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Abstract

Based on a Dissertation read before the Royal Medical Society on Friday, 16th January 1959.

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The possible means of treatment available are :-Surgery, Radiotherapy. Chemotherapy, Serotherapy and Psychobiological methods. Prophylactic measures designed to prevent a person from getting cancer are, of course, of great importance also.

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THE TREATMENT OF CANCER

By JOHN McKENDRICK

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AN overall view of the adequacy of the treatment of cancer at the moment presents a very dismal picture. To be satisfactory this treatment must mean cure, but until the cause or causes of cancer are known this will seldom be achieved.

The possible means of treatment available are:—Surgery, Radiotherapy, Chemotherapy, Serotherapy and Psychobiological methods. Prophylactic measures designed to prevent a person from getting cancer are, of course, of great importance also.

Let us first consider Surgery. The human race has been faced with the problem of cancer for thousands of years. Carcinoma of the breast was described by the Egyptian surgeon Imhotep in the year 3000 B.C. It is mentioned in the papyrus Ebers of the 16th century B.C. and in the remnants of the literature of India and Persia. In those ancient times the mainstay of treatment was excision and caustics and in A.D. 180 Leonides of Alexandria was dissecting out breast cancers extensively, cutting through healthy tissue with knife and cutnery"essentially the same technique as is used to-day. In no other branch of Therapeutics has so little advance been made against a disease known for so long. It is a measure of our ability to conquer the neoplastic process that such a crude and primitive procedure as surgical excision should be the main, and in some cases the only, radical weapon at our disposal.

Surgery is successful in curing cancer in so far as it can get right down to the "roots" and remove the growth, plus the immediately surrounding tissues, where there will be a small number of outlying cancer cells. It is thus effective in removing a superficial tumour where no metastases have occurred, such as one of the skin, uterine cervix, bladder, rectum and a few cases of cancer of the thyroid and parotid glands. In other cases a significant remission may be obtained. A surgical procedure may also be effective in relieving obstruction or pressure, controlling infection or stopping persistent bleeding. But, on the whole, Surgery is not a satisfactory method of treatment, and its possible advantages must be weighed against its many shortcomings, which include: mutilation, inadequate removal of cancer cells, further spread of cancer cells, disturbance of the normal physiological mechanisms of the body and possibly death.

There is now an increasing pressure on the surgeon to "do something about cancer." Articles in lay magazines, the "education" spread forth by the satanic T.V. set, reports of ultraradical operations and the patient's natural desire for cure make it difficult to tell those with certain types of cancer that they cannot be helped by operation. Consideration must be given to the fact that the "something" may do more harm than good. The persistent failure of ultraradical surgery to arrest cancers of high malignancy and the devastating side-effects of these operations make it obvious that it is time to give first thought to the patient as a whole, and to develop operations which control the malignant process as well as possible, but with the minimum

deformity and impairment of function. There is some place for radical operations, especially in treatment of cancer of the head and neck, rectum, colon and cervix, but the initial wave of enthusiasm is now being replaced with more caution. Definite rules must be followed in their procedure: they should only be done by specialists, there must be proper selection of patients, at no time should cancer tissue be cut across and the possibility of seeding into the wound allowed to occur, routes of spread must be sealed off as early as possible, the wound should be washed before closure, possibly using cytotoxins and in the future there may be a possibility of administering cytotoxins parenterally before, during and after the operation.

Surgery by itself, however, has probably reached the stage at which no great advance in method can be expected, but there is a field for its possible use in conjunction with other methods.

X-rays were discovered by Roentgen in 1895 and have been used in therapy ever since. The gamma rays emitted by Radium are most commonly used since they have much the greatest penetrating power. Many advances have been made recently in this form of therapy, and its main advantage is that it does not involve the possibility of cutting into malignant tissue. Critical assessment of the results obtained, however, indicates that there is little justification for complacency. There may result increased comfort and palliation, but the long-term or "cure" rates have shown little improvement.

Radiotherapy is especially effective against actively dividing cells, but normal cells are also damaged to a greater or less extent and not all cancers are affected by it.

