ECP

European Organization
for Cooperation
in Cancer
Prevention Studies

INTERIM REPORT OF ACTIVITIES

1985 - 1986

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C O N T E N T S

I. INTRODUCTION

ECP was established in 1981 with the object of fostering the development of joint studies in cancer prevention on a European basis as the European Organization for Research on Treatment of Cancer (EORTC) was restricting its activities to research on cancer treatment.

The method chosen to achieve this aim was to establish Working Parties to plan studies on particular cancers, or aspects of cancer aetiology, which might result in devising preventive measures, particularly of the "primary" (e.g. smoking control and lung cancer) rather than the "secondary" type (e.g. cytology screening and cervical cancer). The working party members are drawn from different disciplines and countries and are responsible for identifying lines of approach which practicably, and possibly advantageously, may be performed on a joint European basis.

During its initial phase (1981-1984) ECP has set up a minimal and flexible structure as to be able to obtain the cooperation of active European investigators, build the working groups, define its first research projects, and become known as a specific entity. ECP has also established a series of annual symposia drawing attention to fields in which there currently seem to be particular opportunities for progress in regard to prevention.

A short summary of ECP's activities during the years 1985/1986 follows.

WORKING GROUPS

Five previously created Working Groups under the following headings, have been active: AIDS, Colorectal Cancer, Diet, Hormonal and Sexual Factors, Respiratory Tract Cancer (previously Tobacco).

All of them have pursued the active phase of the studies with the exception of the Respiratory Tract Group, who is still searching for financial support to start the already prepared project of study.

Two groups have organized their first meeting: Virus and Cancer, Breast Cancer.

The initial group on Public Information has been specialized into a more specific topic "Healthy Diet Promotion Methods".

SYMPOSIA

Two symposia were held: " DIET AND HUMAN CARCINOGENESIS " in Aarhus-Denmark, in June 1985; and " CONCEPTS AND THEORIES IN CARCINOGENESIS " in Bruges-Belgium, June 1986.

SCIENTIFIC ADVISORY COMMITTEE

The Scientific Advisory Committee met regularly as to supervise the ECP scientific work and to define the general politics regarding its internal structure and external relations.

At the end of this document you will also find:

- The Calendar of the ECP meetings
- The Publications of ECP

II ECP WORKING GROUPS

E C P W O R K I N G G R O U P

" D I E T A N D C A N C E R "

Chairman: Dr. M. HILL
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INTRODUCTION

The European Organisation for Cooperation in Cancer Prevention Studies (ECP) was established as a forum to encourage cooperation between European cancers in the study of cancer prevention. It is now generally thought that 80% or more of all cancers are caused by modifications of the environment, often related to the individual life-style, particularly to smoking or nutrition but also including exposure to occupational and environmental carcinogens. It follows that cancer, which claimed more than half a million lives in Western Europea in 1981, is essentially a preventable disease.

An essential first step in disease prevention is to determine the causes of cancer, and ECP has set up working parties to study cancers with particular subsites (eg. large bowel, breast) or causes (eg. tobacco, endocrine-related, diet related or virus-related cancers). This document concerns the studies of diet-related cancers planned by ECP. In addition to organising multinational, multidisciplinary research projects, ECP also organises symposia, the third of which was on the subject of diet and cancer (held in Aarhus, June 1985).

DIET AND HUMAN CARCINOGENS

ECP has undertaken four studies of the relation between diet and carcinogenesis; two concern the roles of specific dietary components and two concern studies of the role of the overall diet.

1. Intersalt

This is a joint project of the International Society and Federation of Cardiology (ISFC) and ECP. The major part of the project is to study the

relationship between salt intake and blood pressure between and within countries. The ECP part of the project is to study the geographical relationships between gastric cancer incidence and intake of salt and nitrates. Samples from 56 populations living in 32 countries from all 5 continents will be collected and analysed and these have been obtained. It has been postulated that salt is important in the causation of gastric atrophy, the first stage in gastric carcinogenesis; nitrate is metabolised to N-nitroso compounds in the achlorhydric stomach and this might be important in the progression from gastric atrophy to gastric cancer.

(The most expensive part of the study - the selection of subjects within each population and the collection, storage and transport of samples of blood and urine - will be met by funds obtained by ISFC. ECP will only need to find the costs for the nitrate and salt analyses.)

2. Euroselenium project

There have been made epidemiological studies, principally from the United States, suggesting that a low intake of selenium is associated with an increased risk of cancer. Since selenium compounds are antioxidants and would therefore interact with, and inactivate, proximate carcinogens, the observation has credibility and is worth pursuing. The Euroselenium project aims at studying the variation in serum selenium concentrations throughout Europe and at correlating average selenium concentrations with cancer morbidity/mortality data.

3. Diet and the causation of colorectal adenomas

(See : "Colorectal Group")

4. Diet and the causation of intestinal metaplasia of the stomach

(See following report from Dr. West : "ECP-Euronut Intestinal Metaplasia Study")

THE ECP-EURONUT INTESTINAL METAPLASIA STUDY

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This study is co-ordinated in Wageningen on behalf of the Nutrition and Cancer Group of the European Organization for Cooperation in Cancer Prevention Studies and Euronut which is the concerted action programme on nutrition of the Commission of the European Communities. Initially this study was referred to as the ECP atrophic gastritis project but the name has been modified because the primary criterion for the selection of cases is the presence of intestinal metaplasia and because Euronut is co-operating with ECP in providing financial support for co-ordinating the study.

INTRODUCTION

Intestinal metaplasia, which is located invariably in the antrum and sometimes in the fundus of the stomach, is regarded as a precursor lesion of the intestinal type of stomach cancer. It has been suggested by Correa et al. (1975) that the first stage in the development of such cancer is the development of gastric atrophy, in which nutritional factors appear to play a role. One factor thought to be implicated in this step is dietary salt (Joossens & Geboers, 1980). Gastric atrophy results in hypochlorhydria and consequently bacterial overgrowth of the stomach. Bacteria reduce dietary nitrate to nitrite and also catalyse the subsequent N-nitrosation by the nitrate so formed of suitable secondary amino groups: these N-nitroso compounds may be involved in the development of increasingly severe dysplasia and ultimately malignancy. The reduction of nitrate to nitrite is inhibited by vitamin C, vitamin E and selenium which can replace a part of the vitamin E requirement. This hypothesis has generated much interest but it is by no means proven. The purpose of the research which is now getting under way is to examine the first step in the pathway suggested for the aetiology of the intestinal type of gastric cancer.

