INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

WORLD HEALTH ORGANIZATION

LYON
FRANCE

ANNUAL REPORT
1968

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INTRODUCTION

Each year the Director of the International Agency for Research on Cancer is required to present a report on the past year's activities of the Agency. The report is intended to provide a review of the programmes of the Agency, as an expression of the policy and objectives of the Participating States.

To provide a better understanding of the nature and objectives of IARC the Governing Council requested that the report for 1968 should be expanded to include additional background information. This is intended to make it suitable for distribution to other interested bodies as well as to the Agency's two statutory bodies—the Governing Council and the Scientific Council—, which are already conversant with its earlier development. Since the Agency has been in active operation for only a limited period, few results are available and so the report is limited to current programmes of research. Furthermore, the Agency will not be capable of full operation until the completion of its new building. In spite of these limitations, it is believed that the report will permit assessment of the role of an international organization that is so far largely engaged in research into the role of the environment in human cancer.

The present report covers the first full calendar year of the Agency's operation since it entered its present temporary headquarters at Lyon, France, in mid 1967.

Background and origins of the Agency

The International Agency for Research on Cancer was established by the Eighteenth World Health Assembly in 1965 within the framework of the World Health Organization. The statute of the Agency lays down its objective in the following terms:

> The objective of the International Agency for Research on Cancer shall be to promote international collaboration in cancer research. The Agency shall serve as a means through which Participating States and the World Health Organization, in liaison with the International Union Against Cancer and other interested international organizations, may co-operate in the stimulation and support of all phases of research related to the problem of cancer.

The Agency is empowered to develop its own research programmes, including whatever laboratory studies are necessary for the implementation of its field projects. The present Director was appointed in mid 1966. At present there are nine Participating States, listed in Annex 1 along with the names of their representatives at the Fifth Session of the Governing Council of the Agency in October 1968. The Director-General, WHO, is an *ex officio* member of that Council. As well as the Governing Council, there is a Scientific Council appointed by the Governing Council to give technical guidance to the Agency. A list of present and former members of the Scientific Council is given in Annex 2.

The environmental biological aspects of cancer research

In the selection and development of the research programmes of the Agency, two important considerations were prominent. Firstly, advances in molecular biology have opened up many new possibilities for a better understanding of carcinogenic mechanisms at the cellular level and, secondly, epidemiology has contributed to the identification of carcinogenic stimuli in man, thus providing the rationale for modern experimental chemical carcinogenesis. Both considerations are relevant to any balanced cancer research programme.

It was considered desirable by the Governing Council and the Scientific Council that the Agency should direct its efforts to problems particularly suited to its international role, rather than duplicate laboratory investigations that could equally readily be undertaken by national cancer research institutes. In view of its limited resources and the limited number of problems to the solution of which it could as an international body contribute, certain priorities were established, on the basis of available scientific knowledge and in the light of the increasing recognition of the importance of the environment in human disease. Accordingly, it was decided to develop (1) a research programme in environmental cancer biology utilizing a multidisciplinary laboratory and field approach, and (2) a fellowship programme to increase the supply of professional manpower in the field of cancer.

The importance of exploiting the field of environmental biology was further emphasized by a number of other considerations. Firstly, there is evidence that exogenous stimuli play a major role in over 80 % of malignant neoplasms in man. Secondly, many new chemicals are being synthesized each year for use in industry and medicine, and only a few of them are adequately tested for carcinogenicity. Thirdly, since the extrapolation to man of carcinogenic activity observed in experimental animals is a highly complex operation, experimental testing needs to be closely integrated with environmental field studies. For example, such a potent therapeutic agent as isoniazid might have been banned as a potential carcinogenic hazard if present testing regulations had been in force earlier, although the drug is apparently harmless to man at normal dosage levels. Governmental and international organizations will be increasingly required to make decisions regarding the utilization of therapeutic or chemical compounds, sometimes in the absence of adequate supporting data. Thus, society will increasingly have to live with situations involving calculated risks.

The Governing Council and the Scientific Council believed that the Agency was in a suitable position to undertake research in the field of environmental biology. Such research clearly requires extensive collaborative studies and offers the prospect of providing new knowledge in the foreseeable future with practical implications in the field of public health, and it also avoids the danger of the Agency becoming a mere repository of dead statistics. That this decision of the Governing and Scientific Councils was justified is emphasized by the discussions held in the United Nations General Assembly in December 1968 on problems of the human environment, which clearly indicated the increasing international interest in the subject.

The Agency's finances

The Agency has so far been financed by equal annual contributions from each of the Participating States, established for the first quinquennium at the sum of US $150 000. In 1968, the approved budget was US $1.6 million; for 1969, it will be US $1.752 million. The difference between the total annual contributions and the total approved budget has been met by allocations from the Governing Council Special Fund. The first quinquennium will end on 31 December 1969, and during 1969 the financing of the Agency for the second quinquennium (1970-1974) will be considered by the Governing Council.

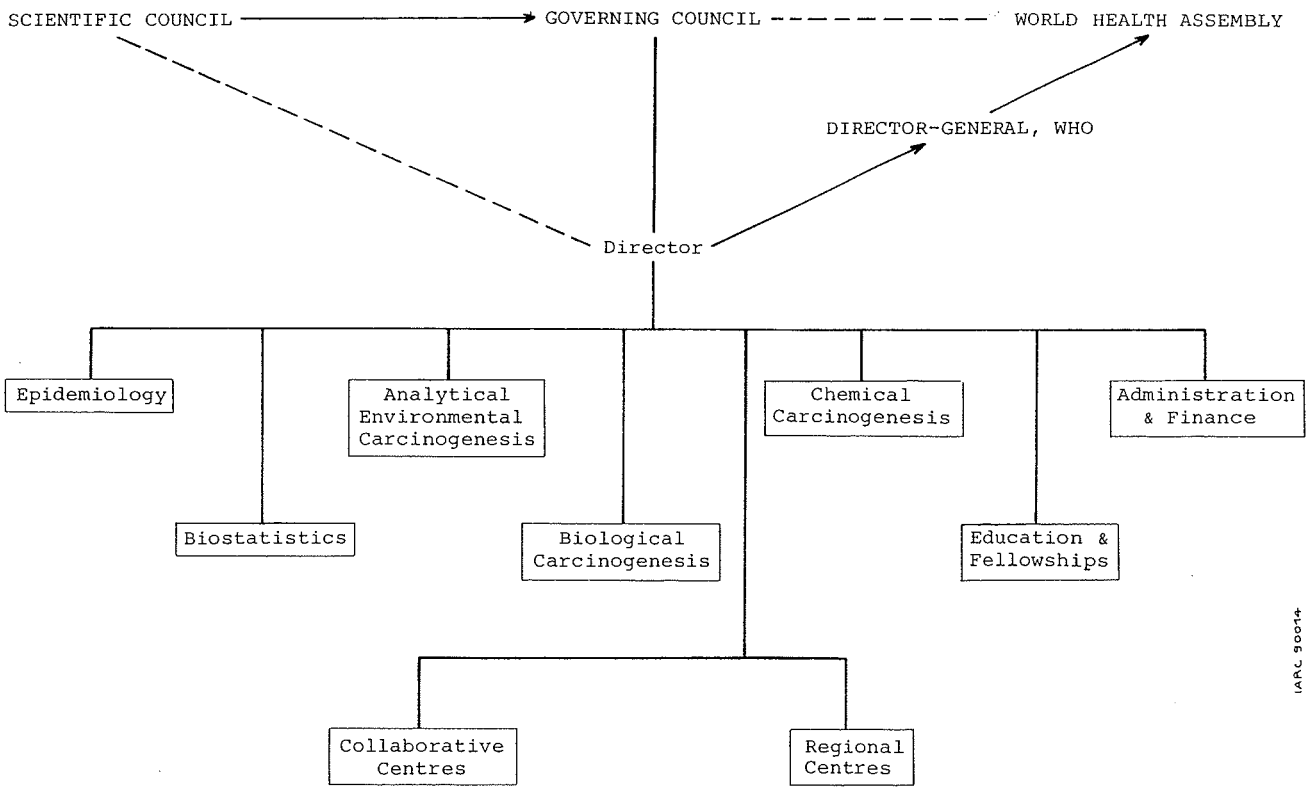

Fig. 1. Structure of the Agency.

Staff

So as to provide a coordinated multidisciplinary approach, the present staff of the Agency (Annex 3) has been selected to include scientists of several disciplines. It is considered that the success of the Agency will depend on its capacity to attract professional staff of high calibre who are not only fully aware of modern research developments but also have the organizational abilities necessary to take advantage of the international potential of the organization. The general structure of the Agency is shown in Fig. 1.

Accommodation

The Agency is at present housed in a temporary office (Fig. 2) put at its disposal by the Municipality of Lyon while the permanent building is being constructed. Laboratory space during this time has been kindly provided under contract to the Agency by Professor R. Sohier, Unité de Virologie, Institut national de la Santé et de la Recherche médicale (INSERM), and Professor M. Dargent, Centre Léon Bérard. The present space available is already fully occupied and further expansion will not be possible until completion of the new building.

Fig. 2. Temporary Headquarters of IARC. Additional offices and laboratories are situated elsewhere in Lyon.

Organization and work of IARC

At present the Agency is organized into five research units, largely on a disciplinary basis. A sixth unit is responsible for education and fellowship programmes. The staff of IARC is listed in Annex 3.

The *Unit of Epidemiology* provides the basic statistics which are fundamental to research studies on human populations. Thanks to the collaboration of numerous national cancer registries, the Agency now has access to cancer statistics from many areas of varied cultural and socio-economic background.

The unit is also making an extensive study, involving several different geographical regions, of the etiology of cancer of the digestive tract. Cancer of this system is of major significance in most countries and yet almost nothing is known of its causation.

The unit is collaborating with the *Unit of Analytical Environmental Carcinogenesis* to establish a limited number of priorities for the study of some of the numerous potential chemical carcinogens, natural and synthetic, in the human environment.

The unit of Analytical Environmental Carcinogenesis is also engaged in developing a collaborative network among existing national laboratories to provide the necessary analytical data to facilitate studies correlating cancer patterns with environmental carcinogens.

The *Unit of Biostatistics* provides the necessary statistical support for the Agency's programmes as well as developing stochastic models of the carcinogenic process.

The *Unit of Chemical Carcinogenesis* is responsible for the development of collaborative laboratory studies, with special reference to the extrapolation of data from animals to man. It has also developed a programme to answer the important question whether pesticides present another cancer hazard in the human environment. This programme is being undertaken by parallel laboratory studies in different countries. In such a programme the Agency can act as a neutral body through which governments can collaborate on problems that may have political or economic implications and, because of the absence of basic data, give rise to a variety of hypotheses.

Unit of Biological Carcinogenesis. The Agency's studies on viruses are already proving of significance in indicating additional tumours in which viruses may be causally implicated.

The *Unit of Education and Fellowships* has, since its inception, awarded 180 travel and research training fellowships. This programme is important in helping to increase the specialized manpower required in cancer research and to create a pool of future collaborators for the Agency's own programmes.

Regional and collaborating centres. The Agency is gradually building up a network of regional centres where it is proposed to study environmental cancer problems in depth over a period of years. Among such problems is one that may have serious socio-economic implications — that of human liver cancer and its possible relation to the presence of aflatoxin in the diet.

The above programmes are discussed in detail in the reports of the separate units. While it is obvious that the programmes are at various stages of development, it is hoped that they suffice to indicate the Agency's long-term objectives in relation to environmental biology.

Relationships with national institutes of cancer research

Experience already indicates that the Agency can develop as a biomedical centre in which scientists of several nationalities can collaborate in scientific research that has important practical applications. In addition, the Agency has a role in facilitating research studies that require collaboration between the industrialized and the emerging countries so as to reveal environmental factors of significance to both. These studies are supported by the Agency's own regional centres, and there is collaboration with existing national cancer research institutes.

Initially, fear was expressed that the Agency would compete with national cancer research institutes for manpower and finance. Happily, this does not seem to be the case; in fact, the Agency has been increasingly approached by research organizations wishing to expand their programmes through international collaboration. Owing to the limited resources of the Agency, however, many of these requests could not be supported, although the programmes were scientifically desirable.

Research agreements

The Agency makes research agreements with established institutions for the performance of specific research projects within the Agency's overall programme. A list of such agreements is found in Annex 4.

Visitors

An important contribution to the Agency's activities is made by the visitors, scientific colleagues from different countries who have visited the Agency in large numbers. These personal contacts and discussions of the Agency's programme have proved extremely valuable. During 1968 the scientists listed in Annex 5 visited Lyon.

Miscellaneous

The scientific meetings organized by IARC in 1968 are listed in Annex 6. The publications of members of the Agency staff are listed in Annex 7, and are followed by the publications of IARC Fellows.

1. UNIT OF EPIDEMIOLOGY

Staff: Dr C. S. MUIR (Chief)
Mr D. K. JAIN
Dr J. KMET
Dr ULRIKE DE JONG
Dr NUBIA MUÑOZ (from August 1969)
Dr H. TULINIUS (from April 1969)
Dr A. J. TUYNS

Supporting staff: 5

The work of the unit of Epidemiology is shown in Fig. 3.

1. DESCRIPTIVE EPIDEMIOLOGY

While the demonstration of differences in the incidence of cancer between different population groups and different countries remains the keystone in the search for etiological factors, the available data from all continents show considerable inadequacies.

1.1 *Morbidity Data*

The unit of Epidemiology continues to collaborate with the UICC Committee on Cancer Incidence in collecting and processing cancer morbidity data. A joint IARC/UICC meeting held in Lausanne, Switzerland, in May 1968 discussed the publication of a second volume of the monograph *Cancer incidence in five continents*.[1] This second volume will contain up-to-date material from most of the 32 registries represented in the first volume, as well as new information from a further 20 registries from Africa, Asia, Europe, North America, and Oceania.

Although the unit maintains close links with many cancer registries, it is not the policy of the Agency to provide long-term financial support to cancer registries, except when necessary for specific Agency programmes (in particular those undertaken in emerging countries). However, the Agency is willing to give advice and to provide consultants on the establishment and running of such registries.

1.2 As a first step towards improving comparability in cancer statistics, an assessment of techniques used by existing cancer registries was begun and is now nearly completed.

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

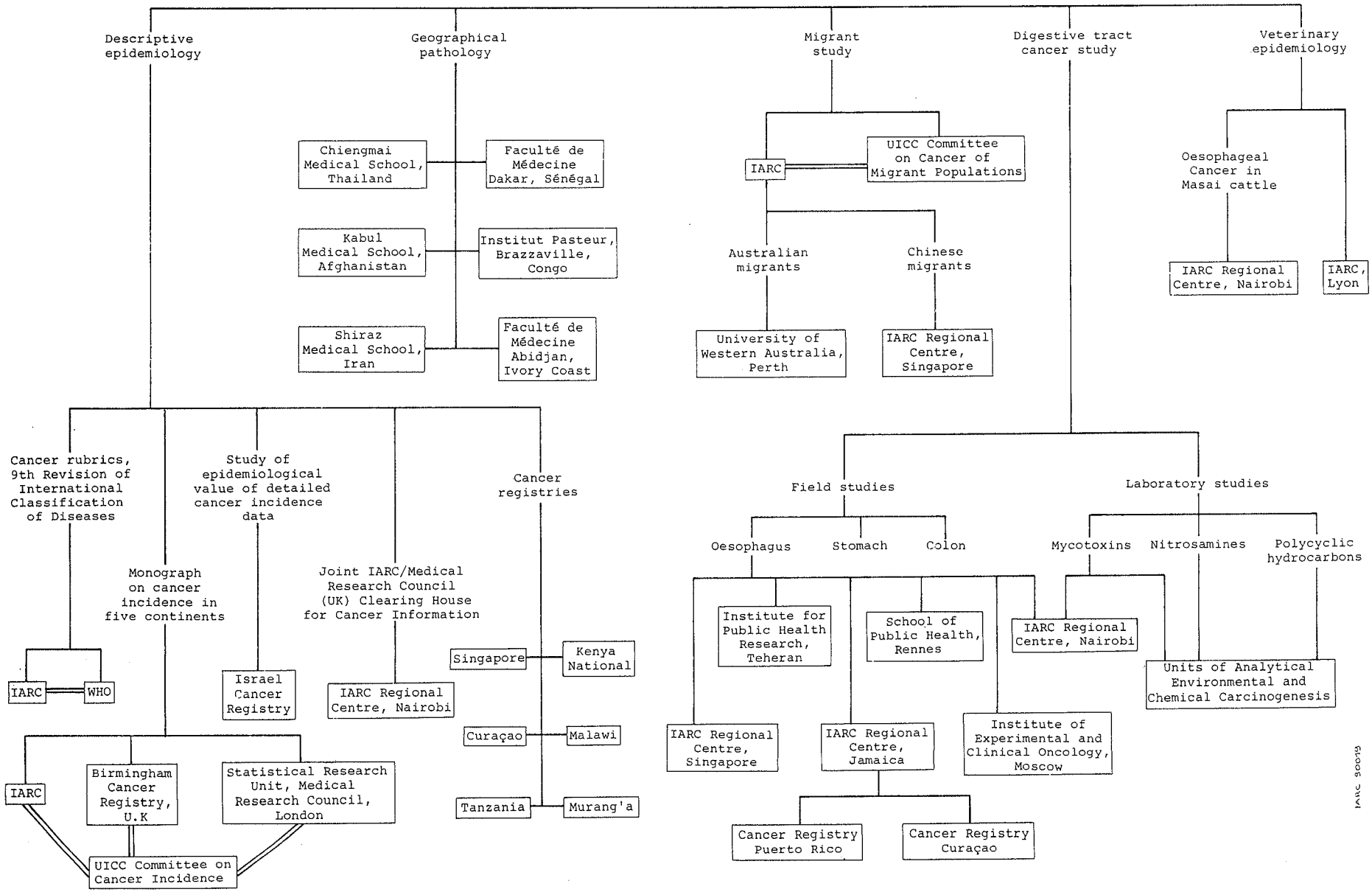

Fig. 3. Unit of Epidemiology.

1.3 *Study of the epidemiological value of detailed cancer incidence data*

Principal Investigator: Dr Ruth Steinitz (RA/67/022)

For such studies large numbers of people are required, hence the three most important sites (breast, stomach, and lung) in the Israel Cancer Registry were chosen. Some 3900 cases of female breast cancer were re-analysed. The preliminary work led to the elimination of 200 cases which proved to have been recorded twice or to affect non-residents. Relevant detailed information has now been put on punched cards for amalgamation with the demographic and identifying items already on magnetic tape. A set of tables has been devised and run. The results have shown several areas which need correction before embarking on the full-scale analysis.

1.4 *Incidence of specific histological tumour types*

As differences in the histological pattern may be of etiological significance, cancer registries have been asked to submit a histological analysis by age and sex for certain cancers (bladder, thyroid, ovary, testis, leukaemia), so that histological age-specific rates may be calculated. This request entails many problems of classification and further underlines the need for an internationally recognized classification acceptable to pathologists and epidemiologists. Close contact continues with the WHO International Reference Centres for the Histological Classification of Tumours.

2. 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. Experience has shown that an unusual cancer incidence is nearly always reflected in a high relative frequency of pathological material. A technique has been developed to improve the comparability of ratio studies by correction for the effects of age.[1]

2.1 The cancer registries at the Regional Centres at Nairobi (Dr M. Rogoff: RA/67/001) and Singapore (Professor K. Shanmugaratnam: RA/67/009) are now well under way. The Nairobi Regional Centre is co-ordinating the results from the IARC-supported registries in Africa with the cancer data obtained by the Medical Research Council of Great Britain. The Kenya registry reports a high frequency of primary cancers of the œsophagus (9.2%), liver (9 %), nasopharynx (7.5 %), and skin (7 %).

2.2 Progress is reported from the minimum incidence registries at Blantyre (Dr J. A. A. Borgstein: RA/68/003) and Dar-es-Salaam (Dr R. Mitchell: RA/68/005).

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[1] Tuyns, A. J. (1968) *Int. J. Cancer*, 3, 397.

2.3 The Registry at Willemstadt, Curaçao (Dr W. J. A. Oostendorp: RA/68/004), is supervised and partially financed by the Jamaica Regional Centre (see page 72).

2.4 A ratio study based on Kabul, Afghanistan, was completed by Professor L. Sobin, acting as an IARC consultant.[1] He reported that oral cancer was virtually absent in a population chewing very large amounts of nasswar (a tobacco/lime mixture). A low frequency of cancer of the uterine cervix was observed, whereas cancers of the uterine body and ovary showed moderate frequency.

2.5 In Chiengmai, North Thailand (Dr Dusdee Prabhasawat: RA/68/009), the ratio study being carried out is combined with registration of clinically diagnosed cases. The results of the first six months of operation are shown in Table 1. A total of 206 cancers was reported (males 88; females 118), of which 197 were in Thais. There was histological confirmation in 78 %, and the X-ray appearance was considered diagnostic in a further 7 %. The very high relative frequency of laryngeal cancer in males is now being investigated.

TABLE 1

PRIMARY MALIGNANT NEOPLASMS DIAGNOSED AT CHIENG-MAI, THAILAND, BY SITE (ACCORDING TO THE INTERNATIONAL CLASSIFICATION OF DISEASES), SEX, AND ORDER OF RANK

Males					Females				
Rank order	ICD no.	Site	Number	%	Rank order	ICD no.	Site	Number	%
1	161	Larynx	14	17	1	171	Cervix	26	23
2	163	Lung	9	11	2	170	Breast	12	11
3	146	Nasopharynx	6	7	3	163	Lung	6	5
4	150	Oesophagus	6	7	4	175	Ovary	5	4
5	177	Prostate	6	7	5	161	Larynx	4	4
		All sites	83	100			All sites	114	100

2.6 The results of a ratio study in Sabah (Borneo) have been published.[2]

2.7 Data on approximately 6000 cases of cancer, obtained from the various pathological laboratories in Dakar, Senegal, are now being processed in Lyon (Consultant: Dr D. Lambert). A collaborative research agreement to extend this work has been signed (Professor C. Quenum: RA/68/015). A ratio study has been also initiated in Abidjan, Ivory Coast (Professor R. Loubière: RA/68/017). These studies are designed to provide background information for the liver cancer programme of the Agency.

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[1] Sobin, L. (1969) *Cancer (Philad.)*, in press.

[2] Muir, C. S., Evans, M. D. E. & Roche, P. J. L. (1968) *Brit. J. Cancer*, **22**, 637.

2.8 The files of the Institut Pasteur, Brazzaville, have been analysed in collaboration with Dr Ravisse. A high frequency of liver cancer was found (41 % in males, 13 % in females), the crude minimum annual incidence rates being in the region of 11 and 4 per 100 000 population respectively.

3. COMPARABILITY OF CANCER STATISTICS

Cancer data are often collected, processed, and published in different ways, making valid comparison difficult. The Agency is attempting to improve the quantity and quality of such information. A Working Group on Sources of Cancer Statistics was held in November 1968 (IARC Technical Report No. 68/003). The Group "noted with satisfaction that the major activity of the IARC lay in the field of multidisciplinary epidemiological studies and re-emphasized the necessity to obtain reliable descriptive information on which to base such epidemiological investigations".

