THE CHEMOTHERAPY OF MALIGNANT DISEASE

—PRACTICAL AND EXPERIMENTAL CONSIDERATIONS

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THE TERM chemotherapy was introduced by Ehrlich to describe the specific and effective treatment of infectious disease by chemical substances. It is currently also applied to the treatment of malignant disease. Unfortunately no aspect of tumour metabolism has been discovered which has allowed the development of drugs capable of acting specifically upon the malignant cell, so that cytotoxic drugs also affect normal cells to a greater or lesser degree. The most susceptible or sensitive of the normal tissues are those with the highest rates of cell turnover and include the hæmopoietic and lympho-reticular tissues, the gastro-intestinal epithelium, the ovary, the testis and the hair follicles.

Cancer chemotherapy may be said to encompass all treatments of a chemical nature administered to patients with the purpose of restricting tumour growth or destroying tumour tissue. It is not proposed however in this article to consider chemical substances active by virtue of their physical emanations (i.e. radioisotopes).

The introduction of nitrogen mustard into medicine in 1946 as a direct result of chemical-warfare research may be said to have heralded the era of cancer chemotherapy, although the inhibitory effect of colchicine on cell mitosis had been recognised since the latter part of the nineteenth century. Subsequently many thousands of naturally-occurring and laboratory-synthesized substances have been examined for anti-tumour potentiality. Of these only a limited number have proved effective in clinical practice. Those in common use are listed below.

A. Chemotherapeutic agents, the actions of which are, at least in part, understood.

1. Alkylating agents

The alkylating agents are synthetic substances of known chemical composition. They react avidly with inorganic and organic radicles by a process known as alkylation, in which negatively charged intra-cellular radicles combine with the

positively charged alkyl (CH_3) radicles of the agent.

- (a) *The nitrogen mustards*: mustine (HN2 'nitrogen mustard', mechlorethamine, mustargen), trimustine (Trillekam), HN3, chlorambucil (*Leukeran*, phenyl butyric mustard), melphalan (*Alkeran*, phenyl alanine mustard), uramustine (*Uracil mustard*), cyclophosphamide (*Endoxan* or *Cytoxan*), mannomustine (*Degranol*).
- (b) *The ethylenamines*: tretamine (triethanmelamine, triethylene melamine, TEM), thiotepa (triethylene thiophosphoramide), triaziquone (*Trenimon*).
- (c) *The epoxides*: triethyleneglycoldiglycidyl ether (*Epodyl*).
- (d) *The sulphonic acid esters*: busulphan (*Myleran*), mannitol myleran.

2. The antimetabolites

The antimetabolites are substances of known chemical composition which closely resemble known naturally-occurring metabolites. Such a substance enters a particular metabolic pathway and interferes with subsequent biosynthetic steps by a process of competitive inhibition.

- (a) *Purine analogues*: 6-mercaptopurine (*Puri-nethol*), 6-chlorpurine.
- (b) *Folic acid antagonists*: aminopterin, methotrexate (amethopterin), pyrimethamine.
- (c) *Pyrimidine analogues*: 5-fluorouracil, 5-fluorodeoxyuridine, 6-azauracil.
- (d) *Glutamine antagonists*: azaserine, diazo-oxo-norleucine (DON).

B. Chemotherapeutic agents with obscure biochemical actions.

1. *Anti-mitotic substances extracted from plants*: colchicine and its derivative demecolcine (*Colcemid*), vinblastine (*Velban*), vincristine (*Oncovin*).
2. *Antibiotics or agents synthesized by living organisms such as fungi and bacteria*: actinomycin C (*Sanamycin*), actinomycin D, mitomycin C.

3. *Miscellaneous cytotoxic chemicals*: urethane, methylhydrazine, sodium vanadate.
4. *Hormones*

Chemical compounds with actions similar to those of natural hormones may be properly regarded as chemotherapeutic agents. This is particularly so when they are used in therapeutic rather than physiological or replacement dosage. Apart from the lympholytic action of the corticosteroids, it is doubtful whether any of the hormones used in cancer chemotherapy affect the malignant cells directly. In the main, tumour cells seem to be inhibited by the withdrawal of certain natural hormones, for example following ovariectomy or orchidectomy. Alternatively, the production of such hormones may be reduced by the suppression of internal secretions responsible for their control. So that the mode of action of many, if not all, hormonal chemotherapeutic agents is possibly by means of a 'medical' hypophysectomy, adrenalectomy, ovariectomy or orchidectomy.

