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WORKSHOP CONFERENCE

SYMPOSIUM ON THE PREVENTION OF CANCER

AT THE ROYAL COLLEGE OF SURGEONS LONDON 1970

EDITED BY RONALD W RAVEN OBE TD FRCS

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SYMPOSIUM ON THE PREVENTION OF CANCER

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AT

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Address of Welcome

SIR THOMAS HOLMES SELLORS, D.M., M.CH.
President of the Royal College of Surgeons of England

It is, Mr. Chairman, Ladies and Gentlemen, a great privilege to be allowed to address you at the start of this Symposium. The name of Marie Curie is of course revered not only in the world of medicine but by humanity as a whole, and this second Meeting of the Memorial Foundation helps keep our thoughts and memories fresh of her great achievements and what they have led to. Your Foundation has reached its coming of age and has given nation-wide domiciliary care both night and day to any patient with cancer. In addition to this valuable marathon work done by more than 2,000 devoted nurses, it has provided more than 400 beds in different nursing homes all over the country. May I add that at least a quarter of the patients in these beds are not terminal patients—they are patients awaiting or undergoing radiotherapy or other treatment. They may be patients who have no relatives to nurse them at home and, last but not least, the Foundation may serve to give relatives a rest from a very trying period of nursing a sick person with this dreadful disease.

The actual Marie Curie Hospital, which is now nothing to do with the Foundation because it became part of the National Health Service in 1948, had an invaluable band of brothers, I should say sisters, who collected money for that institution. They have happily continued to do so and, forming a joint Committee with the Queen's Institute of District Nurses, the Foundation had the good fortune to gain the services of Mr. Ronald D. Raven as its Chairman. Now Mr. Raven, as you know, is not only a surgeon of great expertise in cancer work, but he is a magnificent organiser and I am told and assured that he is very skilled in spending the money that has been collected. You are also aware of the fact that a Research Centre at Limpsfield has recently been started and is engaged on valuable research work, which we hope will lead to some help in treating this problem.

Today we have had registered 389 people to attend this Symposium on the Prevention of Cancer and, the audience includes not only doctors and nurses but social workers, representatives of industry, of Universities and of Public Authorities, and delegates do not only come from this island, they come from all over Europe and indeed from the United States, from Australia, from Brazil, from Thailand, from India and from

Iraq. This is not a national crusade, it is international and I should like to extend my College's most sincere and warm welcome to all. I realise from the programme and from the capacity of the speakers that you will have a very full intellectual feast. All the speakers are people with a high degree of expertise and knowledge in their own special subjects. The title of the Symposium that has been taken, "The Prevention of Cancer", is as challenging as anything can be, for prevention of any disastrous disease is far, far superior than attempts to cure it, and this most certainly applies in cancer work. Surgery, radiotherapy, chemotherapy—any of these means falls into the background if only prevention can take their place. And, although of course, a good many of us have been engaged for years in the study of the discussions concerning cancer, we are still left with large question marks.

What makes the behaviour of a normal body cell suddenly go wild? Why does control of growth or metabolism or immunity suddenly go astray and allow a malignant process to develop? What is the role of viruses? I think these are the different angles that are engaging our thoughts at the present time. We as doctors study the unhappy clinical course of the disease and at times have been able to eradicate or control a growth, but we are still very far from knowing all the causes, and if we did know them, we then might be able to prevent the occurrence of the disease, which after all must be our aim and object. We all know that chronic irritation of the skin or mucous membrane can produce cancer in some parts of the body. We were brought up on the Kangri cancer, caused by charcoal containers that the Indians in the Himalayas used to carry against their bellies to keep warm; we also know of the clay-pipe smoker who would get a cancer on the edge of his lip. These are obvious examples of chronic irritation that in some cases produces malignant change. Now there are a whole group of pre-cancerous conditions which, if recognised, can be dealt with before vicious transformation occurs. These only account for a very small proportion of the actual total.

