Professor McMICAEL: Could I ask one more question, I think of Dr. Suzman again, who has experience of these things in Johannesburg? It is said there that emboli commonly occur in 50% of the cases. How, in fact, do they come? Is thrombosis in the ventricle a common feature?

Dr. DONIACH: It was present in the ventricle in the one or two recorded cases.

Dr. SUZMAN: I showed a case like this with Dr. Evan Bedford in 1943 or 1944. It was a young man, and we eventually made this clinical diagnosis of so-called endomyocardial fibrosis. He ultimately died. We also thought he was a traumatic case, that he might have had an injury to his heart during a boxing bout. He died under an anaesthetic while receiving thiopentone. They quite commonly die suddenly during a minor operation. At necropsy he had a large area of fibrosis with thrombosis in the ventricle; he was a man in his early twenties, a white man.

Professor McMICAEL: We now thank Dr. Campbell for leading this discussion. His clinical approach was splendid, as nobody really knows the answer, either clinically or pathologically.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

CHEMOTHERAPY FOR CANCER BY PERFUSION IN THE U.S.A.*

BY

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Introduction

In attempting to use cytotoxic drugs as a treatment for cancer they must be administered in such a way that they destroy the multiplying cancer cells without injury to the more delicate rapidly dividing marrow cells or other normal cells. If the drugs which are at present available and which are strong enough to inhibit cancer mitosis in the part of the body affected by the growth could be given without damage to the normal cells of the part, and especially without danger to the rest of the body, a new field of treatment would be attained. The method by which this is being accomplished is known as "perfusion."

Klopp *et al.* (1950) gave fractionated doses of nitrogen mustard to specific regions of the body by intra-arterial injections, with more pronounced effects on a tumour than had been possible by intravenous injections. They also suggested employing a heart-lung machine to maintain circulation in a tumour-bearing extremity during injection treatment with its circulation isolated. In the same year Bierman *et al.* (1950) found that if the nitrogen mustard was injected into an artery it was much less poisonous to the whole system than if injected into a vein. They also described methods of injecting a drug directly into the area of the growth. Other workers have conducted similar treatments for

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many types of cancer in different parts of the body. Bergel (1953), working at the Chester Beatty Institute for Cancer Research, Royal Cancer Hospital, reported the anti-tumour activity of phenylalanine mustard and Bergel and Stock (1954) described its preparation. Its L-isomer (melphalan or P.A.M.) has proved most active in this work. Later O. Creech, Jr., *et al.* (1958) reported their first results with perfusion by means of an extracorporeal circulation, and showed that they could give large amounts of a drug to an isolated part of the body under high arterial oxygen tension. Since December, 1957, similar perfusions have been undertaken at the M.D. Anderson Hospital and Tumour Clinic in Houston, University of Texas, by Dr. R. Lee Clark, Jr., Dr. John S. Stehlin, Jr., and their associates (Stehlin *et al.*, 1959).

Method

Perfusion entails:

- (1) Pumps and oxygenator to provide a separate (extracorporeal) artificial circulation for the affected part of the body.
- (2) Operation to isolate the diseased part from the circulation of the rest of the body.
- (3) Electronic or other tests to make sure isolation is efficient.
- (4) A high dose of anti-cancer agent or agents circulated long enough to be effective.
- (5) Restoration to normal after washing out the drug from the region.
- (6) Post-operative care, involving a knowledge of the special complications which may occur.

Apparatus

The apparatus required for a perfusion consisted essentially of two sigmamotor pumps to maintain the flow of the extracorporeal circulation and a Pulmo-Pak oxygenator (Abbott). This is a small disposable transparent plastic bubble oxygenator with a blood-reservoir capacity of 600 ml. Other pieces of apparatus required are varying sizes of catheters to cannulate the blood vessels, with plastic and latex tubings and stainless-steel connexions to complete the circuit. A source of supply of a gaseous mixture of 95% oxygen and 5% carbon dioxide is necessary to bubble through the oxygenator, the rate of flow being controlled by a flowmeter. A 250-watt infra-red lamp is used to warm the blood in the oxygenator to 100° F. (37.8° C.).

To isolate the extracorporeal circuit one or two tourniquets are usually needed. I saw in use an automatic tourniquet which is preset at the required pressure (for a thigh 500 mm. of Hg is advised), and by pressing a button at the required moment the tourniquet inflates.

