



Recent Advances in
CANCER and

RADIOTHERAPEUTICS :
CLINICAL ONCOLOGY

Edited by

KEITH E. HALNAN



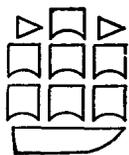
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Introduction

It is now a well known truism that one in five of all of us will develop some form of cancer before we die, often a long time before! This may well be an understatement since the death rate from infections continues to fall. However, the management of human cancer is now at a highly interesting phase of development, and it seemed well worthwhile reviewing some of the more interesting topics in a selective rather than a comprehensive way. The chapters are intended to be readable and critical surveys and are written by authors actively working in these fields. They are designed for undergraduate and postgraduate students as well as consultants and general medical and scientific readers; they are not just for specialists. Clinical management of cancer, neoplasia, or 'oncology' is beginning to coalesce in the English-speaking countries. In many others, especially in Europe, there are already Institutes and Departments of Oncology. It may be a sign of the times that in Britain an Association of Head and Neck Oncologists is now flourishing, and that the Royal Society of Medicine has a newly formed section of Oncology.

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A striking recent feature of clinical work in cancer has been the increasing number of valuable clinical trials undertaken, especially in breast cancer. The first chapter is by Robert McWhirter—himself responsible for stimulating these advances—who reviews and cogently criticises current treatment; much of this chapter can be applied to the orthodox treatment of other tumours.

Many people think of chemotherapy as the future treatment of cancer. Chemotherapy has been used since the early nineteen forties, and is now beginning to make a substantial impact on the clinical problem; new and valuable compounds continue to appear. The outstanding success of chemotherapy in the control of the rare disease, choriocarcinoma, is an inspiration to us all. One of the main fields in which chemotherapy has been applied with valuable though still limited success is leukaemia in children. The clinician himself continues to make important contributions, and the recognition of Burkitt's lymphoma has been one of the major milestones of the last decade. The common lethal varieties of human cancer may seem less interesting but they remain vitally important to their human hosts—our patients—and breast cancer especially is one of these.

03/2/28

INTRODUCTION

For many years excisional surgery was the only sure method of cure for cancer. The major current advance in surgery itself is the possibility of successful organ transplantation. This may not yet be of substantial value for treatment of cancer, but it leads to evaluation and investigation of many intriguing secondary problems. Immunology is one of these which itself is beginning to develop advances in clinical treatment, in leukaemia especially.

Radiotherapy has become the second major method of cure, and over the last 50 years has achieved perhaps the first place for palliative treatment of human cancer. There are at present several highly promising technological advances—'growth points'—in radiotherapeutics. The use of computers is one obvious example. Others depend upon radiobiology, which has taken on a new rational and scientific lease of life. The 'oxygen-effect' (a probable cause of many failures of conventional X-ray therapy) is one of the more important aspects, leading to the exploration of treatment in hyperbaric oxygen, and by fast neutrons. The easy availability of artificial radioactive nuclides as radiation sources has led to endolymphatic radiotherapy—a possible method for improved treatment of the lymphatic spread of a tumour—and to 'after-loading' methods to overcome the main disadvantages of radium treatment, which has already achieved so much especially in gynaecological cancer.

Many other topics might have been discussed if space and time had been more flexible. Very sincere thanks are due to the distinguished contributors to this volume, all of them extremely busy, and most of them refreshingly punctual with delivery of their chapters. Personal thanks are also due to my secretary, Mrs. Z. Willoughby, to the publishers for all their help, and to my wife and daughters for putting up with so much work at home.

K.E.H.

