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PROSPECTS OF CANCER CONTROL*

BY

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I am honoured by the invitation to deliver the Florence Blair-Bell Memorial Lecture in memory of the wife of the illustrious Professor Blair-Bell, of Liverpool University, whose work on the treatment of cancer by lead attracted much attention more than three decades ago. As a student I heard him lecture at St. Bartholomew's Hospital, and sensed the impetus which he gave to work connected with cancer control at that time. His contribution is one of the pioneer attempts in cancer chemotherapy.

We have made progress in our knowledge of cancer since those days. The subject is systematized so that we now have a clearer conception of our goal and the paths to it. There remains a long way to go, however, and many years of hard work lie ahead. On such a journey it is prudent to halt periodically for a review of the situation, and this lecture gives us such an opportunity. The lecturer is a watchman set upon a tower who is asked to declare what he sees, and I welcome your invitation to give you my impressions of the cancer situation. The vision is fleeting and the horizons are distant, with the result that I can only take a glimpse here and there. I will look at the way ahead and indicate certain directions in which we must move so that our generation can make its maximum contribution to cancer control. The present international effort is inadequate to solve the whole cancer problem in a reasonable time. Cancer control could be achieved in the foreseeable future provided the manpower and sufficient money were made available.

Lethal Force of Cancer

Human cancer has created a menacing world situation, for it is second on the list of killing diseases and causes an annual increase in the number of deaths. The medical profession must therefore prepare to deal with many more cancer patients in the future, and hospital facilities should be increased to treat them. Cancer should be given a high priority when the nation's research and medical resources are allocated. The pattern of the disease is changing and its lethal force against the community has altered in direction. Lung cancer is now the greatest menace of all varieties of cancer and the harbinger of death to increasing thousands of people who will die in their prime. But this dark cloud has a silver lining, for the solution of this problem is well known and national and individual action is required. Apart from lung cancer the lethal force of cancer has diminished and the outlook for men and women is better.

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Death rates at all adult ages in both sexes have fallen for cancer of many sites. In men these sites include the buccal cavity; pharynx, larynx, and trachea; intestine and rectum; scrotum; and bone, except the jaw. In women death rates have fallen for cancer of the lip, stomach and duodenum, intestine and rectum, larynx and trachea, vagina and vulva, and jaw. It is noteworthy that the death-rate has fallen in men below 75 years of age for cancer of the stomach and duodenum but has risen at older ages. Death-rates have risen at all, or nearly all, adult ages in men for cancer of the lung and bronchus, pancreas, kidney, bladder and urethra, Hodgkin's disease, and leukaemia. For women they have risen for cancer of the lung and bronchus, pharynx, pancreas, ovary and Fallopian tube, kidney, Hodgkin's disease, and leukaemia. In spite of these changes the cancer situation remains serious and no effort must be spared to control this disease. The prospects are discussed under three headings, research and clinical and public health aspects.

RESEARCH ASPECTS

The solution of the intricate nature of the problems concerning cancer requires a supreme concentrated international effort.

Organization

While nothing must be done to curtail scientific liberty, it is apparent that the work ahead should be developed according to an overall plan and our forces organized to carry it out. The scientist cannot be regimented, but he requires an organized framework for his activities. Future planning should be done now, and I will indicate some of the needs to be met.

The Scientific Force.—It is apparent that the available force is not commensurate with the task to be accomplished. The scientific data required are supplied by much detailed, time-consuming laboratory work with consequential delays in progress. This situation could be ameliorated by increasing the number of laboratory technicians and junior scientists working in the various subjects. An effort must be made to attract to this work those in our schools with good brains, and more attention could be given to the kind of training they should undergo later before embarking on cancer research. There are many scientists in this field who have never seen a case of human cancer. Scientists must be provided with all the equipment they require for their work. Over the past ten years new research techniques have been developed which include the use of radioactive tracers and chromatography of all types.

No doubt in the future other techniques will be discovered, and the search for them should be encouraged. Sufficient financial support must be organized for this expanding task.

