should be less pronounced than those seen in a normal post-ovulatory endometrium. Nonetheless, the endometrium does undergo cyclical changes resembling normal ones, and these changes are probably sufficiently different from the normal to prevent nidation should "escape" ovulation and fertilization occur.

We thank Wyeth, Belgium, and Schering, Berlin, for supplying the contraceptive preparation for this trial. The laboratory facilities are supported in part by grant No. 20.035 from the Belgian

Research Council. We are indebted to Miss M. R. Puttemans who performed all the technical work.

References

- ¹ Noyes, R. W., Hertig, A. T., and Rock, J., *Fertility and Sterility*, 1950, 1, 3.
- ² Johansson, E. D. B., *Acta Endocrinologica*, 1969, 61, 592.
- ³ Hamperl, H., *Klinische Wochenschrift*, 1954, 32, 665.
- ⁴ Kazzaz, B. A., *European Journal of Obstetrics and Gynecology*, 1972, 3, 77.

Today's Treatment

Blood and Neoplastic Diseases

Management of Solid Tumours—Surgery, Radiotherapy, and Chemotherapy

T. J. McELWAIN, M. J. PECKHAM

British Medical Journal, 1974, 4, 645-647

The traditional mainstays of cancer treatment have been surgery and radiotherapy and more recently chemotherapy. Immunotherapy offers hope, but is at present largely experimental. Until recently these disciplines were often found in isolation from each other and some patients were given treatments which were inappropriate for their disease. An important introduction into the investigation and management of cancer has been the concept of oncology as a specialty.

Surgery

Cancer surgery has reached a level of technical achievement beyond which it is unlikely that important advances will be made. Its established role in palliation is, of course, vital, and a newer role in the pathological staging of several tumour types has developed. The use of irradiation as an adjunct in the surgical management of tumours of borderline operability or inoperable tumours at several sites is being intensively investigated. Chemotherapy as an adjunct to surgery in tumours with a high propensity for metastatic spread may be of value in some cases—for example, in osteogenic sarcoma and carcinoma of the breast.

Radiotherapy

During the past two decades rapid technological advances have occurred in radiotherapy; kilovoltage machines have been superseded by megavoltage apparatus generating penetrating beams of high energy x-rays at high dose rates, and the precision, ease, and adaptability of treatment planning methods have been

improved by the introduction of simulators, mould room facilities, and computers. These developments, together with improved tumour localization techniques, have facilitated the treatment of most deep-seated tumours with a high degree of accuracy.

Successful radiotherapy must be based on precise tumour localization. Isotope scanning has achieved some success, ultrasonic scanning now shows considerable promise for obtaining details of tumour localization and volume for planning treatment.

Surgical staging procedures have been particularly useful in Hodgkin's disease, demonstrating occult splenic involvement in about 40% of patients with apparently localized nodal disease. There may be room for further improvement in achieving precise distribution of radiation dose within these accurately identified structures. For example, the possibility of employing proton beams together with x-ray beams to treat inaccessible sites such as the pancreas and the advantages of using beams of negative pi-mesons to achieve the same end is currently under discussion.

When optimal dose distribution has rarely posed a problem—for example, in skin cancer—the cure rate with irradiation has been excellent. The same is true for glottic cancer. Significant advances have, however, also been made in Hodgkin's disease,¹ based on two factors: tumour localization, and the ability to give tumoricidal doses to deeply placed nodes—for example, in the mediastinum and retroperitoneal areas. In bladder cancer radical radiotherapy was impracticable before the introduction of supervoltage irradiation, which can cure about 20% of advanced lesions,² a proportion which is likely to be considerably improved by the planned sequential use of irradiation and surgery. In advanced carcinoma of the cervix, improvements in stage IIB and IIIa have been recorded after the introduction of supervoltage irradiation.³ In localized carcinoma of the prostate, a site previously ignored by the radiotherapist, the Stanford group have reported a five year disease free rate of 72%.⁴ Successive improvements in the curability of testicular tumours have resulted from the introduction of modern treatment and investigative techniques.⁵ About 40% of children with medulloblastoma can be cured using techniques which irradiate the entire neuraxis.⁶