In general the conservative optimal dosage to all organs is 6000r delivered over a period of time depending on several clinical factors, but most tumours have a wide range of lethal dose. Surface applicators containing the Radium can be moulded to a part of the body and applicators can be placed in hollow organs such as the uterus. Interstitial irradiation is obtained by means of Radium or radioactive Cobalt needles, Radon seeds or radioactive Tantalum wire coated with Platinum to absorb the Beta rays. Such methods are effective against superficial or localised growths. For deeper growths the telerradium or radium beam treatment can be used, but this is usually less successful since the risk to surrounding normal tissue is much increased. The best effects are obtained with carcinoma of the cervix and some lympho-sarcomas.

For many years Radiotherapy has been used only for palliation, but it can be curative when properly applied to certain types of cancer. It is now used in the treatment of seminoma of the testis, dysgerminoma of the ovary, medulloblastomas and lymphoepitheliomas of the throat. The results are not good, but are better than those obtained by methods previously used in these cases.

There is a growing necessity for teamwork between surgeons and radiotherapists to ensure maximum chance of cure with the best functional results. Some tumours are now amenable to treatment using either or both surgery and radiotherapy, and radiotherapy is an alternative to surgery in treating carcinomas of the skin, mouth and lip, cervix and bladder.

Sources of super-voltage therapy are now available, including the super-voltage X-ray machine, betatron, thoratron, the linear accelerator and high specific intensity radioactive sources of Cobalt 60 and Caesium 130, by which means sources of radiation are provided which allow a homogeneous dose to be delivered at a definite volume. Radiation can now be produced with a shorter wave-length and higher energy which penetrates more deeply into the tissues, with less damage to the intervening normal tissues and portals can be shaped to shield the normal tissue and allow accurate high dosage to small volumes.

The emphasis in Radiotherapy is tending to shift to the radiobiological aspects of the tumour and attempts are being made to render malignant tissues more susceptible to irradiation without increasing the vulnerability of the normal tissues. Biochemical methods involving thyroid hormone, adrenocorticoids, oestrogens, androgens and oxygen alter the intracellular homeostasis and so enhance the effects of irradiation. Radiotherapy has also been used along with other drugs, such as Synkavit, nitrogen mustards and Actinomycin D.

Artificial radioactive isotopes were first used therapeutically in 1936 and since then a wide variety of applications have been developed. They have not proved so beneficial as was initially expected, though they can be effective in certain forms of malignancy. Radioactive Phosphorus was the first to be used—this localises in body tissues which have a high exchangeable phosphorus content (especially bone), a high metabolic rate and a rapid rate of cellular reproduction. It is still used in the treatment of polycythaemia vera and chronic lymphatic leukaemia. Strontium 90 applicators can be used to irradiate superficial tumours of the eyelids, conjunctivae and cornea. Colloidal chromic phosphate, radioyttrium and radiogold are now widely used for the control of malignant effusions and are being administered interstitially in cases of carcinoma of the prostate after surgical removal of as much of the tumour as possible. Good results have been reported following intracavitary or interstitial application of Cobalt 60 in a variety of tumours, such as carcinoma of the bladder and uterus, but its use as a gamma source of teletherapeutic units of deep penetration is currently of most interest. Recent studies of autoimmunisation indicate that it may be possible to deliver a radiation dose to tumours using radioactive antibodies. Neutron fission therapy in glioblastoma multiforme is another interesting approach. Boron 10 is administered and the patient is subjected to slow neutrons which cause the Boron to disintegrate into Lithium and alpha particles within the tumour. But it is too early to predict the place of this work in cancer therapy. Radioactive isotopes have still only a very limited use, but they constitute a fruitful field for research.

Chemotherapy, as a rational means of treating cancer, has only recently been developed, but various diverse agents have been used at different times in the past, including belladonna, aconite, mercury, antimony, arsenic and potions of animal, vegetable and other ingredients brewed under the charm of magical incantations. A popular application in this country during the 15th century was a powder made by burning together sulphur, lead and "arnement" (a black powder used for making ink) which was applied to the ulcerated surface after it had first been washed with the urine of a male child. In the 18th century live toads were bound over the diseased part and left there for 24 hours. Live kittens, puppies and fowls, pigeons split lengthwise, minced lizards and pounded crabs have all had their vogue. In 1802 a remedy was published which was to dry the corns and pairings from the feet of an uncastrated horse, beat this to a powder and take as much as would lie on a sixpence in a glass of white wine night and morning. Medicine, greatly helped by Science, has made significant advances since then—or so we would hope.

