THE TREATMENT OF MALIGNANT DISEASE BY REGIONAL CHEMOTHERAPY

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THE treatment of cancer by the local application of chemical substances has been practised since the time of Hippocrates. Moore, writing in the *British Medical Journal* of 1866, commented on the failure of occasional applications of caustic pastes in the treatment of cancer and suggested the necessity for a long continued stream of the medicinal agent flowing through the tumour.

Modern chemotherapy of solid tumours began about 1940 when nitrogen mustard was first used in the treatment of the reticuloses. Klopp and his colleagues (1950) first described a method of localised chemotherapy for tumours in an area with an accessible arterial blood supply. Intermittent injections of nitrogen mustard given through a small polythene catheter in the appropriate artery produced regressions of tumour growth which had not been obtained by systemic chemotherapy. The amount of chemotherapeutic agent given by intra-arterial injection was limited, because of the general toxic effects produced after the drug had passed through the tumour circulation.

The ideal agent for this form of treatment would be a substance with a very short effective life in the body after injection so that the drug was completely inactivated by the time it had passed through the tumour circulation. This type of substance has not been produced but research continues along these lines. Two methods have been developed which aim at increasing the local or regional cytotoxic effects and at the same time reducing the general toxic actions of the drugs. The first consists of vascular isolation of the region to be treated with maintenance of the circulation of the isolated area by a pump oxygenator during treatment. The second consists of injecting large doses of the drug intra-arterially and at the same time giving an antagonist to the cytotoxic agent by systemic injection. The highest concentration of the drug occurs in the treated area and severe toxicity is avoided.

The majority of chemotherapeutic agents which have been used fall into two main groups, the alkylating agents and the antimetabolites. All these substances produce their biological effects by interfering with nucleic acid synthesis. The alkylating agents act by direct chemical reaction with the complex nucleic acid molecules and so destroy their normal function. Antimetabolites, on the other hand, interfere with the synthesis of nucleic acids by competing with normal metabolites for enzymes required in nucleic acid production. Alkylating agents act rapidly and most of them exert their maximum effect within minutes of coming into contact with body tissues. These drugs are suitable for single injections or short periods of isolated perfusion.

The antimetabolites act slowly and it is necessary to have the antimetabolite in contact with body tissues for many days before the maximal effect is obtained. These drugs are usually given continuously for days so that the sequentially dividing cells will be exposed to the antimetabolite. Another miscellaneous group consists of plant extracts and antibodies. Limited clinical success has been reported with these substances.

The principal cancer chemotherapeutic agents which are clinically useful in the treatment of solid tumours are listed in Table 1.

TABLE 1.

EXAMPLES OF SOME OF THE DRUGS CURRENTLY IN USE FOR CANCER CHEMOTHERAPY.

ALKYLATING AGENTS:			
NITROGEN MUSTARDS	TRIETHYLENEAMINES	ANTIMETABOLITES	ANTIBIOTICS
Leukeran	T.E.M. (Triethylenemelamine)	6 Mercaptopurine	Actinomycin D
Melphalan (Phenylalanine Mustard)	Thiotepa	5 Fluorouracil	—
Cyclophosphomide (Endoxan)	—	Amethopterin (Methotrexate)	—
Degranol (Mannomustine)	—	—	—
Myleran	—	—	—

REGIONAL PERFUSION.

Creech and colleagues (1958) first published the results of the treatment of localised malignant disease by regional arterial perfusion. Since then regional perfusion has been applied in a variety of ways by many investigators and some of the results have been encouraging.

Extracorporeal perfusion implies the continuous artificial circulation of cytotoxic drugs through an isolated area. When the area can be easily isolated as in a limb the dose of the drug is limited only by the tolerance of the tissues. Where isolation is difficult a varying amount of the drug leaks into the general circulation and the maximum dose of drug is limited by this spill over into the rest of the body.

The drug that has produced the most dramatic regressions of tumours after regional perfusion is melphalan (phenylalanine mustard). This drug is a combination of an alkylating agent with phenylalanine. It is thought that melanin-forming cells have an affinity for phenylalanine and this explains the selective toxicity in melanoma.