The advantages and disadvantages of mortality and morbidity statistics were discussed in relation to epidemiological studies. Special consideration was given to temporary *ad hoc* cancer registries, and the value of relative frequency studies based on pathological and clinical material was stressed. The analysis of the age-specific incidence for certain specified types of neoplasms was considered promising. The report made recommendations to the Agency about work on the reliability and comparability of morbidity and mortality statistics, and considered the Agency to be a suitable organization to solicit and assemble proposals for the cancer section of the Ninth (1975) Revision of the International Classification of Diseases.

4. MIGRANT STUDIES

Consultant: Dr J. Staszewski

While planned experiments in man are difficult, populations migrating from one environment to another provide useful opportunities for cancer epidemiological studies, since the genetic characteristics of such groups are initially unchanged. On the other hand, culturally determined environmental factors such as diet and the preparation of food may change slowly over a period of years.

The unit has prepared a list of existing migrant populations of a size suitable for such studies and has assessed the feasibility of such investigations for presentation at a meeting on the methodological aspects of studies on migrant populations. Regrettably, many countries with advanced health facilities and vital statistical systems do not record the place of birth in the appropriate places, thus making the identification of the population at risk virtually impossible. Inquiry by the unit reveals that 60 % of 44 cancer registries do not record this information either.

4.1 *Mortality in Australia*

Principal investigator: Dr M. J. McCall: RA/67/005

This work is now in its second year. Early difficulties have been overcome and the 1966 census has provided a denominator for the calculation of the differential risk.

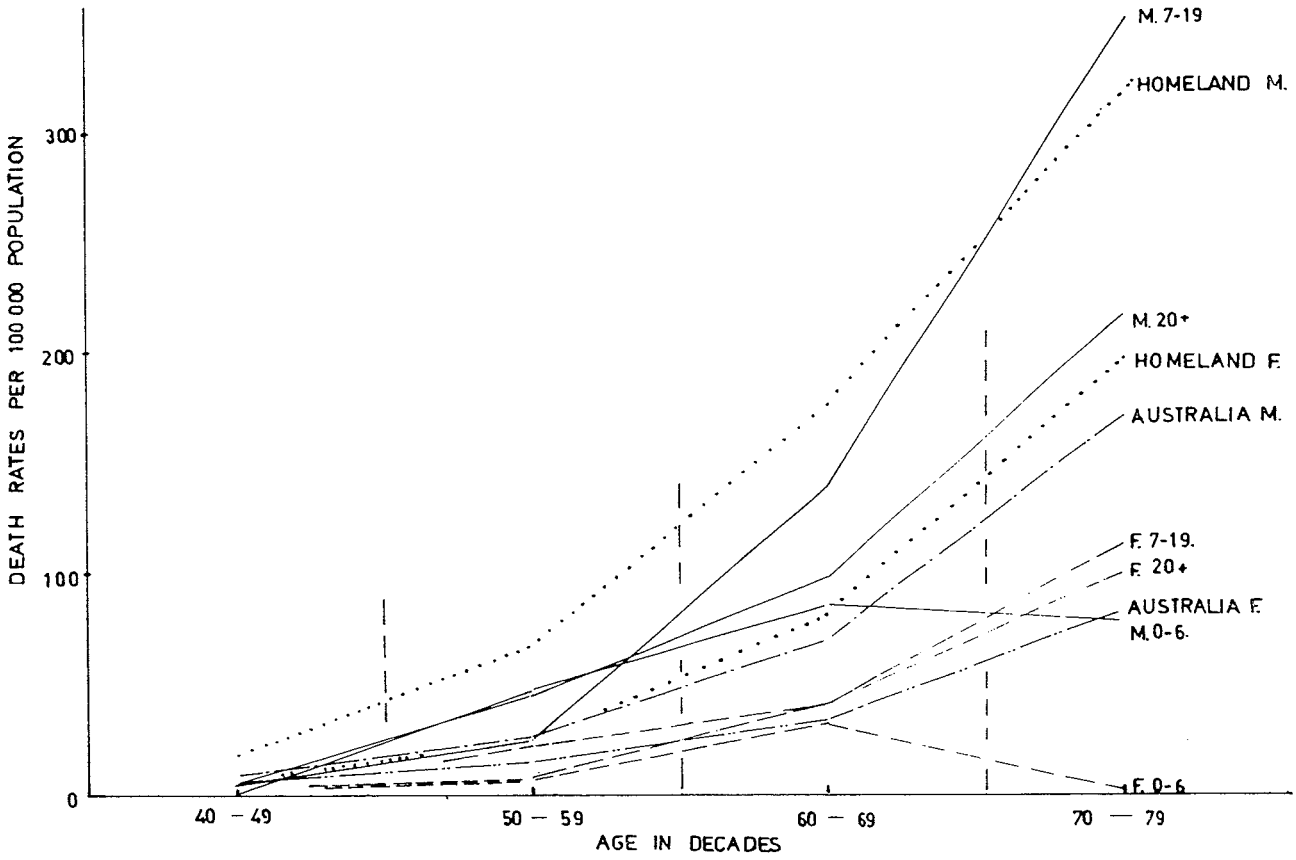

Fig. 4. Death rates from cancer of the stomach for Italians residing in Australia with comparison for native-born Australians, by period of residence in Australia, by ten-year age groups.

The age-specific mortality rates for selected cancer sites for migrants from England and Wales, Italy, and Scotland have been computed by sex and length of residence (0-6 years, 7-19 years, 20+ years), and compared with rates for the Australian-born population. For example, the gastric cancer rates for male Italians (Fig. 4) resident for 0-6 years in Australia are considerably lower than those for Italians in Italy. For those resident for 7-19 years the rates are very close to those for the homeland, whereas for those resident for more than 20 years the rates are much closer to those of the Australian-born population. These findings, which parallel those for arteriosclerotic and degenerative heart disease, indicate that recent migrants are highly selected and that a comparatively long time is required for the environment to alter the mortality risks. The unit believes that migrant studies, although expensive and difficult, need to be expanded.

5. ETIOLOGICAL FACTORS IN DIGESTIVE TRACT CANCER

Digestive tract cancer is one of the major problems in industrialized countries today. The Agency has therefore initiated a long-term programme for its study, attention being initially directed towards the oesophagus. A working group was held in Lyon in July 1968. The report (IARC Internal Technical Report No. 68/001), on which the unit's programme in relation to cancer of the oesophagus is based, emphasized the need for a balanced attack on the problem.

5.1 *Oesophagus*

In general, cancer of the oesophagus has been linked with abuse of strong alcoholic spirits and tobacco. However, these factors probably do not explain the high levels reported in Iran and certain parts of South Africa.

Iran. Principal investigator: Dr E. Mahboubi: RA/68/008

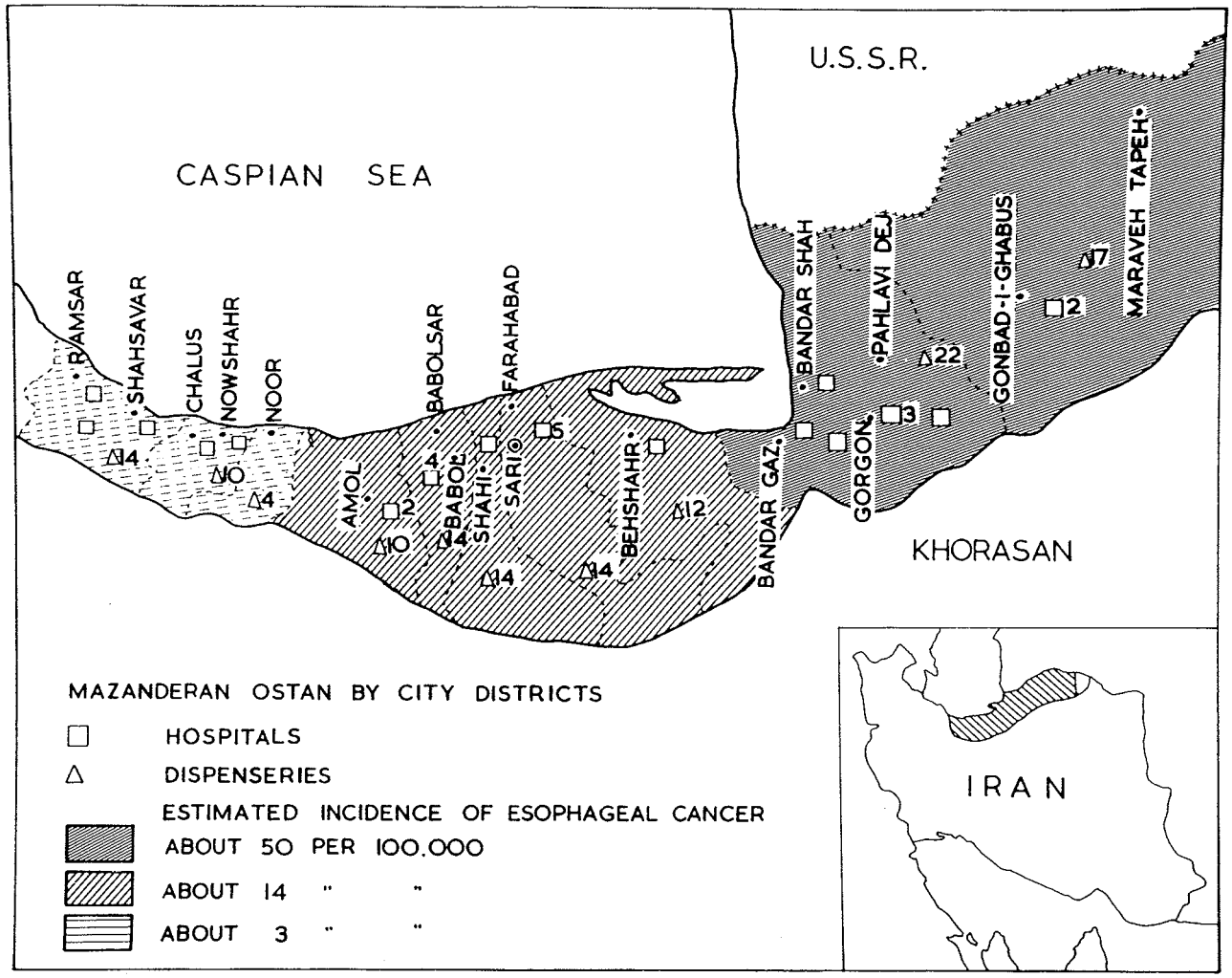

Fig. 5. Estimated incidence of oesophageal cancer in Mazanderan Province, Iran. The figures next to the squares and triangles denote the numbers of hospitals and dispensaries respectively.

Oesophageal cancer has been believed to be common in the Province of Mazanderan (Fig. 5). Preliminary studies of radiologically and clinically diagnosed cases from June to October 1968 suggest a very high incidence in the predominantly desert portion of the Province, the incidence diminishing rapidly towards the West. There is no reason to believe that this is an artefact. In Mazanderan, the consumption of alcohol is slight. Most of the neoplasms in this northern Province are located in the lower two-thirds of the oesophagus. In Shiraz, in the south of Iran, it is believed that a high proportion lie in the upper third of the viscus. A ratio study (Professor W. Dutz: RA/68/010) is under way to confirm whether this is so.

Caribbean region. A meeting was held at the IARC Regional Centre, Kingston, Jamaica, in November 1968, to plan the work to be undertaken in Jamaica, Curaçao, and Puerto Rico (Dr I. Martínez). The high incidence of cancer of the oesophagus in the Caribbean region seems to be related to the consumption of strong alcoholic drinks, a proportion of which are home-brewed. However, in the Netherlands Antilles, where the female rates are higher than those for males, alcohol may not be the causative factor.

France. In Brittany, the very high rates for cancer of the oesophagus seem to be associated with the consumption of distilled cider (Calvados). Professor L. Massé, School of Public Health, Rennes, is collaborating in a study of the situation.

Africa. At Kisumu, on the Kenya-Uganda border, where there are contiguous high- and low-frequency areas, the unit and the Nairobi Regional Centre are conducting a study in collaboration with the Medical Research Council of Great Britain (Miss P. Cook).

The Singapore Regional Centre and the Division of Epidemiology, Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR (Professor A. V. Chaklin) will also participate in the study of oesophageal cancer. A high incidence has been recorded in Singapore Chinese and a high mortality in certain parts of the Kazakh SSR.

5.2 *Nitrosamines and the oesophagus*

In view of the virtually selective action of certain nitrosamines on the rat oesophagus and the fact that diethylnitrosamine has been detected in Malawi gin,[1] the need is evident for a relatively simple screening method to detect the presence of such substances in alcoholic and other drinks and also foodstuffs. At a joint IARC/UICC meeting on quantitative carcinogenesis, it became clear that such a method did not exist. The unit of Analytical Environmental Carcinogenesis is preparing a collaborative programme to facilitate the analysis of alcoholic beverages.

5.3 *Stomach and large intestine*

Consultant: Dr T. Hirayama

Planning for studies of gastric and large bowel cancer has begun.

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[1] Mc Glashan, N. D. et al. (1968) *Lancet*, **2**, 1017.

6. CORRELATION STUDIES

The world-wide and regional differences in the incidence of cancer at various sites (Fig. 6) have been considered to indicate a variation in the exposure to environmental agents, as the genetic influence is likely to be small for most cancers. Moreover, a consideration of age-specific incidence curves suggests that a variety of environmental exposures exist. The observation that cancer of the colon is correlated positively with the level of energy production (an index of industrialization), whereas cancer of the stomach is not, indicates that the correlation of quantifiable aspects of the environment with the observed cancer incidence may provide a source of hypotheses for subsequent testing.

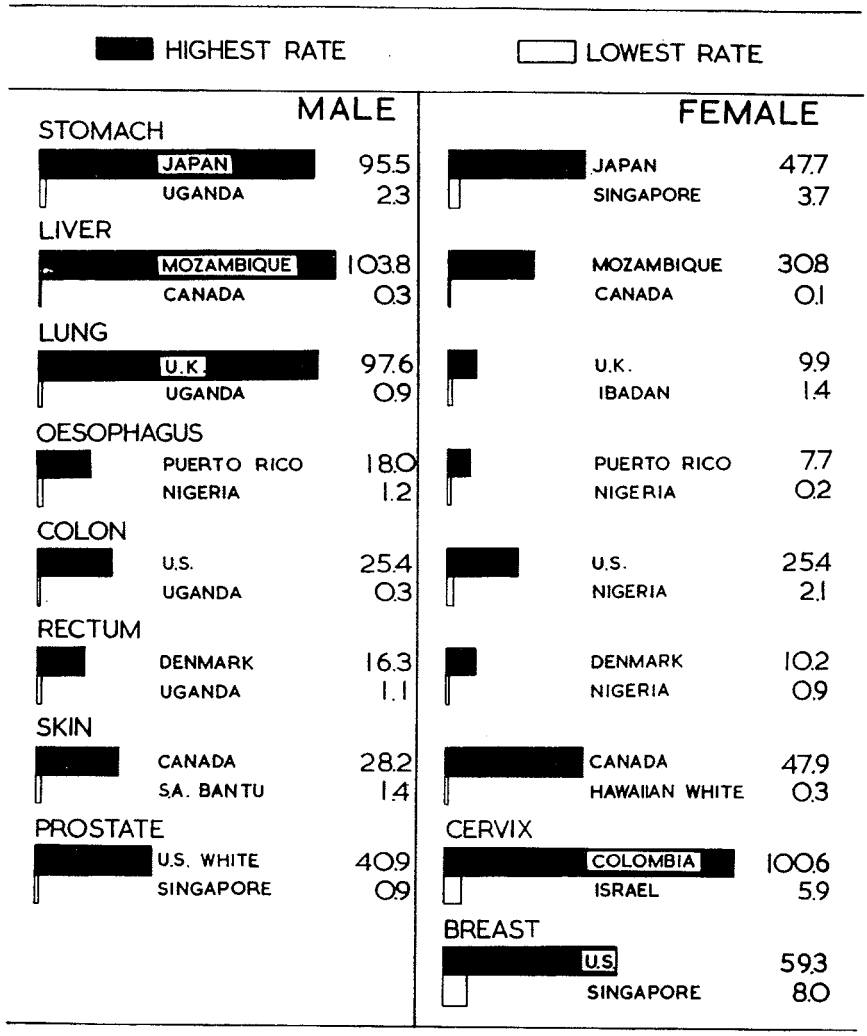

Fig. 6. Highest and lowest observed age-adjusted rates of incidence for selected cancer sites. The wide differences are considered to indicate variations in the exposure to environmental agents.

The unit is preparing a series of studies to correlate aspects of the environment with observed cancer patterns.

7. OTHER STUDIES

7.1 *Tumours in animals*

Dr L. Loomis was a consultant for 11 months in 1968, to advise the Agency on:

(*a*) whether the distribution of certain cancers in domesticated or wild animals is related to the distribution of human cancers in the same regions;

(*b*) whether the study of certain tumours in animals may indicate new methods of approach to the problem of human cancer and throw further light on the nature of certain human cancers; and

(*c*) whether certain specific situations exist in animals which are worthy of investigation in their own right.

Dr Loomis's draft report is now being finalized. His principal conclusions are as follows:

(*a*) the data on animal tumours currently available are inadequate for utilization by the Agency;

(*b*) there is no evidence that the incidence of tumours in animals is related to that of human neoplasms, or *vice versa*; and

(*c*) the Agency should not for the present embark on a programme of epidemiological research in relation to animal tumours.

7.2 *Trophoblastic disease*

The assessment by Professor K. Shanmugaratnam of specimens of microscopically diagnosed malignant trophoblastic disease collected in Norway (by Dr E. Pedersen), in Sweden (by Professor N. Ringertz), in Connecticut (by the late Dr H. Eisenberg) and in Singapore is now completed. The preliminary results (Table 2) confirm the suspected high

TABLE 2

ANNUAL INCIDENCE OF MALIGNANT TROPHOBLASTIC DISEASE PER 100 000 LIVE BIRTHS AND AGE-ADJUSTED INCIDENCE PER 100 000 FEMALES

	Cases per 100 000 births per annum	Cases per 100 000 females per annum
Singapore:		
Chinese	17.7	1.5
Malays	17.7	2.2
Connecticut	2.1	0.09[a]
Norway	6.0	0.22
Sweden	3.7[b]	0.13[a]

[a] Crude rates.
[b] Births and abortions.

incidence per 100 000 births of those neoplasms in Singapore Chinese and Malay women. This incidence, however, is lower than the literature would suggest.

7.3 *Trace elements*

A review of the possible role of trace elements in carcinogenesis[1] was presented at Teheran in June 1968 to a meeting sponsored by the International Atomic Energy Agency on activation analysis in the study of mineral element metabolism in man.

8. THE FUTURE

Completion of the programme outlined above implies a further four to eight years' work.

The unit considers its major future task to be an integrated attack on genital tract cancer. A classical epidemiological approach has finally succeeded in disentangling the many suspect etiological agents obscuring the relationship between sexual intercourse at an early age and this disease.[2] As the facts are consistent with infection as a cause, a combined virological approach is necessary. The world-wide increase in ovarian cancer requires study. The low levels of prostatic and mammary cancer in the Japanese and Chinese indicate the need for a specialist metabolic epidemiology unit to investigate the reasons for them.

Limited though the resources of the Agency are, it has been an encouraging experience to find that in many fields of study a modest investment of funds, when combined with interest and technical advice, evokes a remarkable response in local research workers and often helps induce various groups to contribute to joint international projects.

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[1] Kmet, J. (1969) *Selected aspects of trace metals in cancer research.* In: *Proceedings of the International Atomic Energy Agency Symposium on Activation Analysis, June 1968, Teheran, Iran* (in press).

[2] Rotkin, I. D. & Cameron, J. R. (1968) *Cancer (Philad.)*, **21**, 663.

2. UNIT OF BIOSTATISTICS

Staff: Dr T. WILLIAMS (Chief)
Mr R. NELSEN
Mr B. MORGAN (July-September 1968)

Supporting staff: 3

1. INTRODUCTION

The unit of Biostatistics is responsible for:
(*a*) statistical consulting work for other units of the Agency;
(*b*) data processing and computer programming arising from such co-operation;
(*c*) the formulation of stochastic models for carcinogenesis; and
(*d*) other related basic research.

2. STATISTICAL CONSULTING

The unit has provided consultative services to other units of the Agency. An example of this aspect of its work was a binomial test for determining the sample size necessary to establish a significant difference in the tumour incidence between experimental and control mice in a multi-generation study of carcinogenesis induced by polycyclic hydrocarbons. Another was a non-parametric test for establishing statistically significantly different levels of bound carcinogen on the skin of mice. The cluster-sampling experimental design for determining the relation between aflatoxin ingestion and the incidence of hepatic cancer was examined (page 59).

3. COMPUTER SERVICES

The Agency has access to the IBM establishment at Lyon as well as to the IBM system at WHO Headquarters, Geneva. The shorter debugging runs have been performed locally and the longer production runs at Geneva. An Olivetti 203 machine—a small computer on which autocode programmes can be written—is in use and so, too, is an IBM 029 key-punch. The first collection of UICC data on the world-wide incidence of cancer for all sites for the six five-year age groups from 35 to 65 has been transferred to punched cards, and the logarithm of incidence fitted linearly by the method of least squares.

Data from the Singapore Cancer Registry have been put on punched cards and printed out in tabular arrays together with age-adjusted incidence figures. Similar work was undertaken for Dakar cancer data and a programme written to discover and eliminate duplicate case histories. A computer map given in a recent paper[1] was entirely drawn up by the Calcomp plotter attachment to the IBM 360 computer at WHO Headquarters, Geneva.

4. STOCHASTIC MODELS

Professor H. Drückrey (Freiburg im Breisgau, Federal Republic of Germany) has formulated a biological picture of the carcinogenic process. He assumes that normal tissue cells are continuously being rendered cancerous through the repeated application of a carcinogen and that, once transformation takes place, it is passed on to the daughter cells produced by binary fission. This produces scattered foci of cancerous cells which are held in check until a certain critical threshold is reached (if, indeed, it is ever reached during the lifetime of the host). On the basis of this theory a stochastic model has been developed and its consequences examined mathematically. It is assumed that, since the cells form part of a tissue whose overall size is controlled by the homoeostatic mechanism of the body, the cell fission rate λ is equal to the cell death rate μ during the first stage of this process; however, once the critical threshold is reached, λ becomes greater than μ, with the result that a tumour develops rapidly. If the rate of transformation of normal cells into cancerous cells is δ, and $\alpha = \delta/\lambda$, the moment-generating function of tumour induction time is given by:

$$(\omega/\lambda)^{(\alpha-1)/2} \Big/ \{ \Gamma(\alpha) J_{\alpha-1}(2\sqrt{\omega/\lambda}) \}.$$

The integral transform of this in the complex plane works out in terms of known functions (Jacobi θ -functions) only in the cases where $\alpha = \frac{1}{2}$ or $\frac{3}{2}$. It must be handled on the computer by numerical means in other cases.