Integration of Units.—It is true that memorable discoveries have been made by individuals, often working alone, and history may be repeated for cancer. Some integration of isolated units could prove advantageous; indeed, for the solution of some scientific problems this is essential. It is particularly desirable to establish close liaison between scientists in cancer research and clinicians studying all aspects of human cancer. Our objective is to reach a full understanding of human cancer; clinicians can indicate to the scientists possible investigations and provide clues obtained from patients. The scientists can inform the clinicians of the main results of their experiments and indicate where their work is leading. Integrated teams of specialists are required, for example, in cancer chemotherapy. If this subject is not to remain in its infancy much closer collaboration is necessary: progress in chemotherapy, although modest, should now encourage the clinician to seek closer contact with research workers.

Scientific Communication.—Easy methods of scientific communication are essential between scientific units and individuals throughout the world so that they possess an overall picture of the work and the details of specific experiments. Duplication and overlap should generally be avoided, although certain experiments have to be confirmed by repetition; there can be no wastage of scientific effort. The world literature on cancer is now of enormous dimensions and an individual cannot keep abreast of even a part of it. More précis which are informative and easily read are necessary on different subjects, and more cancer institutions could usefully publish selected papers. Conferences are valuable when well organized, and this method of communication could be expanded. Local conferences of scientists and clinicians are desirable at frequent intervals. National conferences held in different regions are profitable, and international congresses have been established for many years with good results. During recent years the number of personal visits to centres throughout the world has expanded, but they can be time-consuming for the individual, though perhaps the most rewarding.

Scope of Research.—The pattern of cancer research has widened considerably during recent years. It is now subdivided into certain main divisions—laboratory, clinical, and epidemiological. All three are expanding continuously, and this must go on. We need new ideas and clues; we must not exclude those ideas which appear novel or unusual. Our clinical observations should be carefully documented; has not the subject of carcinogenesis developed from the observation of Percivall Pott on the frequency of scrotal cancer in chimney-sweeps? Epidemiological methods are of fairly recent application to the cancer problem and may furnish important aetiological clues. An opportunity for this research is now available in the study of human cancer in Africa; it must be seized, for conditions are changing rapidly in that continent. Every country should make an annual statistical analysis for cancer and report outstanding features of cancer in their people. I recently tried to obtain a world picture of cancer, but the information received from many countries was very incomplete. The geography of cancer is worthy of greater documentation.

Some Fundamental Unsolved Problems

The subject of cancer research with all its ramifications is enormous and it is therefore helpful to narrow it down to what appear to be the most important unsolved problems. The mechanism of normal and abnormal cell division must be worked out; knowledge of the stimuli which make them work is required. During cell growth and division, synthesis of nucleic acids and proteins occurs. The latter consists in the formation of peptide bonds between amino-acids and seems to be the concern of the cell microsomes which are rich in ribonucleic acid (R.N.A.). Nucleic acid synthesis is particularly active in the cancer cell. Many carcinogens react with the proteins, nucleic acids, and enzymes of tissues and may cause the inactivation of enzymes or other compounds, or modify the structure of certain cellular macromolecules. We must know more about these reactions, for cancer may result from such changes in the cellular composition and metabolism. At present no such change or reaction is recognized as the essential feature of cancer induction. If the mechanism of carcinogenesis were understood it might be possible to block the sequence of changes at certain stages.

Much work has been done on the role of hormones in the genesis of cancer and an important outcome is the development of hormone therapy in human cancer. In the chemotherapy of solid tumours by far the most consistent effects have been obtained by the use of hormones and anti-hormones, and the ablation of the pituitary and adrenal glands, ovaries, and testicles in carcinoma of the breast and prostate. Experimental work has shown how an imbalance of hormones may provoke the appearance of a malignant tumour and also how tumour growth may be controlled by the administration of hormones or anti-hormones. A particularly interesting result of this work has been the discovery that tumours may be initially induced, for example, by substantial interference with the supply of a particular hormone to the relevant tissue, but in the early stages restoration of the hormone will cause the tumour to subside. If, however, the hormone deprivation is continued for a longer period we reach a point where restoration of the hormone has no effect on the tumour, and the tumour is then, in contradiction to its former state, a truly malignant and autonomous growth. It would therefore be very important to delve into the biological mechanisms which operate in the tissue before and after this striking change from benign to malignant growth.

For many years the only experimental example of a virus-induced malignant tumour was the Rous sarcoma produced in fowls. However, recently this subject has been revived in a more interesting way by the induction of malignant tumours in small mammals—for example, hamsters—by the administration of a virus preparation obtained from leukaemic mice; this is called the polyoma virus. Further investigations of these mammalian tumours are being actively pursued. It will also be evident that the efforts now being made, mainly in this country and in America, to discover drugs for the treatment of virus diseases may eventually become complementary to the search for anti-cancer drugs.

