the Far East and there is good evidence for the existence of a high frequency of primary intestinal malignant lymphoma in the countries of the Middle East. The foregoing statements are largely based on series that are probably selective, and there has been little attempt to examine, using uniform morphological criteria, all cases of these diseases occurring in defined populations. The unit has arranged for a detailed re-evaluation of the classification of these malignancies in Israel for the years 1964-68, in Norway for 1968, and in Iceland for the years 1955-69.

10.2 *Classification evaluation* (Dr A. J. Tuyns)

Neoplasms of many sites have more than one histological classification scheme, but the reproducibility of these is rarely evaluated. A mathematical model is available for the evaluation both of the classes of the classification and of the criteria on which they are based. Meetings have been held with representatives of the Cancer unit of WHO (Dr L. H. Sobin) and of the European Organization for Research on Treatment of Cancer to plan the application of the model to existing slide collections.

11. OTHER STUDIES

11.1 *Occult carcinoma of the prostate* (Dr H. Tulinius)

It has been suggested that the low rates for prostate carcinoma noted in certain countries are linked with a failure of the so-called "occult" carcinomas to invade and metastesize.

A study has been designed in which prostates removed at necropsy from persons in selected age groups will be examined to assess the conversion rate from occult to invasive carcinoma. This will be done in several areas where there are cancer registries, including Kampala (Uganda), Jamaica, Hong Kong, Israel, Singapore, Homburg-Saar (Federal Republic of Germany), Malmö (Sweden), and Tallinn (Estonian SSR). Extension of the study to include investigation of the role of marital status, cadmium exposure, and changes in the interstitial cell mass of the testis is being considered.

11.2 *Cervical cancer* (Dr J. Kmet)

Dr Kmet continues to act as consultant to the US-Yugoslav team studying the possible venereal nature of cervical cancer in Muslim and Christian populations in Yugoslavia.

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[1] MacMahon, B. (1966) *Cancer Res.*, **26**, 1189.

11.3 *Physiological aging* (Dr H. Tulinius)

Some of the changes associated with aging are considered to be physiological. To examine those factors that may be related to cancer, the physiological aging process has to be better understood. The unit is preparing suggestions as to which parameters, measured at the time of autopsy, would be most useful in elucidating this process.

12. BIOSTATISTICS (Dr N. E. Day, Mr D. K. Jain)

The Biostatistics section has been involved in the planning of the statistical aspects of the laboratory and field programmes. It has also developed the computing and data processing service of the Agency.

12.1 *Collaborative work*

(*a*) *Nasopharyngeal cancer sero-epidemiology*

Assistance was given in the design and planning of the sero-epidemiological survey, now in progress in Singapore and Hong Kong, aimed at elucidating the natural history in human populations of a particular herpes-type virus associated with nasopharyngeal carcinoma (see pp. 48-50).

(*b*) *Prospective study of Burkitt's lymphoma*

Assistance is being given in the design and planning of a prospective study to investigate the role of the Epstein-Barr virus in the etiology of Burkitt's lymphoma. This has necessitated two field trips to the West Nile district of Uganda to enable participants in the study to become fully acquainted with the area and the people who will be involved. The analysis of the basic data for the prospective study, in particular the results of the West Nile Health Survey and all the relevant incidence data, has been completed (see p. 59).

(*c*) *Epidemiology of Burkitt's lymphoma*

Various projects are under way to establish the incidence of Burkitt's lymphoma in other regions of Africa, notably north-west Tanzania, Ghana, and parts of Nigeria, and also to attempt to establish space-time clustering in a region other than the West Nile.

(*d*) *Immunological studies in Burkitt's lymphoma and nasopharyngeal carcinoma*

The extent to which different antibody-antigen components can be separated and identified is of prime importance in serological work in Burkitt's lymphoma and nasopharyngeal carcinoma. Mathematical models to describe the behaviour of a complex antibody-antigen system are being developed, and the experimental results so far obtained are being analysed in terms of these models. The analysis pinpoints both the degree of indeterminacy of the results and the further information needed to establish a unique representation of the system.

(*e*) *Evaluation of serological techniques*

Collaboration is continuing on the design and analysis of experiments to establish the reproducibility of two methods of detecting Epstein-Barr virus-associated antibodies:

(i) paired radioactive-iodine-labelled tests;

(ii) indirect immunofluorescence tests.

(*f*) *Levels of DDT in man and mice*

So far, only peripheral aspects of the DDT investigation have been analysed, i.e., the levels of DDT and its metabolites in human fat tissue from populations in different regions of the world, the concentration of DDT and its metabolites in different organs from the DDT-fed mice of the Lyon experiment, and toxicity trials of the various metabolites. The data processing of the main DDT experiment is under way, and analysis will start when the results are sufficiently complete (see p. 66).

(*g*) *Dimethylbenzanthracene skin-painting experiments*

The analysis of various experiments in which the skin of mice was painted with different levels of dimethylbenzanthracene has demonstrated the existence of two types of tumour induction and suggested a threshold effect for the early type of induction. Experiments are being planned to confirm the existence of this threshold.

(*h*) *Cancer of the oesophagus in Iran*

Work is progressing on the design of future studies in Iran of the etiology of oesophageal cancer and on the analysis of available material, with a view to both the construction of sampling frames and the development of testable hypotheses. Comprehensive models are being constructed to elucidate the relationship of various types of epidemiological investigation (case-control studies, population-based studies) to different parameters.

(*i*) *Cancer of the penis in Uganda*

Data collected in Uganda on the varying incidence of penile cancer by tribe, district, and immigrant status have been analysed, and differences of considerable epidemiological interest have been established (see p. 62).

(*j*) *Aflatoxin survey in Murang'a district, Kenya*

When the environment, or a part of the environment such as diet, is sampled for levels of a particular contaminant, the results often take a form that is unsuitable for conventional types of analysis. The data from the aflatoxin survey illustrate this point clearly, for while most samples collected contained either no aflatoxin or so little that it was undetectable (below 1 part per 10^9), the distribution of the aflatoxin levels in the positive samples was highly skewed. This has necessitated the construction of a statistical model that fits the data well enough to validate any conclusion based on it.

(*k*) *Vaccine trials*

Since it is widely believed that vaccination against cancer is imminent, designs were constructed for testing the efficacy of possible vaccines. From this work, it was clear that there is a wide gap between what is feasible in the laboratory and what is acceptable as an epidemiological study.

12.2 *Development of computer facilities*

During the year, a remote access terminal was installed with connexions both to the IBM 360/40 computer in Geneva and to a similar machine in Lyon. This is providing excellent service and greatly facilitates the development and routine use of programmes. The planned upgrading of the Geneva installation should provide an even better service in the future. Close watch is being kept on all developments that will give the IARC a more economical or efficient service.

12.3 *Development of data processing services*

With the installation of new machinery, the Biostatistics group is now in a position to undertake all the data processing for the Agency. The basic material from Volume II of *Cancer Incidence in Five Continents* has now been stored on disc.

12.4 *Other projects*

(*a*) *Development of factor analysis models*

Models are being developed in which the values of a range of variables when measured on a group of individuals are expressed in the form:

Value of variable i on individual j = Function $(a_i \cdot b_j')$

where a_i and b_j' are vectors of smaller dimension than either the number of variables or the number of individuals.

Two types of model are being considered. The first relates to the situation when the variables are dichotomous. In this case, the function in the above equation is taken as the logistic and interpreted as the probability of a variable taking one of its two possible values. As an application, an attempt is being made to construct a differential diagnosis of Hodgkin's disease on the basis of histological data (supplied by Dr G. Newell, Tulane University, New Orleans, La., USA). Secondly, in conjunction with the immunological studies on Burkitt's lymphoma and nasopharyngeal carcinoma, specific models are being constructed for the uptake of different sera on different cell lines. In this situation, where the factors represent the components of the antigen-antibody system, a unique representation of the sera and cell lines in the factor space is required. For this purpose an extension of normal factor analysis is necessary, as non-uniqueness in the representation of the factor space is

a feature of most forms of factor analysis. By making use of the extra information that can be obtained from serum-cell line systems, methods to obtain the required uniqueness have been developed.

(*b*) *Analysis of age incidence curves*

The patterns that exist among age incidence curves for specific sites are being analysed. This is an extension of previous work by others,[1] in which the age-incidence relationship is assumed to have a particular form. One of the aims is to develop less arbitrary forms of age standardization, both for incidence and for ratio data.

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[1] Doll, R., Cook, P. J. & Fellingham, S.A. (1969) *Int. J. Cancer*, **4**, 93.

2. UNIT OF ENVIRONMENTAL CARCINOGENS

Staff: Dr P. Bogovski (Chief)
Dr E. Boyland (Consultant)
Mr E. A. Walker
Mr M. Castegnaro

Supporting staff: 3

1. INTRODUCTION

Now that the unit has been installed in the Agency's temporary building, it will be able for the first time to develop its own research programme. An analytical chemical laboratory has been staffed and is being equipped and brought rapidly into use. Animal experimental facilities are also available.

Meanwhile, collaborative programmes on the polycyclic aromatic hydrocarbons (PAH), the nitrosamines, and asbestos carcinogenesis have continued, since these were considered as priorities by the joint IARC/UICC committee that met in 1968.

The importance of accurate quantification of environmental carcinogens is evident in any correlation study of carcinogens. In the long-term prospect of a world monitoring system of environmental factors, it is even more vital. The unit is very much concerned with investigating the feasibility of developing standardized analytical techniques capable of providing data on the environment for possible correlation with data gathered from cancer registries.

2. QUANTITATIVE DATA ON ENVIRONMENTAL CARCINOGENS

2.1 *Polycyclic aromatic hydrocarbons*

An "International Bank of Standard PAH Samples" has been organized in the Chemistry Section of the Air Pollution Control Division of the Environmental Health Centre, Ottawa, which has considerable experience in the purification and analysis of PAH (principal investigator: Mr J. L. Monkman—RA/70/025). The Bank will provide purified standard reference samples of carcinogens to laboratories collaborating with IARC. The IARC Working Group on PAH in Air (Geneva, 10-12 December 1969) decided that the following six hydrocarbons were to be analysed in air samples: benzo[*a*]pyrene, benzo[*e*]pyrene, benzo[*k*]fluoranthene, benzo[*g,h,i*]perylene, coronene, and benzo[*a*]anthracene. Standard

reference samples of these compounds can now be obtained from Mr Monkman. Reference samples have so far been despatched to two laboratories.[1]

2.2 N-*nitroso compounds*

(*a*) *Analytical methods for* N-*nitroso compounds in the environment — Forschergruppe für Präventivmedizin, Max Planck Institut für Immunobiologie, Freiburg, Federal Republic of Germany* (RA/68/016)

Principal investigator: Dr R. Preussmann

Considerable progress has been made towards the achievement of standard analytical procedures for nitrosamines. The first step demands adequate separation methods for complex analytical samples of varied origin. The two most useful techniques have been shown to be steam-distillation [2] and subsequent thin layer chromatography.[3]

The application of gel-chromatography has been investigated. It was found that a series of 6 homologous dialkylnitrosamines from dimethyl- to di-n-hexyl-nitrosamines can be effectively separated on Sephadex LH-20.[4]

A major effort has also been made to improve methods for end-determination of nitrosamines. Most available methods are too sensitive to impurities in the sample, and so an improved method, based on the formation of derivatives, was sought. It was found that *N*-nitroso compounds were quantitatively cleaved to form secondary amines and nitrite under very mild conditions (15 min at room temperature, or 12 min at 50°C), using hydrobromic acid in anhydrous acetic acid. The liberated nitrite can be captured by diazotation of sulfanilic acid, which is then coupled to form an azo-dye that can be determined colorimetrically. Thus a new and very sensitive method of nitrosamine determination was developed. Under optimal reaction conditions, a series of 17 nitrosamines was determined with an average recovery of 99.5 %. Nitrosamides can also be determined by this method.[5]

The essential advantage of the new method lies in the possibility of the identification and quantitative determination of the liberated secondary amine, which can be captured and qualitatively and quantitatively estimated in the form of suitable derivatives. The use of the two procedures will thus give a determination of trace amounts of nitrosamines with high specificity and accuracy.

Among other methods being studied is one involving fluorescent derivatives of nitrosamines, which might prove suitable for determination of nitrosamines in the field. Derivatives suitable for gas chromatography and for mass spectroscopy are also being sought.

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 30.
[2] Eisenbrand, G., Hodenberg, A. V. & Preussmann, R. (1970) *Z. anal. Chem.*, **251**, 22.
[3] Eisenbrand, G., Spaczynski, K. & Preussmann, R. (1970) *J. Chromat.*, **51**, 503.
[4] Eisenbrand, G., Spaczynski, K. & Preussmann, R. (1970) *J. Chromat.*, **51**, 304.
[5] Eisenbrand, G. & Preussmann, R. (1970) *Arzneimittel-Forsch.*, **20**, 1513.

(*b*) *Nitrosamines in alcoholic beverages*

Samples of alcoholic beverages have been collected from Puerto Rico, Jamaica, Iran, Singapore, and Brittany. Analysis for nitrosamines has been carried out, in the British Food Manufacturers' Industrial Research Association laboratories, Leatherhead, Surrey, United Kingdom, by Dr C. L. Walters. So far, 47 samples have been analysed, but the results obtained both by polarographic and photolytic methods have been shown to be inconsistent and subject to interference. The application of a cadmium column for nitrite release from nitrosamines is currently being investigated for its possible use as a screening test. Results so far have been somewhat disappointing owing to the limited reduction by the column of nitrosamines of low molecular weight, such as the dimethylnitrosamines. While the extent of possible interference from other compounds is not yet known, present indications are that these should be limited in number. It would therefore appear unwise to abandon this screening technique entirely at this stage.

(*c*) *Catalysis of nitrosamine formation by saliva* (Dr E. Boyland)

The rate of formation of nitrosamines from secondary amines and nitrous acid is known to be increased by many substances. Sodium thiocyanate which is present in human saliva has been shown to have this property, and normal saliva can increase the rate of nitrosamine formation several hundred-fold. The thiocyanate concentration is much higher in the saliva of smokers than in that of non-smokers, and a smoker's saliva could therefore greatly increase the rate of nitrosamine formation in the mouth or stomach.

(*d*) *IARC meeting on nitrosamines*

A meeting was convened (Lyon, 21-22 September 1970) to discuss problems of nitrosamine analysis related to IARC projects. The problems involved in the sampling and storage of samples were discussed, as well as recent trends in the development of analytical methods for alcoholic beverages and food. The need for the determination of nitrosamine precursors (nitrite and secondary amines) was stressed.

2.3 *Determination of precursors of nitrosamines in food and beverages* (Mr E. A. Walker)

In vitro studies have shown that secondary amines can be nitrosated to give nitrosamines under mild physiological conditions.[1] It is therefore important not only to determine the presence of nitrosamines but also that of their precursors. Since secondary amines are widely distributed in food products, the nitrite content becomes the critical factor. For this reason attempts have been made to determine the nitrite content of food and beverages.

Determination of the nitrite content of cider and apple juice (from Brittany and Normandy) has been started. The field of examination has been narrow, and the values

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[1] Mirvish, S. (1970) *J. nat. Cancer inst.*, **44**, 633; International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 52.

found do not differ greatly from those for samples taken from local tap water, being of the order of less than 1 ppm. Similar results have been obtained on a sample of salt from Mashad, used in Iran for salting fish and preferred by consumers to salt from other sources. The values found compare closely with those for samples of table salt purchased locally, and the nitrite content was shown to be of the order of 1 ppm. By use of the cadmium column, determinations of the nitrate content were also made, and it was found to be of a similar order to the nitrite content. Although such small concentrations would be unlikely to give rise to high concentrations of nitrosamines, their presence cannot be entirely ignored.

2.4 *Advisory Committee on Environmental Carcinogens*

The Advisory Committee on Environmental Carcinogens held its first meeting at the Eppley Institute for Research in Cancer, Omaha, Nebr., USA, in June 1970. During the meeting (IARC Internal Technical Report No. 70/004), the continuation and expansion by the IARC of the UICC report on the quantification of environmental carcinogens [1] was discussed. It was proposed that the IARC should produce a compendium on carcinogenic chemicals with special reference to those possibly related to cancer of the gastro-intestinal tract in man. The publication by the Agency of a series of handbooks for analytical chemists was also recommended.

It was decided to hold the next meeting in Teheran, from 10 to 12 May 1971, to discuss carcinogenic compounds possibly related to oesophageal cancer in humans.

2.5 *Working group on analysis and formation of nitrosamines*

A meeting, to be held jointly with the German Cancer Research Centre, will take place in Heidelberg, Federal Republic of Germany, from 13 to 15 October 1971. The group will review the progress made in the detection and determination of nitrosamines since the first meeting held in October 1969 in London and plan future international activity in this field.

The formation of *N*-nitroso compounds *in vitro, in vivo,* and in the environment will also be discussed.

3. ASBESTOS PROJECT (RA/70/014)

Medical Research Council Pneumoconiosis Research Unit, Landough Hospital, Penarth, Glamorgan, Wales

Principal investigators: Dr J. C. Gilson, Dr J. C. Wagner

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[1] Shubik, T., Clayson, D. B. & Terracini, B., ed. (1970) *The quantification of environmental carcinogens.* Geneva (UICC *techn. Rep. Ser.*, vol. 4).

3.1 *Finland*

(*a*) *Retrospective-prospective mortality study of the working population of two anthophyllite-asbestos mines in Finland* (Dr L. Meurman and Dr R. Kiviluoto)

The records for this investigation have now been completed and are being analysed by Dr Matti Hakama of the Finnish Cancer Registry in Helsinki. It is hoped that, in the new analysis, the separation of the miners with more than ten years' service from the rest will give a clearer indication of the effect of exposure to anthophyllite dust. The incidence of carcinoma of the lung appeared to be twice as high in the miners as in the controls.

(*b*) *Pathology of lungs exposed to asbestos dust in the Finnish asbestos area*

Lungs from 84 cases have been examined histologically and "asbestos bodies" counted by the thick section technique. The amount of collagen present has now been estimated chemically by Dr Tudor Morris at the Medical Research Council Pneumoconiosis Unit in South Wales. It is now considered that the number of asbestos fibres should be investigated by the maceration method developed by Dr C. Gold before an attempt is made to establish a relationship between asbestos in the lung tissue, the histological findings, and the chemical collagen estimation. In collaboration with Dr K. Wusteman of the Biochemistry Department, University College of South Wales and Monmouthshire, Cardiff, the pleural plaques are being studied. Dr L. Meurman is continuing his search for mesotheliomas amoug workers in Finnish anthophyllite asbestos mines, but no case has so far been diagnosed.

3.2 *United Kingdom*

(*a*) *Mesothelioma register*

The year was spent in examining material that had not already been seen by the pathology panel and, where necessary, requesting clinical and occupational histories from the epidemiologists reporting the cases. In this way, it is hoped to be able to obtain full pathological/clinical and occupational details on the 700 cases that have been reported in various parts of the United Kingdom. Professor P. C. Elmes, of Belfast, is co-ordinating the clinical and epidemiological aspects of this study. Included in this investigation will be the material from the five major surveys in the United Kingdom mentioned in the previous report. This is the largest series of mesotheliomas that has ever been available for study.

(*b*) *The Ten Centre International Survey*

The lungs of 200 consecutive adult necropsies from Glasgow, Liverpool, East London, West London, Belfast, Dorchester, Nottingham (all in the United Kingdom), Galway (Ireland), Dresden (Democratic Republic of Germany), and Kupio (Finland) have now been prepared in a standard manner and examined by twelve pathologists. IARC support was used in obtaining the material from Galway, one of the non-industrial control areas

from which information on a few cases is still awaited. Material from one control and one heavily polluted area has been examined by Dr F. D. Pooley. Using electron microscopy and electron diffraction, he has confirmed the presence of asbestos fibre in the cases in which "asbestos bodies" had been found by pathologists using optical microscopy. The majority of these "bodies" were formed on crocidolite, or amosite, fibres.