The search continues for the development of suitable stochastic models to explain age-specific curves in relation to different cancer sites in man. This programme has been handicapped by the absence of suitable experimental data for comparative analysis.

5. MISCELLANEOUS RESEARCH PROJECTS

A device commonly used by virologists in plating out experiments is to compute the ratio of the number of plaques or foci observed on two Petri dishes. Thus, if 200 plaques are found on one culture medium and 400 on another, the efficiency of plating (e.o.p) is

[1] Williams, T. (1968) *J. gen. Virol.*, **2**, 13.

stated to be 0.5. However, the observed values of 200 and 400 can only be construed as estimates of the means of two Poisson variates, and are therefore subject to sampling fluctuations. If the experiment was carried out repeatedly, it would be found that in 95 % of cases the true e.o.p lay between the limits 0.42 and 0.59. A technique for obtaining such interval estimates has been described,[1] a computer map being given from which the upper and lower limits may be read immediately without any computation.

A technique for measuring the rate of change of bacterial fission rates *in vivo* has been described [2] and the underlying mathematical analysis presented.[3] It is assumed that cells are each initially labelled with a random number of marks, distributed according to the Poisson Law; that the cells are dividing and dying at rates which may vary with time; that, when a cell dies, the marks it carries are destroyed; and that, when a cell divides, each of the marks it bears passes to either daughter cell, with probability $^1/_2$, independently of the fate of the other marks. By measuring the progressive dilution of the marks amongst the cells, i.e., by measuring the percentage of cells bearing at least one mark at time t, the manner in which the fission rate has varied with time can be determined, since the concomitant death of the cells appear to have no influence on the proportion in question. A contour map from which the results may be read directly has been devised.

A study of queueing systems with unpunctual customers which has applications to patients arriving at physicians' surgeries has been made.[4]

6. RELATIONS WITH WHO

Cordial and stimulating relations have been maintained with the relevant units in WHO Headquarters at Geneva. A number of interesting seminars and colloquia have been attended, and fruitful collaboration has been possible with the staff. In particular, the general stochastic model of an epidemic for homogeneously mixing populations with exponential removal of identified infectives has been examined and a much simpler expression has been obtained for the final total epidemic size than appears in the published literature. Other areas of mutual interest have been explored.

7. TRAINING AND EDUCATION

The unit of Biostatistics collaborated with the unit of Epidemiology in a joint training course for medical research workers held in Lyon at the end of June and beginning of July 1968.

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[1] Williams, T. (1968) *J. gen. Virol.*, **2**, 13.

[2] Williams, T. (1969) *Rev. Inst. Pasteur (Lyon)* (in press)

[3] Williams, T. (1969) *Biometrika* (in press).

[4] Nelsen, R. B. & Williams, T. (1968) *Nature (Lond.)*, **219**, 573.

3. UNIT OF ANALYTICAL ENVIRONMENTAL CARCINOGENESIS

Staff: Dr P. Bogovski (Chief)

Supporting staff: 1

The work of the unit of Analytical Environmental Carcinogenesis is shown in Fig. 7.

1. INTRODUCTION

The unit started operations in February 1968.

The main objective of the unit is to develop techniques and programmes for the quantitation of environmental carcinogens, in order to provide data for correlating the levels of carcinogens and the incidence of cancer.

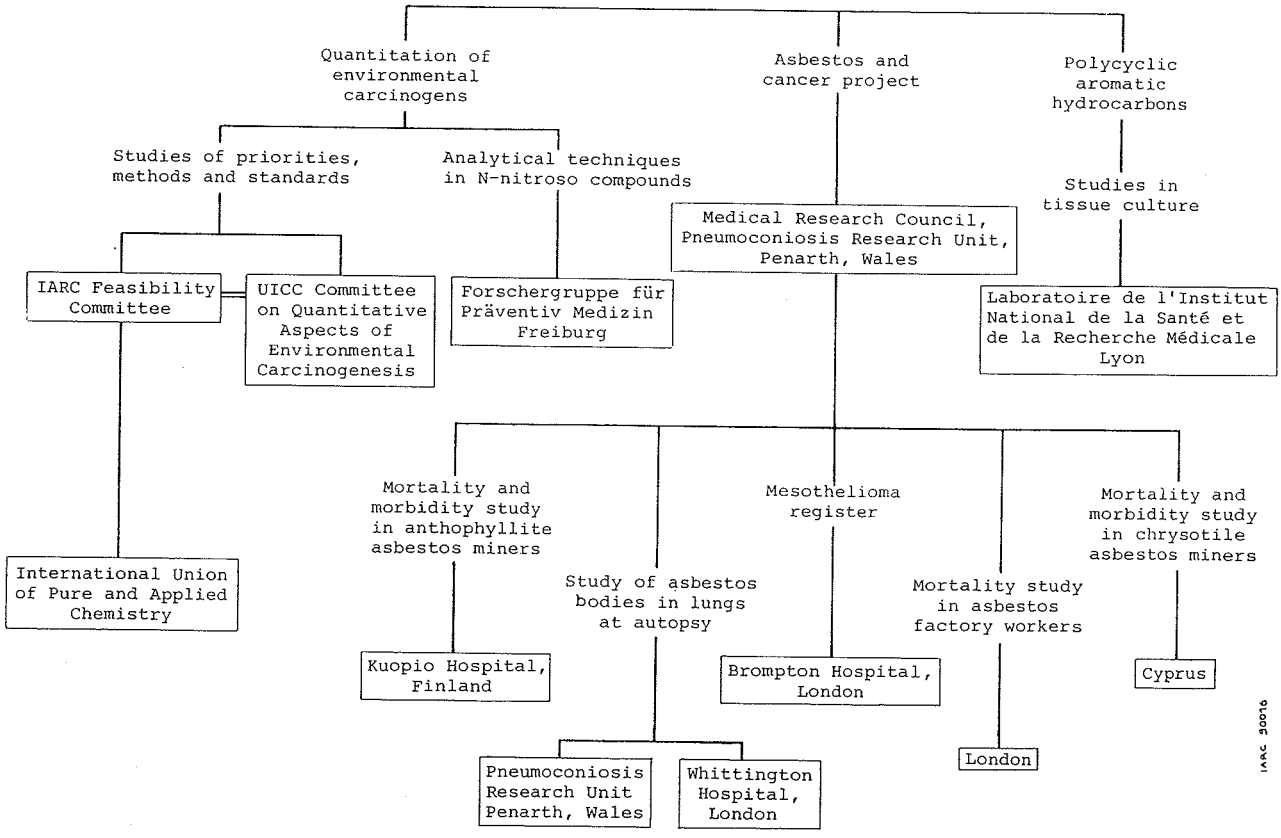

Fig. 7. Unit of Analytical Environmental Carcinogenesis.

2. QUANTITATION OF ENVIRONMENTAL CARCINOGENS

Although most causes of human cancer are environmental, sufficient information is not available regarding the levels of environmental carcinogens to correlate them with the incidence of cancer. No causal relationship has been demonstrated between, for example, cancer mortality in man and exposure to such a well-known carcinogen as benzo [*a*] pyrene.[1] In view of the long latent period of human cancer, it will be necessary to evaluate the whole carcinogenic load and to correlate it with cancer morbidity in selected geographical areas over at least a decade.

Since such a programme is clearly an extremely complicated task, a feasibility committee of scientists experienced in environmental carcinogenesis was created in 1968 to discuss and recommend priorities for the unit's programme. Since the UICC Committee on Quantitative Aspects of Environmental Carcinogenesis was preparing a meeting for the same time at which the standardization of analytical methods for environmental carcinogens would also be discussed, it was decided to organize a joint meeting of both committees. This provided a much larger representation of specialists.

This meeting resulted in a number of recommendations on priorities in the study of environmental carcinogenesis, taking into account the limitation of resources and the fact that the human environment contains many potential chemical hazards. The cancer site, chemicals, and occupational hazards have been considered as bases for establishing priorities.

In the study of oesophageal cancer, it was recommended that nitrosamines, aflatoxins, polycyclic hydrocarbons, and trace metals should be determined. It was also suggested that the Agency should give high priority to surveying a specific environment for aromatic amine and nitrosamine contamination. This will require the development of methods for the identification and quantitation both of amines and of nitrosamines within the environment. A study of methods for the detection and determination of *N*-nitroso compounds is being carried out under a collaborative research agreement by Dr R. Preussman (RA/68/016).

It was also recommended that a system should be developed for the provision of standard reference carcinogenic samples in order to facilitate the standardization of various methods of detecting carcinogens. Further, it was recommended that a survey of the presence and uses of chemical carcinogens in the human environment should be made and correlated with epidemiological and bioassay data.

To implement these recommendations, preparatory work for the establishing of a network of regional laboratories has been started, and a preliminary selection of suitable geographical areas for use in the programme has been carried out.

It is recognized that the Agency will not itself be able to finance as extensive a programme as is required. However, it may well stimulate work and initiate programmes in

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[1] Stocks, P. (1966) *Brit. J. Cancer*, **20**, 595; Waller, R. E. & Commins, B. T. (1967) *Environ. Res.*, **1**, 295; etc.

the field by the establishment of working groups for the development of methods and analytical procedures. Furthermore, the Agency will itself be actively involved in single projects devoted to specific objectives.

Close contact is maintained with the appropriate units of WHO.

3. ASBESTOS PROJECT (RA/67/002)

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

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

3.1 *Finland: Retrospective/prospective mortality and morbidity study in anthophyllite asbestos miners in Finland by Dr L. Meurman and Dr R. Kiviluoto*

Of the population of 1092 workers with three or more months of exposure to anthophyllite asbestos at any time between 1 January 1936 and 1 July 1967, 998 (91.4 %) have been followed up. There have been 244 deaths with 237 death certificates. Replies to a questionnaire have been received from 754 of the 848 workers thought to be alive. The follow-up continued until 1 April 1969. Dr M. Hakama, of the Finnish Cancer Register, is helping in the analysis. The well established differences in death rates from lung cancer between the eastern and western parts of Finland are being taken into account.

The preliminary results suggest that in the asbestos workers the lung cancer and pulmonary tuberculosis death rates are about twice as great as should be expected. No case of mesothelioma has been discovered. An increased risk of bronchial cancer has not been observed previously in the anthophyllite mines. The absence of mesotheliomas of the pleura and peritoneum confirms previous reports from Finland and adds to the evidence that anthophyllite differs in this respect from other types of asbestos.

In addition to the epidemiological study, an investigation is in progress to compare the collagen (estimated as hydroxyproline) content of lungs in relation to the presence and number of asbestos bodies detected by the light microscope. Sixty lungs have been studied by Dr H. Huttunen. The lungs are being analysed chemically at the Pneumoconiosis Research Unit in the United Kingdom.

This is the first detailed epidemiological investigation of a well-defined population of anthophyllite workers. It will provide a much clearer picture of the effects of this type of asbestos. The smoking histories collected from the mining population will be used for comparison with other data in Finland.

3.2 *Great Britain*

(1) *Mesothelioma register*

Support for a secretary and a technician has made it possible to establish a centre in Dr K. F. W. Hinson's Department at the Brompton Hospital, London. Here all the

information on mesotheliomas detected in the United Kingdom is collected. Sections cut from material sent in are distributed to a panel of pathologists. The Centre works in co-operation with the Pneumoconiosis Panels of the Department of Health and Social Security. Mesothelioma has been a compensatable industrial disease in the United Kingdom since August 1967 and hence is notifiable. In addition, the Medical Department of the Department of Employment and Productivity is notified of the cases as early as possible, so that the medical inspectors can make inquiries about the occupations of the patients.

The number of cases identified has been rising steeply in the last four years. Undoubtedly part of the reason for this is greater awareness of the disease, but pathologists who have had experience of mesothelioma over many years think that a real increase in the incidence is occurring. Analysis of the Register cases will be made when sufficiently complete information has been collected.

The Register staff have also assisted in the collection of the pathology reports of 426 deaths in a retrospective/prospective mortality inquiry by Dr M. L. Newhouse and Mr I. D. Hill covering the male population of workers and ex-workers of an asbestos factory in the East End of London. Seven deaths had been certified as due to mesotheliomas. Fifteen additional mesotheliomas were added after reclassification of 301 deaths when more information was received from hospitals and coroners' inquests. Dr Blanche Butler assisted in this work.

(2) *Retrospective study of the prevalence of asbestos bodies in autopsies in London, 1926-1966*

Using improved quantitative methods, Dr Chang Hyun Um has been making a systematic search of a representative sample of lungs from deaths occurring in the years 1936, 1946, 1956, and 1966. The material for this study has been provided by Dr P. C. Marks, Director of Pathology, Whittington Hospital, London, where blocks and full pathological reports have been preserved since 1933; 500 lungs have been examined so far. Preliminary results show that there has been a steady rise over the years in the proportion of lungs in which asbestos bodies and fibres can be detected under the light microscope. An additional sample of the pathological material is being inspected to investigate the change in prevalence with age. Later it is hoped that it will be possible to undertake electron microscope studies and X-ray diffraction analysis of the fibres in a representative sample of this material, to provide additional evidence on the nature of the fibres.

(3) *International study of asbestos bodies*

The Agency has supported an international study, carried out in 12 centres, of the prevalence of asbestos bodies in consecutive autopsies.

3.3 *Cyprus : morbidity and mortality in a chrysotile mine*

Following a pilot inquiry made in Cyprus in 1966 with UICC support, which showed little asbestosis and no detected cancer risks despite heavy dust exposure in the mills, it was decided to look first at the dust.

A dust survey of an old mill, which was about to be replaced, was made by Mr G. Kronides, Assistant Senior Mines Officer. Mr Kronides visited the Pneumoconiosis Research Unit for training in the new techniques used for sampling fibrous dusts. Some of the results confirmed the high dust concentration suspected. Other results need further investigation.

A large group of radiographs of asbestos miners, taken annually over about ten years, requires classification. This is now possible because of a system developed by an international group of radiologists and epidemiologists meeting, with UICC support, in Cincinnati, USA, in 1967. The classification developed has already been applied to 16 000 films of workers and ex-workers in the chrysotile mining area in Quebec, and it is hoped that the Cyprus group of films will be classified by Dr M. G. Constantinides and his staff in 1969. The first case of a pleural mesothelioma has now been reported from Cyprus. The histology has been confirmed by the United Kingdom Panel of Pathologists. Light and electron microscope studies of the dust in the lungs are now being made by Dr Pooley.

3.4 *Southern Africa : chrysotile mines in Swaziland*

Studies of the effects of asbestos exposure on the populations around crocidolite and amosite mines have been reported by Dr G. K. Sluis-Cremer and Dr J. C. Wagner in southern Africa. No comparable studies have been made near chrysotile mines.

An opportunity to start this work arose when Dr Y. S. Kaplan, at present in charge of the National Tuberculosis Control Centre in Swaziland, visited the United Kingdom. It appeared feasible to make a pilot study of the asbestos bodies in sputum samples sent in for the identification of tubercle bacilli.

3.5 *Future projects within the initial three-year period of the asbestos cancer research agreement*

The Agency is at present exploring with the Pneumoconiosis Research Unit the question of further support for the techniques developed by the Unit for the positive identification of the type and quantity of asbestosis in lung sections in concentrates. A method has been developed whereby single fibres can be identified on the basis of their ultrastructural morphology and confirmation achieved by X-ray diffraction analysis. These studies are most pertinent in determining which formations of asbestos are most dangerous for man.

4. UNIT OF BIOLOGICAL CARCINOGENESIS

Staff: Dr G. DE THÉ (Chief)
Dr J.-C. AMBROSIONI
Dr R. SCHMAUZ

Supporting staff: 6

The work of the unit of Biological Carcinogenesis is shown in Fig. 8.

1. INTRODUCTION

The Unit of Biological Carcinogenesis was established in April 1967 to study the role of viruses in the development of human tumours, utilizing the unique opportunity the Agency provides for studying simultaneously in different regions the environmental factors involved in the genesis of the same type of tumour. Three types of tumours are being

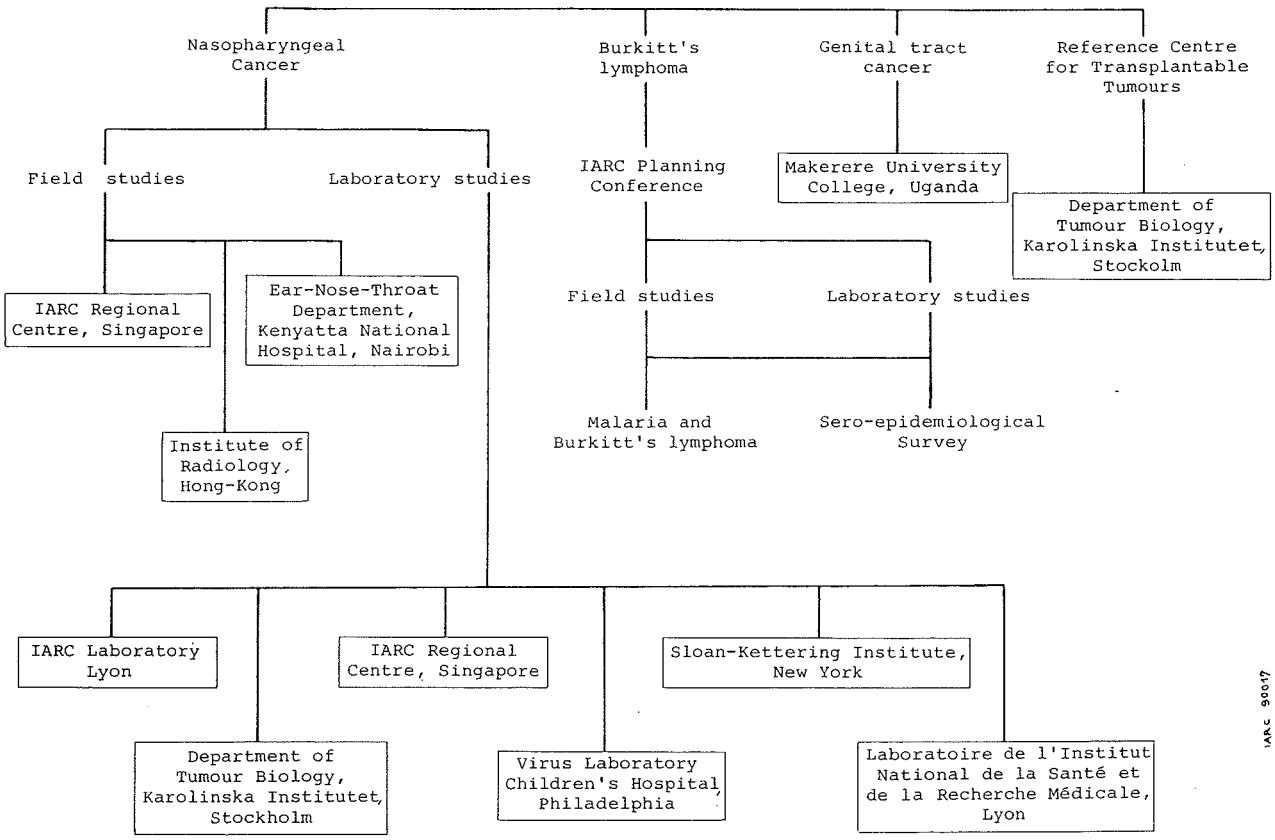

Fig. 8. Unit of Biological Carcinogenesis.

investigated, through integrated field and laboratory studies and in close collaboration with a number of national laboratories. They are:

(1) nasopharyngeal carcinoma, a tumour prevalent in South-East Asia among the Chinese population;

(2) Burkitt's lymphoma, a tumour associated with tropical climatic conditions; and

(3) cancer of the genital tract.

2. STUDIES ON NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma is 60 times more frequent among the southern Chinese than among Caucasians. This apparent relationship between an ethnic group and the prevalence of a tumour is of interest to the Agency, since the role of genetic factors in susceptibility or resistance to experimental viral and chemical carcinogens is well established.

2.1 *Field studies*

(1) *IARC Regional Centre, Singapore*

Principal investigator: Professor K. Shanmugaratnam

Full details of the work in progress are given in the report of the Regional Centre (page 69).

(2) *Institute of Radiology, Kowloon, Hong Kong*

Principal investigator: Dr H. C. Ho, Director of the Institute

A collaborative research agreement was signed in May 1968 for the dispatch of biopsy specimens from Hong Kong to Lyon; between 5 May 1968 and 8 January 1969 245 separate samples were received, including both biopsy specimens and the sera of patients. The biopsy specimens were transmitted in a medium ready for culturing, fixed in glutaraldehyde ready for electron microscopy, and as smears and in formol saline ready for histological examination. Aliquots of the sera were sent to collaborating laboratories in the Department of Tumour Biology, Karolinska Institutet, Stockholm (Professor G. Klein), the Sloan-Kettering Institute, New York (Dr L. J. Old), and the Virus Laboratory, Children's Hospital of Philadelphia (Dr W. and Dr G. Henle).

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

Principal investigator: Mr P. Clifford, FRCS

Mr Clifford is already collaborating with Professor G. Klein, Stockholm, and has extended his collaboration to the Agency.

