An Appraisal of Cancer Chemotherapy By Regional Perfusion *

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CANCER chemotherapy by perfusion was conceived as a method to achieve maximum concentration of anti-tumor drugs locally with minimal systemic toxicity.[1, 6] It was hoped that the effectiveness of cancer chemotherapy would be increased thereby. The term *perfusion* was applied to the method because the circulation of the tumor-bearing region, separated wholly or in part from the systemic circulation, is maintained by a pump-oxygenator during administration of the drug.

The technics described originally have remained essentially unchanged. A disposable bubble dispersion oxygenator with a low priming volume has been used in all cases, and 100 per cent gaseous oxygen has been used to increase the oxygen tension of the blood. The pumps are Sigmamotor, model TM 5. A blood heat exchanger of the Marchand type is incorporated into the arterial line to maintain blood temperature at or near normal.

After cannulation of the major artery and vein supplying a part, a tourniquet is applied above the area to be perfused whereever possible. The method of administering chemotherapeutic agents and the duration of perfusion vary with the agent. Thus, nitrogen mustard (HN_2), which has a short duration of action and is highly neurotoxic, is given in small amounts at two- to five-minute intervals and perfusion is continued for ten minutes after the last dose. L-phenylalanine mustard (Melphalan) and TSPA, as well as most of the other agents, have a longer duration of action and do not appear to be as neurotoxic as HN_2. They are usually given in two to four equal doses every three to five minutes. The duration of perfusion with the longer acting agents is 45 to 60 minutes.

To further minimize systemic toxicity, residual agent is removed by flushing the extremity with one-half liter of whole blood before releasing the tourniquet. Where isolation is not possible this step in the procedure is eliminated.

For a while systemic chemotherapy with HN_2 was administered intra-arterially using the same extracorporeal circuit employed in regional perfusion and was designated *total body* perfusion.[3] In most patients autologous bone marrow replantation was carried out in an effort to reduce depression of hematopoiesis. Sixty-one patients were treated by this method and it was evident that the results were no better than those obtained with large doses of HN_2 administered intravenously. Therefore, the technic was abandoned and the cases so treated have been excluded from this report.

The first patient was treated by regional perfusion on June 11, 1957 and a report

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TABLE 1. *Cancer Chemotherapy by Regional Perfusion*

Type of Tumor	No. Patients	No. Perfusions
Carcinoma	119	124
Sarcoma	56	63
Melanoma	142	186
Glioblastoma	33	38
Totals	350	411

TABLE 2. *Cancer Chemotherapy by Regional Perfusion*

No. Patients	Frequency of Perfusion
305	1
37	2
2	3
4	4
2	5

TABLE 3. *Cancer Chemotherapy by Regional Perfusion. Area Perfused*

Arm	35
Forequarter	30
Leg	140
Hindquarter	34
Lung	4
Head & neck	38
Brain	41
Breast	29
Pelvis	60

TABLE 4. *Tumor Type and Area Perfused—350 Patients*

Area	Carcinoma	Sarcoma	Melanoma	Glioblastoma
Head & neck	29	4	4	—
Brain	—	1	1	33
Breast	26	—	3	—
Lung	4	—	—	—
Pelvis	46	4	6	—
Extremities	14	47	128	—
Totals	119	56	142	33

of the preliminary experiences with 24 cases appeared in October, 1958.[1] Throughout the investigation of this method results have been reviewed periodically and criteria for case selection and drug dosage and operative technics were altered accordingly.[1-6] However, no attempt has been made previously to evaluate results critically because the number of cases and length of follow up were limited. Since the clinical experience with regional perfusion will soon span a five-year period, it seems appropriate now to review the material again to determine the morbidity and mortality and to determine if it has any value as a therapeutic modality in the treatment of cancer. This report is an analysis of the cases of cancer in which regional perfusion was used in treatment prior to March 1962.

Analysis of Cases

Between June 11, 1957 and March 1, 1962, 350 patients with cancer were treated with chemotherapy by regional perfusion. These procedures have been carried out by the staff and residents of the Department of Surgery, Tulane University School of Medicine, under the supervision and direction of the authors. This number represents only a small part of the many patients who have been seen in consultation or have been referred for perfusion. As time has gone by and criteria for treatment have become more restricted the proportion of those referred who receive chemotherapy by perfusion has become smaller.