CLINICAL ASPECTS

While we await the solution of fundamental problems in cancer an all-out clinical effort is required to diagnose the disease early and to use effectively our

present methods of treatment. However inadequate the latter may be as judged in the future, a great deal can be done for cancer patients to-day: even during the last decade the outlook for them has considerably brightened.

Surgical Treatment

Surgery alone or combined with radiotherapy still remains the chief method of treatment for cancer and is responsible for the cure of thousands of patients throughout the world. In many sites this is the only possible treatment, while in others radiotherapy is the alternative. The selection of patients for surgical treatment must be done with judgment, for a patient with cancer must not be left in a worse position after operation. The operation is based upon a clear understanding of the pathology of the disease, including the details of the local and lymphatic spread. It is executed, wherever possible, as a monoblock procedure. Because of modern anaesthesia and antibiotics these operations are no longer dangerous, and owing to advances in reconstructive surgery are not mutilating.

In a number of sites vital organs must be removed and substitutes may have to be provided. In cases where endocrine glands are excised metabolic disturbances will occur unless appropriate substitution therapy is given. The surgeon undertaking major cancer surgery must consider these matters in order to restore the patient to good health so that he may resume his responsibilities in the community. This can be done, for it is illustrated by many patients, even with advanced cancer in relatively inaccessible and vital parts of the body, who have undergone major surgery and are alive and at work many years later. A good example is pharyngo-oesophago-laryngectomy for carcinoma of the hypopharynx and cervical oesophagus. This is an ideal cancer monoblock operation for a serious variety of the disease and gives gratifying results. The results I have obtained in a series of advanced cases are as follows:

Survival Period After Radical Surgical Treatment of 57 Cases of Carcinoma of Hypopharynx and Cervical Oesophagus

Alive (23 cases):	1, 2, 2, 3, 3, 4, 8, 9, 10, 10, 11, 19, 19, 20, 23, 33, 55, 59, 67, 97, 117, 117, and 118 months.
Dead	<div style="display: inline-block; vertical-align: middle;"> Cancer (25 cases): 4, 4, 6, 6, 8, 8, 8, 9, 9, 12, 12, 12, 13, 13, 15, 15, 15, 19, 20, 23, 23, 33, and 66 months Other cause (6 cases): 2, 10, 21, 30, 75, and 91 months Operation (3 cases): 3, 23, and 42 days </div>

Organ Implantation

Substitution therapy is required after several cancer operations, and work is proceeding regarding organ implantation to replace vital glands that have been removed. Reference is made to foetal thyroid and parathyroid implantation after laryngo-oesophago-pharyngectomy which includes a total thyroidectomy, and parathyroid glands are often included. I have a series of 10 patients for whom a foetal thyroid implantation was done, and in two cases it has been successful as shown by radioactive iodine uptake studies in one and histological examination of the implant in the other. This work is being continued.

When a laryngo-oesophago-pharyngectomy is performed the cervical parathyroids are often removed with the specimen and the serum calcium may fall as low as 6 mg./100 ml.; in some patients tetany occurs. The serum calcium and serum proteins are always evaluated before the operation, and measures are taken to prevent the development of calcium imbalance by the administration of A.T. 10, calciferol, and calcium lactate. All patients with a low serum calcium do not develop

tetany; I cannot explain this at present. When I discover a parathyroid attached to the specimen I reimplant it in the sternomastoid muscle. I have no evidence yet of success in the implantation of foetal parathyroids.

Radiotherapy

During the last decade an important advance in radiotherapy has been the development of supervoltage apparatus for clinical use. This implies irradiation with beams of energy of one million volts or more, using x rays generated by particle-accelerating machines, or gamma rays produced from radioactive sources in telecurie units. Apparatus can now produce x rays up to 100 million volts, but this is confined to the experimental field. There is evidence that the optimum clinical voltage is from 2 to 8 million, and its use is chiefly for deep-seated tumours, primary bone tumours, and extensive tumours of the head and neck. Sufficient time has not elapsed for a comparison to be made with the results achieved by the conventional apparatus. There is no evidence that the biological effect on tumours is superior with supervoltage irradiation, but it has greater penetrating power and causes less skin reaction. Great care is required in using this treatment, because serious deep-seated injuries can occur without the warning overlying skin reactions.