Melphalan has been used exclusively in the present studies. Three of the factors which influence the effectiveness of drug perfusion are temperature, flow rate, and oxygen tension. The apparatus is designed so that each can be controlled. The utilization of the drug is related to the temperature of the infusate. A heat exchange unit is connected between the arterial pump and the patient, and the infusate delivered at 40°C.

The venous return from the isolated area is pumped through an oxygenating column and pure oxygen is added. The blood then passes through a defoaming sponge before reaching the arterial inflow pump. High flow rates of 100-120 ml. per minute are maintained in order to achieve a uniform distribution of blood in the peripheral tissues and the pressure in the isolated circuit is maintained below the systemic blood pressure in order to limit the leakage into the general circulation.

The pump system is primed with 1 litre of heparinized blood and the main vessels cannulated. A tourniquet is tightened to isolate the part and the pumps switched on. The first injection of cytotoxic agent is given as soon as the venous return is adequate. Intermittent doses are injected during perfusion, and the total amount given depends on the leakage into the general circulation. This is small in femoral perfusion but higher in forequarter or pelvic perfusion. An estimate of the leak into the rest of the body is obtained by injecting some of the patient's red blood cells labelled with radioactive chromium 51 into the isolated part at the beginning of the perfusion. Samples are taken from a systemic vein at fifteen-minute intervals during perfusion and the percentage leakage calculated.

Clinical Experience.

Isolated regional perfusion has been applied to the limbs and girdles in five patients. The technique has been used by other workers to perfuse the head and neck, liver and lung, but the enormous leakage in these areas reduces the value of the method.

Regional chemotherapy has not been used for new cases of peripheral malignant disease, but has been reserved for cases of locally advanced or recurrent disease. It has been the aim to use perfusion as an adjuvant to further surgical treatment where possible. Regional perfusion has been attempted in six patients and was successfully completed in five. One patient had advanced atheroma and previous dissection in the groin made arterial cannulation difficult and dangerous, and the procedure was abandoned. Two patients had prophylactic perfusion after radical surgery. Four patients had recurrent malignant melanomata and one had a recurring pleomorphic sarcoma. The histories of the individual patients are as follows:

Case 1. This patient, a man aged 29, attended the Department of Dermatology in August, 1961, with a pigmented mole in the interscapular region, which had been present for nine months. A wide excision was carried out and a split skin graft applied. The pathological report was that of malignant melanoma, and the extent of the resection appeared adequate. The patient was re-admitted in May, 1962, with a hard mass in the right supraclavicular fossa. This was the only evidence of spread. Forequarter perfusion was carried out immediately after

dissection and removal of the affected neck glands which contained malignant melanoma. The catheters were threaded into the brachial artery and vein and the subclavian vessels were occluded in the neck. The perfusion was of 100 mg. of melphalan. The post-operative course was uneventful for the first week and then the white cell count fell to less than 1,000 within ten days and remained low for four days. During this period of marrow depression the wound became infected and a staphlococcal septicæmia ensued. The organism was resistant to most antibiotics and the patient died within a few days from septicæmia.

Case 2. This patient, a lady aged 75, had a malignant melanoma locally excised from the sole of the right foot, in August, 1962. She was seen a few months later and was found to have enlarged groin glands and local recurrence of tumour. Isolated regional perfusion lasting one hour was carried out with 80 mg. melphalan and at the same time excision of the groin glands was performed. These glands contained excessive melanin but no malignant cells. The lesion in the foot regressed in the first week after treatment. The white cell count fell to 1,200 per cu. mm. by the twelfth day, but soon rose again. The groin wound failed to heal and became infected. A brisk reactionary hæmorrhage occurred from the femoral artery thirty days after perfusion and femoral ligation was necessary. The right leg required to be amputated a few days later and the patient died from bronchopneumonia two months after perfusion.

Case 3. This patient, a man aged 78, had a painful tumour excised from the sole of the right foot in January, 1963. This was a malignant melanoma and a local recurrence rapidly developed. He was treated in March, 1963, by a block dissection of inguinal glands and isolated regional perfusion of the right leg. 80 mg. of melphalan was given during perfusion which lasted one hour. The local recurrence on the foot was not touched and rapidly regressed after perfusion. The white cell count fell to 1,500 per cu. mm. within twelve days and soon rose again to normal limits. The wound healed satisfactorily and convalescence was uneventful. The patient refused to have a further biopsy and excision at the site of the local recurrence and the regression has persisted. Without excision of the site of recurrence it is difficult to know the effectiveness of treatment in this patient.