1. Incidence. There were 174 males and 176 females ranging in age from two to 88 years, with an average age of 49.7 years.

Melanoma was treated most frequently and glioblastoma least frequently (Table 1). It was possible to repeat perfusion two or more times in 13 per cent of the patients (Table 2). In general, reperfusion was performed when lesions had shown a significant response initially but had recurred

after a period of time. Reperfusion was used most often in the treatment of melanoma and least often in the treatment of carcinoma.

Among the anatomic areas for which perfusion technics were developed, the leg was treated most often and the lung least often (Table 3). Perfusion of the extremities, including the fore- and hindquarters made up almost 60 per cent of the total.

In areas where it was possible to isolate the tumor-bearing region from the systemic circulation by means of a tourniquet or by other means, as in the case of perfusion of the lung, the term isolated perfusion has been applied. For perfusion of all other areas the term *regional perfusion* has been used. It should be pointed out, however, that unless the time course of escape of an indicator from the perfusion circuit into the systemic circulation is monitored continuously, it is not possible to determine if perfusion has been isolated or regional. Studies using RISA (radioiodinated serum albumin) indicated that perfusion of the arm, leg and lungs may be considered isolated. However, the fact that systemic leakage was monitored in only a third of the cases in this series makes it impossible to categorize them in this way.

Distribution of the major pathologic types of tumors according to anatomic area is shown in Table 4. Carcinoma of the pelvis was treated most often followed in order by carcinoma of the breast, head and neck, and extremities. Sarcoma and melanoma were predominantly on the extremities.

The types of carcinoma treated by perfusion varied widely (Table 5). Relatively few were adenocarcinoma arising in the gastro-intestinal tract because early results indicated they were unaffected by agents administered by this technic.

More than 20 histologic types of sarcoma were treated, the most frequent being liposarcoma, rhabdomyosarcoma, and fibrosarcoma (Table 6).

2. Agents. As this has been an exploratory study, many different chemotherapeutic agents have been tried (Table 7). The most frequently used were the alkylating agents, nitrogen mustard, melphalan, TSPA and a combination of melphalan and TSPA.

TABLE 5. *Types of Carcinoma—119 Patients*

Adenocarcinoma:	
Breast	26
Breast (metastatic to arm)	1
Colon and rectum	14
Rectum (metastatic from stomach)	1
Endometrial	8
Ovary	7
Kidney (metastatic to bone)	2
Undifferentiated	1
Parotid	1
Lung (metastatic to scapula)	1
Prostate	1
Urethra	1
Epidermoid:	
Oropharynx	20
Skin	10
Sinus	4
Cervix	3
Lung	2
Anus	1
Vagina	1
Lung (metastatic to leg)	1
Urethra	1
Miscellaneous:	
Bladder	6
Anaplastic lung	2
Lymphoepithelial	1
Seminoma	1
Basal cell skin	1
Anaplastic	1

TABLE 6. *Types of Sarcoma—56 Patients*

Rhabdomyo	7	Spindle Cell	3
Lipo	8	Myxo	2
Fibro	7	Parosteal	2
Osteogenic	5	Neurofibro	2
Chondro	4	Lympho-(localized)	2
Synovial	3	Alveolar cell	1
Kaposi's	1	Leiomyo	2
Ewing's	1	Giant cell	1
Hemangio	1	Reticulum cell	1
Undifferentiated	1	Unspecified	2

TABLE 7. *I. Agents in 346 Perfusions*

pe of Tumor	HN_2	Mel-phalan	TSPA	Mel-phalan & TSPA
Carcinoma	77	0	6	14
Sarcoma	32	13	1	6
Melanoma	8	45	3	123
Glioblastoma	0	0	18	0
Totals	117	58	28	143

TABLE 8. *II. Agents in 63 Perfusions*

VLB	16	AB 100 & ACT D	2
AB 100	9	5 FU & TSPA	2
ACT D	10	AB 100 & HN_2	1
ACT D & HN_2	4	5 FU & ACT D	1
TEM	5	Mitomycin	1
CB 3025 & ACT D	4	A 8103	1
5-FU	2	ACT D, CB 3025, TSPA	1
Dihydro-E73	3	Colchicine	1