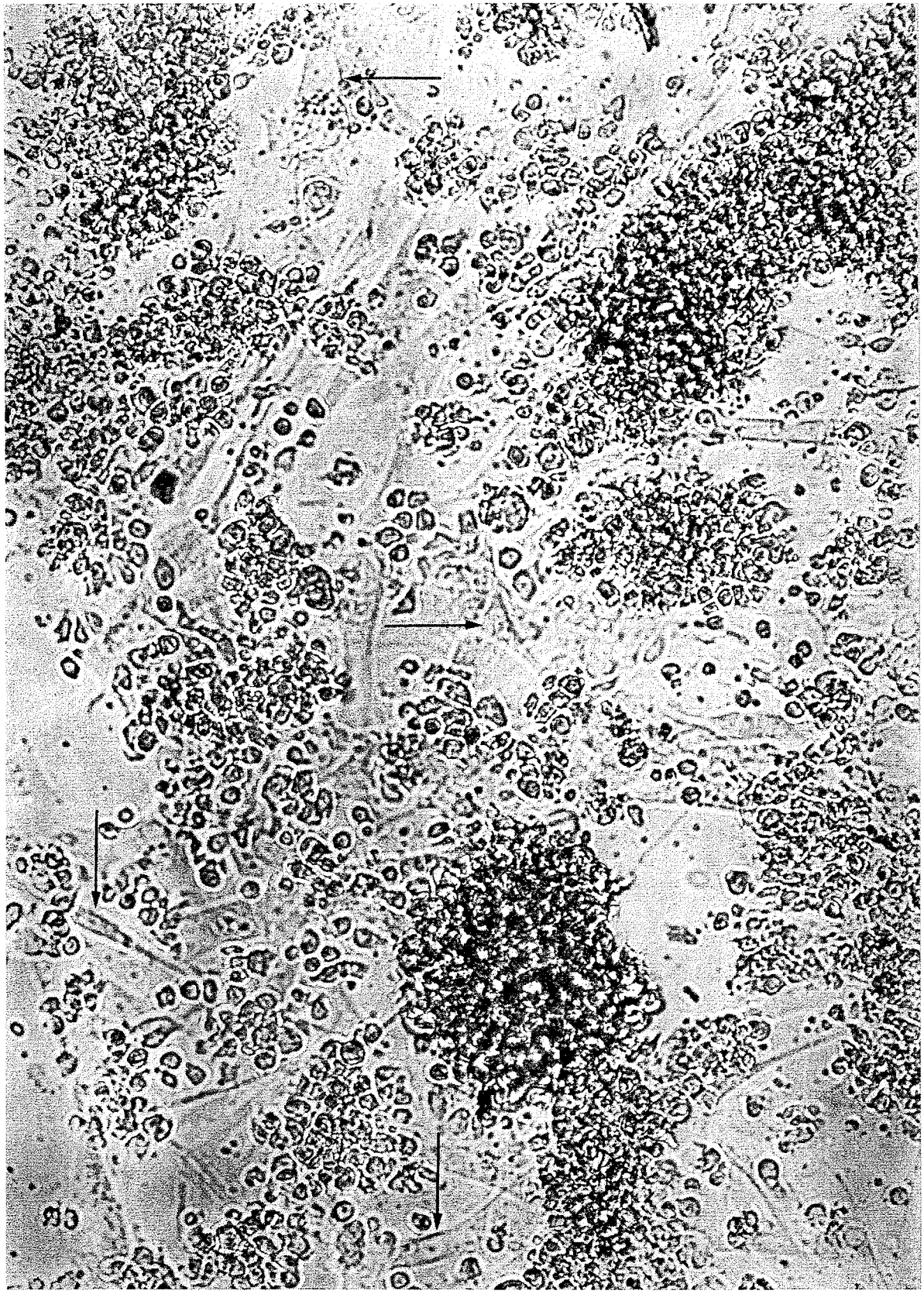

Fig. 9. Microscopic appearance of NPC 866 cell line showing fibroblastic cells in the background attached to the glass (arrows). On top of these cells rounded free-floating cells in large clumps are visible. × 190.

2.2 *Tissue culture studies*

Biopsy specimens of nasopharyngeal carcinoma received from Hong Kong and more recently from Nairobi have been prepared as tissue cultures. Epithelial growth was obtained, fibroblastic elements progressively supplanting the epithelial cells after the first or second subculture. Long-term cultures were obtained in which fibroblastic cells were predominant. A lymphoblastoid transformation was observed in one culture. In this culture epithelial cells were the first to grow and were later replaced by fibroblastic elements, which underwent an apparent lymphoblastoid transformation to give a permanent culture of round free-floating cells (referred to as the NPC/866 line) mixed with fibroblastic elements (Fig. 9).

2.3 *Ultrastructural studies of biopsy specimens and cell cultures*

The preliminary results show that cultures of epithelial cells with nearly full differentiation do survive and divide. Large nuclear inclusions, already noted by Papadimitriou in biopsy specimens, were found in a larger number in the tissue culture preparations. The presence of emperipolesis was also noted in a few cases (page 70).

2.4 *Morphological studies of the lymphoblastoid NPC/866 line*

Comparison of the *in vitro* characteristics of the cell line derived from nasopharyngeal carcinoma and those derived from Burkitt's lymphoma and infectious mononucleosis has been undertaken and reveals some differences. The NPC/866 line appears to have the capacity to alternate from fibroblasts to round free-floating cells and *vice versa*, whilst the others do not. Electron microscopic examination of the NPC/866 line exhibited the presence of herpes-type virus particles in 0.5 to 2 % of the cells (Fig. 10). The relation between this virus and the Epstein-Barr virus is under investigation. The role of arginine deprivation in the tissue culture medium of the three cell lines is being studied.

2.5 *Immunological studies*

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

Collaborators: Professor R. Sohier and Mr T. Greenland

A technique using antibodies labelled with radioiodine is being developed for these studies, since the method promises to be not only extremely sensitive but also highly suitable for the large number of measurements required to deal with the samples derived from field studies.

Studies in collaboration with Professor G. Klein have been started to compare the immunological properties of the NPC/866 cells and of Burkitt's lymphoma cells.

Recent data derived from a study of the sera of 60 patients with nasopharyngeal carcinoma from whom our cultures originated and the sera of patients with Burkitt's

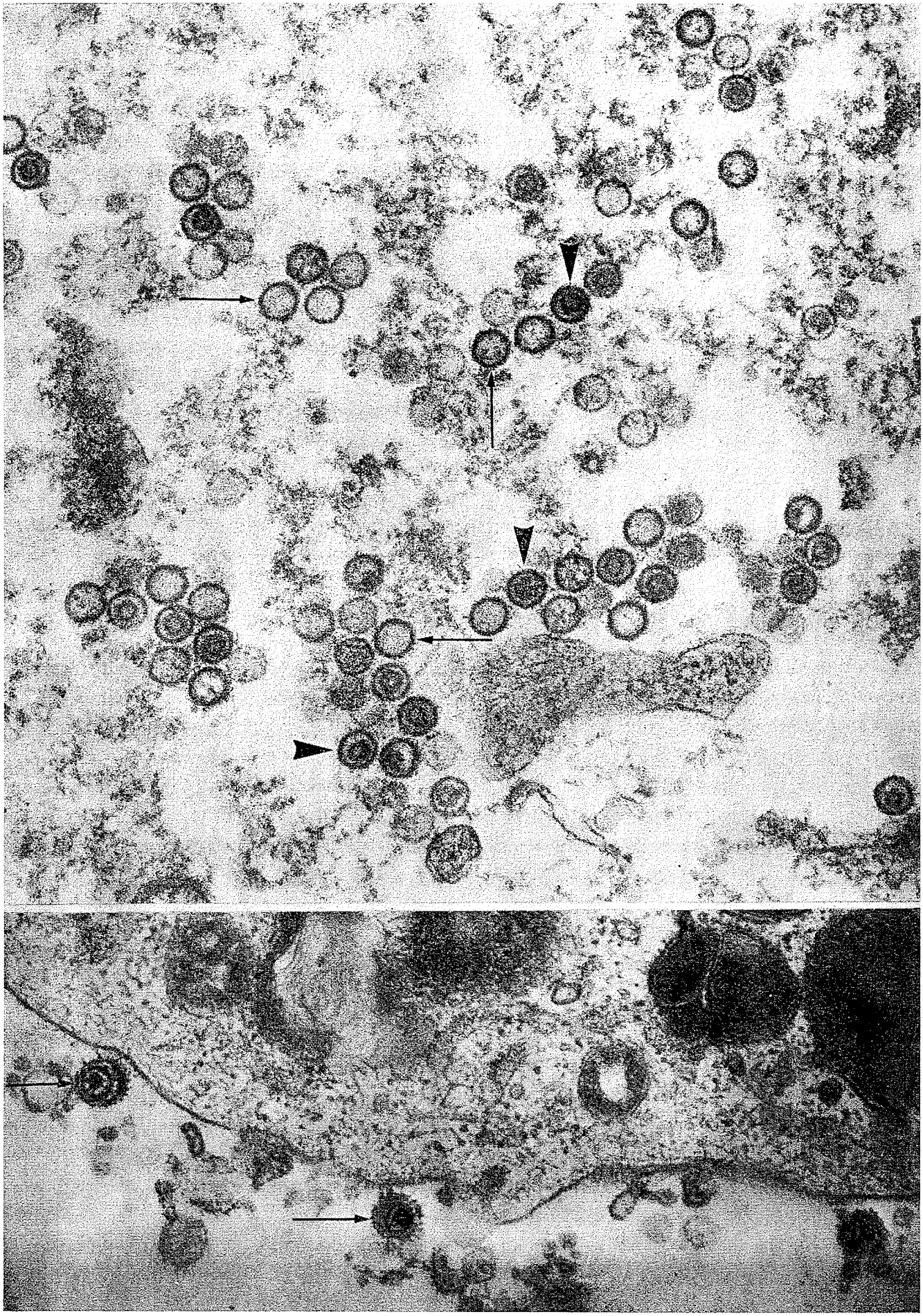

Fig. 10. Electron photomicrograph of NPC 866 free-floating cells showing herpes-type virus particles in the nuclei and extracellular spaces. In the upper photograph empty capsids (thin arrows) and nucleocapsids (thick arrows) are present. In the lower photograph two complete herpes-type virions are visible, in a culture grown on arginine-free medium. × 57 000.

lymphoma suggest that there are some antibodies common to both groups of sera (G. Klein, Stockholm, and W. and G. Henle, Philadelphia—personal communication).

2.6 *Heterokaryon technique*

In collaboration with Professor R. Sohier and his assistant, Mr L. Gazzolo, the recuperation of Rous virus from transformed mammalian cells when cultured and fused with sensitive chicken fibroblasts is being investigated. This model system should eventually provide an important technique for application to the study of viral infection in human tumours.

2.7 *Future studies*

The Round-Table Conference on the possible relationship between Burkitt's lymphoma and infectious mononucleosis (IARC Internal Technical Report No. 68/004) held in Nairobi in December 1968 also discussed the possibly related problem of nasopharyngeal carcinoma. Amongst their proposals are listed three sero-epidemiological studies of that condition in relation to Epstein-Barr or a related virus. The conference proposed a study of the serological patterns in an endemic area, a cluster study, and a similar study to include siblings of patients and matched controls. It was further proposed that a pathology register should be established for nasopharyngeal carcinoma.

Future studies will also include a collaborative research project with the relevant unit at WHO Headquarters, Geneva, and the WHO Regional Immunology Centre in Singapore. It is planned to investigate by tissue typing the possible genetic factor or factors associated with the high incidence of nasopharyngeal carcinoma in Chinese.

Another method will consist in investigating the susceptibility of fibroblastic cells from different ethnic groups to oncogenic viruses such as SV 40.

3. STUDIES ON BURKITT'S LYMPHOMA

Following the establishment of a relationship between infection by the Epstein-Barr virus and the development of infectious mononucleosis, Dr W. Henle and Professor G. Klein suggested that the Agency should organize a round-table conference on the feasibility of sero-epidemiological surveys in Africa for studying the relationship between infection with that virus and the development of Burkitt's lymphoma.

The Round-Table Conference referred to above met and made a number of recommendations (IARC Internal Technical Report No. 68/004).

The main proposal was to study the serological patterns preceding the development of Burkitt's lymphoma and to compare the serological profiles of close relatives of patients with those of controls from neighbouring households matched for age and sex.

Other projects include study of the relationship between malaria and the development of Burkitt's tumour.

Since this tumour is relatively rare, study of the serological pattern of the patients before its development requires a survey of a large number of children who would have to be followed up clinically. Clearly such a study could only be done in the wider context of other simultaneous research projects and of a developing health service.

The implementation of these sero-epidemiological surveys will require a full-time co-ordinator working in Nairobi. He will have to control the activities of the field stations which it is hoped to establish in the West Nile Province of Uganda and the Shirati area of Tanzania (for the study of Burkitt's tumour) and in the Nandi area of Kenya (for the study of nasopharyngeal carcinoma). The serological studies will be carried out in the collaborating laboratories already mentioned and in the Agency's laboratories.

4. CANCERS OF THE GENITAL TRACT

Epidemiological studies have clearly shown the relationship between circumcision and the incidence of cancer of the penis on the one hand and between an early sexual life and cancer of the cervix on the other. Thus the possibility of biological carcinogens playing a role in cancer of the genital tract is a reasonable hypothesis.

Dr R. Schmauz, who was appointed an IARC Research Assistant to work at Makerere University College under Professor M. S. R. Hutt, has been studying the general pathology of tumours in Africa since October 1968. His special research is concerned with cancer of the penis and precancerous lesions in certain tribes of Uganda. He sends biopsy specimens to the Agency for tissue culture and electron microscope studies.

It is intended eventually to develop studies in different parts of the world where epidemiological data on cancer of the genital tract have shown the existence of abnormally high rates.

5. IARC TUMOUR TRANSPLANTATION REFERENCE CENTRE

Originally established by WHO, the IARC Tumour Transplantation Reference Centre under Professor George Klein, at the Department of Tumour Biology, Karolinska Institutet, Stockholm, continued to function during 1968 with the scope of its activities considerably enlarged. The original function of the Centre—the provision of transplantable animal tumours preserved in the frozen state—still remains the main one, but the provision of human tumour tissues and of sera and normal tissues of tumour-bearing patients and controls has become a continuously increasing additional activity during the last three years. This service was originally stipulated in the contract signed with WHO as one of the possible future functions of the Centre, but it was not until 1965-1966 that the demand for it became marked.

Supply of tumours

The number of shipments of tumours during 1966 was 133, to 43 investigators in 14 different countries. In 1967, it increased to 271 shipments, to 65 investigators in 18 countries. For 1968 the analysis of shipments has not yet been made, but the number will certainly show an increase over 1967.

The animal tumour collection

The animal tumour collection maintained at the Centre includes: murine sarcomas induced by methylcholanthrene, dibenzanthracene, the implantation of cellophane films, X-irradiation, radioactive strontium, polyoma virus, adenoviruses of different types, murine sarcoma virus (MSV), and the Schmidt-Ruppin variant of the Rous virus; carcinomas arising spontaneously in strains carrying the mammary tumour agent (MTA) or after inoculation of the MTA into strains that are devoid of it, oestrogen-induced mammary carcinomas, and various carcinomas induced by the polyoma virus. Long-established ascites carcinoma strains include the non-specific Ehrlich and Krebs-2 lines, and the strain-specific ascites carcinomas TA3 and 15091a, of A-strain origin. The collection also includes lymphomas or leukaemia induced by the Gross, Moloney, or Graffi viruses, by X-irradiation, by oestrogen administration, or of spontaneous origin. A number of long-established lymphomas are available as well, propagated in the ascites form, such as 6C3HED or Gardner's lymphoma, DBA or Dalton's lymphoma, and the EL4 lymphoma. Other tumour types include interstitial cell tumours of the testis, induced by oestrogens and some hormone-producing pituitary tumours.

Nearly all mouse tumours (with the exception of a few long-transplanted so-called non-specific lines) have been induced in highly inbred mouse strains that carry known isoantigen markers. Information on strain compatibility and antigenic markers is as a rule provided together with the tumour. A small number of animals of the same genotype is also frequently provided, to facilitate establishment of the line by serial transplantation.

For special studies parallel tumour sublines are available, selectively isolated from the same tumour cell population but differing with regard to isoantigenic expression or the expression of virus-determined, membrane-localized tumour-specific antigen markers. As a rule, such differences in surface antigen expression are paralleled by differences in immunosensitivity *in vivo* or *in vitro*.

Other special strains include the TL antigen system, available in the form of congenic TL+ and TL— lines on the same genetic background and translocation-bearing stocks like T6 or T190. The latter translocation involves the H-2-bearing ninth linkage group. A number of immunoglobulin-producing myeloma lines are available as well.

Human tumour material

The human tumour material provided on a regular basis includes fresh biopsy material from Burkitt's lymphoma, other lymphomas and leukaemia, carcinomas of the naso-

pharynx, and a number of carcinomas and sarcomas. Most of the material comes from Nairobi, but human tumour materials from many types occurring in Sweden can be made available on request as well. There is a very large collection of corresponding patient and control sera. Pre- and post-disease sera as well as bone marrow and white cell samples can also be made available from cases of infectious mononucleosis.

Tissue culture lines

Tissue culture lines include more than two dozen lines of Burkitt's lymphoma, half a dozen leukaemia lines of non-Burkitt origin, lines derived from peripheral white cells of normal donors or mononucleosis cases, MSV-induced hamster, mouse, and rat sarcomas, and 3T3 and BHK 21 cells, not transformed or transformed by various oncogenic viruses.

In addition to its function as a purely service organization, the Centre frequently participates in a more active way in the selection of materials particularly suitable for the study of a given problem. If mutually desired, a collaborative study can be initiated as well.

5. UNIT OF CHEMICAL CARCINOGENESIS

Staff: Dr L. TOMATIS (Chief)
Dr V. TURUSOV
Dr P. SIZARET
Miss B. WITTHOFF
Mr R. CHARLES

Supporting staff: 5

The work of the unit of Chemical Carcinogenesis is shown in Fig. 11.

The objective of the unit is to achieve better understanding of the mechanism of carcinogenesis so that the knowledge can be applied to protection against and the elimination of identified carcinogenic hazards for man. The unit started work on 1 November 1967.

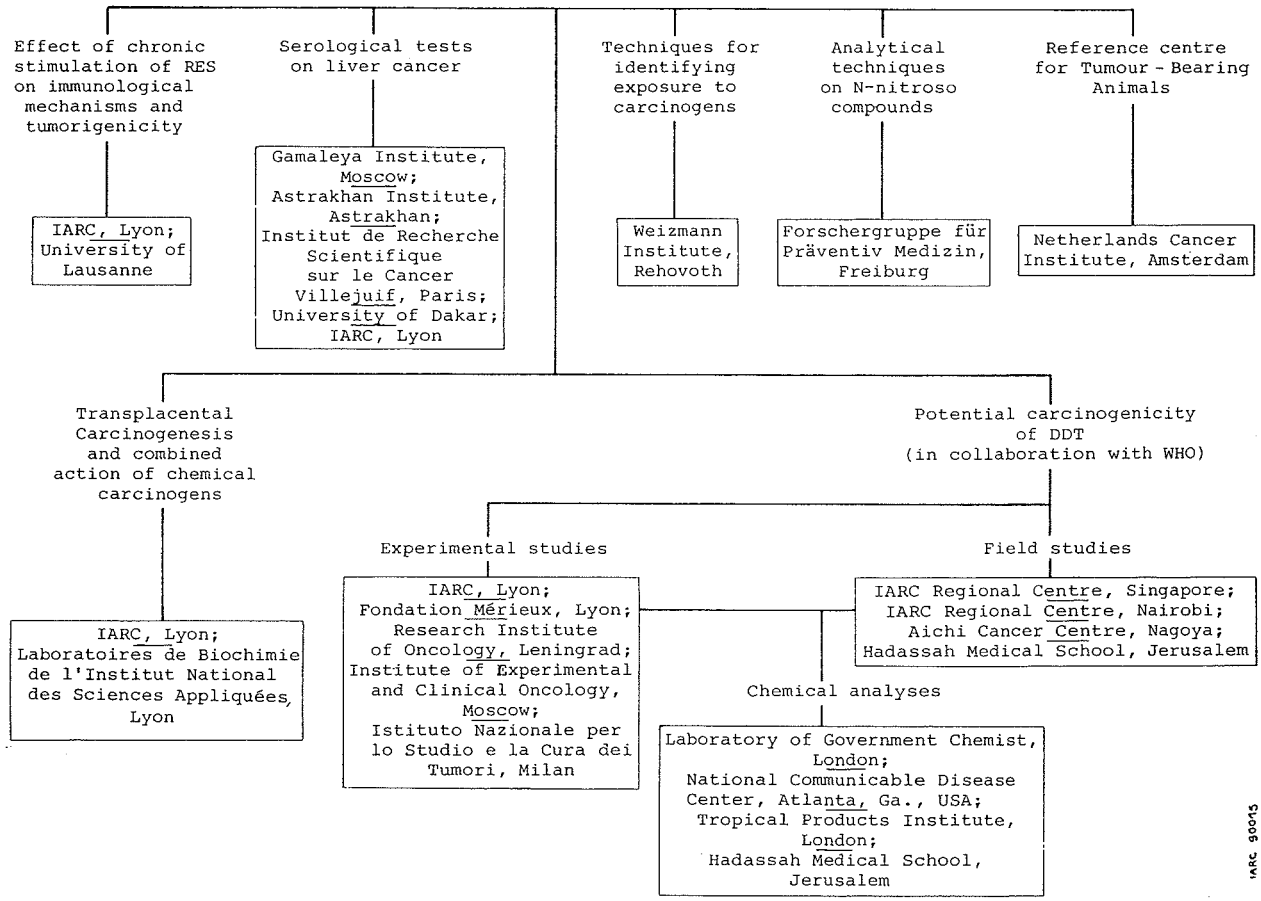

Fig. 11. Unit of Chemical Carcinogenesis.

1. POTENTIAL CARCINOGENIC HAZARD OF PESTICIDES

The potential carcinogenic hazard of the chlorinated hydrocarbon 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)ethane (DDT) has been investigated. Data from the literature had shown that the long-term administration of DDT to rats is followed by the appearance of a few hepatic tumours and of nodular adenomatoid hyperplasia of the liver.[1] More recent reports indicate that the long-term administration of DDT to mice extended for several generations may result in the appearance of a rather high incidence of tumours, beginning at the second generation and increasing in the following generations.[2] The Agency, following the recommendation at the WHO and FAO meeting held in Rome on 4 December 1967, therefore decided to undertake an extensive investigation on the possible carcinogenicity of DDT.

A collaborative study with the financial aid of WHO has been organized to cover both laboratory and field projects. The first three research agreements were concluded within three weeks.

1.1 *Laboratory studies*

The experimental investigation is being carried out in four different laboratories on three different strains of mice and on one strain of rats. Similar experimental conditions are maintained in the four collaborating laboratories. DDT is administered mixed into the food continuously for life and for five consecutive generations at various dose levels. The animal feed used in all four laboratories is periodically checked for possible aflatoxin contamination by the Tropical Products Institute, London. The levels of DDT and its metabolites are periodically checked by the Laboratory of the Government Chemist, London, both in the feed used for control and in the feed containing the DDT. In each generation several animals are sacrificed to check the DDT level in the tissues. The analyses are carried out at the National Communicable Disease Center, Atlanta, Georgia, USA. The laboratories where the trials are carried out are as follows:

(1) *Fondation Mérieux, Lyon, France* (RA/68/HQ.1)

(Under the direct supervision of the unit of Chemical Carcinogenesis)

CF_1 outbred SPF (specific pathogen-free) mice are used. DDT is administered at four dose levels, namely 2, 10, 50, and 250 ppm. As well as a control group of untreated animals, two additional groups of mice, representing positive controls, receive a known carcinogen (urethane) at two different dose levels (see Table 3).

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[1] Food and Agriculture Organization (1965) Report No. PL/1965/10/1, Rome.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 391.

TABLE 3

EXPERIMENTAL STUDY ON THE POTENTIAL CARCINOGENICITY OF DDT

Administration of DDT or urethane at various concentrations to CF_1 mice
(Fondation Mérieux and IARC, Lyon)

Treatment	Sex	Number of animals at start[a]				Survivors at 31.12.68			
		P[b]	F_1	F_2	F_3	P	F_1	F_2	F_3
Controls (untreated)	♂	64	66	57	—	59	64	57	—
	♀	61	61	69	—	57	56	69	—
DDT 2 ppm	♂	60	68	57	—	57	66	57	—
	♀	60	53	65	—	58	51	65	—
DDT 10 ppm	♂	60	59	68	—	58	53	68	—
	♀	59	70	60	—	56	68	60	—
DDT 50 ppm	♂	60	78	68	—	55	75	68	—
	♀	60	52	60	—	57	50	60	—
DDT 250 ppm	♂	60	64	59	—	52	58	59	—
	♀	60	53	59	—	53	45	59	—
Urethane 0.001 %	♂	48	61	63	50	46	61	62	50
	♀	40	38	39	40	36	38	38	39
Urethane 0.01 %	♂	48	45	65	41	42	44	63	41
	♀	48	37	39	43	44	35	39	43

[a] Number at start; for the descendants, the number at weaning.