- (a) *Oestrogens*: stilboestrol, ethinyloestradiol.
- (b) *Androgens*: testosterone and esters, nandrolone (*Deca-Durabolin*).
- (c) *Corticosteroids*: prednisolone, prednisone.
- (d) *Thyroid hormones*: thyroxine, triiodothyronine.
- (e) *Progesterone*: medroxyprogesterone (*Provera*), ethisterone.

General Aspects

Chemotherapeutic agents are most commonly used in cancer to treat disseminated disease unsuitable for surgery or radiotherapy. Radiotherapy remains the most effective means of reducing the volume of a tumour mass and relieving localised bone pain, nerve pressure or superior vena caval obstruction.

Chemotherapeutic drugs may be administered systemically or locally. They may be given by mouth or injected into a vein or muscle. Alternatively an agent may be instilled into an artery or a body cavity, may be injected directly into a tumour mass or applied to its surface. The development of agents which are effective by mouth has greatly simplified the management of patients, many of whom may now be treated as out-patients.

Substantial but temporary palliation has been achieved in acute leukaemia in children, chronic leukaemias, Hodgkin's disease and other

malignant reticulososes, carcinoma of the ovary, uterus, prostate and breast, plasma-cell myeloma, testicular tumours, melanoma and epithelioma. It is of interest that tumours arising from tissues normally most susceptible to chemotherapeutic agents are among those most sensitive to treatment.

Following a remission, most authorities recommend continuing the drug in reduced dosage as maintenance therapy. It has been shown in acute leukaemia and in Hodgkin's disease (Scott, 1963) that the duration of a remission may be lengthened in this way. There is no indication that prolonged use of a low dose hastens the appearance of resistance but the long term administration of potentially very toxic drugs may prove unnecessary in slowly growing tumours. In these cases it would be reasonable to discontinue the drug and await events.

There is little doubt that treatment with chemotherapeutic drugs may prolong life. This has been amply demonstrated in acute leukaemia where life expectancy is short (Haut, Altman, Cartwright and Wintrobe, 1955 and 1959; Bernard and Boiron, 1962). However, when the untreated patient survives three, four or more years, it is more difficult to prove and the usefulness of a particular drug must rest on other criteria such as its ability to bring about subjective and objective improvement. Where improvement is marginal or equivocal or when two drugs of similar potential are to be compared, carefully conducted clinical trials are required.

Hodgkin's disease and other reticulososes unsuitable for radiotherapy by virtue of the degree of dissemination may commonly be controlled for considerable periods by alkylating agents, of which chlorambucil (Scott, 1963), cyclophosphamide (Matthias, Misiewicz and Scott, 1960; Coggins, Ravdin and Eisman, 1960), and melphalan are among those most widely used. Possibly the most rapid response is achieved by intravenous administration although oral therapy is usually effective.

Methylhydrazine (Mathé, Berumen, Schweisguth, Brule, Schneider, Cattas, Amiel and Schwarzenberg, 1963) may be useful when the disease is resistant to the alkylating agents and relapses often respond to vinblastine (Warwick, Darte and Brown, 1960; Frost, Goldwein and Bryan, 1962; Smart, Rochlin, Nahum, Silva and Wagner, 1964) or vincristine (Bohannon, Miller and Diamond, 1963; Whitelaw and colleagues, 1963). Methylhydrazine therapy tends to cause troublesome nausea and vomiting, and the

administration of vincristine is complicated by a high incidence of neurotoxicity. Cyclophosphamide, vinblastine and vincristine possess a relatively high therapeutic ratio as far as the marrow is concerned and in particular may be more safely employed in patients with thrombocytopenia. As a rule maintenance therapy is indicated in Hodgkin's disease, particularly as the remissions induced by single courses of mustine, methylhydrazine, vinblastine and vincristine, are not uncommonly only of four to eight weeks duration.