Modern research is tending to concentrate more on the hormonal side and biochemistry and immunology, and it has certainly been making progress—progress in interesting fields and branches, but this is all too slow and offers very little to the potential victim. The epidemiologist will know variations between race and place. I recently was undertaking a fairly comprehensive study of cancer of the oesophagus, and the racial variation was enormous. In the Transkei district of South Africa, near Natal, the incidence of cancer of the oesophagus among the Bantus, is enormous, a highly malignant disease, and one doctor who is working there told me that the commonest disease in the hospital beds is cancer of the oesophagus. I remember a long time ago spending a year in Scandinavia, and in that full year I saw in several busy clinics

only one cancer of the rectum operated on, but I did see far, far more cancers of the stomach treated than I ever did in a year in this country. There is a very marked racial and environmental difference; whether this is due to dietetic habit, inborn genetic trends or not, we do not know. All these things must be open to study and, of course, the World Health Organisation regards this as one of their most important works.

In this Symposium you will have most, if not all, of these modern aspects reviewed. The role or place of authority in popularising the discoveries and making the public aware of what they can do to prevent and, if they are unfortunate enough to suffer from this disease, to seek early treatment and early recognition will be discussed.

Cancer is a challenge that has to be faced with increasing vigour as our population gets older and older and therefore more liable to these changes that we know are in part degenerative. We all recognise that the surgeon, the radiotherapist and the chemotherapist are happy to see themselves put out of business in this field, if only prevention can be brought to the perfection that all medicine must end.

The Principles of Cancer Prevention

FRANCIS J. C. ROE, D.M.(OXON.), D.SC., F.R.C.PATH.

Non-events hit no headlines. Successful prevention is, in journalists' telegramese—"un-news". This is one reason why so few people realise how important and how rewarding a subject is "Cancer Prevention". Another reason is that, for most doctors and members of paramedical professions, malignant disease is seen as a problem in diagnosis and treatment: their patients already have cancer, and it is too late to consider the possibilities of preventing the disease in them.

In this Symposium we are purposely withdrawing a little from the front line cancer clinic to study the strategy of the whole battle against malignant disease and to pose questions such as "Are we fighting it on the right front?" Today, each of us may be likened to the garage mechanic who, having spent six days doing his best to patch up cars damaged in accidents, sits down on the Sabbath to consider how road accidents might be prevented by the better design of cars, or perhaps, by the better behaviour of the people who drive them.

A modern concept of cancer and of cancer causation

As a professional cancer researcher, I am regularly rendered hypertensive by the sort of question which runs "Have you found *the cause* yet?" For practical purposes cancer is not a single disease but a large and very mixed group of diseases that differ from each other in almost every conceivable way: the part of the body affected, age of appearance, rate of growth and spread, microscopic appearance, etc., are all widely variable. Different types of cancer are associated with exposure to quite different causative factors. In many instances, it is clear that a multiplicity of factors are implicated in the causation of a single cancer.

The definition of cancer

Because cancer is so many different diseases, it is difficult to define. For present purposes it is enough to say of cancer that it is a manifestation of the uncontrolled growth and spread within the body of abnormal cells derived from the body's own cells. I use the word "uncontrolled" rather than "uncontrollable" because therein lies one of the hopes for its effective treatment.

It is necessary to include in the definition "spread within the body" since the ability of cancer cells to invade normal tissues and to spread

to distant sites via the blood or lymph streams and to multiply on arrival in those sites, are the hallmarks of malignancy. Tumours that consist of cells which multiply but do not invade normal tissues or spread to distant sites are *benign* and are usually readily amenable to surgical removal. They are not to be regarded as true cancers, though true cancers, not infrequently, arise in them after they have been present for some time. Mr. Raven later today, will be discussing the possibilities of preventing cancer by looking for and removing benign tumours and other precancerous lesions before they become true cancers.