[b] All parent groups were started between April and June 1968, and the parents were mated after 4 weeks of treatment.

(2) *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, namely 2, 20, and 250 ppm. In addition to untreated controls, a positive control has been established with mice receiving a known chemical carcinogen, dimethylnitrosamine (see Table 4).

(3) *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, namely 2, 10, and 50 ppm.

TABLE 4

EXPERIMENTAL STUDY ON THE POTENTIAL CARCINOGENICITY OF DDT

Administration of DDT at various concentrations or **N**-nitrosodimethylamine (DMN) to BALB/c mice

(Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan)

Treatment	Groups	Sex	P		F_1 [a]	
			Number at start	Number at 31.12.68	Number weaned	Number to be weaned
Controls (untreated)	A	♂	28	24	19	24
		♀	29	29	29	
	B	♂	35	32	25	24
		♀	31	29	23	
DDT 2 ppm	A	♂	30	29	20	9
		♀	35	34	17	
	B	♂	34	29	20	26
		♀	31	31	28	
DDT 20 ppm	A	♂	28	24	17	31
		♀	32	31	17	
	B	♂	30	25	16	26
		♀	32	32	25	
DDT 250 ppm	A	♂	33	24	26	13
		♀	28	27	15	
	B	♂	29	21	12	25
		♀	40	40	13	
DMN 0.0003 %	A	♂	28	24	27	23
		♀	33	32	16	
	B	♂	20	19	9	21
		♀	31	29	11	

[a] Situation at 31 December 1968.

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

Principal investigator: Professor L. Shabad

Mice of the inbred strain A are used and DDT is administered at two dose levels, 10 and 50 ppm. Using a technique developed by Professor Shabad in 1968, this experiment aims at repeating the experiment described above in an *in vitro* system using organ cultures.

1.2 *Field studies*

The objective of the field study is to obtain baseline data on exposure to and storage of DDT in man, by monitoring the DDT levels over a long period. Samples of human fat tissue are collected in different areas of the world: in Singapore, through collaboration with Professor K. Shanmugaratnam, Head of the IARC Regional Centre; in Japan by Professor K. Akazaki, Aichi Cancer Centre, Nagoya; in Israel, Nigeria, and Uganda by Professor Wassermann, Hadassah Medical School, Jerusalem; and in Kenya by Dr M. Rogoff, Medical Research Laboratories, Kenya. Samples are collected from 25 individuals of each sex in the following six age groups: stillborn and foetus, 0-1, 1-5, 6-20, 25-45, and 46-80. The stillborn and foetus group is of particular importance since DDT is known to cross the placental barrier and has been found present in large amounts in stillborn children.[1] The chemical evaluation of the DDT content in human tissues is carried out at the National Communicable Disease Center, Atlanta, Ga., USA (Dr W. Barthel), and at the Department of Occupational Health, Hadassah Medical School, Jerusalem (Professor M. Wassermann).

2. LOW-DOSE CARCINOGENESIS WITH MULTIPLE CARCINOGENS; TRANSPLACENTAL AND PERINATAL CARCINOGENESIS

The effects of exposure to several chemical carcinogens at low doses have significant implications, since man will rarely be exposed to levels as high as those used in experimental studies. Very little is known about the possible significance of the total carcinogenic load to which man is exposed in his environment. Further studies are required to investigate the possibility of synergism when multiple carcinogenic agents are involved.

Investigations on the effects of the exposure of the foetus and newborn to chemical carcinogens via the placenta or the milk are at present under way. The possible effects of prenatal and perinatal exposure to chemical carcinogens on susceptibility later in life to the same or different carcinogens is also being explored. In the present experiment, methylcholanthrene is administered to mice, either alone or combined with diethylnitrosamine.

2.1 *Département de Biochimie, Institut national de Sciences appliquées, Lyon* (RA/68/011)

Principal investigator: Professor H. Pacheco

An investigation is under way to quantify the amount of chemical carcinogens that may reach the foetus by crossing the placental barrier or may reach the newborn via the mother's milk. This collaborative study with Professor Pacheco should later develop into a study on the effect of enzyme inducers on the foetus and newborn in relation to their later response to a carcinogenic stimulus.

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[1] Wassermann, M., et al. (1967) *Pesticides Monitoring Journal*, **1**, 15.

3. TESTING FOR MARKERS INDICATIVE OF PREVIOUS EXPOSURE TO CARCINOGENS

3.1 *Weizmann Institute of Science, Department of Experimental Biology, Rehovoth, Israel* (RA/67/004)

Principal investigator: Dr S. Mirvish

The purpose of this investigation is to determine whether or not metabolic modifications produced by chemical carcinogens may prove of value in identifying exposure in human population groups. Its final goal is to develop field methods for identifying man's exposure to carcinogens. Preliminary work has concentrated on the metabolism of dimethylnitrosamine and diethylnitrosamine in experimental animals. The total radioactivity in the liver proteins and nucleic acids after the injection of ^{3}H-dimethylnitrosamine and ^{3}H-diethylnitrosamine has been evaluated. It was found that, among other labelled purines, ^{3}H-7-methylpurines are excreted not only after injection of the tritiated dimethylnitrosamine but also after the injection of ^{3}H-diethylnitrosamine. The influence of various drugs and pathological states on the incorporation of the radioactive material has also been studied. A survey of human urine for the presence of purines is at present under way and samples are taken from individuals of several population groups in Israel of different countries of origin. Preliminary results have shown similarities in the rate of excretion of purines in different population groups.

4. STANDARDIZATION OF ANALYTICAL METHODS FOR THE DETECTION OF CHEMICAL CARCINOGENS IN THE ENVIRONMENT

The unit is collaborating with the unit of Analytical Environmental Carcinogenesis to promote the standardization of analytical methods for the detection of carcinogens in the environment.

5. STUDIES ON THE RETICULO-ENDOTHELIAL SYSTEM

Consultant: Dr G. O'Conor

Experimental studies are under way to explore the role of stimulation of the reticulo-endothelial system on the pattern and incidence of spontaneously occurring and induced tumours.

The influence that infection with *Plasmodium berghei* (a form of experimental malaria) can have on spontaneous and experimentally induced tumours is being studied. Determinations have been made of the mortality, temperature, parasitaemia, haemoglobin rate, leucocyte count, weight of liver and spleen, gamma-globulin rates, and carbon clearance, and a histological survey has been made of the various tissues. The influence of single or

repeated infections of mice with *Plasmodium berghei* on spontaneous and experimentally induced tumours is under investigation. The carcinogenic agents used are at present the Rauscher virus and the chemical carcinogen urethane.

5.1 *Institut de Biochimie, Université de Lausanne, Switzerland* (RA/67/006)

Principal investigator: Professor H. Isliker

The effects of the stimulation of the reticuloendothelial system on the cellular and humoral immune response and on the spontaneous appearance of tumours in mice are being investigated.

6. COLLABORATIVE STUDY FOR EVALUATION OF A SEROLOGICAL TEST FOR CANCER OF THE LIVER (Fig. 12)

Principal investigators and collaborating centres:

Dr J. Uriel: Laboratoire de Chimie des Protéines, Institut de Recherches scientifiques sur le Cancer, Villejuif, France

Dr G. Abelev: Tumour Immunochemistry Laboratory, Department of Tumour Virology and Immunology, Gamaleya Institute for Epidemiology and Microbiology, Moscow, USSR

Dr J. S. Tatarinov: Medical Institute, Astrakhan, USSR

Dr C. A. Linsell: IARC Regional Centre Laboratory, Nairobi, Kenya

Professor M. Hutt: Department of Pathology, Makerere Medical College, Kampala, Uganda

Dr P. Brisbois: Department of Medicine, University of Lovanium, Kinshasa, Democratic Republic of the Congo

Professor G. Edington: Department of Pathology, Ibadan University Medical College, Ibadan, Nigeria

Professor R. Masseyeff and Professor C. Quenum: Faculty of Medicine, University of Dakar, Senegal

Professor K. Shanmugaratnam: Department of Pathology, University Medical School, Singapore

Professor G. Bras: Department of Pathology, University of the West Indies, Kingston, Jamaica

Dr M. Rives: Faculty of Medicine, Abidjan, Services des grandes Endémies, Ivory Coast.

These studies were initiated by Dr G. O'Conor, who left the Agency in June 1968 and is now acting as a consultant.

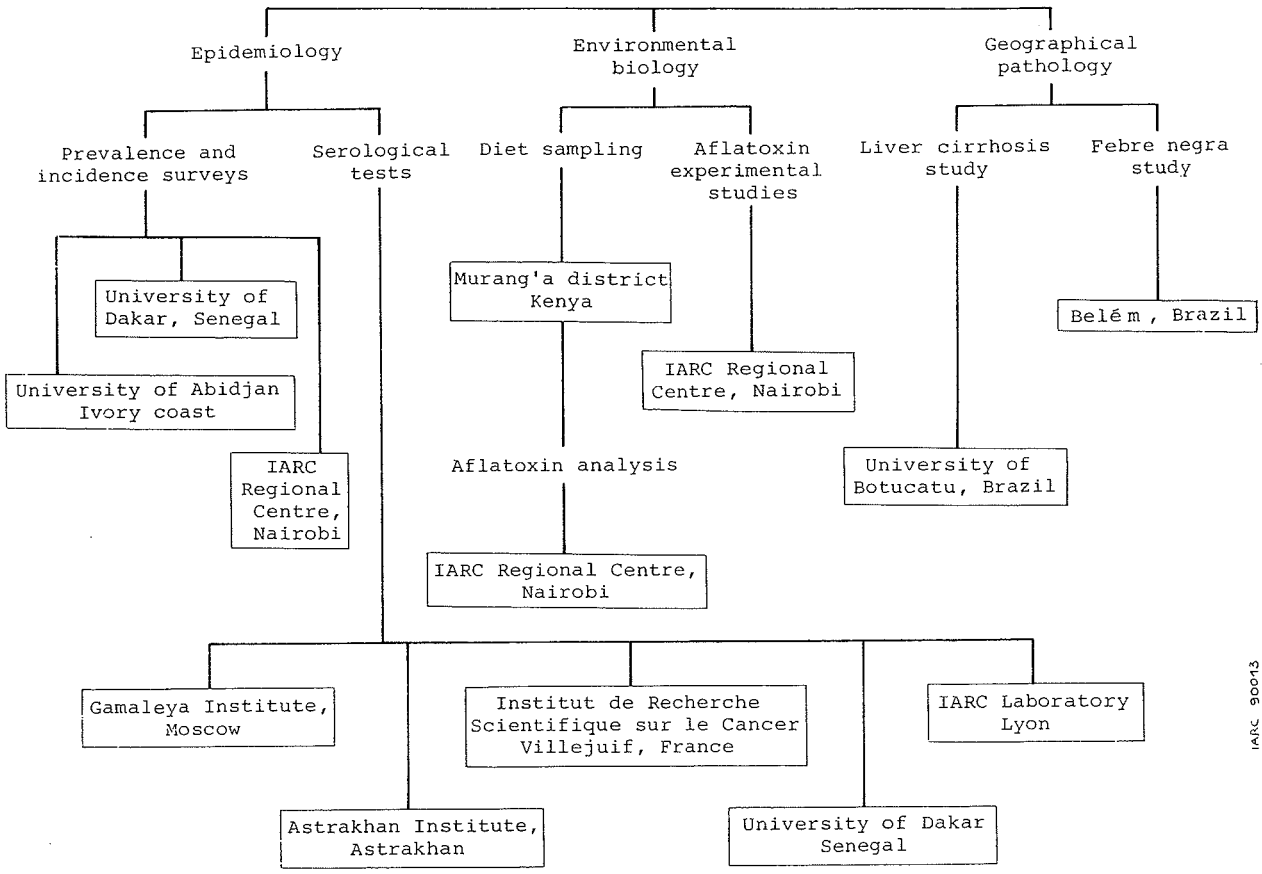

Fig. 12. The liver cancer study.

The reappearance of embryonal proteins in the serum of experimental animals with transplantable or primary hepatomas and in the serum of patients with primary carcinoma of the liver has been demonstrated. This finding has opened the way to numerous investigations which are being carried out or sponsored by the Agency. The investigation was initially intended to confirm the specificity of the α_f-globulin test. Subsequent studies were oriented towards investigation of the possible use of the test for the early detection of primary liver cancer.

6.1 *Objectives of study*

To determine the usefulness of the α_f-globulin test in the diagnosis of primary carcinoma of the liver and its potential value as an epidemiological tool.

The study is designed to:

(*a*) determine the specificity and sensitivity of the test;

(*b*) compare the specificity and sensitivity in areas where environmental and ethnic differences exist;

(*c*) determine the reproducibility of test results in different laboratories; and

(*d*) seek correlations between test results and clinical, chemical, and morphological parameters.

6.2 *Results*

Specimens of sera have been collected from seven collaborating centres and appropriate clinical, biochemical, and histological data have been recorded for each corresponding patient.

Aliquots of each specimen have been tested for the presence of α_f-globulin at three test centres. The results and data sheets have been sent to the IARC project officer for tabulation and analysis.

6.3 *Preliminary conclusions*

Approximately 800 patients have been examined, including over 200 with primary liver cancer. The results of the preliminary examinations are summarized in Table 5. Sera received from Singapore had not been analysed when this report was prepared.

TABLE 5

THE α_f-GLOBULIN TEST: PRELIMINARY RESULTS

Collection centre	No. of specimens	Hepatomas	Serologically positive	False positives
1. Nairobi	113	28	13 (46 %)	0
2. Kampala	118	14	4 (30 %)	1
3. Kinshasa	96	30	23 (77 %)	3
4. Ibadan	43	18	10 (55 %)	1
5. Dakar	198	111	73 (70 %)	11
6. Kingston	98	5	3 (60 %)	3
Total	666	206	126 (60 %)	

The data suggest:

(*a*) a considerable variability in the sensitivity of the test in patients from different geographical areas (the difference in the percentage of positive tests in liver cancer patients in East and West Africa appears to be significant);

(*b*) a very high specificity of the test, as indicated by the infrequency of false positive results; and

(*c*) a high degree of reproducibility in test results from different laboratories.

The following work is in progress and must be completed before firm conclusions are drawn:

(*a*) repetition of the test procedure and follow-up of patients in cases listed as false positive and false negative or where there was disagreement in the results between test centres;

(*b*) histological review of all the available material; and

(*c*) correlation and statistical analysis of the test results with clinical, biochemical, and morphological data.

6.4 *Proposed studies*

A meeting of the principal investigators is planned for July 1969, by when it is expected that sufficient results will be available to meet the primary objectives of the study. It is also expected that the results will justify recommendations along the following lines:

(*a*) studies to confirm differences between East and West Africa in the percentage of positive tests in liver cancer patients;

(*b*) studies to relate these differences to the etiology and perhaps the morphology;

(*c*) studies of the time α_f-globulin appears in high-risk groups; and

(*d*) studies of α_f-globulin in relation to other foetal globulins and specific disease states.

Twenty thousand individuals will be examined and the serum of each will be checked every three months for a period of two years. Part of the serum will be preserved frozen and be available for possible further investigations.

The establishment of an international reference centre for the standardization of the α_f-globulin test is at present under consideration.

7. REGISTRY FOR CARCINOGENS

The unit is investigating ways and means of establishing a registry of all substances that have been tested for their potential carcinogenic hazard. A preliminary feasibility meeting on this subject was held in Geneva in December 1968, following the recommendation of the Scientific Council in 1968. The project was also discussed at the joint IARC/UICC meeting in November 1968. While there is consensus on the necessity of establishing such a registry and the priority that such a project should receive, its establishment depends on the possibility of finding adequate financial support. As was pointed out at the preliminary meeting in December 1968, the registry should be in the form of a data bank and an annual publication. The data should be stored in a computer, from which they could easily be retrieved.

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

Principal investigator: Professor O. Mühlbock

In 1968 the Centre provided a total of 2599 tumour-bearing mice, 8282 healthy mice, and 420 healthy rats to institutes in Austria, Belgium, France, Germany, Greece, Iran, Italy, Japan, Norway, Romania, Switzerland, the United Kingdom, and the USSR.

6. UNIT OF EDUCATION AND FELLOWSHIPS

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

Supporting staff: 1

1. INTRODUCTION

It has been the Agency's policy since its inception to contribute to the raising of standards of cancer research, both clinical and experimental, by providing fellowships for long-term research training and for short-term travel.

The Research Training Fellowships, which are for periods of one or two years, are awarded mainly to younger scientists already established in cancer research who have some postdoctoral experience. The essential requirement is that they should travel abroad to a selected laboratory in another country for the period of research training. Fellowships are awarded to applicants from any country whatsoever and are tenable in any country.

The Travel Fellowships are usually awarded to more senior cancer research workers to enable them to visit laboratories abroad for a maximum period of three months. These visits are intended to permit consultation between scientists, the collaborative planning of research projects, and the acquisition and standardization of new techniques. Like the Research Training Fellowships, they are available for both clinical and experimental cancer research.

Candidates for both types of fellowship apply directly to the Agency, with the consent of the director of their home institution. They are all interviewed, usually in their own laboratory, and their applications are reviewed by the Fellowships Selection Committee, which meets annually in Lyon. The Fellowships Selection Committee places the candidates in order of merit and the final number of awards is determined by the availability of funds. This Committee is composed of five scientists representing different disciplines (who are invited to serve on the Committee for periods of two years at a time), and three staff members of the Agency. At present the five non-Agency members are:

Professor W. U. Gardner (Anatomy)[1]
Dr N. P. Napalkov (Experimental carcinogenesis)
Professor N. F. Stanley (Virology)
Professor U. Veronesi (Clinical research)
Professor G. Wagner (Biostatistics)

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

Since the inception of the programme at the end of 1966, 74 Research Training Fellowships and 106 Travel Fellowships have been awarded.

2. FELLOWSHIPS

In February, April, and July 1968, 79 applications for Travel Fellowships were examined. The advice of the Fellowships Selection Committee was obtained by correspondence and as a result 39 fellowships were awarded. In addition, two supplementary Travel Fellowships were awarded to scientists who had participated in the course on biostatistics and epidemiology in cancer research.

In October 1968, the Fellowships Selection Committee met in Lyon (Fig. 13) to review 68 applications for Research Training Fellowships and 28 for Travel Fellowships. Of these, the Agency was able to award 25 Research Training Fellowships, of which eight are, subject to satisfactory development of the research programmes, for two years.

The WHO Fellowships and Training Grants Review Committee agreed to examine 15 of the applications for Travel Fellowships already chosen by the Fellowships Selection

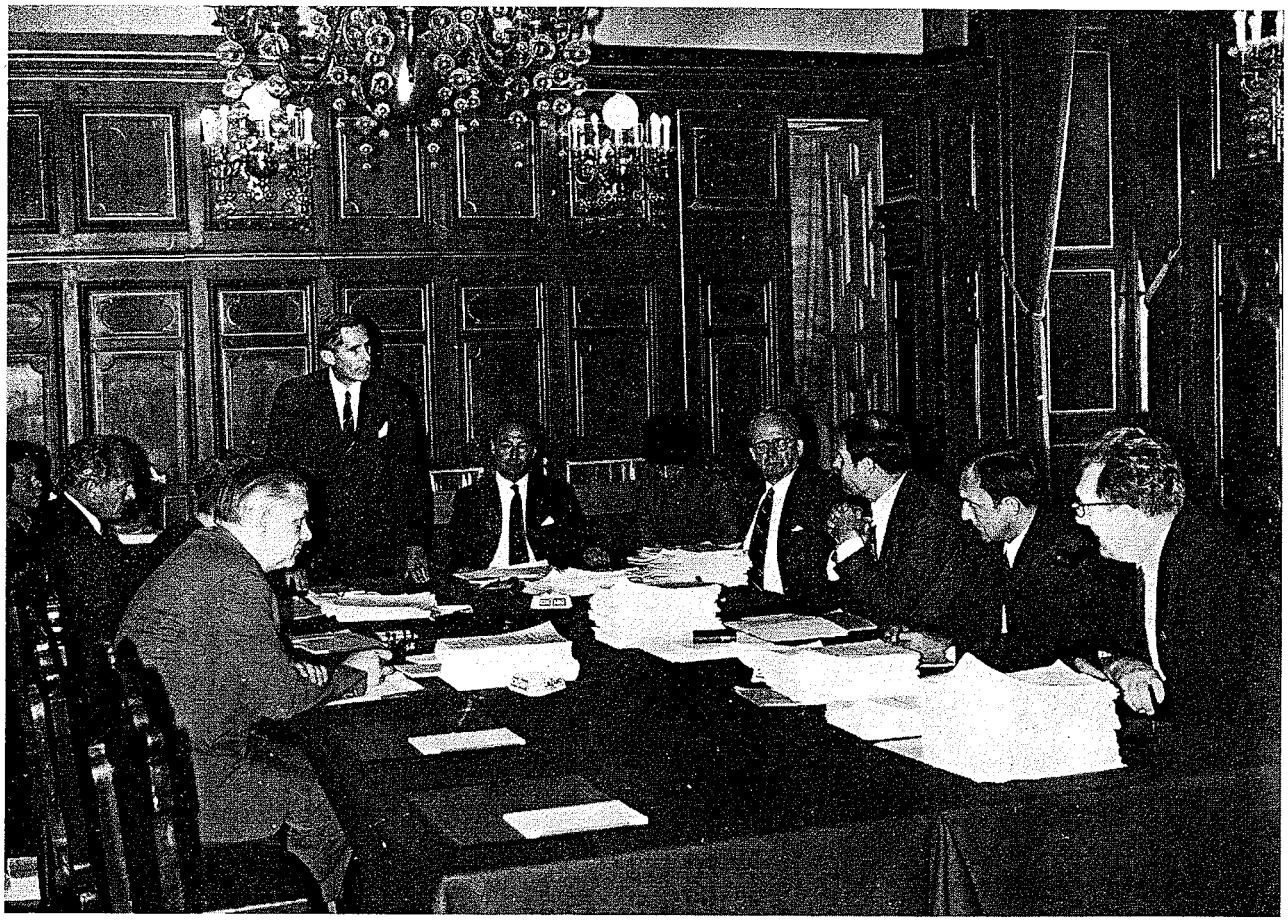

Fig. 13. Director, IARC, opening a session of the Fellowships Selection Committee in a room put at the disposal of the Agency by the Mayor of Lyon.

Committee and WHO awarded appropriate grants to six of them from WHO funds. The remaining nine were financed by the Agency.

The total number of Travel Fellowships awarded in 1968 is, therefore, 50, to which may be added 6 awarded by WHO. This represents just over half the total number of applications received, which was 109.