One of the biggest problems in trying to relate nutritional factors to cancer is that by the time cancer has been diagnosed it is difficult to determine the nature and quantity of food eaten at the critical time for the development of the cancer. This is so for a number of reasons:

* firstly, onset of the disease produces changes in eating patterns; and
* secondly, the critical time for cancer development, that is when cancer is initiated and during the initial stages of promotion, could be many years prior to clinical manifestation of the disease.

As intestinal metaplasia is a very important precancerous lesion, a study aimed at elucidating factors involved in the aetiology of this disease would give information on factors involved in the aetiology of gastric cancer with fewer of the problems referred to above.

AIM OF THE STUDY

The hypothesis to be tested is that there is a significant difference between cases and controls in the intake of foods, nutrients and toxicants with special emphasis being given to those which have been postulated as being associated with either intestinal metaplasia or with gastric carcinoma. A case-control study will be carried out involving 600 persons in each of the countries participating in the project. As it is planned to carry out the studies in about eight countries in Europe, those factors which are found to be associated with atrophic gastritis in a high proportion of countries are likely to be of great importance in the aetiology of this disease and of gastric cancer.

METHODS

Selection of cases and controls:

Cases will be selected from people, aged between 20 and 50 years, attending clinics with gastrointestinal complaints which justify carrying out a gastroscopy. Those found to have intestinal metaplasia will be eligible for inclusion as cases. The remainder of those undergoing gastroscopy will be eligible for inclusion as the first group of controls (gastroscopy controls). A second group of controls will be selected from apparently healthy persons in the population at large (non-gastroscopy controls).

Measurement of intake of foods and toxicants:

From a series of studies carried out in Wageningen and from studies carried out elsewhere, it has been established that the best way to obtain information on dietary patterns in the past is to take the present food intake as starting point. Such a method will be used in this study. Measurements of changes in food intake, based on the food frequency method, which have occurred since the age of 25 years (or at the age of 20 years if the subject is under 30 years of age) will provide sufficient information to allow a previous food pattern to be determined. Since data on food consumption will be collected from more than one country in Europe, it is essential that the food composition tables are compatible and the EUROFOODS organization has been established to do just this. In addition, 24-hour urine samples will be collected for the analysis of electrolytes, nitrate, and a number of other substances. Emphasis ir the study will be directed towards the measurement of intake of nutrients and toxicants thought to be related to the aetiology of either intesinal metaplasia or gastric cancer itself. The electrolyte analyses will be carried out in the Division of Epidemiology of the Sint-Raphael University Hospital at Leuven (Belgium) and the nitrate analyses in the Bacterial Metabolism Research Laboratory of the Centre for Applied Microbiology at Porton (England).

PROGRESS SO FAR

* A series of meetings and workshops resulted in the development of a working plan which was published two years ago (West, 1984).
* A detailed questionnaire was then developed and field tested in the Netherlands. This was then modified and translated to enable it to be used in pilot studies in a total of eight countries in Europe (Federal Republic of Germany, Greece, Italy (including San Marino), the Netherlands, Poland, Portugal, Sweden, United Kingdom).
* Pilot studies involving up to 20 cases and 40 controls were carried out in seven countries during 1985 and the first half of 1986.
* A workshop was held in Wagenungen in May 1986 to evaluate the pilot studies and to modify the working plan of the study. This modified working plan will be published in the near future.

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E C P W O R K I N G G R O U P

" C O L O R E C T A L C A N C E R "

Chairman: Prof. J. FAIVRE
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DIET AND THE CAUSATION OF COLORECTAL ADENOMAS

There is a great deal of evidence implicating excess dietary fat and meat and low intakes of dietary fibre and vitamins A, C and E in the causation of colorectal cancer. Comparisons of populations show this association very clearly but case control studies have been disappointing. Colorectal carcinogenesis can be divided into two stages, namely the formation of the precursor adenoma and the progression of the benign adenoma to malignancy; these two stages may be related to diet in different ways. In the study prepared by this ECP group, centers in 10 European countries will each find 150 patients with colorectal adenomas, 150 colonscoped patients with no adenomas and with no history of adenomas, and 150 controls (matched for age and sex) who have not been colonscoped but have no abnormal colonic symptoms. These patients will be then be used in a study of the relation between diet and (a) adenoma carriage, (b) adenoma size, and (c) adenoma subsite. A subsample of patients will be selected (together with their controls) for the study of the role of bile acids and intestinal bacteria and of cell proliferation defect in colonic biopsies. This a very large and powerfull study that could not be done in any single country and needs an organisation the size of ECP to make it possible.

As of August 1986, pilot studies have been completed for the optimal use of dietary questionnaires (Dijon, Genova) and for the analyses of cell proliferation in the mucosa (Bologna, Dijon, Louvain-en-Woluwe). The study is now active in these four centers and in preparation in the others. Data will be collected throughout 1986 and 1987.

In addition to this study, the ECP colorectal group is preparing a workshop to be held in March 1987, the aim of which being to update present knowledge on the causation of human large bowel cancer, and to prepare the basis for future studies.

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E C P W O R K I N G G R O U P

" H O R M O N A L A N D S E X U A L F A C T O R S A N D C A N C E R "

Chairman: Prof. J.S. SCOTT
University of Leeds

One of the sub-groups working in ECP deals with "Sexual Factors and Cancer". A high proportion of cancers, particularly of the female, affect organs of reproduction and in which hormonal and sexual factors play a part. In this group, cervical cancer is the one with which there has been most attempt at prevention with cervical smear screening and sophisticated techniques of inspection. This allows treatment of abnormal epithelium which has started to change towards a cancerous state but before it has become invasive. This is an example of "secondary prevention", as opposed to "primary prevention" in which the aim is to prevent the abnormality from starting. In the field of secondary prevention of cervical cancer, a vast amount of State-supported and privately organized medical activity has been taking place in recent years. The ECP philosophy has been to prefer primary approaches as these are more fundamental and more economical.

The Group members therefore turned their attention to other pelvic sex organ cancers, particularly those occurring in relatively young women. These are few in number but in importance they rate very high in relation to our objectives. Preventing cancer in someone of over 80 may be desirable but it contributes little to lengthening life-span and the quality of that life may not be high.

