INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

WORLD HEALTH ORGANIZATION

LYON
FRANCE

ANNUAL REPORT
1969

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INTRODUCTION

The report of the Director of the International Agency for Research on Cancer (IARC) for 1968,[1] which dealt with the origin and background of the Agency and its programmes during the first eighteen months of its work in Lyon, has had a favourable reception. It has accordingly been decided to issue the report for 1969 in the same format for the information of interested scientists as well as the Agency's two statutory bodies—the Governing Council and the Scientific Council. In preparing it, an attempt has been made to strike a balance between a highly technical report of interest only to specialists and one in which technical detail is kept to a minimum.

General comments

The original decision of the Governing Council that the research programme should concentrate on the environmental biology of human cancer appears increasingly justified. During the last year there has been marked concern, in both industrialized and non-industrialized countries, about the potential toxic effects of the chemicals to which man may be involuntarily exposed in his environment over prolonged periods. Cancer is regarded as among the most important of these long-term effects.

Although interest in this connexion has centred mainly on certain pesticides and food additives, many other chemicals of socio-economic or health importance are being increasingly used in modern industrial and agricultural societies, and their long-term effects cannot always be forecast. As regards cancer, it does not seem that any large-scale disasters have so far occurred as a result of such environmental factors. However, the fact that accidents have occurred in certain occupations and industries involving relatively short periods of exposure precludes complacency and re-emphasizes the need for continual environmental monitoring to give early warning of the toxicity of certain compounds or to confirm the safety of others. Today, few new chemicals are intentionally introduced into the environment without careful consideration of their ill effects as well as their benefits. Nevertheless, many potentially carcinogenic substances are utilized in industry and elsewhere with insufficient knowledge of their action.

As Clayson [2] has pointed out, animal testing is as yet the only technique available for identifying substances with a potential carcinogenic hazard. The absence of a risk in an experimental animal, however, provides no certainty of its absence in man, and *vice versa*. As long as our knowledge of comparative carcinogenesis and toxicology in animals and

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

[2] Clayson, D. B. (1966) *The induction of cancer.* In: Ambrose, E. S. & Roe, F. J. C., ed., *The biology of cancer*, London, Van Nostrand, p. 156.

man remains insufficient to permit extrapolation, it is essential to monitor environments in which man has been exposed—whether advertently or inadvertently—to a suspected agent for a prolonged period. Such studies should permit a better assessment of the potential risks to humans. Although it is true that initial exposure may have taken place at a time when these risks were less appreciated, it is distressing to note that in many cases relatively little has been done to organize the systematic collection of the necessary data. In this respect, work on chemical carcinogens presents a significant contrast to the very considerable efforts made in the field of radiation carcinogenesis, in which apparently successful control methods, based on sound experimental and epidemiological criteria, have been introduced over the last two decades. The absence of data on chemical carcinogens may require decisions to be taken without the necessary experimental or epidemiological background, and at times the use of a substance has been stopped solely on the basis of a calculated guess. The tragedy here is not that the use of the substance was first permitted and then prohibited or restricted, but that no adequate steps were taken to monitor the situation from the beginning in the absence of conclusive laboratory studies. Investigations to establish a firm biological basis for studying the effects of potentially toxic compounds are still carried out only on a very limited scale.

The reasons for the shortcomings of monitoring systems are essentially financial. Contrary to general belief, laboratory studies are relatively cheap by comparison with environmental and epidemiological studies in man. Nevertheless, the cost of environmental studies is still small in relation to the vast sums that will have to be spent on environmental control during the next decade. Whereas laboratory results may be obtained within two or three years, environmental monitoring may have to continue for up to twenty years. Another drawback to the long-term investigation of population groups is that it enjoys relatively little prestige as a branch of observational science. However, no alternative methods have been established permitting a definite assessment of environmental hazards to man.

It is in this context that the programme of the Agency should be viewed, since it seems to be in an eminently suitable position to initiate and develop research on the effects of the environment on man. As an international body, it can compare environmental and disease patterns in different countries without offending national susceptibilities. It is probable that man will have to live with a certain level of known toxic substances, and the possible risks should be identified and reduced to a minimum. At the same time, situations must be avoided in which the prohibition of useful compounds may cause significant socio-economic distress or increase other health problems. Thus, there is every reason to support organized research in this field in order to provide a wider scientific basis for such decisions as far as possible. In view of the cost of environmental studies, it is highly desirable that duplication should be kept to a minimum and detailed planning established from the outset of each study.

It is also useful to have a neutral agency for acquiring information on environmental problems on which governments or institutions may desire a further opinion or additional

data or on which it is felt that the local scientific community may not have the necessary expertise or information. Expert committees of the World Health Organization and other specialized agencies in relationship with the United Nations make valuable recommendations on such problems, but too often the committee concerned has had to point out that not enough data were available to permit a satisfactory estimate of a given environmental hazard. Moreover, these expert committees lack executive power and are unable themselves to initiate research. Relatively few scientists can be called on who are both competent and willing to undertake the time-consuming and tedious investigations required in environmental studies.

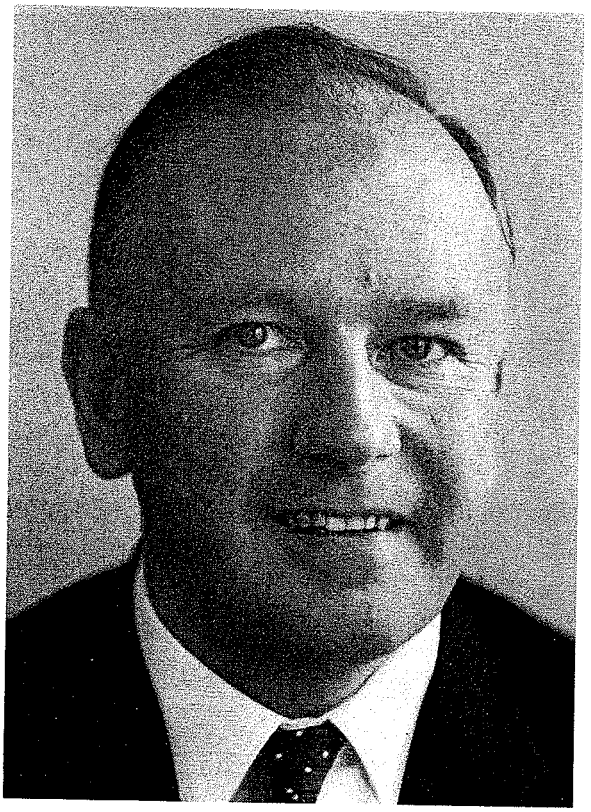


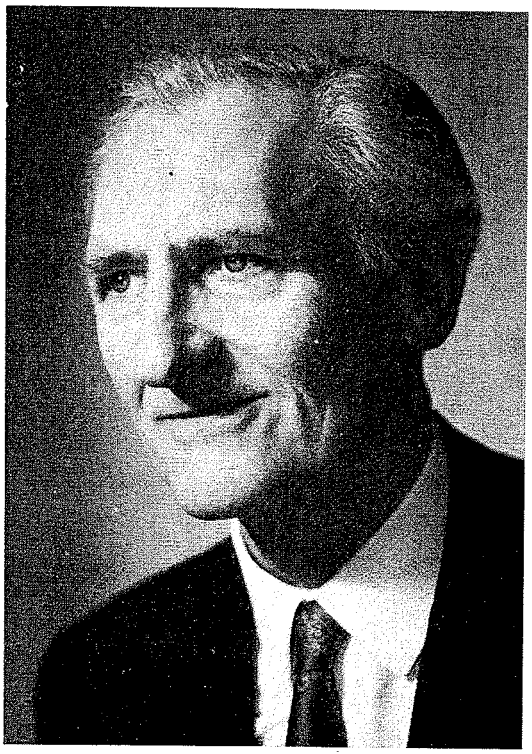
Fig. 1. Dr R. J. H. Kruisinga,
Chairman of the IARC Governing Council.

The IARC has the advantage that its statute permits it to initiate or undertake research on specific problems within its own competence. This type of activity was not foreseen when the Agency was founded, but developments during the last two years suggest that it may form an increasingly important part of the Agency's work. The Agency concentrates on developing research in fields that have been insufficiently explored and on aspects of environmental biology on which new knowledge is urgently required. While the Agency is responsible for the overall control of the research programmes, these are developed as much as possible with the aid of local scientists and often receive local financial or material

Fig. 2. Members of the Scientific Council of the IARC

Professor N. N. Blokhin (1968-70)

Professor P. F. Denoix (1968-70)

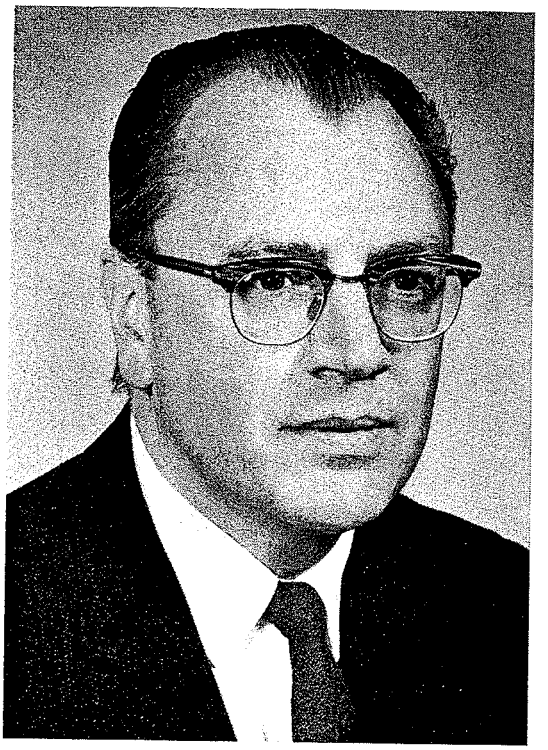


Professor W. R. S. Doll (1968-70)

Professor H. Isliker (1968-70)

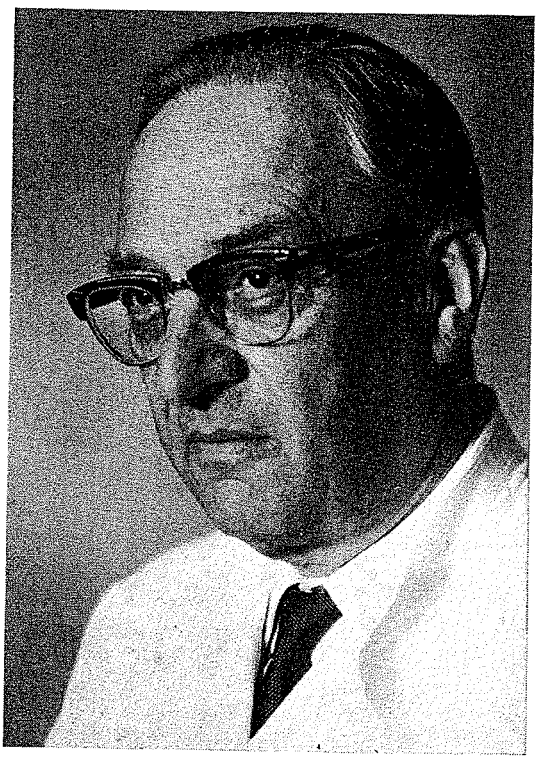
Fig. 2. Members of the Scientific Council of the IARC *(continued)*

Professor G. Klein (1967-69)



Professor B. MacMahon (1969-71)

Dr D. Metcalf (1967-69)

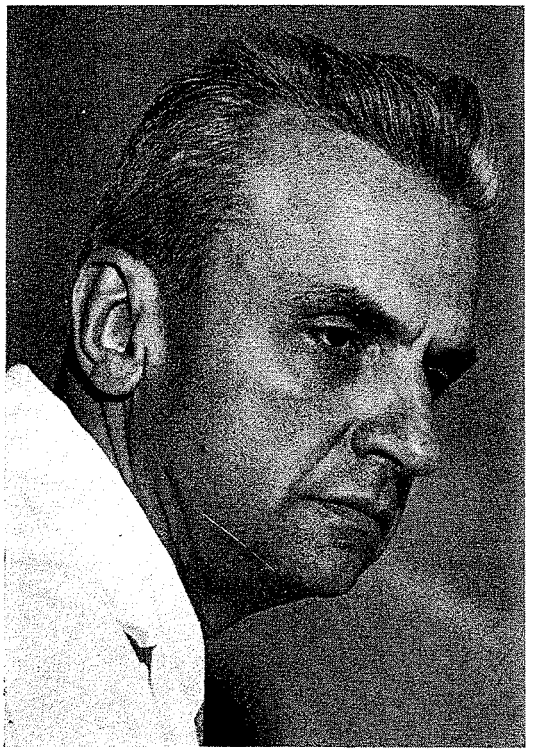


Professor O. Mühlbock (1967-69)

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 P. N. Wahi (1967-69)

support. Such programmes can be described as truly collaborative. While many of them have more specific goals, they are essential for obtaining basic knowledge on cancer problems in man's environment. It has become clear that, to stimulate and develop these studies, the Agency must maintain its own staff of specialists as well as being able to call on outside experts.

Experience during the last year has indicated that there is a considerable shortage of facilities and manpower for the study of chemical carcinogenesis and environmental biology at both the national and the international level. Through its research training programme, the Agency has tried to encourage junior research workers to take up these fields of study, but the number of suitable applicants has been disappointingly small. It is felt by the Fellowships Selection Committee that the manpower situation will not be solved by training unsuitable candidates and that it must be made clear to young scientists that environmental biology can be a worthwhile career.

The immediate aim of the Agency's programme has been to see how successfully it can integrate basic laboratory studies and observational investigations in the field. Care has been taken to avoid repeating what can be done equally well in national laboratories. Programmes on several problems have been initiated, with varying degrees of outside involvement. Few of these problems are of a kind that can be easily or quickly solved and progress to date should be judged in this light.

Relations with the WHO Cancer unit and the International Union against Cancer

Scientists from various national institutions have expressed their willingness to take part in the Agency's programmes, and it is hoped that gradually a network of workers interested in environmental biology will be built up, making it possible to concentrate on the solution of specific problems.

From the report it will be seen that close collaboration has been maintained with the International Union Against Cancer (UICC), and the Agency is continuing some programmes originally undertaken by UICC. The Agency and the UICC keep each other informed on all their activities to avoid overlapping.

The Cancer unit of WHO continues to be responsible for programmes in cancer control and treatment. Since these programmes rely largely on the application of established knowledge or deal with the standardization of terminology and treatment methods, this division of labour has proved satisfactory. Close contacts are maintained with the many other technical units in WHO that deal with subjects related to the Agency's work.

Organization and programmes

The programmes of the individual units of IARC are discussed in detail later in the report, but here we should like to stress the overall unity of the programme. In each unit, all the members are intimately involved with several programmes; where one person is

predominantly responsible for a particular investigation, his name is given so as to facilitate exchange of information.

Epidemiology. Cancer registries have too often been neglected as unrewarding and of little importance. Yet, accurate data on cancer in man are essential for the identification of potential carcinogenic situations. The value of individual registries is markedly improved when the results from several geographical areas can be compared. The Agency has accordingly welcomed the formation of the International Association for Cancer Registries, with which it hopes to work in close collaboration as it has in the past with the Cancer Incidence Committee of the International Union Against Cancer. In assessing the significance of new agents in the environment, it is essential to have data on time trends. This is especially true where the agents are widely distributed in the population at low levels and high risk groups are difficult to identify. Unfortunately, few national cancer registries have been in existence for long enough to permit assessments of morbidity trends during the last two decades. The support of cancer registries during the apparently non-productive period when their work is confined to collecting data tends to have low priority with most financing bodies, and registries may sometimes be terminated just at the time when the results are most likely to become of value. The correlation of cancer trends with well-documented data on changes in environmental carcinogen levels is just beginning to be possible but will certainly prove difficult. Thus, continuing information on specific groups with unusual risks of cancer must be sought.

Environmental Carcinogenesis. This unit is gradually increasing its contacts and is beginning to build up a network of collaborating laboratories in order to acquire accurate data on the distribution of environmental carcinogens.

Chemical Carcinogenesis. The purpose of this unit is to study the mode of action of certain chemical carcinogens in low doses, in order to provide fundamental data for the study of environmental cancer and to determine where carcinogenic hazards are most likely to arise.

Biological Carcinogenesis. This unit is mainly concerned with determining the carcinogenic significance of the herpes-type virus—especially in nasopharyngeal carcinoma. This project will be partly supported by the National Cancer Institute, Bethesda, Md., USA, and by the Ligue nationale française contre le Cancer.

Research Training and Liaison (formerly Education and Fellowships). This unit has had a very successful year and the number of qualified candidates has again exceeded the number it was possible to accept with the funds available.

Administration and Finance. Resources were strained in 1969 by the need for holding additional meetings of both the Governing Council and its sub-committee, to deal with the long-term financing of the Agency. Owing to the inherent uncertainty of the situation, the recruitment of additional staff and the implementation of new programmes were delayed pending the decisions of the Governing Council.

Financing the IARC

During its first quinquennium, the Agency has been supported by equal annual contributions from participating states. Expenditure towards the end of this period was greater than income, and the deficit was met in 1968 and 1969 from the Governing Council's Special Fund. In October 1969, the Governing Council decided that a modified formula relating contributions partly to the gross national product should be introduced in 1971. The basic contribution of US $150 000 was maintained. For 1970 a budget of US $1 925 000 was approved; a rise of 5 % per annum is being permitted to offset inflation and increased statutory costs. The Governing Council approved a total budget for the quinquennium 1971-75 of US $11 168 650, to be financed by the existing nine Participating States. Contributions from any new Participating States may bring this total up to US $15 445 000.

The new system of contributions from the Participating States will involve amendments to the Statutes, and these are being submitted for approval by the World Health Assembly.

During the past year, the Agency has been grateful for contributions received from the Ligue nationale française contre le Cancer and from the National Cancer Institute, Bethesda, Md., USA, as well as gifts from individuals.

Personnel

While the staffing position has improved somewhat during the past year, it is considered that the recruitment of suitable staff will remain a problem as long as space and facilities are limited. There is also a general shortage of applicants suitably trained in the fields of chemical and environmental carcinogenesis.

Future trends and developments

It is anticipated that the Agency will continue to concentrate on environmental biology. The present budgetary level should be sufficient to maintain an adequate staff at Headquarters with research facilities that will permit them to remain competent in their own fields and to speak authoritatively in their dealings with the scientific community. They will thus be in a better position to control outside contracts and take part in the development of collaborative projects. During the next two years, not only will the staff in Lyon be consolidated but an increasing effort will be made to build up the network of collaborating laboratories engaged in specific programmes with different population groups. It is important, however, that the growth of contractual and collaborative programmes should remain proportionate to the size of the Agency's own scientific staff so that the latter can continue to supervise them adequately.

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 S. C. BESUSCHIO (Jan.-July 1969)
Dr L. LEBLANC

Supporting staff: 10

1. INTRODUCTION

To promote closer integration of their work, the units of Epidemiology and of Biostatistics were amalgamated in the course of the year.

In the field of descriptive epidemiology, work continues on the collection of cancer morbidity and relative frequency data and of information on cancer incidence by histological type. Opportunities for studies of differential cancer risks in migrant populations have been examined, and material and opinions gathered on the cancer section of the Ninth Revision of the International Classification of Diseases.

The search for etiological factors in cancer of the oesophagus continues in Iran and Curaçao (where this type of cancer has approximately the same incidence in both sexes) and in Jamaica and France, where the disease, much commoner in males, has been linked with alcohol consumption. A series of studies to evaluate the α-fetroprotein test as a method for screening populations for primary liver cancer are under way in West Africa.

The frequency of "occult" carcinoma of the prostate in relation to the incidence of invasive neoplasms is being evaluated in populations at low, medium, and high risk.

2. DESCRIPTIVE EPIDEMIOLOGY

The collection of data from several areas of the world is continuing. Wherever possible, studies are planned to give background information on cancer patterns in areas where IARC studies are in progress or projected.

2.1 *Morbidity data*

Collaboration with the UICC Committee on Cancer Incidence in the collection and processing of cancer morbidity data continues. As a result of this work, a second volume of the monograph *Cancer Incidence in Five Continents* is being published in 1970. This will contain information on 33 populations which were not covered in the first volume.[1] The facilities provided by the Birmingham Cancer Registry and the University of Birmingham computer have been most valuable in the production of this monograph.

2.2 *The Croatian Cancer Registry*

The unit has given considerable assistance to the Croatian Cancer Registry, Zagreb, Yugoslavia, in the computer handling of their records.

2.3 *Study of the epidemiological value of detailed cancer incidence data—Israel Cancer Registry, Ministry of Health, Jerusalem*

Principal Investigator: Dr Ruth Steinitz (RA/67/002)

The first set of tabulations for cancer of the breast has now been received. It was observed that:

(*a*) The Israel Cancer Registry is a reliable source for epidemiological studies on incidence and mortality by place of origin.

(*b*) The most reliable information is given by a combination of case summary and pathological report. For 90 % of cases, case summaries and/or pathological reports were available.

(*c*) Information on laterality was available in 80 % of cases, but there were serious difficulties with regard to:

(i) delay in seeing doctor, which was reported for 38 % of cases only;

(ii) identification of stage, which was either reported or evident from the clinical and/or pathological descriptions in 68 % of cases;

(iii) identification of the sub-site or quadrant, which was available in only 34 % of cases.

Detailed tables on survival by stage and age at diagnosis, by stage and treatment, by stage and histology, etc. were drawn up, but the data were far from complete. It has not yet been decided how to summarize the information in order to derive valid conclusions.

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[1] Doll, R., Payne, P. M. & Waterhouse, J. A. H. (1966) *Cancer incidence in five continents*, Berlin, Springer-Verlag (International Union against Cancer).

An *ad hoc* detailed code for lung and stomach cancer has been constructed, and the cards for these sites have now been punched. This work has again revealed discrepancies in hospital records on such matters as the dates of certain events. It is extremely important to eliminate inconsistencies of this kind in view of plans for the nation-wide automatic data processing of medical records for linkage purposes.

The codes for ovarian cancer and leukaemia are in preparation.

3. IARC-SUPPORTED CANCER REGISTRIES AND RATIO STUDIES

The Agency supports studies of the relative frequency of cancer in selected areas where reliable incidence data are unlikely to be obtained for some time, as experience has shown that an unusual cancer incidence is nearly always reflected in a high relative frequency of certain cancers in pathological material. In general, such studies are undertaken in areas where the Agency has other programmes.

3.1 *Regional Centres*

Cancer registry work 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 R. Mitchell: RA/68/005) is described in the reports of the Regional Centres (pages 72 and 80).

3.2 *Curaçao*

(Dr J. W. A. Oostendorp: RA/68/004)
See pages 25 and 86.

3.3 *Thailand*

In Chiengmai, North Thailand (Dr Dusdee Prabhasawat: RA/68/009), the ratio study, combined with registration of clinically diagnosed cases, is continuing. The results of the first 18 months of operation are shown in Table 1. There was histological confirmation in 79.7 % of cases and the X-ray appearance was considered diagnostic in a further 6.0 %.

The very high relative frequency of laryngeal cancer in both sexes has been confirmed. A retrospective case control study will determine whether this is associated with the consumption of *keyyo*, a cigar containing home-grown, sun-dried, uncured tobacco and tree bark in approximately equal proportions. The bark has been sent to Professor D. B. Clayson, Leeds, United Kingdom, to determine its carcinogenicity.

The figures in Table 1 pertain to Chiengmai Province as a whole. However, if these histologically diagnosed cases are related to the population at risk in each administrative district, the crude minimum incidence rates (all sites) vary from 63.7 per 100 000 for Chiengmai City to less than 10 per 100 000 in the more remote areas of the Province. This suggests considerable under-reporting.

The analysis of data on 1877 microscopically diagnosed cancers in the files of the Chiengmai University Medical School is now under way. The major difficulty in this work is to eliminate duplication.

An analysis of cancer deaths and cases discharged from hospitals in Thailand in 1965 has been made (IARC Internal Technical Report No. 69/007).