(*c*) *Identification of asbestos in tissue* (Dr F. D. Pooley, Department of Mineral Exploitation, University College of South Wales and Monmouthshire, Cardiff)

In the course of studies partly supported by IARC, the identification of various types of asbestos in tissue has been confirmed. It has been necessary to obtain electron-diffraction patterns on approximately 100 further samples of amphibole asbestos for reference standards against which to check fibres seen in human lungs. All the necessary diffractions have now been taken and measured, and the data are in the final stages of computation. A comparable study using X-ray powder diffraction equipment has also been performed to check the accuracy and sensitivity of the electron diffraction technique employed.

The technique is being used for the identification of types of asbestos seen in cases with mesothelioma and controls from the Netherlands, Sweden, New York, and various centres in the United Kingdom It is hoped to obtain material from Canada and South Africa as well, to enable a full international comparison to be made.

Samples from an asbestos mine in Vermont, USA, where the chrysotile differs in formation from that in the main mines in Canada, are being analysed for comparison with other chrysotile samples.

A significant difference between crocidolite from the Cape and crocidolite from the Transvaal has been confirmed.[1]

(*d*) *Exfoliative cytology in the diagnosis of diffuse mesotheliomas* (Dr Blanche Butler)

The findings from cases of mesothelioma and other tumours producing pleural and peritoneal effusions are being compared by exfoliative cytology. The use of enzyme identification as a means of diagnosing mesotheliomas is being studied in collaboration with Dr H. T. Planteydt (Middelburg, Netherlands).

3.3 *USA*

New diagnostic criteria have been developed by Dr R. Echeverria (University of Florida, Gainsville, USA), who claims that they can differentiate mesotheliomas from other neoplasms. It would be valuable if these criteria could be applied to the classification of mesotheliomas in the asbestos project. It is planned to send samples of human and experimental material to Dr Echeverria.

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[1] Timbrell, V., Griffiths, D. M. & Pooley, F. D. (1971) *Nature* (in press).

3.4 *USSR*

Investigation of the comparative carcinogenic action of shale-oil and chrysotile asbestos dust in rats — Institute of Experimental aud Clinical Medicine, Tallinn (RA/69/017)
Principal investigator: Dr A. Võsamäe

Long-term experiments have been started in Wistar and non-inbred rats. Repeated intratracheal injections of benzo[*a*]pyrene suspensions, with or without shale-oil and chrysotile asbestos dust, have been made. In each of the 9 groups some animals have died, but a sufficient number have survived for 5 months. The first lung tumours were observed in experimental groups.

3.5 *Netherlands* (Dr H. T. Plandeyt)

Histological material from mesotheliomas occurring in dockyard workers at Flushing, Netherlands, has been sent for examination to Dr Pooley in Cardiff.

3.6 *International classification of radiographic appearances of the pneumoconioses*

A classification of the radiographic appearances of the pneumoconioses prepared by a committee of the UICC has now been published [1] and sets of standard films prepared for distribution. This was originally a UICC project, but now has some financial support from the Agency.

3.7 *Proposed working party meeting on asbestos and health, 1972*

It has been suggested that the working group on asbestos cancers which met in New York in 1964, under the auspices of the UICC, should report back on the progress made in the studies recommended and consider what further aspects require investigation. With the change in the policy of UICC, it is hoped that this working group may meet under the auspices of the IARC. Consideration has been given to the organization of such a meeting, and it was agreed that the original three panels—on epidemiology, pathology, and physics and chemistry—should be reconstituted. Persons who have actively contributed to the various studies during the period 1964-70 have been suggested as participants. All aspects of the problem—apart from engineering control, legal matters, and other aspects of compensation—would be discussed. It is intended that preprints by individual participants on their special topics should be circulated before the meeting. These would provide an up-to-date summary of present knowledge on which an authoritative report could be based. In some instances special international studies will be needed beforehand, for example by the panel on pathology for the discussion of criteria and test agreements between observers in the diagnosis of mesothelioma and other pleural and peripheral lung tumours.

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[1] *Chest*, 1970, **58**, 57.

Professor W. T. E. McCaughey, of Dublin, who was appointed to report on the criteria for the diagnosis of mesotheliomas, received support for a visit to Ottawa, where he went through the material collected by Professor D. Magner in collaboration with Canadian epidemiologists.

4. STUDIES IN ORGAN CULTURES ON POLYCYCLIC AROMATIC HYDROCARBONS

The organ culture studies have been temporarily interrupted and are to be resumed in 1971 when new IARC laboratory facilities will be available.

5. CARCINOGENIC AND MODIFYING FACTORS RELATED TO OESOPHAGEAL CANCER

5.1 *Field studies in Iran*

Following a visit to the study area in Northern Iran (provinces of Mazandaran and Gilan) in November 1970, arrangements have been made, in collaboration with the Unit of Epidemiology and Biostatistics, for the collection of samples and the determination of carcinogenic compounds in food, water, and other environmental sources.

Food and water samples will be collected with the assistance of the Public Health Research Institute of the University of Teheran, and within the framework of a collaborative research agreement (RA/70/033) between the IARC and the Food and Nutrition Institute of Iran. The possibilities were discussed of carrying out routine analytical work in local laboratories and of training chemists in the IARC chemical laboratory at a later stage.

Since food habits had changed considerably over the last two decades, it would be necessary to prepare a number of food items, such as dried meat and dried and smoked fish, under the conditions in which they were prepared 10-20 years ago. These could then be examined for the presence of suspected carcinogenic compounds, in order to investigate any possibility of a causal relationship between eating habits in the past and the current incidence of oesophageal cancer.

Some samples of food and water were taken for preliminary determination of nitrosamines and their precursors.

5.2 *Laboratory studies—combined exposure to carcinogens and phenols*

Animal feeding experiments (Charles River CD random-bred rats, albino strain) have been started in order to investigate the effect of ingested water-extractable fractions of tea, which contain large amounts of polyphenols. It is possible that these might have a modifying influence on the carcinogenic action of benzo[*a*]pyrene and *N*-methyl-*N*-nitroso-*N*-pentylamine on the oesophagus.

3. UNIT OF BIOLOGICAL CARCINOGENESIS

Staff: Dr G. Blaudin de Thé (Chief)
Dr A. Geser
Dr D. Šimkovič
Dr Nubia Muñoz
Dr R. Schmauz
Mr J.-C. Ambrosioni
Mr T. B. Greenland
Mrs E. Galatius

Supporting staff: 17

1. INTRODUCTION

The Unit of Biological Carcinogenesis studies the association of viruses with human tumours in general, and with nasopharyngeal carcinoma and Burkitt's lymphoma in particular. Several integrated field and laboratory studies were in progress during the year, and the main event was the launching of the field work in the sero-epidemiological surveys in Hong Kong, Singapore, and Lyon.

The tumour-virus relationship was also studied in cancers of the genital tract (penis and cervix) as well as in lymphomas and related conditions.

2. STUDIES OF NASOPHARYNGEAL CARCINOMA

During 1968 and 1969, information indicated that there was an association between a herpes-type virus infection and nasopharyngeal carcinoma in man. In order to study whether this association could be of a causal nature, the National Cancer Institute, US Public Health Service, Bethesda, Md., USA, and IARC agreed in 1969 to conduct jointly further studies of the relationship between herpes-type virus and nasopharyngeal carcinoma in human populations and in the laboratory.[1]

The contract was signed in June 1970.

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969,* Lyon, p. 43.

2.1 *Conference on the implementation of field sero-epidemiological studies on nasopharyngeal carcinoma*

A meeting was convened by IARC in St Gervais, France, from 11 to 13 January 1970 to consider the implementation of these studies.

It was concluded (IARC Internal Technical Report No. 70/001) that before any prospective study can be attempted of the sequence of events that takes place between the time of virus infection and the onset of nasopharyngeal carcinoma, it is necessary to know more about the epidemiology of herpes-type virus infection—the age-specific prevalence and incidence of infection, the duration of immunity, and the frequency of re-infection. To measure these variables and to compare their magnitude in populations at high and low risk of nasopharyngeal carcinoma, it was agreed that sero-epidemiological surveys should be carried out in Hong Kong, Singapore, and Lyon.

It was further decided that, in order to make valid comparisons between the rate of infection in various sub-groups, approximately 4000 individuals should be studied in both the Hong Kong and Lyon survey areas. In Singapore an additional 3000 persons would be needed, since the Indo-Pakistanis—a low-risk group—present a special problem. It was agreed that the collected sera should be tested for anti-Epstein-Barr type viral capsid antibodies by the indirect immunofluorescence test of Henle and that a sub-sample of the examinees should be re-bled at intervals of 6–12 months over a period of two years in order to study the stability of the antibody levels.

The discussions at the meeting made it clear that the ubiquitous herpes-type virus cannot possibly be the sole cause of a condition as rare as nasopharyngeal carcinoma. The unit has therefore developed plans to initiate studies of genetic and environmental factors (other than viruses) that may play an etiological role in nasopharyngeal carcinoma. Such studies, which will involve the testing of known blood genetic systems in the survey populations (see page 94) and the observation of relevant environmental conditions, will be built into the sero-epidemiological investigations.

2.2 *Co-ordination of the sero-epidemiological studies* (Dr A. Geser, with Dr N. E. Day and Dr D. Šimkovič)

A comparison of measurements of antibody titres, genetic markers, and environmental variables has to be made in different places or in the same place at different times. It is therefore essential that the techniques and methods of observation are uniform throughout. To achieve this, a co-ordinating unit has been created to ensure uniformity in survey techniques (sampling, population coverage, data collection, and data processing) and in laboratory methods. Its tasks have included the preparation of protocols giving details of survey procedures in the field and laboratory, and of record forms for data collection and data processing.

A programme has been prepared for measuring the consistency and reproducibility of the tests carried out in the various participating laboratories.

2.3 *Institute of Radiology, Queen Elizabeth Hospital, Kowloon, and Hong Kong Cancer Society* (RA/70/013)

Principal investigator: Dr H. C. Ho

A field unit under the direct supervision of Dr S. M. Bard, Director of the Hong Kong University Medical Service, has collected 2000 sera since August 1970. These will be tested in the Institute of Radiology, where a new serological laboratory has been established, and will also be sent to IARC, Lyon.

During the period 1 January to 19 October 1970, the following specimens, together with the relevant clinical data sheets, were despatched to Lyon:

For tissue culture: nasopharynx (37)
tonsils (4)
nasopharynx, freeze-dried (72)
tonsils, freeze-dried (5)
For electron microscopy (41)
For histology (118)
Sera from nasopharyngeal cancer patients: before radiotherapy (75)
after radiotherapy (393)
Sera from lymphoma patients (3)
Sera from patients with cervical carcinoma (6)
Sera from other patients (21)

The results obtained with these different specimens in collaboration with Dr Ho are described on pages 52-59.

2.4 *Singapore*

The immunological, immunogenetic, and sero-epidemiological studies on nasopharyngeal cancer were conducted in collaboration with the Unit of Biological Carcinogenesis.

See also the report of the Regional Centre, pages 93-95.

2.5 *Studies in Lyon* (RA/70/021)

Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon (RA/68/102)

Principal investigator: Professor R. Sohier

A series of studies relating to the level of anti-Epstein-Barr type antibodies have been carried out on local subjects in Lyon to provide comparisons with the data from other countries.

(*a*) *Sero-epidemiological study on herpes-type virus infection*

The study has now been completed on 299 sera.[1,2]

A longitudinal retrospective study on the evolution of anti-Epstein-Barr virus antibodies using the indirect immunofluorescence method (IFA test or Henle's test) has been made on at least two blood samples of 55 normal subjects, taken over periods ranging from six months to 12 years. For 40 donors the IFA titre was constant, 8 showed a two-fold or greater decrease, and 7 showed an increase.[3]

(*b*) *Relation between evolution of the IFA titre and illness*

The IFA titre has been determined in the sera obtained from blood donors aged 20–60 years. The samples were taken from each donor at intervals of three, seven, or 12 months. Information was sought from each donor on the history of illness before the first sample and, more important, between the first and second blood donations.

The sera of 146 donors have been thus studied over two or three successive bleedings (Table 4).

TABLE 4. DEVELOPMENT OF ANTI-EPSTEIN-BARR VIRUS ANTIBODIES IN THE SERA OF BLOOD DONORS

Age group (years)	No. of sera examined	Unchanged antibody titres	Increased antibody titres [a]	Decreased antibody titres [b]	Interval between bleedings (months)
18-29	38	29	6	3	3-12
30-39	45	41	1	3	3-12
40-49	50	40	5	5	3-12
50-60	13	11	2	0	3-12
Totals	146	121	14	11	

[a] A four-fold increase or more.
[b] A four-fold decrease or more.

Of those subjects whose sera showed an increase in Henle titre, a few had experienced some illness, but the majority were unaware of having had any symptoms whatsoever.

(*c*) *Evolution of the IFA antibody titre in patients with infectious mononucleosis*

Seventy-six confirmed cases were studied, but unfortunately it was not possible to obtain "early" and "late" sera from the same patients, and therefore it was impossible to demonstrate any change in antibody titre. This study was carried out using three methods in parallel —immunofluorescence, complement-fixation reaction, and gel-immunodiffusion.

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 40.
[2] Sohier, R. (1970) *Path. et Biol.*, **18**, 707.
[3] Sohier, R. (1970) *C. R. Acad. Sci. (Paris)*, **271**, 1231.

(*d*) *Evolution of anti-Epstein-Barr antibody titre during other virus infections*

The anti-Epstein-Barr antibody titre was determined by Henle's technique on sera from 75 donors. The sera were also examined for complement-fixing antibodies for a number of pathogenic viruses [1] and the agent of psittacosis/ornithosis. Ten of the 75 sera showed a significant titre of antibodies against one of the viruses, but only in two cases was there evidence of a correlation between an increase of the anti-Epstein-Barr virus antibody titre and complement-fixing antibodies for one of the other viruses.

(*e*) *Evolution of the antibody titre in patients with sarcoidosis (Besnier-Boeck-Schaumann's disease)*

In only a few of 42 patients has it been possible to obtain a second sample after a known time interval. Where the antibody titre was low during the development of the disease, a higher titre was found when the lesions had regressed markedly and cortisone treatment had been started.

2.6 *IARC Laboratories in Lyon*

(*a*) *Tissue culture*

Table 5 gives the types of tissue cultures obtained from the various specimens put in culture during the period January-August 1970. These represent only about half of the specimens received, as a large proportion did not grow satisfactorily *in vitro*. In contrast with the 1969 investigations,[2] only three cultures gave epithelial growths.

It is important to obtain cultures, if possible of epithelial tumour cells; this may best be achieved by culturing the nasopharyngeal carcinoma specimens in Hong Kong and Singapore, where they can be placed in culture immediately after biopsy.

Two nasopharyngeal carcinoma-derived cell lines were selected for the sero-epidemiological survey in South-East Asia: HK-LY-28, yielding a reasonable amount of herpes-type virus (10 % of the cells are immunofluorescence positive), and HK-LY-2, which does not yield a virus and can therefore be used instead of the Raji line. A micro sero-epidemiological study is at present being conducted to compare the lines derived from Burkitt's lymphoma and from nasopharyngeal carcinoma.

Attempts to clone HK-LY-28 and HK-LY-2, so far unsuccessful, are being continued.

(*b*) *Influence of temperature on virus production* (Mr J.-C. Ambrosioni)

Various lymphoblastoid cultures obtained from biopsies from different sources (nasopharyngeal carcinoma, Burkitt's lymphoma, or peripheral blood from patients with infectious mononucleosis) were examined by immunofluorescence, under standardized tissue culture conditions, for their ability to produce herpes-type virus. The percentage of

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[1] These were: influenza virus types A and B; parainfluenza virus types 1, 2, and 3; mumps virus, respiratory syncytial virus, rubella virus, adenovirus (hexon), herpes virus, and *Mycoplasma pneumoniae*.

[2] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 41.

TABLE 5. TYPES OF CULTURES OBTAINED IN THE IARC LABORATORIES, LYON, JANUARY-AUGUST 1970

Place of origin	Diagnosis	No. of cultures	Epithelial growth	Early lymphocytic production	Fibroblastoid cultures	Long-term lympho-blastoid lines
Hong Kong	Nasopharyngeal carcinoma	12	3	9	9	6
	Ascitic fluid	2	0	0	2	0
	ENT tumours other than nasopharyngeal carcinoma	1	0	0	1	0
	Burkitt's lymphoma	1	0	1	1	0
Kampala	Nasopharyngeal carcinoma	3	0	3	3	1
	Burkitt's lymphoma	3	0	1	1	2
	Pearly penile papules	8	0	0	8	0
	Carcinoma of the penis	4	0	2	4	2 [a]
	Carcinoma of the foreskin	3	0	0	3	0
Nairobi	Nasopharyngeal carcinoma	13	0	11	13	3
	Other ENT tumours	6	0	1	6	0
	Burkitt's lymphoma	4	0	4	1	2
Total	Nasopharyngeal carcinoma	28	3	23	25	10
	Burkitt's lymphoma	8	0	6	3	4

[a] A third culture underwent transformation but reconverted to fibroblastoid culture.

fluorescent cells observed in the indirect immunofluorescence test on fixed cells (Henle method) using a known positive serum was taken as a measure of virus-producing cells.

(i) The majority of cultures derived from nasopharyngeal carcinoma were found to present two peaks in the percentage of fluorescent cells, one at 35°C and a second at 39°C with a well-defined low point at 37°C.

(ii) Cultures derived from Burkitt's lymphoma usually presented only one peak at 33°–35°C.

(iii) All lines derived from infectious mononucleosis or non-malignant nasopharyngeal mucosa showed a single peak at 37°C.

Experiments are being carried out to ascertain whether the two peaks observed for nasopharyngeal carcinoma cultures represent the production of different antigens.

(*c*) *Serology*

The immunofluorescence test of Henle has been set up so that all the long-term lymphoblastoid lines obtained from different sources (nasopharyngeal carcinoma, Burkitt's lymphoma, infectious mononucleosis, and other tumours) have been studied every month to investigate the variations of viral synthesis with time.

Three types of sera also tested by immunofluorescence were:

(i) Sera from untreated nasopharyngeal cases: 89 from Hong Kong, 44 from Singapore, 25 from Kampala (Table 6).

(ii) Sera from patients with tumours other than nasopharyngeal tumours (Table 6).

TABLE 6. IMMUNOFLUORESCENCE TITRES (HENLE'S TEST) OF PATIENTS' SERA FROM HONG KONG, SINGAPORE, AND KAMPALA

Diagnosis of carcinoma	No. of patients	Dilutions [a]										Totals	
		10	20	40	80	160	230	640	1280	2560	5120	< 160	⩾160
Nasopharynx	158	3	0	3	8	12	17	49	25	29	13	14	144
Bronchus	1									1		0	1
Oesophagus	4				2	2						2	2
Cervix	10			1	1	3	4	1				2	8
Penis	13				1	3	8		1			1	11

[a] Titres are expressed as reciprocals of the last dilution showing immunofluorescence positivity.

(iii) Sera from follow-up patients having 3–4 successive bleedings after radiotherapy (Table 7). The results showed reasonable stability with time for Stages I and II and a tendency to decrease for Stages III and IV.