Radioactive Implants.—For certain early circumscribed tumours in the mouth and urinary bladder a radioactive implant of the tumour is a good method of treatment. Radiotantalum can easily be inserted into a tumour of the urinary bladder and removed per urethram. Radioactive gold grains have replaced radon seeds as permanent implants in the mouth, bladder, and elsewhere. This is a valuable adjuvant to surgery where the tumour cannot be completely removed. Examples include residual carcinoma of the oesophagus, stomach, and bronchus. Sometimes a metastatic lymph node is fixed to the internal carotid artery and cannot be completely removed. In such cases I remove the greater part of the lymph node and irradiate the residual tumour with radioactive gold grains. When a primary lesion cannot be excised useful palliation may occur with interstitial gold grains as in carcinoma of the stomach, pancreas, and bile-ducts.

Oxygen Effect in Radiotherapy.—Clinical work is proceeding on this combined method of treatment, and encouraging results were published by Churchill-Davidson (1960), who has described the technique.

Combined Radiotherapy and Chemotherapy.—An attempt has been made to increase the radiation effects on cancer by the simultaneous administration of chemical compounds with anti-tumour properties. Potentiation of radiation response was observed with certain alkylating agents, including nitrogen mustards and tretamine (T.E.M.). Encouraging results were also obtained with actinomycin and azaserine. Another approach is to sensitize the tumour to radiation with a non-carcinostatic compound. Substances like "synkavit," fluorescein, and various inorganic salts were used, but the results were not encouraging. Injections of insulin have increased the percentage of regressions in animal tumours treated with radiation, and some increase in radiosensitivity was found in a tumour treated locally with insulin. Many attempts have been made to increase selectively the radiation dose given to a tumour by metal colloids as secondary radiators, but they are of little value. A search has

been made for radioactive isotopes which would be taken up selectively by primary tumours and metastases and thus deliver large doses of radiation. Not much success has been achieved apart from the limited use of radioactive iodine in carcinoma of the thyroid, and radioactive phosphorus has revolutionized the treatment of polycythaemia (see review by Bane *et al.*, 1957).

Chemotherapy in Cancer

This is the newest method in the treatment of cancer, and many chemical compounds and antibiotic extracts are being tested for any inhibiting effect on tumours. The ultimate objective is to find compounds which can selectively damage cancer cells like the antibacterial agents against bacteria. Cancer cells often proliferate rapidly, and compounds such as the polyfunctional alkylating agents, which interfere with the deoxyribonucleic acid replication, thereby effectively inhibit cell growth in rapidly proliferating tissue. Other compounds, like colchicine, act on the mitotic spindle and are antimitotic agents. Another group of compounds, antimetabolites, may interfere in the synthetic processes required for new cell formation; they include folic acid and pyrimidine antagonists and purine analogues, and are mainly used in acute leukaemia. Other compounds, like the sex hormones or adrenal steroids, affect certain properties which the cancer cell retains from its tissue of origin.

Thyroid cancer can be attacked by radioactive iodine because it retains the ability to concentrate iodine, and adrenal cancer produces a high level of steroid hormone. The search continues for compounds with the capacity to act on specific processes in the cancer cell which are responsible for its malignant behaviour. A beginning has been made in this work, but it is still in its infancy and much more requires to be done. For it is pointed out that none of these chemicals has cured a single case of cancer, although many have ameliorated the disease, sometimes for many years. Until further progress is made I feel that this work should be done in centres where every facility is available for its control. These chemicals are dangerous substances and can be fatal for the patient. They are toxic marrow depressants, they damage normal tissues, and many produce unpleasant side-effects, including stomatitis, nausea, vomiting, and diarrhoea.

Specificity.—There is very little evidence that one nitrogen mustard compound is more specific against a tumour than any other nitrogen mustard. For instance, thiopeta is said to be the agent of choice for carcinoma of the ovary, but remissions are obtained as easily with chlorambucil and cyclophosphamide. There is more evidence of specificity among the antimetabolites—for example, 6-mercaptopurine in acute leukaemia of adults, and methotrexate in acute lymphoblastic leukaemia.