TABLE 1

PRIMARY MALIGNANT NEOPLASMS DIAGNOSED AT CHIENGMAI, THAILAND,[a] BY SITE (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), SEX, AND ORDER OF RANK

Males					Females				
Rank order	ICD no.[b]	Site	Number	%	Rank order	ICD no.[b]	Site	Number	%
1	161	Larynx	43	18.1	1	171	Cervix uteri	71	24.1
2	162-3	Lung	20	8.4	2	170	Breast	25	8.5
3	151	Stomach	12	5.1	3	162-3	Lung	21	7.1
4	145	Oesophagus	12	5.1	4	161	Larynx	15	5.1
5	179	Genitals	12	5.1	5	154	Rectum	11	3.7
6	146	Nasopharynx	11	4.6	6	175	Ovary	10	3.4
7	155	Liver, etc.	10	4.2	7	190	Skin (malignant melanoma)	10	3.4
		All sites	237	100			All sites	295	100

[a] Total population 965 000 (1960 census).
[b] Seventh Revision.

3.4 *Peru*

Dr J. Gálvez Brandon (IARC Fellow, 1968) has established a cancer registry in Lima, based on the Instituto Nacional de Enfermedades Neoplásticas (RA/69/003).

The registration of new cases in the Lima metropolitan area in 1968 has been completed. It is estimated that coverage is now 95 %. The seven most frequent cancers, by sex, are indicated in Table 2. Detailed tabulations of age-adjusted incidence are available by site, age, and sex (IARC Internal Technical Report in preparation). A preliminary report on the frequency of malignant neoplasms in Lima in 1968 has been published.[1]

[1] Gálvez Brandon, J. (1968) *Acta cancer.*, 7, 46.

TABLE 2

PRIMARY MALIGNANT NEOPLASMS DIAGNOSED IN THE LIMA METROPOLITAN AREA IN 1968 BY SITE (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), SEX, AND ORDER OF RANK

Males					Females				
Rank order	ICD no.[a]	Site	Number	%	Rank order	ICD no.[a]	Site	Number	%
1	151	Stomach	144	24	1	180	Cervix uteri	401	37
2	162	Lung	68	11	2	174	Breast	165	15
3	185	Prostate	54	9	3	151	Stomach	86	8
4	204-7	Leukaemia	38	6	4	173	Other skin	32	3
5	161	Larynx	22	4	5	182	Other uterus	28	3
6	188	Bladder	21	3	6	156	Gall bladder & bile ducts	28	3
7	153	Large intestine except rectum	20	3	7	155	Liver & intrahepatic bile ducts (primary)	27	3
		All sites	601	100			All sites	1070	100

[a] Eighth Revision.

Registration continued in 1969, but is incomplete. It is difficult to obtain information on the time elapsing between first interview by a doctor and histological diagnosis and on length of residence in Lima. The work of the registry has been publicized by papers read at the International Congress of Pathology and Oncology, at a symposium on cancer in children, and at a seminar on cancer registries organized in Cali, Colombia, by the Pan American Health Organization, which subsequently agreed to make the appropriate tabulations from the punch cards at Washington, D.C.

3.5 *Sudan*

A cancer registry has been established at Khartoum (Professor A. M. El Hassan and Dr E. H. Daoud: RA/69/004). See the report of the Regional Centre, Nairobi (p. 73).

3.6 *West Africa*

(*a*) *Senegal*

(Professor C. Quenum: RA/68/015)

The processing of data on approximately 6000 cases of cancer obtained from various pathological laboratories in Dakar continues. It has proved particularly difficult to eliminate duplicated material and to obtain further information on imprecise diagnoses.

(*b*) *Ivory Coast*

(Professor R. Loubière: RA/68/017)

A card index of histologically diagnosed cases of cancer has been established in the Department of Pathology, Faculty of Medicine, Abidjan, and 816 cases are now being ana-

lysed. The relative frequency of liver cancer, corrected for age, is considerably greater in the north than in the south (Table 3), whereas tumours of other sites such as the breast, cervix, and prostate are of approximately equal frequency in both regions. This difference between north and south is of importance in connexion with the proposed large-scale serological survey in the Ivory Coast (see page 26).

TABLE 3

RELATIVE FREQUENCY, CORRECTED FOR AGE, OF PRIMARY LIVER CANCER IN THE NORTH AND SOUTH OF THE IVORY COAST, BY SEX

	Males		Females	
	No.	%	No.	%
North	57	31.4	5	2.5
South	22	11.4	0	0.0

(*c*) *People's Republic of the Congo*

The analysis of 508 cases of cancer seen at the Institut Pasteur, People's Republic of the Congo, in 1965-66 has been completed.[1]

(*d*) *Cameroon*

A new ratio study has been initiated in collaboration with the Pasteur Institute, Yaoundé (Dr P. Ravisse).

3.7 *Poland*

(Dr J. Staszewski, Institute of Oncology, Gliwice: RA/69/007)

A critical review of Polish cancer mortality data is to be made, with special attention to the relationship between mortality and the incidence data available for Warsaw, Cracow, Katowice, and four rural areas. The high Polish rates for gastric cancer are well known; the apparently very low rates for prostatic cancer need to be confirmed.

4. INTERNATIONAL CLASSIFICATION OF DISEASES (ICD)

The cancer section of the Eighth Revision of the International Classification of Diseases, Injuries and Causes of Death[2] has aroused considerable criticism. The unit participated

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[1] Tuyns, A. J. and Ravisse, P. (1970) *J. nat. Cancer Inst.* (in press).

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

in a Study Group for the Ninth Revision of the International Classification of Diseases, held in Geneva in October 1969, and has agreed to set up two working parties:

(*a*) to examine the nature, scope, and content of the existing cancer section, removing anomalies where possible;

(*b*) to consider methods whereby information on microscopic morphology (histology) could be added to the existing section by means of a complementary code.

The proposals of these working parties will be field tested and the recommendations forwarded to the Committee for the Ninth Revision.

Over 200 national statistical offices, cancer registries, and interested individuals were asked to give their opinion on the cancer section of the ICD. The replies, which have been circulated to all those who answered, will be most useful in preparing the Agency's proposals to the Revision Committee. The Division of Health Statistics at WHO Headquarters has been most helpful in this work.

5. COMPARABILITY OF CANCER STATISTICS

The assessment of the techniques used by existing cancer registries has been completed and will appear as a chapter in the monograph *Cancer Incidence in Five Continents.* Very wide and fundamental differences have been revealed in registry practice on such matters as "date of onset", cases diagnosed only at necropsy, and utilization of death certificates, as well as in the range of information collected, e.g., place of birth, histological diagnosis.

5.1 *International Association of Cancer Registries*

Close liaison has been maintained with the International Association of Cancer Registries. Problems of comparability will be discussed at a meeting to be held in Houston, Tex., USA, in May 1970.

5.2 *A registry code*

A simple code for cancer registries has been designed using the WHO code numbers for countries, followed by a code number which identifies registries covering the entire country, provinces, and towns and those concerned with particular tumours, e.g., bone, female genital tract, etc.

5.3 *Incidence of selected histological tumour types* (Dr H. Tulinius)

Hitherto, information on histological tumour types has been restricted to data on relative frequency from the files of individual pathology departments; these have inevitably

reflected the interests of surgeons and hospital admission policies. Cancer registries contributing to the second volume of *Cancer Incidence in Five Continents* were asked to submit a histological analysis by age and sex of tumours of the ovary, testis, bladder, and thyroid and of histologically confirmed leukaemia. Although it has proved possible to collect this type of information on a population basis, the lack of standardization in diagnosis and the varying interpretations of the suggested classification reduce its value. Nevertheless, areas where further controlled comparative studies might be rewarding have been delineated. Table 4 shows ratios between the age-adjusted incidence rates for urothelial and squamous cancer of the bladder in selected registries. The range of values is so large that the differences observed are likely to be genuine.

This investigation has once again shown the need for an internationally recognized classification acceptable to pathologists and epidemiologists and readily convertible into a numerical code.

TABLE 4

COMPARISON OF THE UROTHELIAL/SQUAMOUS RATIOS FOR BLADDER NEOPLASMS IN SELECTED REGISTRIES: CRUDE NUMBERS AND AGE-STANDARDIZED RATES [a]

Registry	All bladder neoplasms		Histologically confirmed bladder neoplasms			
			Urothelial:[b] Squamous			
	Standardized incidence rate	Histological confirmation (%)	No. of cases	Ratio	Age-standardized rates	Ratio
Bulawayo [c]	13.1	96	8 : 13	0.6	3.10 : 9.26	0.33
Natal, Africans	3.6	93	1 : 9	0.1	0.72 : 1.46	0.49
Natal, Indians	7.3	83	5 : 5	1.0	2.84 : 2.81	1.01
Cali	10.6	88	36 : 11	3.3	6.04 : 1.91	3.16
Jamaica [c]	10.6	100	10 : 6	1.7	2.98 : 1.95	1.53
Alameda, Caucasian	17.9	91	340 : 11	30.9	15.03 : 0.47	31.98
Alameda, Negro	10.9	82	15 : 1	15.0	7.24 : 0.34	21.29
El Paso, Latins	8.3	95	15 : 0	—	5.59 : 0	—
El Paso, others	11.8	88	38 : 1	38.0	8.39 : 0.25	33.56
Sweden [c]	9.8	94	2083 : 32	65.1	9.04 : 0.13	69.54
Sheffield [c]	13.4	71	658 : 48	13.7	5.57 : 0.41	13.56
Liverpool	13.8	74	404 : 33	12.2	5.89 : 0.48	12.27
Scotland	11.4	82	381 : 24	15.9	2.95 : 0.18	16.39
Birmingham [c]	—	—	1313 : 112	11.7	10.28 : 0.91	11.30
Birmingham	11.5	73	766 : 112	6.9	6.40 : 0.91	7.03

[a] All rates are age-standardized to the world population.
[b] Urothelial: benign papilloma (if included), plus papillary carcinoma, plus transitional (cell) carcinoma.
[c] Includes benign papilloma.

6. MIGRANT STUDIES

(Consultant: Dr J. Staszewski)

The study of changes in cancer risk in population groups after their migration to a new environment can provide useful etiological indications. For example, the rapid rise in

large bowel cancer rates in persons from Japan after their emigration to the USA suggests that the causative factors are predominantly environmental, whereas the breast cancer risk, which has remained unaltered, is probably related more to host factors. The unit believes that such studies should be expanded.

6.1 *Review of studies*

The unit presented a review of previous migrant studies, a list of existing migrant populations of a size suitable for such studies, and a study of their feasibility to a meeting on Methodological Aspects of Studies on Migrant Populations, held at the East West Centre, Honolulu, in February, 1969.[1,2]

The Singapore Regional Centre contributed papers on differential risks of primary hepatic cancer and nasopharyngeal cancer in Chinese migrant populations: the former neoplasm was commoner in those born in China (1.7:1) and the latter in those born in Singapore (1:1.8).

The efficiency of cancer registration in several areas of Canada and the United Kingdom where there are large migrant populations makes these countries suitable for such investigations. The Dominion Bureau of Statistics in Canada, the WHO Centre for the Classification of Diseases in London, and the Birmingham Cancer Registry have been approached in this connexion.

6.2 *Mortality in Australia*

Principal investigator: Dr M. G. McCall (RA/67/005)

Dr McCall's co-investigator, Dr N. S. Stenhouse, Director of Medical Statistics, University of Western Australia, was a consultant in Lyon for three months in 1969. He presented the Agency with a very detailed computer tabulation for selected cancer sites[3] giving cause of death by sex and place of birth and standardized mortality rates. Similar information was provided for cerebrovascular and cardiovascular diseases (ICD 400-458).

6.3 *Collection of death certificates*

National statistical offices throughout the world have been requested to submit death certificates, census schedules, and census reports. So far these have been received from 72 countries. Unfortunately, although information on place of birth is collected, this may not be coded and, if coded, may not be tabulated. Death certificates are often in two parts:

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[1] Kmet, J. (1970) *J. chron. Dis.* (in press).

[2] Staszewski, J., Muir, C. S., Slomska, J. & Jain, D. K. (1970) *J. chron. Dis.* (in press).

[3] Buccal cavity and pharynx, oesophagus, stomach, colon, rectum, liver and bilary passages (including secondary cancers), pancreas, larynx, lung (ICD 162 and 163 separately), breast, cervix uteri, corpus uteri, ovary etc., prostate, bladder and kidney, skin (malignant melanoma), all skin and brain, etc.

a medical certificate of cause of death and a certificate of the fact of death, or burial permit. The portion containing the cause of death usually does not indicate the place of birth. When the two parts become separated, it is often impossible to link them afterwards.

7. ETIOLOGICAL FACTORS IN DIGESTIVE TRACT CANCER

Cancer of the oesophagus, in those areas where it is found predominately in males, has generally been 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)

Principal investigator: Dr E. Mahboubi (RA/68/008 and RA/69/008)

(a) The Mazandaran Cancer Registry

The first year of operation of the Mazandaran Cancer Registry was completed in June 1969. The results have confirmed the suspected differences between high and low incidence areas. The crude rates for oesophageal cancer are shown below. Although the 1966 census figures, by age and sex, are available for the various districts in Mazandaran, they have not yet been issued for the sub-districts. Considering that the mean age is close to 21 years and that 56 % of the population are under 20 years of age, these crude incidence rates, when age-adjusted to a European population structure, would be approximately doubled (see Table 5).

TABLE 5

PROVINCE OF MAZANDARAN CANCER REGISTRY: NUMBER OF OESOPHAGEAL CANCERS REPORTED IN FIRST YEAR OF OPERATION, WITH CRUDE AND AGE-ADJUSTED RATES

	Population (1966 census)	Cases of oesophageal cancer	Crude incidence rates per 100 000	Age-adjusted incidence rates [a]	Crude incidence for age group 35-64
Males	940 342	204	21.7	53.4	70.8
Females	901 304	182	20.2	45.7	78.3

[a] Rates age-adjusted to a European population structure.

(b) Appointment of a pathologist

The appointment of Dr Salmasizade, a pathologist, by the Institute of Public Health Research, Teheran, should lead to improved diagnostic facilities and better cancer registration. He will serve at Babol and provide all practitioners in the Province with a free biopsy service.

(*c*) *Extension of cancer registration*

Cancer registration has been extended to the Caspian coast of Western Iran, since the low incidence areas seem to include Gilan Province.

(*d*) *Correlation with physical characteristics*

When the crude incidence rates for oesophageal cancer are superimposed on maps indicating soil characteristics, it appears that the high incidences in the desert and semi-desert areas of Gorgan and Gonbad, largely settled by Turkomans, are found in areas where the soil is predominantly saline. Relatively low crude incidences are located in the rainbelt area where the soil is predominantly heavy, leached, and acid. In the centre of the Province, where saline and non-saline soils are mixed, the incidence rates are intermediate between high and low.

Miss Paula Cook, a medical geographer, visited Iran as a consultant in November 1969 to help prepare for studies of the physical and biotic characteristics of the high and low incidence areas. These will begin in 1970. A considerable amount of relevant information is available in various Iranian institutes (geography, soil, geology, statistics) but it needs collation and reworking before it can be applied. A detailed enquiry into feeding practices and personal habits is to begin in 1970.

(*e*) *Personal habits of cancer patients*

A small-scale investigation was undertaken to ascertain the consumption of alcohol, tobacco, and opium in oesophageal cancer patients. The results suggest that these factors are probably of no importance, particularly as, in the high risk areas, this type of cancer is commoner in females than in males (Table 6).

TABLE 6

PERSONAL HABITS OF 31 PATIENTS WITH RADIOLOGICALLY DIAGNOSED OESOPHAGEAL CANCER IN MAZANDARAN

	No. of patients	Alcohol consumption			Tobacco consumption			Opium consumption		
		Nil	Light to moderate	Heavy	Nil	Light to moderate	Heavy	Nil	Light to moderate	Heavy
Males	19	14	4	1	6	6	7	7	6	6
Females	12	12	0	0	9	3	0	11	1	0
Total	31	26	4	1	15	9	7	18	7	6

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

(*a*) *Oesophageal cancer* (Professor L. Massé: RA/69/015)

A review of mortality data on oesophageal cancer in Europe in 1965-66 has revealed distinctive patterns in different countries. A more detailed geographical analysis in Brit-

tany has defined foci of very high oesophageal cancer mortality with a crude rate of 60 per 100 000 per annum. These are often contiguous with areas where mortality is much lower. This work is being extended to neighbouring areas, and to other cancer sites.

(*b*) *Correlation with alcoholism*

A study [1] has been made at departmental level of mortality data on oesophageal cancer in France. The known correlation with mortality from "alcoholism" plus cirrhosis has been confirmed (r = .54). It has further been shown that the correlation with "alcoholism" alone (r = .64) is greater than with cirrhosis alone (r = .37). As "alcoholism" as a cause of death is associated with spirit drinkers rather than wine or beer drinkers, this finding is consistent with the hypothesis that oesophageal cancer is linked with heavy spirit drinking in France, particularly in the west of the country.

7.3 *The Caribbean* (Dr Ulrike de Jong)

Oesophageal cancer is a problem throughout the Caribbean region, being common in Jamaica (males: 17.2 per 100 000; females: 5.5 per 100 000), Puerto Rico (males: 18.0; females: 7.7), and Curaçao. The importance of the role of alcohol (particularly when illicitly distilled), tobacco, and spices in Puerto Rico has been shown,[2] but it remains to be seen whether these factors operate in other parts of the Caribbean.

Arrangements for a case-control study to determine the role of alcohol and tobacco in Jamaica have been finalized. The collaboration of the IARC Regional Centre and the Jamaica-based Epidemiological Research Unit of the Medical Research Council of Great Britain has been most useful.

In Curaçao, where the incidence of oesophageal cancer is approximately the same in both sexes—in 1968-69 the Curaçao Cancer Registry recorded 20 male and 15 female cases of oesophageal cancer in a population of 130 000—, it has been attributed to the consumption of hot *funchi* (maize porridge). Consumption of *funchi* is still common among the older people, but the younger generation stop eating it as soon as they can afford to. Preliminary investigations suggest that Curaçao women consume rather more alcoholic drinks than women in neighbouring Caribbean territories. Other possible factors are awaiting study.

In conjunction with the unit of Environmental Carcinogenesis, alcoholic beverages —preferably those that are home-brewed and illicitly distilled—have been collected in Jamaica, Curaçao, Puerto Rico, Iran, Brittany, and Singapore. After purchase, the samples are placed in identical brown glass containers, given randomly chosen code numbers, and sent for analysis of their nitrosamine content (see p. 32).

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[1] Tuyns, A. J. (1970) *Int. J. Cancer*, **5**, 152.

[2] Martínez, I. (1969) *J. nat. Cancer Inst.*, **42**, 1069.

7.4 *Comparative studies* (Dr Nubia Muñoz)

Consultant: Dr T. Hirayama

Studies in Colombia and Mexico have shown that there are two main types of gastric cancer: the "intestinal" and the "diffuse".[1] These differ not only morphologically but epidemiologically. Arrangements have been made with pathologists in Yugoslavia, Israel, and Norway to study the population groups for which different gastric cancer risks have been reported.

8. EPIDEMIOLOGICAL AND SEROLOGICAL SURVEYS FOR LIVER CANCER IN AFRICA (Dr A. J. Tuyns)

8.1 *Dakar* (Dr L. Leblanc)

Principal investigator: Professor R. Masseyeff (RA/68/013)

A serological survey aimed at covering 6000 male adults has been initiated in Dakar; subjects will be tested three times a year over a period of two years. The study is expected to provide an estimate of the prevalence and incidence of liver cancer in the population examined and to clarify the time relationships between a positive fetoprotein test and the appearance of clinical symptoms.

Difficulties have been encountered in re-examining the same persons, but measures have been taken to follow up absentees. Most of the groups under study have been examined twice already and some three times. One unsuspected case has been detected by the test so far, and the diagnosis was later confirmed by clinical and pathological examination.

8.2 *Ivory Coast*

Principal investigator: Dr F. Sérié (RA/69/001)

A population survey has been designed to establish the prevalence and incidence of liver cancer among adults in representative samples of villages in the north and in the south, using the α-fetoprotein test on serum samples.

A co-ordination committee has been set up at the Faculty of Medicine of Abidjan (Dean: Professor P. Pène) under the chairmanship of Professor E. Bertrand. It includes all interested research workers at the Ministry of Health (Services des Grandes Endémies) and at the Faculty of Medicine, as well as WHO staff in the Ivory Coast and IARC staff-members. This group has worked out a general plan and detailed protocols for determining the population sample, as well as technical procedures for handling the material and for the testing itself.

The collection of serum started early in 1970 (see Fig. 3); 20 000 adults will be examined three times a year over a period of two years. It is anticipated that an aflatoxin survey of

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[1] Muñoz, N., Correa, P., Cuello, C. & Duque, E. (1968) *Int. J. Cancer*, **3**, 809.

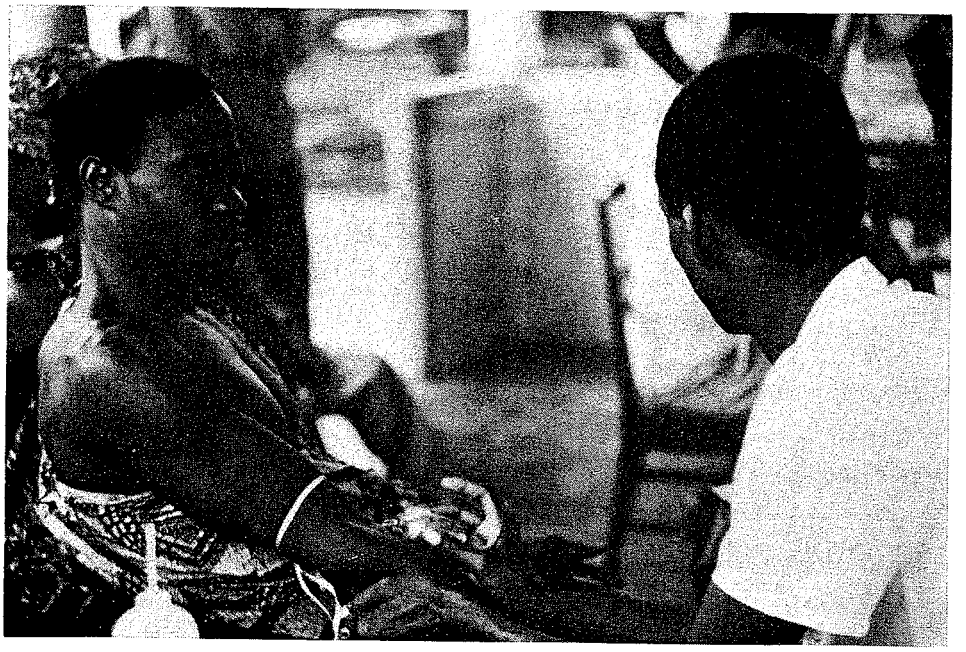

Fig. 3. Taking blood sample during liver cancer survey in the Ivory Coast.

the Murang'a type (see p. 73) will be organized parallel to the serological survey. Further pathological and clinical studies are contemplated.

This comprehensive study involves several units of the IARC. The unit of Chemical Carcinogenesis and the Regional Centre at Nairobi actively co-operate with the unit of Epidemiology and Biostatistics in this multidisciplinary research project.

9. OTHER STUDIES

9.1 *Cervical cancer* (Dr J. Kmet)

Dr J. Kmet is a consultant to the US-Yugoslav team studying the possible venereal nature of cervical cancer in Muslim and Christian populations. Case-control techniques and serology are being used, and the role of herpes-type virus is being studied.

9.2 *Prostatic cancer* (Dr H. Tulinius)

Wide differences in age-adjusted rates of cancer of the prostate have been noted, ranging from 40.9 for US Caucasians in Connecticut to 0.9 for Singapore Chinese. Prostatic cancer is the most frequent cancer in Swedish males. It has been suggested that the low rates in certain countries are linked with a failure of the so-called "occult" cancers to become invasive.