Progressive lymphoproliferative disorders such as lymphosarcoma and chronic lymphatic leukaemia are generally relatively more sensitive than Hodgkin's disease to the alkylating agents so that smaller doses should be used initially. Corticosteroids may be used alone or in conjunction with cytotoxic drugs. However, they are usually less effective in reducing the lymphocyte count and the volume of tumour masses but are often preferred in the face of a significant thrombocytopenia because of their effect in reducing capillary permeability. Nevertheless if the deficiency of platelets is due to interference with the megakaryocytes in the marrow by tumour cells, a case may be made for the cautious use of cytotoxic agents.

The frequency of troublesome side effects due to long-term therapy, such as osteoporosis, vertebral collapse, myopathy, diabetes mellitus and steroid obesity, suggests that corticosteroids should not be used too readily in patients with a relatively good outlook.

Corticosteroids are also of value for treating the anaemia of cancer. This common complication is in part haemolytic and the incidence of both anaemia and undue haemolysis increases as the disease progresses. Prednisone or prednisolone in therapeutic doses will often reduce the rate of fall of, and sometimes increases, the haemoglobin level. The explanation for this effect is almost certainly complex but in part may be due to a reduction of losses of red cells from the circulation (Matthias, 1964a).

There seems little value in using doses of prednisolone or prednisone larger than 40-60 mg. a day in the treatment of malignant disease. Indeed it has been shown that doses in the range of 250 mg. a day in acute leukaemia are associated with an increased risk of overwhelming infection (Medical Research Council Working Party, 1963).

The most successful drugs in plasma-cell myeloma are cyclophosphamide (Matthias, Misiewicz and Scott, 1960; Algenstaedt,

Gerhartz and Kortge, 1963; Rivers, Whittington and Patno, 1963; Matthias, 1964b), and melphalan (Bergsagel, Sprague, Austin and Griffith, 1962; Eridani, Carrara and Testero, 1963; Brook, Bateman and Steinfeld, 1964; Waldenstrom, 1964; Speed, Galton and Swan, 1964). This is possibly explained in part by the fact that either is well tolerated and may be persevered with for considerable periods rather than to any other reason. Some 50-60% of patients will improve objectively and one third may be returned to gainful occupation.

Busulphan induces consistent and worthwhile remissions in chronic myelocytic leukaemia. It is more easily controlled and more consistent than mercaptopurine (Shullenberger, 1961) and should be continued in maintenance doses. Prednisolone (or prednisone) is the drug of choice in acute leukaemia. 70-80% of children and 10-20% of adults will remit. If a remission is not achieved, mercaptopurine or methotrexate should be added and on occasion cyclophosphamide (Hoogstraten, 1962; Fernbach and colleagues, 1962) or vincristine (Selawry and Hananian, 1963; Whitelaw and colleagues, 1963) may be effective. Corticosteroid remissions can be extended by the addition of mercaptopurine in maintenance doses, and Zuelzer (1964) has shown that there is some advantage in ringing the changes at regular intervals between mercaptopurine and methotrexate. In 1963 Elion and her co-workers introduced the xanthine oxidase inhibitor, hydroxypyrazole pyrimidine (HPP or allopurinol). It is not of itself effective in inducing remissions but potentiates the action of mercaptopurine several fold. HPP inhibits the degradation of 6-mercaptopurine to 6-thiouric acid.

In general the response of the solid tumours to cytotoxic drugs is disappointing. Ovarian carcinoma responds with reasonable regularity to alkylating agents and worthwhile responses occur from time to time in a number of other conditions including mammary and lung carcinomata. Adenocarcinoma of the alimentary system has proved extremely resistant to therapy, although it is claimed that successful palliation may be achieved in 20-30% with 5-fluorouracil or related compounds (Wilson, 1960; Ansfield and Curreri, 1963). 5-fluorouracil is toxic and must be used with particular care. 5-fluorodeoxyuridine has a more favourable therapeutic index but it is expensive and not generally available.

Cytotoxic drugs and radiation usually produce additive effects but there is some

indication that actinomycin D (D'Angio, Farber and Maddock, 1959) and 5-fluorodeoxyuridine (Foye, Willett, Hall and Roth, 1960) may potentiate the effects of radiotherapy in a synergistic fashion. Such combinations may prove useful in resistant solid tumours. However, it is doubtful whether tumour cells are sensitised in preference to normal cells.