Distinction between cancer prevention and cancer control

This distinction is made in Table 1. There is confusion in the literature to the point that many people think that prevention and control mean the same thing and that the possibilities of prevention are limited

TABLE 1

Distinction between Cancer Prevention and Cancer Control

Prevention	Control
(1) Practice of eugenics	(1) Early diagnosis
(2) Reduction or abolition of exposure to causative factors	(2) Effective treatment
(3) Recognition and treatment or removal of precancerous lesions	(3) Palliative treatment

to the recognition and treatment or removal of precancerous conditions, and the early diagnosis of true cancer and its treatment. Much of today's discussion, however, will be concerned with what I regard as true prevention, namely the reduction or abolition of exposure to causative factors. However, before I pass on to this topic, I should like briefly to consider the role of genetic factors and the possibility of preventing cancer by means of eugenics.

Role of genetic factors and eugenics

The medical student is instructed to regard diseases as either congenital or acquired. Early in his medical training he comes to realise that genetic and environmental factors are commonly both implicated in the causation of a single disease. This generalisation applies to the causation of cancers.

At present we know relatively little about the genes that favour cancer development in man. However, examples can be given of cancerous diseases in which genetic factors play a major role. *Xeroderma pigmentosa*, characterised by a skin that is abnormally sensitive to the

cancer-inducing activity of sunlight, is associated with the inheritance of a particular abnormal recessive gene. In an individual who has inherited only one of the abnormal genes, the skin is normal. But if two individuals, each carrying one abnormal gene, marry and have a child, there is a one in four chance that the child will inherit the abnormal genes from both parents and, as a result, will suffer from the disease.

Familial polyposis, on the other hand, is associated with the inheritance of a dominant gene. The disease is characterised by the development of multiple polyps in the lining of the colon and rectum and a high risk of the development of cancers in these polyps.

Both these conditions are rare and most other examples of association between genes and cancer are even rarer. Thus, we have very little knowledge concerning the effect of genes on the risk of developing most of the more common types of cancer, such as stomach, lung, breast, etc.

In laboratory animals, especially in the mouse, it has been possible to obtain many genetically pure strains by close in-breeding (i.e. successive brother-sister mating for more than 20 generations). Under these circumstances it is clear that genetic factors play an important role in determining susceptibility to a wide variety of cancers. It becomes increasingly difficult, however, to detect the role of specific genetic factors, as the system of breeding moves from close in-breeding to deliberate non-inbreeding. Man is, for the most part, so out-bred that the influence of genetic factors is difficult either to see or to predict. Our experience from the laboratory, however, must lead us to expect that genetic factors are at work, and I prophesy that we shall one day be more knowledgeable about them. The need to practice eugenics may then become more obvious and more pressing in relation to the prevention of cancer.

A note on cancer families

There has, in the past, been much talk of so-called cancer families. In Table 2, I seek to show that one must expect multiple cases of cancers in single families merely as a result of chance. On average each of us has approximately a 1 in 4 chance of developing one or other form of cancer before we die and we have at least a 1 in 5 chance of dying from malignant disease. Simple arithmetical calculations based on these figures indicate that there is a greater than 1 in 12 chance that 4 or more members of a family of eight (i.e. parents, brother, sisters and children) will develop cancer of one type or another before all are dead. Five or more cases of cancer are to be expected in 1 out of every 43 families of 8, and 6 cases in 1 out of every 260 families of 8.

It should be pointed out that these calculations are only theoretical, and certainly do not apply retrospectively. Only a few years ago, the

risks of death from infectious disease were much higher than now, so that amongst the older generations of present day families death from cancer was less frequent than 1 in 5.

Nevertheless, the calculations do suggest that the occurrence nowadays of multiple cancer deaths in the same family should not lead directly to the conclusion that genetic susceptibility is to blame. Of course, the likelihood of there occurring multiple cases of cancer of the *same type or site* in a single family is much less, so that if this happened it would be justifiable to suspect more strongly that genetic factors were implicated.

TABLE 2

Life-time Expectation of Cancer in 8-Member "Families"

Assumptions

(1) Risk of developing cancer is 25%.
(2) Cancer attacks individuals at random.
(3) 8 members of a family are equivalent to 8 individuals selected at random from the entire population.