A study has been designed in which prostates removed at necropsy from persons in selected age groups will be examined in several areas of the world where there are cancer registration schemes to assess:

(*a*) the frequency of occult carcinoma in the necropsy sample of each age group;

(*b*) the incidence of invasive cancer in that age group;

(*c*) the estimated conversion rate from occult to invasive cancer.

So far, workers in five study areas have been approached, and two have definitely accepted.

10. BIOSTATISTICS

Dr T. Williams resigned from the Agency to become Professor of Statistics at the University of Bristol. The unit of Biostatistics has, therefore, been incorporated in the unit of Epidemiology, so that programmes and statistical services are now more closely integrated.

Dr N. S. Stenhouse, Director, Department of Medical Statistics, University of Western Australia, acted as a consultant to the Agency for three months until the arrival of Dr N. E. Day.

10.1 *Data processing*

The statistical services have been reviewed, and equipment suitable for the present data-processing needs of the Agency has been selected. The future computing needs of the Agency are being assessed in relation not only to the scientific programmes but also to the administrative and financial services so that suitable facilities may be provided in the new building.

10.2 *Singapore cancer statistics*

The amended data from the Singapore Cancer Registry for the quinquennia 1950-54, 1955-59, and 1960-64 have been recorded on punch cards and tabulated. The ratio studies mentioned earlier in this report have been similarly processed.

10.3 *Correlation studies* (Mr D. K. Jain)

The wide variations in morbidity from cancer of various sites indicates that environmental factors are of high etiological significance. An attempt has been made to correlate morbidity rates of cancer (age-adjusted to world population distribution) with different environmental factors. Data from 17 cancer registries throughout the world were used, and attention was confined to the 16 sites for which they provided adequate information. Dietary, socio-economic, and environmental data were obtained for the countries to which the registries belonged. These variables were correlated with the age-adjusted morbidity rates for each cancer site. The finding of greatest interest was a high positive correlation between meat intake and cancer of the colon and of the rectum. In all studies of this kind, the limitations of the data should be kept firmly in mind.

2. UNIT OF ENVIRONMENTAL CARCINOGENESIS

Staff: Dr P. BOGOVSKI (Chief)
Dr E. BOYLAND (Consultant from March 1970)

Supporting staff: 2

1. INTRODUCTION

The objectives of the unit are:

(*a*) to develop and standardize methods and techniques for collecting quantitative data, suitable for use in international studies, on carcinogenic substances in the environment;

(*b*) to decide the environmental carcinogens related to cancer sites under investigation in IARC to which priority should be given;

(*c*) to collect data on the distribution of such carcinogens in selected geographical areas;

(*d*) to initiate and carry out projects to demonstrate the significance of specific environmental carcinogens.

2. QUANTITATIVE DATA ON ENVIRONMENTAL CARCINOGENS

2.1 *Analytical problems*

Of the five main groups of presumptive carcinogens in the human environment (IARC Internal Technical Report No 68/006), the polycyclic aromatic hydrocarbons (PAH) and the N-nitroso compounds—nitrosamines (NA)—are very active in experimental conditions and are widely distributed. The methods required for their chemical analysis are in greater need of development and standardization than those for the other groups—aromatic amines, mycotoxins, and metals. The immediate programme, therefore, deals primarily with ways of analysing PAH and NA and their application in specific epidemiological research projects of IARC.

2.2 *Polycyclic aromatic hydrocarbons in food*

(*a*) *IARC working group*

A special working group was held in Lyon on 6 March 1969 to discuss practical problems of PAH analysis in food, especially in field conditions (IARC Internal Technical

Report No. 69/002). The nature of the sampling problem was well demonstrated when it was calculated that, to detect two parts per thousand million, a minimum representative sample of 250 g would be necessary for each analysis over a range of PAH. The group also discussed problems of extracting PAH from foodstuffs and their stability. It suggested that some questions should be referred to the International Union of Pure and Applied Chemistry (IUPAC) for evaluation.

(*b*) *XXVth Conference of IUPAC*

At the XXVth Conference of IUPAC (30 June 1969-8 July 1969), which the unit chief, Dr Bogovski, attended as an observer, the questions put forward by the IARC working group were discussed by the Trace Substances Commission of the Food Section. It was not found appropriate to seek a single extraction system to isolate groups of potentially carcinogenic compounds, which exhibit widely divergent physical and chemical properties (e.g., non-polar PAH, polar nitrosamines, semi-polar aflatoxins).

The Commission was not familiar with the problem of the stability of PAH following prolonged storage and took note of the Research Agreement arranged by the IARC with Professor G. Grimmer to provide data on this subject (see below). The Commission reaffirmed that top priority should be given to establishing standardized methods for the quantitative analysis of PAH.

(*c*) *Laboratory of Biochemistry, Hamburg, Federal Republic of Germany* (RA/69/006)

Principal investigator: Professor G. Grimmer

A study of the fraction of eight polycyclic aromatic hydrocarbons recoverable from a meat homogenate has been carried out by Professor Grimmer, using his own published method.[1]

The hydrocarbons were added in known amount to 200 g of homogenized meat mixed either with an excess (1000 ml) of methanolic 1N-KOH or with a minimal amount (250 ml methanol + 25 g KOH). With the first solvent mixture, neither previous heating nor storage at different temperatures (4°C and 35°C) resulted in substantial losses of PAH.

The results with the second solvent are given in Table 7.

2.3 *Polycyclic aromatic hydrocarbons in air*

A Working Group was convened by IARC in Geneva (10-12 December 1969) to discuss the standardization of sampling and analytical procedures for the estimation of PAH in air (IARC Internal Technical Report No. 69/009). The Agency was requested to organize an international reference centre for the provision of standard compounds to laboratories investigating PAH as environmental pollutants. It was also decided that IARC

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[1] Grimmer, G. & Hilderbrandt, A. (1965) *J. Chromat.*, **20**, 89; (1967) *Z. Krebsforsch.*, **69**, 223.

TABLE 7

RECOVERY OF EIGHT POLYCYCLIC AROMATIC HYDROCARBONS ADDED TO HOMOGENIZED MEAT (200 g) MIXED WITH METHANOL AND KOH (25 g) AFTER STORAGE IN DARKNESS FOR 28 DAYS AT 35°C

Compound	Added	Recovered	
	(μ)	(μ)	(%)
Phenanthrene	1.22	1.58	129
Pyrene	1.08	1.00	93
Fluoranthene	1.22	1.00	82
Benzo[*a*]anthracene	1.01	0.88	87
Chrysene	0.91	0.84	92
Benzo[*e*]pyrene	1.03	0.78	76
Benzo[*a*]pyrene	0.98	0.69	70
Benzo[*g,h,i*]perylene	1.07	0.78	73

should publish during 1970-71, in collaboration with WHO, a manual of recommended methods of sampling and analysis for PAH in air. The Editor-in-Chief (Dr E. Sawicki) and an editorial board were elected.

2.4 *N-nitroso compounds in food*

(*a*) *Forschergruppe für Präventivmedizin, Max Planck Institut für Immunobiologie, Freiburg, Federal Republic of Germany* (RA/68/016)

Principal investigator: Dr R. Preussman

The investigations aimed at developing: (*a*) adequate nitrosamine separation techniques for more or less complex mixtures of different origins, and (*b*) reliable methods for the quantitative determination of nitrosamines. In the case of fatty food, a liquid-liquid partition in acetonitrile/n-heptane resulted in 95 % recovery of the nitrosamine in the acetonitrile phase.[1]

Steam distillation (at atmospheric pressure and under vacuum) of 16 nitrosamines in two steps—from alkaline (0.2 N NaOH) or neutral medium and subsequently from an acid medium (0.2 N tartaric acid)—was evaluated quantitatively and found to provide good separation. The use of thin-layer chromatography as a clean-up process was investigated, and recoveries were found to be dependent on layer thickness, temperature, and the method of applying the solution to the chromatograph. Optimum recovery was obtained using a a 0.6 mm layer (kiesel gel Pf 254) and developing at 4°C. Alternating-current polarography can be used for the determination of nitrosamines, and 4 μg quantities of the lower nitrosamines can be detected without difficulty. If no detectable waves are found at the highest sensitivity of the instrument, the nitrosamine content in a 1 kg sample must be below 4 parts

[1] Preussman, R. (1969) *Z. analyt. Chem.*, **247**, 54.

per thousand million. For positive identification, gas chromatography, mass spectrometry, and, if possible, derivative formation should be used.

(*b*) *Nitrosamines in alcoholic beverages*

A study of the nitrosamine content of alcoholic beverages is planned in collaboration with the Epidemiology and Biostatistics unit. Samples will be sent from six geographical areas (Puerto Rico, Jamaica, Curaçao, Brittany, Iran, and Singapore) with differing incidences of oesophageal cancer. The nitrosamine analysis will be carried out in the British Food Manufacturers' Industrial Research Association laboratories in Leatherhead, Surrey, United Kingdom (Dr C. L. Walters). See also page 25.

The first samples have arrived from Puerto Rico.

(*c*) *Analytical problems in the estimation of traces of nitrosamines in food*

A meeting was convened (London, 23-24 October 1969) to examine the problems involved in the extraction and clean-up of nitrosamines from food samples and in their identification and estimation (IARC Internal Technical Report No. 69/008). Two groups for collaborative studies were set up: one will examine the effectiveness of acetone as an extraction solvent under field conditions (Co-ordinator: Dr R. Preussman); the other will compare techniques of gas chromatography for the detection and estimation of nitrosamines (Co-ordinator: Mr J. K. Foreman). The meeting will be re-convened in 1971.

2.5 *Standing Committee on Environmental Carcinogens*

An IARC Standing Committee on Environmental Carcinogens (Chairman: Dr P. Shubik) has been appointed. Its main aims will be:

(*a*) to discuss carcinogens in relation to specific cancer sites and the priority they should be given in the epidemiological programmes of IARC;

(*b*) to advise the unit of Environmental Carcinogenesis on the development of specific programmes; and

(*c*) to discuss other problems related to environmental carcinogenesis.

3. ASBESTOS PROJECT

Principal investigators: Dr J. C. Gilson, Dr J. C. Wagner (RA/67/002)

On 25 February 1969 a meeting on the co-ordination of work on asbestos cancer was convened in Lyon with the participation of Dr J. C. Gilson, Dr J. C. Wagner, and representatives from Italy (IARC Internal Technical Report No. 69/001). It was decided, after reviewing the investigations carried out as various parts of the research agreement, that many questions still remain to be solved. The possible participation of Italian specialists

was discussed. In a further co-ordination meeting held in Cardiff, United Kingdom, in June 1969, it was decided to continue the research agreement for a second three-year period, because of the international importance of the problem.

3.1 *Finland*

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

The collection of data on a population of 1902 asbestos workers has continued, and by May 1969 a 95.33% coverage had been obtained. Only 51 of the miners employed between 1936 and 1967 have not been traced. An analysis of the death certificates of 254 asbestos workers who had died up to May 1969 showed that 21 died of lung cancer, compared with 12 in a control group. Of the group of miners who had worked for more than ten years, 33 have died: of these, 19 had asbestosis and 8 carcinoma of the lung. A statistical analysis of the data is awaited from Dr Matti Hakama, Finnish Cancer Registry, Helsinki.

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

In conjunction with Dr Tudor Morris, the biochemist at the Pneumoconiosis Unit of the Medical Research Council of Great Britain, chemical analyses of the lungs of asbestos workers have been compared with pathological findings. Eighty-four pairs of lungs are being studied. Preliminary results show that there is a relationship between the amount of hydroxyproline, the amount of fibrosis, and the number of asbestos bodies present.

3.2 *Great Britain*

(*a*) *Mesothelioma register*

IARC has provided support for a secretary and a technician for the mesothelioma register, and a centre has been established in Dr K. F. W. Hinson's department at the Brompton Hospital, London. During the year, 125 cases of mesothelioma were referred to the Mesothelioma British Panel for diagnosis. Information on over 600 cases has been collected since the establishment of the register in 1965. The members of the British Panel met in January 1970 and decided that, in association with the epidemiologists and the various government departments concerned, a complete investigation of the data in hand should be carried out before collecting further material.

The centre has also been responsible for the pathological aspects of the five major epidemiological surveys on links between asbestos and cancer in Great Britain.

Material for a retrospective study of the prevalence of asbestos bodies in autopsies in London has been prepared for Dr Chang Hyun Um by the register's technician.

Dr Blanche Butler, a former IARC Research Fellow, is now Senior Lecturer in Cytology in the University of Manchester and is working on criteria for the diagnosis of diffuse mesotheliomas from the study of the cells seen in pleural and peritoneal effusions. This is particularly important as a survey in the British Navy has revealed a number of cases of recurrent asymptomatic effusions which require investigation.

(*b*) *Retrospective study of the prevalence of asbestos bodies in autopsies in London, 1936-66*

Dr Chang Hyun Um has completed his retrospective survey of samples of lungs from people who died in the years 1936, 1946, 1956, and 1966. The samples have been provided by Dr P. C. Meyer, Director of Pathology, The Whittington Hospital, London. There has been an increase over each decade in the number of asbestos bodies seen in the lungs surveyed and this correlates with the increased importation of asbestos into Britain. The 1966 results match the findings of the Ten Centre Survey in London (see below). A detailed analysis of the material is planned to see if there has been any change in the type of fibre found in the lungs over the thirty-year period. The epidemiological distribution of the cases in the survey is now being investigated.

(*c*) *Ten Centre International Survey*

This survey has been partly supported by the IARC, particularly as regards obtaining material from Galway, Ireland, which has been used as a non-polluted control area. The preliminary results of a survey of the incidence of asbestos bodies in lungs in ten European towns—eight industrial and two rural—show that the high incidence in Finland has been maintained. Incidences in the industrial cities are similar, being well above the levels in the rural control areas of Galway, Ireland, and Dorchester, England. The survey has been challenged by certain investigators who suggest that the so-called "asbestos bodies" might not, in fact, contain asbestos. A statistical sample of the material submitted is being studied by Dr F. D. Pooley, who has so far confirmed that asbestos fibres were present in the "bodies" observed by the pathologists.

(*d*) *The identification of asbestos in tissue*

Dr F. D. Pooley, of the Department of Mineral Exploitation, University College of South Wales and Monmouthshire, Cardiff, working in conjunction with Dr V. Timbrell of the Medical Research Council Pneumoconiosis Unit, Penarth, has developed techniques using electron microscopy and electron diffraction methods that have made it possible to differentiate between the major types of asbestos as seen on routine histological sections. The study has been partly supported by IARC.

3.3 *Cyprus*

Following earlier investigations, Dr J. C. Gilson, Dr V. Timbrell, and Dr F. D. Pooley visited Cyprus. Dr Gilson read the radiographs of 1000 miners, and the Cypriot authorities are now producing the service records of the miners concerned.

One definite case of mesothelioma of the pleura has been diagnosed in a woman who lives near the mines. Dr Pooley's investigation of lung sections from this patient showed no chrysotile, but amphibole was suspected. The investigation at the mine revealed that there were considerable amounts of tremolite in the ore; this had not previously been reported.

3.4 *Southern Africa*

(*a*) An International Pneumoconiosis Conference, held in Johannesburg in April 1969, was attended by Dr J. C. Gilson, Dr J. C. Wagner, Dr V. Timbrell, Dr F. D. Pooley, Dr L. Meurman, and Dr K. Kiviluoto. Papers were presented on the investigations that have been in part, or fully, supported by the asbestos and cancer research agreement of the IARC.

(*b*) Dr Gilson and Dr Wagner visited the amosite mining area in the Northern Transvaal and confirmed that, although the crocidolite and amosite ores are remarkably similar, so far mesotheliomas have only been associated with the crocidolite areas.

Even though doctors in the rural hospitals in the amosite area were well aware of the mesothelioma tumour problem in asbestos workers, only one definite case had been diagnosed over the previous ten years; another possible case was still being investigated.

(*c*) Samples of asbestos were obtained from the whole of the South African amphibole asbestos fields extending from the Orange River in the south to the Northern Transvaal, in order to compare fibre diameters. Results obtained by Dr Timbrell and Dr Pooley suggest that Transvaal crocidolite is more closely related to amosite than it is to Cape crocidolite.

3.5 *USSR*

Professor L. Shabad and Dr L. N. Pylev (Moscow) are repeating the intrapleural experiments carried out at the Pneumoconiosis Unit of the Medical Research Council of Great Britain, using identical dusts and equipment. Professor Kogan (Sverdlovsk) has sent samples of asbestos fibre to Dr Timbrell and Dr Pooley for comparison with the UICC standard samples.

3.6 *Netherlands*

Dr J. Stumphius has discovered a group of asbestos-related cases of mesothelioma in the Flushing shipyards.[1] He is continuing the enquiry with Professor J. Zielhuis, testing whether there is, in fact, a special association between mesothelial tumours and workers engaged in welding.

4. STUDIES IN ORGAN CULTURES ON POLYCYCLIC AROMATIC HYDROCARBONS

Explants of adult mouse skin and oesophagus were cultivated in various modifications of nutrient media with the addition of benzo[*a*]pyrene, caffein, and dimethylsulphoxide. Preliminary results have shown that a higher proportion of binucleated epithelial cells and fibroblasts is found five days after the addition of a 0.01 % solution of caffein. Benzo[*a*]-pyrene (0.1 μg/ml of medium) induces a higher mitotic activity and more cellular polymorphism than are observed in control explants.

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[1] Stumphius, J. & Mayer, P. B. (1968) *Ann. occup. Hyg.*, **11**, 283.

3. UNIT OF BIOLOGICAL CARCINOGENESIS

Staff: Dr G. BLAUDIN DE THÉ (Chief)
Dr A. GESER
Dr D. SIMKOVIC
Dr NUBIA MUÑOZ
Dr R. SCHMAUZ
Mr J. C. AMBROSIONI
Mr T. B. GREENLAND
Mrs E. GALATIUS

Supporting staff: 9

1. INTRODUCTION

The Unit of Biological Carcinogenesis is continuing to study the oncogenic role of viruses, especially in man.

(*a*) Integrated field and laboratory studies are being continued on:
(i) nasopharyngeal carcinoma;
(ii) Burkitt's lymphoma;
(iii) cancer of the genital tract (penis and cervix).

(*b*) An international reference centre for avian tumour viruses is being planned for Lyon.

(*c*) Various sero-epidemiological techniques are being explored in order to establish methods convenient for field studies.

2. STUDIES OF NASOPHARYNGEAL CARCINOMA

The programme on nasopharyngeal carcinoma involves collaboration with field centres in South-East Asia and Africa and laboratories in Europe and the USA.

2.1 *Collaborating field centres*

(*a*) *Medical and Health Department Institute of Radiology, Kowloon, Hong Kong* (RA/68/007)

Principal investigator: Dr H. C. Ho, Senior Specialist in charge of the Institute.

The collaborative research agreement initiated in 1968 was continued. Eighty-two biopsy specimens from nasopharyngeal carcinoma, 11 from other tumours of the ear, nose, and throat, 16 from tonsilitis, and 12 from clinically normal nasopharynxes were sent from Hong Kong to Lyon for tissue culture studies. Three hundred and fifty-one sera from patients with nasopharyngeal cancer, 189 from such patients after radiotherapy at different intervals, 29 from families of patients, and 189 from various controls were also collected and sent to Lyon. Aliquots of these sera were sent to collaborating laboratories at the Virus Laboratory, Children's Hospital of Philadelphia, Penn., USA (Dr W. Henle and Dr G. Henle), and to the Department of Tumour Biology, Karolinska Institutet, Stockholm (Professor G. Klein). The results obtained with this material are given in sections 2.2 (*a*) and (*b*) and 2.3.

The close collaboration of Dr Ho has been invaluable for IARC. In 1970 it is planned to carry out some of the laboratory work in the Institute of Radiology in Hong Kong.

(*b*) *IARC Regional Centre, Singapore* (RA/67/008)
WHO Regional Immunology Research and Training Centre, Singapore (RA/69/012)

Principal investigators: Professor K. Shanmugaratnam, Director of the IARC Regional Centre

Dr D. S. Nelson, Director of the WHO Regional Immunology Research and Training Centre

Full details on the work in progress at the Regional Centre are given in its report (page 80).

A serum collection of 343 samples from selected age groups of the Chinese and Indo-Pakistani populations living in Singapore was completed and sent to IARC. Aliquots were given to the Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon (Professor R. Sohier). They are being tested for complement-fixation titrations against different adenoviruses and by immunofluorescence for the detection of antibodies against herpes-type virus, to see if there is any correlation between the pattern of infection by these viruses and the prevalence of nasopharyngeal carcinoma (see section 2.2(*c*)).

(*c*) *Ear, Nose and Throat Department, Kenyatta National Hospital, Nairobi*

Principal investigator: Mr P. Clifford, F.R.C.S.

Mr Clifford has sent a number of nasopharyngeal carcinoma biopsies *via* Professor G. Klein of Stockholm. This material has been used in tissue culture studies.

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

Principal investigator: Professor M. S. R. Hutt

Under the supervision of Professor Hutt, epidemiological investigations on nasopharyngeal carcinoma were carried out by Dr R. Schmauz, Research Assistant of IARC, with

serum collections and biopsies. Dr Schmauz also carried out investigations on cancer of the penis and cervix (see page 45).

2.2 *Collaborating laboratories*

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

Principal investigator: Professor G. Klein

Specific immunological work on the sera of nasopharyngeal carcinoma patients and on the permanent lines derived from such carcinomas in the IARC laboratories has been carried out in Professor Klein's laboratory. The sera of nasopharyngeal carcinoma patients showed the presence of membrane reactive antibodies (Klein test) and, when established cell lines derived from either Burkitt's lymphoma or nasopharyngeal carcinoma were used as target cells, these sera showed a high blocking activity against fluorescein-labelled reference sera.[1]

Another study [2] had shown that when the Klein test was used there was no major difference between the LY-1 cell line derived from nasopharyngeal carcinoma and those derived from Burkitt's lymphoma or infectious mononucleosis.

(*b*) *Virus Laboratory, Children's Hospital of Philadelphia, Penn., USA*

Principal investigators: Dr W. Henle and Dr G. Henle

The majority of the nasopharyngeal carcinoma and control sera from Hong Kong have been tested in the Children's Hospital of Philadelphia.

The main results were as follows: all the nasopharyngeal carcinoma patients had antibodies against herpes-type virus (closely related to Epstein-Barr virus), as measured by the Henle test; 84 % of the patients had high titres (equal or superior to 1:160), while the various control groups had much lower titres. Another interesting finding was that the titre of antibodies, as measured by indirect immunofluorescence (Henle), appears to increase with the stage of the disease. Only 5 out of 10 patients with nasopharyngeal carcinoma confined to mucosa had high titres, while 92 out of 115 patients with local extension of the tumour or involvement of the regional lymph nodes and 57 out of 58 patients with involvement of nodes in supra-clavicular fossae and other metastases had high titres.[3]

(*c*) *Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon* (RA/68/012)

Principal investigator: Professor R. Sohier

Sera, mostly from Singapore, have been tested for complement fixation and immunofluorescence against different adenoviruses and herpes-type virus. The results are shown in Tables 8 and 9. Plans are in hand for providing some of the laboratory tests required for

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[1] de Schryver, A., Friberg, C. S., jr, Klein, G., Henle, W., Henle, G., de Thé, G., Clifford, P. & Ho, H. C. (1969) *Clin. exp. Immunol.*, **5**, 443.

[2] de Schryver, A., Klein, G. & de Thé, G. (1970) *Clin. exp. Immunol.* (in press).

[3] Henle, W., Henle, G., Burtin, P., Cachin, Y., Clifford, P., de Schryver, A., de Thé, G., Diehl, V., Ho, H. C. & Klein, G. (1970) *Clin. exp. Immunol.* (in press).

