REGIONAL PERFUSION FOR CARCINOMA*

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A great deal of interest has been aroused by the technique of regional perfusion, suggested by Klopp and introduced by Creech of New Orleans,[1] in the treatment of malignancy. Creech[1] has demonstrated that it is feasible to exclude regions of the body temporarily from the general circulation, and to take over the circulation of such areas by means of an extracorporeal heart-lung system. Cancericidal agents, such as the alkylating agents of the nitrogen-mustard series, can then be added to this isolated circuit in much higher concentration than can be tolerated by systemic administration. For example, the dog's hind limb, which constitutes $^{2}/_{15}$th - $^{1}/_{20}$th of the total body volume, can safely be perfused with twice the total body dose of these drugs. With the isolated perfusion method of treatment effective concentration of the chemotherapeutic agent may be largely confined to the tumour-bearing area. Isolation in many areas can be made so complete that the dose of the drug is limited by the local tissue tolerance, rather than systemic toxicity. High systemic concentrations are particularly toxic to normal tissues of the haematopoietic system and the gastro-intestinal tract.

It has been shown that the cytotoxic effects of these drugs closely resemble the effects of X-rays. Radiation is more effective at high tissue-oxygen tensions, and it is logical to conclude that a high tissue-oxygen tension is advisable in regional perfusion. This indicates that it is necessary to provide oxygenated blood to the excluded regions by means of an oxygenator rather than to rely on short periods of simple exclusion.

Cancericidal Drugs

I am not presenting a brief for the efficacy of the cancericidal drugs. The experience of other workers must be carefully analysed. The Tulane results[2] suggest that this technique is of value as adjunctive therapy in localized lesions and as palliation of advanced lesions; none of the anti-cancer drugs at present available is considered to be curative. I have become involved in this work purely because of my possession of a heart-lung apparatus, and its utilization in open-heart surgery at Wentworth Hospital. I do not profess to be an expert in this form of cancer therapy. However, I believe that this form of therapy may prove to be of great significance and benefit, and its possibilities must be explored. The techniques involved are relatively simple, and we have shown, to our own satisfaction, that amazingly complete isolation of a limb can be achieved.

Drugs of the nitrogen-mustard series have mainly been used in this work. Current thought favours 'thio-tepa' in ovarian cancer, phenylalanine mustard (PAM), or AB 100 for the pelvis, and nitrogen mustard for limbs. Actinomycin-D is claimed to increase the sensitivity of rhabdomyosarcoma to deep therapy. More effective drugs will probably be discovered, as well as tests to indicate sensitivity of different neoplasms to individual drugs. The same type of neoplasm in different individuals may exhibit different sensitivities.

Use of Isolation-perfusion Method

Creech and others have used the isolation-perfusion method on all the extremities, the pelvis, breast, brain, intestine and liver. Even the lungs have been perfused, employing one extracorporeal circuit to maintain the systemic circulation and a second to perfuse the lesser circulation. Total exclusion of a region is relatively easily accomplished in the limbs. Exclusion in other areas is more difficult and less effective. Fairly extensive dissection is required to occlude temporarily as many collaterals as possible, but this principle may have further application. Creech has employed total body perfusion after sequestration of bone marrow for later retransfusion. Cooley of Houston has been interested in irradiating blood in the extracorporeal circuit in the treatment of leukaemia. Perfusion with high concentrations of antibiotics has been suggested in the treatment of osteomyelitis.

Technique of Limb Perfusion

We have confined our attempts to the relatively simple one of limb perfusion, and have used the technique in 3 cases. Each patient had had a melanoma of the lower limb excised a short time before, and in each instance the cancericidal agent employed was nitrogen mustard. Lugol's iodine was administered pre-operatively in an attempt to protect the thyroid. An attempt was made to include the groin in the area of perfusion. The external iliac vessels were exposed, and cannulated in a distal direction after heparinization of the patient, using 3 mg. of heparin per kg. bodyweight. The venous blood was drained by gravity into the oxygenator, oxygenated, and returned into the external iliac artery in a distal direction. The oxygenator was kept warm by infra-red lamps, since it is believed that the cytotoxic effect of the drugs is more pronounced at normal body temperature. A simple rubber tourniquet was tightened around the groin in an attempt to occlude superficial collateral vessels. The tourniquet was kept high in the groin by means of a Steinmann pin inserted into the iliac crest.

Nitrogen mustard, 1 mg. per kg. bodyweight, was then injected into the arterial line in 6 divided doses at 5-minute intervals. Each ampoule of the solution was prepared immediately before injection, since it is unstable. The efficacy of the exclusion of the limb was determined by injecting Evan's blue dye (T-1824) into the isolated limb, and then testing samples of blood taken from an arm vein for calorimetric

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evidence of dispersal of the drug. In 2 cases no trace at all of the dye was found, and in the third case, merely a trace after 5 minutes. Tracer drugs may be more efficient in determining the efficacy of complete exclusion. It was unnecessary to drain the limb of blood at the conclusion of the perfusion because of the short-acting nature of the nitrogen mustard. Bio-assay methods have indicated that nitrogen mustard retains its activity for about 8 minutes following mixture with whole blood, while PAM remains active for about 2 hours. With longer-acting drugs it becomes necessary to drain the limb of blood, and perhaps irrigate with 'dextran'.

The blood was fully oxygenated and perfused at about 700 ml. per minute, low flow rates being probably adequate and possibly preferable. The cannulae were removed and the vessels repaired. Protamine or 'polybrene' was then given to counteract the heparin. Postoperatively the limbs became somewhat reddened and swollen, but neither venous nor arterial thrombosis occurred. Daily red-cell, white-cell and platelet counts were performed to ensure that no serious damage had occured to the haematopoietic system. Sodium thiosulphate is recommended if much leakage occurs into the systemic circulation.

Complications

Specific complications may be due to 2 factors.

1. *Local tissue intolerance.* This may result in erythema, petechiae, blistering, or gangrene. Toxic absorption following massive necrosis of the tumour has been reported.

2. *Leakage into the systemic circulation.* This may result in depression of the bone marrow, thyroid gland, gastro-intestinal system, etc.

Apparatus

We have utilized a simple roller-pump with the Melrose drum oxygenator, which is a filming oxygenator. This is unnecessarily extravagant in the amount of priming blood required, and a small bubble oxygenator would be adequate; we have constructed a simple stainless steel model. We have utilized the 'pulmo-pak' disposable bubble oxygenator experimentally, and it is being used in the Department of Surgery at the University of Natal. With this, the priming volume is much less. We have recently perfused a fourth patient with our stainless steel bubble oxygenator, and only 2 pints of blood were required to prime the apparatus.

Conclusions

It is impossible to draw any conclusions from these few cases. They all recovered very rapidly and were discharged home after 7 - 10 days. Two of the patients are well and do not demonstrate any evidence of recurrence. The third patient developed a small mass in the groin 5 months after perfusion. This was explored by Mr. A. Copley and was found to be a melanoma in the muscle. He considers that this may have been implanted while removing the inguinal glands.

A most dramatic case is that of a female patient under the care of Mr. E. M. Barker. Numerous satellite melanomata rapidly disappeared after perfusion with nitrogen mustard.

This technique must be considered of great significance, and its possibilities must be fully explored.

REFERENCES

1. Creech, O. jun. *et al.* (1958): Ann. Surg., **148**, 616.
2. *Idem* (1959): *Ibid.*, **149**, 627.