(*d*) *Immunology*

Studies on the herpes-type virus associated antigens in lymphoblastoid cell-lines using radio-iodinated antibodies (Mr T. B. Greenland)

1. An indirect method for the detection of the antibody taken up by lymphoblastoid cells analogous to the indirect immunofluorescence method used by Henle has been developed, where a mixture of ^{125}I-labelled rabbit antihuman IgG and ^{131}I-labelled rabbit normal globulin replaced the goat antihuman IgG antiserum. The ratio ^{125}I : ^{131}I (R) was then determined.

Experiments showed that:

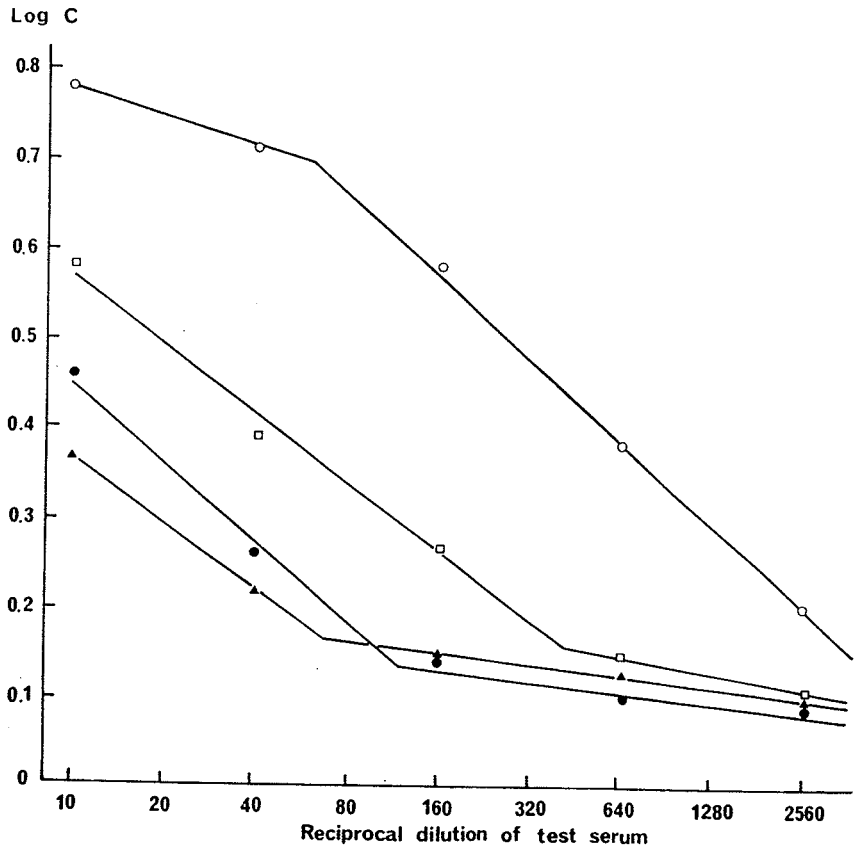
(i) The uptake of test serum onto the cells was dose-dependent. In a few cases, there was a high-level plateau at strong concentrations of high-titre sera, and the log R

TABLE 7. CHANGES IN HENLE TITRE AFTER RADIOTHERAPY OF NASOPHARYNGEAL CARCINOMA PATIENTS (HONG KONG)

	Total no. of patients	Henle titre					
		Increased by at least one dilution		Decreased by at least one dilution		Unchanged	
		No.	%	No.	%	No.	%
Stage I	6	—	—	1	16.7	5	83.3
Stage II	14	1	7.1	4	28.6	9	64.3
Stage III	43	4	9.3	22	51.2	17	39.5
Stage IV	3	—	—	2	66.7	1	33.3
Stage V	1	—	—	—	—	1	100.0
Total (stages I-V)	67	5	7.5	29	43.3	33	49.2

then fell off linearly with dilution until a low-level plateau was reached corresponding to non-specific uptake of ordinary gammaglobulin (Fig. 6).

FIG. 6. DOSE-DEPENDENCE OF TEST SERUM UPTAKE*



* $C = \frac{R}{R_0}$ where R_0 is the initial isotopic ratio of the labelled serum mixture.

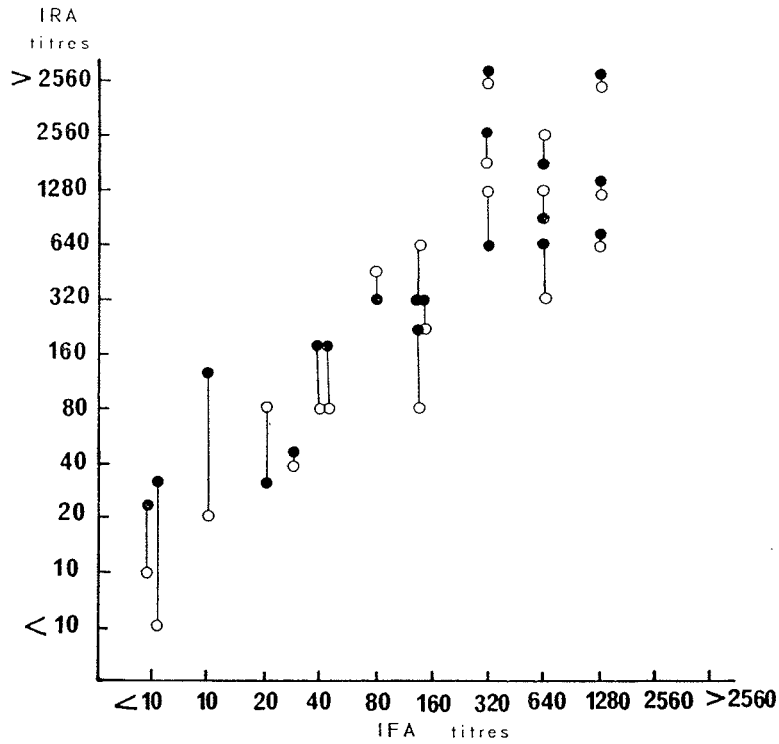
(ii) Jijoye cells contained enough antigen so that when 10^5 cells were treated with 0.1 ml of serum at minimum dilution 1:10 the high-level plateau was only rarely seen, even with high-titre sera.

(iii) Quadrupling dilutions of serum could be used; extrapolation of a titre to the nearest doubling dilution was quite possible. This factor, coupled with that mentioned in (ii) above, means that the technique employed fewer cells for the titration of a given number of sera than the classical Henle technique.

(iv) The slopes of the plot of log R against dilution were generally nearly parallel whether the serum had a high or a low titre. Occasional sera appeared to give a markedly different slope, perhaps indicating qualitatively different antibody contents.

(v) The titres found by this technique corresponded well with those found for the same sera using the Henle technique (Fig. 7). The isotope technique appeared to be rather more sensitive, however, as it allowed the detection of reactivity in some sera that were negative by the Henle technique.

FIG. 7. GRAPHICAL CORRELATION BETWEEN THE TITRES FOUND FOR 20 SERA BY THE INDIRECT RADIO-LABELLED ANTIBODY TECHNIQUE (IRA) * AND THE INDIRECT IMMUNOFLUORESCENT ANTIBODY TEST (IFA)



* Two series of determinations were made with the IRA technique, one being represented by circles and the other by dots in the diagram.

2. A panel of six selected sera has been used to study the relative antigenicity of several lymphoblastoid lines. In these experiments each serum was divided into two portions: one was labelled with ^{125}I and the other with ^{131}I. The labelled sera were then mixed

in pairs to provide 36 mixtures, each containing one serum labelled with each isotope. The uptake of radioactivity from these mixtures by different cell lines allowed a determination of the different relative strengths of each serum for each cell line. Furthermore, the actual amount of gammaglobulin fixed from each serum by each line could be determined by the use of suitable standards. Preliminary results indicated that there were several independent antigenicities expressed by the different lines, and correspondingly the sera contained antibodies to only some of the antigens. It appeared that there was one antigen that was always present in "Henle positive" cell lines but absent from "Henle negative" lines. A second was absent in "Henle positive" and present in "Henle negative" lines. A third antigen was found in all lymphoblastoid lines derived from nasopharyngeal carcinoma, but never in those from Burkitt's lymphoma or infectious mononucleosis. There was at least one further antigen that was not found to correlate with any other factor.

The results so far obtained are being analysed to determine whether they may be due to artifacts in the simple mathematical analysis used, and also to determine the degree of ambiguity in the system described.

Experiments will be carried out to determine whether the antibodies in the different sera can be selectively absorbed out by using suitably matched cells. Eventually it is hoped to investigate the changes in expression of the different antigens by changing culture conditions.

(*e*) *Electron microscopy*

(i) *Studies on nasopharyngeal carcinoma biopsies*

Comparative studies were made of the ultrastructure of nasopharyngeal carcinoma biopsies, three normal nasopharynx biopsies, and Burkitt's lymphoma biopsies. In the normal nasopharyngeal mucosa, three types of cells were encountered—epithelial cells, fibroblasts secreting collagen, and lymphoid cells. The last two categories were found mostly in the subepithelial layer of the mucosa. A few lymphoid cells, however, were also found in the epithelial layer.

The nasopharyngeal carcinoma biopsies included three well-differentiated tumours, three poorly differentiated, and four undifferentiated. In the tumours, fibroblasts and lymphoid cells were intimately mixed with the epithelial cells. The nature of the undifferentiated tumour cells was difficult to ascertain when no keratin tonofibrils or functional complexes were visible. They could be either of epithelial or lymphoreticular origin. The fibroblastic cells in the tumours presented abnormal nuclei, with fibrillar, concentric nuclear bodies, as well as nuclear sheets, the nature of which was unclear.

(ii) *Studies on cultures obtained from nasopharyngeal carcinoma*

The epithelial nature of these cells was established by the presence of junctional complexes and desmosomes. Their ultrastructure did not vary greatly from that of the original *in vivo* tumour cells. No virus particle was detected in these cultures.

In contrast, most of the long-term lymphoblastoid cultures obtained from nasopharyngeal carcinoma, Burkitt's lymphoma, or other sources, showed the presence of herpes-type virus at some time in the culture.

One of the long-term cultures (HK-11) was followed at different intervals, by both electron microscopy and immunofluorescence. The number of virus-producing cells was larger than immunofluorescence tests would suggest.

It was found that the virus was released on maturation, either following the cell degradation (producing mostly capsids and nucleocapsids) or, in ultrastructurally normal cells, by budding processes through the nuclear membrane and migration in cytoplasmic channels towards the extracellular spaces.

Staining of the lymphoblastoid cells by the ruthenium red test showed that their cell membranes were covered with a mucopolysaccharide layer, 200 Å thick.

(*f*) *Histopathological studies* (Dr Nubia Muñoz)

The histological characteristics of 57 nasopharyngeal carcinoma cases were studied in relation to the tissue culture and serology results. No correlation was found between the degree of lymphoplasmocytic infiltration in the neoplastic tissue or non-neoplastic tissue. The infiltration of the tumour was always mild, whatever the degree of infiltration of the stroma.

No correlation was found either between the degree of lymphoplasmocytic infiltration of the stroma and the frequency of lymphoblastoid transformation in tissue culture.

The cases with good demarcation between the tumoral tissue and the stroma had a slight tendency to reveal more lymphoblastoid transformation in tissue culture but showed no special correlation with the Henle titre.

Little difference was observed between the frequency of lymphoblastoid transformation in well-differentiated or in undifferentiated carcinomas.

A correlation was observed between the frequency of lymphoblastoid transformation and of early lymphocytic production in tissue culture and the stage of the disease.

No correlation was found between the Henle titre and either the frequency of lymphoblastoid transformation or early lymphocytic production, or the degree of lymphoplasmocytic infiltration in the primary tumour.

In conclusion, neither the peculiar serological pattern of nasopharyngeal carcinoma patients nor the lymphoblastoid transformation observed *in vitro* was related to the degree of lymphoplasmocytic infiltration of the tumour.

(*g*) *Other studies*

Purification of herpes-type virus from cultures derived from nasopharyngeal carcinoma

The optimum conditions for viral production have been studied. The virus has been grown on a substrate containing tritiated thymidine and purified by differential centrifu-

gation or flotation on sucrose gradient. Preliminary results showed that purification of the virus can be achieved, but its infectivity has not yet been tested.

3. BURKITT'S LYMPHOMA

3.1 *Studies of the etiological role of the Epstein-Barr virus in Burkitt's lymphoma in the West Nile district, Uganda* (see page 36)

At a meeting held in St Gervais, France, from 15 to 18 January 1970 (IARC Internal Technical Report No. 70/002), it was considered whether a longitudinal sero-epidemiological survey should be carried out to study the possibility that a virus plays an etiological role in relation to Burkitt's lymphoma.

The group concluded that the accumulated data show that there is an association between Epstein-Barr virus infection and Burkitt's lymphoma and that further knowledge about the possible etiological role of the virus can now be obtained only in large-scale follow-up studies in human populations where the time sequence of infection and tumour development can be observed.

The participants also realized that, before such a follow-up study could be designed, it would be necessary to know whether the Epstein-Barr virus antibody levels are sufficiently stable to permit a meaningful classification of the studied population. The final decision on an etiological study was therefore deferred until the stability of virus antibody levels had been studied in the health survey initiated in the West Nile district in 1968 by the East African Virus Research Institute, Entebbe (Dr G. W. Kafuko) together with the Department of Preventive Medicine, Makerere University, Kampala, Uganda, and Dr W. Henle, Children's Hospital, Philadelphia, Penn., USA.

The results (in terms of Henle titres) of the repeated Epstein-Barr virus antibody determination became available in September 1970, by courtesy of Dr Henle and Dr Kafuko (personal communication).

It appeared that approximately 90 % of the Henle titres were unchanged or only slightly changed (less than 2 dilutions) and were therefore sufficiently stable to permit a follow-up study to be carried out.

A meeting was convened in Uganda in November 1970 to formulate plans for the study in the West Nile district. As a prerequisite for the study, attention will be paid to the problem of establishing co-operation with the population by keeping them continuously informed about the purpose of the work.

A prospective sero-epidemiological study is proposed in which approximately 35 000 children under the age of 5 years will be bled during a period of 5 years. The Epstein-Barr virus antibody level will be determined in the sera of those children who subsequently develop Burkitt's lymphoma. It is also proposed to carry out sequential re-bleeding on a small random group drawn from that population in order to study the epidemiology of Epstein-Barr virus infection in the West Nile district in more detail.

3.2 *An epidemiological study of Burkitt's lymphoma in the North Mara district, Tanzania* (Dr A. Geser and Dr M. Pike)

A relatively high incidence of Burkitt's lymphoma has been reported from the North Mara district in Tanzania.[1]

The area has been revisited and it was confirmed that the incidence is as high in the North Mara district as in the West Nile district of Uganda. The medical officers of Shirati Hospital, where the Burkitt's lymphoma cases have been diagnosed, have agreed to co-operate in a more detailed epidemiological study to determine the true incidence of the disease and its distribution in place and time. Later it may be possible to conduct etiological studies in North Mara.

3.3 *Hyperendemic malaria and Burkitt's lymphoma*

A high incidence of Burkitt's lymphoma is found only in tropical countries, and only up to an altitude of about 1500 metres. Burkitt's lymphoma is also largely absent in large towns (Kinshasa, Mombasa, Kampala) where malaria control has been effective for years, while the surrounding countryside remains hyperendemic. This distribution corresponds closely with that of hyperendemic malaria and it is therefore relevant to ask whether malaria infection may be a causal factor in Burkitt's lymphoma.

In order to make it possible to test the hypothesis that malaria is one of the factors necessary for the development of Burkitt's lymphoma, a field trial has been designed which could show whether malaria suppression (with antimalaria drugs) could reduce the incidence of Burkitt's lymphoma in children living in an area of hyperendemic malaria.

Table 8 shows the size of study population that would be needed to show a significant effect of malaria prophylaxis under three different assumptions regarding the effect of malaria control on the incidence of Burkitt's lymphoma.

TABLE 8. CALCULATION OF THE POPULATION SIZE REQUIRED TO STUDY THE EFFECT OF MALARIA PROPHYLAXIS ON THE INCIDENCE OF BURKITT'S LYMPHOMA

Reduction in no. of Burkitt's lymphoma cases due to control	Required no. of Burkitt's lymphoma cases		Sample size[a] needed, based on incidence of $10/10^5$	Sample size[a] needed, based on incidence of $25/10^5$ (approx.)
	In malaria control group	In untreated group		
50 %	30	60	240 000	100 000
67 %	10	30	120 000	50 000
75 %	6	24	100 000	40 000

[a] Number of children in sample, including "controls"; the children should be 2-5 years old at the beginning of the trial.

[1] Eshleman, J. L. (1966) *E. Afr. med. J.*, **43**, 273.

It is realized that it may be impossible to establish a malaria prophylaxis group and an untreated comparison group. The trial therefore may have to rely on the comparison of Burkitt's lymphoma incidence in an area before and after malaria control. For such a study it is of paramount importance to know the base-line values of Burkitt's lymphoma incidence and it is therefore intended to observe carefully the incidence of Burkitt's lymphoma in a few areas like the West Nile and Shirati, with a view to conducting a malaria-Burkitt's lymphoma trial in these areas at some time in the future.

4. OTHER LYMPHOMAS AND RELATED TUMOURS

Collaborating field centres

(*a*) *Instituto de Medicina Tropical, Universidade de São Paulo, São Paulo, Brazil* (RA/70/016)

Principal investigator: Dr R. Carvalho

A collaborative research agreement was initiated in August 1970, with financial assistance from the Brown Hazen Fund Committee Research Corporation, New York, N.Y., USA. Sero-epidemiological and tissue culture studies of lymphoma, leukaemias, and other tumours to determine the role of herpes-type viruses in the development of these tumours were initiated two years ago by Dr G. Dalldorf. These studies continue and a sero-epidemiological study will be carried out in an isolated Indian population.

(*b*) *Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru* (RA/69/003)

Principal investigator: Dr A. Solidoro

Arrangements have been made to start the collection of sera from patients with Hodgkin's disease and nasopharyngeal carcinoma. These sera will be sent to Lyon for Henle testing, together with duplicates of the histological preparations.

(*c*) *Departamento de Patología, Universidad del Valle, Cali, Colombia* (RA/70/005)

Principal investigator: Dr Carlos Cuello

The collection of sera from patients with Hodgkin's disease and from controls matched for sex and age has been started.

5. ORGANIZATION OF A SYMPOSIUM ON ONCOGENESIS AND HERPES-TYPE VIRUSES

Collaborating Centre: Houghton Poultry Research Station, Houghton, Huntingdon, United Kingdom (RA/70/008)

Principal investigator: Dr Peter M. Biggs

Herpes-type virus has been shown to be the cause of Marek's disease of the fowl and of renal carcinoma in the frog. It is considered therefore that a comparative approach may be useful to those engaged in studying oncogenesis and herpes-type viruses.

It has been decided to hold a symposium of some 150 participants from 20 to 25 June 1971 in Cambridge, United Kingdom, jointly organized by the Houghton Poultry Research Station and IARC. The proceedings will be published by IARC.

6. CANCER OF THE PENIS (Dr R. Schmauz)

Department of Pathology, Makerere University, Kampala, Uganda (RA/69/002)

Principal investigator: Professor M. S. R. Hutt

Epidemiological investigations on the incidence of pearly penile papules in hospital populations showed a possible correlation in the geographical distribution of both pearly penile papules and penile cancer. Further studies have therefore been undertaken.

6.1 *Material for laboratory studies*

(*a*) Sixteen cases of pearly penile papules were biopsied and the specimens cultured. Only fibroblastic growths were obtained.