Measurement of Leakage

The success or failure of perfusion depends upon accurate estimations of leakage from the perfused area into the main blood-stream. Special apparatus is required for testing the efficiency of the degree of isolation of the perfusion circuit—that is, detecting the degree of cross-circulation or "leakage." This involves the use of a radioactive iodinated serum albumin (R.I.S.A.) in the circuit, and its detection requires a scintillation probe linked with a counter and continuous recording device. The scintillation probe consists of a

photomultiplier tube (1,100 volts), a scintillation crystal 2 in. (5 cm.) diameter $\times$ 1½ in. (3.8 cm.) deep, and a pre-amplifier. Extra lead is used round this to avoid scatter from around and above, and it is rendered spark-proof. A gantry holds this heavy apparatus, which costs \$500, over the base of the patient's heart and great vessels. It connects with a precision ratemeter which carries with it a Recti-riter recording device.

In conjunction with a calibration chart it is possible to assess the percentage of leakage—the leakage factor—between the two circulations. If such an apparatus is not available frequent estimations of blood levels of radioactivity must be made, but they take more time and are less accurate than the electronic apparatus.

Operation

The object of operation is to isolate the part of the body which contains all the cancerous process in such a way that the circulation of that part shall be separated as completely as possible from the circulation of the rest of the body. The completeness depends on the surgeon's knowledge of anatomy of the local arteries and veins, their branches and tributaries respectively, and all the routes by which they and their collaterals connect with all other vessels in the neighbourhood to reach the rest of the circulation. In addition to his skill as a surgeon it also depends upon the availability of plenty of time by himself and his assistants, to ensure that every possible collateral vessel is dealt with.

In the preliminary stages (removal of the primary growth, dissection of regional lymph nodes, approach to the vessels, etc.) care must be taken to secure every bleeding-point to ensure absolute haemostasis, because heparin is to be used.

Isolation of the distal part of a limb is relatively easy because only the main artery and vein need to be catheterized, and virtually all collaterals can be dealt with by a satisfactory tourniquet. In several cases there was no leakage at all.

To perfuse the whole of a limb including the axilla or the groin is not so easy without leakage, but in the case of the lower extremity the use of a Steinmann pin driven into the iliac crest at an acute angle and the application of a firm Esmarch bandage round the pin and the gluteal fold succeeded in about 90% of isolation. The pelvis, head and neck, breast, and liver all have their own special anatomical problems; they need long and tedious care for their isolation, because all collateral vessels must be occluded by multiple clips or ligatures.

Two tapes are passed round the main artery and two round the vein. The two artery tapes are threaded through two red rubber tubes and the vein tapes through blue ones. When all the anatomical work has been carried out and the wound rendered very dry, the patient is given heparin into the general circulation in a dose of 2 mg./kg. body weight (100 B.P. units per mg.).

Before any cytotoxic drug is introduced into a perfusion circuit careful tests must be made to determine what degree of leakage is taking place via collateral vessels between the isolated and the general body circulations. The scintillation counter is suspended over the base of the heart and great vessels of the patient, and counts per minute stabilized and recorded

on the graph in an adjoining room. The physicist and two assistants were present and had the scintillation meter working before the anaesthetist injected 2 microcuries (R.I.S.A.) intravenously into the general circulation. It then took ten or twelve minutes to stabilize the readings of the scintillation counter for that amount of R.I.S.A. by graph and by formula. When the reading was constant and at a low level on the graph the surgeon proceeded with the insertion of the catheters into the taped main vessels. Meanwhile the bubble oxygenator had been primed with 500 ml. of blood to which 18 mg. of heparin has been added and the mixture of oxygen and carbon-dioxide bubbled through this blood at a rate of 4-5 litres per minute.

A small transverse incision is made into each vessel between the tightened proximal and distal tapes and a suitable catheter inserted past the distal tape, the surgeon using a larger-sized catheter for the vein to allow easy return of the blood from the venous side of the circulation.

Fifteen minutes after heparinization the primed oxygenator is attached to the two catheters, the preset proximal tourniquet blown up, and the two sigmamotor pumps switched on and synchronized. A solution of papaverine (180-300 mg.) is now injected into the arterial line of the extracorporeal circulation to produce vasodilatation. The rate of flow is adjusted to suit the anatomical site. In general a low rate of flow is maintained because of the difficulty of securing venous return and to allow better mixing of the drug with the tumour, a lower leakage factor, and a reduction of local and general complications.