In the past few years many new chemicals have been developed for use in the treatment of cancer, but in actual practice the therapeutic gains have been very little. No chemotherapeutic agent has been shown to cure a patient of cancer, though in some cases drugs may relieve symptoms, reduce time spent in hospital, prolong life and increase the possibility of eventual cure by other means.

As with other methods of treatment, the efficacy of Chemotherapy depends on the differential sensitivity of tumourous as against normal tissue, and

there is often a slight margin of safety between the effective dosage and that which will cause degeneration of the haemopoietic system and the development of an aplastic bone-marrow.

The chemicals which are available can be divided broadly into three groups: the alkylating agents, the antimetabolites and a small miscellaneous group mainly of vegetable origin.

The alkylating agents comprise a vast number of drugs, including "TEM," "Myleran," "Tretamine," "Chlorambucil" and the nitrogen mustards. Studies on similar substances have proved that they are effective on certain malignant tumours of mice, human carcinoma of the breast and some C.N.S. tumours. However, nitrogen mustards and other alkylating agents are used mainly in the treatment of the chronic leukaemias and widely disseminated Hodgkin's disease, and may produce remissions of several months or even a year. Direct instillation of nitrogen mustards may decrease or eliminate reaccumulation of malignant effusions and they are of some benefit in the terminal stages of bronchogenic carcinoma, especially of the small cell type. The indications for using nitrogen mustards include: radioresistance, severe radiation sickness, exhaustion of the skin portals, intractable systemic symptoms, acute mediastinal compression, advanced disease and metastatic lesions not amenable to X-ray therapy.

Antimetabolites such as "Aminopterin," "6-Mercaptopurine," "Pyrimethamine" and "Urethane" are used mainly in the management of acute leukaemia. However, the length of remission obtained is very variable, and these drugs are liable to have serious toxic effects, such as damage to the bone-marrow and alimentary epithelium, and the neoplastic cells are able to develop resistance to them.

The miscellaneous group have two things in common—none of them is of great value and most of them are still undergoing trial. "Colcemid" may have some success against chronic myeloid leukaemia. Actinomycin D is effective to some extent in the treatment of soft tissue sarcomas and some epithelial tumours. Actinomycin C gets a response in a few cases of Hodgkin's disease. Cyanocobalamine has been recommended for disseminated neuroblastoma, particularly in infants.

It has been suspected since about 1925 that Insulin may cause some inhibition in the growth of malignant tissue. Glucagon also has this action and the two combined give an even greater carcinostatic effect. Experiments have been done on rats, and the greatest limitation seems to be that the retardation of tumour growth persists only during the period of administration. These investigations must be carried much further before they can have any application to treatment in humans.

A new method of using drug treatment is now being tried. In the case of certain tumours the blood supply to the tumour-bearing area is isolated, and by using a pump oxygenator system the viability of the limb or organ can be maintained while at the same time it can be perfused with high concentrations of chemotherapeutic agents sufficient to destroy the cancer cells but unable to destroy the normal host tissue cells. The temporary isolation of the blood supply prevents the passage of the agent into the bloodstream and thus prevents bone-marrow depression.

Better results may be obtained using a combination of drugs, or of drugs with radiotherapy. The normal physiological activity of the cancer cell is disturbed either by direct alkylation of cell constituents, blocking essential metabolic pathways, interfering with the normal enzymatic reactions, altering the hormonal milieu of the cell or by the effect on the mitotic activity and chromosomal structure produced by ionising radiation. Thus different

methods of treatment may have a synergistic effect when applied in combination.

The use of specific hormones is another aspect of Chemotherapy, and combined with endocrine ablation therapy has proved of value in the palliative treatment of breast and prostatic carcinomas. Oestrogens may favourably affect the primary growth on the soft tissue metastases and also relieve the pain of bony metastases. They should be reserved for inoperable breast cancers in women who are at least 5 years past the menopause, and for prostatic cancers when the testes are known to be producing androgens. Androgens are of little use and may in fact exacerbate tumour growth, probably due to conversion of oestrogens. About 50% of mammary carcinomas are oestrogen dependent and will respond favourably to removal of endogenous sources of oestrogens, such as the ovaries, adrenals and hypophysis.