(*b*) More than 200 sera were collected in high and low incidence areas of carcinoma of the penis. The cases were age-matched, and in each area half of the sera collected had pearly penile papules.

(*c*) From January 1969 to August 1970, material was collected from 33 cases of possible nasopharyngeal carcinoma and 54 of penile carcinoma. Clinical records and histological slides were kept of all these cases. Tissue culture results are given in Table 5, page 53. Penile carcinomas gave rise only to fibroblastoid cultures, with two lymphoblastoid transformations.

6.2 *Epidemiological studies*

The geographical distribution of carcinoma of the penis in Uganda has been determined (see page 37).[1] The incidence of penile carcinoma in migrants was investigated further. It appears that different tribes living in one area tend to have similar incidence rates, which would stress the influence of environment on the genesis of this cancer.

From the material available at the Kampala Cancer Registry, 30 cases were found that were considered to be precancerous lesions of the penis. The histopathology of these cases is at present being studied.

6.3 *Related studies*

The histology and epidemiology of carcinoma of the nasopharynx in Uganda have been determined. In collaboration with Dr A. C. Templeton, all malignancies of the head, face,

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[1] Schmauz, R. & Jain, D. K. (1971) *Brit. J. Cancer* (in press).

and neck have been reviewed.[1] The histological appearances of nasopharyngeal carcinoma were compared with those of other head and neck carcinomas found in the Kampala Cancer Registry.

7. CANCER OF THE CERVIX

7.1 *Collaborating field centres*

(*a*) *Departamento de Patología, Universidad de Valle, Cali, Colombia* (RA/70/005)

Principal investigator: Dr Carlos Cuello

Seven biopsy specimens from cervical carcinoma, two from dysplasia, two from chronic cervicitis, 25 from condyloma accuminatum of vulva, vagina, and cervix, and three from condyloma of the penis were sent from Cali to Lyon, together with 39 sera from the corresponding patients and 34 from age- and sex-matched controls. The biopsy specimens were cultured *in vitro* and examined by electron microscopy.

(*b*) *Cadeira de Anatomia Patologica, Universidade Federal de Pernambuco, Recife, Brazil*

Principal investigator: Dr Adonis R. L. de Carvalho

Preliminary arrangements have been made with the Cancer Hospital and the University Dermatological Service of Recife to collect biopsy specimens from perianal carcinoma and condyloma accuminatum, and sera from the corresponding patients.

7.2 *The effects of Enovoid and* Herpesvirus hominis *type 2* (Dr Nubia Muñoz)

The experiment reported last year [2] has been continued. The mice that had received an oral contraceptive (Enovoid) were given an intravaginal inoculation of *Herpesvirus hominis* type 2. One cervical carcinoma has been found in the group treated with œstrogens and the virus. This tumour was transplanted subcutaneously in five BALB/c mice. Tumoral growth has been observed in four mice, three weeks after transplantation. This experiment will continue for another six months.

7.3 *Other studies*

Dr Muñoz is a consultant to the US-Yugoslav team on cervical carcinoma with special reference to herpes genital virus. Sero-epidemiological studies are being carried out in Muslim and non-Muslim groups.

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[1] Templeton, A. C. & Schmauz, R. (1971) *E. Afr. med. J.* (in press).

[2] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 46.

8. GASTRIC CANCER (Dr Nubia Muñoz)

An attempt is being made to correlate the histological types "intestinal" and "diffuse" (see page 31) with the carcinoembryonic antigen test carried out by Professor François Martin, Faculty of Medicine, Dijon, France. In the 18 cases of gastric cancer so far studied, no correlation has been found between histological type and antigen.

9. ROUS SARCOMA VIRUS (Mr L. Gazzolo)

Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon

The electron microscopic studies described last year [1] were continued. None of the six lines originating from *in vitro* transformation of BHK 21 clone 13 cells by Rous sarcoma virus (Schmidt-Ruppin or Bryan strains) showed the presence of C-type particles. In contrast, two lines that originated from *in vivo* transformation by the Schmidt-Ruppin strain showed either C-type virions or A-type particles, associated with mitochondria. R-type particles were present in all the hamster-derived cell lines examined.

Rat cell lines were also studied. The WERC line (from the Institute of Oncology, Bratislava, Dr D. Šimkovič), a spontaneously transformed line, contained a murine C-type virus, identified both by electron microscopy and by tritiated-uridine labelling. This virus was not infectious for chicken cells. When the WERC cell line had been transformed by Rous sarcoma virus it did not produce any virions. Another line, the 17RBI77 originating from a rat sarcoma induced *in vitro* by B77 Rous sarcoma virus, produced a virus infectious for chicken cells, shown to be also of murine C type.

Thus, it appeared that in 17RBI77 cells the avian Rous sarcoma virus underwent a phenotypic change to a murine-type envelope while retaining its infectivity for chicken cells.

The studies of the recuperation of Rous sarcoma virus from heterokaryons formed by transformed hamster cells and permissive chick cells were continued. Separation of the different cell types—hamster cells, chick cells, and heterokaryons—was achieved by using Ficoll density gradient centrifugation.

10. INSTITUT DE CANCÉROLOGIE ET D'IMMUNOGÉNÉTIQUE, VILLEJUIF, FRANCE

(Director: Professor G. Mathé)

Dr de Thé continued to act as consultant in electron microscopy at the Institute. His activities included collaborative studies aimed at the analysis of the particles found in plasma of leukaemic patients.

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[1] *Ibid.*, p. 47.

11. IARC TUMOUR TRANSPLANTATION REFERENCE CENTRE

Department of Tumour Biology, Karolinska Institutet, Stockholm (RA/67/003)

Principal investigator: Professor G. Klein [1]

The reference centre continued to function during 1970 with no decrease in activities, in spite of a reduction of funds.

(*a*) *Animal tumours*

The animal tumour collection has been maintained and includes murine sarcomas and carcinomas induced by a wide variety of known agents.

Nearly all mouse tumours have been induced in highly inbred mouse strains that carry known isoantigen markers. As a rule, information on strain compatibility and antigenic markers is provided together with the tumour.

(*b*) *Human tumours*

Human tumour material has also been provided on a regular basis, including fresh biopsy material from Burkitt's lymphomas, other lymphomas and leukaemic carcinomas of the nasopharynx, and a number of carcinomas and sarcomas.

During previous years most of the material came from Nairobi, but human tumour material from hospitals in Sweden has become increasingly available during 1970. There is a very large collection of corresponding patient and control sera. Pre- and post-disease sera, as well as bone marrow and white cell samples, can also be made available from cases of infectious mononucleosis.

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[1] This section is an abstract of a report by Professor Klein.

4. UNIT OF CHEMICAL CARCINOGENESIS

Staff: Dr L. TOMATIS (Chief)
Dr V. TURUSOV
Dr C. AGTHE (from August 1970)
Dr P. SIZARET (until June 1970)
Dr R. MONTESANO (from September 1970)
Miss B. WITTHOFF
Mr R. CHARLES
Mrs C. PARTENSKY (from September 1970)

Supporting staff: 8

1. INTRODUCTION

The unit has continued the long-term investigation of the potential carcinogenic hazard of two pesticides, DDT and lead arsenate, and has further studied the effects of the combined administration of several carcinogens and of transplacental carcinogens.

In parallel with the work of the Unit of Environmental Carcinogens on the nitrosamines, studies have been made on the comparative metabolism of nitrosamines in rodents and human tissues and on the kinetics of nitrosation of secondary amines.

Plans for the preparation of a manual on the pathology of tumours in laboratory animals are well in hand, as are those for the preparation of a series of monographs in which the carcinogenic risk to man of a series of chemicals is evaluated.

2. POTENTIAL CARCINOGENIC HAZARD OF PESTICIDES

The collaborative study on the potential carcinogenic hazard of DDT has been continued and expanded.

2.1 *Laboratory studies*

(*a*) *IARC, Lyon* (Animal housing provided for CF_1 mice by Institut Mérieux, Lyon—RA/68/HQ.1)

Principal investigator: Dr V. Turusov

Observations, extended to the 104th week for the parent generation and to the 90th week for the first generation descendants (F_1), confirm the increased incidence of tumours in DDT-treated mice already reported in 1969. This was most evident in the mice receiving the highest dose of DDT, and the tumours were mainly hepatomas. A slight increase of lung adenomas was also observed at all dose levels (Table 9). The hepatomas appeared at

TABLE 9. CUMULATIVE DATA ON MORTALITY AND TUMOUR INCIDENCE OF CF_1 MICE (MALE AND FEMALE) RECEIVING DDT AT VARIOUS CONCENTRATIONS, AT 104 WEEKS FROM THE BEGINNING OF THE EXPERIMENT FOR THE PARENT GENERATION (P) AND AT 90 WEEKS OF AGE FOR THE FIRST GENERATION DESCENDANTS (F_1)

DDT concentration	Generation	Number of animals		Died		Tumour-bearing animals		Animals with more than one tumour		Number of tumours		Animals with									
												Lymphomas		Lung Adenomas		Hepatomas		Osteomas		Other tumours	
		At start	Effective no. [a]	No.	% [b]	No.	% [c]	No.	% [c]	Total	Average per animal [c]	No.	% [c]	No.	% [c]	No.	% [c]	No.	% [c]	No.	% [c]
Control	P	125	116	74	59.2	48	41.3	17	14.6	67	0.57	30	25.9	16	13.8	7	6	8	6.8	6	5.2
	F_1	127	115	62	48.8	34	29.6	9	7.8	45	0.39	24	20.8	12	10.4	0	0	2	1.7	6	5.2
2 ppm	P	120	116	70	58.3	55	47.4	21	18.1	79	0.68	24	20.6	26	22.4	11	9.5	6	5.2	12	10.3
	F_1	121	117	59	48.7	40	34.2	13	11.1	53	0.45	23	19.6	13	11.1	7	5.9	3	2.6	7	5.9
10 ppm	P	120	117	84	70	69	58.9	24	20.5	98	0.83	38	32.4	34	29	12	10.2	4	3.4	10	8.5
	F_1	129	118	59	45.7	41	34.7	14	11.8	58	0.49	19	16.1	19	16.1	8	6.7	8	6.7	4	3.4
50 ppm	P	120	111	76	63.3	57	51.3	27	24.3	90	0.81	29	26.1	27	24.3	12	10.8	6	5.4	16	14.4
	F_1	130	125	62	47.7	47	37.6	22	17.6	72	0.57	25	20	20	16	12	9.6	6	4.8	9	7.2
250 ppm	P	120	99	104	86.6	73	73.7	39	39.4	127	1.28	25	25.2	34	34.3	55	55.5	5	5.1	8	8.1
	F_1	117	99	82	70.1	60	60.6	33	33.3	98	0.98	19	19.2	17	17.2	45	45.5	6	6.1	11	11.1

[a] Number alive at time of appearance of first tumour.
[b] In relation to the number at the start.
[c] In relation to the effective number.

an earlier age in the F_1 generation, which were exposed to DDT from intra-uterine life, than in their parents whose exposure started only at the eighth week of extra-uterine life. Lung metastases of hepatomas have been observed in only two cases, both in DDT-treated mice. Several unsuccessful attempts have been made to transplant the induced hepatomas into adult and newborn mice.

Additional groups have recently been added to the main experiment to investigate: (1) the possible regression and/or drug dependency of the liver lesions induced by DDT; and (2) the possible carcinogenic effect of two of the main metabolites of DDT, namely *pp'*-DDD[1] and *pp'*-DDE.[2]

A preliminary investigation of the possible teratogenic effect of DDT was carried out on mice of the F_5 generation, where the preceding four generations had been exposed to 50 ppm of DDT. No increase in malformation was seen in the DDT-treated group when compared with the untreated controls.

DDT-treated mice had a higher body weight than the controls. In prepuberal mice of the F_5 generation, exposed to 50 ppm of DDT, the weight of the liver in both female and male mice and of the uterus was higher than in the untreated controls.

(*b*) *Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy* (RA/68/HQ.2)

Principal investigator: Dr B. Terracini

This experiment has now reached the fifth generation and several hepatomas have been observed in the DDT-treated mice (Table 10).

TABLE 10. CUMULATIVE DATA ON MORTALITY AND TUMOUR INCIDENCE IN BALB/c MICE RECEIVING DDT AT VARIOUS CONCENTRATIONS, AT 100 WEEKS OF AGE FOR THE PARENT GENERATION (P) AND AT 80 WEEKS OF AGE FOR THE FIRST GENERATION DESCENDANTS (F_1)

DDT concentration	Generation	Effective number of mice	Mice dead [a]	Total number of mice dying with tumours [b]	Number of mice dying with hepatomas [c]
Control	P	104	60	39	0
	F_1	92	41	25	1
2 ppm	P	103	68	38	0
	F_1	86	29	22	1
20 ppm	P	100	67	41	1
	F_1	80	26	19	0
250 ppm	P	80	50	32	13
	F_1	71	34	22	12

[a] At 100 weeks of age for parents; at 80 weeks of age for F_1 generation.
[b] Gross diagnosis, histology not yet completed.
[c] Histologically confirmed.

[1] 1,1–dichloro–2,2–bis–(*p*–chlorophenyl)ethane.
[2] 1,1–dichloro–2,2–bis–(*p*–chlorophenyl)ethylene.

(*c*) *Research Institute of Oncology, Leningrad, USSR* (RA/68/HQ.3)

Principal investigator: Dr N. P. Napalkov

A high dose-level group (250 ppm) has been added to the original plan. These rats will receive DDT for their life span. Further generations will not be followed up. Within the other groups, a few tumours have been observed, including reticulum cell sarcomas of the lungs in the DDT-treated animals.

(*d*) *Institute of Experimental and Clinical Oncology, Moscow* (RA/68/HQ.4)

Principal investigator: Professor L. M. Shabad

The observation of early biological changes and preneoplastic lesions, using organ cultures in an *in vitro* system, has been expanded to organ cultures of fetal lungs of the F_1, F_2, and F_3 generations of mice receiving 10 ppm of DDT. Focal epithelial hyperplasia was observed in lungs of fetuses of mice receiving 10 ppm of DDT. Similar results had previously been achieved only at 50 ppm. A higher frequency of hyperplastic foci was observed in the fetuses of mice of the F_3 generation that had been exposed to 10 ppm of DDT.

(*e*) *US Public Health Service Food and Drug Administration, Chamblee, Ga., USA* (Mr W. Barthel)

The storage of DDT and its metabolites has been evaluated in the fat tissue, reproductive organs, liver, brain, and kidney of DDT-treated mice; *op'*-DDT has now been found in mouse tissues in addition to the previously reported *pp'*-DDT, *pp'*-DDE, and *pp'*-DDD. The statistical evaluation of the data (Dr N. E. Day) indicated that there is a linear relationship between the concentration of each metabolite in each organ and the dose to which the animal was exposed. The fat was the tissue with the highest concentration of all metabolites, followed by the reproductive organs, the kidney and liver together, and lastly the brain. There was no evidence of any difference in storage levels between the parent mice and their adult descendants, and the concentration of the metabolites in the fetuses was directly related to the concentration fed to the mothers.

2.2 *Field studies*

The evaluation of DDT and its metabolites in human fat tissues is in progress in the following countries: Japan, Singapore, Uganda, Argentina, Brazil, Ceylon, Israel, Nigeria, and South Africa. The results for Israel, Nigeria, and South Africa are summarized in Table 11. Collaborating in the project are: Professor K. Shanmugaratnam, Head of the IARC Regional Centre, Singapore; Professor K. Akazaki, Aichi Cancer Centre, Nagoya, Japan; Professor M. Wassermann, Hadassah Medical School, Jerusalem; Dr M. Rogoff, Medical Research Laboratories, Nairobi; and Dr C. A. Linsell, Head of the IARC Regional Centre, Nairobi. The chemical evaluation of the DDT content of human tissues obtained

TABLE 11. AVERAGE DDT CONTENT IN HUMAN FAT TISSUE IN VARIOUS COUNTRIES, BY AGE AND SEX, EXPRESSED AS PARTS PER MILLION (PPM) OF TOTAL DDT

	Age group													
	Months		Years											
	0-11		1-4		5-14		15-24		25-44		45-69		70+	
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
South Africa (Caucasians)	—	—	6.89	3.46 ± 1.85	—	3.29 ± 0.33	5.59 ± 1.02	7.73 ± 3.66	14.35 ± 5.42	19.72 ± 11.54	6.99 ± 0.95	6.46 ± 0.82	7.09 ± 0.19	—
South Africa (Bantus)	—	—	5.26 ± 1.11	5.85	5.69 ± 1.29	2.76 ± 0.60	10.35 ± 5.45	4.73 ± 1.81	14.11 ± 5.70	8.22 ± 1.53	5.45 ± 1.01	7.87 ± 1.52	—	11.37 ± 3.41
Nigeria	2.50 ± 0.47	3.83 ± 0.85	6.03 ± 1.00	7.03 ± 0.90	8.45 ± 2.56	6.61 ± 2.29	4.34 ± 1.40	4.40 ± 1.61	7.83 ± 1.68	8.53 ± 2.17	4.33 ± 0.96	4.94 ± 0.92	—	1.33
Israel	6.40 ± 1.34	5.34 ± 0.93	—	—	18.26 ± 3.4	18.68 ± 4.56	11.43 ± 2.80	14.33 ± 1.96	31.86 ± 18.97	15.93 ± 2.59	15.08 ± 1.68	19.39 ± 1.83	15.60 ± 1.63	20.92 ± 3.06

from Singapore and Japan is carried out by Mr W. Barthel, and tissues from other countries are evaluated by Professor M. Wassermann.

A working group of all collaborators in the experimental and field studies met in Lyon (November 1970) to review the programme and the results so far obtained.

2.3 *Rijks Instituut voor de Volksgezondheid, Utrecht, Netherlands*

Principal investigator: Dr G. van Esch

The study of the possible carcinogenic effect of the long-term administration of lead arsenate to rats has continued. The lead content of the experimental animal organs is being determined at the Institute in Utrecht; the arsenic content is determined through the co-operation of the International Atomic Energy Agency, Vienna.

3. EXPERIMENTAL CARCINOGENESIS WITH MULTIPLE CARCINOGENS: TRANSPLACENTAL AND PERINATAL CARCINOGENESIS

3.1 *Combined exposure to different chemical carcinogens* (Dr V. Turusov)

Methylcholanthrene and diethylnitrosamine have been administered to CF_1 mice at different dose levels and at different ages. The experiments are not yet sufficiently advanced to permit a sound evaluation of the results.

3.2 *Combined exposure to X-irradiation and a chemical carcinogen*

(*a*) *Institute of Experimental and Clinical Oncology, Moscow*

Principal investigator: Professor L. M. Shabad

A preliminary experiment has been started to investigate the possible carcinogenic effect of a single whole-body X-irradiation on the progeny of X-irradiated mice. In a short-term test to establish the experimental dosage, single whole-body irradiation has been given at doses between 25 and 400 roentgens in the last period of pregnancy.

(*b*) *Research Institute of Oncology, Leningrad, USSR*

Principal investigator: Dr N. P. Napalkov

The effect on mice of the combined administration of ethylnitrosourea and X-irradiation is being studied.

3.3 *Transplacental carcinogenesis with methylcholanthrene*

(*a*) *IARC, Lyon*

Methylcholanthrene has been administered to pregnant mice during the last period of pregnancy. The first experiment, in which a group of pregnant mice received a dose

of 8.4 mg *per os*, has been completed. A very high incidence of tumours (97 %-100 %) in the treated mice and in their descendants has been confirmed, regardless of whether the offspring were nursed by their own mothers or by untreated foster-mothers. The descendants of untreated mice that were foster-nursed by methylcholanthrene-treated females do not so far show a higher incidence of tumours than untreated controls (Table 12). A second experiment using 1 mg of methylcholanthrene has been started.