After waiting a further 15 minutes for stabilization 20 μ c. of R.I.S.A. was injected into the arterial side of the extracorporeal regional circulation. Now is the important time for the physicists to estimate by the scintillator the leakage-factor. After 15 to 20 minutes in more than one case which was having the lower three-quarters of the leg perfused there was no increase in the scintillation count, showing that the leakage factor was nil. In another case in which the whole limb from the groin was being perfused the count increased by only 5% in 15 minutes.

As the perfusion progresses in time so the leakage factor tends to rise, as it did at Houston in one case of extensive melanoma of the leg from 5% to 12% at the end of 45 minutes. This was considered to be a satisfactory isolation, and 100 mg. of P.A.M. was inserted proximal to the arterial pump and the whole limb perfused for upwards of 60 minutes. The level of blood in the larger section of the Pulmo-Pak must be kept constant in volume, flow rate, and temperature.

To protect the thyroid gland Lugol's iodine is given for two days before perfusion.

Dosage

The leakage is only one factor which regulates the quantity of drug which can be safely given. The second is the tolerance of the local tissues to the poisonous effects of the drug. At present the latter can be estimated only by experiments on animals and from clinical experience.

Where the leakage factor is nil or negligible, as in a limb, dosage depends solely on tissue tolerance. In other parts of the body as in aortic or carotid perfusion

the leakage factor and the local tissue tolerance have practically equal importance in determining the doses of drugs.

If the leakage factor is proved to be high (60%–100%) it is dangerous to give the recommended dosage. Either the project must be abandoned or a smaller dose used, after taking steps to protect the marrow by an autologous bone-marrow transplantation. 400–500 ml. of bone marrow is aspirated prior to the perfusion from the sternum and ilium, and diluted with 250 ml. of equal parts of Ringer's and acid citrate dextrose. Some hours after the perfusion the bone marrow is replaced.

Nitrogen mustard (HN_2) is introduced into the circulation in divided doses of 10 mg. at five-minute intervals and perfused for 20 minutes after the last dose has been added. Perfusion with a longer-acting drug such as phenylalanine mustard is continued for 60 to 90 minutes. This is given dissolved in propylene glycol 5 mg. of powder per 1 ml. of solution, and to this solution is added an equal portion of normal saline. The total amount of this drug is introduced at one injection.

Dr. Creech uses HN_2 or P.A.M. for limbs. HN_2 has also been used for bladder and breast. Thio-tepa seems best for ovarian cancer; for the pelvis generally P.A.M. or A.B.100, and for colon and rectum 5-fluorouracil. Actinomycin-D renders rhabdomyosarcoma more sensitive to x rays.

Restoration to Normal

When the treatment is finished the region is washed out with 500 ml. of dextran followed by 500 ml. of heparinized blood. This is carried out through a T-connexion inserted into the arterial side of the circuit. The blood containing the drug already in the circuit is thereby washed out and must not be allowed to re-enter the limb. The catheters are removed and the blood vessels repaired with silk sutures after testing the lumen with a Backus probe. The tapes and tourniquets are released and an anti-heparin drug such as "polybrene" (Abbott) 1 mg. per 100 B.P. units is given intravenously. Finally the wound is closed without drainage.

Dangerous quantities of drug in the general circulation can be counteracted with sodium thiosulphate.

Post-operative Complications and Care

The chief complications of perfusion are related to (1) local tissue tolerance, and (2) leakage factor.

If local tissue tolerance is exceeded, petechiae, erythema, mild oedema, tanning, blistering, or even gangrene may occur. Methyl prednisolone is advised to counteract the oedema.

If leakage is high, depression of bone-marrow occurs.

If the haemoglobin is less than 10 g. per 100 ml., give a blood transfusion. If the platelets are less than 30,000 per c.mm., transfuse with platelet-rich plasma. For leucopenia and fever give broad-spectrum antibiotics and cortisone.

Haemolysis of red cells may cause haemoglobinuria and anaemia.

All cases must therefore have daily blood counts, careful observation, and notes recorded on them.

Local tissue tolerance is a very individual, variable factor, but blistering of the skin and gangrene can occur. Gangrene may be produced by the trauma of handling the vessels or the use of the tourniquet, especially in patients with arteriosclerosis. These complications may precipitate the decision for amputation.

Complications are more likely to occur after a second perfusion, which should therefore be performed with smaller doses of drugs.