TABLE 8

TITRES OF ANTIBODIES AGAINST HERPES-TYPE VIRUS (HENLE TEST) IN SERA COLLECTED IN SINGAPORE

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

Henle test titre	Sources of sera			
	Nasopharyngeal carcinoma (NPC)		Non-NPC cancer (12 samples)	Non-malignant disease (6 samples)
	Confirmed cases (33 samples)	Biopsy negative (19 samples)		
< 10	0	1	0	0
10	0	3	3	0
40	1	4	5	2
80	4	5	1	1
160	3	1	1	0
320	8	1	1	3
640	7	2	1	0
1280	5	1	0	0
2560	5	1	0	0

TABLE 9

LEVELS OF COMPLEMENT FIXATION AGAINST GROUP-SPECIFIC ADENOVIRUS ANTIGENS IN SERA COLLECTED IN SINGAPORE

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

Dilutions [a]	Sources of sera			
	Nasopharyngeal carcinoma (NPC)		Non-NPC cancer (12 samples)	Non-malignant disease (6 samples)
	Confirmed cases (33 samples)	Biopsy negative (19 samples)		
2	17	11	6	5
± 2	5	3	3	0
2	4	0	2	1
± 4	0	0	1	0
4	0	1	0	0
± 8	4	1	0	0
8	0	1	0	0
±16	0	1	0	0
16	1	0	0	0
±32	1	1	0	0
64	1	0	0	0

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

the large-scale sero-epidemiological study of nasopharyngeal carcinoma which will be developed in South-East Asia. A pilot study on the sera collected in France from the general population has been completed (Table 10).

TABLE 10

SERO-EPIDEMIOLOGICAL STUDY ON HERPES-TYPE VIRUS INFECTION IN SERA COLLECTED IN FRANCE, USING HENLE TEST: DISTRIBUTION OF ANTIBODY TITRES BY AGE GROUP

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

AB titres	Age group											
	Months			Years								All ages
	0-6 (6 sera)	7-12 (24 sera)	12-24 (48 sera)	2-5 (25 sera)	6-10 (25 sera)	11-20 (25 sera)	21-30 (25 sera)	31-40 (25 sera)	41-50 (26 sera)	51-60 (25 sera)	>60 (25 sera)	(279 sera)
<10	5	21	25	11	10	3	6	8	4	5	2	100
10	1	2	10	7	6	10	6	9	11	5	5	72
40	0	0	5	4	3	4	5	7	4	5	4	41
80	0	0	4	2	3	4	4	0	4	5	5	31
160	0	1	2	0	3	3	3	1	3	3	8	27
320	0	0	2	1	0	1	1	0	0	2	1	8
% AB ⩾ 10	16.6	12.5	47.9	56	60	88	76	68	84	80	92	

(*d*) *Sloan-Kettering Institute, New York, N.Y., USA*

Principal investigator: Dr L. J. Old

A limited number of sera have been tested for immuno-precipitating antibodies. A similarity between sera from nasopharyngeal carcinoma and Burkitt's lymphoma patients was noted, with an extra precipitating line in the former not present in the latter.

(*e*) *Institut de recherches scientifiques sur le cancer, Centre national de la Recherche scientifique, Villejuif, France*

Principal investigator: Dr P. Dubouch

Some preliminary experiments are being carried out in this institute on nasopharyngeal carcinoma material. Attempts are being made to infect baboon cells *in vitro* with herpes-type virus from irradiated tumour cells.

2.3 *Studies in IARC laboratories*

Experimental studies on nasopharyngeal carcinoma biopsies and corresponding sera were carried out in the laboratories put at the disposal of the IARC by the Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon (Director: Professor R. Sohier).

(*a*) *Tissue culture studies*

Biopsies of nasopharyngeal carcinoma received mainly from Hong Kong and, to a lesser extent, from Nairobi and Kampala were grown *in vitro*. Four different types of culture were obtained:

(i) epithelial growth, which was limited in time (4-12 weeks) and in size (a few mm around the explants);

(ii) early lymphocytic production lasting for one to three weeks;

(iii) fibroblastic cultures (either primary or secondary to the epithelial growth) occasionally showing a criss-cross growth; and

(iv) "lymphoblastoid transformation", which occurred in 28 % of the cultures and resulted in the establishment of long-term free-floating cell lines.

Table 11 shows the proportions in which these types of culture were obtained from the nasopharyngeal carcinoma biopsies received in Hong Kong between January and August 1969. A few lines were intermittently dependent upon the presence of fibroblasts, but most of them were entirely independent.

TABLE 11

TYPES OF CULTURES OBTAINED FROM 69 NASOPHARYNGEAL CARCINOMA BIOPSIES BETWEEN JANUARY AND AUGUST 1969

	Number	Percentage
Epitheloid growth	18	26
Early lymphocytic production	47	70
Fibroblastoid cultures	53	76
Long-term lymphoblastoid cultures	19	28

Control cultures derived from biopsies of ear, nose, and throat tumours other than nasopharyngeal carcinoma, from inflamed tonsils of children, and from clinically tumour-free nasopharynxes gave rise to similar types of culture with lymphoblastoid transformation and the establishment of long-term free-floating cell lines. These results from controls do not confirm or preclude the oncogenic action of a transforming virus, since it is well-known that DNA and RNA oncogenic viruses can infect and replicate in non-tumorous tissues. Furthermore, what is specific for nasopharyngeal carcinoma patients is that they are all infected with herpes-type virus, giving a strong immunological response, whereas about 80 % of the general population are positive for this virus with averagely low antibody titres.

The relationship was analysed between the degree of lymphoplasmocytic infiltration of the nasopharyngeal carcinoma biopsies, their properties in tissue culture, and the Henle titres of the corresponding sera. As shown in Table 12, the only parameter which evolved in parallel with lymphoplasmocytic infiltration of the tumour was the frequency of early lymphocytic production. Neither the Henle titre nor the frequency of lymphoblastoid transformation was related to the degree of lymphoplasmocytic infiltration.

TABLE 12

NASOPHARYNGEAL CARCINOMA BIOPSIES: DEGREE OF LYMPHOPLASMOCYTIC INFILTRATION COMPARED WITH FREQUENCY OF EARLY LYMPHOCYTIC PRODUCTION, FREQUENCY OF LYMPHOBLASTOID TRANSFORMATION, AND HENLE TITRES[a] OF THE CORRESPONDING SERA

Degree of lymphoplasmocytic infiltration of the tumour	Cases evaluated	Early lymphocytic production	Lymphoblastoid transformation and long-term cultures	Low Henle titre	High Henle titre (1 : 160)
Moderate	21	14 (67 %)	7 (33 %)	2 (9.5 %)	19 (90 %)
Marked	14	13 (93 %)	4 (28 %)	2 (14 %)	12 (86 %)
Total	35	27 (77 %)	11 (31%)	4 (12 %)	31 (88 %)

[a] The results shown here were obtained from the Virus Laboratory, Children's Hospital of Philadelphia, Penn., USA (Dr W. Henle and Dr G. Henle).

Table 13 shows the frequency of lymphoblastoid transformation in cultures derived from nasopharyngeal carcinoma and from the so-called "control patients" in the different age groups.

TABLE 13

FREQUENCY OF LYMPHOBLASTOID TRANSFORMATION IN CULTURES DERIVED FROM NASOPHARYNGEAL CANCER PATIENTS AND FROM CONTROLS, BY AGE GROUP

Age group	Nasopharyngeal carcinoma patients [a]		Control patients [a, b]	
	Males	Females	Males	Females
0-14	—	—	2/7	0/1
15-29	0/1	1/5	1/3	1/6
30-49 [c]	10/31	3/9	0/5	1/2
50 and over	4/20	1/3	1/3	1/1
Sub-total	14/42 (33 %)	5/17 (29 %)	4/18 (22 %)	3/10 (30 %)
Total	19/69 (27.5 %)		7/28 (25 %)	

[a] In each pair of figures, the first indicates the number of cultures showing lymphoblastoid transformation and the second the total number of cultures.
[b] The control group includes patients with ear, nose, and throat tumours (other than nasopharyngeal), inflamed tonsils, and clinically tumour-free nasopharynxes.
[c] This age group represents the high-risk group for nasopharyngeal carcinoma in male Chinese.

(*b*) *Electronmicroscopy*

Ultrastructural studies have been carried out on the biopsy specimens and the tissue cultures derived from them. The nuclear inclusions and presence of emperipolesis reported last year have been confirmed. The presence of a herpes-type virus in all permanent lines,

regardless of their origin, was established. Preliminary experiments on the most favourable conditions for viral synthesis have been initiated.

(*c*) *Immunological studies*

The technique to facilitate the antigenic analysis of tumours and the corresponding antibodies in the sera of patients and comparisons with the Henle and Klein tests has been developed further by Mr T. Greenland. It consists of using antibodies labelled with radioiodine. It is also hoped to develop an automatic test that could be used for large numbers of samples derived from field studies.

To assess the feasibility of detecting multiple but different antibody activities in each serum, the technique was extended so that each serum to be tested was paired with every other serum in the experiment in a checkerboard pattern. This method has proved very sensitive indeed. Minute differences in the reactivity of either antigen or antibody have been detected, and absolute titres of antibody activity—expressed as weight of gamma globulin in a given volume of serum—have been determined. The lack of certain antibodies in some of the sera has been demonstrated. Nevertheless, where they were present, these antibodies appeared to be directed towards tumoral antigens. Furthermore, not all the cell lines have the same antigen spectrum. It is hoped eventually to be able to demonstrate that several antigen/antibody systems are present in patients with nasopharyngeal tumours and to compare clinical findings with titres of antibody of specific activity for a single antigen.

Investigations using the same technique have been carried out on experimental models. These covered the lytic cycle of SV 40 virus on vervet monkey kidney cells, the reproductive and transforming cycle of the Rous sarcoma virus on either chick fibroblasts or on hamster cells, and the study of heterokaryons formed by Rous-transformed hamster cells with permissive chick cells. In the models, the sensitivity of the radioiodine technique also appeared to be satisfactorily high, since small cell samples and very low antibody concentrations were sufficient for accurate measurements.

2.4 *Further development of studies on the relationship between nasopharyngeal carcinoma and herpes-type virus* (in collaboration with the National Cancer Institute, National Institutes of Health, Bethesda, Md., USA)

Through its Special Cancer Virus Programme, the National Cancer Institute, US Public Health Service, is joining forces with the Agency to study the relationship between nasopharyngeal cancer and herpes-type virus in the field as well as in the laboratory. A proposal for a cost-sharing contract has been accepted.

The objectives of the proposed studies have been defined as follows:

(*a*) to obtain a sero-epidemiological pattern of herpes-type virus infection in human groups known to differ in their risk of nasopharyngeal carcinoma;

(*b*) to determine the positive conversion rate by direct measurement in selected groups followed for two years;

(*c*) to study the variations in serum titres over a two-year period;

(*d*) to study the immunological and biological properties of the herpes-type virus associated with nasopharyngeal carcinoma;

(*e*) to investigate the extent of the relationship between this virus and the Epstein-Barr virus associated with Burkitt's lymphoma;

(*f*) to study the immunological pattern of nasopharyngeal carcinoma patients after treatment and eventual recurrence;

(*g*) to investigate cell-bound immunity in nasopharyngeal carcinoma patients;

(*h*) to investigate, through tissue typing, the possible existence of a genetic marker associated with susceptibility to nasopharyngeal carcinoma.

A conference was convened in January 1970 to finalize plans for the collection of sera in Singapore, Hong Kong, and Lyon. Dr Hirayama, from the National Cancer Centre, Tokyo, reported on the work of the Japan/Taiwan co-operative study group which is investigating nasopharyngeal carcinoma in Taiwan. Plans were made to co-ordinate the two studies.

3. STUDIES ON BURKITT'S LYMPHOMA

A round-table conference was convened from 14 to 18 January 1970 to re-assess the situation of the African studies on Burkitt's lymphoma and to determine priorities. The participants were mostly epidemiologists and scientists with a sound knowledge of conditions in East Africa. The epidemiological situation in the West Nile district was reviewed, and a report was presented on the current health serological survey undertaken by the East African Virus Research Institute (Dr G. N. Kafuko) and the Department of Preventive Medicine, Makerere University (Dr R. H. Morrow). Complete serological results were not yet available on the first bleeding, but it was agreed that once the second bleeding of the same individuals had been carried out and the results analysed, it would be possible, by conducting a longitudinal study, to test the hypothesis that Epstein-Barr virus is an essential etiological factor in Burkitt's lymphoma. The participants estimated that a five-year follow-up of about 50 000 children in the West Nile district should yield enough cases of Burkitt's lymphoma to answer basic questions concerning the etiological relationship.

The second bleeding will be made in April/May 1970, and it was proposed to convene a working group in East Africa in September 1970 to consider whether the results obtained in the small-scale serological survey justify starting the large-scale longitudinal study.

IARC will keep in close touch with Dr Kafuko and Dr Morrow, and any request for help with the second bleeding will be given high priority by the Agency. In the meantime, it will prepare a detailed proposal for the long-term longitudinal study, so that, if a favourable decision is taken in September, it can be implemented as soon as funds become available.

4. CANCER OF THE GENITAL TRACT

Epidemiological data on the relationship between circumcision and a lower incidence of cancer of the penis and between an early sexual life and a higher incidence of cancer of the cervix suggest that oncogenic viruses may play a part in the development of these cancers.

4.1 *Cancer of the penis*

Dr R. Schmauz, IARC Research Assistant, continued to study the general pathology of tumours in Africa at Makerere College, Kampala, Uganda, under Professor M. S. R. Hutt, with special reference to cancer of the penis and pre-cancerous lesions. The geographical distribution of carcinoma of the penis in different tribes of Uganda where this tumour is very frequent has been studied (Fig. 4).

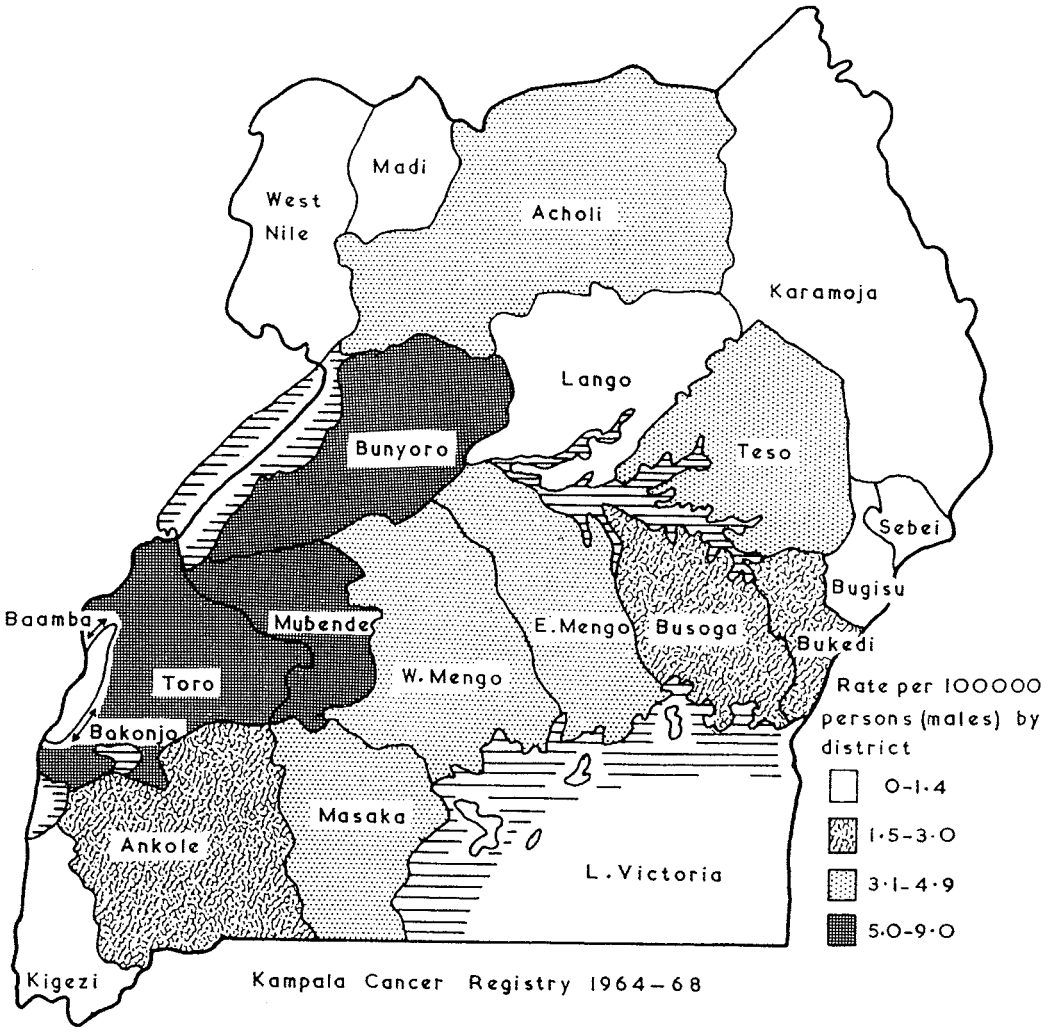

Fig. 4. Incidence of cancer of the penis (based on biopsies) in Uganda.

The incidence of the tumour varies considerably between the different tribes of the country, being higher in those that do not practise circumcision. However, other etiological factors, related more to the place of residence than to tribal origin, appear to be involved.

An attempt was made to correlate the frequency of carcinoma of the penis with specific benign tumours, such as papilloma and pearly penile papules; 700 males from various hospitals all over Uganda were examined for these papules and smegma accumulation and phimosis. No direct correlation was found between the incidence of the two latter conditions and the incidence of carcinoma of the penis. Pearly papules were not found in boys under the age of 10 and only occasionally in adults over 50. The appearance of these lesions seemed to coincide with the beginning of sexual activity in adolescence.

The histopathological and biological nature of these papules is under study, and further epidemiological studies are required to establish whether they bear any relation to the later development of carcinoma of the penis.

Tissue specimens and sera from 22 patients with carcinoma of the penis were sent from Mulago Hospital to Lyon, together with some foreskins and condylomata acuminata. Four long-term fibroblastic cultures were obtained from these biopsy specimens. Electron-microscopic investigation of this material is under way with the aim of finding evidence of viral infection.

4.2 *Cancer of the cervix* (Dr Nubia Muñoz)

Previous studies have shown an association between cancer of the cervix and herpes virus hominis type 2, but the nature of this association is unknown.

An *in vivo* experiment to study the role of this virus and hormonal imbalances on the induction of cervical carcinoma in mice has been started. The hormones were administered as subcutaneous pellets of a hormone-cholesterol mixture. The mice treated with the virus had previously been immunized with UV-inactivated herpes virus hominis type 2.

The viral infection of the cervix was achieved by introducing a cotton pellet soaked in a virus dilution into the vagina. Twelve groups of 20 BALB/c mice were treated with different combinations of hormones and viruses. Periodic vaginal smears were taken at first to check the level of viral infection, which disappeared after 2 weeks. Subsequently, they have been taken for the detection of early neoplastic changes. The experiment will continue for 12 months.

5. AVIAN TUMOUR VIRUSES

5.1 *International reference centre for avian tumour viruses* (Dr D. Simkovic)

During 1967, various investigators in the field of avian tumour viruses felt that the creation of an international reference centre for these viruses would be very bene-

ficial for the development of work in this field because of the great number of immunologically variant viruses involved. Dr R. J. C. Harris, Imperial Cancer Research Fund, London, suggested that IARC should be responsible for establishing the centre. This suggestion was discussed with different groups of investigators attending the VIth International Symposium on Comparative Leukaemia Research at Cherry Hill, N. J., USA, in September 1969, and the meeting of the European Tumour Virus Group in Bratislava, Czechoslovakia, in October 1969. Several valuable suggestions were made and both European and American laboratory workers agreed on the value of such a centre. The aim of the reference centre, which it is hoped to establish in 1970, will be to provide laboratories with reference prototype avian tumour viruses and corresponding antisera, and possibly also with genetically defined chick cells.

5.2 *Study of the recuperation of the Rous sarcoma virus in mammalian cells transformed by this agent* (in collaboration with Mr L. Gazzolo, Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon)

A number of Rous-transformed lines from hamsters, rats, and primates were studied by electronmicroscopy for the presence or absence of C-type virus particles. *In vitro* transformed lines lacked C-type particles, which were often found contaminating *in vivo* transformed cells.

An interesting finding in this study was the presence in the hamster-derived line (HS) of nucleocapsids associated with mitochondria (Fig. 5). This was associated with a high group-specific antigen content and with great difficulty in recuperating the Rous virus by cultivation. It appears that the presence of these intramitochondrial particles indicates a failure in the synthesis of the virus particles.

The ultrastructural study of the heterokaryons formed by X-irradiated transformed cells and permissive chicken cells has shown the presence of virus 4 days after fusion, but it could not be established whether this new virus was formed by the heterokaryons.

Using iodine-labelled antibodies, it was possible to follow the synthesis of group-specific antigen in chick fibroblasts infected by Rous sarcoma virus (Schmidt-Ruppin strain), in X-irradiated mammalian transformed cells, and in heterokaryons. The kinetics of group-specific antigen synthesis show two peaks in these three types of cells, and it seems that the first peak appears earlier in heterokaryons than in Rous sarcoma virus-infected chick fibroblasts.

6. CONSULTANTSHIP AT THE INSTITUT DE CANCEROLOGIE ET D'IMMUNOGENETIQUE, VILLEJUIF, FRANCE (Director: Professor G. Mathé)

During 1969, Dr de Thé has acted as consultant in electron microscopy at the above-mentioned institute and is collaborating with it in some of its programmes.

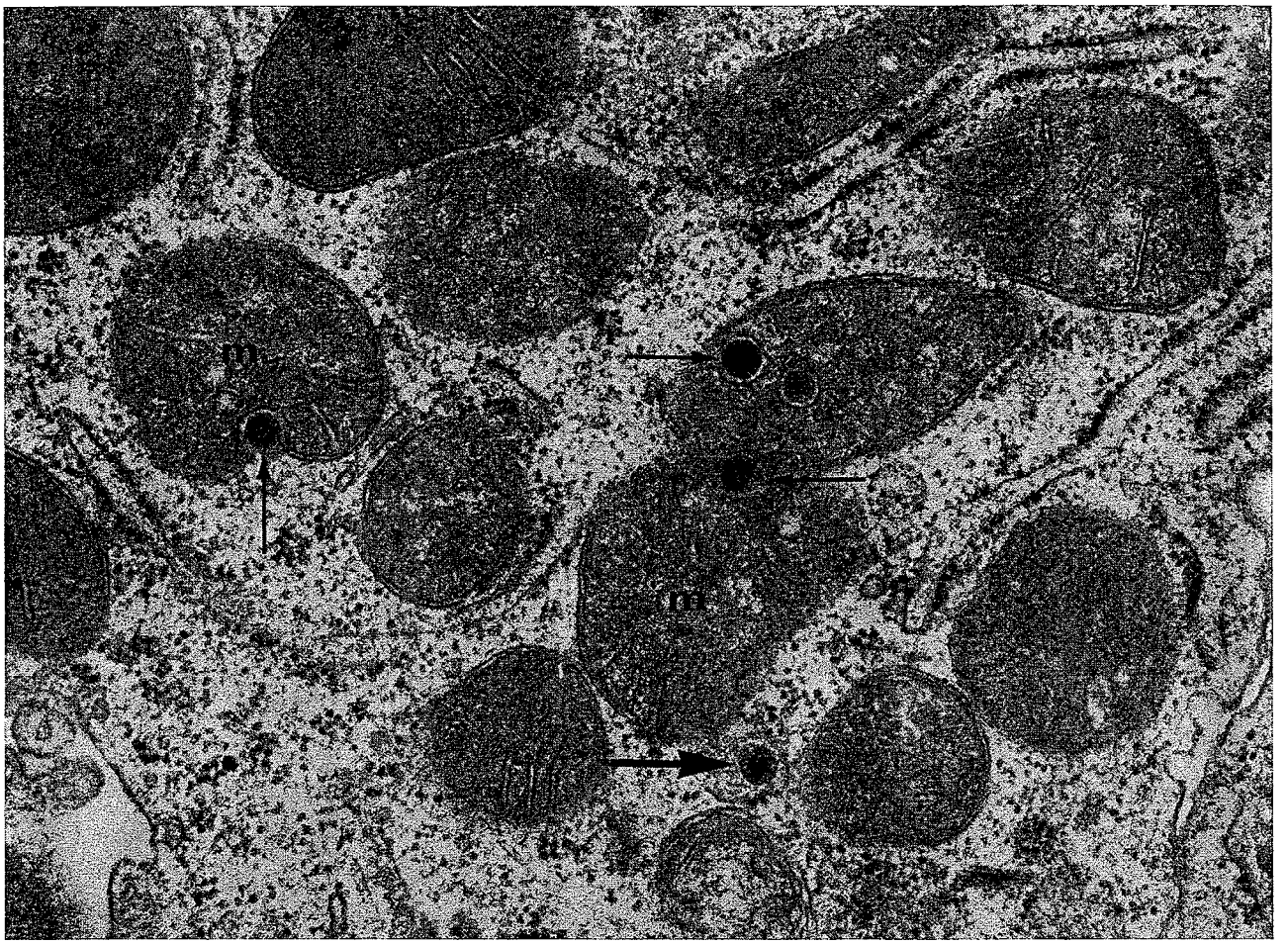

Fig. 5. Cytoplasm of a cell of the hamster-derived line showing *particles* (fine arrows) which appear to be *nucleocapsids* associated with mitochondria (m). The darker arrow indicates an *R-type particle* (often found in hamster tumour cells). × 40 000.