TABLE 12. INCIDENCE OF TUMOUR-BEARING ANIMALS FOLLOWING THE *PER OS* ADMINISTRATION OF 8.4 mg OF METHYLCHOLANTHRENE (MC) DURING THE LAST PERIOD OF PREGNANCY (CF_1 MICE)

Group [a]	Number at start	Tumour-bearing animals		Number of tumours	
		Total	%	Total	per mouse
1 MC administered during pregnancy (adult females)	35	34	97	60	1.7
2 Descendants of Group 1	99	97	98	142	1.4
3 Descendants of Group 1 foster-nursed by untreated females	68	68	100	99	1.5
4 Descendants of untreated pregnant mice foster-nursed by MC-treated females	91	41 [b]	45	52	0.6
5 Untreated controls	89	36 [b]	40	48	0.5

[a] All mice from Groups 1, 2, and 3 died within 80 weeks. At 100 weeks, 38 mice of Group 4 and 39 mice of Group 5 were still alive.

[b] At 100 weeks.

(*b*) *Département de Biochimie, Institut national de Sciences appliquées, Lyon* (RA/68/001)

Principal investigator: Professor H. Pacheco (assisted by Miss Guibbert and Mr Malaveille)

Analysis of the concentrations of methylcholanthrene in fetal tissues is being carried out in parallel with the studies described above. A first series using a dose of 10 mg of methylcholanthrene has been completed.[1] In a second series, 3.3 mg or 1 mg of methylcholanthrene has been given to CF_1 mice in the late period of pregnancy (Table 13). There appears to be a higher concentration of methylcholanthrene in the thymus than in the lungs, liver, and the rest of the body. The results of a study of methylcholanthrene concentration in the fetus at different times following administration to the mother are summarized in Fig. 8. A preliminary investigation of the metabolism of ^{14}C-labelled methylcholanthrene in the fetus has been carried out.

[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 56.

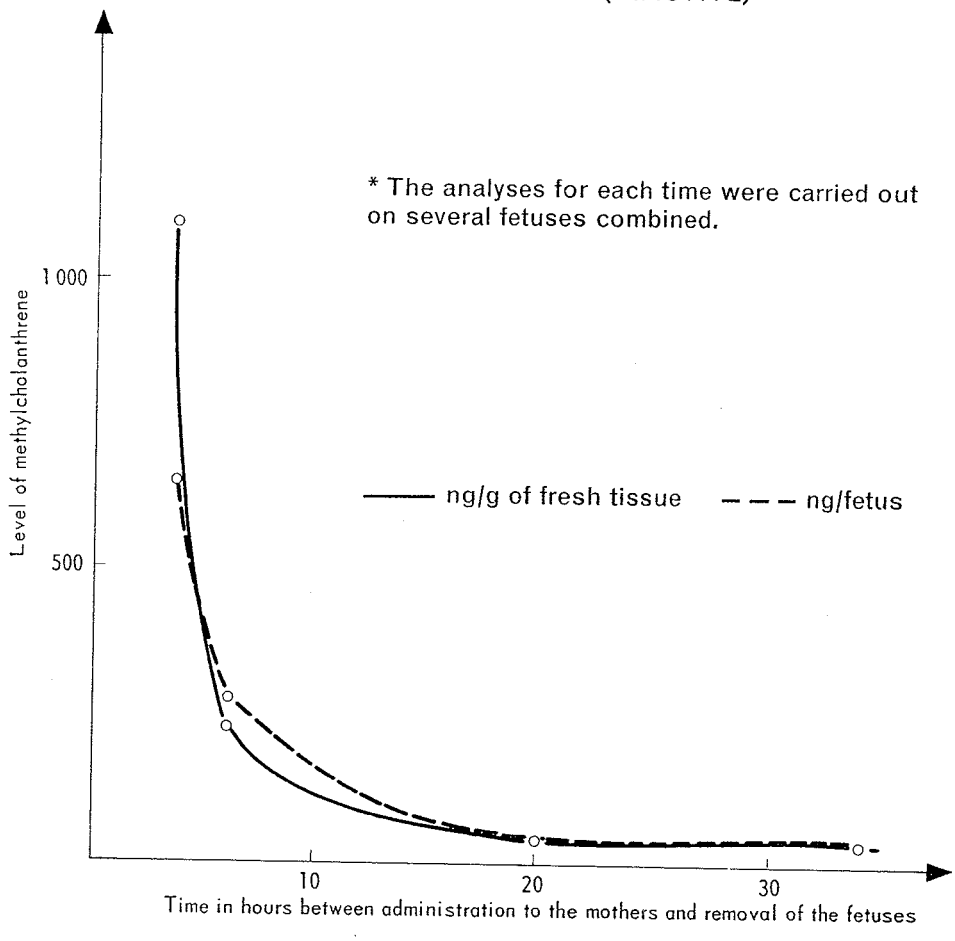
TABLE 13. AMOUNT OF METHYLCHOLANTHRENE RECOVERED FROM FETUSES 6 HOURS AFTER ADMINISTRATION OF VARIOUS DOSES TO THE MOTHERS (CF_1 MICE)

Methylcholanthrene			
Dose administered to the mother (mg)	Average amount in fetus (ng)	Average level per g fresh tissue (ng)	Average level per fetus (ng)
10 [a,b]	1350	130	135
3.3 [b]	6030	830	580
1	1460 (±1300)	140 (±130)	130 (±120)

[a] The 10-mg dose was given in three equal portions of 3.3 mg every 6 hours. The fetuses were taken 6 hours after the last injection.

[b] For both the 10-mg and 3.3-mg doses, the analyses were performed on several fetuses combined. The calculation of the maximum deviation from the mean was therefore not possible. The mean values given correspond to at least 6 fetuses combined.

FIG. 8. THE VARIATION OVER TIME OF THE LEVEL OF METHYLCHOLANTHRENE IN THE FETUSES AFTER ADMINISTRATION TO THE MOTHER OF A DOSE OF 3.3 mg OF METHYLCHOLANTHRENE (INACTIVE)*



The results (Table 14) indicate that three hours after administration to the mother 14 % of the methylcholanthrene is present unchanged; six hours after administration the figure has fallen to 5 %. Further studies are being carried out to investigate the intracellular targets of methylcholanthrene and its metabolites.

TABLE 14. LEVEL OF METABOLISM OF METHYLCHOLANTHRENE (MC) IN THE FETUS: A COMPARATIVE STUDY OF THE RADIOACTIVITY OF THE UNCHANGED MC AND OF ITS METABOLITES IN WHOLE FETUSES 3 AND 6 HOURS AFTER ADMINISTRATION OF 1 mg OF RADIOACTIVE MC TO THE MOTHER *

Time between administration of MC and removal of the fetuses	Total radioactivity		Radioactivity of unchanged MC		Distribution of the radioactivity	
	cpm/g tissue	cpm/fetus	cpm/g tissue	cpm/fetus	Unchanged MC (%)	Metabolites (%)
3 hours	6 400 (±1 700)	3 600 (±1 000)	900 (±700)	500 (±200)	14 (±7)	86 (±7)
6 hours	10 700 (±3 700)	9 600 (±3 900)	510 (±460)	470 (±440)	5 (±4)	95 (±4)

* In the 3-hour series the specific activity of MC was 0.52 μc/mmol. In the 6-hour series it was 0.44 μc/mmol.

(*c*) *Medizinische Hochschule; Pathologisches Institut, Abteilung für experimentelle Pathologie, Hanover, Federal Republic of Germany* (RA/70/002)

Principal investigator: Professor U. Mohr

An investigation has been started into the morphological changes in fetal organs following the transplacental administration of methylcholanthrene. On the 16th day of the gestation period, three-month-old BALB/c female mice received a single administration of 3.3 or 1.0 mg of methylcholanthrene. Three days later the fetuses were dissected and the ovary, testis, thymus, spleen, liver, lung, and parotid gland examined. Semi-thin sections of the tissue embedded in epon were used.

In conjunction with the European Committee for the Protection of the Population against the Hazards of Chronic Toxicity (Eurotox) and the University of Hanover, the unit is organizing a meeting on transplacental carcinogenesis to be held in Hanover from 5 to 7 October 1971.

(*d*) *First Institute of Pathology, Medical University, Budapest* (RA/70/003)

Principal investigator: Professor K. Lapis

The effect of methylcholanthrene on cells cultured *in vitro* is being investigated. Primary cultures obtained from the lungs of newborn mice (CBA T6 T6 strain) are used. Preliminary studies have been carried out with concentrations of methylcholanthrene in the culture medium, ranging from 0.1 to 100 μg/ml. Initial results indicate that asynchronous cells treated with methylcholanthrene for 24 hours survive better than synchronized cells treated for only two hours. The plating efficiency of cells treated in G_1 phase was much lower than that of cells treated in S phase.

4. KINETICS OF NITROSATION OF SECONDARY AMINES

Eppley Institute for Research in Cancer, University of Nebraska College of Medicine, Omaha, Nebr., USA (RA/69/014)

Principal investigator: Dr S. Mirvish

The induction of lung adenomas in Swiss mice was found to be a very sensitive test for exposure to dimethylnitrosoamine and diethylnitrosamine.[1] This system was used for testing whether nitrosamines are formed *in vivo* after administration of nitrite together with various amines. Positive results were observed for piperazine, morpholine, and *N*-methylaniline but not for dimethylamine.[2]

It was shown that simple alkylureas and alkylurethanes were very readily nitrosed to give nitrosamides and the kinetics of this reaction were established. Nitrosation of the naturally occurring alkylurea, citrulline, proceeded fairly rapidly to give *N*-δ-nitroso-citrulline. Nitrosation of naturally occurring methylguanine gave methylnitrosourea, but at a slower rate.

The fate of nitrite in the rat stomach was also studied. It was shown that most of a dose of nitrite disappeared from the rat's stomach within four hours, mainly owing to decomposition in the acid conditions of the stomach.

5. STUDIES ON THE METABOLISM OF *N*-NITROSO COMPOUNDS

(Dr R. Montesano)

Nitrosamines are a potential carcinogenic hazard for man, and it is possible that they require metabolic conversion to form an active carcinogenic intermediate. The metabolism of dimethylnitrosamine by human liver slices *in vitro* has therefore been investigated. A first study indicated that human liver could metabolize dimethylnitrosamine at a rate comparable to rat liver and that similar levels of nucleic acid methylation were found in human and rat liver slices.[3] In another study, using isotope-labelled materials, the metabolism of dimethylnitrosamine and diethylnitrosamine was measured in the liver, kidney, oesophagus, lung, and small intestine of the rat and the hamster. The data obtained suggested a correlation between the degree of metabolism of either of the two nitrosamines in an organ and the distribution of induced tumours in the two species.[4]

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[1] Mirvish, S. S. & Kaufman, L. (1970) *Int. J. Cancer*, **6**, 69.

[2] Greenblatt, M., Mirvish, S. S. & So, B. (1971) Nitrosamines studies: Induction of lung adenomas by concurrent administration of sodium nitrite and secondary amines in Swiss mice (submitted for publication).

[3] Montesano, R. & Magee, P. N. (1970) *Nature*, **228**, 173.

[4] Montesano, R. & Magee, P. N. (1971) *Proc. Amer. Soc. Cancer Res.* (in press).

6. MANUAL ON THE PATHOLOGY OF TUMOURS IN LABORATORY ANIMALS (Dr V. Turusov)

The preparation of a series of monographs on the pathology of tumours in the mouse, the rat, and the Syrian hamster is continuing. The monographs will aim to provide a standardized interpretation of results obtained in research and carcinogenicity testing.

The authors selected by the Editorial Board have agreed to contribute, and manuscripts are already being received at the Agency. Publication of the manual is expected in 1972.

7. EVALUATION OF CARCINOGENIC RISK OF CHEMICALS TO MAN (Dr C. Agthe)

The Advisory Committee on Environmental Carcinogens, at its meeting in Omaha, Nebr., USA from 2 to 4 June 1970 (see p. 43), recommended the production of a series of monographs, each evaluating the potential carcinogenic risk to man of a chosen substance. These monographs, which will replace the list that was previously envisaged,[1] will each consist of a summary of the available information on the carcinogenic action of the relevant substance in man and/or animals, with an assessment of the possible relevance of the animal tests to man agreed upon by an international group of experts. A working group was convened in Lyon in December 1970 to prepare definitions and examine preliminary drafts (IARC Internal Technical Report No. 70/009). The first series of about 20 monographs on the evaluation of carcinogenic risk of chemicals to man will be published following the 1971 meeting on this subject.

8. SEROLOGICAL STUDY ON PRIMARY LIVER CANCER (Dr P. Sizaret)

Detection and standardization of α_1*-fetoprotein* (Dr G. Abelev, Gamaleja Institute, Moscow, USSR; Dr P. Burtin, Institut de Recherches scientifiques sur le Cancer, Villejuif, France; Dr D. Rowe, International Reference Centre for Human Immunoglobulins, Lausanne, Switzerland; and Dr J. Uriel, Institut de Recherches scientifiques sur le Cancer, Villejuif, France)

A standard test system for α_1-fetoprotein detection is being prepared for distribution. For this test system, the necessary tested reagents (antiserum and antigen) have been put into ampoules.

At the same time an international standard of α_1-fetoprotein is being prepared.

The starting material will be cord blood sera, and a collection is being made in Lyon at the Hôtel Dieu (Professor Notter) and the Hôpital Edouard Herriot (Professor Magnin).

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 61.

This material will be put into ampoules and submitted to accelerated degradation at raised temperature for six months. This will ensure the stability of the final standard.

It is now possible to measure α_1-fetoprotein in amounts down to 1 μg/ml both in patients and in fetal sera, using a purified standard provided by Dr Abelev as comparison in the electro-immunodiffusion technique.

9. INVESTIGATION ON THE POTENTIAL CARCINOGENICITY OF DRUGS

Istituto di Anatomia e Istologia Patologica, Perugia, Italy (Dr C. Biancifori)

The antitubercular drug ethambutol is at present being tested in mice and rats to determine its carcinogenic potential, if any. The drug is being given for life span at different dose levels.

10. IARC INTERNATIONAL CENTRE FOR EXPERIMENTAL ANIMALS IN CANCER RESEARCH, NETHERLANDS CANCER INSTITUTE, AMSTERDAM (RA/67/019)

Principal investigator: Professor O. Mühlbock

The Centre maintains 35 pure strains of mice, five of which are kept under germ-free conditions, and four pure strains of rats. The Centre has provided tumour-bearing animals and healthy mice and rats to institutes in various countries. It maintains links with collaborating centres in Tokyo, Bombay, and Santiago.

5. UNIT OF RESEARCH TRAINING AND LIAISON

Staff: Dr W. Davis (Chief)
Mrs S. Rubin

Supporting staff: 2

1. INTRODUCTION

The fellowships programme is now entering its fifth year and the pattern is firmly established. The Fellowships Selection Committee, meeting in Lyon in October 1970, discussed the general policy of the programme and proposed some changes that seemed necessary in the light of experience.

The duration of Research Training Fellowships has been reviewed on several occasions, and this year the question was again thoroughly ventilated. It was decided that, if the available funds are to be used to the best advantage, the maximum number of such fellowships should be awarded, and it was therefore agreed that, for the time being, their duration would be strictly limited to one year.

In the light of this decision, the Committee further proposed that in future it should not normally accept applications from scientists already studying abroad with the aid of a fellowship from another organization.

It was recommended that Travel Fellowships should no longer be awarded to supplement funds for sabbatical leave. In the past, the Committee had recommended awards of three-month Travel Fellowships to scientists, knowing that they were in fact completing research during a sabbatical year. While such awards were in most cases well merited, the Committee felt that they did not fulfil the aims of the Travel Fellowships programme and the practice will therefore be discontinued.

A final and important organizational change was proposed with regard to the meeting for the selection of Research Training Fellows. The Selection Committee has traditionally met in October. However, there have always been a certain number of applicants wishing to start their fellowships at the beginning of the academic year, and the timing of the selection meant that they would have to wait almost another year before starting. Furthermore, in the interest of co-ordination with the American Cancer Society/Eleanor Roosevelt International Cancer Fellowships programme administered by UICC, it would be an advantage to fix the closing date of the IARC programme later than theirs, since it is only very rarely that applicants to IARC are referred to UICC for the more senior programme, whereas the reverse procedure is fairly common. For these two major reasons, the Committee agreed to change its date of selection and will in future meet in Lyon in May.

The members of the Fellowships Selection Committee invited from outside the Agency are:

Professor H. Isliker (Molecular biology)
Professor K. Munk (Virology)
Professor N. F. Stanley (Microbiology)
Professor U. Veronesi (Clinical oncology)
Dr D. Wood (Experimental and clinical oncology)

2. TRAVEL FELLOWSHIPS

As in previous years, Travel Fellowships were reviewed in February, April, and June by correspondence, as well as at the Fellowships Selection Committee's meeting in October 1970. During the year, a total of 103 applications were received, 41 being successful.

3. RESEARCH TRAINING FELLOWSHIPS

The Fellowships Selection Committee reviewed 59 applications for Research Training Fellowships and recommended awards in 25 cases. Since then two Fellows have declined their awards in order to take up other fellowships.

Once again the quality of the applications received was high, and the final selection proved a delicate and difficult task.

The distribution of the scientific disciplines represented showed little change and, as can be seen from Table 15, over half the fellowships awarded are in the allied fields of

TABLE 15. DISTRIBUTION OF FELLOWSHIPS BY SCIENTIFIC DISCIPLINE, 1970

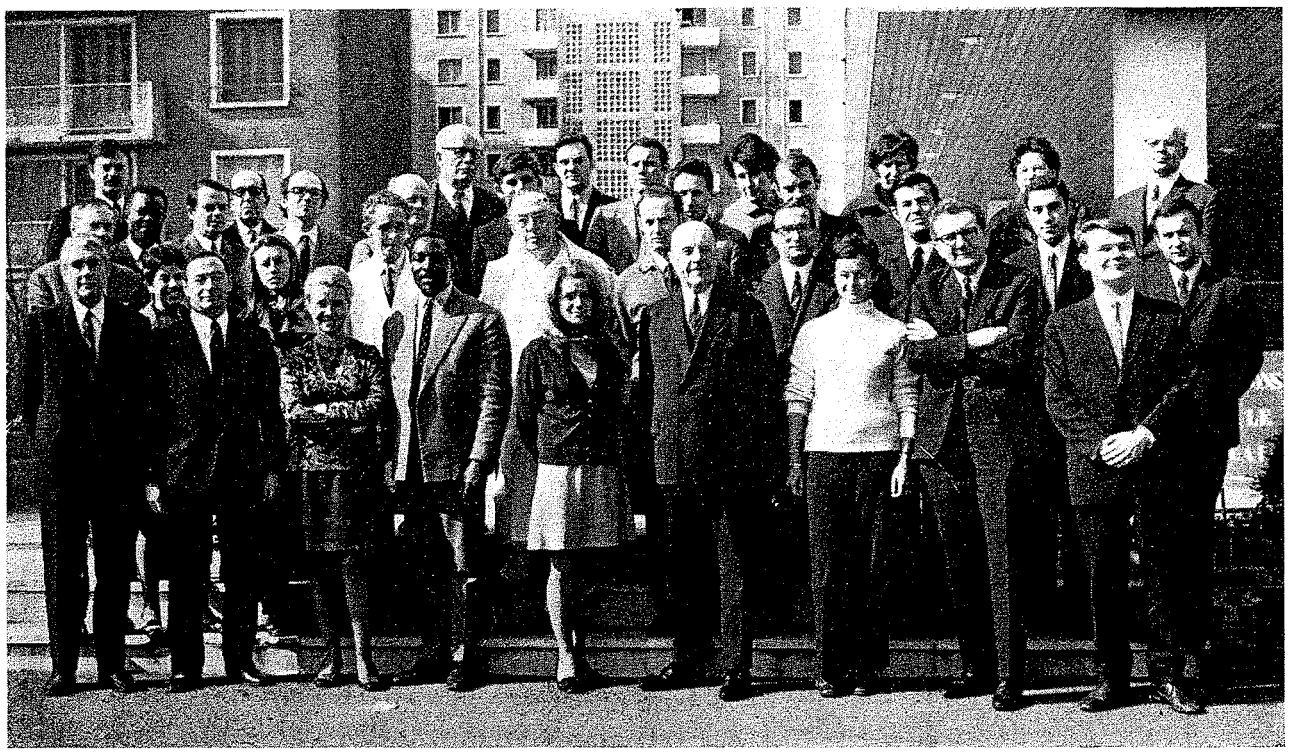
Research Training Fellowships		Travel Fellowships	
Biochemistry	1	Biochemistry	3
Cell biology	2	Cell biology	7
Cytogenetics	1	Chemical carcinogenesis	1
Electron microscopy	1	Cytogenetics	1
Epidemiology	2	Endocrinology	1
Experimental carcinogenesis	3	Epidemiology	4
Experimental pathology	1	Experimental carcinogenesis	1
Genetics	1	Experimental chemotherapy	2
Immunology	5	Experimental endocrinology	2
Molecular biology	4	Immunology	4
Virology	4	Molecular biology	4
		Oncology	1
		Pathology	1
		Radiology	1
		Radiodiagnostics	1
		Virology	7

virology, immunology, and molecular biology. This year again, two Fellows are being trained in epidemiology. One of the virology fellowships will be tenable at the Agency where the Fellow will work in the Unit of Biological Carcinogenesis. It is hoped that this is the beginning of a new trend that will develop as more laboratory space becomes available in the Agency.