Number of "family" with cancer	Frequency
0/8	1 in 10 "families"
1/8	1 in 4 "families"
2/8	1 in 3 "families"
3/8	1 in 5 "families"
4/8	1 in 12 "families"
5/8	1 in 43 "families"
6/8	1 in 260 "families"
7/8	1 in 2,731 "families"
8/8	1 in 65,536 "families"

Calculations by Dr. L. I. Hart, June 1970.

Vertically-transmitted viruses

Study of inbred strains of mice has led not only to the discovery of genes that favour the development of cancer, but also of vertically-transmitted cancer viruses—that is to say of viruses that are transmitted from parent to offspring via the placenta and that increase the risk of specific forms of cancer arising in the progeny. At present we have no indication that there exist vertically-transmissible cancer viruses in man, but our lack of knowledge in this area probably stems more from our inability to detect them than from their rarity or non-existence.

The importance of the environment in the causation of human cancers

I have said enough about genes and cancers, and now turn to the much more important subject of environmental causes of cancers.

A survey of the mortality from cancers of different organs and types shows remarkable differences between countries. Different standards of diagnosis account for some of the differences, but by no means for all of them. Theoretically, the differences may be due to either genetic or environmental factors, but studies on migrants from one country to another have repeatedly shown that environmental factors are likely to be far more important than genetic ones.

TABLE 3

Changes in Cancer Risk for Japanese MEN who migrate to U.S.A.

Standardised Mortality Ratios (Japan = 100) for	Japanese-born	Japanese-born Migrants to U.S.A.	U.S.A. born Japanese	U.S.A. White
Stomach	100	72	38	17
Colon	100	374	288	489
Lung	100	306	166	316
Leukaemia	100	314	—	265

From Haenszel and Kurihara, 1968.

TABLE 4

Changes in Cancer Risk for Japanese WOMEN who migrate to U.S.A.

Standardised Mortality Ratios (Japan = 100) for	Japanese-born	Japanese-born Migrants to U.S.A.	U.S.A. born Japanese	U.S.A. White
Stomach	100	55	48	18
Colon	100	218	219	483
Breast	100	166	136	591
Ovary	100	337	—	535
Cervix Uteri	100	52	33	48

From Haenszel and Kurihara, 1968.

In many ways the most impressive study on migrants has been that of Haenszel and Kurihara (1968). These workers compared age-standardised mortality from cancers of different types in Japanese in Japan, Japanese who migrated to the United States or Hawaii, the children of Japanese migrants to the United States or Hawaii, and white U.S. citizens living in the United States. Tables 3 and 4 illustrate that, for cancer of the stomach, the high mortality in Japan is dramatically lower in Japanese migrants to the U.S.A. and lower still in their children;

whereas the risk of death from cancer of the colon is dramatically higher in Japanese migrants and their children than in stay-at-home Japanese. In both cases the cancer experience of the migrants rapidly changes in the direction of that of the population in the country to which they migrate. These data provide strong evidence for the greater importance of environmental as opposed to genetic factors. The same conclusion applies to cancer of the lung in males and to cancers of the ovary and uterine cervix in females. Only in the case of cancer of the breast does it seem that genetic factors are of greater importance than environmental ones.

It has been variously estimated that between 70% and 80% of human cancers are primarily of environmental rather than of genetic origin. These figures are necessarily based mainly on guesswork but, in the light of current knowledge, I personally believe that they are fairly close to the truth.

Carcinogens and the environment

Twenty years ago it was more or less reasonable to regard carcinogens as *unnatural* agents which convert cells or tissues from the normal to the cancerous state. It is now abundantly clear that even the most natural environment has innumerable components that are to be regarded as carcinogens in this sense.