The best results in breast cancer developing before the menopause or in the subsequent five or ten years are achieved by measures which reduce the output of natural oestrogens such as ablative surgery and the administration of androgens and corticosteroids. When the disease arises ten or more years after the menopause, oestrogen therapy is usually preferred. The controlling factor in the choice of therapy is the degree of natural oestrogen activity present at the time. On occasion hormonal therapy may stimulate rather than suppress tumour growth so that the patients should be followed carefully. Recently some separation of the anabolic and virilising activities of androgens has been achieved and it has been found that relatively non-virilising preparations may retain their ability to arrest breast cancer. It is often said that hormonal measures are most effective in the control of metastases in bone but it should be remembered that whereas a relatively minor reduction in the volume of a bone secondary may be associated with the relief of pain, a comparable effect on metastases in soft tissues and organs may pass unnoticed. Chemotherapeutic agents are usually advocated for this type of disease and some success may be expected from thiotepea (Moore, 1958; Sears, 1961), methotrexate (Wright, Cobb, Golomb, Gumpert, Lyall and Safadi, 1959) or 5-fluorouracil (Ivy, 1962; Dao and Grinberg, 1963) in 15-30% of patients.

Measures designed to reduce the output of natural androgens (castration and oestrogen therapy) continue to be the treatment of choice in disseminated carcinoma of the prostate. Recently attempts have been made to enhance the effectiveness of treatment by deliberately stimulating the tumour with testosterone prior to the administration of radio phosphorus. It has been known for many years that a small percentage of patients with well-differentiated tumours of the thyroid respond to the administration of thyroid hormones, the limiting factor being the general metabolic effects. (Balme, 1954; Crile, 1957; Thomas, 1957). There is hope that the antithyroid and metabolic effects may eventually be successfully

divorced. This has to some extent already been achieved in the propionic and acetic acid derivatives of thyroxine and triiodothyronine. Progesterone derivatives have been claimed to bring about objective remissions in one third of patients with disseminated carcinoma of the body of the uterus (Baker, 1961) and also to be useful on occasion in carcinoma of the kidney.

The concept of 'cure' by chemotherapy

Until the advent of radiotherapy, surgery offered the only possibility of 'cure' in cancer. Already radiotherapy has replaced surgery in the treatment of some malignant conditions (e.g. basal cell carcinoma). In others it has produced comparable results and cases unsuitable for surgery show increasing numbers surviving five, ten or even twenty years without recurrence after treatment. In particular, conditions previously considered of multifocal origin and therefore 'incurable', such as the reticuloses, are showing impressive survival figures when treated as if they were of unicentric origin. Large doses of radiation are given to the site of disease and the adjacent regions of lymphatic drainage are also treated. Using this principle Peters and Middlemiss claim a 71% five-year survival, a 58% ten-year survival and 33% twenty-year survival in Hodgkin's disease confined clinically to one lymphatic region at the time of presentation and treatment (Peters, 1950; Peters and Middlemiss, 1958). The Manchester results are equally impressive (Easson and Russell, 1963).

Wide dissemination, however, may occur before local control can be achieved. It is logical therefore to attempt the elimination of such cells even when the disease is localised clinically and apparently amenable to curative surgery or radiotherapy. In practice it has proved difficult to demonstrate that a combination of chemotherapy and curative surgery (Curreri, 1962; Higgins and colleagues, 1962; Holden and Dixon, 1962; Longmire, 1962), or radiotherapy improves the patient's chances of survival. However, the published series suggest that 'adjuvant' chemotherapy (Shapiro and Fugmann, 1957) may be of value in particular instances; for example, the use of thiotepea with radical mastectomy in carcinoma of the breast (Noer, 1962), thiotepea and surgery in ovarian carcinoma (Masterton, 1962), actinomycin D and radiation in Wilm's tumour (Farber, D'Angio, Evans and Mitus, 1960; Altman, 1961), and tretamine (TEM) and radiation in retinoblastoma (Reese and

colleagues, 1958; Hyman, Elsworth and Reese, 1962).