The Royal Marsden Hospital, Sutton, Surrey

T. J. McELWAIN, M.B., M.R.C.P., Consultant Physician
M. J. PECKHAM, M.D., F.F.R., Professor of Radiotherapy

RADICAL IRRADIATION

In broad terms small or medium sized tumours at many sites are well controlled by radical irradiation. Considerable attention has recently been paid to securing improved control of locally advanced tumours. Roughly 10% of patients dying of cancer in the United States do so because irradiation has failed to control the primary lesion. This represents 30% of deaths in patients actually treated with radiation. In head and neck cancer, the relation between tumour volume and curability is striking: as the tumour volume increases, the radiation dose necessary for its eradication inflicts an increasing amount of damage on the normal tissues. The curve relating the probability of controlling the tumour to the total dose is steep so that relatively small changes in dose may be associated with important changes in the chances of cure. Possibly inadequately vascularized (hypoxic) cells may explain these observations, since in the presence of oxygen, cells are almost three times as sensitive to radiation.

ROLE OF HYPOXIA

Approaches to the solution of this problem include hyperbaric oxygen as an adjunct to irradiation, chemical radiosensitizers, and fast neutrons. In many animal tumours roughly 20% of the total cell population are hypoxic, and the presence of necrosis in many human tumours strongly suggests that the situation is similar. Nevertheless, during experimental fractionated radiotherapy hypoxic cells may spontaneously become reoxygenated, though whether this occurs in man is unknown.

The results of treatment of patients with radiotherapy and hyperbaric oxygen have been largely inconclusive, though the Cardiff group⁷ has shown a significant improvement in local control of patients with head and neck cancer. The development of chemical agents which specifically sensitize hypoxic cells to radiation has shown promising advances, particularly the so-called oxygen mimics, which may sensitize almost as effectively as oxygen itself. Since the biological effect of fast neutrons is altered by a factor of only about 1.6 by oxygen these particles are of considerable interest as a means for improving local tumour control. Preliminary studies are being carried out at the Hammersmith Hospital,⁸ but it is premature to assess the usefulness of this treatment.

Radiotherapy and Chemotherapy

Combined radiotherapy and chemotherapy offer considerable promise. These two modalities can be employed in various ways. Irradiation of the skull and spinal cord is routinely practised in patients with acute lymphoblastic leukaemia after remission induction with chemotherapy and has proved to be one of the most important factors in changing the prognosis. Its use is based on the observation that meningeal infiltration becomes increasingly common with increasing survival in patients treated with chemotherapy alone and the value of the technique has been established in some carefully executed studies by Pinkel and his colleagues.⁹

In tumours such as Ewing's sarcoma where survival after treatment to the primary tumour by irradiation or surgery is about 10%, disseminated occult disease may be assumed to be present at diagnosis. A policy of irradiation of the tumour-bearing bone combined with intermittent multiple-drug chemotherapy has been adopted and preliminary results suggest that the survival rate will be considerably improved.¹⁰ As yet, the use of combined irradiation and chemotherapy has not been shown to improve the control of locally advanced carcinomas, but this possibility is being explored at several different sites.

Radiotherapy and Surgery

The failure of radiation therapy consistently to control bulky, locally extensive carcinomas and the failure of surgical excision (due either to spillage of tumour cells at operation or to occult local extension remaining after the procedure) argue in favour of a combined approach. The objective of the combined approach may be to eradicate metastases, to reduce tumour bulk, or to render non-viable the superficial cells of the tumour and thus prevent local recurrence: often the aim will be to realize all three objectives. On the whole, workers have preferred pre-operative rather than postoperative irradiation, though there are no conclusive data in man to support this approach. Moreover, few controlled studies have been carried out on the use of the combined approach in several sites. Nevertheless, Roswit *et al.*¹¹ reported that the number of lymph nodes infiltrated by tumour was significantly reduced in those patients with carcinoma of the rectum and rectosigmoid colon receiving 2,000 to 3,000 rads preoperatively. In this controlled study the life table survivals at five years were 40.4% for the combined group and 27.5% for the surgical group and the favourable effect appeared to be dose related.