Nitogen mustard is most commonly used in the treatment of carcinoma, melphalan in melanoma and sarcoma, and the combination of melphalan and TSPA has been used most often in treatment of melanoma. In addition to the alkylating agents, many others have been used including the antibiotics, plant alkaloids, and antimetabolites (Table 8). Vinblastine (VLB) has been used exclusively for glioblastoma; AB 100 has been used for adenocarcinomas of the pelvis and in some cases of melanoma. Actinomycin D has been used most often in the treatment of tumors occurring in children and renal carcinoma. On one occasion perfusion was performed without the use of a chemotherapeutic agent in an effort to determine the effect of oxygenated whole blood alone. On another occasion the total therapeutic dose of x-ray was delivered to an osteogenic sarcoma of the leg simultaneous with perfusion using oxygenated whole blood alone. Twice perfusion was carried out on two extremities simultaneously in an effort to determine the efficacy of oxygenating the blood in the perfusion circuit. In the first instance, there was epidermoid carcinoma involving both lower extremities and perfusion was carried out with nitrogen mustard, but in only one extremity was the blood oxygenated. A similar study was done in a case of epidermoid carcinoma involving both upper extremities except in this instance melphalan was the chemotherapeutic agent used. In all four cases the results were inconclusive.

TABLE 9. *Early Results—303 Patients*

Type of Tumor	No. Patients	% Improved
Carcinoma	105	55
Sarcoma	48	67
Melanoma	123	84
Glioblastoma	27	48
Totals	303	68

TABLE 10. *Results—Carcinoma*

Years	Patients	Controlled
1	92	23 (25%)
2	63	10 (16%)
3	40	4 (10%)
4	4	0

3. Results. Evaluation of the treatment of cancer is unsatisfactory unless there is an adequate period of follow up. For most tumors this period should be five years and for melanoma and carcinoma of the breast ten years. No patient treated by regional perfusion is eligible for a five-year evaluation and a majority have been followed for a relatively short period. Many of the patients, however, have presented with advanced malignancies or with lesions that were rapidly growing so the results during shorter periods of time may be of significance.

Among the 350 patients in the series, 313 were treated six months ago or longer and are eligible for evaluation. No recent follow up could be obtained in ten patients and these have been excluded from evaluation (Table 9). Assessment of early results of regional perfusion has been based on criteria used for evaluation of systemic

chemotherapy, namely, measurable reduction in size of lesions, relief of pain, increase in a sense of well-being, and a gain in weight. By these criteria, at least 50 per cent of patients are considered to be improved following treatment. In our experience approximately 10 per cent of patients with solid tumors respond to systemic chemotherapy; thus, it is evident that more frequent response occurs with regional chemotherapy by perfusion. As with systemic chemotherapy, however, response is usually short-lived following perfusion of advanced solid tumors.

Although tumor response following perfusion was greater than the response following systemic therapy, more exact criteria must be used to evaluate perfusion since it is potentially more hazardous to the patient. Further, cancer chemotherapy should be measured by the same standards as other forms of therapy if its value is to be accurately assessed. For these reasons the results have been analyzed in terms of

TABLE 11. *Data Concerning Patients with Carcinoma now Controlled Following Regional Perfusion and Excision*

Patient Age, Race Sex	Type and Site Lesion	Drug/Dose mg./ kg./Total Dose	Additional Therapy	Time Control
A. B. 55 CF	Adenocarcinoma breast	HN_2/0.4 mg./30 mg.	Radical mastectomy	45 mos.
L. H. 64 CF	Adenocarcinoma breast	HN_2/0.38 mg./35 mg.	Radical mastectomy	24 mos.
E. J. 68 CF	Adenocarcinoma breast	HN_2/0.4 mg./22.4 mg.	Radical mast. x-ray therapy	45 mos.
E. N. 39 CF	Adenocarcinoma breast	TSPA/0.4 mg./30 mg. Melphalan/1.5 mg./102 mg.	X-ray therapy Simple mastectomy**	24 mos.
A. P. 62 CF	Adenocarcinoma breast	TSPA/0.7 mg./51 mg. Melphalan/1.25 mg./91 mg.	Radical mastectomy	29 mos.
O. V. 42 WF	Adenocarcinoma breast	Act D/50 mcg./2,600 mcg.	Radical mastectomy	43 mos.
S. B. 56 WF	Adenocarcinoma breast to axilla	TSPA/0.34 mg./25 mg. Melphalan/0.69 mg./50 mg.	Deep x-ray therapy* Axillary dissection	19 mos.
M. C. 54 CF	Epidermoid, both lower extremities	HN_2/0.4 mg./30 mg./leg	Bilateral groin dissection*	29 mos.
B. W. 88 CF	Epidermoid lower extremity	HN_2/0.8 mg./30 mg.	Amputation**	34 mos.
L. F. 57 WM	Hypernephroma metastasis to arm	HN_2/0.37 mg./30 mg. Act D/11.25 mcg./900 mcg.	Amputation**	31 mos.
G. T. 60 WF	Epidermoid lower extremity	Mit-C/0.4 mg./25 mg. HN_2/40 mg.	Amputation*	12 mos.
V. G. 67 CF	Adenocarcinoma endometrium	HN_2/0.53 mg./40 mg.	Extensive hysterectomy*	19 mos.
I. Y. 61 CF	Adenocarcinoma endometrium	HN_2/0.6 mg./40 mg.	Extensive hysterectomy*	21 mos.
A. H. 62 WM	Epidermoid oropharynx	HN_2/0.3 mg./27 mg.	Further excisional surgery**	29 mos.
T. L. 63 WM	Basal cell, lip	HN_2/0.3 mg./15 mg.	No other therapy	24 mos.