B W
H 12

Contents

- 1 AN ANALYSIS OF THE TREATMENT OF BREAST CANCER,
Robert McWhirter 1
Introduction—present uncertainty. Review of treatment—radical mastectomy, more radical approaches, conservative attitudes—Crile. The Influence of Delay. Bond's suggestions. The National Death Rate. Discussion—endocrine and chemotherapy, immunological control. A comprehensive treatment policy. Comparison of different treatments—factors influencing survival, adequate numbers. Results from an Edinburgh trial with randomly selected sub-groups receiving identical treatment. Summary.
- 2 CANCER CHEMOTHERAPY—THE PRESENT POSITION,
I. D. H. Todd 25
Hodgkin's Disease, single and combined treatment. Chronic myeloid leukaemia. Polycythaemia Vera. Multiple Myeloma. Solid tumours. Intra-arterial chemotherapy. Local applications in skin cancer. Combination with radiotherapy. Combinations with hormones.
- 3 CHORIOCARCINOMA AND TROPHOBLASTIC TUMOURS,
K. D. Bagshawe 45
Trophoblast biology. Chorionic Gonadotrophin—a tumour index substance. Hydatidiform Mole. Malignant Sequelae. Invasive Mole, treatment. Choriocarcinoma, morphology, arteriography, immunological factors, chemotherapy—methods and drugs used.
- 4 MANAGEMENT OF CHILDHOOD LEUKAEMIA,
M. L. N. Willoughby 71
Induction of remission, criteria, combination of drugs. Remission maintenance chemotherapy. Intensive chemotherapy, drug schedules. High-dose combination chemotherapy. Continuous infusion techniques. Immunotherapy. Extramedullary leukaemic deposits. Supportive treatment. Myeloblastic, myelomonocytic and chronic granulocytic leukaemia. Chronic myeloid leukaemia. Growth points—identification of residual cells during remission, use of cell kinetics, drug selection by in-vitro tests.
- 5 BURKITT'S LYMPHOMA, *Peter Clifford* 113
Epidemiology. Possible association with viruses—Reovirus, Epstein-Barr virus. Other aetiological factors—domestic animals, malnutrition, genetics, transplacental and arthropod transmission. Incidence. Clinical features. Origin of multiple tumours. Immunological aspects. Treatment—radiotherapy, chemotherapy, present drug schedules, central nervous system involvement, immunotherapy. Results of treatment.

- 6 TRANSPLANTATION AND CANCER, *P. R. F. Bell* 159
 Recognition of foreign and aberrant cells and their destruction. Prevention of rejection, enhancement, immunological tolerance. Immunosuppression—chemotherapy, steroids, anti-lymphocyte serum, tissue typing. Relative immunity of cancer cells, enhancement, tolerance, antigen modification, decreased immune reactivity. Spontaneous tumour occurrence during immunosuppression. Transplantation as a treatment for cancer. Conclusions.
- 7 IMMUNOTHERAPY OF CANCER, *J. Maxwell Anderson* 193
 Nomenclature. Basic immunotherapy. Indications—suitable tumour types. Methods: non-blocking antibody, cellular augmentation, specific antigenic stimulus, non-specific lympho-reticular stimulation.
- 8 PROSPECTS FROM RADIOBIOLOGY, *N. M. Bleehen* 217
 Current techniques and results—assessment of cell survival, sub-cellular action of radiation, repair of radiation damage, normal tissue and tumour growth. Applications to radiotherapy. The oxygen-effect—oxygen therapy, anoxic therapy, high L.E.T. radiation, ultra-high dose rate radiation, chemical sensitisation. Fractionation. Synchrony. Dose rate changes. Chemical sensitisation and protection. Conclusions.
- 9 FAST NEUTRONS IN RADIOTHERAPY, *William Duncan* 251
 Introduction. Neutrons and the oxygen effect. Criteria for neutron sources—nuclear reactors, cyclotrons, d-t generators, the Hiletron. Physics—shielding, scatter, penetration, quality, RBE, OER, attenuation, skin sparing. Biology—cellular, gain factor, time, recovery, skin, blood, gut, lens. Experimental radiotherapy. Clinical work—Stone 1932-42, Hammersmith 1964- , Manchester 1969- . Radio-chemical sources—Californium-252, Caesium-242/Beryllium. Future trials.
- 10 RADIOTHERAPY IN HYPERBARIC OXYGEN, *Sasha Morris* 309
 Introduction. Techniques—Vickers chamber, oxygenation, beam direction. Other methods. Hazards—fire, non-cooperation by patients, pressure difficulties, oxygen convulsions. Results—M.R.C. trials, head and neck cancer in Cardiff, cancer of uterine cervix, trials in Australia, cancer of lung and bladder in Portsmouth, importance of fractionation. Conclusions.
- 11 ENDOLYMPHATIC RADIOTHERAPY, *Gerald E. Flatman* 323
 Techniques. Lymphography apparatus—radiography, monitoring, radiation protection. Radioactive materials used—colloidal gold-198, iodine-131 lipiodol, phosphorus-32 lipiodol, yttrium-90 sources. Suitable tumours—testicular, lymphoma, gynaecological, urinary bladder, melanoma. Dosage distribution. Complications—radiation hazards, effects on blood, lungs, thyroid, subcutaneous tissue, lymphoedema. Histological changes. Conclusions.
- 12 AFTER-LOADING METHODS IN RADIOTHERAPY, *C. A. Joslin* 353
 Advantages—reduction of exposure to staff. Dosimetry control. Treatment applicators. Afterloading for gynaecological cancer, source pencils, rectal dose measurement, transit dose, combination therapy. Clinical considerations. Radiobiological implications. Post-operative vaginal treatment. Other tumours—oesophageal, laryngeal, brain, bone cavities. Interstitial uses. Surface mould uses. Future developments.