On the other hand, a cancer occurring in a relatively young woman of child-bearing years is likely to be an appalling tragedy and if this can be prevented the individual is likely to have many years of fruitful life, possibly with raising a family who might otherwise be orphaned.

ECP therefore established in 1983 a study of the background factors involved in women who developped cancer of the ovary or cancer of the lining of the womb (endometrial) while still aged under 40. The evidence from this was that the occurrence of pregnancy provided a high degree of protection against the likelihood of both cancers. It also indicated that use of the oral contraceptive pill was associated with a lower incidence. These cancers in young women are of such frequency that adequate numbers to perform a significant study are not available in one

country, so the international European cooperation was an important factor in relation to this work.

The conclusion arrived at was that the approach hitherto adopted in relation to analysis of the cancer-inducing effects of the contraceptive pill have been wrong. At the outset, a matter of 25 years ago, there had been great fears that "The Pill" might have cancerous ill effects.

All the monitoring performed had been designed to detect any increase in any cancer. No account had been taken of the possibility arising from our new evidence - and supported by other modern studies - that with certain important cancers, some highly fatal like ovarian, the incidence is in fact reduced.

The commonest cancer of the female sexual organs is that of the breast and it is now becoming evident that this has an epidemiological background very similar to that of cancer of the ovary so that measures to improve the "milieu interieur" (internal climate) in respect of ovarian cancer risk may at the same time be beneficial with regard to breast cancer.

The group has therefore organized a workshop to study "Optimalization of the Influence of Ovarian Steroid Consumption on Cancer Risk". This will include not only the use of "The Pill" but also the widespread use of similar hormones to adjust the endocrine climate for women who have passed the menopause. These are two situations in life in which large proportions of the population take powerful endocrines for non-therapeutic reasons. It would be unthinkable to prescribe hormones to prevent cancer. However, the evidence is now beginning to suggest that where these hormones are being used, subtle variations in proportion (oestrogen and progestogen), and variations in age and child-bearing status when they are prescribed, may have a major impact on the ultimate incidence of cancers. There are good grounds to anticipate that the experts meeting in October 1986 in Frankfurt to study this matter will come up with proposals which will lead to advance in this field.

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E C P W O R K I N G G R O U P

" A I D S A N D C A N C E R "

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SPREAD OF THE AIDS VIRUS IN EUROPE

The ECP Working Group on AIDS has evaluated data on seropositivity to LAV/HTLV-III supplied by members in 11 Western European countries. The period covered is 1981-1984. A constant increase in the rate of seropositivity was observed in all screened population groups. For instance, sera collected from healthy male homosexuals at sexually - transmitted disease clinics were anti-LAV positive in 1 to 9 % of the cases in 1981; these figures rose to 19 to 26 % in 1984. Data for drug addicts progressed from 0 -3 % to 21 - 36 %. Similarly high figures were found in prison inmates. Although these figures only reflect the prevalence of anti-LAV seropositivity in selected populations from large European cities, they indicate that LAV/HTLV now spreads freely within Europe and this spread has become less dependent upon promiscuity. The epidemic is about to enter Eastern Europe. Intravenous drug abusers appear to be the risk group experiencing the most rapid spread at present. Furthermore, seropositivity in males and females outside the traditional risk groups seems on the rise.

Due to the high incidence of cancer in AIDS patients, this disease is rapidly becoming a major cause of cancer in young adults. A coordinated European preventive effort is urgently needed. A vaccine maybe some years off. It is, therefore, mandatory that mass education about the AIDS problem is pursued throughout Europe. ECP is now planning to organize research on the preventive strategies used in different countries with the purpose of identifying the most profitable approach.

The fifth annual ECP Symposium which will take place in May 1987 will be devoted to this subject.

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E C P W O R K I N G G R O U P

" R E S P I R A T O R Y T R A C T C A N C E R "

Chairman: Prof. F. OESCH
University of Mainz

COLLABORATIVE STUDY PROPOSAL ON RESPIRATORY TRACT CARCINOGENESIS

Background

The respiratory tract including nasal cavities, larynx, trachea, bronchi and alveoli and the upper digestive tract including pharynx and oesophagus are complex organ systems involved in air transport, filtration and clearance.

As the first border to the external environment, the highly specialised epithelial lining of the respiratory tract has a remarkable capacity to repair damage caused by exposure to harmful and toxic compounds. However, local or systemic effects of chemicals may lead to irreversible changes of the epithelial lining, leading to various types of cytotoxicity including neoplastic growth. The importance of these cytotoxic effects are seen in context of increasing air pollution, some forms of occupational exposure and the inhalation of tobacco smoke. The evidence that cigarette smoke is dangerous to health is now irrefutable and there is no question that the use and consumption of tobacco smoke would be highly restricted if the combustion products were considered chemicals or drugs. Cigarette smoke is one of the few cases of an environmental pollutant where there is adequate epidemiological and experimental evidence to demonstrate an association with the development of vascular disease and respiratory tract carcinogenesis. The experimental evidence on the carcinogenicity of tobacco smoke are based on studies using tobacco smoke condensates and its fractions and the exposure of experimental animals to total tobacco smoke, to single constituents mainly found in the particle phase (for example toxic and carcinogenic polycyclic aromatic hydrocarbons (PAH)) or in the volatile phase (for example toxic and carcinogenic nitroso compounds).

A large number of 3000 chemicals found in tobacco smoke show cytotoxic, mutagenic and carcinogenic effects in many different biological systems. Tobacco smoke is actively inhaled by the smoker (main stream smoke), but the non-smokers in the same room are also involuntarily exposed to the combustion products. There is epidemiological evidence which indicates an increased incidence of lung cancer in such passive smokers; the air they inhale

is to some degree filtered by the active smokers who retain up to 80 % of the particulate matter and 50 % of the volatile phase present in the smoke they inhale. Side stream smoke which is not inhaled by the smoker contains certain chemicals including some carcinogenic compounds at much higher concentration than the main stream. For example nitrosamines are present at 52 times the concentration found in the main stream. Even after dilution of this smoke in the air of the room, a considerable risk remains to all present.

Several possibilities to improve the current problems associated with tobacco-induced carcinogenesis can be envisaged. The first possibility is trying to break or circumvent the dependence on tobacco smoking. However, the results of efforts in this direction suggest that it is very difficult to change this habit.

The present proposal focused on the acquirement of sufficient knowledge of the mechanism underlying the toxic and carcinogenic effects of tobacco smoking to allow either the removal of constituent(s) which are especially critical for the toxic and carcinogenic effect in man, or the addition of an effective antidote.