* Excision at time of perfusion.
** Excision for recurrence following perfusion.

TABLE 12. *Results—Sarcoma*

Years	Patients	Controlled
1	41	13 (32%)
2	26	9 (35%)
3	18	7 (39%)
4	8	3 (37%)

duration of control of a tumor. Control as here used implies complete or partial regression of tumor with no evidence of growth.

There were 92 patients with carcinoma followed from one to four years after perfusion (Table 10). The disease was controlled in 25 per cent of the patients at the end of one year and in 16 and 10 per cent at two and three years, respectively. Of the four patients followed for four years there is evidence of tumor growth in all. There were 15 patients with carcinoma followed one year or more after perfusion in whom the disease is now controlled (Table 11). Fourteen had excisional therapy in conjunction with perfusion or afterward when there was evidence of tumor growth.

Among 41 patients with sarcoma treated by regional perfusion, 13 were free of disease or showed no evidence of tumor activity at the end of one year (Table 12).

TABLE 13. *Data Concerning Patients with Sarcoma now Controlled Following Regional Perfusion and Excision*

Patient Age, Race Sex		Type and Site Lesion	Drug/Dose mg./ kg./Total Dose	Additional Therapy	Time Control
P. C.	55 WM	Liposarcoma upper extremity	Melphalan/1 mg./70 mg.	Excision*	31 mos.
E. L.	70 CF	Liposarcoma shoulder	Melphalan/1.3 mg./103 mg.	Excision*	45 mos.
E. R.	76 CF	Liposarcoma lower extremity	HN_2/0.4 mg./26 mg.	Excision*	50 mos.
P. K.	56 CF	Liposarcoma retroperitoneal	HN_2/0.6 mg./30 mg.	Re-excision*	19 mos.
R. N.	47 WF	Rhabdomyosarcoma lower extremity	Melphalan/2 mg./134 mg. + TSPA/0.3 mg./20 mg. Melphalan/103 mg. + TSPA/155 mg.	Radical excision	45 mos.
H. E.	21 WM	Alveolar cell sarcoma, lower extremity	HN_2/0.4 mg./30.8 mg.	Wide excision*	51 mos.
M. B.	52 WF	Fibrosarcoma upper extremity	Melphalan/1.2 mg./101 mg.	Amputation*	44 mos.
C. F.	63 WF	Fibromyxosarcoma upper extremity	Melphalan/1.2 mg./60 mg.	Escision*	12 mos.
F. D.	46 WF	Spindle cell sarcoma foot	HN_2/0.9 mg./60 mg.	Amputation*	25 mos.
E. K.	58 WM	Reticulum cell sarcoma axilla	HN_2/0.38 mg./30 mg.	Axillary dissection Amputation**	17 mos.
J. T.	15 WM	Neurofibrosarcoma lower extremity	TSPA/0.8 mg./26 mg. + Melphalan/1.7 mg./57 mg. HN_2/25 mg. +	Amputation**	37 mos.
M. W.	61 WF	Myxosarcoma leg	Melphalan/1.9 mg./138 mg.	Excision*	48 mos.
O. N.	56 WF	Osteogenic leg	Melphalan/1.2 mg./90 mg.	Excision*	12 mos.