Case 4. This patient, a woman aged 34, had an ulcerated mole excised from the outer aspect of the right leg in February, 1961. This was found histologically to be a malignant melanoma. Recurrence occurred at the site of excision within six months and a further wide local excision and skin graft was performed. Three weeks later a radical block dissection of the groin glands was performed, and the glands were found to be free of tumour. However, a further local recurrence was noted one month later. This was a small black nodule at the edge of the previous skin graft.

The right leg was perfused with 75 mg. of melphalan for a period of 1 hour 20 minutes. The white cell count subsequently fell to 2,000 per cu. mm. and erythema developed in the perfused limb. The recurrent nodule did not regress immediately and it was excised two weeks later and found to be an epidermoid cyst containing organised blood clot. The patient has remained free of recurrence for two years after excision and perfusion. Regional perfusion in this patient turned out to have been prophylactic and really should have been done at the time of regional gland dissection.

Case 5. This patient, a man aged 72, had a large lump removed from the right gluteal region in 1948. This recurred and was again locally excised in February, 1961, July, 1961, and June, 1962. The histological picture was that of a pleomorphic sarcoma. A further wide excision of gluteal muscle and scar tissue was carried out, and the hind quarter was perfused with 80 mg. of melphalan in July, 1962. The catheters were threaded into the common iliac vessels which were occluded at their origins during perfusion. The limbs were protected by femoral cuffs which were inflated during perfusion. The patient had an uneventful convalescence and has remained free of recurrence for over one year.

Serious complications occurred in two patients. Severe bone marrow depression occurred in one man due to an excessive leak and in the other patient local healing was impaired. Tumour response was observed in two patients. The result in the two patients treated prophylactically is difficult to assses at this stage, but both are free of tumour at one and two years respectively.

Krementz (1962) reported their experience with 350 perfusions and claimed that twelve out of forty-five patients with malignant melanoma remained under control after two years. Irvine and Noon (1960) have also reported dramatic regressions of malignant melanomata.

Continuous Intra-Arterial Infusion.

This term is applied to the administration of drugs by an intra-arterial drip. The drug which is not fixed or inactivated by the tissue in the infused area returns to the rest of the body by the venous drainage of the part. The folic acid antagonist methotrexate has been used in this form of treatment. Methotrexate interferes with the conversion of folic acid to folinic acid which is in turn necessary for nucleic acid synthesis.

It is possible to combat any methotrexate which enters the circulation by giving folinic acid systemically, and because of this very large doses of the antimetabolite can be given into the tumour-bearing area. Maximum concentration of the drug occurs in the infused area and the excess which recirculates causes little damage because of the circulating folinic acid. Cells vary in their sensitivity to antimetabolites depending upon the phase of mitosis. A high concentration of drug must be maintained in the tumour-bearing area for a prolonged period, so that all the cells will pass through a sensitive phase when the drug is present.

This treatment is simpler to carry out than regional perfusion and has been more widely used. Head and neck cancer and advanced pelvic tumours have been suitable for this form of therapy.

Malignant disease of the head and neck often remains localised and produces severe pain and disability by local tissue infiltration. Some of the arterial branches of the external carotid artery are easily entered and it is in the treatment of this form of malignant disease that the most encouraging results have been obtained. Sullivan (1962) found that 50 per cent. of patients with advanced head and neck cancer obtained relief of symptoms, and partial regression of growth after infusion therapy. Westbury (1962) and Espiner (1962) have had similar experiences. The

reports of these workers contain a few cases of relatively early disease in which total regression of tumour occurred after infusion and in some cases this has been maintained for more than one year. These observations of total regression in a few patients raises the question of the use of infusion for the treatment of the early rather than the advanced case.

Clinical Experience.

Twenty-four patients with epidermoid carcinoma of the head and neck have been treated in the surgical Professorial Unit, Royal Victoria Hospital. The disease was unilateral and confined to the distribution of the external carotid artery in every case. The superficial temporal artery was cannulated in sixteen patients. The superior thyroid artery was used five times, the facial artery once, and the external carotid in the remaining two patients. There were no complications from the minor surgical procedure of cannulation which was always carried out under general anæsthesia.