Indications.—Acute leukaemia should be treated by chemotherapy; radiotherapy is used only for local deposits such as those occurring in the central nervous system. The chemical compounds used are 6-mercaptopurine, and methotrexate combined with corticosteroids or A.C.T.H. Chronic leukaemia is treated by chemotherapy or radiotherapy according to the condition present. Chlorambucil and busulphan are given. Lymphosarcoma and Hodgkin's disease are treated by radiotherapy when the lesions are localized. When the disease is generalized, nitrogen mustard, chlorambucil, cyclophosphamide, and other nitrogen mustards are used. Polycythaemia is treated with

radioactive phosphorus; busulphan is used in resistant cases, and careful supervision is required. Widespread or recurrent ovarian carcinoma can respond to the nitrogen mustards, but remissions normally do not last more than eight months. Nitrogen mustard, chlorambucil, thiopeta, and cyclophosphamide are used. When choriocarcinoma has spread, methotrexate can cause regression; frequent urinary gonadotrophin estimations should be done. Nitrogen mustards can cause regression of metastasis from seminoma of the testis. High doses of chemotherapeutic drugs are required in carcinoma of the breast and lung and are very dangerous; alkylating agents are not of value in these patients at present.

Combination Therapy

The possibilities of using combined chemotherapeutic drugs are being considered. The use of paired antibiotics has claimed considerable attention for several years, and this problem is not yet settled. Certain of these combinations have the advantage of synergic action on bacteria, and new combinations which are stated to have this effect are periodically produced. Another advantage of the method is the discouragement of acquired bacterial resistance. The ideas that several drugs acting in different ways in cancer might be more effective than any used alone and the possibility that emergence of drug resistance might be delayed are well worth further elucidation. Some work is being done with a combination of actinomycin D, chlorambucil, and mercaptopurine in the treatment of malignant disseminated teratoma of the testis, and a proportion of patients have shown some response to this combined treatment but never to any drug used alone. In another series of cases of teratoma and other highly malignant tumours mercaptopurine in this combination has been replaced by methotrexate. The real difficulty in this work is that the combinations are very toxic, and it is never possible to attribute toxic effects to any one of the ingredients, so that all three must be withdrawn on the appearance of toxicity. The dose is really guesswork and must be very small if toxic effects are to be avoided.

Another combination used is chlorambucil and busulphan, for the combined effect nearly reproduces the effects of total body x-irradiation on the haemopoietic organs and peripheral blood count in the rat. Clinical trials have begun for patients with advanced metastatic disease and in several types of other serious tumours. Two dosage systems are being used—intermittent therapy with single large doses, and continuous therapy with smaller doses. It is too early to report the results.

Steroid therapy is often usefully combined with an alkylating agent in the treatment of resistant febrile Hodgkin's disease, in acquired haemolytic anaemia supervening on malignant lymphoma, and to achieve the non-specific rise in neutrophils or platelets when these are too low to permit treatment with an alkylating agent.

I have treated a series of patients who had carcinoma metastases in the liver with insulin and prednisolone. This treatment developed out of my experience with a patient having hepatic metastases from a primary carcinoma in the pelvic colon which was removed. This patient was extremely ill when treatment began, and with a daily injection of 45 units of insulin she gained 4 stone (25.4 kg.) and lived four years; during most of this time she was able to work. The clinical impression is that such patients eat well and live longer in comfort.

Chemotherapy of Solid Tumours

The most encouraging results are achieved in carcinoma of the breast and prostate, and chemotherapy (in which I include endocrine surgery) has given amelioration of symptoms to many patients.

Carcinoma of the Breast

It is a matter for concern that 25% of patients with stage 1 disease are dead in five years after radical mastectomy. Could they be saved by combined methods of treatment? Bilateral oophorectomy and adrenalectomy or hypophysectomy do influence the course of later stages of the disease and perhaps should be carried out for certain patients with early disease. The question is which patients should receive this treatment, and new biochemical tests are required to identify them. I perform bilateral adrenalectomy (and oophorectomy if this has not been done) on the first appearance of a recurrence or metastasis after primary treatment for breast carcinoma. The administration of synthetic hormones is now deferred until these operations cease to influence the disease. Bilateral adrenalectomy has an important place in the treatment of patients up to the age of 65 and about 50% benefit, especially those with osseous metastases or recurrent carcinoma of the skin and deeper tissues of the chest wall. Information is now required why the disease subsequently becomes uncontrolled and new treatment methods are necessary to gain further control. The results achieved in a series of 187 cases at the Royal Marsden Hospital are shown in the graph.