The Fellowships Selection Committee remarked on the overall high quality of the applicants, which made the task of selection correspondingly difficult. As can be seen from Table 6, the number of applications increased markedly in 1968; there was a rise of $33^1/_3$ % in Research Training Fellowships applications and one of 50 % in Travel Fellowships applications.

TABLE 6

APPLICATIONS RECEIVED, FELLOWSHIPS AWARDED, AND COST

Research Training Fellowships			
	1966	*1967*	*1968*
Applications received	41	51	68
Fellowships awarded	22	27	25
Fellowships activated	20	27	—
Cost	$ 209,436	$ 290,672	$ 186,129
Average cost per year per Fellowship	$ 7,480	$ 8,074	$ 7,755
Travel Fellowships			
	1966	*1967*	*1968*
Applications received	32	73	109
Fellowships awarded	16	40	56[a]
Fellowships activated	16	37	—
Cost	$ 43,570	$ 63,760	$ 81,378[b]
Average cost per year per Fellowship	$ 2,723	$ 1,723	$ 1,850

[a] Of these, six fellowships were awarded by WHO.
[b] Cost of 44 fellowships only.

The scientific disciplines of the successful candidates are given in Table 7.

During 1968, 14 fellowships were completed that had been awarded in 1966 and activated in 1967 and the Fellows have now returned to their home laboratories. In each case, a report is required from the Fellow concerned covering the work done during his fellowship. The quality of work reported is generally good. Fellows have been uniformly satisfied with the training facilities offered them in the host laboratories and supervising scientists have been very happy with the quality of the Fellows sent to work in their laboratories.

TABLE 7

DISTRIBUTION OF FELLOWSHIPS BY SCIENTIFIC DISCIPLINE

Research Training Fellowships		*Travel Fellowships*	
		Cell biology	11
Cell biology	8	Biochemistry	10
Biochemistry	7	Virology	15
Virology	6	Molecular biology	4
Molecular biology	2	Epidemiology	6
Epidemiology	3	Clinical	3
Radiobiology	2	Pathology	7

Amongst the many interesting reports received, there was a detailed study of the carcinogenic process in the mouse, using derivatives of xanthurenic acid and *0*-aminoazotoluene as carcinogens; a study of the effect of laser beams on tumour cell lines; a study of the ultrastructure of the yellow fever mosquito (a possible vector of the Shope fibroma

Fig. 14. Participants and lecturers at the first IARC course, on the biostatistics and epidemiology of cancer research. M. Louis Pradel, Mayor of Lyon, is in the centre. (Photograph by courtesy of Lyon Reportage.)

virus); and a study of cell surface and intracellular structure using the advanced techniques of electron cytochemistry and electron autoradiography.

One Fellow who was trained in epidemiological techniques during his fellowship is now organizing a cancer registry in Lima, Peru.

Titles of publications by Fellows are given at the end of the list of publications by the staff of the Agency (Annex 7).

3. BIOSTATISTICS AND EPIDEMIOLOGY IN CANCER RESEARCH

The first course organized by the Agency was held in Lyon from 24 June to 5 July 1968. The unit of Epidemiology, the unit of Biostatistics, and WHO staff members co-operated in the planning and in the teaching. The number of applications to participate in the course was 56. Of these, 23 were given full support by the Agency and two others received partial support. In addition, five applicants who did not require any support were invited to participate free of charge in the course. The 30 candidates spent ten working days attending lectures and participating in practical working sessions (Fig. 14).

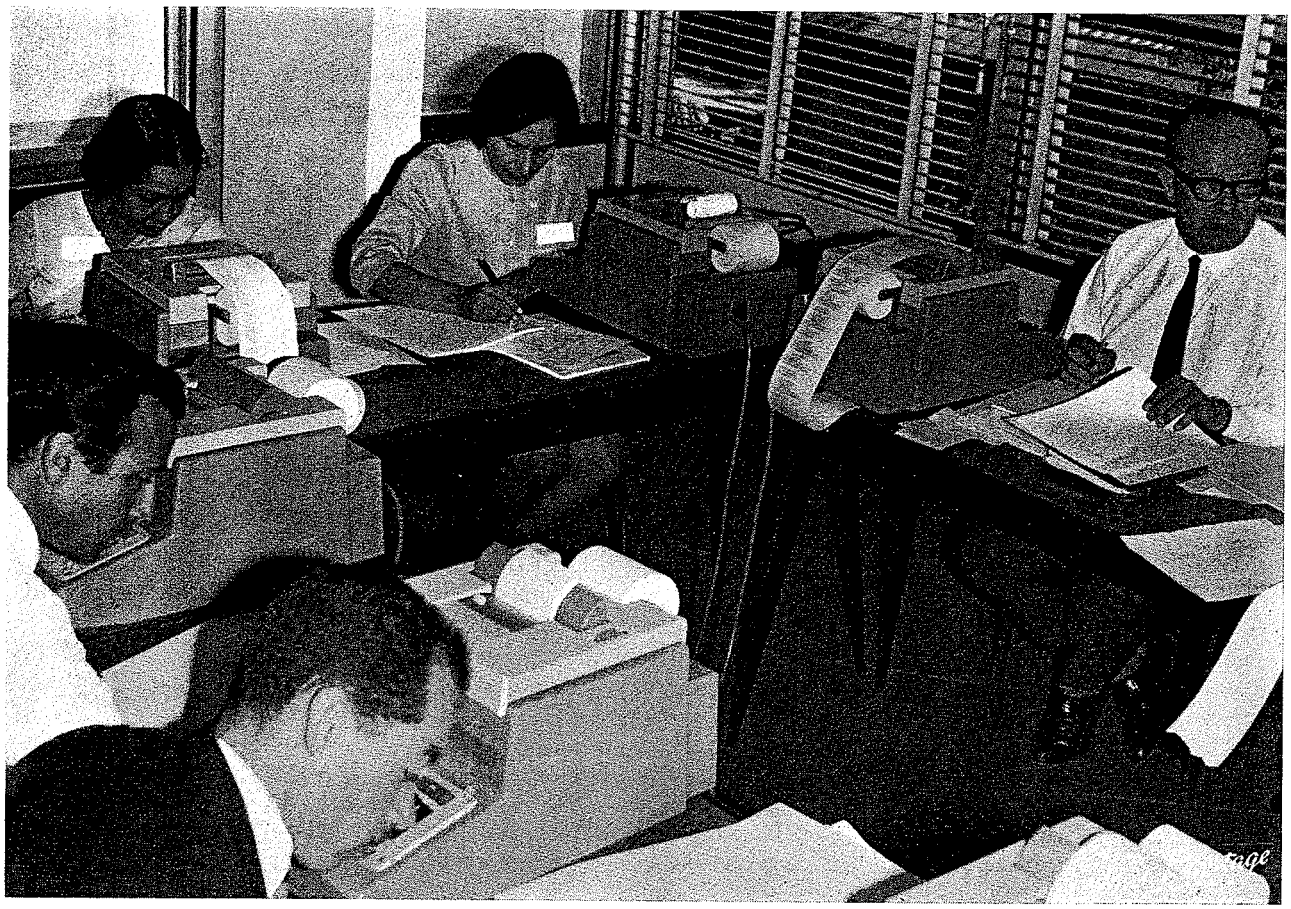

Fig. 15. Participants at the first IARC course learning to use desk calculators in solving specific statistical problems. (Photograph by courtesy of Lyon Reportage.)

The Agency was very fortunate in receiving the co-operation in the course of a number of experts from outside the staff of the Agency or WHO. They included: Dr W. R. S. Doll, Dr P. J. Lawther, Dr T. Mork, Professor D. D. Reid, and Professor G. T. Stewart.

The Agency also gratefully acknowledges the very generous loan of 30 desk calculators by Messrs Olivetti Ltd, Lyon (Fig. 15).

4. TECHNIQUES WITH EXPERIMENTAL ANIMALS IN CANCER RESEARCH

The second course to be organized by the Agency will be held in Amsterdam on 12-23 May 1969. The course director is Professor O. Mühlbock, Netherlands Cancer Institute.

A large number of teachers have been invited. Six lecturers are from cancer research institutes outside the Netherlands and, since it is intended to provide ample opportunity for practical work, several members of the staff of the Netherlands Cancer Institute will be assisting as demonstrators as well as lecturers. Six lecturers from other institutes in the Netherlands will also be included among the teachers.

5. THE USE OF EPIDEMIOLOGICAL TECHNIQUES IN CANCER RESEARCH

Preliminary discussions have already been held with Professor Daniel Schwartz (Unité de Recherches statistiques, Villejuif, France) for a course to be held in the French language early in 1970, on the use of epidemiological techniques in cancer research.

6. COORDINATING COMMITTEE FOR HUMAN TUMOUR INVESTIGATION (CCHTI)

In addition to his responsibilities for the Education and Fellowships Programme, Dr Davis has been able to continue as Secretary to the Coordinating Committee for Human Tumour Investigation, a position he has held since the Committee was set up in 1961. The activities of this Committee, which is under the sponsorship of the UICC, are clearly related to the overall programme of the Agency.

The Committee's aim is to bring together clinical research workers and cancer research workers engaged in experimental studies on human tumours in order to encourage collaborative projects in this difficult field.

Under the aegis of the Committee, a number of study groups have been established on subjects including: cell proliferation, tissue and organ culture, human carcinogenesis, cytogenetics, and cell biology.

Two international symposia under the general title of « Biological Characterization of Human Tumours » have been held at the Abbaye de Royaumont, near Paris (May 1965) and at the Accademia Nazionale dei Lincei, Rome (April 1967). The Third International Symposium was organized in April 1969 in the Consejo Superior de Investigaciones científicas, Madrid, Spain.

7. UNIT OF ADMINISTRATION AND FINANCE

Staff: Mr A. G. B. SUTHERLAND (Chief)
Mr Y. POLLET (Translation Services)

Supporting staff: 11

1. INTRODUCTION

The unit is responsible for all the financial, travel, and supply services to the scientific programmes, for the administration of the Agency Headquarters, and for the recruitment of personnel. It maintains liaison with the French Government and the municipal authorities of Lyon, with special attention to legal questions. Included within the Unit are the translation services, the registry, and the drivers and messengers.

The unit is directly responsible for the preparation of meetings of the Governing and Scientific Councils. At present, it carries a major part of the responsibility for questions arising from the construction of the Agency's new building.

The work load in the administrative and financial services has reached the point where a detailed review of the staffing pattern will very soon be required. Every effort has been made to keep the overhead costs low and, wherever possible, modern up-to-date equipment has been used and procedures devised to economize in manpower.

2. PERMANENT ACCOMMODATION OF THE AGENCY

During 1968 the final plans for the new building were completed and approved (Fig. 16). Construction begins in 1969. The delay in starting construction during 1968 was due to changes in French law affecting the safety requirements of tall buildings. This entailed a complete review of the original plans and the production of new drawings. The cost of the building will be shared between the Government of France, the Département du Rhône, and the city of Lyon.

The Agency was honoured by the special interest shown in the proposed new building by the President of the French Republic, who visited Lyon on 24 March 1968. He examined the model of the new building along with representatives of the Participating States and the Director-General of WHO.

The building will consist of 14 storeys and a basement and sub-basement, and will provide the Agency with administrative offices, a library, laboratories—including animal areas—, a cafeteria restaurant and an auditorium (Fig. 17). It is planned, as far as possible, on a

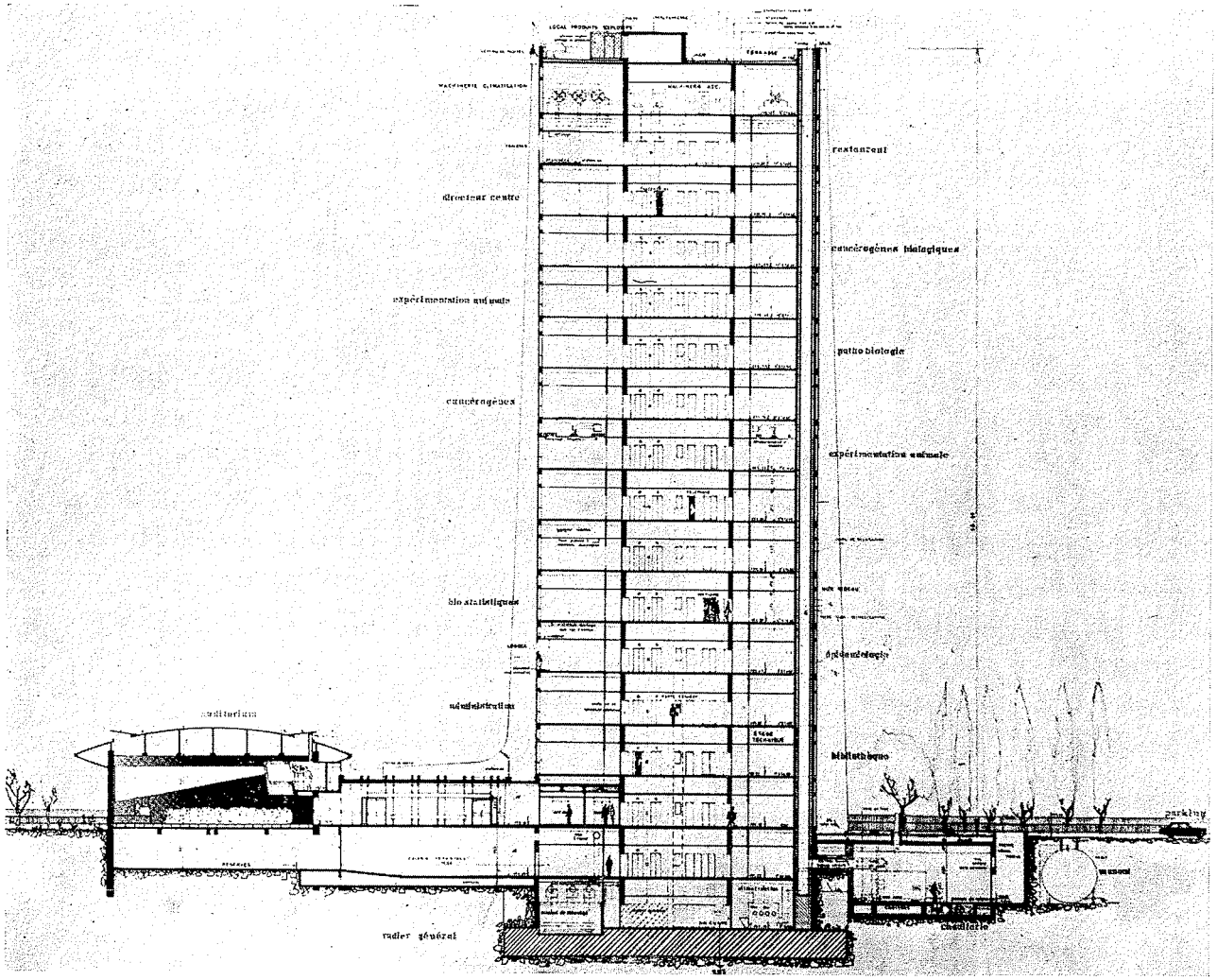

Fig. 16. Elevation of the proposed new building for the International Agency for Research on Cancer, Lyon.

modular basis with the maximum flexibility possible for converting the space from one use to another with the minimum of expense and time. It has been decided not to use movable partitions for corridors and walls inside the building, because of the additional cost and because they are not as sound-proof as light internal walls constructed with prefabricated hollow concrete blocks. The pipes and services will be housed in a false ceiling.

The main tower of the 14 storeys will have a core in which will be housed passenger lifts, a goods lift, an animal lift, and a small documents lift as well as stairways, toilets, and small service or store rooms. The usable space will be all round the core on all four sides of the building and, as a result of the flexibility of the plans and designs, it can serve either for laboratories or for offices. In the basements will be housed the machinery of the building, together with storage areas and delivery and loading platforms. Animals can be delivered directly to the animal lift from the delivery platforms.

The auditorium will be used as a multipurpose building, equipped with cabins and simultaneous interpretation equipment for five languages and a sound-recording cabin.

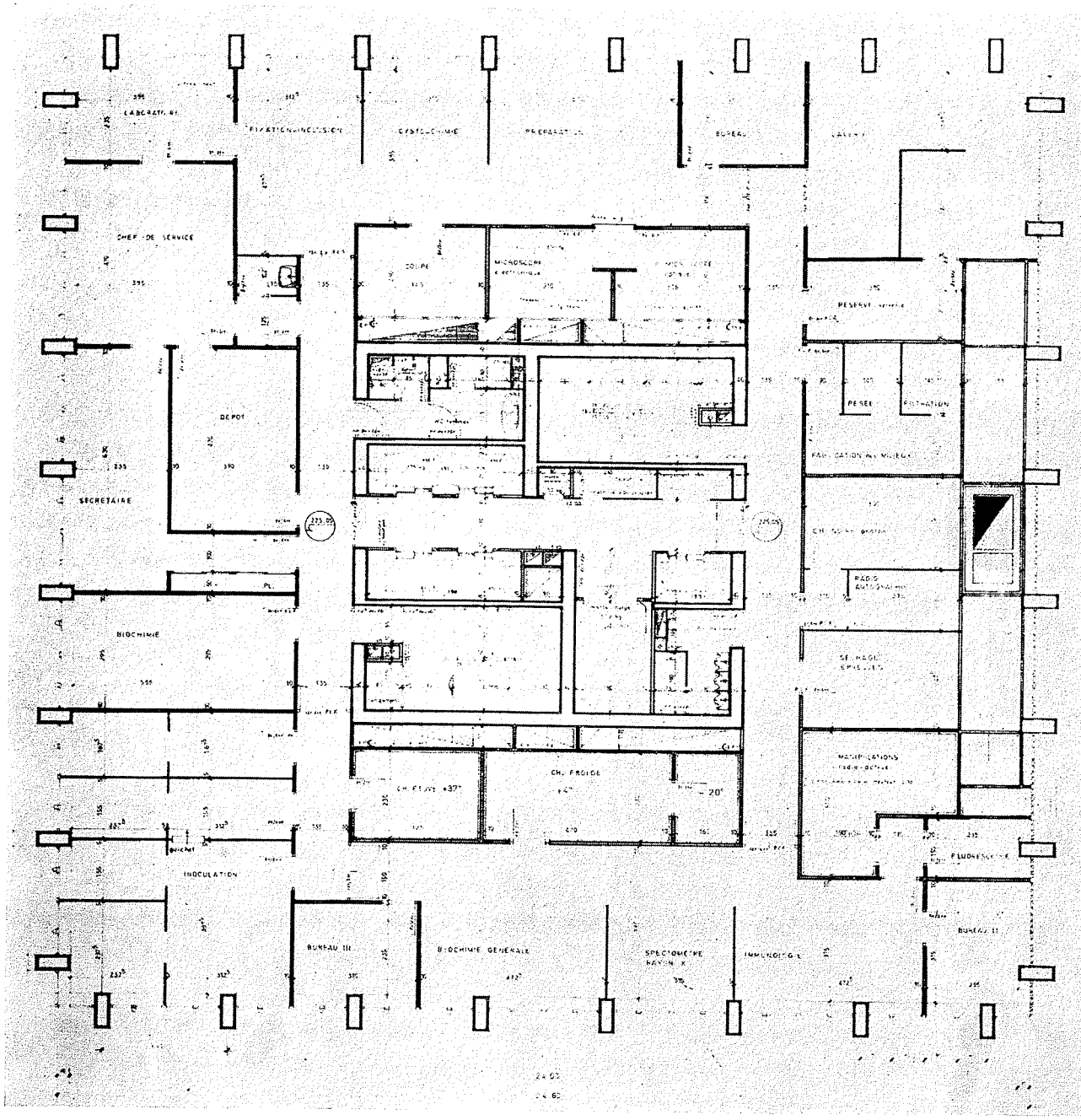

Fig. 17. Typical floor plan of proposed new building. The walls can be removed to meet any modifications required.

It will be equipped with movable unit type furniture which can be moved to a store by means of a platform lift. Thus the auditorium can be used for Council and other meetings, lectures, official receptions, and the showing of films. When it is not needed for the Agency's purposes, it will be available for use by other international organizations, by the Medical Faculty of the University, and by other scientific institutes or bodies in Lyon.

It is hoped that the building will provide the facilities and surroundings the Agency needs for its efficient operation, and that it will accommodate not only the Agency's own staff

but also visiting scientists and research workers. It is intended eventually to provide adequately air-conditioned space for a computer installation and/or linkage with the 360/40 computer in WHO Headquarters, Geneva. A special area is being provided for an electron microscope and a high degree of flexibility is being maintained in the laboratory space to permit changes as required. Initially, two floors will be left completely empty without inside walls so that they can be adapted to future needs and to the changing emphasis of the Agency's programme.

3. THE MICROFORM STUDY

At the request of the Director, WHO made a study of the application of the microform technique in the Agency and produced a management survey report and flow chart for a proposed system. Action was immediately taken to purchase the recommended equipment —a camera, readers, and a printer-developer. This system will be introduced operationally in the first part of 1969 and is geared to a long-term plan for a more sophisticated use of the microform technique in the new building. The possibility of incorporating the microform installation in a system of closed-circuit internal communication is being considered.

4. TELECONFERENCES

The traditional conferences to which scientists travel from different parts of the world are both expensive and time-consuming. Moreover, busy scientists often cannot spare the time to leave their laboratories. In some parts of the world, notably in the USA, teleconferences are being successfully arranged by the national and international telephone lines, and there seems to be no doubt that such teleconferences will become standard features of international scientific life. To enable the staff of the Agency and its collaborating centres, institutes, and laboratories throughout the world to profit from this innovation, advice has been sought from experienced organizations on the feasibility of such a system for the Agency. It is hoped that the first trials will take place during 1969.

8. 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

The Nairobi Regional Centre was established in 1967 to develop and supervise the programmes of the Agency in East and Central Africa. The staff is supported by the Agency. The Centre also maintains close contacts with local research institutes, some of which collaborate in programmes of mutual interest. The present programmes are largely of a short-term nature with limited objectives. It is intended, however, to develop the Centre further in relation to the Agency's long-term environmental studies. The Government of Kenya has been most helpful in assisting with the development of the Centre.

2. AFLATOXIN STUDY (Murang'a district)

One of the major interests of the Centre has been to develop a programme on primary liver cancer in Africa with special reference to the role of aflatoxin in the diet. This programme was initiated by Dr G. O'Conor and is now under the control of the Head of the Centre.

2.1 *Basis of the programme*

Primary carcinoma of the liver and its possible relation with ingested aflatoxin were chosen as an appropriate subject for study by the Agency since:

(*a*) the frequency of liver cancer shows very striking geographical differences that are undoubtedly related to environmental factors;

(*b*) mycotoxins are known to be potent experimental hepatotoxic and hepatocarcinogenic agents; and

(*c*) on circumstantial evidence, a relationship between primary liver cancer and exposure to mycotoxins has been suggested which, if it exists, would profoundly affect present public health and nutritional programmes, as well as the economic life in some areas.