It is important that the catheter tip lies in such a position that the infusate reaches the desired area. A slow injection of 1 - 2 cc. of 5 per cent. fluorescein solution is given and the area examined under ultraviolet light. The fluorescence persists in the capillary bed of the irrigated area for about thirty minutes. When the catheter is in the external carotid supply, fluorescence occurs in the skin of the face, neck, scalp, and the mucosa of the mouth and tongue. If the infusate is reaching the internal carotid supply fluorescence occurs in the eye, eyelids, and forehead. The position of the catheter is adjusted until fluorescence is observed in the required area. Methotrexate (50 mg.) is dissolved in 500 ml. of physiological saline and placed in a plastic bag containing heparin. The plastic pack is inserted into the pouch of the Fenwal pressure infusor, which consists of an air-filled cuff, surrounding the polythene bag. The pressure in the cuff is kept above the patient's arterial pressure and the drip rate adjusted so that the contents of the plastic pack are infused slowly over twenty-four hours. The drip rate and the pressure in the infusion cuff are checked each fifteen minutes during treatment by the duty nurse. This method of arterial infusion has proved very satisfactory, and is easier to manage than infusion by the gravity feed or an arterial pump described by others (Sullivan, 1962; Espiner, 1962). The danger of air embolism is eliminated. The patient can move freely about the ward during treatment since the apparatus is very light and can be easily fixed to the buttonhole of a dressing-gown.

A full blood count is checked daily and the dose of 50 mg. of methotrexate per day continued until the white cell count falls below 2,000 per cu. mm. or toxic signs appear. The usual early toxic signs consist of painful mouth ulcers. Folinic acid (citrovorum factor) is given daily by intramuscular injection (6 mg. four-hourly). The average duration of infusion in the present series was 5 - 6 days, by which time 250 - 300 mg. of methotrexate had passed through the growth. The catheter was withdrawn at the end of the treatment and light pressure applied for five minutes. Bleeding from the infusion site did not occur after withdrawal of the catheter.

The results of the treatment are shown in Table 2. Total regression was defined as the complete disappearance of all visible tumour, but without histological confirmation. This occurred in two patients and has persisted for three and six months respectively. The treatment was considered to have been worthwhile in the patients who had partial reduction of tumour size and relief of symptoms. Pain relief was observed by the second day of infusion and analgesic requirements were reduced. The remissions did not last longer than 5 - 6 weeks in most instances which is rather disappointing. The incidence of tumour response and pain relief was greatest in the patients who did not have prior treatment with radiotherapy. Espiner, Vowles, and Walker (1962) record a similar observation.

TABLE 2.

CASES OF CARCINOMA OF THE HEAD AND NECK TREATED WITH METHOTREXATE AND THOSE SHOWING REGRESSION AND/OR SUBJECTIVE IMPROVEMENT.

LESION	NO. TREATED	PARTIAL REGRESSION	TOTAL REGRESSION	SUBJECTIVE IMPROVEMENT
Carcinoma:				
Tongue	2	–	–	–
Buccal Mucosa	7	3	1	5
Neck Glands	7	4	–	3
Skin of Face	2	1	1	2
Sinuses	2	1	–	1
Malignant Tumours of Salivary Glands	4	–	–	1
TOTAL	24	9	2	12

The incidence of complications in a palliative procedure is important when assessing the value of the treatment. Complications occurred in eight patients. (A reduction in white cell count alone was not counted as a complication.) Very marked ulceration of the buccal mucosa with œdema occurred in two patients. One patient developed a complete hemiplegia during treatment and died. Two others had transient signs of contralateral hemiplegia which cleared up in 5 - 6 days. The hemiplegia is presumably due to thrombi forming around the catheter in the external carotid artery and breaking off into the internal carotid circulation. One patient developed a severe bronchopneumonia during treatment and died. Severe mental depression was associated with infusion in a further four patients. Six patients developed a generalised macular skin rash after 4 - 5 days. This was severe enough to cause the treatment to be discontinued in each case. The majority of complications occurred in patients who had had previous radiotherapy.