Results of bilateral adrenalectomy in 187 cases of disseminated carcinoma of the breast.

Adjuvant Chemotherapy in Cancer Surgery

The detection and incidence of cancer cells in the blood-stream are of practical significance and efforts are made to diminish their number by minimum handling of tumours at operation and early ligation of blood vessels supplying the affected organ. Circulating cancer cells are more vulnerable to chemotherapeutic drugs than established cells, and transplanted tumours are more susceptible to their action during the first days. Nitrogen mustard analogues can destroy cancer cells before they are established in tissues. Chemotherapeutic drugs are required which will destroy or inactivate circulating cancer cells or prevent tissue inoculation without damaging normal cells. Little progress has been made in preventing metastases with adjuvant intravascular chemotherapy. Another possible use of chemotherapy with surgery is the treatment of residual tumour tissue with drugs after the greater part has been removed. It may also be possible to find a drug to destroy small metastases after excision of the primary tumour.

Regional Perfusion

Systemic chemotherapy has the handicap that quantities of the drug necessary to affect tumours also affect other rapidly dividing cells, such as those of the haemopoietic system and gastro-intestinal mucosa. Low dosages are therefore used, and courses have often to be terminated owing to agranulocytosis or gastro-intestinal symptoms. With a pump oxygenator system for an extracorporeal circulation an independent circulation can be maintained in the tumour area and anti-tumour drugs can be added to this circulation. Three advantages are gained: a high concentration of drug in the perfused region; protection of the remainder of the body from the effects of the drug; and the normal tissues in the perfused region remain viable, owing to oxygenation of the arterial blood. Melphalan is the most satisfactory compound used so far, especially in malignant melanoma. Others, including the ester of melphalan, mannitol-busulphan, and methotrexate, are awaiting trial. The dosage of the drug is difficult to determine and at present is estimated on the total body weight of the patient. Nitrogen mustard is given in a dosage of 0.3 to 0.5 mg./kg. body weight and melphalan 1 to 1.5 mg./kg. We must find a dosage system that relates the dose to the particular region to be perfused.

Regions for Perfusion.—The full advantages of the method can be obtained in those areas where the leak back into the systemic circulation is a maximum of 5%. The limbs, using a proximal pneumatic tourniquet to 400 mm. Hg, are the best regions, together with organs with an endarterial supply like the lungs, kidneys, spleen, and liver. High leak rates occur with the pelvis, head and neck, and chest wall. The leak is estimated by tagged Cr-51 erythrocytes.

Experimental Studies

Experiments with chlorambucil were carried out by M. D. Staunton (1960, personal communication) at the Royal Marsden Hospital with the following conclusions. Oxygenation is necessary to protect normal tissues. The use of 5% CO₂ and 95% O₂ prevents the complete removal of CO₂ from the perfused blood and keeps the blood pH from shifting to the alkaline side. To maintain a constant level the drug should be added in divided doses. A high level of drug for a short period can cause normal tissue necrosis apart from the total amount used. Temperature is the most important factor in varying the uptake of the drug. Thus a dose of 180 mg. at 38° C. has the same effect as 130 mg. at 42° C.; for every rise of 10° C. the drug doubles its action. Low temperatures (24° C.) inhibit the uptake of the drug. By using higher temperatures it may be possible to increase the effectiveness in incompletely isolated regions; for example, a temperature gradient or barrier might be established—a warm circuit around the tumour and a cold circuit for the rest of the body.

Continuous blood-pressure recordings should be made; abnormally high pressures signify vascular spasm due to the drug, which usually causes severe tissue damage. The signs of tissue damage are a high arterial pressure; reduced venous drainage; the blood becomes blacker and thicker, more difficult to oxygenate; the normal tissues swell and the skin becomes pink and develops purpuric spots; and, finally, exudation of blood occurs through muscle and fascial planes. Drugs with a powerful specific action against various cancers are required. To find them necessitates the testing of various drugs for their action

against cancer cells growing in tissue culture. For instance, malignant melanoma cells were cultured *in vitro*, and it was found they were killed by melphalan but not by chlorambucil or methotrexate.

PUBLIC HEALTH ASPECTS

The following subjects must be considered by those responsible for the nation's health.

Cancer Education

There is an increased demand for cancer teaching throughout the world and some universities have appointed professors in cancerology to develop it.