7. IARC TUMOUR TRANSPLANTATION REFERENCE CENTRE (Karolinska Institutet, Stockholm)

Principal investigator: Professor G. Klein (RA/67/003)[1]

The IARC Tumour Transplantation Reference Centre has maintained its original function—the provision of transplantable animal tumours preserved in the frozen state. In addition, the provision of human tumour tissues and of sera and normal tissues of tumour-bearing patients and controls has been continually increasing over the last three years.

The number of shipments during 1969 was 225, serving 62 investigators in 16 different countries. The shipments are made with no charge to the investigator concerned.

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

(*a*) *Provision of experimental tumour materials on a service basis*

The demand for this type of service has increasingly shifted in emphasis from the old lines of "transplantable tumours" to tumours that have arisen and are being propagated in highly inbred strains that are of known iso-antigenic constitution and/or carry other marker characteristics of interest. The old "non-specific" tumour lines are now mainly requested by investigators in developing countries.

(*b*) *Active assistance in the selection of suitable experimental tumour materials and, if mutually desirable, initiation of collaborative studies*

In many cases, at the request of investigators undertaking immunogenetic and immunopathological studies on tumour growth, the Centre has been able to assist in providing suitable materials. Sometimes this has meant that tumours have had to be produced or the necessary animal or virus stocks obtained. Projects in this category include: the provision of serum cells for antigenic typing of mouse leukaemias; the provision and characterization of immunosensitive and immunoresistant sublines selected from the same original neoplasm for studies on the role of immunosensitivity in influencing responsiveness to chemotherapy or radiotherapy; the provision of sera to trace serum allotype relationships between different inbred strains; the selection of chemically induced sarcomas, antigenic in genetically compatible hosts as well as being adapted to tissue culture, for studies of the action of sensitized lymphocytes on monolayer-grown target cells; the provision of suitable antigenic cell systems and typing sera for ultrastructural and biochemical studies on cell membrane associated transplantation and tumour-specific antigens; the provision of very weak antigenic sarcomas for studies on autoimmune reactions against tumours and ways of strengthening them; the provision of typing sera to identify possible H-2 antigen bearing cell membrane components incorporated into the capsid of the mammary tumour virus particle; the provision of antigenic tumours grown *in vivo* to study the fixation of complement components to the cell surface, as a means of tracing antigen-antibody reactions *in vivo*; the provision of strain specific and non-specific sublines derived from the same original tumour, for studies on the possible significance of certain biochemically characterized surface patterns in the ability of a tumour cell to overcome rejection reactions; the provision of spontaneous mammary carcinomas for the comparison of long-transplanted tumours having certain characteristic biochemical patterns with primary tumours in the autochthonous host; the provision of mouse tumours with known H-2 markers for cell fusion experiments to study antigenic expression in the hybrid cell product; the provision of tumours grown *in vivo* and carrying known tumour-specific antigens and of the corresponding tumour-specific antisera, for *in vivo* localization studies of radioiodine-labelled antibodies.

(*c*) *Provision of human tumour and serum material on request*

A large number of requests for human tumour and serum material have been received during the last two years. These have been met mainly thanks to the regular weekly shipments of viable biopsies and sera sent from Nairobi by Mr P. Clifford. Various investi-

gators have been provided with a considerable number of biopsies from Burkitt's tumours and from carcinomas of the nasopharynx, bone marrows, and peripheral white cell cultures and other tissue culture preparations from tumour patients or from African controls. It has also been possible to supply a large number of sera from African donors with or without malignant diseases. In addition, sera have been collected from cases of African glandular fever or infectious mononucleosis and distributed. New Burkitt's lymphoma lines have been established, characterized with regard to Epstein-Barr virus reactivity and cell membrane reactivity, and shipped on request. Non-African tumour materials, particularly from Swedish leukaemia and lymphoma cases, have also been supplied, though to a more limited extent.

(*d*) *Provision of human tumour materials to laboratories working on collaborative studies with the Centre*

Numerous collaborative studies are in progress. They include work on Burkitt's lymphoma in all its biological aspects, with special reference to its virological and immunological characteristics. In collaboration with IARC, studies are being made of the cellular and serum activity of nasopharyngeal cancer patients.

4. UNIT OF CHEMICAL CARCINOGENESIS

Staff: Dr L. Tomatis (Chief)
Dr V. Turusov
Dr P. Sizaret
Miss B. Witthoff
Mr R. Charles

Supporting staff: 5

1. INTRODUCTION

The unit of Chemical Carcinogenesis is responsible for studying the application of knowledge of chemical carcinogenesis to man, with special reference to the mechanisms involved. This involves a consideration of the practical and theoretical implications of the simultaneous action of several carcinogenic stimuli at low doses, since comparatively little is known about the possible significance of "total carcinogenic load".

(*a*) The unit has been concerned with the potential carcinogenic hazard presented by pesticides, notably DDT. The effects of DDT administered over several generations are being investigated in a large-scale international study.

(*b*) Increasing attention is being paid to the nitrosamines and to the effects of chemical carcinogens administered transplacentally.

(*c*) Steps have been taken towards the publication of a much needed standard reference text on the pathology of tumours in laboratory animals. A list of chemicals with generally recognized carcinogenic properties is in preparation.

(*d*) In collaboration with the unit of Epidemiology and Biostatistics and the Regional Centre, Nairobi, work is being continued on the serological aspects of primary liver cancer.

2. POTENTIAL CARCINOGENIC HAZARD OF PESTICIDES

The collaborative study on the potential carcinogenic hazard of the chlorinated hydrocarbon 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl) ethane (DDT) has been continued. Since

1968, two further reports on the occurrence of tumours in mice following the long term administration of DDT have appeared.[1,2]

The study initiated by the IARC consists of both laboratory and field projects.

2.1 *Laboratory studies*

Details of the methodology of the experiments are given in the report for 1968.[3]

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

Principal investigator: Dr V. Turusov

The original plan to investigate the effect of DDT given continuously for five consecutive generations was expanded to include two additional generations. As the investigation was largely based on the possibility of DDT having a cumulative effect over several generations, it seemed important to ascertain if this possible effect would disappear after the administration of DDT was suspended. The sixth generation will receive DDT only during intra-uterine life, via the mothers' milk, and until weaning, while the seventh generation will not receive DDT at all. The extension to two additional generations has been limited to the groups receiving levels of 2, 10, and 250 ppm respectively, to the untreated control, and to the group receiving urethane (0.001 %). The DDT concentration in animal feed is periodically controlled by the Government Chemist, London.

Fecundity and fertility did not appear to be affected by the DDT treatment. The neonatal weights were similar in controls and in the first three DDT-treated groups, but lower in the 250 ppm group. The average litter size was the same in all groups. Neonatal and overall mortality was higher in the group of mice receiving DDT at a dose level of 250 ppm as compared with the other DDT-treated groups and the untreated controls. The incidence of tumours in DDT-treated and untreated mice was similar in animals which died within one year of birth. At a later age, however, a higher incidence of hepatomas was observed in the DDT-treated mice. Preliminary observations carried out on the parent generation up to 78 weeks of age do not indicate a marked difference between DDT-treated and control groups in the number of tumour-bearing animals. However, the number of animals bearing more than one tumour was higher in the DDT-treated groups than in the control groups. This was due principally to the higher frequency of hepatomas in three of the treated groups. Moreover, the animals exposed to the highest dose of DDT had also a markedly higher incidence of lung tumours (see Table 14). A similar pattern seems to occur in the F_1 generation.

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[1] Tarjan, R. & Kemény, T. (1969) *Food Cosmet. Toxicol.*, 7, 215.

[2] Innes, J. R. M. et al. (1969) *J. nat. Cancer Inst.*, 42, 1101.

[3] International Agency for Research on Cancer (1969) *Annual report, 1968*, Lyon, p. 40.

TABLE 14

EXPERIMENTAL STUDY ON THE POTENTIAL CARCINOGENICITY OF DDT

Cumulative data on mortality and tumour incidence at 78 weeks from birth for the parent generation (males and females) of CF_1 mice receiving DDT at various concentrations

	Generation	Number of animals		Died		Tumour-bearing animals		Animals with more than one tumour		Number of tumours		Animals with						
												Lymphoma		Lung adenoma		Hepatoma		Other tumours
		At start	Effective number	No.	% [a]	No.	% [b]	No.	% [b]	Total	Average [c]	No.	% [b]	No.	% [b]	No.	% [b]	No.
Control	P	125	116	35	28.0	22	19.0	2	1.7	24	0.21	16	13.8	3	2.6	1	0.9	4
DDT-2 ppm	P	120	116	26	21.7	18	15.5	3	2.6	21	0.18	9	7.8	5	4.3	3	2.6	4
DDT-10 ppm	P	120	117	38	31.7	27	23.0	8	6.8	36	0.31	18	15.4	10	8.5	4	3.4	4
DDT-50 ppm	P	120	111	33	27.5	17	15.3	4	3.6	22	0.2	12	10.9	5	4.5	0	—	5
DDT-250 ppm	P	120	99	52	43.25	23	23.2	8	8.1	36	0.37	11	11.1	11[d]	11.1	12	12·1	2

[a] In relation to the number at start.
[b] In relation to the effective number (number alive at time of appearance of first tumours).
[c] Average number of tumours per animal (in relation to the effective number).
[d] The difference between this figure and the figure for lung adenomas in control animals is statistically significant ($\chi^2 = 5.7$, $p<0.025$).

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

Principal investigator: Dr B. Terracini

BALB/c mice are used, and DDT is administered at three dose levels: 2, 20, and 250 ppm. In addition to untreated controls, a positive control consisting of mice receiving a known chemical carcinogen, dimethylnitrosamine, has been established.

In spite of preventive measures, fighting was a major cause of death among males of all groups. In addition, several males and a few females in the 250 ppm group died with symptoms of acute intoxication by DDT. DDT treatment had no persistent effect on fecundity, fertility, average litter size, or neonatal mortality. A few tumours were observed in animals which died or were killed, both in the control and DDT-treated groups, but no difference between the various groups in the incidence of tumours was noted. Liver tumours and lung adenomas were frequently observed in mice receiving dimethylnitrosamine.

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

Principal investigator: Dr N. P. Napalkov

Outbred rats are used, and DDT is administered at three dose levels: 2, 10, and 50 ppm. The experiment is at present at the F_3 generation. So far, no differences have been found between the various groups in fecundity and fertility rates and average litter size. Neonatal mortality has been slightly higher in the 250 ppm group. No tumours have yet been observed in the rats which have died in the various groups. Enlargement of the thyroid was noted in some of the animals which died in the 10 ppm and 50 ppm groups.

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

Principal investigator: Professor L. M. Shabad

Mice of the inbred strain A are used, and DDT is administered at two dose levels: 10 and 50 ppm. The experiment aims at identifying early biological changes and preneoplastic lesions using organ cultures in an *in vitro* system.[1] Focal epithelial hyperplasia was observed in lungs explanted *in vitro* from fetuses pertaining to the 50 ppm group, while no such change was observed in lungs explanted *in vitro* from fetuses pertaining to the 10 ppm group. The mice appeared particularly sensitive to the toxic effects of DDT and few of those receiving DDT at a dose level of 50 ppm were suitable for long-term observation.

(*e*) *US Public Health Service Consumer Protection and Environmental Health Service, Atlanta, Ga., USA* (Mr W. Barthel)

The analysis of the DDT content of the animal fat tissues indicates a good correlation between levels of exposure and levels of storage. Mice appear to convert completely the

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[1] Shabad, L. M. (1968) *Z. Krebsforsch.*, **70**, 198.

technical DDT to which they are exposed, to pp'-DDT, pp'-DDE,[1] and pp'-DDD.[2] In the mice of the CF_1 strain used in Lyon, of the total pp'-DDT stored in the fat tissue, 3 %-9 % is DDE, 5 %-18 % is DDD, and 78 %-87 % is DDT. The results of this preliminary analysis indicate, therefore, a different DDT metabolic pattern and rate in man and in mice; op'-DDT and op'-DDE are always found in man, and DDE represents about 70 % of the total DDT.

(*f*) *Laboratoire d'Histologie et de Biologie tissulaire, Faculté des Sciences, Université de Lyon*

Principal investigator: Mr Pavans de Ceccaty

An investigation by electron microscope of liver cell lesions in the DDT-treated animals has been started. Dilation of the rough endoplasmic reticulum and vesiculation of the smooth endoplasmic reticulum were seen in the 2 ppm group. In the 10 ppm group, these were more evident and combined with the appearance of lipid droplets. In the 250 ppm group, there was a marked increase in the lipid vesicles and destruction of the mitochondria. Numerous lipid droplets and occasional myelinic figures were present in the liver cells of newborns of the fifth generations receiving DDT at a dose level of 10 ppm.

2.2 *Field studies*

Preliminary data show that there are strong individual variations in the storage levels of DDT in all countries considered. These levels appear to be higher in people from Israel than in people from Nigeria, Japan, or South Africa. In Israel, in the age group 6-20 years, the average DDT content in fat tissue was 16.49 in men and 13.55 in women; in Nigeria, it was 4.51 in men and 4.50 in women; in Japan, 4.54 in men and 4.56 in women; among Bantus, 5.20 in men and 4.69 in women; among Caucasian South Africans, 9.18 in men and 5.02 in women. These differences have not as yet been reflected in any observable changes in the cancer patterns of these populations.

The collection and analysis of samples are continuing and will be extended to include Argentina, Brazil, Uganda, and Singapore. 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 (who will cover also Nigeria, Uganda, South Africa, Argentina, and Brazil); Dr M. Rogoff, Medical Research Laboratories, Nairobi; and Dr A. Linsell, Head of the IARC Regional Centre, Nairobi. The chemical evaluation of the DDT content of human tissues obtained from Singapore and Japan is carried out by Mr W. Barthel at the US Public Health Service Consumer Protection and Environmental Health Service, Atlanta, Ga., USA, and tissues from other countries are evaluated by Professor M. Wassermann.

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

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

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

Principal investigator: Dr G. van Esch

An investigation of the possible carcinogenic effect of the long-term administration of lead arsenate was recently started. Lead arsenate is administered to rats at two different dose levels, either alone or in combination with low doses of the carcinogen dimethylnitrosamine.

3. EXPERIMENTAL CARCINOGENESIS WITH MULTIPLE CARCINOGENS: TRANSPLACENTAL AND PERINATAL CARCINOGENESIS (Dr V. Turusov)

The effect of exposure to multiple chemical carcinogens is being investigated in mice. Preliminary studies have been started using the carcinogens methylcholanthrene and diethylnitrosamine. At the dose levels used in the first series of experiments, the incidence of tumours following the combined administration of the two carcinogens during neonatal and adult life has so far not differed significantly from the incidence observed after the administration of only one of the two carcinogens. An increase in early mortality was seen, however, in mice exposed to methylcholanthrene during fetal life and treated at birth with diethylnitrosamine.

The effect of exposure to a chemical carcinogen during prenatal and early postnatal life is being investigated. Methylcholanthrene administered to pregnant mice during the second part of pregnancy resulted in a very high incidence of tumours in the descendants. A similar incidence of tumours was observed in the descendants of methylcholanthrene-treated pregnant mice fostered immediately after birth by untreated mothers. No effects were detected, however, in descendants of untreated mothers fostered immediately after birth by mothers treated with the same carcinogen in the second period of pregnancy.

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

Principal investigator: Professor H. Pacheco

Parallel with the above experiments, the amount of methylcholanthrene reaching the fetus after administration to pregnant mice has been determined. The mice were treated in the last days of pregnancy and killed 6 or 20 hours later. The fetuses were isolated, weighed, ground, and homogenized. After extraction in cold and warm benzene, the dry residue was separated by thin layer chromatography. The area containing methylcholanthrene was identified by its fluorescent spectrum under ultra-violet light, scraped off, redissolved in warm benzene, and then estimated by gas chromatography. A more intensive extraction of the residue showed that approximately 66 % of the carcinogen had been removed in the first extractions. A summary of the first series of results is given in Table 15.

TABLE 15

LEVELS OF METHYLCHOLANTHRENE IN ALL LITTERS 6 HOURS AND 20 HOURS FOLLOWING THE ADMINISTRATION OF 10 mg OF METHYLCHOLANTHRENE TO PREGNANT MICE

No. of litters analysed	Average weight of litters	Total quantity of MC	Levels of MC
	(g)	(ng per litter)	(ng/g fresh tissue)
After 6 hours: 8	7.98 (5.0-11.3) ±1.84	911 (590-1310) ±240	115 (73-148) ±23
After 20 hours: 8	4.04 (3.1-7.0) ±1.27	819 (375-1900) ±467	232 (83-620) ±169

In addition, the distribution of methylcholanthrene in various fetal organs has been evaluated 6 and 20 hours after its administration to pregnant mice. A summary of the results is given in Table 16. Further studies are being carried out using methylcholanthrene labelled with radiocarbon.

TABLE 16

DISTRIBUTION OF METHYLCHOLANTHRENE IN VARIOUS FETAL TISSUES 6 HOURS (6 LITTERS = 60 FETUSES) AND 20 HOURS (7 LITTERS = 80 FETUSES) FOLLOWING THE ADMINISTRATION OF 10 mg METHYLCHOLANTHRENE TO PREGNANT MICE

Tissue analysed	Weight of fresh tissue		Total quantity of MC		Level of MC	
	After 6 hours	After 20 hours	After 6 hours	After 20 hours	After 6 hours	After 20 hours
	(g)		(ng)		(ng/g fresh tissue)	
Lungs	1.71	1.70	820	590	480	345
Liver	3.26	4.00	1000	795	320	200
Heads with salivary glands	16.60	18.10	3200	1740	195	96
Rest of body	35.70	35.00	2400	3300	70	96

The results so far show that the amount of carcinogen entering the fetus is small and there is at present no correlation between its distribution in the tissues and tumour incidence.

4. TESTING FOR MARKERS INDICATIVE OF PREVIOUS EXPOSURE TO CARCINOGENS

Eppley Institute for Research in Cancer, University of Nebraska College of Medicine, Omaha, Nebr., USA (RA/67/004)

Principal investigator: Dr S. Mirvish

Individual urine specimens from 72 healthy adult males were analysed for the presence of purines. In addition, 24-hour urine specimens from 32 hospital patients, including some

with liver cirrhosis or various types of cancer, were analysed. The healthy individuals showed similar results for urinary adenine, 7-methylguanine, hypoxanthine, and xanthine. The differences observed for some of the minor methylated purines were probably due to artefacts. The hospital patients showed low values for hypoxanthine and xanthine excretion, while values for adenine and 7-methylguanine excretion appeared normal. A group of patients, including some with liver cirrhosis and primary liver cancer, had high excretion rates of 8-hydroxy-7-methylguanine, 1-methylhypoxanthine, and occasionally 1-methyladenine. Similar rates have already been reported in primary and secondary gout and leukaemia.

5. KINETICS OF NITROSATION OF SECONDARY AMINES

Principal investigator: Dr S. Mirvish

In view of the potential cancerogenic hazard of nitrosamines for man, the kinetics of nitrosation of a secondary amine has been investigated *in vitro*. The nitrosation of dimethylamine in buffer aqueous solutions has been studied with the aid of a tritium-labelled amine.[1] At pH 3.4 the rate of dimethylnitrosamine formation was proportional to the dimethylamine concentration and to the square of nitrite concentration, consistent with third-order kinetics of the reaction. The rate of formation was maximal at pH 3.4 and decreased to low levels above pH 5. The rate constants were used to estimate the amounts of dimethylnitrosamine which might be formed in the contents of the stomach after the ingestion of food containing various concentrations of dimethylamine and nitrite. It appeared that, following a 300 gm meal containing 40 mg of dimethylamine hydrochloride and 200 mg sodium nitrite per kg of food, about 3 μg of dimethylnitrosamine might be formed in the stomach.

6. RETICULO-ENDOTHELIAL STUDIES (Dr P. Sizaret)

Infections of mice infected with *Plasmodium berghei* have resulted in stimulation of the reticulo-endothelial system. A variety of parameters relative to these infections have been studied.

In an attempt to determine the influence of stimulation of the reticulo-endothelial system on the carcinogenic process, infected mice have been subjected to the chemical carcinogen urethan and the Rauscher oncogenic virus. No significant difference in mortality has been observed between the groups treated only with carcinogenic agents and those also infected with the parasite. The tumour incidence remains to be studied.

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[1] Mirvish, S. (1970) *J. nat. Cancer Inst.* (in press).

7. SEROLOGICAL STUDY ON PRIMARY LIVER CANCER (in collaboration with the unit of Epidemiology and Biostatistics—Dr P. Sizaret)

A meeting of all those collaborating in the serological study of primary liver cancer patients was held in Lyon in July 1969 to assess the previous year's progress. It was confirmed that the proportion of positive serological tests in liver cancer patients varied from 50 % to 80 % between different regions. On the other hand, the test was highly specific, false positives being practically unknown. It also showed excellent reproducibility in different laboratories.

Attempts to find any parallel between the macroscopic and microscopic aspects of a given tumour and its biochemical characteristics and serum positivity had not been successful. The level of α_1-fetoprotein found in the sera of primary liver cancer patients ranged between 5 and 5000 μg/ml and did not remain stable for any given individual. β-fetal proteins are also often identified in patient sera but, as these occur in a number of different diseases, they are of little interest.

The meeting agreed on a proposed classification, by species, of the fetal proteins having α-electrophoretic mobility (Table 17).

It was further recommended that an international reference centre be established for the study of cancer serology and that, with regard to α_1-fetoprotein, it should supply standard reagents to enable research workers to check their methods and also provide an international standard. The following investigators are collaborating in putting these proposals into effect:

Professor G. Abelev	Gamaleya Institute, Moscow
Dr P. Burtin	Institut de Recherches scientifiques sur le Cancer, Villejuif, France
Dr H. Goodman	Immunology Unit, WHO, Geneva, Switzerland
Professor R. Masseyeff	University of Nice, France
Professor Sankalé	University of Dakar
Dr L. L. Purves	South African Institute of Medical Research
Dr D. Rowe	International Reference Centre for Human Immunoglobulins, Lausanne, Switzerland
Dr J. Uriel	Institut de Recherches scientifiques sur le Cancer, Villejuif, France
Dr L. Leblanc	IARC, Dakar

TABLE 17

PROPOSED TERMINOLOGY FOR SERUM FETOPROTEINS WITH α-ELECTROPHORETIC MOBILITY [a]

Species	Suggested systematic name [b]	Suggested trivial name [c]	Previous designations [d]
Man	α_1-fetospecific serum protein	α-fetoprotein [e]	X-component (1) ESA-globulin (2) α_1-fetoprotein (3, 4, 5)
Monkey	α_1-fetospecific serum protein	α-fetoprotein [e]	α-fetoprotein (6)
Cow	α_1-fetospecific serum protein	fetuin	fetuin (7)
	α_2-fetospecific serum protein	α-fetoprotein [e]	α-fetoprotein (8)
Dog	α_3-fetospecific serum protein	α-fetoprotein [e]	α_3-embryospecific protein (9)
Rat	α_1-fetospecific serum protein	α-fetoprotein [e]	post-albumin (10) LA-protein (11) α-globulin (12) fetal α_1-globulin (13)
	α_2-fetospecific serum protein	α_M-fetoprotein	slow α_2-globulin (14, 19) abnormal serum component (15) α_2-glycoprotein (11, 16) α_2-macroglobulin (17) α_2-acute phase globulin (18)
Mouse	α_1-fetospecific serum protein	α-fetoprotein [e]	α_F-globulin (20)

[a] Recommendations aimed at establishing a uniform terminology, proposed by a meeting of research workers to discuss the evaluation of a serological test for the diagnosis of liver cancer, IARC, Lyon, France, 7-9 July 1969.