Chemotherapy

Until recently cytotoxic drugs were really of much use only in treating leukaemia and lymphomas. Recently, however, we have seen the prolongation of useful life in patients with other tumours when they are treated with optimal chemotherapy. The best results have usually been obtained when drugs are used as part of a co-ordinated attack on the tumour by specialist groups in which there is the fullest integration of medical, radiotherapeutic, and surgical services. But it still remains true that the common tumours—such as those of the stomach, colon, cervix, and lung—are usually insensitive to chemotherapy, though responses are sometimes seen and life is occasionally prolonged.

The ideal cytotoxic drug would be the one which killed only cancer cells and spared the normal host tissues. Such an agent does not, of course, exist. Drugs used in cancer therapy interfere in one way or another with the synthesis of DNA, RNA, or protein. They are thus toxic to all cells, normal and malignant, to a variable extent. Their apparently selective action on certain tumours depends partly on the paradox that many tumour cells proliferate less rapidly than normal tissues (and are thus less capable of repairing the damage that the drugs inflict upon them), and partly on the innate chemosensitivity of some tumours.

Tumour growth also differs from that of normal tissues in that the rate of cell loss from the system is less than the rate at which cells are added to the system. Cytotoxic drugs act by tipping this balance in favour of cell loss by killing some of the proliferating cells in the tumour. In experimental systems the fraction of tumour cells killed by a drug is proportional to the dose of the drug: the higher the dose, the greater the fraction of tumour cells killed.

A given dose always kills a fixed proportion of cells irrespective of the actual number of cells that are present and for this reason just as much drug is needed to eradicate a few cells in a small tumour as is needed to eradicate many in a large one. In clinical practice this means that doctors must continue to use chemotherapy aggressively long after a tumour is no longer detectable clinically if they hope to eradicate every tumour cell.

At present tumours are eradicated very seldom owing to many factors—among which are the innate resistance of some of the tumour cells to the drugs; failure of the drugs to gain access to the tumour; our inability to know how long to continue treatment; and the dose-limiting side effects of the drugs. Unfortunately, high doses of drugs are more toxic than low doses to normal rapidly dividing cell systems such as the gut mucosa and bone marrow. Nevertheless, since these tissues

have a greater capacity for rapid repair than most tumours, intermittent administration of high doses of drugs can result in a stepwise loss of tumour cells at the cost of transient reversible toxicity to the host. But the bone marrow, gut, skin, liver, kidney, and gonads may all be damaged by cytotoxic drugs and this has to be remembered when treatment schedules are being designed; this has resulted in very large doses of drugs being given to patients over short periods with rest periods between treatments, rather than small doses of drugs being given continuously as was the practice in the past.

The latter type of treatment has been called "relapse orientated" since, though it may produce remissions and prolong life, there is little hope of tumour eradication. High-dose intermittent chemotherapy is "cure oriented" since it is aimed at total tumour eradication—though this seldom occurs except in special cases, such as chorioncarcinoma.

Combination Chemotherapy

If effective agents are given together, their antitumour effects may be additive while their side effects may not. This can be partly achieved by choosing drugs whose major side effects are different from one another. Combinations also have the advantage that one drug in the combination may kill tumour cells which are resistant to one of the other drugs and vice versa. Since drug combinations are usually used on a high-dose intermittent basis, this method of treatment should result in a much increased tumour cell kill—and in fact this is the case. Significant responses are seen, for example, in tumours of the breast, bronchus (oat-cell), skin, ovary, testis, and in many of the embryonal tumours of childhood. This suggests that if such chemotherapy was applied earlier in these diseases, subclinical foci of cancer might be permanently eradicated. The term adjuvant chemotherapy is usually applied to this addition of drug treatment to primary treatment with either radiotherapy or surgery. There are two ways of doing this.