In this proposal, a concerted collaborative effort on this problem is envisaged where functional and morphological changes in model systems are related to underlying molecular alterations which occur during tobacco smoke-induced carcinogenesis.

Moreover, it is anticipated that in the long term the study will provide information on the basic mechanisms of chemically-induced carcinogenesis which will not be exclusively confined to tobacco smoke and lung cancer but rather may render some step(s) in carcinogenesis amenable to modulation for general preventive measures.

Specific Aims

Amongst chemical compounds which are known to induce cancer, tobacco smoke is responsible for the greatest number of chemical-induced cancer in man. In order to learn whether elimination or addition of a few chemical substances could reduce or eliminate the problem, knowledge of the mechanism of tobacco-induced cancer and definition of the responsible constituents are the prime prerequisite.

Both the mechanism as well as the responsible constituents can only be efficiently and unambigously studied in a combination of studies in vitro and in vivo. The in vitro experiments are necessary to analyse particular steps and to understand the relative importance of the various contributing factors. In this way, it can then be verified whether the information gained in vitro also holds in the in vivo situation. Both pieces of information are ultimately needed for the extrapolation to man. To this end, carcinogenesis and the responsible constitutents of tobacco will be studied in organ and cell culture with rat, hamster and human lung, bronchus and trachea in vitro and compared to results obtained in whole animal studies. The relationship of the findings in vitro with those in vivo shall help to establish the significance of the findings in the in vitro system with human tissue.

In view of the complexity of tobacco smoke, it is planned to study the biological effects of cigarette smoke at various levels. These include studies using gaseous and the particulate fraction from low and high tar cigarettes as well as pure chemical carcinogens and potential tumour promoters present in tobacco smoke. The compounds in question include polycyclic aromatic hydrocarbons, aromatic amines, nitrosamines, aldehydes and phenols. The respective roles of these components in respiratory tract carcinogenesis will be investigated.

In addition to the initiating and promoting effects of tobacco smoke constitutents, another important factor in chemical carcinogenesis is the potential synergism due to other environmental contaminants. In this regard, epidemiological studies have showed asbestos to be of outstanding signifi-

cance. It has been shown that the risk for bronchogenic carcinoma was increased 92 times by combined cigarette smoke and asbestos exposure. It is therefore planned to evaluate the synergistic effect of tobacco smoke and asbestos as well as potential asbestos-replacing mineral fibres in the experimental systems used in this study. Such data will provide insight into the mechanism of the obvious synergism between inert materials and chemical carcinogenic or co-carcinogenic activity, which therefore could serve as substitute materials.

An understanding of the mechanism of the damage produced by the above described constituents is a pre-requisite for both the extrapolation to human and the proposition of effective preventive measures against tobacco-smoke induced lung cancer which may even yield tools for generally interrupting the chain of events leading to cancer.

Experimental approach

The proposed studies are by necessity very complex and since no single team possesses all the required expertise a combined approach using the expertise of laboratories in several European countries is proposed. These teams are: Drs. Michiels and Prof. Chouroulinkov, Villejuif; Prof. Althoff and Dr. Richter-Reichhelm, Hannover/Berlin; Drs. Wilmer and Feron, Zeist; Dr. Baeckmann and Prof. Oesch, Mainz; Drs. Wolf and Hayes, Edinburgh.

In our exprimental approach to this problem it is planned to study the sequential changes following exposure in vitro and in vivo in the structure of the genetic material, the consequent changes in gene expression, and the relationship of changes in carcinogen-metabolising enzymes and molecular as well as morphological markers of early stages of carcinogenesis. It is hoped that in this way it will be possible to identify the carcinogenic compounds in tobacco smoke which are most critical for human cancer and to propose measures of either eliminating or preventing their adverse effects.

Moreover, the study of the sequential early effects should allow the discovery of early markers which would facilitate very early diagnosis of patients with cancers of the respiratory tract and therefore significantly improve their prospects of survival.

Trachea, bronchus and lung from human and rat fetuses and hamster (Villejuif, Berlin) will be cultured. The cultures will be treated with complete cigarette smoke condensates from normal, low tar and high tar cigaretts as well as purified fractions. Pure carcinogens and co-carcinogens, of known chemical structure, which occur in tobacco smoke (polycyclic aromatic hydrocarbons, aromatic amines, nitrosamines, aldehydes, phenols) will also be used. Whole animals (rat, hamster) will be treated intratracheally using similar regimens (Zeist, Villejuif, Berlin). The changes of sequence in the cultures and in the whole animals will be followed morphologically (Villejuif, Zeist, Berlin) by electron microscope (Hannover), biochemically (Edinburgh, Villejuif) and at a molecular biological level (Mainz).

Morphological level. The test is using fetal respiratory tissue brought in vitro shortly before or after term. Exposure takes place in vivo (transplacentally) or in vitro. Once an effect is established, which is caused by a single compound the modifying enhancing or inhibiting effect of other materials may be examined. For animal studies, hamster and/or rat tissue appears to be appropriate, human fetal tissue needs to be examined for establishing the relevance of data obtained with animal tissues. For documentation of morphological changes and lesions, routine histology by graded sections or scanning electron microscopy will be used.

(i) 28 days after exposure, inhibition or accelleration of epithelial differentation will be estimated indicating toxic effects of the test material.

(ii) 28 days after exposure, changes of the respiratory epithelium will be diagnosed indicating the potential for cellular transformation.

(iii) 28 days after exposure, morphologically recognized lesions associated with dysplasia and carcinoma in situ may be found indicating pre- or neoplastic transformation. In such cases, reimplantation studies have to confirm the findings.

Biochemical level. The biological changes to be studied will focus in the following areas.

(i) Changes in the enzymes responsible for the control of carcinogenic and co-carcinogenic metabolites such as microsomal monooxygenases, microsomal and cytosolic epoxide hydrolases and glutathione transferases. This will include histochemical localization and quantitation of enzyme protein using specific antibodies raised to the enzymes which had been purified to apparent homogeneity.

(ii) The enzyme activities will be determined in most cases by the use of radioactive substrates. The radiosynthesis of them has already been completed.

(iii) Modification of distinct members of the keratin protein family.

Molecular biological level

The molecular biological changes to be investigated focus on the alterations of gene expression.

(i) DNA-level: Changes of the content and/or pattern of 5-methylcytosin. Comparison of different parts of the respiratory tract.