4. COURSE ON EPIDEMIOLOGICAL TECHNIQUES IN CANCER RESEARCH FOR FRENCH-SPEAKING PARTICIPANTS

The first course organized by the Agency for French-speaking participants took place in Lyon from 2 to 14 March 1970 (see Fig. 9). The course was organized in close collaboration with the Centre d'Enseignement de la Statistique appliquée à la Médecine, Paris,

FIG. 9. IARC COURSE ON EPIDEMIOLOGICAL TECHNIQUES IN CANCER RESEARCH, LYON, MARCH 1970



Lecturers and participants in the course. Mr L. Pradel, Mayor of Lyon, is in the centre of the front row.

whose director, Professor Daniel Schwartz, lectured several times during the course. Other members of his staff and members of the Unit of Epidemiology and Biostatistics took the major responsibility for the organization of the programme, and Dr A. J. Tuyns acted as scientific director. There were 25 participants in the course, the success of which can best

be judged by the fact that in the succeeding six months no less than 16 of the participants made further contact with the Unit of Epidemiology and Biostatistics in connexion with their own work.

The Agency is indebted to Professor R. Sohier for permitting the course to be held at the Institut national de la Santé et de la Recherche médicale.

5. COURSE ON CANCER EPIDEMIOLOGY AND REGISTRATION

The programme for the first regional course organized by the Agency in the Regional Centre, Singapore, is now complete and 44 participants from Asia and Australasia have been selected. The course, which will take place from 7 to 14 March 1971, is being organized in collaboration with the International Epidemiological Association.

6. PUBLICATIONS

The Proceedings of the Working Conference on Liver Cancer, held in London in July 1969, are expected to be published in the summer of 1971.

Every effort is being made to ensure that the Proceedings of the forthcoming Symposium on Oncogenesis and Herpes-Type Viruses (see pp. 61-62) are published with the shortest possible delay.

It has been decided to make a selected number of the IARC Internal Technical Reports available for wider distribution. These monographs, in offset form, will be sent free of charge to all who now receive the Annual Report in order to provide them with more detailed information about specific IARC programmes.

6. UNIT OF ADMINISTRATION AND FINANCE

Staff: Mr A. G. B. SUTHERLAND (Chief)
Mr W. A. PRICHARD (Administrative Officer)
Mr Y. POLLET (Translation Services)
Mr N. P. CUMMINS (Library)
Mr B. BORGSTRØM (Administrative Services Officer)

Supporting staff: 9

1. INTRODUCTION

The unit continues to provide the administrative services that give essential support to the scientific programmes. Mr W. A. Prichard has been working alongside Mr A. G. B. Sutherland whom he will replace when the latter retires in June. He has also gained experience at WHO Headquarters and at the Regional Office for Europe in order to familiarize himself with the work and methods of WHO.

2. TEMPORARY ACCOMMODATION

At the end of 1969 the planning of a prefabricated building to provide laboratory and office space had already begun. Construction started in April 1970, and the building was ready for occupation in August. It contains an analytical laboratory for the Unit of Environmental Carcinogens, a biochemical laboratory for the Unit of Chemical Carcinogenesis, a histology laboratory, immunology laboratories, and animal rooms. Provision has also been made to house a tissue culture group. Besides the laboratory space, extra offices have been provided for the Unit of Environmental Carcinogens and the Units of Chemical and Biological Carcinogenesis.

The experience gained in the installation of the laboratories will be invaluable in planning the larger laboratory installations in the new building.

3. PERMANENT ACCOMODATION

The reinforced concrete tower structure that will house the Agency was finished in August, and by the end of 1970 work had started on the foundations of the auditorium. The architects have been co-ordinating the planning of the installations of the building

and it is anticipated that work will be completed in the late spring of 1972. Much valuable advice and criticism has been given by the staff of the Conference and Office Services unit of WHO Headquarters.

Close liaison has been maintained with the architects and engineers through the participation of Dr W. Davis (Chairman of the Building Committee) and Mr B. Borgstrøm in the meetings on the building site. The Governing Council Building Committee met in May 1970, visited the site, and presented a report to the Governing Council at its Eighth Session in October. At that time members of the official delegations also visited the site.

4. LIBRARY

Despite difficulties due to the cramped accommodation, the IARC Library continues to provide a service to the scientific staff. The subscriptions to journals now number 180, and approximately 2000 monographs are available.

To permit more efficient handling of the material in the Library, the catalogue has now been converted to conform to the US Library of Congress classification and a subscription to Library of Congress catalogue cards has been obtained. The Library has become a member of the US Book Exchange, and by exchanging some of the duplicates in its stock has obtained more needed volumes, including a set of *Advances in Cancer Research* for the IARC Regional Centre, Nairobi.

With the housing of three of the unit Chiefs and two of the units in the prefabricated building, a special library service has been established there so that all the currently needed journals are on hand.

7. IARC REGIONAL CENTRE, NAIROBI

Dr C. A. LINSELL (Head)
Dr F. G. PEERS (Consultant under Research Agreement RA/68/006 with the Tropical Products Institute, London)

Supporting staff: 11

1. INTRODUCTION

The expansion of the Centre's programme has continued. Its principal current projects are:

(*a*) cancer registration in East and Central Africa;
(*b*) studies on dietary carcinogens and human liver cancer;
(*c*) a review of liver disease in Africa;
(*d*) the animal tumour programme, covering
  (i) oesophageal tumours in cattle;
  (ii) vitamin B6 deficiency in baboons.

2. CANCER REGISTRATION IN EAST AND CENTRAL AFRICA

The objectives of this programme are:

(*a*) to determine the overall cancer pattern in East and Central Africa;
(*b*) to indicate sites suitable for further study by the Regional Centre;
(*c*) to give reliable cancer frequencies for the Centre's current projects;
(*d*) to study the methodology of cancer registration in developing countries.

The year 1970 was the third in which the Regional Centre collected data from the Kenyan, Tanzanian, Malawian, and Zambian national cancer registries. The information is, of necessity, incomplete, covering biopsy cases handled by the national histology service and all cases, including clinical diagnoses, seen at the major hospitals where the registries are located. Clinical information collected by the British Medical Research Council from peripheral hospitals has been added to this material, and all case data for 1968 and 1969 have been transferred to 80-column cards and magnetic tape.

The 1970 data will be collated and ready for evaluation by mid-1971. The material from the Ugandan cancer registry is also available to the British Medical Research Council,

so, within the present limitations of medical care and registration, the cancer pattern in East and Central Africa, regardless of political boundaries, can be determined. It will also be possible to assess the various biases that have been associated with purely hospital, biopsy, or clinical series reported from the area. Preliminary evaluation has shown considerable differences: for example, between the number of tumours registered at the central hospitals as a percentage of all tumours registered in the country—Kenya, 40 %; Malawi, 28 %; Tanzania, 11 %—and a bias of this nature may have greatly affected the cancer patterns previously reported from these countries. It has also been shown that the presence of clinicians expert or interested in particular cancers has had a very marked influence on the crude frequencies reported.

It has been suggested that in the Sudan cancer patterns change markedly and abruptly from those seen in Africa south of the Sahara to those seen in the Arab countries. The Khartoum registry was finally established in 1970, and preliminary registrations—analysed in Table 16—do in fact show interesting differences from patterns of cancer in sub-Saharan Africa.[1]

It is hoped to keep up this registry after the present study has finished and to attempt an incidence survey in the City of Omdurman.

TABLE 16. PRIMARY MALIGNANT NEOPLASMS DIAGNOSED BY SITE (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), SEX, AND ORDER OF RANK, SUDAN, 1970

MALES					FEMALES				
Rank order	ICD no.[a]	Site	No.	%	Rank order	ICD no.[a]	Site	No.	%
1	191	Skin	42	11.7	1	170	Breast	121	27.5
2	181	Bladder	25	7.0	2	171	Cervix	57	12.9
3	200.1	Lymphosarcoma	24	6.7	3	191	Skin	41	9.3
	197	Connective tissue (19)	24	6.7					
	197	Kaposi sarcoma (5)							
4	142	Salivary gland	21	5.9	4	172	Corpus uteri	28	6.4
	146	Nasopharynx	21	5.9					
5	190	Malignant melanoma	17	4.7	5	175	Ovary	23	5.2
6	196	Bone	16	4.5	6	142	Salivary gland	14	3.2
	192	Eye	16	4.5		197	Connective tissue	14	3.3
7	179	Penis	14	3.9	7	194	Thyroid	12	2.7
	140-205	All sites	359	100.0		140-205	All sites	440	100.0

[a] Seventh Revision.

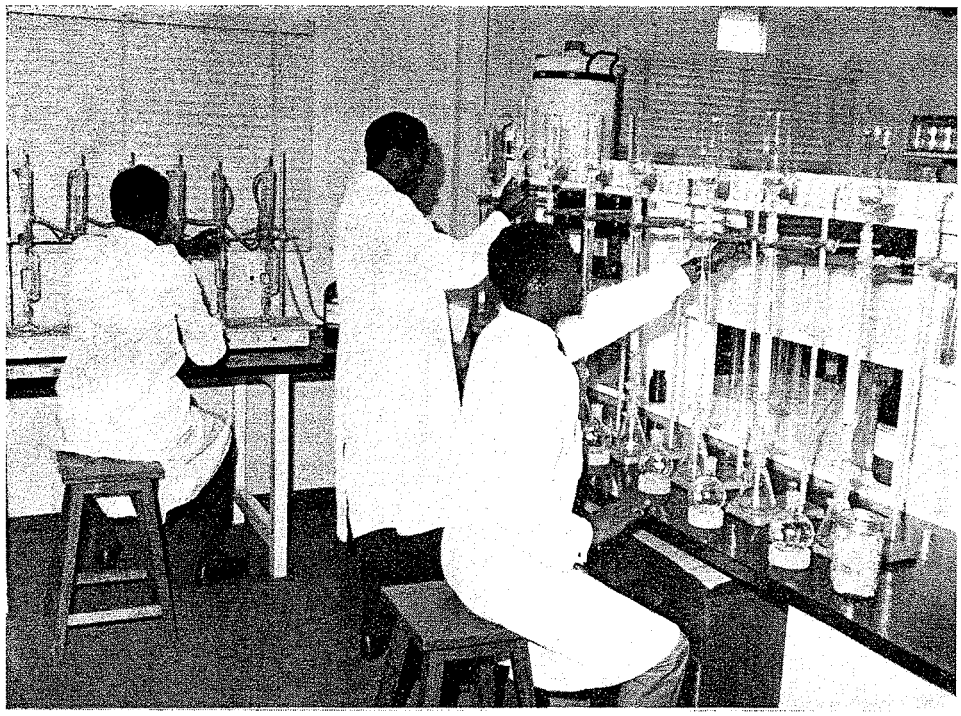
[1] Doll, R., Muir, C. & Waterhouse, J. ed. (1970) *Cancer incidence in five continents*, Geneva, UICC, vol. II.

3. DIETARY CARCINOGENS AND HUMAN LIVER CANCER

3.1 *Aflatoxin exposure in the Murang'a district (Kenya)*

The analytical examination of plate samples collected over a period of eighteen months is complete (Fig. 10). Cancer registration has continued and the α_1-fetoprotein test was made available to physicians working in the district. The precise location of the home of each liver cancer patient was traced in 43 out of 44 cases registered between 1967 and 1970.

FIG. 10. FOOD SPECIMENS BEING EXAMINED FOR AFLATOXIN IN THE LABORATORY OF THE NAIROBI REGIONAL CENTRE



Cases were accepted in the study if there was positive histology, a positive α_1-fetoprotein test (50 %-60 % of histologically proven cases in East Africa are positive), or a competent clinical diagnosis with death within six months. An evaluation of the aflatoxin levels and other data is currently being made with the assistance of the Unit of Epidemiology and Biostatistics. As indicated previously, there appears to be a definite correlation between aflatoxin levels and current liver cancer cases in the three sub-areas of differing altitude in Murang'a (Table 17).

The registration of cases will continue in the district with the assistance of the Department of Pathology of the University of Nairobi, which will in future co-ordinate the activities of the Kenya cancer registry. The Murang'a project has shown that methods can be devised for the detection of aflatoxin in "plate" samples, and that these can be used

TABLE 17. AFLATOXIN CONTAMINATION OF PLATE SAMPLES IN MURANG'A, KENYA

	Average altitude of area		
	High	Medium	Low
Aflatoxin content of food samples (μg/kg)	3.5	5.9	10.0
Proportion of positive samples	39/808	54/808	78/816
Hepatoma incidence:			
Total no. cases 1967-1970	1	19	12
No. cases per 100 000 adults per year	1.3	6.3	8.0

to measure exposure in a rural population in Africa. However, it is necessary to extend this study to other areas in the world with differing cancer rates and levels of aflatoxin contamination, if the hypothetical association between aflatoxin ingestion in man and hepatocellular cancer is to be adequately tested.

3.2 *Food storage survey in Murang'a*

Consultant: Mr G. A. Gilman, Tropical Products Institute, London

Detailed knowledge of harvesting and food storage practices is vital to any field study on mycotoxins. The Murang'a district had been divided into three sub-areas, available agricultural, sociological, and meteorological data being used to determine whether methods and conditions of storage were sufficiently different to justify the suggestion that mould contamination would vary significantly. The survey showed that mould contamination was most likely to occur in cereals stored in the low altitude areas. The knowledge of storage methods acquired in Murang'a has permitted the selection of the most appropriate time and area for the collection of market samples in Murang'a itself and will enable a rapid evaluation to be made of other areas where liver cancer rates are thought to be high.

3.3 *Market sample survey in Murang'a*

Harvesting, marketing, home storage, and cooking methods in Murang'a have also been observed. Published data on levels of aflatoxin in African foodstuffs are based on the examination of market samples or export crops, ignoring the possibility of housewife selection or changes during cooking. The need to make a clear distinction between market and plate samples of cereals is supported by the preliminary findings, as positive samples are more frequent among the cereals available in the market. The assessment of contamination levels is still in progress.

3.4 *Aflatoxin levels in other East African diets*

Thirty-six samples were obtained from the Nutrition Research Unit of the Medical Research Council located at Kampala. These lyophilized samples were taken from diets known to contain a high proportion of groundnuts, and a significantly high number of them were positive for aflatoxin. On completion of this study, consideration will be given to the question whether other areas within East Africa warrant a Murang'a-type study.

3.5 *Studies outside East Africa*

Plans are already in hand for similar studies to be made in India, the Ivory Coast, Mozambique, and the Philippines.

(*a*) *India*

The Tata Memorial Centre, Bombay is undertaking a prospective study at Alibag, 113 km south of Bombay.

(*b*) *Ivory Coast*

See pages 21 and 32.

(*c*) *Mozambique*

Active negotiations for a project have started in Mozambique, where the world's highest incidence of liver cancer has been reported.

(*d*) *Philippines*

A food collection study is being planned on the island of Cebu where maize, but not rice, is eaten and where the rate of liver cancer is reported to be higher than elsewhere in the Philippines.

3.6 *Examination of mycotoxins isolated from food in Hong Kong*

As part of the mycology study by the Massachusetts Institute of Technology in the Far East, samples of foodstuffs from Hong Kong were examined for mycotoxins other than aflatoxin. Isolates from this investigation were returned to Hong Kong for carcinogenicity testing. This work is now being continued by Dr Lily Ma, Department of Pathology, Hong Kong University, under contract with the IARC.

4. LIVER DISEASE IN KENYA

The Agency has supported studies in the Department of Medicine, University of Nairobi, the National Cancer Institute Solid Tumour Centre, Kampala, and the Faculty of Medicine, Dakar. The long-term follow-up study of liver disease is continuing at the

Nairobi Medical School. In Kenya viral hepatitis is a more severe disease than in Europe and America [1] and hepatitis associated antigens (HAA) were found in 54 % of cases; [2] 14 % of hepato-cellular cancers in Nairobi were also HAA-positive. A much higher percentage of such tumours were positive for HAA in Kampala (40 %) [3] and Dakar (42 %).[4] In Nairobi 20 % of patients with cirrhosis are positive for HAA, as compared with 23 % in Kampala.

The fact that liver cancer can occur, at least in Africa, without cirrhosis and that some cases are HAA-positive raises the question whether the hepatitis virus is directly involved in neoplasia, particularly as such a high percentage of proven liver cancers are positive for HAA. The varied geographical pattern of the percentage of liver cancer cases in Africa showing a positive α_1-fetoprotein test, reported in 1969, is confirmed by current studies. It has been found, however, that there is a tendency for α_1-fetoprotein positivity to occur more often in younger cancer patients, and this may be a factor influencing the considerable differences between α_1-fetoprotein positivity in Africa, the United Kingdom, and the USA.[5,6] Although the appearance of α_1-fetoprotein is now recognized as a diagnostic serological test for hepato-cellular cancer, there is clearly much to be learned about its pathogenesis both in man and experimental animals.

5. ANIMAL TUMOUR PROGRAMME

5.1 *Rumenal cancer in Kenyan cattle*

The occurrence of rumenal cancer at a minimum yearly rate of 15 histologically proven cases for the isolated cattle population of Kenya, totalling 1000 cattle, has been reported.[7] No cases have occurred so far in the animals introduced by the Regional Centre to the area. The botanical survey continued throughout 1970, as plants must be observed at various seasons before final identification. The screening, by means of thin-layer chromatography, of a number of suspect plants for gross contamination by nitrosamines gave negative results.[8] The cancer chemotherapy screening programme of the United States National Cancer Institute has supplied details of plants in other areas of Kenya with a similar botanical background, including any with carcinogenic properties. The plant collection from the suspect high-altitude areas continues, and the material is submitted to biological and phytochemical testing.