[b] Composite term expressing the electrophoretic mobility of the protein according to the species considered and its serum fetospecific character.

[c] Uniform terminology based on immunological cross-reactivity between species.

[d] The figures in parentheses refer to the list of sources below.

[e] The first α-protein to appear in mammalian sera during development, and the dominant serum protein in early embryonic life. It reappears in the adult serum in several situations, principally in patients with hepatocellular carcinoma.

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The meeting further recommended the planned distribution of sera collected for research purposes. A population survey has been designed to establish the prevalence of liver cancer in the Ivory Coast and, as part of the programme, it is planned to take blood samples from 20 000 adults three times a year over two years (see p. 26). These samples will be divided into five aliquots, one of which will be examined on the spot by the double immunodiffusion technique for α_1-fetoprotein. Another aliquot will be sent to the Gamaleya Institute, Moscow (Professor G. Abelev), where the more sensitive techniques of passive haemagglutination, autoradiography, and radio-immunology will be applied in the hope of achieving an early diagnosis of primary liver cancer and a greater percentage of positives. This survey may make it possible to find a correlation between the incidence of primary liver cancer and certain factors such as race, age, environment, and diet.

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

The unit has agreed to prepare a series of monographs on the pathology of tumours in the three species most commonly used in cancer research—the mouse, the rat, and the Syrian hamster. The aim is to promote uniformity in the interpretation by different laboratories of the results obtained in research and carcinogenicity testing with these experimental animals.

An *ad hoc* working party of several pathologists appointed by the Agency considered standards for the preparation of the monographs and established an Editorial Board, composed of Dr F. C. Chesterman, Dr G. Della Porta, Dr C. F. Hollander, Professor U. Möhr, Professor L. M. Shabad, Dr M. F. Stanton, and Dr V. Turusov (Chief Editor/Co-ordinator). The names of acknowledged experts who might contribute different chapters were put forward. The manuscripts will be reviewed by an Editorial Committee to ensure consistency of form and content and to prevent duplication. Each volume will deal with the tumours of one species and will be divided into chapters on the basis of the organs affected. Emphasis will be placed on the histological structure of naturally occurring and experimentally induced tumours and their classification. Basic information on methods of tumour induction and data on comparative oncology will also be given. The classification proposed should provide a basis for the coding of experimental tumours.

9. ESTABLISHMENT OF A LIST OF CHEMICAL CARCINOGENS

On the recommendation of a working group convened in Lyon on 27 November 1969, the IARC has decided to sponsor the publication of a list of chemicals universally agreed to be carcinogenic in man or in experimental animals. It is envisaged that a second list will be prepared including compounds that need additional testing.

10. IARC INTERNATIONAL REFERENCE CENTRE FOR THE PROVISION OF TUMOUR-BEARING ANIMALS, NETHERLANDS CANCER INSTITUTE, AMSTERDAM (RA/67/019)

Principal investigator: Professor O. Mühlbock

In 1969, the Centre provided several thousand tumour-bearing and healthy mice and several hundred healthy rats to institutes in various countries. In addition, the Director and staff of the Reference Centre collaborated with the unit of Research Training and Liaison to organize an international course on techniques with experimental animals in cancer research (see p. 64).

5. UNIT OF RESEARCH TRAINING AND LIAISON

Staff: Dr W. DAVIS (Chief)
Mrs S. RUBIN

Supporting staff: 2

1. INTRODUCTION

The work of the unit has continued satisfactorily. The Fellowships Selection Committee met in Lyon in October 1969 to review a total of 102 applications. The five non-Agency members were:

Professor W. U. Gardner (Endocrinology) [1]
Dr N. P. Napalkov (Experimental carcinogenesis)
Professor N. F. Stanley (Microbiology)
Professor U. Veronesi (Clinical oncology)
Professor K. Munk (Virology)

The meeting marked the end of service on the Committee for both Professor Gardner and Dr Napalkov, who had been members since the start of the programme at the end of 1966. Professor Gardner is President-elect of UICC and will assume the office of President at the Tenth International Cancer Congress in Houston, Tex., USA, in 1970. The Director and the Fellowships Selection Committee recorded their appreciation of the valuable guidance that Professor Gardner and Dr Napalkov had given to the programme during its formative years.

2. TRAVEL FELLOWSHIPS

Reports from Fellows confirm that, for senior scientists, the Travel Fellowships programme meets a real need.

Eighty-nine applications for Travel Fellowships were received during the year, and 41 awards were made. Two of the successful candidates later declined their awards, having received funds from other sources.

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[1] Professor Gardner has also provided liaison with the American Cancer Society Eleanor Roosevelt International Cancer Fellowships programme administrated by the UICC.

During the first half of the year, 40 applications were received. These were reviewed with the Fellowships Selection Committee by correspondence, and fellowships were awarded to 21 of the applicants. Four grants for additional travel were made to scientists who had participated in the IARC course in Amsterdam, Netherlands (see below).

By the time that the Fellowships Selection Committee met in October 1969, 49 more applications had been received since the last review in June. Voting on 21 of these was postponed until the first selection in 1970, and, of the remaining 28 applications, 17 were successful. Travel Fellowships were also awarded to three applicants who were considered too senior for the Research Training Fellowships they had applied for.

3. RESEARCH TRAINING FELLOWSHIPS

The number of applications for Research Training Fellowships in 1969 was 65 compared with 68 in 1968; 23 applicants were successful.

The Fellowships Selection Committee was most favourably impressed by the quality of the applicants, but was concerned about the uneven distribution of the scientific disciplines represented, no less than 10 of the 65 applicants being molecular biologists, while 5 were biochemists.

Once the Agency is established in its own laboratories and equipped and able to train young scientists in its current programmes of cancer epidemiology, environmental biology, and chemistry of carcinogens, it is hoped that the influence of these programmes will be reflected in the research projects proposed by applicants for fellowships.

During 1969, 22 Fellows completed their fellowship work, but only 14 of them have returned to their home institutions so far. Five are continuing their training with support from other funds. One Fellow, after completing two years' research training in cell biology and in epidemiology, is, with the consent of the director of her home institute, now working as a Research Assistant in the Agency's biological carcinogenesis programme.

The scientific disciplines covered by both the Travel and Research Training Fellowships are listed in Table 18. Table 19 shows the number of fellowships of both kinds awarded from 1966 to 1969 and the comparative costs.

Titles of publications by Fellows are given at the end of Annex 7.

4. TECHNIQUES WITH EXPERIMENTAL ANIMALS IN CANCER RESEARCH

A most successful course on techniques with experimental animals in cancer research was held in collaboration with the IARC International Centre for the Provision of Tumour-Bearing Animals in The Netherlands Cancer Institute, Amsterdam, from 12 to 23 May 1969 (see Fig. 6). The course was organized by Professor O. Mühlbock, Director of the Centre, assisted by two of his staff, Dr L. M. Boot and Dr G. Röpcke.

TABLE 18

DISTRIBUTION OF FELLOWSHIPS BY SCIENTIFIC DISCIPLINE, 1969

Research Training Fellowships		Travel Fellowships	
Biochemistry	4	Biochemistry	1
Biomathematics	1	Cell biology	13
Cell biology	4	Clinical	7
Clinical	2	Electronmicroscopy	1
Cytochemistry	1	Epidemiology	1
Epidemiology	2	Experimental carcinogenesis	6
Experimental carcinogenesis	2	Experimental chemotherapy	1
Molecular biology	4	Genetics	1
Virology	3	Immunology	4
		Molecular biology	2
		Virology	2

TABLE 19

APPLICATIONS RECEIVED, FELLOWSHIPS AWARDED AND TAKEN UP, AND COSTS, 1966-69

Research Training Fellowships				
	1966	1967	1968	1969
Applications received	41	51	68	65
Fellowships awarded	22	27	25	23
Fellowships taken up	20	27	24	—
Cost	$209 436	$290 672	$186 129	$180 348
Average cost per year per fellowship	$ 7 480	$ 8 074	$ 7 755	$ 7 841
Travel Fellowships				
	1966	1967	1968	1969
Applications received	32	73	109	81
Fellowships awarded	16	40	48	39
Fellowships taken up	16	37	48	31
Cost	$ 43 570	$ 63 760	$ 93 068	$ 83 589
Average cost per year per fellowship	$ 2 723	$ 1 723	$ 1 938	$ 2 143

The majority of the lecturers were from universities and research institutes in the Netherlands, but seven of them came from overseas.

There were 28 participants from 17 different countries. An unexpectedly high number of applications was received from the Scandinavian countries, as the result of an announce-

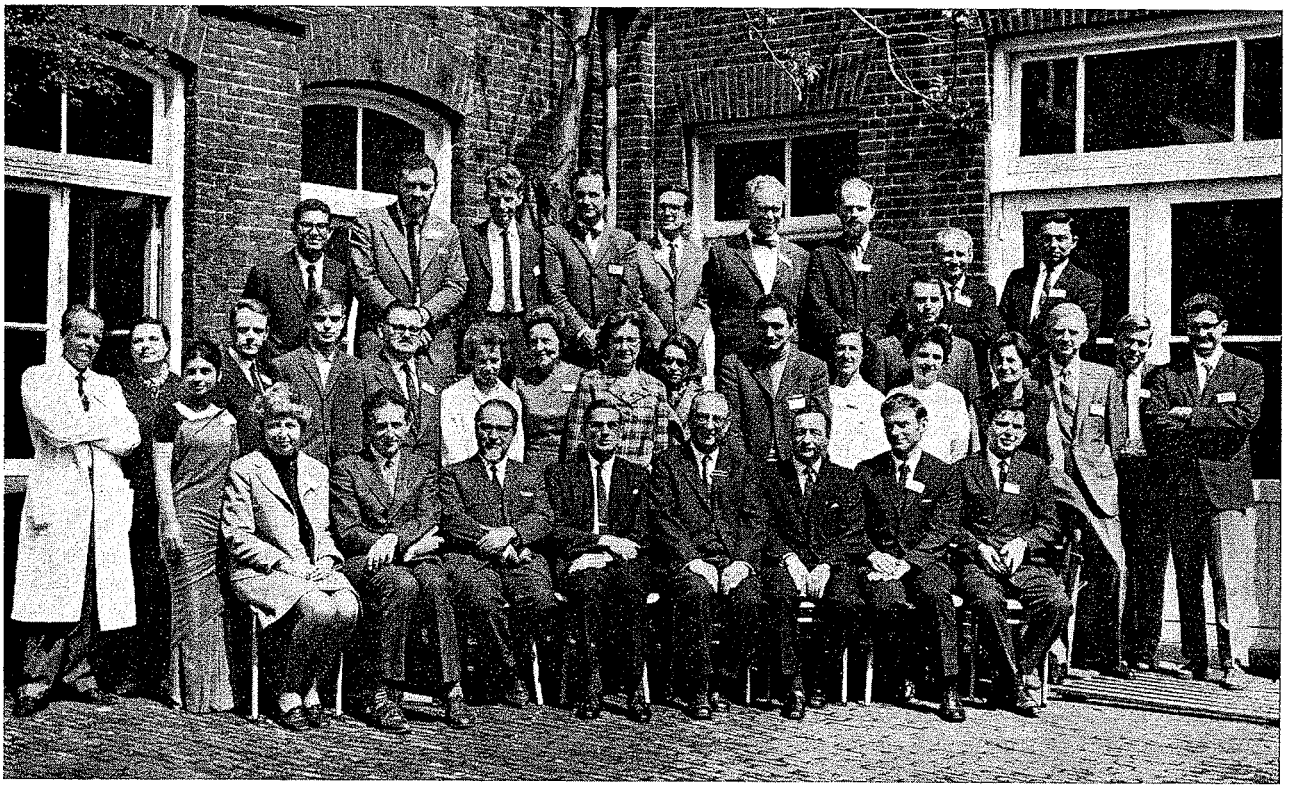

Fig. 6. Participants and lecturers at the IARC course on techniques with experimental animals in cancer research, held at the Netherlands Cancer Institute, Amsterdam, in May 1969.

ment of the course made at a seminar in Sweden earlier in the year. Seven of these applications were successful, and the Scandinavian participants made a noteworthy contribution to the course.

The IARC and all the participants are extremely grateful to the staff of the Netherlands Cancer Institute for their efficient organization of the course and for their kind hospitality. The Agency also expresses its gratitude to the Director and Staff of the International Centre of the Royal Tropical Institute, where the participants stayed while in Amsterdam.

It is planned to publish the lectures as an IARC monograph.

5. CELL PROLIFERATION KINETICS: COLLABORATION WITH UICC

In March 1969, a course on cell proliferation kinetics was organized by the International Union against Cancer (UICC) in Tübingen, Federal Republic of Germany. The IARC was approached by the Executive Director of UICC for assistance in financing some of the participants. The Agency was glad to collaborate with the International Union in this way and provided fellowships to enable four scientists to attend the course. It is hoped that, in the future, specialist courses of this kind will be organized jointly by the IARC and the UICC.

6. COURSE ON EPIDEMIOLOGICAL TECHNIQUES FOR FRENCH-SPEAKING STUDENTS

A course for French-speaking students on the use of epidemiological techniques in cancer research is being held jointly with the Centre d'Enseignement de la Statistique appliquée à la Médecine (Director, Professor D. Schwartz) at Lyon, from 2 to 14 March 1970.

7. EPIDEMIOLOGY AND REGISTRATION OF CANCER

The first regional course on the epidemiology and registration of cancer will take place in 1971. Preliminary discussions have been held with the IARC Regional Centre, Singapore (Head, Professor K. Shanmugaratnam), and with the International Epidemiology Association (Secretary, Professor Roy Acheson), which are prepared to plan and co-ordinate the teaching.

8. CO-ORDINATING COMMITTEE FOR HUMAN TUMOUR INVESTIGATION

Dr Davis has continued to serve as Secretary to the Co-ordinating Committee for Human Tumour Investigation. In April 1969, the Third International Symposium organized by the Committee in conjunction with the Spanish Association against Cancer (AECC) took place in Madrid.

The Fourth Symposium is now at the programme-planning stage and will be held in Heidelberg, Federal Republic of Germany, in 1971, with the co-operation of the staff of the Deutscher Krebsforschung Zentrum.

6. UNIT OF ADMINISTRATION AND FINANCE

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

Supporting staff: 9

1. INTRODUCTION

The unit is responsible for all the legal, budgetary, financial, personnel, language, supply, and office and conference services, and for the administration of the Agency Headquarters. Above all, it is responsible for providing all the support necessary for the smooth and effective working of the scientific programmes. The unit is also administratively responsible for the library.

It maintains liaison with the French Government and the municipal authorities of Lyon, especially on legal questions. Included within the unit are documents services, travel services, building services, the registry, and the drivers and messengers serving the main Headquarters building and the other temporary laboratories and offices.

The unit is directly responsible for the administrative preparation and running of meetings of the Governing and Scientific Councils. It is also responsible, subject to the overall authority of the Building Committee (Chairman, Dr W. Davis), for all questions relating to the construction of the Agency's permanent headquarters and of the temporary prefabricated building.

2. TEMPORARY ACCOMMODATION

The Governing Council, at its seventh session, approved the construction of a prefabricated building, and a contract for the work was signed in December. The building will ease space problems in the Agency by providing additional laboratory space and some offices, so that some expansion will be possible before the permanent building is completed. The temporary building, on two floors, will provide approximately 600 m^2 of working space, in which will be installed a biochemistry laboratory (unit of Chemical Carcinogenesis), a chemistry laboratory (unit of Environmental Carcinogenesis,) an immunology and histology laboratory, and animal rooms. The unit of Biological Carcinogenesis will also have its office in this building, which is expected to be ready for occupation by 30 June 1970.

3. PERMANENT ACCOMMODATION

The construction of the reinforced concrete structure of the 14-storey tower block which will house the Agency was started in July 1969 (Fig. 7). The concrete framework will be completed in July 1970.

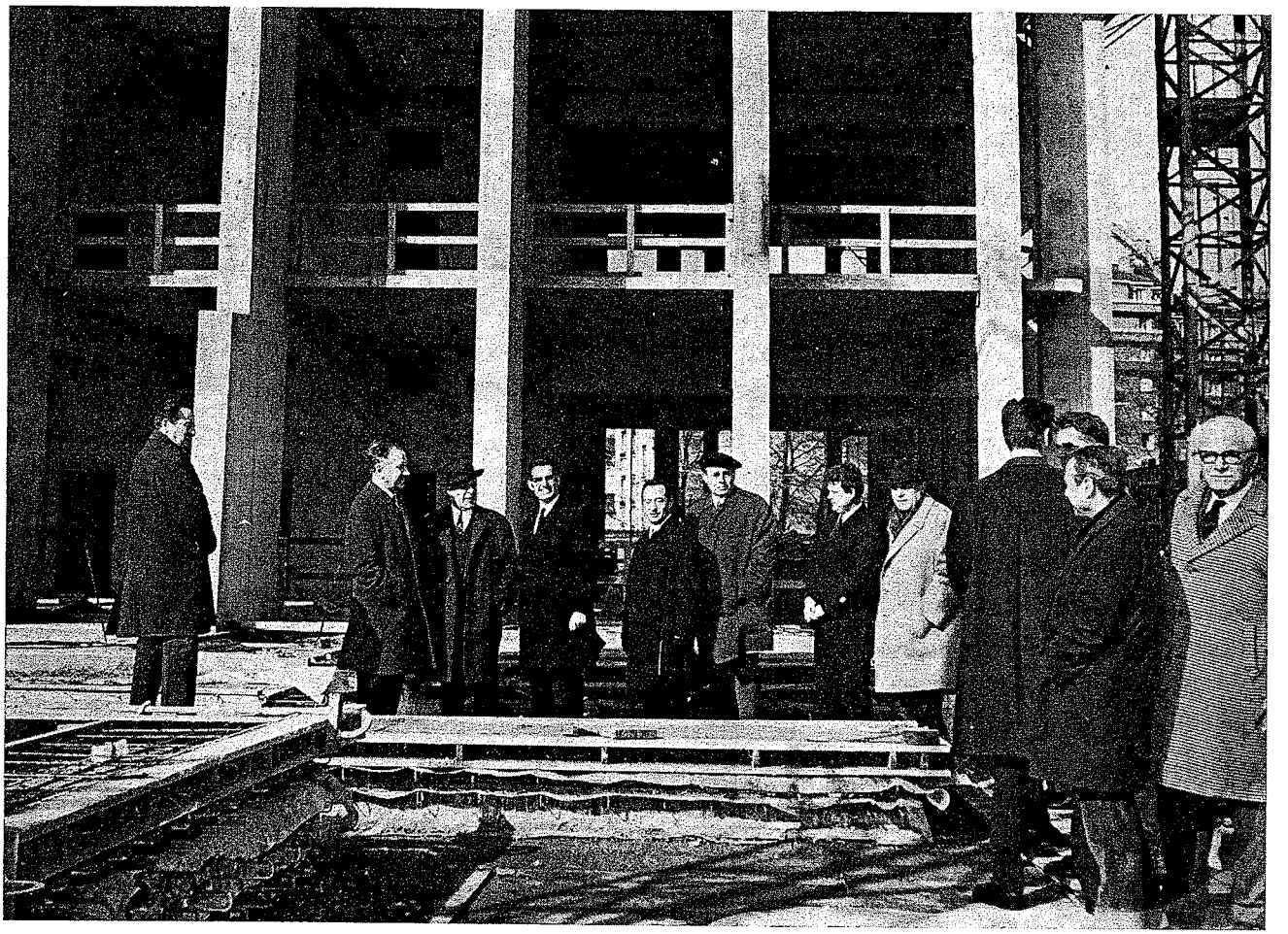

Fig. 7. Dr R. J. H. Kruisinga, Chairman of the IARC Governing Council, on a visit to the site of the Agency's new building in Lyon. Dr Kruisinga is second from the left and Mr L. Pradel, Mayor of Lyon, is third from the left.

At the beginning of the year, as a result of consultations between the architects and the French authorities in Paris, the existing plans were modified. The building module was reduced from 90 cm to 80 cm which involved a corresponding reduction in the size of the building. At the same time the central core was strengthened and increased in size to comply with new fire regulations for tall buildings.

The consequent reduction in the size of the laboratories, animal areas, conference room, and cafeteria floor required a revision of the arrangement of the internal partitions to permit more efficient utilization of the reduced space.

The whole building will now be air-conditioned—the laboratories and animal floor and the restaurant by a double-duct system, the offices and other areas by ejecto-convectors.

The Governing Council Building Committee met in May and October 1969 and visited the site.

4. TELECONFERENCES

The first telephone conference was carried out successfully between Omaha, Lyon, and London on 2 December 1969. The experiment was repeated between Omaha, Bethesda, London, and Lyon on 20 January 1970.

5. LIBRARY

Mr Cummins took up his duties in April 1969. Since that time, a complete reorganization of the IARC library has been undertaken.

New acquisition procedures have been negotiated with the Librarian at WHO Headquarters; periodical and annual subscription orders have been computerized through agents in Amsterdam; a new system of circulating periodicals within the Agency has been initiated; and new photocopy policies have been adopted. These measures are greatly accelerating the acquisition of the materials required for the Agency's research programmes.

Some 1750 bound journals and 1500 monographs form the nucleus of a research collection. It is anticipated that journal subscriptions will eventually reach 200 per year; the acquisition of monographs will remain constant at 250-330 a year.

The classification scheme of the US National Library of Medicine has been adopted, and an author, title, and subject catalogue is being prepared.

6. PERSONNEL

During 1969 three professional staff were recruited, while six more were selected for recruitment in January 1970. Ten general service staff were recruited. One trainee appointment was made. Two consultants were engaged for three months each. Many temporary advisers were appointed.

The Chief of the unit of Biostatistics resigned from the Agency to take a Chair at Bristol University.

Five general service category staff left the Agency during 1969.

It was found necessary to have a nucleus of temporary staff available to help out at peak times, to act as holiday reliefs, and to be trained to take over senior secretarial positions in case of illness.

Nine general service staff-members sat for the United Nations language examination in English, and eight were successful. One of the Agency secretaries was first out of all entries and another tied for second place. Five staff-members sat for the United Nations language examination in French, and all five passed.

7. OFFICE EQUIPMENT

The equipment purchased for the microform installation has now been delivered and a start has been made in using it. It is hoped that, during 1970, it will be in full operation and that virtually all storage of documents will be on microform.

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 : 8

1. INTRODUCTION

A fundamental question raised when the regional centres of the Agency were established was whether they should be concerned solely with local problems or with specific programmes involving a number of geographical areas. During the last year, the Centre in Nairobi has adopted the second approach, having taken over the major portion of the Agency's programme on liver cancer and extended its sphere of interest beyond the African Region. For example, the project on oesophageal cancer in cattle, which would certainly not have been developed if the Centre had not been located in Kenya, may in the future involve workers outside Africa.

The Centre's immediate programme requires considerable support in the chemical field. It is fortunate that the Chemistry Department of the Nairobi University College, the research organizations of the East African Community, the Tropical Products Institute, London, and the WHO specialist services in Kenya are equipped and prepared to work in close co-operation with the Agency's staff in Nairobi.