The case histories of the two patients who had a total regression of growth are as follows:—

Case 6. This patient was a lady aged 57 who was first seen in May, 1962, complaining of a large solid tumour over the right parotid region. The growth was widely excised and was found to be a squamous carcinoma. A skin flap was taken from the forehead to cover the defect, and the bare area on the forehead was then covered with split skin grafts. The growth recurred six months later and she was re-admitted with a large recurrent solid tumour at the site of the previous excision, with no evidence of glandular spread.

A catheter was inserted in the superficial temporal artery and 375 mg. of methotrexate infused during eight days. The bulk of the tumour became necrotic within 2 - 3 days and there was a rapid reduction in size. The white cell count fell to 1,500 per cu. mm. after eight days. The drug was stopped for four days to allow the white cell count to recover and further 200 mg. of methotrexate was given. The white cell count fell sharply again and the treatment was stopped. There was complete regression of the growth after four weeks and there has been no local recurrence after three months.

Case 7. This was a man aged 74 who complained of a painful ulcer in the roof of the mouth for four months. This was an ulcerating squamous carcinoma, one inch in diameter, in the right side of the hard palate. A catheter was placed in the superficial temporal artery and fluorescence was noted in the margins of the ulcer. The infusion was continued for one week and a total dose of 350 mg. of methotrexate was given. The patient was free of pain within a few days of starting treatment, and the ulcer was half its original size at the end of one week. Regression continued and after three weeks a course of radiotherapy was commenced, because the patient had had no previous conventional therapy. The regression continued and the ulcer healed. The patient has remained well and is free of any recurrence nine months later.

Discussion.

There is no doubt that regional perfusion and infusion offers a degree of control over locally advanced malignant disease, particularly the malignant melanoma. However, no patient appears to have been cured of advanced disease by these methods.

There would appear to be reasonable grounds for believing that these new methods may improve the prognosis in many patients when combined with current conventional forms of treatment. The existing evidence suggests that if arterial infusion is being considered then it should be given before and not after radiotherapy or surgical excision.

There are many fields of future advancement in this subject. For example, there is no way of knowing whether a tumour will respond to any particular drug. Some tumours respond dramatically while their exact histological counterpart in another patient shows no response. Techniques require to be developed whereby cancer cells obtained at biopsy can be grown in tissue culture and the sensitivity to various chemotherapeutic agents assessed before any treatment is given.

The results of combining drugs with different cytotoxic actions appears to be another fruitful field of investigation and the inter-relationships between the combination of surgical radiotherapeutic and chemotherapeutic methods requires detailed study. It is also possible that a new type of specialist may emerge in the next decade—the chemotherapist-oncologist who will advise on the application of the advancing knowledge in the treatment of individual cases. It is to be hoped that developments in this field will help to unite rather than separate the specialist treatment of the cancer patient. The surgeon, radiotherapist, and chemotherapist should all combine their interest and experience so that the individual cancer patient will have the best possible chance of cure or control of his disease.

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REFERENCES.

CREECH, O., KREMENTZ, E. T., RYAN, R. F., WINBLAD, J. N. (1958). *Ann. Surg.*, **148**, 616.

ESPINER, H. J., VOWLES, K. D. J., and WALKER, R. M. (1962). *Lancet*, **1**, 177.

IRVINE, W. T., and NOON, C. F. (1961). *Proc. roy. Soc. Med.*, **54**, 483.

KLOPP, C. T., ALFORD, T. C., BATEMAN, J., BERRY, G. N., and WINSHIP, T. (1950). *Ann. Surg.*, **132**, 811.

KREMENTZ, E. T., CREECH, O., RYAN, R. F., and REEMTSMA, K. (1962). *Ann. Surg.*, **156**, 417.

MOORE, C. H. (1866). *Brit. med. J.*, **2**, 548.

SULLIVAN, R. D. (1962). *Methotrexate in the Treatment of Cancer.* (Edited by Porter, R., and Wiltshaw, E.) Bristol: John Wright & Sons Ltd.

WESTBURY, G., NEWTON, K. A., HUMBLE, J. G., FORD, H. T., PEGG, D. E., and WHITE, W. F. (1962). *Brit. med. J.*, **1**, 1238.