CONTENTS

xi

13 USE OF COMPUTERS IN RADIOTHERAPY, *J. S. Orr*

387

The basic parts of a computer—Output, Input, Memory, Arithmetic Unit, Control. Calculation of Dose Distribution. Methods of visual presentation. Presentation in three dimensions. Use of small 'dedicated' computers. Optimisation—visual, mathematical. Automation of treatment. Computer based record systems. Radio-biological models. Organisation.

INDEX

405

1 An Analysis of the Treatment of Breast Cancer

ROBERT McWHIRTER

Some thirty to forty years ago it appeared as if the treatment of breast cancer had been finalized. There was universal agreement that radical mastectomy was the best method of treatment and, indeed, it was generally regarded as the only method which offered any prospect of cure. The operation was held in such high regard that any suggestion that there might be other methods worthy of consideration was treated almost as heresy and the introduction of new methods was vigorously opposed.

In spite of opposition, many other methods have been introduced with the result that now the conflicting claims put forward by protagonists of each procedure have given rise to great confusion. To add to the confusion it has been stated that the survival rates will be the same whatever method of treatment is employed. It has even been suggested that none of the methods has the slightest influence on the natural course of the disease.

Progress cannot be made if there is unquestioning acceptance of all that has gone before but a state of complete uncertainty is not immediately helpful. In the long run, however, a state of uncertainty may be advantageous because it provokes a critical re-appraisal of:

- (A) the treatment methods we employ,
- (B) the procedure adopted when we attempt to compare the value of different methods of treatment.

A. REVIEW OF TREATMENT METHODS

With advantage we can begin our appraisal of treatment methods by trying to ascertain just why so many conflicting proposals have come to be made. It soon becomes evident that our inability to determine the precise extent of the disease in any patient is a factor of major importance. Clearly the extent of treatment should be governed by the extent of the disease and it is interesting to reflect that if we could determine with certainty the extent of spread from the primary site, our whole approach to treatment could be rationalized immediately. Patients with distant metastases would be spared the unnecessary discomfort of radical treatment. Assessment of the value of the methods

employed in the eradication of local disease would be greatly simplified. Methods of controlling distant metastases could be instituted while the patient's general health was still good and therefore at a stage when some measure of control would be far more likely to be achieved.

Unfortunately we have no means of determining the precise extent of the disease in any patient although, as we shall see presently, some progress has been made in respect of lymph node involvement. We are still a long way however from being able to detect more distant metastases unless of course the involvement is gross. Radiographic examination is still the best method of recognizing metastases in the skeleton and lungs but the method fails to detect early involvement. This is not surprising when we recall that one thousand million cells can fit into a sphere 1 cm. in diameter. A 1 cm. osteolytic deposit in the spine, which is a common site of involvement, is most unlikely to be detected and post-mortem examination shows that deposits of this size in the lungs are not always visible. Radio-isotope bone scans may be of some assistance but they are never a substitute for first class radiographs, and it is important to note that a positive scan does not necessarily indicate the presence of a metastatic deposit. Bone marrow examination is so seldom of value that it has been largely abandoned.