2.2 *Justification for the field study*

Early impressions suggested that, although primary liver cancer exists in East Africa, the frequency rates were much lower than those reported for Mozambique and Senegal. It appears most unlikely that areas can be defined within East Africa with marked statistically significant variations in the incidence of the disease. However, in view of the favourable local conditions, it was decided that a dietary survey, coupled with intensified efforts at cancer registration in East Africa, could be used to test and develop methods of sampling, analysis, and data collection and to provide a baseline for later comparison with areas with a higher incidence of liver cancer. The determination of such a baseline of aflatoxin exposure and disease incidence is considered an essential part of any programme designed to test a possible association of aflatoxin ingestion with primary cancer of the liver.

Murang'a district of the Central Province of Kenya was chosen for the following reasons.

(*a*) It is close to Nairobi, where a suitable analytical laboratory could easily be established.

(*b*) There are excellent relations, established by various WHO teams, with the health officials in this area.

(*c*) The sociological, geographical, and meteorological data for the area suggested that it could be divided into three for comparative purposes.

(*d*) There is a high-density rural population mostly living traditionally on food that is almost entirely produced within the area.

(*e*) An accurate census of the district down to the sublocation level (a unit of approximately 2500 persons) was carried out in 1962 and a new census is expected to be compiled shortly.

(*f*) No ground-nuts are used in the area and most of the dietary components are included in a small evening meal.

(*g*) There is evidence that the incidence of liver cancer is higher than in Europe but lower than in Southern and West Africa.

2.3 *Results of the first six months of sampling*

The collection of diet and native beer samples began on 1 April 1968, and by the end of September a total of 768 diet samples and 96 beer samples had been collected by a random sampling method (Fig. 18). The samples are representative of the actual food consumed by 4494 people, of whom 2509 were children.

The food and beer samples have been analysed by sequential solvent extraction and column chromatography followed by the separation of extracted components by thin-layer chromatography (TLC). In this final separation the TLC plates were eluted with 3% methanol in chloroform, diethyl ether, and 10% acetone chloroform (Fig. 19). All samples

Fig. 18. Field team from the Nairobi Regional Centre collecting sample foodstuffs in a village for the aflatoxin cancer research programme.

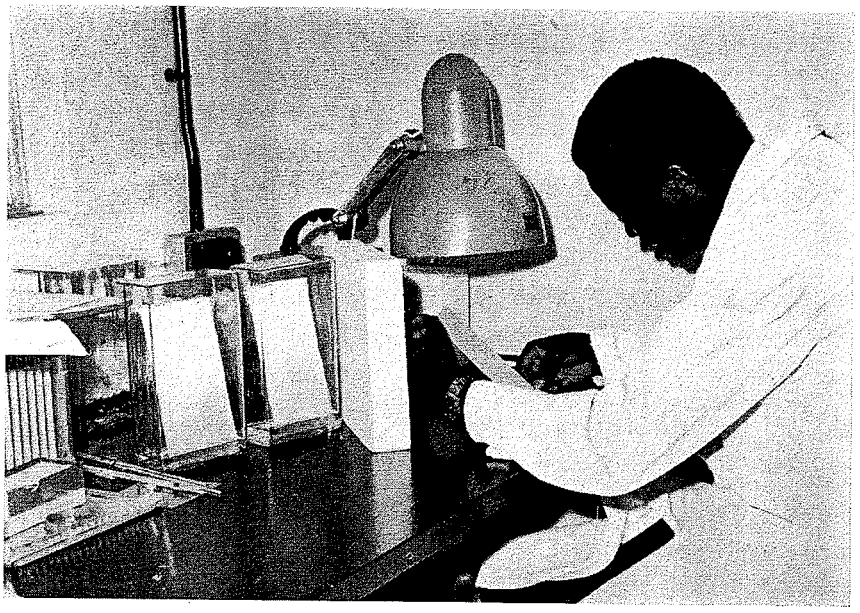

Fig. 19. Reading of TLC plates of food samples in the aflatoxin cancer research programme of the Nairobi Regional Centre.

that showed positive fluorescent spots under ultra-violet irradiation were subjected to a confirmatory test[1] in which the recombined extracts were acetylated before TLC examination. The results obtained in the first six months are given in Table 8.

TABLE 8

READING OF FOOD SAMPLES IN AFLATOXIN SURVEY

	No. of samples	No. of positives	No. of doubtful positives
April	144	5	4
May	144	5	4
June	144	4	3
July	144	3	1
August	144	5	3
September	144	3	5

Out of the 864 samples examined, 25 were definitely positive and a further 20 doubtfully positive. By using the method of doubling the dilution to extinction, the amount of aflatoxin in these 45 samples (three of which were of beer) was determined (Table 9).

TABLE 9

EXAMINATION OF FOOD SAMPLES IN AFLATOXIN SURVEY

16 to 32 μg/kg	2 positive
8 to 16 μg/kg	2 positive
4 to 8 μg/kg	9 positive
2 to 4 μg/kg	11 positive and 5 doubtfully positive
1 to 2 μg/kg	0 positive and 15 doubtfully positive

The months of collection and the areas determined by altitude in the Murang'a district from which the positive samples came are analysed in Table 10.

The results obtained so far seem to indicate a rather low exposure to aflatoxin by ingestion in this population. The data tend to show a difference between the areas of high, middle, and low altitudes but are not yet sufficient to indicate any seasonal variations. It is of interest that a similar pattern seems to be developing in the numbers of primary liver cancer cases recorded so far this year.

Lastly, the study has confirmed that such investigations are possible in rural Africa.

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[1] Andrellos, P. J. & Reid, G. R. (1964) *J. Ass. off. agric. Chem.*, **47**, 801.

TABLE 10

SEASONAL DISTRIBUTION OF 45 POSITIVE AND DOUBTFULLY POSITIVE SAMPLES IN RELATION TO ALTITUDE

	High altitude		Middle altitude		Low altitude	
	+[a]	±[b]	+	±	+	±
April	—	1	3	1	2	2
May	1	—	—	2	4	2
June	—	1	1	1	3	1
July	1	—	1	—	1	1
August	1	—	2	2	2	1
September	—	1	1	1	2	3
Total	3	3	8	7	14	10
	6		15		24	

[a] + = positive.
[b] ± = doubtfully positive.

3. CANCER REGISTRATION (Murang'a district)

When the Murang'a district was selected as a study area, a cancer register was established to investigate the general cancer pattern in the district and to define in detail the location of liver cancer cases.

Initially, all cancer cases detected at the Fort Hall Hospital from 1945 to 1951 had been analysed and compared with the national figures as found in the Kenya Cancer Registry from 1957 to 1963, from which they did not vary significantly, liver cancer being the fifth most commonly diagnosed cancer. The hospital figures were taken from both clinical and biopsy registration. The national figures are mainly those of cancers confirmed by biopsy.

A cancer registrar has been appointed as a member of the field team and is responsible for visiting all hospitals, dispensaries, and health centres within the district as well as those in the surrounding administrative districts that draw patients from the study area. An examination of the records of many of the hospitals bordering on the area was made to assess the extent to which patients are drawn away and it was possible to check the validity of the conclusions by including a certain amount of sociological data in the specimen collection survey.

It would appear that, with the biopsy and clinical cases registered in the three main hospitals—Fort Hall, Thika, and Nairobi—, over 90 % of all cancer cases coming under medical care in the district are covered.

Cases registered from January to September 1968 (see Table 11) give an expected registration of 25 per 100 000 total cancer cases, and a liver cancer rate of 6 per 100 000 in males and 2 per 100 000 in females.

TABLE 11

CANCER CASES FROM MURANG'A DISTRICT, KENYA, JANUARY - SEPTEMBER 1968

	All cancers		Liver cancer			
	Histologically proven	Clinically identified	Histologically proven		Clinically identified	
			Male	Female	Male	Female
Murang'a Hospital	46	6	4	1	2	—
Thika Hospital		18	—	—	2	1
Nyeri Hospital	—	4	—	—	—	—
Tumutumu Hospital	—	1	—	—	—	—
Total	46	29	4	1	4	1

It has been possible to define the residence of most of the patients with liver cancer down to the location and with further investigation it will be possible to obtain a sublocation address.

In general terms, these cases seem to follow the distribution of the positive aflatoxin samples, but at present the cases are far too few to be able to make any firm assessment.

4. LIVER SEROLOGY STUDY

The Regional Centre took part in this study and was able to submit 113 specimens, 28 of which were from patients with hepatomas (page 47).

5. LIVER DISEASE SURVEY (Kenyatta National Hospital, Nairobi)

During 1968, a survey of all patients admitted with liver disease was initiated by the new Nairobi Medical School. Both clinicians and pathologists have been engaged in this study and the Centre has advised on data collection and prepared the record forms for this survey. Approximately 400 patients have been admitted and most of them are now being followed up. Fortnightly clinicopathological assessments are made and these meetings are attended by staff from the Centre.

6. AFLATOXIN EXPERIMENTAL STUDIES

Acute toxicity experiments with aflatoxin have been carried out on baboons to assess the damage to the liver and to provide data for long-term experiments (Fig. 20). Data

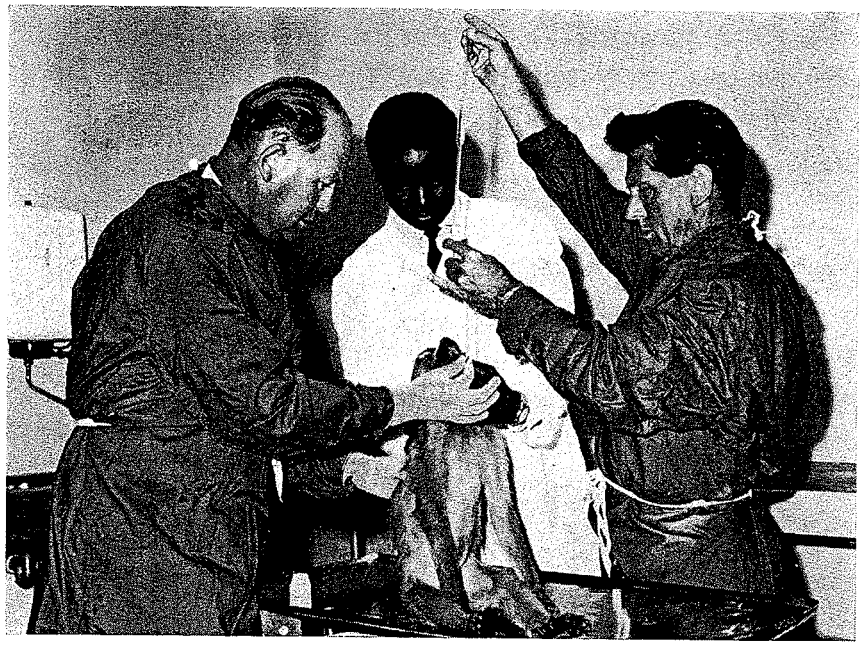


Fig. 20. Intragastric intubation of baboon with aflatoxin at the Nairobi Regional Centre.

TABLE 12

ACUTE TOXICITY EXPERIMENTS WITH AFLATOXIN ON BABOONS

	Dose	Baboon No.	Sex	Survival	Biochemical status[a]	
					SGOT	SGPT
Intubation Experiments						
1.	3.6 mg/kg	68	M	11 days	49	150
2.	3.6 mg/kg	71	M	6 days	132	150
3.	3.6 mg/kg	73	M	6 days	—	—
4.	3.6 mg/kg	109	F	6 days	—	—
5.	2.1 mg/kg	65	M	8 days	197	150
6.	2.1 mg/kg	81	M	3 days	—	—
7.	1.7 mg/kg	69	M	8 days	145	150
8.	1.7 mg/kg	74	M	6 days	—	—
9.	1.3 mg/kg	75	M	still alive	210	150
10.	1.3 mg/kg	86	M	still alive	114	150
Intraperitoneal Experiments						
11.	3.6 mg/kg	60	M	1½-2 days		
12.	2.1 mg/kg	72	M	4 days		

[a] The examinations were carried out approximately 7 days after intubation. Baboons Nos. 3, 4, 6 and 8 died before assessment of their biochemical status. Normal range (23 observations) — SGOT = 27 units: SGPT = 11 units. All animals weighed approximately 10 lb and were 2 years of age.

have been obtained on the survival time at different dose levels and the serum glutamic oxalacetic (SGOT) and pyruvic transaminase (SGPT) titres have been determined as a measure of liver function (Table 12). A complete histopathological examination was made post mortem or on biopsy specimens.

7. HUMAN FAT AND DDT RESIDUES

A co-operative study between the Medical Research Laboratory, Nairobi (Dr M.Rogoff) and the Hadassah Medical School, Jerusalem (Professor M. Wassermann) has been set up to estimate the DDT residues in human fat specimens obtained post mortem from various age groups in Kenyan Africans.

8. CANCER REGISTRATION

Research agreements have been signed with the Kenya Cancer Research Fund, Nairobi (RA/67/001), the Ministry of Health and Housing, Tanzania (RA/68/005), and the Ministry of Health, Malawi (RA/68/003) (it is also hoped that one will be concluded with the Sudan Government) to set up cancer registration in co-operation with the Cancer Frequency Study of the Medical Research Council of Great Britain. Surgeons in Zambia have also co-operated, although not financed by the Agency. This project is difficult to assess at present as the starting of the peripheral registers has been delayed, but the general *modus operandi* with the Medical Research Council has been agreed and data collection is proceeding satisfactorily. The material from the national cancer registries will be processed by the WHO epidemiological unit in Nairobi and that from the hospital frequency study by the statistical unit of the Medical Research Council. A report of activities in Kenya was presented at the recent Cancer Detection Congress in Brussels. It is considered that one of the great advantages of this basic study is that it opens up the possibility, if so desired, of carrying out more detailed studies in these East and Central African countries.

9. CHILDREN'S TUMOURS IN KENYA

Four hundred specimens from the Kenya Cancer Registry were made available through the Centre to Professor J. N. P. Davies, Albany Medical College, New York, USA, to complete his study of the tumours of East African children.

10. OESOPHAGEAL CANCER

An ecological study planned by the Medical Research Council and the Agency will be initiated in the Kisumu area of Kenya as a result of the recent meeting in Jamaica. A

study of the drinking habits of the people and chemical examination of the alcohol consumed in the Luo and Nandi districts of Kenya are contemplated, as these two contiguous populations have widely different frequencies of oesophageal cancer.

10.1 *Oesophageal cancer in cattle*

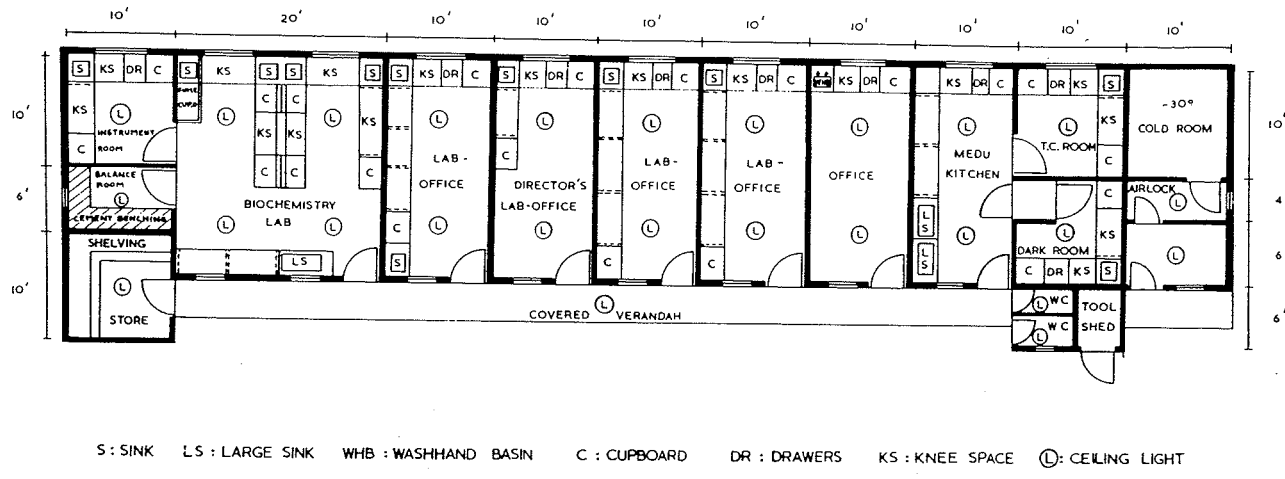
A study of oesophageal cancer in cattle is planned in the Masai district of Kenya, in co-operation with the East African Veterinary Research Organization. For some years, 10 % of cattle in a limited area have been reported to die of oesophageal or rumenal cancer. A pilot survey will be initiated to test the validity of these reports of what is considered to be a rare cancer in bovines.

11. SURVEY OF URINARY PURINES

A co-operative study is being conducted with the Weizmann Institute of Science, Rehovoth (principal investigator: Dr S. Mirvish), to estimate the rate of excretion of different purines in the urine of selected African populations, including patients with liver and oesophageal cancer (page 44).

12. BUILDING FOR THE REGIONAL CENTRE

Plans have been completed for the accommodation of the Regional Centre, including offices and laboratories. The total cost of the building, plus its internal fittings and furniture, is under US $20 000. It is hoped that the building will also enable the Centre to offer accommodation to visiting workers from the Agency Headquarters and to workers from



S : SINK LS : LARGE SINK WHB : WASHHAND BASIN C : CUPBOARD DR : DRAWERS KS : KNEE SPACE Ⓛ: CEILING LIGHT

Fig. 21. Laboratory and office block for the new building of the IARC Regional Centre, Nairobi.

other cancer research institutes. Priority for the use of accommodation at the Centre will be allotted as follows:

(*a*) to projects connected with the Centre;

(*b*) to projects connected with Headquarters units of the Agency; and

(*c*) to visiting scientists from other organizations who wish to work on problems associated with cancer.

The accommodation has been planned to emphasize the possibilities of virological and chemical cancer research in East Africa with a background of registration and epidemiology (Fig. 21).

13. OTHER ACTIVITIES

Lectures have been given on cancer epidemiology to students of the Nairobi Medical School.

9. IARC REGIONAL CENTRE, SINGAPORE

Professor K. SHANMUGARATNAM (Head)

1. INTRODUCTION

The Regional Centre was established in the University of Singapore in 1967.

2. SINGAPORE CANCER REGISTRY

Principal investigator: Professor K. Shanmugaratnam (RA/67/009).

The Registry is managed by a local committee consisting of Professor K. Shanmugaratnam (Chairman and Supervisor), Dr Chia Kim Boon (Radiotherapist), Dr Goon Sek Mun (Obstetrician and Gynaecologist), Mr T. Nadarajah (Hospital Records Officer), Dr S. R. Sayampanathan (nominee of the Ministry of Health), Dr Tan Kheng Khoo (Pathologist), and Mr Tye Cho-Yook (Statistician).

The preliminary arrangements were completed in 1967 and comprehensive registration of all cancer cases diagnosed in Singapore began on 1 January 1968. The Registry has operated satisfactorily and 1850 new cancer cases were registered during the year. The data from these cases are being coded and will be transferred to IBM punched cards in the near future.

The Registry has received excellent co-operation from the medical profession in Singapore and has been given access by the respective authorities to records of hospital admissions, pathology reports, radiotherapy referrals, and death certificates. Singapore, with its reliable vital statistics and well developed medical services, is ideally suited for the operation of a cancer registry, and it is hoped that the Registry will be able to provide data on the multiracial Asian population of Singapore that will be comparable with those provided by established registries in western countries.

As many of the older members of the Singapore population were born in China or India, the establishment of accurate statistics of incidence is of primary importance for studies of the effect of migration on cancer incidence. Earlier work suggested that primary liver cancer was much commoner in China-born Chinese than in the Singapore-born, whereas this appeared not to be so for nasopharyngeal cancer.

3. VIRUS STUDIES ON NASOPHARYNGEAL CANCER (RA/67/007)

Principal investigators: Professor Lim Kok Ann and Dr Mrs M. Y. Murphy (Department of Bacteriology, University of Singapore). Consultant: Professor N. F. Stanley (University of Western Australia).

The Regional Centre has arranged to conduct a series of investigations to determine the possible relations between nasopharyngeal cancer and the adenoviruses. Although available evidence suggests that the high incidence of nasopharyngeal carcinoma in East and South-East Asia may be due to a genetic susceptibility to this disease, the possibility remains that environmental carcinogens—e.g., oncogenic adenoviruses—may be etiologically involved.

Methods of investigation at the Centre include: (*a*) virus isolation from biopsy material; (*b*) fluorescent antibody studies; and (*c*) serological studies. Some aspects of this project were reviewed by consultants from the Agency and local investigators in March 1968. It was agreed that the existing research programme on virus studies in Singapore (conducted by Dr Murphy under the guidance of Professor Stanley and the responsibility of Professor Lim Kok Ann) should be continued and extended. It was also agreed that biopsy material and sera should be sent to the Headquarters laboratory in Lyon for sero-epidemiological studies, the detection of T antigen in tumour cells, and the examination of T antibody levels in patients.

Virus isolations have been attempted from biopsies of nasopharyngeal carcinoma, throat garglings, and rectal swabs.

Sera taken from patients at the time of sampling biopsy material and at six-month intervals thereafter will be tested for adenovirus group-specific complement-fixing antibody and for neutralizing antibodies to types 7 and 12 adenoviruses. Only the first sera have so far been received.

4. OTHER STUDIES ON NASOPHARYNGEAL CARCINOMA

4.1 *Electron microscope studies :*

Regional Centre, Singapore, and Department of Pathology, University of Western Australia

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

Biopsy material from a series of nasopharyngeal cancer cases was embedded in Singapore and sent to Perth for electron microscopic examination. The purpose of this investigation was to clarify the ultrastructure of the neoplasm with special reference to (*a*) the histogenesis of the neoplastic cells; (*b*) variations in neoplastic cell morphology; (*c*) relationships of neoplastic cells to each other and to other cell types, particularly to cells of the lymphocyte/plasma-cell series; and (*d*) the nature of the (possibly viral) inclusions which are sometimes found within the neoplastic cells. By December 1967 material from 49 cases had been sent to the University of Western Australia. In addition, osmium-fixed blocks and gluteraldehyde-fixed material from 30 cases of nasopharyngeal carcinoma were sent to he Headquarters laboratory in Lyon. These studies have confirmed the epithelial nature of these tumours.

A striking feature is the almost invariable presence of a fibrillar nuclear body. Similar nuclear inclusions have been reported in some other human neoplasms, especially malignant tumours of lymphoid tissue.

Lymphocytes are closely applied to the neoplastic cells, and in some instances a pseudopod from a lymphocyte can be seen invaginating the cytoplasm of the epithelioid cell.

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

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

Reports from Kenya suggest that endocrine abnormalities may be implicated in the etiology of nasopharyngeal carcinoma in African males. This possibility was investigated in Singapore, where the incidence is some 10 to 21 times higher than in Kenya and where there are significant differences in the incidence between the various races comprising the population. Since Chinese and Malays have a predisposition to this form of cancer which Indians do not, it was of interest to measure some aspects of the endocrine environment in the three racial groups.