2. CANCER REGISTRATION IN EAST AND CENTRAL AFRICA

Co-operating registries: Kenyatta Hospital (Kenya Cancer Research Fund—RC4/0006/N1): Dr M. Rogoff

Muhimbili Hospital (Ministry of Health and Housing, Tanzania—RA/68/005): Dr R. Mitchell

Queen Elizabeth Hospital (Ministry of Health, Malawi—RA/68/003): Dr J. A. A. Borgstein

Central Hospital, Kitwe, Zambia

Central Hospital, Lusaka, Zambia

Central Registry, Sudan (Ministry of Health, Sudan—RA/69/004): Professor A. M. El Hassan and Dr E. H. Daoud

A standardized method of reporting is being used in all six cancer registries, as well as in the Uganda Registry, which at present is supported by the British Empire Cancer Campaign. In addition, current data on clinically diagnosed up-country cases from the Medical Research Council of Great Britain's hospital cancer survey (under Mr D. Burkitt, F.R.C.S.) are being supplied to the Regional Centre and to the national registries. Complete data will, therefore, be available at the national level, both for detailed tribal and geographical studies, and at the Regional Centre for an overall study of cancer patterns in East and Central Africa. The Regional Centre project was designed to obtain cancer patterns based on two years' registration preceded by a pilot period of approximately six months. Details of cases of cancer, however diagnosed, including home and hospital addresses and tribal data, have been requested. The study will be completed in 1970 for Kenya, Tanzania, Malawi, and Zambia. The Sudan Registry has only just started but, apart from its contribution to the overall study of cancer patterns, it hopes to undertake an incidence rate study in the city of Omdurman which is well served by diagnostic and treatment facilities for cancer. The Regional Centre sponsored a visit by Dr E. H. Daoud of Khartoum to Kenya, Uganda, and Tanzania, to enable him to review the work of the registries there.

A preliminary evaluation of data from the principal hospitals in Kenya, Tanzania, Malawi, and Zambia has been completed. Most cancer patterns previously put forward by clinicians were based on hospital material, and earlier observations can now be compared with findings based on country-wide reporting.

If the common cancers in the Kenyatta Central Hospital and in the Kenya Registry are ranked, the patterns are similar; this shows the practical value of elementary registration methods in cancer epidemiology in Africa. The more precise registration afforded by the current project will be most useful, however, in providing detailed tribal and geographical background material for specific etiological investigations. The data indicate that cancer of the bronchus is higher in Kitwe, which is a mining area. Bladder cancer is somewhat more common in Tanzania, Malawi, and Zambia; so too is schistosomiasis. Relatively few Burkitt's tumours are reported from Malawi, Tanzania, and Zambia, whereas they are common in Kenya.

3. LIVER CANCER PROGRAMME

3.1 *Aflatoxin exposure study in Kenya*

The collection of samples was completed by December 1969, and the field staff have been withdrawn. In all, 2432 dietary specimens and 304 samples of locally brewed beer have been processed. Work in the laboratory is now concentrated on the checking of positive samples found on thin-layer chromatography, the preparation of derivatives of positive

samples for confirmation, and the more precise assessment of levels of aflatoxins in these samples. The general levels of aflatoxin found in diets from the Murang'a area are similar to those given in the 1968 report. Analysis has shown that the frequency of positive samples and the levels of contamination agree with the predictions in a preliminary study of dietary habits, crop husbandry, and possible microclimates to which stored cereals could be exposed, i.e., aflatoxin contamination is higher and more frequent in the hotter, drier, low altitude areas of the Murang'a district.

The field collections have been organized so that not only can levels in the three areas differing in climate and storage hazards be compared but the findings can be related to administrative districts, thus providing an alternative check on the relationship between the incidence of liver cancer and aflatoxin exposure within the Murang'a area, especially if the data on cancer incidence can be refined.

It was previously considered that the district could only be treated as a whole, for comparisons with other areas. An analysis of the Murang'a data suggests a significant relationship between positive samples and the incidence of liver cancer. However, numbers are small and registration is known to be incomplete. It is proposed to continue cancer registration in Murang'a for some years by appointing a field cancer registrar, who will be responsible for registration and follow-up in hospitals and dispensaries. The Ministry of Health of Kenya has already agreed to this.

In addition, the α_1-fetoprotein serological test can now be performed locally, permitting positive diagnoses of cases to be made without histological confirmation (often so difficult to arrange in small up-country hospitals).

The suggestion that aflatoxin ingestion might be responsible for a high liver cancer rate was based on the results of market sampling of foodstuffs and sampling of export products, mainly peanuts. The general low frequency of aflatoxin contamination in Murang'a was expected, as peanuts are not part of the diet, but, nevertheless, it is thought that a very clear distinction must be made between market sampling, the sampling of household stores, and "plate" sampling. Many factors may influence the levels of the plate sample, which is obviously of most interest in the present context, and the housewife's selection of cereals during cooking, certainly in Murang'a, is important. A loss of aflatoxin in African cooking would appear to be unlikely, as sufficiently high pH values will not be attained. However, this factor will be further investigated in Murang'a; a storage expert from the Tropical Products Institute, London, with considerable experience of African farming, will act as a consultant in this connexion. Samples are being collected from areas in East Africa, where storage studies have shown aflatoxin contamination to be common, and also from areas of peanut consumption. If the aflatoxin levels in these areas are found to be high, the possibility of starting cancer registration there will be considered.

3.2 *Future aflatoxin field studies*

The examination of food samples for aflatoxin has been greatly facilitated by the development in the Regional Centre of a method whereby a food sample can be dried and trans-

ported without loss of aflatoxin. It is therefore feasible for the Regional Centre to consider participating in the liver cancer survey in the Ivory Coast (p. 26), and preliminary studies have been made. In addition, Gambia, India, and Brazil have been visited to assess the possibilities of setting up comparable studies there.

3.3 *The α_1-fetoprotein test*

Following the IARC meeting in Lyon in July 1969 (p. 59), the serology test for α_1-fetoprotein was set up in the Physiology Department of University College, Nairobi, in co-operation with the unit of Chemical Carcinogenesis. Owing to lack of staff, the test is available only to physicians in the Murang'a area, to the liver disease study group in the Kenyatta National Hospital, Nairobi, and for experimental work on baboons (see below).

An IARC Special Award has been made to a biochemist at Makerere University, Kampala, Uganda, to enable him to spend three weeks in the laboratory of Professor G. Abelev, Gamaleya Institute, Moscow, and ten days at the Agency in Lyon. He will study the application of the very sensitive technique of immunofluorescence to the detection of α_1-fetoprotein and will subsequently be able to co-operate in the Regional Centre study.

3.4 *Aflatoxin and trout in Kenya*

In 1969, an outbreak of hepatoma in trout was reported by local hatcheries and fishermen. An investigation indicated that approximately 5 % of the stock had macroscopic tumours. This was interesting since it was stated that peanut meal was not included in the diet. Pellet feeds in the factory and in hatchery stores were analysed. Aflatoxin was found in some stored foodstuffs which were, in fact, found to contain peanut meal additives. The Ministry of Agriculture has been advised that another protein source should be sought and that stores should be inspected frequently to avoid secondary mould contamination.

3.5 *Possible role of aflatoxin in* febra negra *of the Amazon*

A visit, in which a representative from the Tropical Products Institute, London, took part, was made to the Belem area of Brazil. The study of *febra negra* and its relation to mycotoxin ingestion has been taken over by the Brazilian Government and staff from the Armed Forces Institute of Pathology of the USA, with a grant from the Rockefeller Foundation.

3.6 *Experimental studies with baboons and monkeys*

The feeding of aflatoxin to baboons and vervet monkeys has continued, and a number of animals that have received amounts close to the lethal dose are still under observation. In co-operation with the Wellcome Trust, the sera of all baboons on a diet deficient in pyridoxine and riboflavin were repeatedly tested for α_1-fetoprotein in Nairobi and at the IARC

in Lyon. Four of the eight pyridoxine-deficient baboons gave a positive test, whereas the riboflavin-deprived animals and controls were negative. Positivity did not depend on the length or severity of the deficiency. One of the positive cases was seen at post-mortem and a "tumour" of the liver demonstrated.[1] The histology of this liver specimen has been variously interpreted, but if the serological evidence can be accepted—and this was the feeling of the meeting in Lyon in July 1969—, then liver tumours have been produced in baboons exposed to a dietary pyridoxine deficiency. On the other hand, if the positive α_1-fetoprotein test is not inevitably associated with cancer, a positive result must be due to some other biochemical lesion. Further work is continuing in Nairobi. Professor G. Abelev (Gamaleya Institute, Moscow) has been sent all sera from the baboons for testing by more sensitive techniques.

3.7 *Liver disease study — Kenyatta National Hospital, Nairobi*

A long-term follow-up of all cases of liver disease seen by the Department of Medicine and Surgery in the Kenyatta National Hospital, Nairobi, has been undertaken by the staff of University College, Nairobi. Over 500 patients are included in the study, which will be restricted to the following diseases: hepatitis, cirrhosis with histological confirmation, liver cancer with histological confirmation, and portal hypertension.

Tests for the Australian antigens or the SH antigen will be used to assess the pattern of hepatitis antigens in Nairobi. Patients with positive α_1-fetoprotein tests will be sought in the hepatitis and cirrhosis groups, in which the cancer risk is possibly high, and the proportion of histologically proven cases of liver cancer in Nairobi with a positive α_1-fetoprotein test will be studied. Differences between the percentages in the USA and the United Kingdom, on the one hand, and Africa, on the other, of liver cancer cases showing a positive serological test have been demonstrated, and this may have etiological significance.

3.8 *Geographical study of cirrhosis*

Five centres taking part in the International Liver Study have provided fifty consecutive cirrhosis specimens, and further material will be obtained from African and Far Eastern sources. This material will be examined in Nairobi to see if the morphology of cirrhosis varies between areas of high and low liver cancer incidence.

4. OESOPHAGEAL CANCER IN CATTLE

A high incidence of oesophageal or rumenal cancer in the Enesempolai valley of the Narok district of Kenya was reported over ten years ago by Dr Plowright of the East African Veterinary Research Organization.

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[1] Foy, H., Kondi, A., Linsell, C. A., Parker, A. M., & Sizaret, P. (1970) *Nature (Lond.)* (in press).

Preliminary studies in late 1968 showed that the situation had not greatly changed in this isolated valley of the Masai tribal area, whose vernacular name may be translated as "the valley where cattle salivate". The Masai tribesmen observe their cattle very carefully, and they claim that they are able to recognize the disease about six months before death ensues. It is sufficiently common to have acquired a vernacular name: *embonget.*

Maps were prepared by the Survey of Kenya from existing aerial photographs, and a field worker from the local population was established in the valley. Animal counts in the area recorded a total of 961 cattle in February 1969 and 997 in November 1969. The grazing pattern of each herd was mapped, and the field representative visited all herds frequently. He was present, when possible, at the post-mortem examination of all animals that died or were slaughtered. Such examinations are current practice among the Masai. The Regional Centre purchased some animals in which the disease had been diagnosed clinically, to ensure that post-mortem material was well preserved. So far, the local clinical diagnosis has always been supported by subsequent post-mortem examination (see Fig. 8).

Field records have been complete only since March 1969, but the minimum crude death rate from histologically confirmed cancer of the rumen and oesophagus in the cattle population of this valley is 1500 per 100 000. As it was suggested that the disease affects wild animals in the area, two wild forest hogs (*Hylochoerus meinertzhageni*, Thomas) were cap-

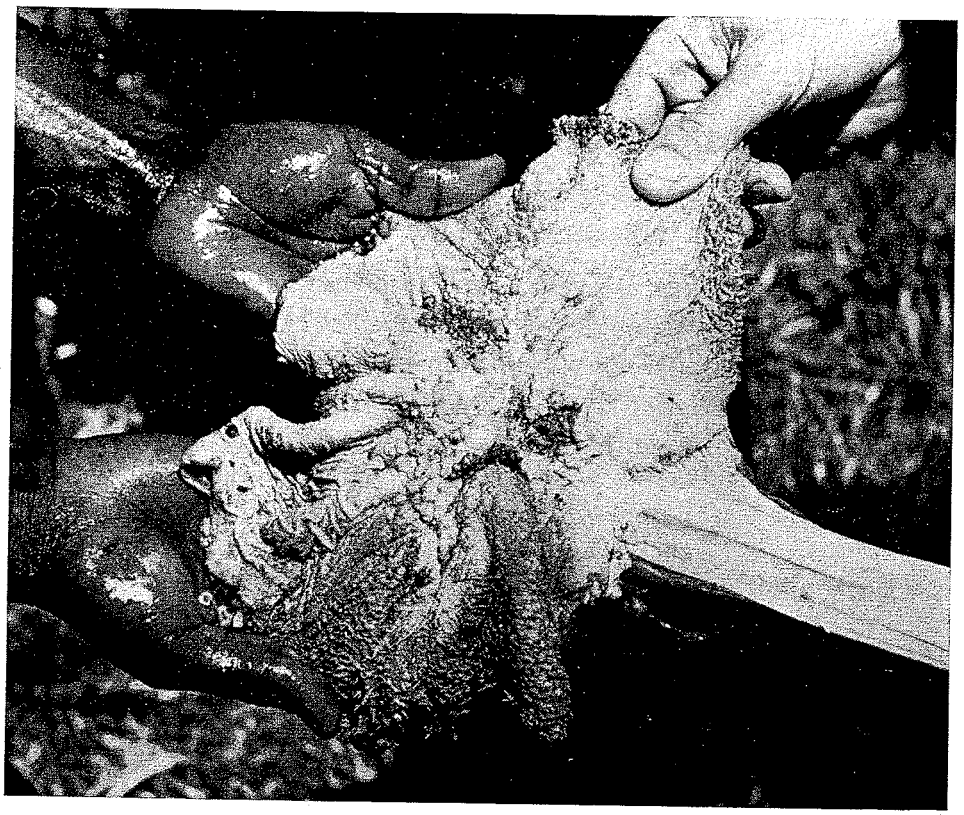

Fig. 8. Post-mortem specimen showing oesophageal cancer in cattle.

tured in a moribund condition and slaughtered. Both these animals showed oesophageal cancer. Thus, the disease can also occur in monogastric animals. From the study of herd-grazing areas and location of the *bomas*—farms belonging to family units—that had suffered the highest losses, it became clear that grazing in the forest areas surrounding the valley was suspect. The valley floor is overgrazed by goats and as the farmers are restricted by their land tenure to the locality of the valley, they are forced to use the forest grazing. Visits in the company of the local farmers and a botanist from the East African Agricultural and Forestry Research Organization implicated 25 plants which were said to form the major part of this rather unusual grazing. These have been identified by their botanical and local vernacular names, and specimens from nine of them have been tested for gross levels of nitrosamines. Arrangements were made for the field work to be intensified, and five cows diagnosed as having the condition have been transferred to the East African Veterinary Research Organization laboratories at Muguga for detailed study and a more thorough post-mortem examination than is possible in the field. Cattle have been introduced into the valley by the Regional Centre, and they are being intensively fed in the suspected areas. The local Masai are convinced that the disease is limited to these areas, and they also state that cattle introduced from other areas contract the disease from time to time.

In Brazil, upper intestinal cancer has been reported in cattle suffering from enzootic haematuria possibly due to bracken-fern poisoning. Although bracken fern is found in the Masai forest, according to the local farmers it is not eaten by their cattle, and there have been no reports of bladder lesions.

5. FUTURE STUDIES FOR FOOD CARCINOGENS

All food samples collected in Murang'a for aflatoxin analysis, together with those from any other relevant collection, will be retained for subsequent examination for other chemical carcinogens. They will be stored in the cold-room at the Regional Centre at a temperature of —30°C. In collaboration with the Chemistry Department of Nairobi University, these samples, as well as suspect plants from the bovine oesophageal study, will eventually be analysed. Particular attention will be paid to their nitrosamine content.

6. BUILDING OF THE REGIONAL CENTRE

The new building of the Regional Centre (Fig. 9) was opened in June 1969 by Dr J. Higginson, Director, IARC, in the presence of local representatives of Participating States.

All the Centre's activities are now accommodated in this building, although animal experimentation is continuing in the Wellcome Trust Laboratory and Baboonery. An office and some laboratory space equipped for chemical and virological work are available.

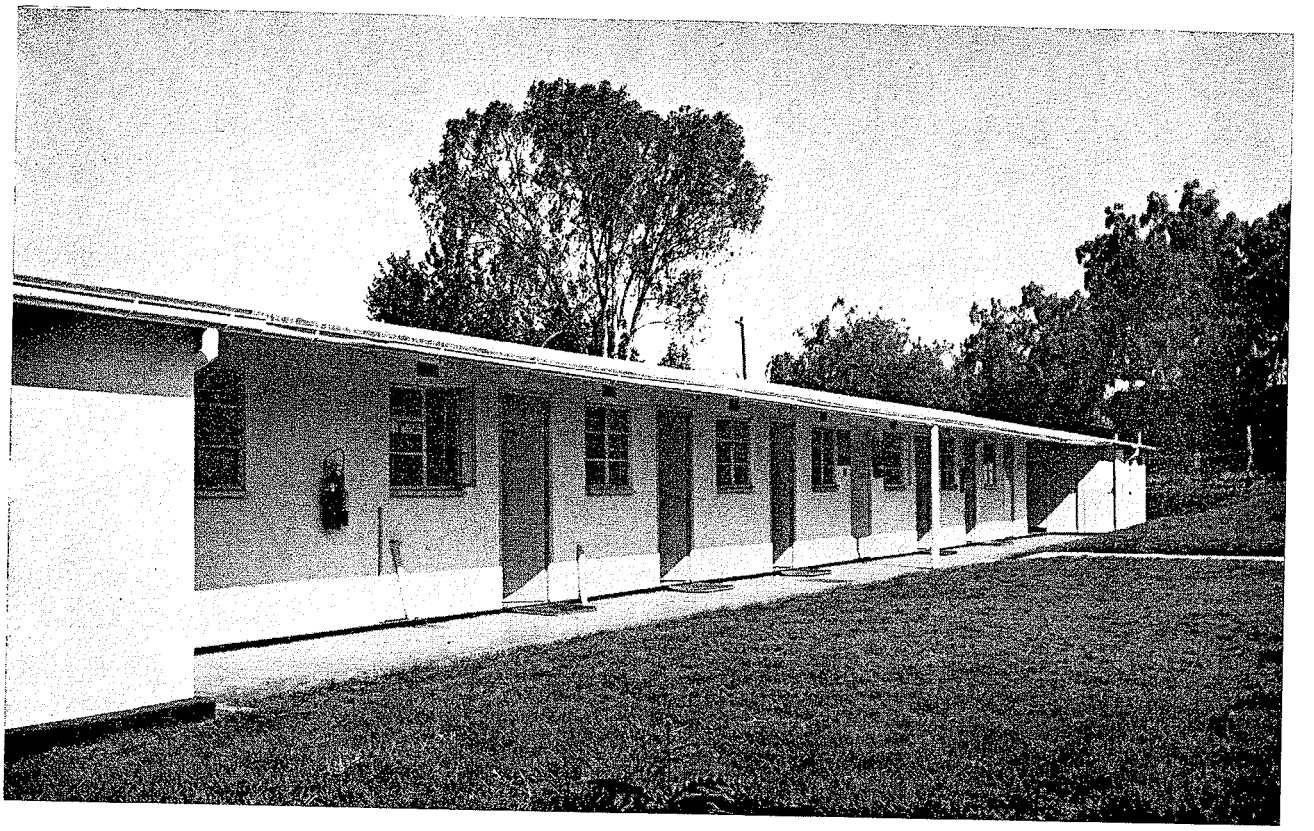

Fig. 9. New building of the IARC Regional Centre in Nairobi.

8. IARC REGIONAL CENTRE, SINGAPORE

Professor K. SHANMUGARATNAM (Head)

1. THE SINGAPORE CANCER REGISTRY (RA/67/009—RC4/0006/S1)

Principal investigator: Professor K. Shanmugaratnam

The Registry is managed by a committee (see IARC *Annual Report, 1968*, p. 69).

A total of 2550 cases were registered in 1969, on the basis of notifications received from all sectors of the medical profession in Singapore. The Registry scrutinizes all death certificates, hospital records, and pathology records in Singapore to ensure that notifications are as complete as possible. Incidence figures and other information derived from the first two years of operation (1968-69) will be published in 1970.

2. ADENOVIRUS STUDIES ON NASOPHARYNGEAL CANCER (RA/67/007—RC4/0006/S2)

Principal investigators: Dr M. Y. Murphy

Professor Lim Kok Ann (Department of Bacteriology, University of Singapore)

Consultant: Professor N. F. Stanley (University of Western Australia)

These studies were undertaken to investigate the possible relationship between nasopharyngeal cancer and adenoviruses or other oncogenic viruses. Virus isolations and serological tests were carried out on a total of 73 patients between September 1967 and October 1969. Adenoviruses were not isolated from the specimens tested, although some patients had adenovirus antibody at the time of biopsy.

2.1 *Virus isolations*

Virus isolations were attempted from throat garglings, rectal swabs, and biopsies from clinically diagnosed nasopharyngeal carcinoma cases. Each specimen was inoculated into primary tissue cultures of monkey kidney, human amnion, and HeLa cells.

The attempted virus isolations from the human amnion and HeLa cell cultures were all negative. The inoculation of monkey kidney cell cultures gave a number of cultures showing cytopathogenic effects. The results are given in Table 20.

TABLE 20

RESULTS OF INOCULATION OF MONKEY KIDNEY CELL CULTURES

Source of specimen	Number of specimens taken from 73 patients	Number of cultures showing positive cytopathogenic effects
Throat gargling	73	18
Rectal swab	36	16
Biopsy	45	23

No haemadsorbing viruses were detected.

Of the 57 cultures showing cytopathogenic effects, 16 were found to yield SV5 (MK I) viruses. The remaining 41 isolates are being investigated in the Centre; they have also been sent to Dr M. F. Warburton, Commonwealth Serum Laboratories, Victoria, Australia and Dr S. S. Kalter, Southwest Foundation for Research and Education, Tex., USA, for further studies.

2.2 *Serology*

Sera from 72 patients were examined for adenovirus group-specific complement-fixing antibodies. Complement-fixing antigens were prepared from type 5 and type 7 adenoviruses (MK I and MK II). Sera were also tested for neutralizing antibodies to oncogenic adenovirus, types 7 and 12. The results are given in Table 21.

TABLE 21

TESTING OF SERA FOR ADENOVIRUS GROUP-SPECIFIC ANTIBODIES

Number of specimens tested from 72 patients	Positive titre	Negative	Test antigens
72	13 (1/8-1/32 dilution)	59	Adenovirus
72	—	72	MKI and MKII
32	2 (1/10 dilution)	30	Adenovirus type 7
26	5 (1/5-1/20 dilution)	21	Adenovirus type 12

3. SERO-EPIDEMIOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA

A total of 343 serum samples from selected age groups of the Chinese and Indian-Pakistani populations in Singapore were sent to the IARC for testing by the Unité de Virologie, Institut national de la Santé et de la Recherche médicale, Lyon. These samples were sent for determination of the complement fixation titres against different adenovirus groups and herpes-type virus as a preliminary to the proposed sero-epidemiological studies on the relationship between herpes-type virus and nasopharyngeal carcinoma (see page 38).

4. IMMUNOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA (N3/2/Singapore)

Principal investigator: Dr D. S. Nelson (Chief, WHO Immunology Research and Training Centre, Singapore)

The main aim of these studies is to determine whether patients with nasopharyngeal carcinoma have an immune response to their own tumours. Much work on tumours in experimental animals suggests that a cell-mediated immune response would be more effective in controlling tumour growth, or preventing a recurrence, than a humoral immune response. The sure detection of a cell-mediated response requires the long term cultivation of nasopharyngeal carcinoma cells *in vitro*; so far this has not proved possible, as the cells are rapidly overgrown by fibroblasts. However, humoral antibodies directed against antigens of autologous epithelial tumour cells have been detected in the sera of some patients by means of immunofluorescence. Further work is required to determine: (*a*) the true incidence of these antibodies; (*b*) whether they are directed against individual tumour-specific antigens, against antigens present in all or most nasopharyngeal carcinomas, or against more ubiquitous antigens (e.g., antigens determined by a passenger virus).