RADICAL MASTECTOMY

When we come to examine the classical Halsted operation in the light of the above remarks we find that frequently the scope of the operation is not commensurate with the extent of the disease. In many it is unnecessarily extensive whereas in others it is inadequate. Thus in patients with negative axillary nodes, dissection of the axilla cannot improve the survival rate and in patients where the disease has spread beyond the axilla there is no possibility of the operation being successful. The percentage of patients in whom axillary dissection may be life-saving is difficult to determine exactly but clearly it must be small. The following calculations give some indication of the proportion of patients in whom cure may depend on axillary dissection. Of the patients nowadays regarded as suitable for radical mastectomy, the axillary nodes are negative in approximately 60%, and in this 60% axillary dissection may be omitted without any disadvantage. In the remaining 40%, the axillary nodes are positive and of these patients some 60% are either dead or have clinical evidence of distant metastases within five years of the operation. The percentage continues to rise in subsequent years and accordingly we can say that in at least 24% (60% of 40%) of the total patients dissection of the axilla fails in its purpose. Combining these observations it may now be stated that in some 84% (60%

plus 24%) of the total patients dissection of the axilla is not a life-saving procedure. Simple mastectomy alone would be just as effective in all but 16% of the patients we regularly treat by radical mastectomy.

The overall survival rates from radical mastectomy have always been encouraging and because of the great importance attached to the dissection of the axilla, it is often assumed that axillary dissection is largely responsible for the success achieved. It is only on closer inspection that it has come to be appreciated that the reputation of the operation has depended, in large measure, on the excellent results in patients with negative nodes. On the basis of the calculations just made and assuming an 80% five year survival rate in patients with negative nodes, the overall survival rate would be 64% (80% of 60% plus 16%) but it will now be evident that in at least three quarters of the survivors axillary dissection played no part in their survival.

Negative nodes are not a test of the value of axillary dissection; the test comes when the nodes are positive and it is in this group of patients that almost every surgeon has expressed disappointment with his results. Handley (1952) has provided one reason why the failure rate is so high in patients with positive axillary nodes. His observations, now amply confirmed by other workers, have shown that by the time the axillary nodes are invaded, the internal mammary nodes are also invaded in approximately 50% of the patients. In addition it has been demonstrated by biopsy of the supraclavicular nodes and by follow up studies after radical mastectomy that the supraclavicular nodes are also commonly involved by the time the axillary nodes are invaded. Both observations help to explain why the survival rates are low in patients with positive axillary nodes.

When the internal mammary and supraclavicular nodes are invaded, standard radical mastectomy does not offer any chance of cure. Recognizing this point, Haagensen (1956) carries out a biopsy of the internal mammary nodes and of the apical axillary nodes before accepting a patient for treatment by radical mastectomy. If the biopsy taken from either site is positive, radical mastectomy is not performed because, as Haagensen rightly says, involvement of these sites places the patient beyond the scope of the operation. In terms of lymph node involvement he has defined very clearly the useful limits of radical mastectomy and his observations are of great importance in the rationalization of treatment. As might be expected from the restriction of the operation to patients with less advanced disease, the survival rates he presents are excellent. Within the limits proposed by Haagensen, radical mastectomy may well remain the best method of treatment.

Our ultimate objective must always be a reduction of the mortality from breast cancer. So far we appear to have failed because the mortality rates, or more correctly the fatality rates, in our national statistics

are the same today as they were at the beginning of the century. While we will not reduce the mortality by continuing to perform radical mastectomy in patients beyond the scope of the operation we must, at the same time, note that restriction of the operation to more favourable patients will not save the life of a single additional patient. From all that has been said it would appear that if we are to attempt to reduce the mortality from breast cancer we must examine more extensive methods of treatment capable of application to more patients and in particular capable of application to patients with positive internal mammary and/or supraclavicular nodes.