The investigation, restricted to males, was conducted in two stages. The first stage involved the estimation of the plasma dehydroepiandrosterone sulfate (DS), androsterone sulfate (AS), hydrocortisone, and transcortin in Chinese, Malay, and Indian males in Singapore. This has been completed and the results show that the levels of AS, DS, hydrocortisone and the degree of plasma hydrocortisone binding are the same in all the racial groups studied. This suggests that the above hypothesis is untenable.[1]

The next stage of the investigation is now in progress and involves the estimation of these hormones and of urinary oestrogens in cases of nasopharyngeal cancer, other cancers, and other diseases, and in normal controls. A pilot study on the plasma of four nasopharyngeal cancer cases showed low androgen and high corticoid levels, but more work is necessary to determine whether these levels are lower than in relevant control groups and to determine whether this abnormality is caused by or precedes the disease.

5. EVALUATION OF A SEROLOGICAL TEST FOR LIVER CANCER (RA/67/010)

During 1968, the Regional Centre in Singapore collected samples from 120 cases (38 liver cancers, 25 cirrhosis cases, and 57 other controls); these samples have been sent as part of the collaborative study. Correlative clinical and histological data from these cases have been assembled in Singapore and the results will be evaluated in Lyon during 1969.

6. EVALUATION OF DDT IN HUMAN DISEASE

During 1968, the Regional Centre in Singapore collaborated with the unit of Chemical Carcinogenesis in the evaluation of DDT in human disease. The pilot studies have indicated that lipid tissues stored in plastic bottles are not suitable for analysis, a fact which had not been realized in studies of this type. It is expected that this project will be completed during 1969.

[1] Wang, D. Y., Bulbrook, R. D. & Shanmugaratnam, K. (1969) (in press).

10. IARC REGIONAL CENTRE, JAMAICA

Professor G. BRAS (Head)

1. INTRODUCTION

Arrangements to establish an IARC Regional Centre in the University of the West Indies, Kingston, Jamaica, were finalized towards the end of 1967. The present report covers work carried out since that time (RA/68/001).

2. CANCER REGISTRY

2.1 *Jamaica*

The Cancer Registry is financed by the British Empire Cancer Campaign and has continued to function well. It provides the basic statistical information on which additional programmes in the environmental biology of cancer will be developed.

2.2 *Curaçao*

A Cancer Registry has been established in Willemstadt, Curaçao. Unfortunately progress, as a result of the resignation of the pathologist in Curaçao and Aruba, has not been as fast as was anticipated. However, a new pathologist has been appointed and will take up his duties during 1969. In the meantime, the members of the medical profession in Curaçao have assured Professor Bras that the Cancer Registry is fulfilling a real need and they all hope it can be continued. The Registrar from Curaçao spent two weeks in Jamaica in order to become acquainted with the techniques of cancer registration. In Curaçao there would appear to be a high incidence of carcinoma of the oesophagus, without any male or female ratio differences. The total rate is 19.8 per 100 000; for males, 18.3 per 100 000; for females, 20.9 per 100 000.

3. SEROLOGICAL TEST FOR LIVER CANCER (RA/67/016)

The Jamaican part of the collaborative study for the evaluation of the serological test for liver cancer was completed and the results of the 100 specimens despatched are given in the report of the serological study. In view of the small number of cases of primary

carcinoma, it has been decided to obtain additional biopsy specimens from cases of liver cancer diagnosed clinically only and to investigate further false positives and false negatives. Every effort is to be made to find as many additional cases of primary hepatoma as possible, in view of the increasing evidence that the proportion of patients whose sera give positive tests varies in different areas.

4. WORKING GROUPS

In November 1968 Jamaica was host to the UICC conference on chemical carcinogenesis, the IARC conference on oesophageal cancer, and the combined working group on priorities in chemical carcinogenesis. These two groups were timed to precede the Second Caribbean Cancer Conference; thus the existence of the Regional Centre and its objectives have become more widely known in the Caribbean area.

11. MISCELLANEOUS RESEARCH STUDIES

1. CANCER OF THE LIVER

1.1 *International liver study*

Consultant: Professor M. Montenegro, Botucatu, Brazil

Professor Montenegro has continued to collect samples of livers for the international liver study and has now a sufficient number available from five different areas to permit assessment of geographical differences in pathological patterns.

1.2 *Febre negra*

Dr H. Torloni, WHO, visited Belém, Brazil, on behalf of the Agency to investigate the possible significance of the so-called *febre negra* and its relation to mycotoxin ingestion. The disease was first described by Dr J. Boshell in children in Làbrea, Brazil. The livers of the patients show acute fatty toxic necrosis with evidence of venous changes, and the local conditions are such as to suggest the cause to be a naturally occurring agent. After discussion with local workers, it was concluded that there was no related increase in primary liver cancer in the area. However, it was considered important to investigate further the possible etiology involved since, if a suspected carcinogenic mycotoxin was identified, a hepatocarcinogenic action in man would then appear unlikely.

2. EXPERIMENTAL GASTRIC CANCER

Tumours of the glandular stomach are rare in experimental animals. However, such tumours are not infrequent in the multimammate mouse *(Praomys natalensis)* and the possible use of this species as a test system for human studies is clearly important.

Groups of these animals have been fed various experimental diets for up to three years and, as tissues from the experimental animals were available in the Agency, they were made available to Dr C. F. Hollander, Experimental Gerontological Unit, Rijswijk, Netherlands. He found the frequency of gastric cancer to be similar in all the experimental and the control groups. A small colony of this unusual species is now being maintained in Lyon in case further studies become necessary.

12. IARC LIBRARY

Librarian : Mrs P. DU TONNAC (up to October 1968)
Mr N. P. CUMMINS (from April 1969)

Assistant Librarian : Miss R. TISSOT

The Library of the IARC caters for the day-to-day needs of the scientific staff in their different disciplines and provides an excellent service as a specialized library in the field of cancer research in general, more especially in the fields of carcinogenesis, environmental biology, and epidemiology.

The Agency has built up in less than two years a still small but extremely useful library which now subscribes annually to 160 journals and has already acquired 800 books and works of reference.

The work of the library is guided by a Committee under the chairmanship of Dr. W. Davis.

13. STAFF ASSOCIATION

Chairman : Dr W. DAVIS

At the end of 1966, the Director asked Dr W. Davis to accept responsibility for establishing a Staff Association in the Agency on the lines of the WHO Staff Association.

Considerable advice and guidance were received from the WHO Staff Association and from the President of the Federation of International Civil Servants Associations. In July 1967 the first meeting of the Staff Association took place in Lyon, with Dr W. Davis acting as provisional chairman. In September 1967 the Committee was elected and charged with the responsibility of developing the work of the Association. Draft statutes have been prepared, based on the statutes of the WHO Staff Association, and will come into force when ratified by a General Meeting of the Staff Association. Excellent relations have already been established between the Staff Association and those of WHO and UNESCO.

The Staff Association has been concerned with many aspects of the well-being of the staff and its relations with the Administration are cordial.

A staff common room established on the top floor of the Agency building is available as a rest room and has sufficient cooking facilities for the preparation of light snacks.

Through the Staff Association, Agency personnel have been able to take advantage of the facilities offered by various sports and cultural groups in Lyon.

During October 1968, the Staff Association co-operated with the Administration in a review of local salary scales.

Annex 1

PARTICIPATING STATES AND REPRESENTATIVES AT THE FIFTH SESSION OF THE IARC GOVERNING COUNCIL, 29-30 OCTOBER 1968

Australia

Dr Graham ROUCH
Assistant Chief Medical Officer
Australian High Commission
London

Miss J. H. BARNETT
First Secretary
Australian Permanent Mission to the United Nations
Geneva

France

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

Dr J. C. MEILLON
Division des Relations internationales
Ministère des Affaires sociales
Paris

Federal Republic of Germany

Dr J. STRALAU
Director General
Bundesministerium für Gesundheitswesen
Bad Godesberg

Dr H. KAISER
Regierungsdirektor
Ministry of Finance
Bonn

Israel

Dr M. FELDMAN
Head, Department of Cell Biology
Weizmann Institute of Science
Rehovoth

Italy

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

Dr L. SANTI
Professor of Experimental Oncology
University of Genoa
Genoa

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. SCHALY
Head, Section World Health Organization
Ministry of Social Affairs and Public Health
The Hague

Dr G. LAMSVELT
Head, Division for International Health Affairs
Ministry of Social Affairs and Public Health
The Hague

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 K. ENDICOTT
Director
National Cancer Institute
Bethesda, Md.

Union of Soviet Socialist Republics

Dr B. P. DANILOV
Deputy Minister of Health
Moscow

Professor A. W. CHAKLIN
Deputy Director
Institute of Experimental and Clinical Oncology
Moscow

World Health Organization

Dr M. G. CANDAU
Director-General

Annex 2

MEMBERS OF THE SCIENTIFIC COUNCIL

Until 1969

Professor G. KLEIN
Institute for Tumour Biology
Karolinska Institutet
Stockholm, Sweden

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

Professor O. MÜHLBOCK
Netherlands Cancer Institute
Amsterdam, Netherlands

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

Until 1970

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

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

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

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

Until 1971

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

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

Professor C. G. 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

FORMER MEMBERS OF THE SCIENTIFIC COUNCIL

Until 1967

Professor B. KELLNER
Oncopathological Research Institute
Budapest, Hungary

Professor G. MATHÉ
Institut Gustave-Roussy
Villejuif, France

Until 1968

Professor I. BERENBLUM
Department of Experimental Biology
Weizmann Institute
Rehovoth, Israel

Professor P. BUCALOSSI
Director, Instituto Nationale per lo Studio e la Cura dei Tumori
Milan, Italy

Professor H. HAMPERL
Director, Pathological Institute, Venusberg,
Federal Republic of Germany

Professor A. LILIENFELD
Division of Chronic Diseases
Johns Hopkins University School of Hygiene and Public Health
Baltimore, USA

Annex 3

STAFF OF IARC

Dr J. HIGGINSON, Director

Dr G. BLAUDIN DE THÉ	Chief, Unit of Biological Carcinogenesis
Dr P. BOGOVSKI	Chief, Unit of Analytical Environmental Carcinogenesis
Mr R. T. CHARLES	Unit of Chemical Carcinogenesis
Dr W. DAVIS	Chief, Unit of Education and Fellowships
Mr D. K. JAIN	Unit of Epidemiology
Dr J. KMET	Unit of Epidemiology
Dr C. A. LINSELL	Head, IARC Regional Centre, Nairobi
Dr M. S. MUIR	Chief, Unit of Epidemiology
Mr Y. POLLET	Unit of Administration and Finance (Translator)
Mrs S. RUBIN	Unit of Education and Fellowships
Dr P. SIZARET	Unit of Chemical Carcinogenesis
Mr A. G. B. SUTHERLAND	Chief, Unit of Administration and Finance
Dr L. TOMATIS	Chief, Unit of Chemical Carcinogenesis
Dr V. TURUSOV	Unit of Chemical Carcinogenesis
Dr A. TUYNS	Unit of Epidemiology
Dr T. WILLIAMS	Chief, Unit of Biostatistics
Miss B. WITTHOFF	Unit of Chemical Carcinogenesis

STAFF JOINING IN 1969

Mr N. P. CUMMINS	Unit of Administration and Finance (Librarian)
Dr U. DE JONG	Unit of Epidemiology
Dr. N. MUÑOZ	Unit of Epidemiology
Dr H. TULINIUS	Unit of Epidemiology

RESEARCH ASSISTANTS

Dr J.-C. AMBROSIONI	Unit of Biological Carcinogenesis
Dr L. LEBLANC	Unit of Epidemiology
Mr B. MORGAN	Unit of Biostatistics
Mr R. NELSEN	Unit of Biostatistics
Dr R. SCHMAUZ	Unit of Biological Carcinogenesis

Annex 4

RESEARCH AGREEMENTS MADE BY IARC WITH VARIOUS INSTITUTIONS UP TO 31 DECEMBER 1968

RA/67/001	Kenya Cancer Research Fund, Nairobi (Cancer registry at Nairobi)
RA/67/002	Medical Research Council Pneumoconiosis Research Unit, ~~Penarth, Wales~~ (Asbestos study programme)
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/67/006	Institut de Biochimie, Lausanne (Effect of chronic stimulation of the reticulo-endothelial system on immunological mechanisms and tumorigenesis in experimental animals)
RA/67/007	IARC Regional Centre, University of Singapore (Virus studies on nasopharyngeal carcinoma)
RA/67/008	IARC Regional Centre, University of Singapore (Studies on nasopharyngeal carcinoma)
RA/67/009	IARC Regional Centre, University of Singapore (Cancer registry at Singapore)
RA/67/010	IARC Regional Centre, University of Singapore (Collaborative study for the evaluation of a serological test for liver cancer)
RA/67/011	Gamaleya Institute for Epidemiology and Microbiology, Moscow (Collaborative study for the evaluation of a serological test for liver cancer)
RA/67/012	Medical Institute, Astrakhan, USSR (Collaborative study for the evaluation of a serological test for primary cancer of the liver)
RA/67/013	University of Ibadan, Nigeria (Collaborative study for the evaluation of a serological test for liver cancer)

RA/67/014	Institut de Recherches scientifiques sur le Cancer, Villejuif, Seine, France (Collaborative study for the evaluation of a serological test for liver cancer)
RA/67/015	Université Lovanium, Kinshasa, Democratic Republic of the Congo (Collaborative study for the evaluation of a serological test for liver cancer)
RA/67/016	Medical College of the University of the West Indies, Mona, Kingston, Jamaica (Collaborative study for the evaluation of a serological test for liver cancer)
RA/67/017	Medical College of the University of the West Indies, Mona, Kingston, Jamaica (Collaborative epidemiological studies relative to liver cancer)
RA/67/018	Faculty of Medicine, University of Dakar, Senegal (Collaborative study for the evaluation of a serological test for liver cancer)
RA/67/019	Netherlands Cancer Institute, Amsterdam (IARC International Reference Centre for the provision of tumour-bearing animals)
RA/67/020	Centre Léon Bérard, Lyon (Laboratory facilities in Lyon for IARC)
RA/67/021	Cell-Cancer-Virus Study Group (CCV), Lyon (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/67/023	Makerere University Medical College, University of East Africa, Kampala, Uganda (Collaborative study for the evaluation of a serological test for liver cancer)
RA/68/001	University of the West Indies, Mona, Kingston, Jamaica (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 (Investigation to establish cancer incidence ~~data in Curaçao and Aruba~~)
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 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 Mazanderan Province, with special reference to oesophageal cancer)
RA/68/009	University of Chiengmai Medical School, Chiengmai, Thailand (Study of cancer patterns in Chiengmai)
RA/68/010	Department of Pathology, Medical School, Pahlavi University, Shiraz, Iran (Cancer ratio study in Shiraz, Iran)
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 foetus and newborn by the transplacental passage of enzyme-inducing substances)
RA/68/012	CCV, Lyon (Sero-epidemiological studies)
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 Immunbiologie, Freiburg, Federal Republic of Germany (Contribution towards a study of analytical methods for identification and quantitation of *N*-nitrosocompounds in various environmental media)
RA/68/017	Faculty of Medicine, University of Abidjan, Ivory Coast (Collaborative study on the geographical distribution of cancer in Abidjan and the Ivory Coast)

There are also four agreements on the multi-generation study on the potential carcinogenicity of DDT in rodents which have been signed between WHO and the following:

RA/68/HQ.1	Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan
RA/68/HQ.2	Fondation Mérieux, Lyon
RA/68/HQ.3	Research Institute of Oncology, Leningrad
RA/68/HQ.4	Institute of Experimental and Clinical Oncology, Moscow

Annex 5

VISITORS TO IARC IN 1968

Professor G. ABELEV	Gamaleya Institute, Moscow, USSR
Dr M. BOEVA	Institute of Oncology, Sofia, Bulgaria
Dr J. BOSHELL	Belém Virus Laboratory, Belém, Brazil
Dr A. BOUÉ	International Children's Centre, Paris, France
Dr M. BRUNET	Cancer Statistics Unit, Institut national de la Santé et de la Recherche médicale, Paris, France
Mrs M. CHAPPLE	Connecticut Tumour Registry, Connecticut, USA
Dr N. W. CHOI	Department of Social and Preventive Medicine, University of Manitoba, Winnipeg, Canada
Dr J. CLEMMESEN	Finsen Institute, Copenhagen, Denmark
Dr V. COMES	Institute of Oncology, Cluj, Romania
Dr P. CORREA	Pathology Department, University of Valle, Cali, Colombia
Professor M. CRESPI	Regina Elena Institute, Rome, Italy
Dr G. DELLA PORTA	National Cancer Institute, Milan, Italy.
Dr G. DRAPER	Department of Social Medicine, Oxford University, England
Professor L. A. ELSON	Chester Beatty Research Institute, London, England
Dr R. FLAMANT	Institut Gustave Roussy, Villejuif, France
Mr M. FRESON	Secretary-General, FNRS, Brussels, Belgium
Dr J. GALVES BRANDON	National Cancer Institute, Lima, Peru
Professor L. GILLO	Committee for the Promotion of Scientific Research, Brussels, Belgium
Dr J. HAKKINEN	Department of Pathology, University of Turku, Finland
Dr M. J. HARTGERINK	Department of Epidemiology and Analysis, Ministry of Health, The Hague, Netherlands
Dr C. F. HOLLANDER	Experimental Gerontological Unit of the Organization for Health Research TNO, Rijswijk, Netherlands
Dr JAIN	Kinshasa, Democratic Republic of the Congo
Dr T. A. KHWAJA	Department of Biochemistry, Punjab Laboratory, Lahore, Pakistan
Dr R. KINOSITA	City of Hope Medical Center, Duarte, Cal., USA
Dr J. T. KOFI DUNCAN	Department of Radiation Biology and Radiotherapy, University of Lagos College of Medicine, Nigeria
Dr W. KRETSCHMER	Tropenmedizinisches Institut der Universität, Tübingen, Federal Republic of Germany

Dr D. LAMBERT	Institut Gustave Roussy, Villejuif, France
Dr L. LEBLANC	Laboratoire de Biochimie, Faculté de Médecine, University of Dakar, Senegal
Dr J. A. H. LEE	Department of Preventive Medicine, University of Washington, Seattle, Wash., USA
Dr C. L. LEESE	Chester Beatty Research Institute, London, England
Professor A. LLOMBART	Department of Pathology, University of Valencia, Spain
Professor C. MALTONI	Institute of Cancer Prevention, Bologna, Italy.
Dr E. MASCIAS	Spanish Cancer Association, Madrid, Spain
Professor G. G. MEYNELL	Lister Institute of Preventive Medicine, London, England
Mrs E. MEYNELL	Medical Research Council Unit of Bacteriology, London, England
Dr S. MIRVISH	Department of Experimental Biology, Weizmann Institute of Science, Rehovoth, Israel
Professor M. MONTENEGRO	Faculdade de Ciencias Médicas e Biológicas, Botucatu, Brazil
Professor H. R. MORGAN	Department of Bacteriology, University of Rochester, New York, USA
Dr N. P. NAPALKOV	Vice-Director, Research Institute of Oncology, Leningrad, USSR
Professor NUNN	Department of Organic Chemistry, Grahamstown, Rhodes University College, South Africa
Dr G. PORETTI	Head, Radium Institute, University of Berne, Switzerland
Dr K. J. RANADIVE	Indian Cancer Research Centre, Bombay, India
Dr N. RETANA	Spanish Cancer Association, Madrid, Spain
Dr ROACH	Transkei, South Africa
Dr J. C. SALOMON	Institut de Recherches scientifiques sur le Cancer, Villejuif, France
Professor W. SANDRITTER	Department of Pathology, Freiburg, Federal Republic of Germany
Professor L. M. SHABAD	Institute of Experimental and Clinical Oncology, Moscow, USSR
Dr M. B. SHIMKIN	Temple University Health Sciences Center, Philadelphia, USA
Dr P. SHUBIK	Eppley Institute for Research on Cancer, Omaha, Nebraska, USA
Dr L. H. SOBIN	Department of Pathology, Cornell University Medical College, New York, USA
Dr J. STASZEWSKI	Institute of Oncology, Gliwice, Poland
Dr M. STUKONIS	Vilnius, USSR
Professor Y. S. TATARINOV	State Medical Institute, Astrakhan, USSR
Dr B. TERRACINI	National Cancer Institute, Milan, Italy
Professor M. TORTORA	University of Ferrara, Italy
Professor R. TRUHAUT	Faculty of Pharmacy, University of Paris, France

Dr J. URIEL	Institut de Recherches scientifiques sur le Cancer, Villejuif, France
Dr J. VACHER	Medical Research Council, Carshalton, Surrey, England
Dr F. DE WAARD	Nederlands Huisartsen Instituut, Utrecht, Netherlands
Dr G. WARWICK	Chester Beatty Research Institute, London, England
Dr R. J. G. WILLIGHAGEN	Department of Pathology, University of Leiden, Netherlands

The Agency also received official visits from the following:

Miss J. BARNETT	First Secretary, Permanent Mission of Australia to the United Nations Office at Geneva
Dr J. S. BOXALL	International Health Section, Commonwealth Department of Health, Australia House, London, England
Dr R. J. H. KRUISINGA	Secretary of State for Public Health, Ministry of Social Affairs and Public Health, The Hague, Netherlands
Professor Boris PETROVSKI	Minister of Health of the USSR, Moscow
Sir William REFSHAUGE	Director-General of Health Services, Canberra, Australia
Dr J. STRALAU	Director-General, Bundesministerium für Gesundheitswesen, Bad Godesberg, Federal Republic of Germany
Mr C. TRUNINGER	Consul-General of Switzerland at Lyon.

Annex 6

LIST OF SCIENTIFIC MEETINGS ORGANIZED BY IARC IN 1968

				IARC Internal Technical Report No.
1.	16-19 July	Lyon	Working Group to discuss the programme on gastro-intestinal tract cancer, with particular reference to the oesophagus	68/001
2.	28-30 October	Lyon	IARC Working Conference on studies of the role of aflatoxin in human disease	68/002
3.	4-8 November	Lyon	IARC Working Group on sources of cancer statistics	68/003
4.	18-22 November	Kingston, Jamaica	Joint IARC/UICC Meeting on chemical carcinogenesis	
5.	20-22 November	Kingston, Jamaica	Meeting of investigators of oesophageal cancer in the Caribbean Area	
6.	23 November	Kingston, Jamaica	Meeting of Heads of IARC Regional Centres	
7.	16-18 December	Nairobi, Kenya	Round-Table Conference on the possible relationship between Burkitt's lymphoma and infectious mononucleosis	68/004

Annex 7

PAPERS PUBLISHED AND SUBMITTED FOR PUBLICATION BY IARC STAFF AND FELLOWS 1967-1968

IARC staff

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IARC Fellows [1]

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

Gamaleja, N. F. et al. (1969) The alteration of the cells in tissue culture with the green laser light. II. Microirradiation of the single mitochondria in the myocardial cells. *J. Cell. Biol.* (in press)

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