A man living in the backwoods of parts of Africa is exposed to the cancer-inducing effects of sunlight. The cereals he grows and eats contain variable amounts of aflatoxin—a potent carcinogen produced by a common mould, *Aspergillus flavus*. He inhales carcinogens in the smoke of fires and recent work suggests that carcinogens of the nitrosamine type are sometimes formed during the brewing of alcoholic beverages, such as Malawi gin, which he needs to survive his village rat race. He is liable to infection with the potentially carcinogenic virus that is thought to give rise to Burkitt's lymphoma, and he may further voluntarily add to his burden of carcinogen exposure by smoking tobacco.

In this country more by design or accident, we are less exposed to the risk of Burkitt's lymphoma, or to hazard from sunlight or aflatoxin, and London Gin is doubtless free from nitrosamines. But we have a very big tobacco cancer problem, and our state of industrialisation has introduced a galaxy of new hazards, mainly for small groups of workers who are exposed to particular chemical agents, but in some cases also for persons living in the vicinity of factories or even for the general populace through the pollution of air and water. The products of the incomplete combustion of fuels for domestic heating and for driving machinery and vehicles pollute not only the air we breathe but, by the fall-out of particles, the food we grow and our water supplies. The asbestos worker is at increased risk of developing cancer of the lungs

and pleura, especially if he inhales enough dust to develop the fibrotic condition of the the lungs known as asbestosis. But this is not the limit of the hazard from asbestos: asbestos-induced cancers have occurred in women whose only occupational contact with dust is that they wash their husbands overalls. The air of big cities is polluted with asbestos dust particles and so is the air downwind from asbestos mines and factories, sometimes heavily so.

I hope I have said enough to make it clear that man cannot escape exposure to agents capable of inducing cancer, and that exposure to carcinogens is not new in the history of the human race. He has always been exposed to the carcinogenic products of incomplete combustion (e.g. 3,4-benzopyrene) and to the cancer-inducing effects of the sun's rays. It is impossible to conceive of an environment that is totally free from carcinogens.

Finally, it is necessary to say that cancer is not a uniquely human problem. Cancers are seen in every animal species, and in the laboratory species of which we know most, cancers are sometimes seen in very high incidence in the absence of deliberate exposure to known carcinogenic agents. In some cases the vertically-transmitted viruses about which I spoke earlier are implicated. In other cases, it has been shown that cancers are caused by aflatoxin or other known carcinogens in the ordinary diet fed to animals. But in no experiment is it possible to define the causation of all the cancers that arise in either the treated or the control groups in terms of identified agents.

Identification of carcinogens

The identification of agents that cause cancer in man is difficult. The most convincing way to do so is by epidemiological studies in man. These may be retrospective or prospective; what proportion of patients with a particular form of cancer have a history of exposure to X or Y as compared with comparable non-cancer subjects? What is the incidence of a particular form of cancer, year by year, in a group of workers exposed to X or Y as compared with non-exposed workers? The retrospective method is open to error because of bad memory and because a positive result may arise as a result of exposure to X being associated with exposure to Z which is the agent really responsible and about which there is no information. The prospective method if less open to these errors but is expensive. Moreover, in the case of drugs and food additives, the commercial life of the product is frequently less than the minimum time required for the induction of cancer in man.

Tests on laboratory animals therefore frequently offer the only practical way of looking for possible cancer hazards. Except in the case of arsenic, it has proved relatively easy to induce cancers in animals with every agent known to cause cancer in man. So that provided tests are

adequately conceived and executed, there is not much danger that a human cancer hazard will be overlooked.

The difficulty with animal tests is of another kind. Tests are necessarily undertaken against a background spontaneous incidence of cancer, so that if exposure to a test agent is associated with a raised incidence of tumours, it is difficult or impossible without further study to distinguish between a true carcinogenic effect and a non-specific enhancement of the development of tumours caused by vertically-transmitted viruses or exposure to carcinogens in the background environment.

Despite the limitations of both epidemiological and experimental methods, we are, year by year, slowly gaining knowledge of the significant causes of cancers in man.