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[1] Jindani, A., Bagshawe, A. F. & Forrester, A. T. T. (1970) *E. Afr. med. J.*, **47**, 138.
[2] Bagshawe, A. F., Parker, A. M. & Jindani, A. (1971) *Brit. med. J.*, **1**, 88.
[3] Vogel, C. L. et al. (1970) *Lancet*, **2**, 621.
[4] Prince, A. M. et al. (1970) *Lancet*, **2**, 717.
[5] Vogel, C. L. et al. (1970) *Lancet*, **2**, 621.
[6] Bagshawe, A. F. & Parker, A. M. (1970) *Lancet*, **2**, 268.
[7] Plowright, W., Linsell, C.A. & Peers, F. G. (1971) *Brit. J. Cancer* (in press).
[8] Dossaji, S. F. (1970) *Toxins in certain indigenous Kenya plants*, Nairobi, University College (Thesis).

5.2 α_1-*fetoprotein-positive, vitamin-B6-deficient baboons*

The study started last year at the Wellcome Trust baboon colony has continued.[1] The histology of the liver in α_1-fetoprotein-positive baboons has been interpreted as atypical hyperplasia similar to the pre-cancerous changes seen in long-term studies of rats fed aflatoxin. The α_1-fetoprotein positivity appears to be irreversible even when normal vitamin balance is restored.

The work will continue partly in the Regional Centre's laboratories, where a new baboonery has been built, and partly in the Veterinary Department of the University of Nairobi, under contract to the Agency. Karyological studies on biopsy and post-mortem material from the baboons are being carried out in the Centre's laboratories by Dr P. B. McCulloch of McGill University, Montreal, Canada.

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[1] Foy, H. et al. (1970) *Nature*, **225**, 952.

8. IARC REGIONAL CENTRE, SINGAPORE

Professor K. SHANMUGARATNAM (Head)

1. THE SINGAPORE CANCER REGISTRY (RA/67/009)

Principal investigator: Professor K. Shanmugaratnam

This is a comprehensive population-based registry for the island of Singapore. Notifications are received from all sections of the medical profession and the registry ensures that notifications are as complete as possible by scrutinizing all hospital records, pathology records, and death certificates in Singapore. The registry has received excellent co-operation from the medical profession and from the Ministry of Health.

Registration began in January 1968,[1] and 6852 cancer cases have been registered to date. An analysis of 2321 cancer cases diagnosed in 1968 among permanent Singapore residents is given in Table 18. A paper based on the findings was presented at the Tenth International Cancer Congress in Houston, Tex., USA.[2]

The age-standardized incidence of cancer as a whole in Singapore is comparable with that any country in the West. There is a particularly high incidence of cancers of the naso-pharynx, oesophagus, stomach, liver, and lung, and a relatively low incidence of cancers of the rectum, breast, and prostate. The age-standardized incidence of lung cancer in Singapore males is higher than that of most countries in Asia; the incidence in Singapore females, standardized for age, is probably the highest recorded for females in any part of the world.

In 1968, the rank order for all cancers diagnosed in Singapore was as follows:

	Males	*Females*
1.	Lung (18.7 %)	Breast (12.6 %)
2.	Stomach (17.2 %)	Stomach (11.6 %)
3.	Liver (13.7 %)	Lung (11.2 %)
4.	Nasopharynx (8.1 %)	Cervix uteri (10.3 %)
5.	Oesophagus (6.4 %)	Ovary (6.0 %)

This is significantly different from the rank order among cases diagnosed histologically (biopsies plus necropsies) in 1960-64. While the difference is partly due to bias in the selection of cases for histological examinations, there has undoubtedly also been a significant

[1] International Agency for Research on Cancer (1969) *Annual report, 1968*, Lyon, p. 69.

[2] Shanmugaratnam, K. (1971) *Patterns of cancer occurrence in the Far East.* In: *Proceedings of the Tenth International Cancer Congress, Houston, Texas, May 1970*, Chicago, Year Book Medical Publishers (in press).

TABLE 18. NUMBERS OF CANCER CASES, SELECTED SITES (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), DIAGNOSED IN THE SINGAPORE POPULATION (ALL RACES), AND RATES PER 100 000 PERSONS AGE-STANDARDIZED TO THE WORLD POPULATION, 1968

ICD no.[a]	Site	Male		Female	
		Cases	Age-standardized rate	Cases	Age-standardized rate
141	Tongue	17	3.1	3	0.5
143-5	Mouth	17	3.2	5	0.8
147	Nasopharynx	110	14.7	47	6.7
150	Oesophagus	89	15.5	42	6.6
151	Stomach	242	40.0	109	17.3
153	Colon	63	10.8	51	7.9
154	Rectum	37	6.2	39	6.1
155	Liver	189	28.5	33	5.2
157	Pancreas	18	2.9	13	2.0
161	Larynx	44	7.5	1	0.1
162	Lung	257	42.9	102	16.4
172-3	Skin	36	5.4	21	3.7
174	Breast	1	0.2	119	17.6
180	Cervix	—	—	97	14.3
182	Uterus	—	—	28	4.0
183	Ovary	—	—	55	7.4
185	Prostate	12	2.7	—	—
187	Penis	8	1.0	—	—
188	Bladder	29	4.9	5	0.8
189	Kidney	9	1.3	10	1.3
191	Brain	19	1.7	8	1.0
193	Thyroid	10	1.3	33	4.1
200-202	Lymphomas	31	4.7	15	2.1
204-209	Leukaemias	42	4.9	23	2.7
140-209	All sites	1 390	218.4	931	138.9

[a] Eighth Revision.

change in cancer patterns in recent years. In 1960-64 and 1968, the ten commonest cancers among biopsies on both sexes were as follows:

	1960-64	*1968*
1.	Nasopharynx (11.0 %)	Lung (11.4 %)
2.	Cervix uteri (10.2 %)	Stomach (10.7 %)
3.	Stomach (9.1 %)	Nasopharynx (10.1 %)
4.	Lung (7.2 %)	Liver (7.8 %)
5.	Breast (5.6 %)	Breast (6.2 %)
6.	Oesophagus (5.4 %)	Cervix uteri (6.1 %)
7.	Liver (5.1 %)	Oesophagus (5.5 %)
8.	Rectum (4.9 %)	Colon (5.2 %)
9.	Skin (4.1 %)	Rectum (4.1 %)
10.	Colon (2.8 %)	Skin (3.5 %)

The figures for 1969 are now being analysed and the results will be available in January 1971.

2. CARCINOMA OF THE OESOPHAGUS (RA/70/023)

Principal investigators: Mr J. Goh Ewe Hong, Mr M. Sridharan

A questionnaire survey on oesophageal cancer is being carried out in collaboration with the Unit of Epidemiology and Biostatistics (Dr Ulrike de Jong). Subjects with oesophageal cancer and controls in Government and private hospitals in Singapore will be interviewed. The project began in November 1970.

3. IMMUNOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA

Principal investigators: Dr M. J. Simons, Dr Kwa Soon Bee

During the first half of the year, Dr D. S. Nelson continued investigations initiated in 1969.[1] The objects were to determine if any patients made an immune response to their own tumours and, if so, whether the antigens to which they reacted were common to all tumours, as in virus-induced animal tumours, or individual-specific.

Sera obtained from patients with nasopharyngeal carcinoma and from healthy Chinese subjects were tested by indirect immunofluorescence, using frozen sections of nasopharyngeal biopsies, for antibodies to tumour cells and normal nasopharyngeal cells.

Of 28 sera tested against autologous tumour, four reacted strongly with nuclei, nine with membranes, and two with cytoplasm of tumour cells. These sera also reacted with similar constituents of other patients' tumours. Antibodies to nuclei and membranes reacted with occasional lymphocytes and epithelial cells in normal biopsies. Anti-cytoplasmic antibodies reacted strongly with normal epithelial cells. Of 10 normal sera, one reacted strongly and three weakly with tumour cell nuclei, none strongly and one weakly with membranes, and none with cytoplasm.

The findings are consistent with the reported association between a herpes-type virus and nasopharyngeal carcinoma, but do not indicate whether a virus is the causative agent or merely grows opportunistically in tumour cells. The nuclear antigen and the membrane antigen are common to all tumours but are also present in some normal cells. They could represent virus antigen and virus-determined antigen respectively, and the few normal cells stained could be infected but not transformed into malignant cells. The cytoplasmic antigen is common to tumour cells and normal epithelium; antibodies to this antigen may be auto-antibodies to a normal tissue-specific antigen.[2]

During the second half of the year, facilities and conditions essential for short-term cultures of lymphocytes in a controlled-gas-phase environment have been established. Lympho-responsiveness to stimulation by phytohaemagglutinin is being measured by incor-

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, p. 82.
[2] Nelson, D. S. (1971) *Clin. exp. Immunol.* (in press).

poration of radioisotopic precursors (tritiated thymine and uracil and ^{125}I-labelled iodouridine). The main objectives of these studies are as follows:

(*a*) to investigate general cell-mediated immune competence in nasopharyngeal carcinoma patients;

(*b*) to establish whether lymphocyte-mediated immunity specific to tumour cell antigens exists in nasopharyngeal carcinoma patients;

(*c*) to determine whether serum factors interfere with lymphocyte tumour cell interaction.

Current progress with the long-term culture of nasopharyngeal carcinoma cells, with the separation of tumour from other cells in lymph node biopsies, and with propagation of tumour cells by transplantation into the cheek pouch of immuno-suppressed hamsters will facilitate the achievement of these objectives.

4. IMMUNOGENETIC STUDIES ON NASOPHARYNGEAL CARCINOMA

Principal investigators: Dr M. J. Simons, Dr Kwa Soon Bee

IARC Visiting Scientist: Mr A. Ting

The main aim of these studies is to establish genetic profiles of the ethnic group (Chinese) amongst whom the incidence of nasopharyngeal carcinoma is high and of the group (Indo-Pakistani) in whom the incidence is very low. The available epidemiological data suggest that the Chinese have a genetically determined susceptibility to nasopharyngeal carcinoma. This predisposition can be investigated by typing the known blood genetic systems. A tissue typing laboratory for the analysis of lymphocyte-HLA antigens has been established with the assistance of the WHO Tissue Typing Reference Laboratory for South-East Asia. Early results indicate a significant difference between the HLA patterns of Chinese and Caucasians. Red-cell and red-cell enzyme genetic systems and immunoglobulin and other serum protein polymorphisms will be examined in collaboration with laboratories in Australia and France. It is proposed to store white cells, red cells, and sera in liquid nitrogen for future population genetics studies.

5. SERO-EPIDEMIOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA

Principal investigators: Dr Kwa Soon Bee, Dr M. J. Simons

IARC Visiting Scientist: Mr I. Jack

During the latter half of 1970 the study on the relationship between nasopharyngeal carcinoma and herpes-type virus was commenced. The objectives of the study have been

outlined previously.[1] Under the direction of Mr I. Jack, conditions necessary for the testing of sera for Epstein-Barr virus antibody by the Henle technique have been established. In addition, cell cultures have been initiated from biopsies of nasopharyngeal tissue obtained both from subjects histologically positive and negative for nasopharyngeal carcinoma and from biopsies of cervical lymph nodes. These cultures comprise cells of lymphoblastoid, fibroblastic, and epithelial type morphology. Facilities and culture conditions essential for the continuation of these cultures into permanent cell lines are being developed. In this way full advantage will be taken of the short time (approximately 30 minutes) between biopsy and initiation of cultures, thus eliminating the delay that occurs when material has to be sent from one country to another.

Before commencement of the serological study involving 4800 Chinese and 2400 Indians and Pakistanis, several practical issues had to be resolved, including the appointment of suitable staff and the preparation of sampling, storing, and analytical materials. This has now been done and the survey will commence in January 1971.

6. CARCINOMA OF THE PROSTATE

The Regional Centre (with the participation of Dr Lee Yoke Sun) is collaborating with the IARC Unit of Epidemiology (Dr H. Tulinius) in a study of latent carcinoma of the prostate.

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[1] International Agency for Research on Cancer (1970) *Annual report, 1969*, Lyon, pp. 43-44.

9. IARC REGIONAL CENTRE, JAMAICA

Professor G. BRAS (Head)

1. KINGSTON AND ST ANDREW CANCER REGISTRY

The Kingston and St. Andrew cancer registry, largely supported by the British Empire Cancer Campaign with some help from the IARC, continues its work. From October 1969 to November 1970, a further 1223 cases were registered, of which 679 were from Kingston and St Andrew (males 265, females 414). Although a census was conducted in 1970, the results are not yet available for the calculation of rates.

2. CURAÇAO AND ARUBA

Staff from the Centre visited Curaçao in January and April 1970 to follow up the work of the cancer registry. During the year, the Chief of the Public Health Service, Dr Oostendorp, was replaced by Dr Gielen, and the pathologist, Dr de Koning, was replaced by Dr Van Leeuwen.

The results of cancer registration in Curaçao in 1968-69 are given in Table 19.

For males and females respectively, the age-standardized rates for all sites were 168.3 and 162.0 per 100 000 per annum; the corresponding rates for oesophageal cancer were

TABLE 19. PRIMARY MALIGNANT NEOPLASMS DIAGNOSED, BY SITE (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), SEX, AND ORDER OF RANK, CURAÇAO, 1968-69

Males					Females				
Rank order	ICD no.[a]	Site	No.	%	Rank order	ICD no.[a]	Site	No.	%
1	151	Stomach	25	16.6	1	174	Breast	46	24.0
2	150	Oesophagus	22	15.6	2	180	Cervix uteri	46	24.0
3	162	Lung	15	9.9	3	150	Oesophagus	15	7.8
4	153-4	Colon, rectum	10	6.6	4	151	Stomach	11	5.7
		All sites	151	100.0			All sites	192	100.0

[a] Eighth Revision.

26.3 and 12.0. Although oesophageal cancer was generally considered to be of equal frequency in both sexes, the rates for males are twice those for females, after age-standardization. It must be stressed that these rates were calculated on the basis of rather small numbers.

Registration in Aruba is still incomplete.

The case-control study of oesophageal cancer in Jamaica has now been extended to Curaçao.

3. BARBADOS CANCER REGISTRY

Principal investigators: Dr A. C. Fraser, Dr H. White (RA/70/006 and RA/70/037)

The Barbados cancer registry forms part of a larger clinical and pathological registry for the Eastern Caribbean at the Queen Elizabeth Hospital, Barbados. Although registrations are received from the other islands in the Eastern Caribbean region, special attention is being paid to cancer registration in Barbados, which has a population of just over 250 000.

Figures are now available for the Barbados registry's first three months of operation, during which 93 cases of cancer (males, 38; females, 55) were diagnosed histologically, the most frequent neoplasm being cervix uteri (31 %). It already seems probable that oesophageal cancer is common in both sexes.

4. JAMAICA (Dr Ulrike de Jong)

Principal investigator: Professor G. Bras (RA/70/001)

In Jamaica, patients likely to have oesophageal cancer are being interviewed, often before the diagnosis has been histologically confirmed. Using part-time staff, 20 confirmed oesophageal cancer cases and an equal number of hospital controls have now been interviewed. In relation to 14 of the cancer cases, 28 neighbourhood controls have been interviewed.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE EIGHTH SESSION OF THE IARC GOVERNING COUNCIL, 19-20 OCTOBER 1970

Australia

Dr B. E. WELTON
Chief Medical Officer
Australia House
London

Mr B. F. HURLEY
Director, Office of the Australian Treasury
Geneva

Mr A. BROWN
First Secretary, Australian Permanent Mission to the United Nations
Geneva

Belgium

Professor S. HALTER
Secrétaire général de la Santé publique
Brussels

Federal Republic of Germany

Professor J. STRALAU
Director-General, Ministry of Youth, Family, and Health
Bonn

Dr H. KAISER
Federal Ministry of Finance
Bonn

France

Professor E. J. AUJALEU
Directeur général honoraire de l'Institut national de la Santé et de la Recherche médicale
Conseiller d'Etat
Paris

Dr J. C. MEILLON
Médecin-Inspecteur principal, Division des Relations internationales
Ministère de la Santé publique et de la Sécurité sociale
Paris

Mr J. C. PANSARD
Ministère des Affaires étrangères
Paris

Israel

Dr J. SILBERSTEIN
Director, Department of Chronic Diseases and Rehabilitation
Ministry of Health
Jerusalem

Italy

Professor R. VANNUGLI
Director, Office of International Relations
Ministry of Health
Rome

Professor L. SANTI
Professor of Experimental Oncology
University of Genoa

Professor F. NOBILE
Ministry of Health
Siena

Netherlands

Dr R. J. H. KRUISINGA (Chairman)
Secretary of State for Social Affairs and Public Health
Ministry of Social Affairs and Public Health
The Hague

Netherlands (continued)

Miss J. SCHALIJ
Acting Head, Division for International Health Affairs
Ministry of Social Affairs and Public Health
The Hague

Union of Soviet Socialist Republics

Dr V. V. KOVANOV
Vice-President, Academy of Medical Sciences
Moscow

Dr G. NOVGORODCEV
Counsellor, Permanent Delegation of the USSR
Geneva

Dr N. NAPALKOV
Deputy Director, N. Petrov Research Institute of Oncology
Ministry of Public Health of the USSR
Leningrad

Dr M. SAVELIEV
External Relations Board
Ministry of Public Health of the USSR
Moscow

United Kingdom

Dr J. A. B. GRAY
Secretary, Medical Research Council
London

Mr G. F. HAWKER
Principal, Department of Education and Science
Lewes

United States of America

Dr C. G. BAKER
Director, National Cancer Institute
National Institutes of Health
Bethesda, Md.

Dr B. BLOOD
International Health Attaché
US Permanent Mission
Geneva

Mr R. B. ALLEN
Department of State
Washington, D. C.