INITIAL ADJUVANT THERAPY

Chemotherapy may be given first to relieve symptoms or to make the surgery or radiotherapy technically simpler. Examples are the use of nitrogen mustard to relieve rapidly superior vena caval obstruction by carcinoma of the bronchus before radiotherapy, and the use of methotrexate or bleomycin to reduce the volume of head and neck tumours before surgery or radiotherapy, which makes the subsequent treatment easier and reduces damage to normal structures.

SUBSEQUENT ADJUVANT THERAPY

The second sort of adjuvant chemotherapy is where the drugs are given after primary treatment with surgery and radiotherapy to prevent the appearance of metastases and thus to increase the proportion of patients surviving disease free. This type of chemotherapy has found its widest application in the treatment of children's tumours, many of which, though apparently localized at the time of presentation, give rise to distant metastases later.

In theory, the time to eradicate the metastases is when they are composed of very few cells and are clinically undetectable rather than when they are clinically obvious and composed of many tumour cells—and this has proved true in practice. The

use of adjuvant chemotherapy in Wilm's tumour, Ewing's tumour, and rhabdomyosarcoma has significantly increased the proportion of long survivors and the principle is currently being tested in the management of testicular teratoma, cerebellar medulloblastoma, and breast cancer—where adjuvant combination chemotherapy has now been shown to increase survival in selected patients known to be at high risk for recurrence of tumour.

Though adjuvant chemotherapy has proved successful, it is a crude approach to the problem, since there is no way of knowing which patients will develop metastases and which will not. Hence it is necessary to overtreat some patients who will not develop metastases for the sake of those who will. One may hope that developments in subclinical tumour detection—through, for example, index substances—may help to solve this problem.

Immunotherapy

The demonstration of specific tumour-associated antigens and of host response to them has provided a rational basis for immunotherapy, but this is still an experimental area at present and the casual administration to patients with cancer of killed tumour cells or their products, or adjuvant substances such as B.C.G. has little to commend it and much against it. The technique is potentially dangerous, unlikely to be effective, and serves mainly to confuse the issues in an already much confused area. Nevertheless, some success has been achieved, mainly in acute leukaemia, and there is every justification for properly conducted controlled clinical studies in which not only clinical but proper immunological measurements are made. The subject has been well reviewed by Currie.¹²

Conclusions

Progress in controlling solid tumours has been slow and until recently results have been disappointing. We are now hopefully on the brink of new advances, as scientists and clinicians increasingly band together to tackle the many problems that cancer presents.

In particular, the recognition that cancer is frequently a generalized disease which should be treated early with methods aimed at eradicating subclinical foci of disease should improve the prognosis for some patients in the future.

References

- 1 Smithers, D. A., and Peckham, M. J., in *Hodgkin's Disease*. London and Edinburgh, Churchill Livingstone, 1973.
- 2 Morrison, R., and Deeley, T. J., *British Journal of Radiology*, 1965, **38**, 449.
- 3 Fletcher, G. H., *British Journal of Radiology*, 1962, **35**, 5.
- 4 Ray, G. R., Cassady, J. R., and Bagshaw, M. A., *Radiology*, 1973, **106**, 407.
- 5 Smithers, D. W., Wallace, E. N. K., and Wallace, D. M., *British Journal of Urology*, 1971, **43**, 83.
- 6 Bloom, H. J. G., Wallace, E. N., and Henk, M., *American Journal of Roentgenology*, 1969, **105**, 43.
- 7 Henk, J. M., in *Proceedings of the 5th International Hyperbaric Conference*, Simon Fraser University, Canada, 1974.
- 8 Catterall, M., and Vonberg, D. D., *British Medical Journal*, 1974, **3**, 137.
- 9 Pinkel, D., *Cancer*, 1971, **27**, 247.
- 10 Johnson, R. E., and Pomeroy, T. C., *American Journal of Roentgenology*, 1972, **114**, 532.
- 11 Roswitt, B., et al., *Radiology*, 1973, **108**, 389.
- 12 Currie, G. A., in *Modern Trends in Oncology*, ed. R. W. Raven, Part I, p. 129. London, Butterworths, 1973.