The possibility that the body has effective defences against the effects of exposure to carcinogens is a highly topical subject. It is likely, certainly in the case of carcinogens that occur naturally and to which man has always been exposed, that defences exist. Until we know more about these defences and how to strengthen them, true cancer prevention must depend on the reduction or abolition of exposure to identified carcinogens.

Preventable cancer in Britain

Figures 1 and 2 are designed to show the proportion of cancers in men and women that might, theoretically, be prevented in the light of present knowledge. By far the most dramatic contribution to the lists

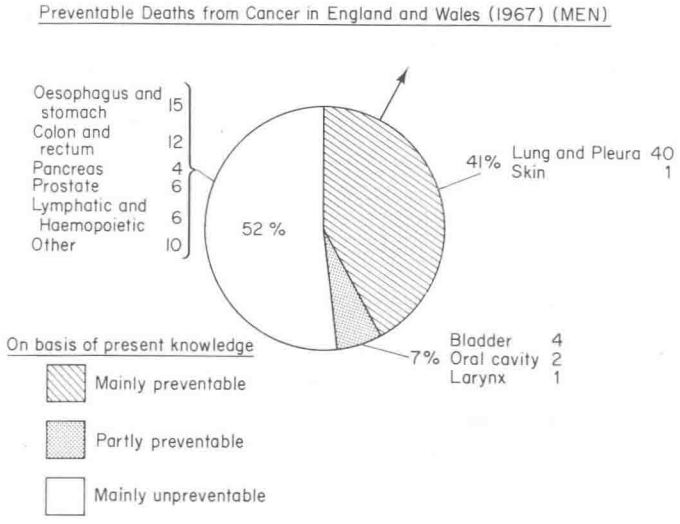

FIG. 1.

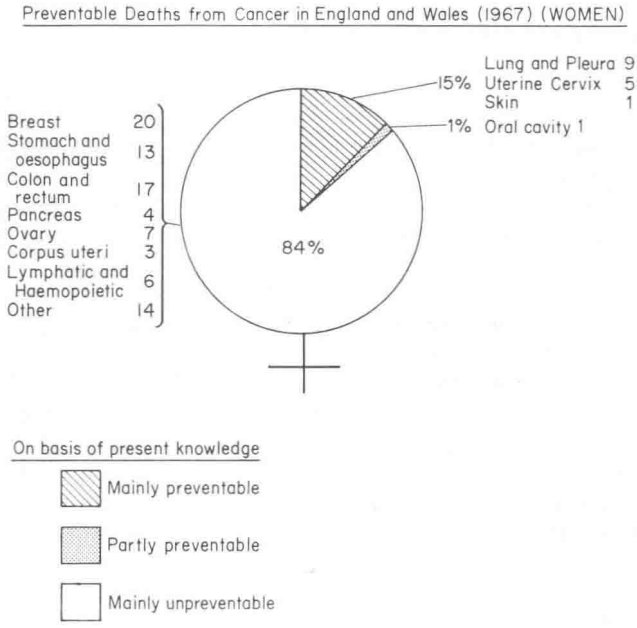

FIG. 2.

of preventable cancers in both sexes concerns cancers of the lung, larynx and pleura. Two out of every five cancer deaths in men are deaths from lung cancer. Occupational exposure to asbestos and other dusts are implicated in a few cases and exposure to general air pollutants is also a contributory factor, but almost everyone who studies the problem agrees that tobacco smoking, especially the smoking of cigarettes, is by far the most important contributory cause in both men and women.

Industrial agents are involved in the causation of cancers of the skin and bladder, and factors loosely bracketed together under the heading "poor sexual hygiene" are important determinants in the case of cancer of the uterine cervix.

We do not yet have useful knowledge of causation in respect of 50% of cancers in men and over 80% of cancers in women.

Cancer prevention—subdivision of the subject

Until recently cancer prevention suffered by being confused with cancer control and it still suffers because different organisations involved in practising cancer prevention do not understand how their work fits into the subject as a whole. Table 5 is an attempt to subdivide cancer prevention logically into its important components.