(ii) RNA level: Isolation of messenger RNA. *In vitro* protein synthesis should give information by which mechanism genexpression is regulated. As a model system elements of the cytoskeleton e.g. actin, keratin will be used.

(iii) Comparison of the structure and expression of keratin genes and oncogenes in transformed and non transformed cells.

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E C P W O R K I N G G R O U P

" B R E A S T C A N C E R "

Chairman: Prof. F. DE WAARD
National Institute for Public Health
Bilthoven

Report and conclusions of the 1st Meeting of the E.C.P. Breast Cancer Group, held in S. Margherita (Italy) April 21-22, 1986.

The first meeting of the Breast Cancer Group of the European Organization for Cooperation in Cancer Prevention Studies (E.C.P.) was organized by the Unit of Clinical Epidemiology and trials of the Istituto Nazionale per la Ricerca sul Cancro in Genova (I.S.T.), Italy.

It was financially supported by I.S.T., E.C.P., and several participants who were able to find coverage for their traveling expenses. Twenty-eight scientists (see enclosed list) from twelve European countries attended the meeting, which was chaired by Dr. F. De Waard (NE).

During the first session (April 21), each participant introduced himself and briefly discussed his research experiences and projects in breast cancer epidemiology. It was acknowledged that, in terms of number of Institutions, number of potentially available cases to be studied, and quality and variety of scientific competence, knowledge and experience, the group represents worldwide a unique opportunity for achieving major improvements in our understanding of breast cancer etiology.

The 2nd session was devoted to the presentation and discussion of study proposals.

The first series of proposals was introduced by Dr. De Waard, who discussed his findings related to the association between Wolfe's Mammographic Patterns (which have been shown to be associated with specific histologic features) and reproductive history, which is a known determinant of breast cancer risk.

In the following discussion several points were made, concerning reproducibility of Wolfe's patterns, the significance of ALAs,

and the fact that P_2 an Dy are associated with a relative risk comparable to that of parity (while, as a proximal risk factor, mammographic patterns should show a stronger association with breast cancer risk).

Suggestions were made about the need for looking at autoptic material, or for more refined studies on biopsied patients.

A second discussion was introduced by F. Bruning, who presented data concerning endocrine factors in breast cancer etiology (specifically the association between free fatty Acids ; and the proportion of free E_2). He also showed evidence relating type of diet (western vs eastern) with type of obesity (abdominal vs gluteo-femoral), and illustrated the differences in terms of endocrinology, metabolic significance, of the two types of obesity, and possible association with various diseases.

A further topic for discussion was introduced again by De Waard, who presented data on the increased proportion of cancers positive for Estrogen Recptors among obese women, which indicates a role of obesity in the promotion of hormone-dependent initiated breast cells, and on the relationship between prognosis of breast cancer and degree of obesity.

He suggested the need for clinical trials of weight reduction in an adjuvant setting, which could provide useful information for preventive interventions. It was anticipated by several participants that such a trial might face severe feasibility problems, since most breast cancer cases are already treated with some form of adjuvant therapy.

At the end of the discussion, various study proposals were presented, and eventually seven research topics were identified.

1) Correlation between Dy-P_2 Wolfe's Mammographic patterns and histology in non-cancerous breasts (Presence of ALAs). Relationship with known risk factors for breast cancer.
2) Case-control study on the distribution of fat (abdominal vs gluteal-femoral) in various countries and a case-control study to test its association with breast cancer risk.

3) Demographic data and time trends on age at 1st and subsequent births in various countries.
4) Meta-analysis of data from case-control studies on breast cancer, in order to obtain pooled information on the role of various risk factors.
5) A case-control study of breast cancer in men.
6) Clinical trial of nutrition intervention in breast cancer cases.
7) A follow-up study of B.B.D. patients, in order to confirm the increased risk in specific histologic subgroups.

It was agreed that these seven topics represent relevant research areas, suitable for cooperative research, and participants were invited to notify their interest and potential availability in participating to any of these studies (see enclosed list). The following were indicated as responsible for drafting a temptative protocol for each study, (seeking any help or support they believe useful) and/or for further exploring its feasibility:

1) Dy/P_2 - Histology (F. De Waard - H. Tulinius).
2) Distribution of fat and Breast Cancer (F. Bruning).
3) Demographic Data on age at 1st and subsequent births (M. Ewertz).
4) Pooling of Data from case-control studies (C. La Vecchia, S. Franceschi, P. Bruzzi).
5) Case control study of B.C. in men (D. Trichopoulos, R. Saracci).
6) Clinical trial of nutrition intervention in breast cancer cases (F. De Waard, M. Ewertz, E. Donath).
7) B.B.D. (M. Rosselli Del Turco, E. Donath).

It was decided that the drafts of the protocols should be circulated among all participants and that the next meeting will be scheduled only after (at least) some of these protocols have been circulated, criticisms and suggestions returned and possibly included in the protocol itself.

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E C P W O R K I N G G R O U P

" V I R U S A N D C A N C E R "

Chairman: Prof. G. de THE
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Dr. de Thé presented the European Organization for Cancer Prevention studies and its different committees.

The discussion on the possibility of European collaboration in the field of "virus-cancer-prevention" covered three different topics :

1) Papilloma viruses and genital cancers :

Dr. Gérard Orth presented the epidemiological project aimed at establishing the prevalence of the different types of papilloma viruses in France. He would be happy to collaborate on the extension of such a study to North Africa, if well focused projects were to develop. He offered to train in his laboratory someone from Morocco within the framework of the existing French-moroccan collaboration. This was well received by Dr. Kettany who expressed his personal interest in genital cancers and especially on cervical cancer. Dr. Kettany proposed three steps :

a. An epidemiological survey of the genital cancers (cervical and penile) in Morocco, and in parallel, the study of the prevalence of different types of papilloma viruses in Morocco, and the study of the Moroccan sexual habits. This could be conducted in pregnant women and probably in their husbands.

On the suggestion of Gérard Orth, he agreed to provide specimens to evaluate the possible role of papilloma viruses the mouth and throat cancers.

b. He would be prepared to initiate a specimen bank including biopsy specimen and sera from patients with genital cancers, and other cancers where a virus is involved, especially NPC, Primary Liver Carcinoma, lymphomas...

c. He will look for a young scientist from the Faculty of Sciences in Rabat to go and work for a few months in Dr. Orth's laboratory in Paris, as well as in Dr. Gissman's laboratory.