4.1 *The immunoglobulins*

Nasopharyngeal carcinomas arise and grow in an area rich in lymphoid cells, including plasma cells, some of which are known to be producers of the more recently discovered immunoglobulins, IgD and IgE. Since the stroma of the tumours frequently contains large numbers of plasma cells, it seemed worth while to estimate IgD and IgE levels in the sera of patients with nasopharyngeal carcinoma and of controls. Mean IgD levels were higher in patients with nasopharyngeal carcinoma than in other patients or normal controls, but the range of levels was so wide that the difference did not appear to be significant. Mean IgE levels were higher in patients biopsied for suspected nasopharyngeal carcinoma, whether the biopsy was positive or not, than in other patients or in normal subjects, but again the statistical significance of the differences was doubtful. Immunoelectrophoresis showed non-

specific changes in the sera of many patients with nasopharyngeal carcinoma or other malignant or inflammatory diseases: the appearance of C-reactive protein and of increased amounts of α_1-globulin with slightly changed mobility.

4.2 *Haemadsorption test*

It has been reported that some species of red blood cells will undergo haemadsorption to frozen sections of some mouse tumours. Frozen sections of 6 nasopharyngeal carcinomas were tested with human, sheep, rat, rabbit, guinea pig, and mouse red cells, with uniformly negative results.

4.3 *T-antigen test*

Attempts were made to detect T-antigens of the oncogenic adenoviruses, types 7 and 12 in frozen sections of 6 tumours by immunofluorescence with hamster antisera. The results were uniformly negative.

4.4 *Anti-sheep and anti-rabbit red cell test*

Because of the suspected association between nasopharyngeal carcinoma and Epstein-Barr virus, which causes infectious mononucleosis accompanied by a positive Paul-Bunnell test in Caucasians, the titres of anti-sheep red cell antibodies were measured in the sera of nasopharyngeal carcinoma patients and controls. The titres were uniformly very low, generally less than 1:16. In contrast, titres of antibodies to rabbit red cells were high, generally 1:80 to 1:640, but there were no differences between the sera of the carcinoma patients and the controls.

4.5 *Sera collection*

The following sera have been collected for dispatch to IARC, Lyon: patients with nasopharyngeal carcinoma (bled at the time of biopsy), 55; patients biopsied and found not to have nasopharyngeal carcinoma, 30; second and later bleeds from patients with nasopharyngeal carcinoma, 24; recurrence of nasopharyngeal carcinoma, 2; suspected recurrence, negative biopsy, 2; normal Chinese, 20; patients with other diseases, 20; diagnosis from biopsy not yet confirmed, 13.

5. OTHER STUDIES ON NASOPHARYNGEAL CARCINOMA (RC/4/0006/S3)

5.1 *Electron microscopic studies — Regional Centre, Singapore, and Department of Pathology, University of Western Australia*

Principal investigators: Dr J. M. Papadimitriou
Professor K. Shanmugaratnam

Biopsy material from 22 cases of nasopharyngeal carcinoma was examined. The neoplastic cells from all these cases showed characteristics of squamous epithelia such as cytolo-

gical aggregates of tonofibrils, bodies resembling "membrane-coating vesicles", and desmosomes between adjacent cells. The more undifferentiated neoplasms showed thin nuclear projections similar to those described in cells of Burkitt's lymphoma and other human lymphoma. A striking feature was the presence of "nuclear bodies" or inclusions. These varied in size from 0.6 to 1.8 μ and were often multiple within any one nucleus. Most were roughly circular in outline while others merged with adjacent inclusions. Most were composed of fine fibrillar material measuring 45-55Å, while some exhibited in addition more electron-dense and granular components measuring 150-250Å which were randomly scattered. The significance of these nuclear bodies cannot at present be assessed.

5.2 *Hormonal studies on nasopharyngeal cancer — Regional Centre, Singapore, and Imperial Cancer Research Fund, London*

Principal investigators: Professor K. Shanmugaratnam
Dr R. D. Bulbrook
Dr D. Y. Wang

Studies completed in 1968 showed no significant differences in hormone levels and plasma cortisol binding between the different racial groups in Singapore.[1]

During 1969, these investigations were extended by making comparisons between patients with nasopharyngeal carcinoma, those with other cancers, those with other diseases, and normal healthy controls. Preliminary results show that the cancer patients have lower levels of plasma androgens than patients with other diseases and normal controls.

6. EVALUATION OF THE α_1-FETOPROTEIN TEST FOR LIVER CANCER (RA/67/010)

The Regional Centre in Singapore collaborated in this study, co-ordinated by Dr G. O'Connor, by submitting serum specimens from 120 hospital patients. A report based on the 120 cases from Singapore has been published locally.[2]

7. EVALUATION OF DDT IN HUMAN DISEASE

The Regional Centre collaborated with the unit of Chemical Carcinogenesis by submitting tissue samples from 188 routine necropsies to Mr William F. Barthel, US Public Health Service, Consumer Protection and Environmental Health Service, Atlanta, Ga., USA. It is expected that the collection of specimens under this project will be completed in 1970.

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[1] Wang, D. Y., Bulbrook, R. D. & Shanmugaratnam, K. (1969) *Singapore med. J.*, **10**, 18.
[2] Shanmugaratnam, K., Chua, K. L. & Seah, C. S. (1969) *Singapore med. J.*, **10**, 230.

9. IARC REGIONAL CENTRE, JAMAICA

Professor G. BRAS (Head)

1. KINGSTON AND ST ANDREW CANCER REGISTRY

The Cancer Registry, largely supported by the British Empire Cancer Campaign with some help from the IARC, has continued to function as before. The new registration card now in use will permit card punching and better data retrieval. The Registry enables incidence rates to be calculated for each age group. Registrations are available for the period 1958-69 in the parishes of Kingston and St Andrew. Table 22 shows the order of rank for the commonest neoplasms, by sex, in this period.

TABLE 22

PRIMARY MALIGNANT NEOPLASMS DIAGNOSED, BY SITE (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), SEX, AND ORDER OF RANK, KINGSTON AND ST ANDREW, 1958-69

Males					Females				
Rank order	ICD No.[a]	Site	No.	%	Rank order	ICD No.[a]	Site	No.	%
1	151	Stomach	332	13.8	1	171	Cervix uteri	1032	27.8
2	162	Lung	219	9.1	2	170	Breast	667	18.0
3	190-1	Melanoma, other skin	202	8.4	3	152-4	Small intestine, colon & rectum	273	7.4
4	177	Prostate	192	8.0	4	190-1	Melanoma, other skin	210	5.7
5	202	Reticulosis	185	7.7	5	151	Stomach	195	5.3
6	152-4	Small intestine, colon & rectum	170	7.1	6	175	Ovary	165	4.5
7	150	Oesophagus	145	6.0	7	202	Reticulosis	135	3.6
	140-205	All sites	2410	100.0		140-205	All sites	3712	100.0

[a] Seventh Revision.

From October 1968 to October 1969, a total of 1188 cases were registered, of which 569 were from rural areas and 619 from Kingston and St Andrew. Histological confirmation ranged from 86.1 % in the University Hospital to 69.2 % in private hospitals and general practice.

The Jamaican contribution to the collaborative study on the serological test for liver cancer has been expanded to include a total of 120 specimens. Follow-up biopsies have been attempted on false negatives and false positives.

Professor Bras is directing a case history study of cancer of the oesophagus.

2. CURAÇAO

The cancer registry in Curaçao is progressing satisfactorily. Professor Bras visited it in April. Local doctors are collaborating. Dr Ulrike de Jong visited Curaçao to examine the problem of cancer of the oesophagus, in respect of which it is hoped to develop a retrospective case history study.

3. ARUBA

Mrs G. Monsanto has registered cancers in the Island of Aruba since 1968, and accurate figures for 1964-68 have been obtained from Dr O. Ten Thije. During this period, 158 malignant tumours were registered in males and females. The most common malignant tumour, i.e., of the skin, was not registered, as histological investigation was not usually carried out. The most common tumour seen was carcinoma of the cervix, but only 8 cancers of the oesophagus were observed (6 in males and 2 in females) in contrast to Curaçao where the frequency is higher in females than in males. It is estimated that 36 cases would have been seen if the incidence had been the same as in Curaçao.

4. BERMUDA

Professor Bras visited Bermuda where cancer has become the commonest cause of death. A local voluntary organization, originally instituted to combat tuberculosis, has now expressed an interest in the investigation of cancer, and Professor Bras has pledged the assistance of the Regional Centre in Jamaica to develop a programme taking the medical priorities of the population into account.

5. GUYANA

Mr Goolkahn visited Guyana, as it appears that medical staff in Georgetown are eager to establish a cancer registry. The cancer mortality rate was given as 42 per 100 000 in 1967.

6. BARBADOS

The possibility of a cancer registry in Barbados is being further explored.

10. MEETINGS

1. AN INFORMAL MEETING OF SENIOR CANCER RESEARCH WORKERS

In order to discuss the scientific direction of cancer research in the light of recent developments, a small group of scientists concerned with institutional administration was invited by the Director, IARC, to meet at Nice, France, on 10 October 1969. The following attended the meeting:

Professor G. J. V. Nossal, Australia
Dr L. Siminovitch, Canada
Professor A. Lwoff, France
Professor C. G. Schmidt, Federal Republic of Germany
Professor D. W. van Bekkum, Holland
Professor M. Feldman, Israel
Professor A. Caputo, Italy
Professor M. G. P. Stoker, United Kingdom
Dr N. P. Napalkov, USSR

Dr F. L. Horsfall, jr., USA, was unable to attend owing to illness.

Each participant presented a brief resumé of needs and problems in his own institute, and the group reviewed certain problems of scientific administration relating to cancer research as a whole.

All were agreed that cancer research should not be divorced from the patient with cancer. It was also emphasized that national cancer institutes should play an active role in training personnel for the care and treatment of cancer patients in hospitals in each country.

The difficulties and problems of selecting and attracting young and talented scientists to cancer research were considered in relation to long-term prospects and obsolescence.

The group was also particularly interested in the relative value of long-term versus short-term research and, in connexion with the latter, stressed the importance of carefully planned evaluation.

Several fields and problems in which increased research efforts were considered necessary were discussed, but no specific field on which these efforts should be concentrated could be singled out.

The group agreed that, in some cases, solutions may already be possible—for example, in that of cigarette smoking and lung cancer. In addition, it was considered that, in relation to the resources available, excellent work was being done in the field of viruses and cancer.

The group concluded that the direction of cancer research involved unique problems of institutional management and organization, and that these should be continually reviewed.

2. A WORKING CONFERENCE ON LIVER CANCER—HUMAN AND EXPERIMENTAL STUDIES

In mid-1968, Dr G. P. Warwick of the Chester Beatty Research Institute, London, suggested that it would be valuable to review the significance of laboratory studies on experimental liver cancer in the light of recent work on hepatic cancer in man. This proposal fitted in well with the current stage of development of the Agency's programme on primary liver cancer. It was accordingly agreed to set up a working party to suggest a basis for future collaboration between laboratory and field workers.

There have been two main approaches in laboratory studies on liver cancer: (*a*) to gain fundamental knowledge of the carcinogenic process through the investigation of rodent hepatoma, and (*b*) to use laboratory models as a means of identifying problems of liver cancer in man.

The working conference was held in July 1969 at the Chester Beatty Research Institute, London, which provided the necessary facilities. Ten clinicians and scientists were invited to prepare working papers on subjects relating to their own fields, and these were circulated one month before the meeting. For the first two and a half days, the working papers were discussed in turn. The problems of aflatoxin and α-fetoprotein received special attention. During the remaining day and a half, which were devoted to research proposals, the participants worked in sub-committees dealing respectively with human carcinogenic studies, biochemical and metabolic studies, and studies in morphology, epidemiology, and comparative pathology. The working papers and reports of the sub-committees are at present being prepared for publication by the Agency. A summary has been published in the form of a leading article in the *British Medical Journal*.[1]

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[1] *Brit. med. J.*, 1970, **1**, 381.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE SEVENTH SESSION OF THE IARC GOVERNING COUNCIL, 28-29 OCTOBER 1969

Australia

Dr R. WELLS
First Assistant Director General
Commonwealth Department of Health
Canberra

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

Mr B. F. HURLEY
Director
Commonwealth Internal Treasury
Geneva

Federal Republic of Germany

Dr B. E. ZOLLER
Director, International Relations Section
Federal Ministry of Health
Bonn

Dr H. KAISER
Federal Ministry of Finance
Bonn

Dr H. B. A. VOSSHENRICH
Federal Ministry for Youth, Family, and Health
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

Israel

Dr R. GJEBIN
Director General
Ministry of Health
Jerusalem

Italy

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

Netherlands

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

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

Professor A. V. CHAKLIN
Chief Oncologist
Ministry of Public Health
Moscow

United Kingdom

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

Mr J. I. JONES
Department of Education and Science
London

United States of America

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

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
Chairman-elect of the IARC Scientific Council

Dr J. F. DELAFRESNAYE
Executive Director
UICC

Professor P. F. DENOIX
Outgoing Chairman of the IARC Scientific Council

Dr S. HALTER
Secrétaire général
Ministère de la Santé publique
Belgium

Professor J. H. F. MAISIN
Président du Conseil supérieur de Cancer
Belgium

Annex 2

MEMBERS OF THE SCIENTIFIC COUNCIL AT ITS FIFTH SESSION, 11-13 JUNE 1969

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

Dr W. R. S. DOLL
Head, Statistical Research Unit
Medical Research Council
London

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

Professor G. KLEIN
Institute for Tumour Biology
Karolinska Institutet
Stockholm

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

Dr D. METCALF
Walter and Eliza Hall Institute for Medical Research
Melbourne, Australia

Professor O. MÜHLBOCK
Netherlands Cancer Institute
Amsterdam, Netherlands

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

Professor G. C. SCHMIDT
Deutscher Zentralausschuss für Krebsbekämpfung und Krebsforschung e.V.
Essen-Holsterhausen, Federal Republic of Germany

Professor L. SEVERI
Director, Institute of Pathological Anatomy and Histology
Perugia, Italy

Professor P. N. WAHI
Head, Department of Pathology
Sarojini Naidu Medical College
Agra, India

MEMBERS OF THE SCIENTIFIC COUNCIL ELECTED TO TAKE OFFICE IN 1970

Professor J. H. F. MAISIN
Président du Conseil supérieur du Cancer
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
The Norwegian Radium Hospital
Oslo

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

Annex 3

STAFF OF IARC

Director	Dr J. HIGGINSON
Secretaries:	Miss S. BLUNDELL Miss S. HUCKLE
Unit of Epidemiology and Biostatistics	
Chief	Dr C. S. MUIR
	Dr A. J. TUYNS Dr J. KMET Dr H. TULINIUS Dr N. E. DAY Dr ULRIKE DE JONG Mr D. K. JAIN Dr S. C. BESUSCHIO (Jan.-July 1969) Dr L. LEBLANC
Technical Clerk	Mme J. NECTOUX
Secretaries:	Mme J. NIELSEN-KOLDING Mlle D. MAGNIN Mrs S. GARSIDE Miss S. GRANDY Mlle A. BROC Mlle C. DERIOL Mme G. DAHANNE Miss W. KIRWIN Mlle A. RESSICAUD Mlle C. BONNARDEL
Unit of Environmental Carcinogenesis	
Chief	Dr P. BOGOVSKI
Secretary	Mme M. MAINAUD
Unit of Biological Carcinogenesis	
Chief	Dr G. BLAUDIN DE THÉ
	Dr A. GESER Dr NUBIA MUÑOZ Dr R. SCHMAUZ Mr J. C. AMBROSIONI Mr T. B. GREENLAND

Technical Officer	Mrs E. GALATIUS
Secretaries:	Mlle C. BARDON Mme A. ROMANOFF

Unit of Chemical Carcinogenesis

Chief	Dr L. TOMATIS
	Dr V. TURUSOV Dr P. SIZARET
Histology Technician	Miss B. WITTHOFF
Research Assistant for Animal Experimentation	Mr R. CHARLES
Bibliographic Researcher	Mme C. PARTENSKY
Secretaries:	Miss E. EVANS Mme L. OSSETIAN

Unit of Research Training and Liaison

Chief	Dr W. DAVIS
Administrative Officer	Mme S. RUBIN
Secretaries:	Mlle M. DELORME Mlle D. BIZOUERNE

Unit of Administration and Finance

Chief	Mr A. G. B. SUTHERLAND
Translator	Mr Y. POLLET
Administrative Services Officer	Mr B. BORGSTRØM
Accountant	Mr G. DALSTON
Registry Assistant	Miss M. LYCETT
Supplies Assistant	Miss S. BOWDITCH
Secretaries:	Mrs P. MALANDINE Mme A. ESCOFFIER Mlle M. RIBORDY Mlle M. COMTE Mlle M. COGOLEGNHE
Other services:	Mlle M. BELOT Mme N. SANTONI Mr C. MAGNIARD Mr S. MARTIN Mr G. BARBERO

Library

Librarian	Mr N. P. CUMMINS
	Mme D. MIETTON
	Mlle V. SUTTER

IARC Regional Centre, Nairobi

Head	Dr C. A. LINSELL
	Dr F. G. PEERS
Technical Assistant	Mrs S. GRAHAM
Secretary	Mrs E. WYER

Annex 4

RESEARCH AGREEMENTS IN OPERATION BETWEEN IARC AND VARIOUS INSTITUTIONS IN 1969

RA/67/001	Kenya Cancer Research Fund, Nairobi (Cancer registry at Nairobi)
RA/67/002	Medical Research Council Pneumoconiosis Research Unit, Cardiff, United Kingdom (Research study programme on asbestos)
RA/67/003	Department of Tumour Biology, Karolinska Institutet, Stockholm (Provision of frozen transplantable tumour strains)
RA/67/004	Weizmann Institute of Science, Rehovoth, Israel (Study of metabolism of carcinogens with a view to developing field methods for identifying exposure to carcinogens in man)
RA/67/005	University of Western Australia Medical School, Perth (Study of differential cancer mortality of migrants in the Australian population)
RA/67/009	IARC Regional Centre, University of Singapore (Cancer registry at Singapore)
RA/67/011	Gamaleya Institute for Epidemiology and Microbiology, Moscow (Collaborative study for the evaluation of a serological test for liver cancer)
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/67/022	Israel Cancer Registry, Ministry of Health, Jerusalem (Investigation of epidemiological value of detailed cancer incidence data)
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/68/003	Ministry of Health, Malawi (Cancer registry at Malawi)

RA/68/004	Curaçao and Aruba Cancer Registry, West Indies (Investigation to establish cancer incidence)
RA/68/005	Ministry of Health and Housing, Tanzania (Cancer registry at Tanzania)
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/68/008	Institute of Public Health Research, Teheran (Pilot study of cancer in Mazandaran Province with special reference to oesophageal cancer)
RA/68/009	University of Chiengmai Medical School, Thailand (Study of cancer patterns in Chiengmai)
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	Gamaleya Institute for Epidemiology and Microbiology, Moscow (Collaborative study in the application of the fetuin test to epidemiological studies on liver cancer)
RA/68/015	Faculty of Medicine, University of Dakar (Collaborative study on the relative frequency of cancer at Dakar and in Senegal)
RA/68/016	Forschergruppe für Präventivmedizin, Max Planck Institut für Immunobiologie, Freiburg, Federal Republic of Germany (Analytical methods for identification and quantitation of N-nitroso compounds)
RA/68/017	Faculty of Medicine, University of Abidjan (Collaborative study on the geographical distribution of cancer in Abidjan and the Ivory Coast)
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 Neoplásticas, Lima (Cancer registry in Lima)
RA/69/004	Stack Medical Research Laboratories, Khartoum (Sudan cancer registry)
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/69/006	Laboratory of Biochemistry, Hamburg, Federal Republic of Germany (Study on the recovery of polycyclic aromatic hydrocarbons in meat)
RA/69/007	Institute of Oncology, Gliwice, Poland (Critical analysis of cancer mortality in Poland)
RA/69/008	University of Teheran (Study of etiological factors in oesophageal cancer in the Caspian coastal area of Iran)
RA/69/009	Institut de Recherches scientifiques sur le Cancer, Villejuif, France (Collaborative study on the utilisation of cultures of human and monkey hepatocytes in the production of α-fetoprotein)
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	Ministry of Public Health, Abidjan (Serological survey on the prevalence of liver cancer in the Ivory Coast)
RA/69/012	WHO Immunology Research and Training Centre, University of Singapore (Study on cell-mediated immunity in nasopharyngeal carcinoma)
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/69/015	Ecole nationale de la Santé publique, Rennes, France (Epidemiology of oesophageal cancer in Brittany and Normandy)
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, Tallin, USSR (Investigation of the comparative carcinogenic action of shale and chrysotile asbestos dust in rats)

Annex 5

VISITORS TO IARC IN 1969

Professor G. ABELEV	Gamaleya Institute for Epidemiology and Microbiology, Moscow
Dr R. M. ACHESON	Yale University, New Haven, Conn., USA
Dr G. ANDERSON	National Institute for Medical Research, London
Dr E. ANGLESIO	Piedmont Tumour Registry, Turin, Italy
Professor E. BERTRAND	Hôpital de Treichville, Abidjan
Dr C. BIANCIFIORI	Institute of Pathological Anatomy and Histology, Perugia, Italy
Dr J. BIELECKI	Ecole nationale de la Santé publique, Rennes, France
Professor E. BOYLAND	Chester Beatty Research Institute, London
Professor G. BRAS	University of the West Indies, Jamaica
Mlle A. BRUNET	Institut national de la Santé et de la Recherche médicale, Paris
Dr G. BYLENGA	UNSF/FAO, Mexico
Dr D. A. CAMPOLO	Reggio Calabria, Italy
Professor D. CLAYSON	University of Leeds, United Kingdom
Dr K. R. COX	University of Melbourne, Parkville, Australia
Dr J. F. DELAFRESNAYE	UICC, Geneva, Switzerland
Professor G. M. EDINGTON	Department of Pathology, University of Ibadan, Nigeria
Dr E. ENGELHARDT	Gamaleya Institute for Epidemiology and Microbiology, Moscow
Mr A. ESTÉVEZ	Director, Department of Experimental Investigations, Havana
Dr F. FAGNANI	Institut national de la Santé et de la Recherche médicale, Paris
Dr S. FIALA	Veterans Administration Hospital, San Fernando, Calif., USA
Mrs L. FORTI	President, National Secretaries Association, USA
Dr A. FRAPPIER	Directeur de l'Institut de Microbiologie et d'Hygiène de l'Université de Montréal, Canada
Professor W. U. GARDNER	Yale University, New Haven, Conn., USA
Dr J. GAVILONDO	Department of Radiological Protection, Havana
Dr J. C. GILSON	Medical Research Council Pneumoconiosis Research Unit, Penarth, Glamorgan, United Kingdom
Dr G. A. GLOBER	Department of the Regius Professor of Medicine, University of Oxford, United Kingdom
Dr H. C. GOODMAN	Immunology unit, WHO, Geneva, Switzerland

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Dr N. STENHOUSE	University of Western Australia, Perth
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Mrs M. YALICH	President, Junior Leagues of America, USA
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Annex 6

INTERNAL TECHNICAL REPORTS UP TO JANUARY 1970

IARC Internal Technical Report No.	
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 absestos cancer (Lyon, 25 February 1969)
69/002	Report of Meeting on standardization of sampling and analytical procedures for polynuclear 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 Carcinogenesis unit, IARC)
69/004	Report by Dr D. B. Clayson of Leeds University, United Kingdom, on his visit to IARC (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	Evaluation of a serological test for the diagnosis of 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 (St Gervais, France, 11-13 January 1970)
70/002	Studies in Burkitt's lymphoma (St Gervais, France, 15-18 January 1970)

Annex 7

PAPERS PUBLISHED AND SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS, 1968-1969

IARC staff

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[1] The names of Fellows are given in bold type.

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