While a more radical approach may be indicated in some patients the survey also shows that there is a place for more conservative treatment. We have seen that a conservative approach requires consideration in patients with negative axillary nodes and possibly also in patients still in the operable category, but where there is a high probability of distant metastases being present.

Both the more radical approach and the more conservative approach require careful consideration. It is convenient to discuss the more radical approach in the first place.

THE MORE RADICAL APPROACH

As already noted some 50% of the patients in the clinically operable category with positive axillary nodes also have involvement of the internal mammary nodes. Involvement of the internal mammary nodes is comparatively rare in patients with negative axillary nodes but may occur in subareolar tumours and in tumours situated in the medial half of the breast. Supraclavicular involvement is very rare indeed if the axillary nodes are negative but when the axillary nodes are positive, biopsy shows that the supraclavicular nodes may also be invaded in patients ordinarily regarded as operable.

Both surgery and radiotherapy have been employed in the treatment of secondarily involved internal mammary and supraclavicular nodes.

The feasibility of complete surgical excision of the internal mammary and supraclavicular nodes was explored by Wangenstein (1956) but the high morbidity and mortality associated with this extensive operation render it unlikely to become a routine method of treating breast cancer. In an operation associated with little or no morbidity, Urban (1964) has resected the internal mammary nodes in continuity with the breast. The results he has obtained are encouraging and the extension of treatment beyond the scope of the standard radical operation would appear to be worth undertaking.

In patients where standard radical mastectomy has been performed, the scope of treatment may be extended by irradiating, immediately

after the operation, the internal mammary and supraclavicular nodes. The value of radiotherapy given immediately after radical mastectomy was examined by Paterson and Russell (1959) who found that the survival rates were no better than those obtained when radiotherapy was given only if and when local recurrence took place. In Edinburgh, from 1935-40, radiotherapy was given routinely immediately after radical mastectomy. The local recurrence rate was markedly reduced but unfortunately there was little improvement in the five year survival rate.

In 1941, following a discussion with the senior surgical staff of Edinburgh Royal Infirmary, it was decided to substitute radiotherapy for surgery in the treatment of all the regional lymph nodes. A clinical trial was proposed but was rejected because in those days any trial involving patients was not considered to be ethical. At a time when radical mastectomy was the unchallenged method of treatment, it was admittedly a bold decision to substitute radiotherapy for surgery in the treatment of all the lymph nodes and some account must be given of the reasons leading up to this decision. Keynes (1937) had shown earlier that radium implantation of the regional nodes yielded results comparable to surgical dissection and it was thought that X-ray treatment might be even more effective because of the much better dose distribution. X-ray treatment had already been shown to be effective in the treatment of local recurrence. Prophylactic radiotherapy given immediately after radical mastectomy had markedly reduced the incidence of recurrences on the chest wall and parasternal masses due to internal mammary node involvement had become exceedingly uncommon. In a small number of patients treated by simple mastectomy and radiotherapy in the period 1935-40, the results were encouraging. The decision had the full support of the late Sir John Fraser (1939) who had recently reviewed the patients he had treated by radical mastectomy and had found that the survival rates, especially in patients with positive nodes, were disappointing. We were also encouraged by the fact that the new method of treatment would offer exactly the same prospect of cure as radical mastectomy if the axillary nodes were negative. The decision to continue to remove the breast before irradiating the nodes was based on the findings in patients with advanced disease who had been treated entirely by radiotherapy. In these patients the response in the nodes was always much better than in the breast and, indeed, it was only rarely that the primary tumour disappeared entirely.

With few exceptions (axillary tail tumours, lymph nodes in continuity with the primary tumour, patients with pulmonary tuberculosis and patients with severe peripheral vascular disease of the arm) it was found that simple mastectomy and radiotherapy could be undertaken in all patients suitable for the standard radical operation. Table I shows the

TABLE I
ALL PATIENTS UNDER 65 YEARS OF AGE TREATED BY SIMPLE MASTECTOMY
AND RADIOTHERAPY.
INTERNATIONAL STAGING.