For the Public.—There is now a more enlightened public attitude to cancer resulting from free discussions and the presentation of information in the press and on sound-radio and television. It has been shown that cancerphobia is not produced by careful methods which emphasize preventive action against the disease, health examinations, and the warning symptoms and signs which require immediate medical advice. In this work general practitioners, medical officers of health, nurses, and health visitors are integrated, and work is proceeding in different parts of the country with the help of national organizations and local cancer committees. These efforts should now be unified on a national scale and form part of the scheme of general health education.

For the Medical Profession.—Doctors must be given all the new information about cancer to help their work. In addition to published articles, lectures, discussions, and demonstrations should be arranged in centres throughout the country similar to those at the Royal Marsden Hospital for consultants, registrars, and general practitioners. Specialist joint consultation is a good method of teaching as well as benefiting patients regarding diagnosis and treatment. Meetings of clinicians and research workers as arranged at the Royal Marsden Hospital are also helpful. Medical students should be given cancer instruction, including diagnosis, treatment, prevention, and the methods of educating and handling the public and what to tell patients and relatives.

For the Nursing Profession.—Cancer education should be given to student nurses, and further teaching is required for nurses engaged in home nursing and health visiting. This is recognized by the Royal College of Nursing and the Queen's Institute of District Nursing, who include cancer lectures in their postgraduate courses. Lectures are given to other groups of nurses throughout the country, and I receive district nurses and health visitors in my out-patient clinics at the Royal Marsden Hospital to show them what is being done. Postgraduate courses for nurses should be given in our special cancer hospitals; a start is being made at the Royal Marsden Hospital.

Cancer Diagnostic Centres

Conflicting reports of the value of the work of these centres have been published in the U.S.A. and other countries. Arguments for and against them have been advanced (Raven, 1958; Garland, 1958). We cannot be satisfied with present conditions, for too many patients consult doctors with advanced cancer, and we must make better use of present knowledge concerning its prevention and diagnosis, and treatment of pre-malignant and early cancerous lesions.

I visualize a new unit to provide doctors with a cancer diagnosis service, to include also an information

department working on cancer education, nursing, socio-economic and welfare subjects, and teaching and records departments. There would also be a research department investigating clinical, biochemical, and histology problems concerning human cancer. I suggest that the College of General Practitioners should be associated with this centre, for general practitioners are early concerned with cancer problems and the centre must work in close collaboration with them. Doctors would refer patients with symptoms and those without symptoms who desire an examination, and full reports would be furnished. The centre would be associated with one or more hospitals, which would admit patients at once who required operative investigations or cancer treatment. In this plan there is complete concentration on cancer; our present methods are yielding results that are not good enough; so let us debate no longer, but try this new experiment, for I believe worth-while results will materialize.

Cancer Prevention

Prevention is the most desirable method of cancer control, and the disease can be prevented in many sites if the right action is taken. Aetiological factors must be recognized, neutralized, or eliminated. Many are already known, and our knowledge should now be applied to the lives of nations. Carcinogenesis is linked with cancer prevention and will increase in importance because of the large number of persons in contact with carcinogens for occupational, dietary, habits, and other reasons. These are responsible for cancer of the skin and of the respiratory, urinary, osseous, and haemopoietic systems. The occupational-hazard group in the world is of impressive size, and more people will be exposed to new chemical compounds introduced into industry. Concern is expressed regarding the possible carcinogenic effects of certain food additives and pesticides used in increasing amounts. They must be tested for carcinogenic activity before use, and the subject has already received the attention of the Ministry of Health. The development of atomic energy in peace and war is an added threat because of the carcinogenic action of radiation on tissues. Any rise in the incidence of leukaemia, bone sarcoma, and other malignancies is being watched as indicative of this hazard.

Pre-malignant lesions, common in the skin, alimentary tract, and female reproductive organs, must be detected and treated before invasive and metastasizing cancers develop. For instance, at the Gordon Hospital in 372 cases of ulcerative colitis the incidence of bowel cancer was ten times the expected figure for a healthy population of the same age and sex structure (I. Macdougall, 1960, personal communication). Carcinoma-*in-situ* can be recognized in the skin, in the gastro-intestinal, respiratory, and urinary systems, and in the female reproductive organs; supervision and treatment are required.

The association of habits and customs with cancer is fairly well documented, and much of this knowledge applies to other nations, but special mention must be made of lung cancer.