World Health Organization

Dr M. G. CANDAU
Director-General

Mr F. GUTTERIDGE
Chief, Legal Office

Dr L. VERHOESTRAETE
Director, Health Protection and Promotion

Observers

Professor N. N. BLOKHIN
Outgoing Chairman of the IARC Scientific Council

Professor M. DARGENT
Representative of the UICC

Professor J. H. F. MAISIN
Chairman-elect of the IARC Scientific Council

Annex 2

MEMBERS OF THE SCIENTIFIC COUNCIL AT ITS SIXTH SESSION, 15-17 JUNE 1970

Professor N. N. BLOKHIN
Director, Institute of Experimental and Clinical Oncology
Academy of Medical Sciences
Moscow

Professor P. F. DENOIX
Director, Institut Gustave Roussy
Villejuif, France

Professor W. R. S. DOLL
Regius Professor of Medicine
University of Oxford
Oxford, United Kingdom

Professor H. C. ISLIKER
Institut de Biochimie
Université de Lausanne
Lausanne, Switzerland

Professor B. MACMAHON
Department of Epidemiology
Harvard School of Public Health
Boston, Mass., USA

Professor J. H. F. MAISIN
Institut du Cancer
Université de Louvain
Louvain, Belgium

Dr G. J. V. NOSSAL
Director, Walter and Eliza Hall Institute of Medical Research
Melbourne, Australia

Dr E. PEDERSEN
Director, Cancer Registry of Norway
Oslo

Professor L. SACHS
Head, Genetics Section
Weizmann Institute of Science
Rehovoth, Israel

Professor C. G. SCHMIDT
President, German Cancer Society, and Director, Department of Internal Medicine (Tumour Research)
Ruhr University
Essen, Federal Republic of Germany

Professor L. SEVERI
Dean and Professor of Morbid Anatomy and Histology
Perugia University Medical School
Perugia, Italy

Professor T. SUGIMURA
Chief, Biochemistry Division
National Cancer Centre Research Institute
Tokyo

MEMBERS OF THE SCIENTIFIC COUNCIL ELECTED TO TAKE OFFICE IN 1971

Professor R. LATARJET
Institut du Radium
Laboratoire Pasteur et Fondation Curie
Paris

Dr N. P. NAPALKOV
N. Petrov Research Institute of Oncology
Leningrad, USSR

Professor M. G. P. STOKER
Director, Imperial Cancer Research Fund
London

Professor D. W. VAN BEKKUM
Director, Radiobiological Institute of the Organization for Health Research TNO,
Rijswijk, Netherlands

Annex 3

RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS IN 1970

RA/67/003	Department of Tumour Biology, Karolinska Institutet, Stockholm (Provision of frozen transplantable tumour strains)
RA/67/009	IARC Regional Centre, University of Singapore (Cancer Registry at Singapore)
RA/67/019	Netherlands Cancer Institute, Amsterdam (WHO International Reference Centre for the provision of tumour-bearing animals)
RA/67/020	Centre Léon Bérard, Lyon, France (Laboratory facilities in Lyon for IARC)
RA/67/021	Cell-Cancer-Virus Study Group (CCV), Lyon, France (Laboratory facilities in Lyon for IARC)
RA/68/001	University of the West Indies, Mona, Kingston (Contribution to the maintenance of an IARC Regional Centre at the University of the West Indies)
RA/68/002	University of Singapore (Contribution to the maintenance of an IARC Regional Centre at the University of Singapore)
RA/68/004	Curaçao and Aruba Cancer Registry, West Indies (Investigation to establish cancer incidence)
RA/68/006	Tropical Products Institute, Ministry of Overseas Development, London (Contribution towards the provision of a research biochemist—Dr F. G. Peers, Nairobi—to supervise and carry out technical and analytical work for field studies on mycotoxins in Kenya)
RA/68/007	Hong Kong Anti-Cancer Society (Studies on nasopharyngeal carcinoma)
RA/68/011	Institut national des Sciences appliquées, Villeurbanne, France (Study of transplacental passage of polycyclic hydrocarbons in rodents and of enzyme induction in the fetus and newborn by the transplacental passage of enzyme-inducing substances)
RA/68/013	Faculty of Medicine, University of Dakar (Collaborative study for the evaluation of a serological test for liver cancer)
RA/68/014	Gamaleja Institute for Epidemiology and Microbiology, Moscow (Collaborative study on the application of the fetuin test to epidemiological studies on liver cancer)

RA/69/001 Rijks Instituut voor de Volkgezondheid, Utrecht, Netherlands
(Experimental investigation of the potential carcinogenicity of various inorganic substances)

RA/69/002 Makerere University College, Kampala, Uganda
(Studies on nasopharyngeal carcinoma and on cancer of the penis)

RA/69/003 Instituto Nacional de Enfermedades Neoplásicas, Lima
(Cancer Registry in Lima)

RA/69/005 Department of Occupational Health, The Hebrew University-Hadassah Medical School, Jerusalem
(Analysis of fat and other tissue for the presence of chlorinated hydrocarbons)

RA/69/008 University of Teheran
(Study of etiological factors in oesophageal cancer in the Caspian coastal area of Iran)

RA/69/010 Institut national des Sciences appliquées, Villeurbanne, France
(Study on infracellular targets and metabolism of carcinogenic hydrocarbons in the fetus and newborn)

RA/69/011 Ministère de la Santé publique, Abidjan
(Serological survey on the presence of liver cancer in the Ivory Coast)

RA/69/013 University of Lyon, France
(Study of ultrastructural modifications in rodent hepatic cells after DDT administration)

RA/69/014 Eppley Institute for Research in Cancer, University of Nebraska College of Medicine, Omaha, Nebr., USA
(Search for markers indicative of a previous exposure to nitrosamines in the environment and *in vivo*)

RA/69/016 Aichi Cancer Centre Research Institute, Nagoya, Japan
(Collection and shipment of 300 samples of human tissues for analysis of their DDT content)

RA/69/017 Institute of Experimental and Clinical Medicine, Tallinn, USSR
(Investigation of the comparative carcinogenic action of shale and chrysotile asbestos dust in rats)

RA/70/001 IARC Regional Centre, Jamaica
(Case-control study of oesophageal cancer)

RA/70/002 Medizinische Hochschule, Hanover, Federal Republic of Germany
(Investigation of the effects of chemical carcinogens administered transplacentally on the foetal reproductive organs)

RA/70/003 Medical University, Budapest
(Investigation of the effects of minute doses of chemical carcinogens on cells cultured *in vitro*)

RA/70/004 Institute of Experimental and Clinical Oncology, Moscow
(Study of the effects of irradiation of pregnant mice on their descendants)

RA/70/005 School of Medicine, University of Valle, Cali, Colombia
(Studies of precancerous and cancerous lesions of the cervix and of the penis)

RA/70/006	IARC Regional Centre, Jamaica (Pilot project in connexion with the expansion of the regional centre's activities to Barbados)
RA/70/007	Dr L. Leblanc, University of Dakar, Senegal (Serological survey for the detection of liver cancer)
RA/70/008	Houghton Poultry Research Station, United Kingdom (Symposium on Oncogenesis and Herpes-type Viruses)
RA/70/009	Chester Beatty Research Institute, London (Provision of secretarial services for IARC consultant in connexion with establishment of a chemical analytical laboratory)
RA/70/010	Institut Pasteur du Cameroun, Yaoundé (Determination of the relative frequency of various forms of cancer in Cameroon)
RA/70/011	National Institutes of Health, Bethesda, Md., USA (Sero-epidemiological carcinoma study)
RA/70/012	Ministère de la Santé publique, Abidjan (Survey on the frequency of aflatoxin contamination of foodstuffs in the Ivory Coast)
RA/70/013	Hong Kong Anti-cancer Society (Studies on the relationship between herpes-type virus infection and nasopharyngeal carcinoma)
RA/70/014	Medical Research Council Pneumoconiosis Research Unit, Cardiff, United Kingdom (Research study programme on asbestos cancers)
RA/70/015	School of Medicine, University of Ljubljana, Yugoslavia (Studies of intestinal metaplasia and gastric cancer)
RA/70/016	Instituto de Medicina Tropical de São Paulo, Brazil (Sero-epidemiological and tissue culture studies on lymphomas, leukaemias, and other tumours)
RA/70/017	University of Singapore (Studies on the relationship between herpes-type virus infection and nasopharyngeal carcinoma)
RA/70/018	University of Hong Kong (Relationship of strains of fungi isolated from Hong Kong foodstuffs to human liver cancer)
RA/70/019	Medical Research Council, London (Short-term technical services in connexion with oesophageal cancer studies in the Caspian littoral and Mazandaran Province, Iran)
RA/70/020	University of Teheran (Contribution to the maintenance of an IARC regional centre at the Institute of Public Health Research)
RA/70/021	Cell-Cancer-Virus Study Group (CCV), Lyon (Epidemiological studies of the herpes-type virus (type EB) in the population of Lyon)

RA/70/022 Ministry of Health, Jerusalem
(Investigation of the epidemiological implications of differences in cancer mortality as reported by a Central Bureau of Statistics and as seen from a cancer register)

RA/70/023 IARC Regional Centre, Singapore
(Case-control study of etiological factors in oesophageal cancer in Singapore)

RA/70/024 University of Teheran
(Study on the incidence of cancer in the Caspian littoral of Iran)

RA/70/025 Environmental Health Centre, Ottawa
(Organization and operation of an International Bank of Standard PAH Samples)

RA/70/026 Institut für experimentelle Toxikologie und Chemotherapie, Heidelberg, Federal Republic of Germany
(Study for the elaboration of analytical methods for identification and quantitation of *N*-nitroso compounds in the environment)

RA/70/028 Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London
(Synthesis of radioactive nitrosamines to be used in metabolic and carcinogenesis studies)

RA/70/029 Institute of Genetics, Cambridge, United Kingdom
(Investigation of the possible mutagenic effect of DDT in mice)

RA/70/030 Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan
(Investigation on DDT storage levels in various tissues of DDT-treated and control mice)

RA/70/031 Research Institute of Oncology, Leningrad, USSR
(Study on the combined effect of the administration of ethylnitrosourea and X-ray irradiation)

RA/70/032 Ecole nationale de la Santé publique, Rennes, France
(Epidemiology of oesophageal cancer in Brittany and Normandy)

RA/70/033 Institute of Food and Nutrition, Teheran
(Study of nutritional status and dietary factors in the Caspian littoral of Iran)

RA/70/035 Wellcome Research Laboratories, Nairobi
(Influence of aflatoxin on vitamin-B6-deficient baboons)

RA/70/037 University of the West Indies, Barbados
(Cancer registration in the Eastern Caribbean)

Annex 4

VISITORS TO IARC IN 1970

Dr E. ACHILLE	Hôpital civil, Strasbourg, France
Dr S. ALI	International Cancer Centre, Neyyoor, Kerala, India
Mr J. I. ARMSTRONG	Director, Division of Administrative Management and Personnel, WHO, Geneva, Switzerland
Dr J. E. ASVALL	Norwegian Radium Hospital, Oslo
Dr N. T. J. BAILEY	Division of Research in Epidemiology and Communications Science, WHO, Geneva, Switzerland
Professor C. BARONI	University of Rome
Dr G. BERRY	Medical Research Council, Penarth, Glamorgan, United Kingdom
Dr P. M. BIGGS	Houghton Poultry Research Station, Houghton, Huntingdonshire, United Kingdom
Dr B. BLOOD	United States Mission, Geneva, Switzerland
Dr P. BURTIN	Institut de Recherches scientifiques sur le Cancer, Villejuif, France
Professor R. CAMAIN	Faculté de Médecine, Nice, France
Dr B. W. CARNAW	University of Illinois, Chicago, Ill., USA
Dr M. R. CHORAZY	Institute of Oncology, Gliwice, Poland
Miss P. COOK	Medical Research Council, University College Hospital, London
Dr P. CORREA	University of Valle, Cali, Colombia
Dr R. DAOUST	Institut du Cancer, Montréal, Canada
Dr J. N. P. DAVIES	Albany Medical School of Union University, Albany, N.Y., USA
Dr E. DEMIAN	Member, International Academy of Pathology, *formerly* Chief Pathologist, Ministry of Health, Cairo
Dr R. H. DEPUE	National Cancer Institute, Bethesda, Md., USA
Dr K. DIETZ	Division of Research in Epidemiology and Communications Science, WHO, Geneva, Switzerland
Mr J. ELLICE	East Africa Virus Research Institute, Arua, West Nile, Uganda
Dr H. GADOMSKA	Institute of Oncology, Warsaw
Professor C. H. GALLAGHER	University of Sydney, Australia
Dr R. GLADSTONE	Division of Research in Epidemiology and Communications Science, WHO, Geneva, Switzerland

Professor D. M. GONZÁLEZ TORRES	National University of Asunción
Dr C. M. GOODALL	University of Otago, Dunedin, New Zealand
Dr N. GRAY	Victoria Anti-Cancer Council, Melbourne, Australia
Mr W. HAENSZEL	National Cancer Institute, Bethesda, Md., USA
Miss A. HANAI	Centre for Adult Diseases, Osaka, Japan
Dr M. J. HARTGERINK	Leidschendam, Netherlands
Dr T. HIRAYAMA	National Cancer Centre Research Institute, Tokyo
Dr T. HIROHATA	UN Scientific Commission on the Effects of Atomic Radiation, New York, USA
Dr J. H. C. HO	Institute of Radiology, Queen Elizabeth Hospital, Kowloon, Hong Kong
Dr A. R. KAGAN	Epidemiology of Non-Communicable Diseases, WHO, Geneva, Switzerland
Dr E. KAILEY	60 rue de Clichy, Paris 9e
Dr R. J. H. KRUISINGA	Secretary of State for Social Affairs and Public Health, The Hague, Netherlands
Dr Z. KULCAR	School of Public Health, Zagreb, Yugoslavia
Dr A. LEVINE	Division of Research in Epidemiology and Communications Science, WHO, Geneva, Switzerland
Miss E. J. MACDONALD	M. D. Anderson Hospital and Tumor Institute, Houston, Texas, USA
Dr P. N. MAGEE	Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London
Dr E. MAHBOUBI	Institute of Public Health Research, Teheran
Dr I. MARTÍNEZ	Cancer Registry, Puerto Rico
Dr N. MARUCHI	Faculty of Medicine, University of Tokyo, Tokyo
Dr I. MATKO	University of Ljubljana, Yugoslavia
Dr Y. MEDVEDKOV	Ecology, WHO, Geneva, Switzerland
Dr J.-P. MENU	School of Medicine, Dar-es-Salaam
Dr L. MESHALKIN	Numerical Analysis, WHO, Geneva, Switzerland
Dr A. B. MILLER	Medical Research Council, Brompton Hospital, London
Dr F. K. MOSTOFI	Armed Forces Institute of Pathology, Washington, D.C.
Dr K. NAZERIAN	US Department of Agriculture, East Lansing, Mich., USA
Dr D. S. NELSON	WHO Immunology and Research Training Centre, Singapore
Professor P. M. NEWBERNE	Massachusetts Institute of Technology, Cambridge, Mass., USA
Dr K. NEWELL	Director, Division of Research in Epidemiology and Communications Science, WHO, Geneva, Switzerland
Dr K. NISHIOKA	National Cancer Centre Research Institute, Tokyo
Dr M. OBRADOVIĆ	Centre de Cytologie et de Dépistage du Cancer, Geneva, Switzerland

Dr R. OOTA	Faculty of Medicine, University of Tokyo, Tokyo
Dr A. PARAF	Institut de Biologie moléculaire, Paris
Dr G. I. PARDOE	Medical School, University of Birmingham, United Kingdom
Mr A. VAN PERNIS	Insurance and Pensions, WHO, Geneva, Switzerland
Dr J. H. POPE	Queensland Institute of Medical Research, Herston, Australia
Mr L. RAYMOND	Centre de Cytologie et de Dépistage du Cancer, Geneva, Switzerland
Dr G. RIOTTON	Centre de Cytologie et de Dépistage du Cancer, Geneva, Switzerland
Mr R. ROC	Centre de Cytologie et de Dépistage du Cancer, Geneva, Switzerland
Dr B. ROIZMAN	University of Chicago, Chicago, Ill., USA
Mr R. J. ROSE	National Cancer Registry, Department of Health, Wellington, New Zealand
Dr G. RUDALI	Fondation Curie, Paris
Mr I. SABOURIN	Honorary Counsel, Quebec Asbestos Mining Association, Canada
Professor M. SANKALÉ	Faculté mixte de Médecine, Dakar
Dr M. N. SAVELIEV	USSR Ministry of Public Health, Moscow,
Professor D. SCHMÄHL	Director, Institut für experimentelle Toxikologie und Chemotherapie, Heidelberg, Federal Republic of Germany
Dr M. SIMONS	WHO Immunology Research and Training Centre, Singapore
Mr J. SØRENSEN	Statistical Department, National Health Service of Denmark, Copenhagen
Dr M. STAQUET	Institut Bordet, Brussels
Dr J. STASZEWSKI	Institute of Oncology, Gliwice, Poland
Dr R. STEINITZ	Head of Cancer Registry, Jerusalem, Israel
Dr J. SUGAR	Research Institute of Oncopathology, Budapest
Dr T. SUGIMURA	National Cancer Centre Research Institute, Tokyo
Dr T. THORGEIRSSON	University of Iceland, Reykjavik
Dr E. THORPE	Tunstall Laboratory, Sittingbourne, Kent, United Kingdom
Professor H. UNGAR	Hebrew University—Hadassah Medical School, Jerusalem, Israel
Mr A. VALOT	Conference and Office Services, WHO, Geneva, Switzerland
Dr F. DE WAARD	Institute of Social Health, University of Utrecht, Netherlands
Dr J. C. WAGNER	Medical Research Council, Penarth, Glamorgan, United Kingdom
Dr J. H. WEISBURGER	National Cancer Institute, Bethesda, Md., USA
Mr J. W. WRIGHT	Vector Biology and Control, WHO, Geneva, Switzerland

Annex 5

INTERNAL TECHNICAL REPORTS UP TO DECEMBER 1970

IARC Internal Technical Report No.	
68/001	Report of the Working Group to discuss the programme on gastro-intestinal tract cancer with particular reference to the oesophagus (Lyon, 16-19 July 1968)
68/002	IARC Working Conference on studies of the role of aflatoxin in human disease (Lyon, 28-30 October 1968)
68/003	Report of the Meeting on sources of cancer statistics (Lyon, 4-8 November 1968)
68/004	Proceedings of a Planning Conference for epidemiological studies on Burkitt's lymphoma and infectious mononucleosis (Nairobi, 16-18 December 1968)
68/005	Notes on Meeting of Heads of IARC Regional Centres (Kingston, 23 November 1968)
68/006	Joint Meeting of the UICC Committee on quantitative carcinogenesis and the IARC Feasibility Committee on priorities for chemical carcinogens (Kingston, 18-22 November 1968)
69/001	Report of Meeting on co-ordination of work on asbestos cancers (Lyon, 25 February 1969)
69/002	Report of Meeting on standardization of sampling and analytical procedures for poly-nuclear aromatic hydrocarbons in the environment: Working Group on food (Lyon, 6 March 1969)
69/003	International study on the estimation of environmental carcinogenesis in selected geographical areas (Working paper by Dr P. Bogovski, Chief, Environmental Carcino-genesis Unit, IARC)
69/004	Report by Dr D. B. Clayson of Leeds University, United Kingdom, on his visit to the IARC (Lyon, 13-16 April 1969)
69/005	Manual on the pathology and histological classification of tumours in laboratory animals (Working paper by Dr V. Turusov, Chemical Carcinogenesis Unit, IARC)
69/006	Meeting of investigators for evaluation of a serological test for liver cancer (Lyon, 7-9 July 1969)
69/007	Hospital cancer cases in Thailand (Working Paper by Dr A. J. Tuyns, Epidemiology and Biostatistics Unit, IARC)
69/008	IARC Meeting on analytical problems in the estimation of traces of nitrosamines in food and other environmental media, with special reference to clean-up methods (London, 23-24 October 1969)
70/001	Epidemiological studies on the association between herpes-type virus infection and incidence of nasopharyngeal carcinoma (Report on a Round Table Conference, St Gervais, France, 11-13 January 1970)

70/002 Studies on Burkitt's lymphoma (Report on a Round Table Conference, St Gervais, France, 15-18 January 1970)

70/003 Cancer morbidity and mortality data in the USSR (Dr A. J. Tuyns, Epidemiology and Biostatistics Unit, IARC)

70/004 Meeting of the Advisory Committee on environmental carcinogenesis (Omaha, 1-2 June 1970)

70/005 Etudes internationales sur le cancer du sein par le Professeur B. McMahon (Exposé fait au Conseil Scientifique du CIRC, le 17 juin 1970)

70/006 Cancer morbidity and mortality statistics: comparison of material published by WHO, by Segi & Kurihara, and in *Cancer Incidence in Five Continents* (Janine Nectoux and Dr C. S. Muir, Epidemiology and Biostatistics Unit)

70/007 Geographic study on oesophageal cancer in Europe (Dr A. J. Tuyns, Epidemiology and Biostatistics Unit)

70/008 Etude de géographie comparée sur le cancer de l'œsophage en Europe (Dr A. J. Tuyns, Service d'Epidémiologie et de Biostatistiques)

Annex 6

PAPERS PUBLISHED AND SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS, 1970

IARC staff:

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Gazzolo, L. & de Thé, G. (1971) Investigations on the presence of viral particles in Rous transformed hamster cell lines. *Int. J. Cancer,* **7**, 119-130

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