Dr. Gissman presented his interest in comparing the prevalence of the human papilloma viruses in European countries and in North Africa. He stressed the point that the ideal situation will be that scientists from different countries be trained in specialized laboratories so that most of the screening work could be done locally in the concerned countries using similar and well-standardized techniques.

2) Epstein-Barr virus and related malignancies

Participated in this discussion Dr. de Thé, Dr. Kettany, Dr. A. Hubert, Dr. A. Sasco.

The association between EBV and NPC is already applicable for the early detection of the tumor in the People's Republic of China, and for differential diagnosis in intermediate and low incidence areas such as Europe and North Africa. Three projects were discussed :

Project 1 : Application of the IgA/VCA diagnosis test in the Maghreb to family members of NPC patients : Such a project would permit to discover early cases of NPC, and to assess the level of familial aggregation of such a tumor in intermediate risk areas such as North Africa. Dr. Kettany will explore the feasibility of such screening in NPC families in Morocco.

He suggested that a technician be trained in Lyon to learn the IgA/VCA test to be established in Rabat.

Project 2. Descriptive epidemiology of NPC in European countries : A better knowledge of the geographical distribution of the NPC in Europe is needed. In France, a registry of the cases which have been treated by radiotherapy centres is being planned by Dr. A. Sasco. A similar investigation was proposed for Italy, Germany, the Netherlands, and Switzerland to get an idea of prevalence of this cancer in Europe and to search for possible aggregations. In France, this project will also be aimed at comparing Caucasian cases with Arabs of the Irst and 2nd generation immigrants.

Project 3. Case control study of NPC in Europe : The extension of the case control study being presently implemented in South China and Tunisia, could be extended after project 2 is completed, to certain centres in Europe. The aim is to characterize environmental factors other than EBV which are likely to play a role in this tumor. For such a study, adolescent cases of NPC would be studied to increase the likelyhood of finding critical environmental factors.

Dr. Kettany accepted to help to implement an anthropological food survey by Dr. A. Hubert in a way similar to that conducted among Cantonese Chinese and Tunisian Arabs in the past. Such an anthropological survey should be preceeded by the establishment of the geographical distribution of NPC in Morocco. This could be done in early 1986 by Malika Elhamdaoui, a student in geography interested in cancer and who will work at the Cancer Centre in Rabat. The ethnographic survey could take place in the Fall of 1986.

3) Retrovirus :

Two projects were discussed.

Project A. Retroviruses and preleukemic conditions :

This project proposed by Dr. A. Burny, who could not come, was presented by his colleague, Dr. R. Kettmann : Chromosomal abnormalities can be observed in a number of leukemias as well as bone marrow dysplasias which often represent preleukemic conditions. Cells of preleukemic conditions can be grown in vitro and in situ hypridization experiment could be performed to search for onc-gene expression. Preliminary results indicate that a few cells of such preleukemic conditions contain activated onc-genes, as detected by in situ hybridisation of smeared cells.

Some contacts have already been taken by Dr. Burny in Europe, such as Dr. P. Stryckmans at the Bordet Institute in Brussels, Dr. H. Van Den Berghe University of Leuven, Dr. N. Muller-Berat in Copenhagen, etc...

This project was felt to be of great interest from the fundamental point of view and a protocole by Dr. Burny should be sent in the coming month. Dr. de Thé suggested to contact hematologists at Saint Louis Hospital in Paris for such a project.

Project B:

Dr. R. Kurth stressed the need of stronger cooperation between European groups involved in human tumor retro-virology and that ECP should provide means to exchange of working visit and informal meetings, to improve collaboration. Specific collaboration was proposed in the area of retroviruses in Africa especially in isolating retroviruses from different HTLV-I and HTLV-III associated syndroms in various African regions.

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E C P W O R K I N G G R O U P

"H E A L T H Y D I E T P R O M O T I O N M E T H O D S"

Chairman: Prof. A. BRUCE
Naerings Laboratoriet Statens Livmedelsverk
Uppsala

ECP's preliminary meeting on Healthy Diet Promotion Methods held in Geneva at the offices of the World Health Organization on May 2/3, 1986

Present:

Dr. A. Giacosa	Istituto Tumori	Genoa	I
Dr. J. Stjernswaard	W.H.O. - Cancer Unit	Geneva	CH
Dr. V. Koroltchouk	W.H.O. - Cancer Unit	Geneva	CH
Dr. J.A. Hanley	W.H.O. - Nutrition	Geneva	CH
Dr. Gurney	W.H.O. - Nutrition	Geneva	CH
Dr. M. Andrien	Institut Communautaire pour l'Alimentation et la Nutrition	Liège	B
Prof. A. Bruce	Naeringslaboratoriet Statens Livsmedelsverk	Uppsala	S
Dr. A. Maskens	E.C.P.	Brussels	B
Dr. B. Herity	University College	Dublin	EI
Dr. L. Arab	Bundesgesundheitsamt	Berlin	D
Prof. R. Hermus	CIVO-TNO Institute of Nutrition	Zeist	NL

Apologies were received from:

Prof. E. Parodi	Istituto Tumori, Genoa
Prof. L. Santi	" " "

Interest had been expressed by:

Mr. D. Cordingley	BBC, London
Dr. Vassilianos	Health Ministry, Greece
Dr. G. Ziant	Association Contre le Cancer, Brussels
Prof. E.B. Thorling	Cancer Research Institutes, Aarhus, DK
Dr. J.A. Amorin Cruz	National School of Public Health, Portugal

The first meeting was held in Geneva in conjunction with the WHO. Its aims are to define the general outline of a European research group on ways to promote healthy dietary habits among the populations.

The meeting decided to start with a multi-step program and the first was to take a look at reality to see what was actually going on in the different countries. The second was to find a research area where pilot studies could be launched from a local point of view and then to make larger studies involving national projects.

The immediate task was to develop a questionnaire designed to find out what the public knows about diet and particularly healthy diet.

Second, was to create a depository of all available material on this subject which it was hoped to be able to locate in the WHO headquarters in Copenhagen, possibly holding exhibitions during future symposia so that people would be able to see what material was available covering different needs in the various countries.

Thirdly, it was agreed to establish an inventory of ongoing projects in different countries.

These preliminary ideas will be discussed at a meeting of a small group which will be held in Genova in November 1986.