* Excision at time of perfusion.
** Excision for recurrence following perfusion.
† Reperfusion.

The lesions were controlled in nine of 26 patients followed for two years and in seven of 18 followed three years. Three of eight patients followed for four years have no evidence of disease. It should be pointed out that where the growth of sarcoma has been controlled, perfusion was combined with exicision of the tumor in almost every instance (Table 13).

There were 103 patients with melanoma followed from one to four years after perfusion (Table 14). The disease was controlled in 40 per cent of the patients at the end of one year and in 30 per cent at two and three years respectively. In one of five patients followed for four years there was no evidence of tumor.

Perfusion was carried out as a part of the surgical treatment of primary melanoma of the extremities in 20 of the 103 cases (Table 15). (In 17 of these the primary lesion had been removed prior to referral for perfusion and in 7 of these reexcision of the primary site was carried out at the time of perfusion. In 5, regional node dissection was performed at or shortly after perfusion.) In 17 there was no evidence of melanoma at the end of one year and seven of 12 patients followed for two years were apparently free of disease. Two of four patients were free of disease after three years. One of five patients treated four or more years ago was free of disease.

There were 71 patients with secondary melanoma of the extremities treated for palliation (Table 16). Included in this group are those with local recurrence and regional cutaneous or nodal metastasis. Whenever feasible the secondary lesions were removed at the time of or following perfusion but because of the extensive nature of the disease this was possible in less than one-third of the cases. There was no evidence of tumor growth in 34 per cent of those followed for one year, 26 per cent of those followed for two years and 30 per cent of those followed for three years.

TABLE 14. *Results—All Melanoma*

Years	Patients	Controlled
1	103	41 (40%)
2	63	19 (30%)
3	27	8 (30%)
4	5	1 (20%)

TABLE 15. *Melanoma of the Extremities—Primary Tumor*

Years	Patients	Controlled
1	20	17 (85%)
2	12	7 (58%)
3	4	2 (50%)

TABLE 16. *Melanoma of the Extremities—Secondary Tumor*

Years	Patients	Controlled
1	71	23 (34%)
2	45	12 (26%)
3	21	6 (30%)
4	5	1 (20%)

4. Deaths and Complications. Of 350 patients in the series, 199 have died (Table 17). Death has been a result of operation or chemotherapy in 34, progression of disease in 161 and other diseases in four. Among these, patients dying as a result of operation or chemotherapy deserve special comment.

TABLE 17. *Causes of Deaths in 199 Patients*

Type	Carcinoma	Sarcoma	Melanoma	Glioblastoma	Totals
Tumor	66	23	56	16	161
Operative	12	1	1	10	24
Chemotherapy	1	2	7	0	10
Other	1	2	1	0	4
Totals	80	28	65	26	199

TABLE 18. *Complications Related to Operation*

Wound—61	
Seroma	11
Hematoma	13
Dehiscence	3
Ischemic necrosis	6
Infection	28
Genitourinary Tract—14	
Infection	13
Uremia	1
Pulmonary—21	
Pneumonitis	19
Pleural Effusion	2
Cardiovascular—19	
Thrombophlebitis	11
Arrhythmia	7
Cardiac arrest	1
Gastro-intestinal—2	
Bleeding ulcer	1
Paralytic ileus	1

There were 34 deaths as a result of operation or chemotherapy. In ten instances, death was due to depression of hematopoiesis followed by septicemia. Seven of these patients had melanoma and were perfused with relatively large amounts of melphalan and TSPA in combination. In six the combined doses of melphalan and TSPA ranged from 1.5 mg./kg. body weight to 2.0 mg./kg. body weight. At the beginning of the series melphalan was dissolved in water but because of its poor solubility, propylene glycol was used instead. The increased solubility of melphalan in propylene glycol necessitated a reduction in the amount of melphalan administered.

There was one instance of acute renal cortical necrosis and necrosis of the mucosa of the gastrointestinal tract following hindquarter perfusion with melphalan and TSPA in a total dose of 1.3 mg./kg. body weight. Since severe leukopenia also developed it is assumed that all of the changes observed at necropsy were a result of chemotherapy. In one case death occurred from septicemia following perfusion of the oropharynx with only 15 mg. of nitrogen mustard.