Results

The majority of cases so far perfused have previously had all modern methods of surgery and radiotherapy and have recurrence or extension of the disease. Results after only a little over two years cannot yet be assessed in survival figures, but I saw examples of the following: relief of pain in pelvic lesions, almost immediately; regression of recurrent and sometimes large and widespread melanomata; the saving of a limb which would, without perfusion, have required amputation; large inoperable tumours becoming small and operable.

Other values of perfusion may be: malignant cells in large tumours may be damaged enough to diminish their capacity to disseminate or become implanted; loose cells may be destroyed within regional lymphatics; as an adjunct to surgery, prophylactic perfusion of isolated organs commonly the sites of metastases may be feasible; a useful research method on the biological response of tumours to chemotherapeutic agents.

Recommendations

I feel that further research along these lines is highly desirable. Surgeons who have this type of patient to treat should, I believe, have ample and continuing laboratory accommodation for animal work to test the many drugs available. In the treatment of the large numbers of patients who might receive benefit much help will be needed from pathologists, physicists, nursing staff, and surgical assistants during long operating hours. Every facility for carrying out this work should be at the disposal of surgeons. Frequent consultations between all branches working on all types of cancer seem fruitful.

I was impressed with the simplicity, cheapness, and freedom from complications of the Pulmo-Pak. I was told that transistor scintillations should be cheaper and more mobile than valve equipment. I saw clear anatomical diagrams of difficult collateral circulations. I saw recovery rooms fully staffed and equipped with a visual E.C.G. attached to each serious operation case. A cardiac pace-maker was available for each patient. I gathered that ballooned catheters had not proved efficacious in preventing leakage in the aorta and vena cava in pelvic perfusion, but that, in Boston, work for liver perfusion was being investigated with these devices. I learned that work is being undertaken to assess the effect of "physiological" agents—for example, altered pH, variable glucose blood levels, high O_2 tension, and lactic-acid factor, both without

any drug at all and also with longer hours of perfusion with drugs.

At informal conferences I suggested that it might be possible to provide for a series of intradermal tests of a drug of varied strengths in an endeavour to assess pre-operatively local tissue tolerance; it might be worth while making a study of any possibly remaining collateral vessels by operative arteriogram taken on the table before the drug is perfused; something might be learned about cross-circulation if the leakage factor was tested in the opposite direction; vasodilators other than papaverine might be tried—for example, procaine; a model with two separate circulations might be made with a cross-connexion which could be opened and closed; not only might pumps, oxygenators, connexions, and electronic devices be tested, but the effects of different flow rates and blood-pressures be assessed, and, especially for beginners in this field, much animal work and time saved.

All who have had the privilege of seeing our American colleagues at work and partaking of their unending and overwhelming hospitality and friendship know how difficult it is adequately to express one's admiration and gratitude. I was recently privileged to spend about three days at New Orleans, Houston, Texas, and Boston, Mass. In each of these cities I received the greatest kindness and consideration from everyone I met.

At the first Dr. Oscar Creech is professor of surgery at Tulane University and the Charity Hospital of 3,800 beds. Among his many associates I met Dr. Krementz, Dr. Robert Ryan, Dr. Schramel, and Dr. Reemstma, and also the chief surgeon at the U.S. Marine Hospital, Dr. Lloyd Elliott. At the second I had a most friendly reception from Dr. Lee Clark, Dr. E. C. White, Dr. John S. Stehlin, Jr., and Dr. John E. Healey, and their many associates at the M. D. Anderson Hospital (350 beds).

At Boston I had recently met Professor Francis Moore, and now talked with some of his associates working on livers; also with Dr. Farber, and with him was working my colleague, Professor Franz Beigel, at the Boston Children's Hospital. I am very grateful to everyone.

REFERENCES

- Bergel, F. (1953). *British Empire Cancer Campaign Annual Report*.
— and Stock, J. A. (1954). *J. chem. Soc.*, 2409.
Bierman, H. R., Byron, R. L. Jr., Miller, E. R., and Shimkin, M. B. (1950). Fifth International Congress of Cancer, Paris, Herman, 186. Abstract. *Amer. J. Med.*, 8, 535.
Creech, O., Jr., Krementz, E. T., Ryan, R. F., and Winblad, J. N. (1958). *Ann. Surg.*, 148, 616.
Klopp, C. T., et al. (1950). *Ibid.*, 132, 811.
Stehlin, J. S., Jr., Clark, R. L., Jr., and White, E. C. (1959). *Amer. Surg.*, 25, 595.