		No. of Patients	Percentage Alive		
			5 yrs	10 yrs	15 yrs
Stage I	T.1 N.O	206	79	64	47
	T.2 N.O	394	68	48	40
	Total	600	72	54	43
Stage II	T.1 N.1	116	67	51	43
	T.2 N.1	375	55	41	32
	Total	491	58	43	35
Stage III	Total	690	37	24	17

No correction made for deaths from intercurrent disease.

crude survival rates of all patients treated by simple mastectomy and radiotherapy. The patients have been classified according to the international form of staging adopted in 1960. The analysis has been confined to patients under 65 years of age so as to lessen the effect of death from intercurrent disease on the long term survival rates.

The Table shows the survival rates to be expected when all the regional lymph nodes are treated entirely by radiotherapy. The results in Stages I and II appear to be comparable to those obtained by radical mastectomy but a clinical trial is obviously essential before a decision can be reached regarding the relative value of surgery and radiotherapy in the treatment of lymph nodes. The findings in the more advanced patients in Stage III will be discussed later.

It is important before going further to try to decide if the extension of treatment to the internal mammary and supraclavicular nodes is likely to be of any value. There is plenty of evidence to show that as the extent of the local disease increases the frequency of distant metastases increases. Thus it is well known that distant metastases are relatively infrequent in patients with negative axillary nodes but are common in patients with positive nodes. It has also been shown that the frequency of distant metastases increases as the number of nodes involved increases. If it could be shown that distant metastases are present in all patients with positive internal mammary and/or supraclavicular nodes then the development of more extensive methods of treatment would not be worth attempting. The following evidence appears to support the view that the attempt should be made.

As already stated, Urban (1964) has demonstrated that positive internal mammary nodes may be successfully removed by surgery. In a clinically operable series of 86 patients with histologically proven metastases in the internal mammary nodes he obtained a five year survival rate of 46.5% and a recurrence free rate of 40%.

In another clinically operable series of 123 patients with histologically proven metastases in the nodes at the apex of the axilla or in the internal mammary nodes, Guttmann (1966), employing two million volt X-ray therapy as the sole means of treatment, obtained a five year survival rate of 52%.

Even in patients with more advanced disease full treatment of all the regional lymph node areas would still appear to be indicated. It may be presumed that a high proportion of Stage III patients have internal mammary node involvement. (It is interesting that there is rarely clinical evidence of this pre-operatively and that parasternal masses indicative of extracapsular spread from the internal mammary nodes are almost entirely confined to patients who have been surgically treated). In many of the Stage III patients in Table I the axillary nodes were fixed and in some the supraclavicular nodes were enlarged. Fortunately fixation of the axillary nodes and enlargement of the supraclavicular nodes do not interfere with full radical treatment by radiotherapy and all patients placed in Stage III have been included provided always that simple mastectomy could be performed without cutting through obvious disease. It will be noted from Table I that the five year survival rate for this group of patients was 37%.

In an analysis confined to patients with enlarged supraclavicular nodes (and often with fixed axillary nodes in addition) a five year survival rate of 17% was obtained in Edinburgh following treatment of all the regional nodes by radiotherapy (McWhirter, 1964).

These findings suggest that distant metastases may not be present in all patients with internal mammary and supraclavicular node involvement, and that more extensive treatment appears to be worth attempting not only in patients who are clinically operable but also in patients who are inoperable because of the presence of gross local disease.

THE MORE CONSERVATIVE APPROACH

We must now turn from these more extensive methods of treatment and examine the conservative approach to the management of breast cancer. More conservative measures have been advocated for many years but they have often been dismissed as a form of treatment to be used only in patients unsuitable for radical mastectomy. Thirty years ago Fitzwilliams (1940) in this country advocated the adoption of

conservative surgery in patients with disease of limited extent but, in spite of the results he was able to present, his work received little support from his surgical colleagues. Surprised by the good survival rates obtained in patients they had treated conservatively, other surgeons went to considerable length to explain them away, so firmly did they believe that radical mastectomy was the only method by which breast cancer might be cured.