Serotherapy has yet to become a practical procedure and may not do so until the cause or causes of cancer have been better elucidated. There is now much research into the theory involving a transmissible viral-like particle found in the cell cytoplasm. A serum specific to the virus of avian myeloblastic leukemia has been developed and this is able to neutralise the infectivity of the virus. Research into the application of this theory to treatment has, as yet, produced equivocal results.

Psychobiology is another way of regarding the chemical, nervous, hormonal or electromagnetic environment of the cancer cell. Since both the host and a cancer draw on a common nutritional substrate and share a common vascular supply, it seems desirable that attention should be given to the metabolic equilibrium and growth partition which exists between them. This contest can be turned in favour of the host cells by spontaneous activity of the body itself without any apparent assistance, but the phenomenon of spontaneous regression is still a complete mystery. Perhaps some people are able to develop antibodies against a possible cancer virus or have hormonal changes which lead to death of the malignant cells. Such possibilities are all remote, but the fact that the body sometimes knows how to kill cancer may some day show the way to a method by which all cancers can be killed.

In general, treatment should be directed at the patient-tumour system and not at the tumour in imaginary isolation. The difficult question of the relationship between stress and host resistance has been slightly clarified recently and it appears that an unavoidable accompaniment of the disturbed physiology of the stressed organism is diminished resistance to disease, including cancer. A definite inverse correlation between psychotic withdrawal from reality and the incidence and progression of malignant tumours has been noted; in withdrawn patients' response to therapy, if any is required at all, is usually excellent and they can expect much longer remissions than their anxiety-ridden fellow sufferers. This is added proof that cancer is not a predictable, irreversible process and that every effort should be made to improve the patients' emotional state. Confidence in the healing ability of something or someone has proved curative in many organic lesions, including cancer.

Of supreme importance in the treatment of cancer is the physician who meets the patient as an individual with a problem, whether he be suffering from cancer or cancerphobia. This latter is a powerful new disease, insidious, contagious and crippling and its increasing incidence is greatly contributed to by the medical propagandists who have in the past consistently used the weapon of fear in their relations with the public. The question arises whether or not to educate people about cancer, and since "scare them

out of their wits" is nearer what actually happens, it is certainly undesirable. Instilling knowledge into people about cancer will probably have the opposite effect to that desired, will do no good to their mental health and may cause great suffering. Stimulated by fear we may find Man reverting to the time of the ancient Egyptians and diverting all his efforts to the building of tombs.

Some education about cancer is necessary—that regarding avoidance of those factors which are known to be liable to initiate a cancerous growth. Some of these are occupational hazards such as tar and aniline dyes and assorted factors such as X-radiation, cigarettes, clay-pipes and atomic bombs.

Gallstones and chronic gastritis should be promptly treated, as should lesions with a definite malignant potentiality such as some bone growths, papillomatous growths (especially of the large bowel), some glandular hyperplasias and hydatidiform moles. But there is a danger in the so-called "prophylactic operation" which may, in fact, over a large number of cases cause more deaths than would have resulted had the operations not been done.

An important new development in prophylactic treatment is the routine examination of cervical smears when women over about 30 are under examination for some other gynaecological complaint. Many "carcinoma in situ" may be detected by this means, and it is reckoned that 50% of these will eventually progress if not treated at this stage, though actual symptoms may not be experienced for about ten years and the diagnosis not made for a further five years. Also in the case of a persistent pneumonia, especially in a middle-aged male, it is advisable to do chest X-rays, bronchoscopy and examination of the sputum for malignant cells. These, at the moment, are the only two routine procedures which can be recommended, since the technique is simple, the patient need not be unduly disturbed and the number of cases in which a diagnosis of malignancy is made will be relatively high. Routine medical check-ups on healthy individuals involving thorough physical examination, X-rays of the whole body, bronchoscopy, gastroscopy, cystoscopy, proctoscopy, colposcopy, etc., etc., etc., as are often recommended, should in fact be discouraged since the procedure is more likely to breed neuroticism than complacency.

At the moment surgeons and radiotherapists are well aware of the many defects in their particular forms of treatment and, along with the other members of the team, these and many other difficulties are being attacked with optimism and enthusiasm, and so: "O Tempus Futurum, te magna spe expectamus!"