Nova et Vetera

NAPOLEON DISSECTED

Of the making of books on Napoleon there is no end. As early as 1824 Walter Scott complained of all the published books that he had to read before he wrote the emperor's life. Napoleon's medical history has also been studied in detail by many, and most authoritatively by Dr. Arnold Chaplin. Yet even now, as Mr. Kemble's study shows, new light can be thrown on Napoleon's maladies, especially from the standpoint of modern medicine.*

Napoleon Bonaparte had exceptional physical and mental energy. He could endure great fatigue, as in the Russian

campaign, and sometimes would walk for five or six miles without feeling tired. He was frugal and temperate in his habits and an enemy to excess. But his health was far from satisfactory during the whole of his meteoric career. As a young man he contracted pulmonary tuberculosis. In 1789 he had prolonged feverish attacks when stationed at Auxonne and Valence; he suffered from cough in the Italian campaign and had haemoptysis in 1803. Antommarchi, at necropsy, reported signs of tuberculosis in the left side of the chest and small tuberculous cavities in the upper lobe of the left lung. Napoleon's son, the Duke of Reichstadt, died of consumption at 21 years of age. Napoleon's scabies dated from the siege of Toulon and persisted until his return from Egypt, when Corvisart cured him. His painful micturition has been attributed to stricture, but was more likely due to cystitis and stone. At necropsy several small stones were present in his bladder. Napoleon III, his nephew, had the same condition and died after an operation for it.

There is evidence that at infrequent intervals Napoleon suffered from angina and epileptiform attacks; the latter ranged from temporary loss of consciousness resembling petit mal to more prolonged seizures accompanied by convulsions. These attacks seized him at critical moments: for instance, at Aspern in 1809, where he was defeated by the Austrians; at Borodino in 1812, where he almost collapsed during the battle; at Düben during his wonderful campaign of 1813-14 against amazing odds, where, half-stuporose, he wasted four days when every hour was of importance; at Fontainebleau, when after taking opium he fell into a fit of prolonged stupor which led to the rumour that he had attempted suicide; and after Ligny in 1815, when he neglected to pursue the defeated Prussians and Wellington withdrawing from Quatre Bras. On the morning of Waterloo he slept when the heavy rain had ceased and it was imperative to strike swiftly. Mr. Kemble, on the evidence of King Jerome, ascribes the emperor's inertia here chiefly to an attack of haemorrhoids. At Paris and Malmaison he displayed apathy and indecision. He again abdicated, delayed to escape to the United States, and was taken a prisoner to St. Helena. Here he appeared to be in good health until the onset of the disease from which he died in 1821. Dr. Chaplin from the evidence at necropsy held that Napoleon died of cancer supervening on a chronic gastric ulcer; Mr. Kemble, from the clinical course of the illness, considers that it arose as a primary carcinoma of the stomach.

What was the mysterious illness which was partly responsible for Napoleon's downfall? Corvisart regarded the attacks as epileptic. Dr. Leonard Guthrie suggested that Napoleon suffered from some form of dyspituitarism which ended in hypopituitarism, as shown by his later obesity, etc., a view which Mr. Kemble favours. Such patients have a slow pulse and are subject to cerebral seizures. Napoleon's sustained vigour, energy, and intellect render this diagnosis doubtful. Madame de Rémusat said that Corvisart informed her that Napoleon had an exceptionally slow pulse, only 40 beats to the minute. Sir William Osler and Sir Arthur Keith held that Napoleon had Stokes-Adams disease, a view to which Mr. Kemble briefly alludes on p. 125. If so, the emperor's case was a mild one. The heart muscle was not involved extensively, and as a rule the syncopal and epileptiform attacks caused by cerebral anaemia were of brief duration, not severe, and infrequent. When complete heart-block has been established, the ventricles tend gradually to adapt themselves to the condition and the symptoms of the disease cease. This may have occurred in Napoleon's case, for he seems to have had few attacks after 1815 and his pulse-rate was quicker. Dr. Chaplin considered that in the absence of graphic records the diagnosis of heart-block must remain a supposition. This is true, but the slow pulse, if accepted, the anginal attacks, and seizures are significant. Mr. Kemble's book, based on the original sources of information, is a valuable contribution to Napoleonic history.

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**Napoleon Immortal. The Medical History and Private Life of Napoleon Bonaparte.* By James Kemble, Ch.M., F.R.C.S. (Pp. 307+xi; illustrated. 28s.) London: John Murray. 1959.