A number of workers have maintained that small tumours can be treated adequately by local excision and radiotherapy. In addition to advising that the regional lymph nodes be treated by radium implantation, Keynes (1957) also advised that small primaries should be treated by local excision and that the whole breast should be removed only if the tumour was large. Mustakallio (1954) for many years has treated small breast cancers by local excision followed by X-ray therapy to the breast and lymph nodes, and in a series of 127 patients he obtained a five year survival rate of 84% and a ten year survival rate of 72%. Porritt (1964) advised that the breast should not be removed if the primary tumour was small and showed that his results from local excision followed by radiotherapy, when this appeared to be indicated, were superior to those he obtained by radical mastectomy. Hedley Atkins has set up a clinical trial to compare local excision and radiotherapy with radical mastectomy in the treatment of tumours of limited extent. His findings are awaited with great interest.

When radical mastectomy was being discussed we noted in patients with negative nodes that dissection of the axilla was unnecessary. We also noted that spread beyond the axilla could be presumed in more than half the remaining patients with positive axillary nodes and that axillary dissection in these patients could not be curative. It was then estimated that the same survival rates would have been obtained in some 84% of the patients if they had been treated by simple mastectomy alone. If now conservative measures (simple mastectomy or even only local excision of the tumour) are restricted to patients with very early disease it should not occasion surprise if the survival rates are found to be identical or almost identical to those obtained by radical mastectomy.

The comments just made in respect of radical mastectomy apply with equal force to the routine use of the still more radical forms of treatment discussed earlier. These methods will not be any more effective when all the regional lymph nodes are negative and will still fail if distant metastases are already present.

In spite of the fact that distant metastases to the skeleton and elsewhere may not be detected pre-operatively, it is the presence or absence of distant spread which largely determines the outcome of treatment. When metastases are present the length of survival will depend on the sites involved, the extent of metastatic spread at the time of operation

and very importantly, on the rate of growth of the tumour. As a general rule, tumours which are well-differentiated grow slowly and tumours which are undifferentiated grow rapidly. In addition to these inherent or intrinsic factors there is now increasing evidence that the reaction of the host to the tumour may exert an important controlling influence.

The fact that tumours continue to grow after the aetiological factors have ceased to act, and the ability of cells to maintain their identity as malignant cells through many cell divisions, is strong evidence in favour of the somatic mutation theory of the origin of tumours. Chromosomal aberrations have been identified in many tumours and if it is ultimately established that malignant cells are genetically different from the host cells of origin, it would not be surprising if tumours did excite an immunological response similar to that encountered when a tissue transplant has been performed. Good evidence of an immunological response has certainly been found in experimental animals and the presence of tumour antibodies has now been firmly established.

Crile (1967) has stressed the possible importance of the host reaction in the treatment of breast cancer and his stimulating observations have gained increasing support as our knowledge of tissue and organ transplantation has extended. In his laboratory studies on mice, he has shown the important role which the regional lymph nodes play in the development of systemic immunity to tumour cells, and how this immunity may be lost if the regional lymph nodes are removed. This experience has led him to advise against the removal of uninvolved axillary nodes. He states "Since systemic immunity to the spread of small cancers may reside largely in the regional lymph nodes, such cancers should probably be treated first by local excision or local radiation, sparing the nodes. Perhaps it is only in the treatment of large and advanced cancers that lymph nodes, involved or uninvolved, can be removed with impunity. In such circumstances, as much of the tumour as possible should be removed or destroyed in the hope that the host might regain immunologic competence against the tumour".

Recognizing the unreliability of clinical examination in the determination of the state of the axillary nodes, Crile inserts a finger into the axilla at the time of the operation and has shown that the error rate in assessing the state of the nodes, as judged by the appearance of enlarged nodes subsequent to treatment, is reduced to 8%. If the nodes seem to be uninvolved, the axilla is not dissected and only a simple mastectomy is performed. If and when enlarged nodes are discovered, they are removed and this delayed removal does not appear to impair the patient's prognosis. If the nodes are found to be involved and are still operable a modified radical mastectomy is performed with preservation of the pectoral muscle. The axillary dissection is deliberately less extensive than that usually performed in the standard radical operation