However, in general it has not been shown clearly to be of use and in view of the hazards accompanying the administration of such agents it should be considered an experimental procedure and restricted to carefully conducted clinical trials. The injudicious use of chemotherapeutic agents at the time of surgery may increase the morbidity and mortality of the procedure and there is some suggestion that on occasion the natural immunological defence of the body against the tumour may be impaired. Further, with particular regard to radiotherapy, the effects of the systemic agent on the bone marrow may severely limit the amount of radiation that can be given to the tumour.

Some forms of malignant disease in animals may be cured by chemotherapeutic agents alone. In patients, survival in good health without evidence of recurrence for five years or more has been achieved in choriocarcinoma and allied conditions (Hertz and colleagues, 1959, 1961, 1963; Bagshaw, 1963). These tumours arise from homologous foetal tissue and are almost certainly less securely established and more easily influenced than autologous tumours. Large doses of methotrexate are required. 20 or 30 mg. are given intramuscularly on each of five consecutive days. In some resistant cases as many as ten or fifteen courses have been given. Despite a complete clinical response the gonadotrophin output may remain elevated. In some of these patients it has fallen to normal after hysterectomy and residual tumour has been found in the resected specimen. The particular sensitivity of this tumour to chemotherapeutic agents is evidenced by the high percentage of subsequent remissions (40-50%) which can be obtained by the use of other agents such as actinomycin D, chlorambucil, vinblastine or DON (Hertz, Lipsett and May, 1960; Ross, Stolbach and Hertz, 1962). In contradistinction gonadotrophin-producing tumours in the male are usually resistant to treatment.

It has been suggested that the judicious use of currently available drugs may be able to eliminate malignant cells in other cancers. Experimental work, however, suggests that tumours contain a spectrum of cells of varying sensitivity and that it becomes progressively more difficult to destroy all the neoplastic cells (Hauschka, 1957). There is evidence that the higher the dose the more effective the treatment (Ferrebee and Thomas, 1960; Skipper, Schabel and Wilcox, 1964) but the systemic use of large

doses of cytotoxic drugs is extremely hazardous requiring the provision of adequate supportive measures such as red cell and platelet transfusions, electrolyte replacement and protection against infection by pathogens (reversed-barrier nursing) and commensals. The usefulness of marrow transplantation is controversial (Mathé, 1960; Kurnick, 1962). It seems that ultimate recovery is little improved even following the use of autologous marrow although the rate of recovery may be accelerated (Sprague, 1960). The administration of testosterone may allow larger doses of chemotherapeutic drugs to be given with less than the expected degree of depression of the peripheral count (Brodsky, Dennis and Khan, 1964).

The volume of tumour present has been shown to have a considerable effect on the cure rates achieved by chemotherapeutic agents in animals. When the tumours are small and of recent origin the greater the chance of cure. In patients the principle may be exploited by the earlier treatment of a recurrence or metastasis and by the excision of tumour masses. Further, the effect of a drug may be greatly modified by varying the intervals between doses quite apart from any consideration of the total dosage employed (Jones, Woodrow, Lessner and Rane, 1962). For example, in the case of mitomycin, correct spacing of the dose prolongs the survival time of animals even when the total dosage is reduced.

A combination of chemotherapeutic drugs may be more likely to succeed than a single agent (Martin, 1960). Some workers are using as many as five drugs simultaneously in the treatment of acute leukaemia, and some success has been reported with a combination of chlorambucil, actinomycin D and methotrexate in resistant testicular (Li, Whitmore, Golbey and Grabstald, 1960) and ovarian tumours.

Nevertheless, it may be possible by such measures to reduce the number of malignant cells to such a degree that there may be a chance of eliminating residual cells by other means. Animal experiments have shown that antitumour antibodies enhance the effectiveness of chemotherapy but little has been achieved to date in patients (Graham and Graham, 1959; Buinaskos, McCredie, Brown and Cole, 1959). However, the circumstances are complex and it may well be necessary to prepare a specific antiserum for each tumour. Further, the antigenic determinants of a tumour may change during the course of the disease.