Professor BRUCE from Sweden was elected Chairman during this preliminary phase and Dr. GIACOSA from Genova agreed to act as Secretary.

The group will organize its second general meeting in '87.

III SYMPOSIA

Two official symposia have been organized during the period under review. The following one is currently being prepared.

Third annual ECP Symposium

"DIET AND HUMAN CARCINOGENESIS"
Aarhus - Denmark
June 19 - 21, 1985

This Symposium was prepared by the corresponding ECP working group and attracted more than one hundred and forty scientists from twenty countries.

A book of abstracts has been published; in addition, the full proceedings were published by Elsevier as No 2 of a series on ECP Symposia.

This Symposium was preceeded by a two-day workshop jointly organized by the Internationnal Union of Nutritional Sciences (IUNS) and ECP. The proceedings of this workshop have been published in "Nutrition and Cancer", 1986 (p. 1-40). A consensus statment on provisional dietary guidelines has also been issued. These recommendations follow.

Recommendations

To the Public

- Decrease the intake of saturated and unsaturated fat in countries where, on average, fat constitutes more than 30% of total food energy (calories). In other countries, people should maintain their lower fat intake. Consumption of fat can be decreased a) by lowering the intake of butter, margarine, cooking oil, salad oils, and dressings; b) by selecting fish, poultry, leaner meat products, and low-fat dairy products; and c) by broiling, baking, and steaming foods, rather than frying.
- Eat a varied diet that contains different types of vegetables and fruits, especially green leafy and root vegetables and citrus fruits; these foods can supply an adequate intake of vitamins and minerals, so that supplements do not need to be used.
- Consume foods that are rich in complex carbohydrates (i.e., starch and fiber) that are known to promote healthy bowel function.
- Maintain appropriate body weight. If a lower energy intake is desirable, eat foods with complex carbohydrates, including whole-grain cereal products, fruits, and vegetables, instead of the higher-energy fatty foods.
- Consume a low-salt diet. A desirable goal is less than 5 g of salt per day as recommended in relation to cardiovascular diseases.
- Use fresh or minimally processed foods rather than cured, pickled, or traditionally smoked foods. Do not eat moldy foods.
- Drink alcohol only in moderation, if at all.

To the Food Industry

- The meat, dairy, baking, and other processed food industries should produce more foods with lower fat and lower salt contents.
- The processed food industries should label foods for their salt and fat content, including the types of fat.
- The agriculture and food industries should develop products that have a lower nitrate content.

To the Scientific Community

- In assigning priorities for research on the relation between diet and human carcinogenesis, pay particular attention to elucidating the effect of individual components of the diet, their interactions, and their mechanisms of action. In this regard, the potential impact on human health of mutagens and carcinogens formed during cooking and of carcinogens formed endogenously needs further investigation.
- Give priority to developing better methodology for studying the interrelationships of diet and human carcinogenesis. In particular, design feasible intervention studies.
- Develop a better understanding of food consumption patterns and the precise composition of foods; undertake research to elucidate factors that determine food habits.
- Give priority to cooperative, multinational, and multidisciplinary research.

To Governments and Other Organizations

- Undertake information and education campaigns to implement the recommendation to eat a varied diet with a high nutrient density that has a low-fat and low-salt content.
- Encourage food service establishments, including cafeterias in schools and other public places, to use low-fat foods and less salt.
- Promote labeling of processed foods for their salt and fat content through legislation and other incentives.
- Promote the sale of low-fat and low-salt foods.
- Support research on the association between fat, fiber, salt, and other dietary components and human carcinogenesis.
- Maintain surveillance of mutagens and carcinogens in the food supply.

Fourth Annual ECP Symposium

"CONCEPTS AND THEORIES IN CARCINOGENESIS"
Bruges-Belgium
June 11 -13, 1986

This Symposium was a success, with one hundred and fifty six participants from nineteen different countries.

A book of abstracts has been published in a special issue of "Cancer Letters". The full proceedings are being published by Elsevier as No 3 of the ECP Symposium series.

Fifth Annual ECP Symposium

"PREVENTIVE STRATEGIES FOR CANCER RELATED TO IMMUNE DEFICIENCIES"

May 1987

The fifth ECP Symposium will be organized by the "AIDS and cancer" Working Group. This conference has tumor development resulting from an interplay between immune deficiency states and viral and non-viral carcinogens as its first topic. Thereafter projections into the future are presented. On this background the conference participants will discuss strategies for cancer prevention and forward recommendations for scientific and science-political actions in the European area.

PRELIMINARY PROGRAM:

1. Etiology and pathogenesis:

Immune surveillance
Oncogenes
Congenital immune deficiency
Immune suppressors as carcinogens
Drugs as virus activators
Epstein-Barr virus

Cytomegalovirus
Papilloma virus
HTLV-I/II
Kaposi's sarcoma in pre-AIDS, Europe
Hepatitis virus

2. Forecasts:

Mathematical models for spread of virus-related diseases
Spread of HIV in Europe
HIV-induced tumors in the future
The hepatitis epidemic and the vaccine
Cervical cancer in the next decade

3. Strategies for prevention:

Correction of immune defects
Modified medical use of immune depressing treatments
Antiviral treatments
Vaccinations
ECP Working Group report on AIDS-preventive strategies in Europe
Influencing the public / the press / the bureaucrats / the politicians
The international health organizations

4. Recommendations

Scientific programs in need of implementation
Administrative restructuring
Possible political initiatives in the European community

IV SCIENTIFIC ADVISORY COMMITTEE

The scientific commitee has met on three occasions, in Brussels, February 8-9, 1985; Aarhus, June 21st, 1985 and Bruges, June 13, 1986.

The first meeting was particularly important: a critical review of the first phase of ECP's activities from November 81 to December 84 was made and new goals were set.

As for the organization it was decided to ease the work load of the Medical Coordinator, Dr Maskens, by delegating the coordination between groups to Professor Scott for "Hormones" and "Breast", to Dr. Ebbesen for "AIDS" and "Virus" ,and to Dr. Hill for "Diet" and "Colorectal".

The composition of the scientific commitee was modified. The following is the present membership list:

CHAIRMAN

Prof. J.S. SCOTT	Department of Obstetrics and Gynecology University of Leeds LEEDS, United Kingdom.