Lung Cancer

The serious rise in the incidence of cancer of the lung in Great Britain and other countries is a tremendous challenge to preventive medicine. In men aged 50 to 54 the death-rate from this form of cancer is now nearly half the total male cancer death-rate at that age (Case,

1958). In women also, the death-rate from lung cancer has increased considerably. The extensive statistical and epidemiological evidence associating tobacco smoking and lung cancer is clear for all to study. Much attention has been directed to carcinogens produced by tobacco combustion; the possible effects of nicotine on the tissues in relation to cancer should now be investigated.

If it were shown that metabolic changes are caused by smoking tobacco, and since it is known that nicotine can pass through the placental circulation, the effects of nicotine on the developing foetus should be studied. Is it possible that cellular changes may be caused *in utero* which manifest their effects in later life?

In the prevention of lung cancer people should be dissuaded from beginning to smoke and smokers persuaded to stop. This is a great challenge to all, and doctors should help people to overcome a severe form of drug addiction. I have made some practical suggestions to help towards a solution of this problem (Raven, 1957), for I feel that elimination of the tobacco habit could be one of the greatest benefits conferred by preventive medicine.

Conclusion

The prospects of cancer control are hopeful, but much work still remains to be done before we reach our objective. A greater international effort is required, more effective use should be made of our present knowledge, and new ideas and clues are urgently required.

I wish to thank Mr. P. M. Payne and Mr. M. D. Staunton for kindly analysing the results of adrenalectomy, and I appreciate the kindness of my colleagues at the Royal Marsden Hospital for allowing me to publish them. I am grateful to Dr. H. E. M. Kay for supplying the foetal thyroids.

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Twelve identical travelling exhibitions on Britain's care of the blind are being sent by the British Council to more than 50 countries overseas. The exhibitions will be touring in Europe, the Middle and Far East, Australasia, Africa, South America, and the West Indies during the next two years. The exhibitions, prepared by the Council with the help of blind welfare organizations, each consist of over 100 photographs showing how blind people in Britain are helped and taught to help themselves. With the exhibitions go periodicals in Braille and Moon type and the publications of official and voluntary organizations for the blind. The majority of countries will show films on the care and treatment of the blind in Britain and the Commonwealth. The exhibitions are intended primarily to show welfare workers and social workers what can be done for people with no sight, but there is also material of wide general interest. There are sections devoted to the following aspects of the subject: the responsibility of the Government, local authorities, and voluntary organizations towards the blind; work for blind children and young people; the rehabilitation of the newly blind; training and employment of blind people here and in the Commonwealth, and equipment for the blind—ranging from bread-cutters for blind housewives to "talking books" recorded on tape.

FACTORS INFLUENCING* RESPONSE TO HYPOPHYSECTOMY FOR ADVANCED CANCER OF BREAST

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The value of hypophysectomy in the treatment of patients with advanced cancer of the breast has been well established. There is not, however, general agreement about which patients are most likely to respond, and many who undergo operation do not benefit from it.

Several factors appear to have influenced the result in some series. The most discriminating so far reported is a function, calculated from the levels of 17-hydroxy-corticosteroids and aetiocholanolone in the urine, which shows a close correlation with the clinical result (Bulbrook *et al.*, 1960). The method, however, involves elaborate chemical procedures, which are not generally available, and the conclusions await confirmation.

Analyses of other factors, obtained by clinical methods, by simple diagnostic procedures, or by observation of the effects of simple therapeutic measures, have been reported.

Age.—The age of the patient at the time of operation appears to be unimportant. Thus Pearson and Ray (1960) found that the results tended to improve with increasing age, while others (Baron *et al.*, 1958; Luft *et al.*, 1958; Evans *et al.*, 1959; Atkins *et al.*, 1960) have not observed that age has any effect.

Relation to Menopause.—Several authors have reported that patients who are still menstruating are more likely to respond favourably to operation than those who have passed the menopause or who have undergone oophorectomy; while others (Atkins *et al.*, 1960) have not observed any such influence. The results which have been published in comparable form are shown in Table I. The bulk of the evidence seems to support the contention that the pre-menopausal state has a favourable influence on the outcome of hypophysectomy.

*In this paper the word "influencing" is to be understood as "associated with and preceding in time." It does not necessarily imply a cause-and-effect relationship.