Regional Chemotherapy

High concentrations of chemotherapeutic

agents in the region of the tumour may be more safely achieved by introducing the drug directly into the arterial supply. Drugs given in this way are more likely to be effective than when used systemically so the techniques are to be recommended for inoperable but relatively localised tumours. Two methods are used. The first is known as infusion, when the drug is instilled into the arterial supply of the tumour without recirculation. A single injection may be given, or alternatively an indwelling catheter may be introduced and a continuous infusion or repeated injections given over a period of time. (Freckman, 1963; Oettgen, Clifford and Candler, 1963; Sullivan, Miller, Chrysoschoos and Watkins, 1962; Sullivan and Zurek, 1964). Systemic effects are restricted by dilution in the general circulation and inactivation of a proportion of the drug during its passage through the tumour—thus drugs with a short action are favoured. Alternatively, antidotes may be given systemically to inhibit the general effects, for example, folinic acid may be given when using methotrexate (Sullivan, Miller and Sykes, 1959; Duff and colleagues, 1961; Trussell and Mitford-Barberton, 1961), thymidine with 5-fluorodeoxyuridine (Miller, Sullivan, Young and Burchenal, 1961), and thiosulphate or cysteine when using radiomimetic drugs. Protection of the body may also be attempted by hypothermia.

The second method is that of perfusion (Crech, 1959, a and b). The tumour vasculature is isolated as completely as possible and the drug is circulated mechanically in a closed circuit by means of a pump in association with an oxygenator. When the region can be isolated completely, the tolerance of normal tissues proves the limiting factor to the amount of drug that can be used. However, except with peripherally situated limb lesions, considerable leakage into the general circulation cannot be avoided. The advantages of the perfusion techniques lie in the relative isolation and the possibility of some control over the local environment. For example, the anti-tumour effects of some agents may be enhanced by increasing the temperature, oxygen tension or glucose concentration or by lowering the pH (Krementsz, Harlin and Knudsen, 1960).

Many ingenious methods have been introduced for the infusion and perfusion of the limbs, the head and neck including the brain, the liver, the pelvis and the lungs: the most commonly employed techniques are the intermittent or continuous infusion of cancers of the head and neck with methotrexate, 5-

fluorouracil or a short acting alkylating agent such as mustine or *Epodyl*, alone or in combination, and the perfusion of malignant melanoma of the limbs with melphalan. The development of micro-pumps which can be attached to the person or implanted subcutaneously has allowed the ambulant patient to avoid spending prolonged periods in hospital (Rose and Nelson, 1955; Sullivan and Zurek, 1964).

Regional chemotherapy is usually a palliative procedure. It is consistently successful in relieving pain and obstruction. It may prove a valuable means of improving the results of surgery and perhaps may eventually become the curative treatment of choice for some tumours (for example, peripherally situated melanomata, see Stehlin, Smith and Clark, 1960).

However, the crux of the problem lies in the development of drugs with a specific action on malignant tissue. It has already been shown that it is possible to separate to some degree the cytotoxic effects of such drugs on tumour and normal tissue. In animals, if the minimum dose which effectively prolongs life (MED) or cures (MCD) is compared with the minimum lethal dose (MLD), the figures for mustine, chlorambucil and melphalan in moles/kg. are respectively, MCD/MLD, 16/15, 50/174 and 50/140 and MED/MLD, 5.2/15, 1.7/174 and 19/140 (Jones and colleagues, 1960), showing the superiority of chlorambucil and melphalan over mustine.

It must be emphasised that to date no patient with malignant disease may be said to have been cured by chemotherapeutic drugs. There is, nevertheless, high hope that success will eventually be realised. Already the elimination of malignant trophoblastic disease may have been achieved and regional chemotherapy has been advocated as the definitive treatment for malignant melanoma of the extremities.

Undoubtedly at the present time, in those situations in which surgery or radiotherapy offer a reasonable chance of cure, such treatment should be advised. However, it seems likely that the cure rates of both surgery and radiotherapy may be improved in certain circumstances by the judicious use of adjuvant chemotherapy designed to destroy undetected disseminated disease, to prevent the dissemination of viable malignant cells at operation and to reduce the site of the tumour to facilitate the technical aspects of operation. Possibly the preoperative administration of therapeutic drugs will allow the more extensive

and mutilative forms of surgery to be replaced by lesser procedures without prejudicing the patient's chances of survival.

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