MEMBERS

Prof. J. ALTHOFF	Centre International de Toxicologie EVREUX, France.
Prof. G. de THE	Laboratoire d'Epidémiologie et Immunovirologie des Tumeurs, Faculté de Médecine Alexis Carrel LYON, France.
Prof. F. DE WAARD	National Institute for Public Health Division of Epidemiology BILTHOVEN, The Netherlands.
Dr. L. DOBROSSY	WHO Regional Office for Europe COPENHAGEN, Denmark.
Dr. P. EBBESEN	The Institute for Cancer Research Danish Cancer Society AARHUS, Denmark.

Prof. J. FAIVRE	Registre des Tumeurs Digestives Faculté de Médecine DIJON, France.
Mr. J. GEBOERS	Division of Epidemiology School of Public Health LEUVEN, Belgium.
Dr. A. GIACOSA	Istituto Scientifico per lo Studio e la Cura dei Tumori GENOVA, Italy.
Dr. M. HILL	Bacterial Metabolism Research Laboratory Public Health Laboratory Service SALISBURY, United Kingdom.
Mr. P JEANDRAIN	Secretary-Treasurer ECP Brussels
Prof. J.V. JOOSSENS	Division of Epidemiology School of Public Health LEUVEN, Belgium
Prof. E.G. KNOX	Department of Social Medicine University of Birmingham BIRMINGHAM, United Kingdom.
Dr. A.P. MASKENS	Medical coordinator ECP BRUSSELS, Belgium
Prof. F. OESCH	Pharmakologisches Institut der Universitat Mainz MAINZ, F.R.G.
Prof. M. ROBERFROID	Unité de Biochimie Toxicologique et Cancérologique Université Catholique de Louvain LOUVAIN-en-WOLUWE, Belgium.
Dr. H. SANCHO-GARNIER	Institut Gustave Roussy VILLEJUIF, France.
Prof. L. SANTI	Istituto Scientifico per la Studio et la Cura dei Tumori GENOVA, Italy.
Dr. Cl. WEST	Agricultural University Department of Human Nutrition WAGENINGEN, The Netherlands.

V ACTIVITY CALENDAR

(For the period Jan. 1985 - Nov. 1986)

1985	Jan.	8-9	Group "AIDS and Cancer" Brussels
	Jan.	30-31	Group "Respiratory Tract Cancer" Villejuif
	Feb.	1-2	Group "Sexual Factors and Cancer" Gatwick
	Feb.	8-9	Scientific Advisory Committee Brussels
	March	14	Administrative Council Brussels
	June	17-18	Joint ECP-IUNS Workshop on "Diet and Human Carcinogenesis" Aarhus
	June	19-21	3rd ECP Symposium "Diet and Human Carcinogenesis" Aarhus
	June	21	Scientific Advisory Commitee
	Sept.	25	Group "Colorectal Cancer" Geneva
	Oct.	25	Group "Virus and Cancer" Paris
	Oct.	29	Group "AIDS and Cancer" Brussels
1986	March	13	Administrative Council Brussels
	Apr.	21-22	Group "Breast" S. Margherita-Italy
	May	2-3	Group "Healthy Diet Promotion Methods" Geneva
	May	5-7	Group "Diet" (Atrophic gastritis project) Wageningen

June	11-13	4th ECP Symposium "Concepts and theories in Carcinogenesis" Bruges
June	13	Scientific Advisory Committee Bruges
June	20-21	Group "Colorectal Cancer" Dijon
Oct.	16-17	Workshop "Optimisation of Influence of Ovarian Steroid Consumption on Cancer Risk" Frankfurt
Nov.		Group "Healthy Diet Promotion Methods" Genova

VI PUBLICATIONS

Third Annual ECP Symposium "DIET AND HUMAN CARCINOGENESIS". Book of Abstracts. ECP, Brussels, 1985

DIET AND HUMAN CARCINOGENESIS. Proceedings of the Third Annual ECP Symposium, by J.V. Joossens, M.J. Hill and J. Geboers, Eds., Elsevier Excerpta Medica, Elsevier, Amsterdam 1985

European collaborative study on the role of diet and other factors in the aetiology of atrophic gastritis: a precancerous lesion of gastric cancer, Clive E. West, Ed. Wageningen: Stichting Nederlands Instituut voor de Voeding - EURO-NUT report 4, Dec. 1984

EUROFOODS: Towards Compatibility of Nutrient Data Bánks in Europe. Clive E. West. Ann. Nutr. Metab. 29 (Suppl.1), 1-72, 1985

Proceedings of a Joint ECP-IUNS Workshop on Diet and Human Carcinogenesis. (Aarhus, Denmark, June 1985). Nutrition and Cancer 8 (1), 1-40, 1986

"Fourth Annual ECP Symposium "CONCEPTS AND THEORIES IN CARCINOGENESIS" Abstracts of free communications and summaries of invited lectures. Cancer Letters 30, S1-S108, 1986

Selenium Status in Europe - Human Data - A multicenter Study", E.B. Thorling, K. Overvad and J. Geboers, Eds. Ann. Clin. Res. 18: 3-7, 1986

"Report of Activities. First Phase: Dec. 81 - Dec. 84" (ECP, Brussels, 1985)

ECP NEWS 3 (April 1985)
ECP NEWS 4 (October 1985)
ECP NEWS 5 (March 1986)
(ECP, Brussels)

ECP Study of Ovarian Cancer and Endometrial Cancer in Women under 80 Years of Age. M. Booth. Cancer Letters 30: S88, 1986

Experimental Skin Carcinogenesis: a critical Review. MC Gueur, AP Maskens, P Maes. Cancer Letters 30: S64, 1986

The Oncogenes: History of a Concept. P Maes, A Maskens, MC Gueur, A Burny. Communication to the Fourth Annual ECP Symposium, Bruges, June 1986.

VII ACCOUNTS

E C P A C C O U N T S - 1 9 8 5 -

RECEIPTS

Brought forward	92.451
Private Sponsorship	165.852
ECP Foundation	950.000
Symposium	2.536
	1.210.839

EXPENSES

Expenses on research

- Groups	Nutrition	195.529	
	Sex	90.016	
	Colon	75.759	
	Tobacco	105.266	
	AIDS	46.622	
	Virus	133.421	
- Scientific Committee		150.062	
- Medical Coordination		111.874	
			908.549

Operating expenses

- Secretariat	100.922	
- Operating expenses	64.102	
- Bank charges	350	
		165.374
Reimbursement of advance to associates		60.000
Paid out		62.000
Cash in Hand		14.916
Total		1.210.839