TABLE 19. *Complications Related to Perfusion*

Complication	No. Patients
Persistent edema	16
Venous thrombosis	8
Arterial thrombosis	3
Pulmonary embolus	1
Postoperative bleeding	3

A majority of operative deaths occurred in patients with carcinoma who were treated early in the study. These patients were debilitated and would have been poor operative risks under any circumstance. In one instance death followed perfusion of a large lymphosarcoma of the thigh. During the first three days after operation extensive necrosis of the tumor occurred and on the fourth day the patient died in shock and renal failure. It was not clear whether death was a result of chemotherapy (HN_2) or was related to tumor necrosis.

Complications resulting from chemotherapy by regional perfusion have been divided into those which might accompany any major operative procedure, those arising from perfusion technics and those resulting from the use of chemotherapeutic agents. The incidence of wound complications was high, representing more than half the total of complications occurring as a result of operation itself (Table 18). The formation of seromas and hematomas and necrosis of skin flaps occurred following regional node dissection for the most part. Wound infections involved predominantly wounds of the extremity. A majority of genito-urinary tract complications were cystitis. Atelectasis or patchy pneumonitis occurred in 19 patients and in all instances were thought to be primarily obstructive rather than infectious in nature. Eleven patients developed thrombophlebitis following perfusion which was considered to be unrelated to venous cannulation and repair.

In most instances this was deep venous thrombosis involving an unperfused extremity and was manifest by edema and pain.

Complications believed to be directly related to perfusion were persistent edema, venous thrombosis, arterial thrombosis, pulmonary embolus and postoperative bleeding in order of frequency (Table 19). Although a majority of patients developed mild to moderate edema of the extremity following perfusion it was of short duration and there were no sequelae. However, in 16 patients edema was severe and persisted beyond the usual period of convalescence and in some instances has been permanent. Thrombosis of the vein cannulated for perfusion is known to have occurred in eight instances and probably occurred in others but went unrecognized. Arterial thrombosis at the site of cannulation and repair was observed in three instances. In each case repair had been difficult because of the small size of the vessel or because of atherosclerosis. Nonfatal pulmonary embolism occurred in one instance and there were three cases in which bleeding from the wound occurred. These were thought to be due to heparinization.

The most serious complications were those resulting from chemotherapy (Table 20). Among ten patients developing complete or partial alopecia after perfusion only three had regional perfusion of the head and neck. The remainder had perfusion of lesions involving extremities, pelvis or breast, and melphalan and TSPA were the agents used. Gastro-intestinal symptoms were severe in ten patients although many others had nausea and vomiting during the first 12 to 24 hours. Stomatitis was observed following perfusion in eight patients with five different agents.

One of the most distressing complications of chemotherapy was nerve injury resulting from the neurotoxicity of the alkylating agents. Nitrogen mustard proved to be the most toxic particularly when administered in large amounts. There were five instances of brachial plexus paralysis of which four had some degree of permanent injury In one case it was necessary to perform shoulder joint disarticulation because of persistent pain and motor weakness of the upper extremity. Seventh nerve injury occurred in four instances following perfusion of the head and neck and two of these have been permanent.

TABLE 20. *Complications Related to Chemotherapy*

Complication	No. Patients
Alopecia	10
Persistent nausea and vomiting	5
Persistent diarrhea	5
Stomatitis	8
Brachial plexus palsy	5
Peripheral nerve injury	3
Cranial nerve injury	6
Muscle weakness of perfused extremity	4
Erythema, ecchymosis or necrosis of skin	50
Dermatitis	8
Severe depression of hematopoiesis	35
Septicemia	10*
Chemical arteritis—gangrene	2

* Included in operative deaths.

Although slight erythema of the skin of the perfused part is usual after regional perfusion, persistent discloration or the development of blebs or superficial necrosis are indicative of severe soft tissue damage by the chemotherapeutic agent. In many instances discoloration has been permanent and is not unlike that observed following irradiation.

Severe depression of hematopoiesis was observed in 35 patients, in ten of whom fatal septicemia developed. In a majority

TABLE 21. *Leukocyte Depression in 278 Perfusions*

WBC	No.	%
Above 3,000/cu. mm.	192	69
1,000–3,000	57	21
Below 1,000	29	10

of patients, however, the leukocyte count did not fall below 3,000 cells/cu. mm. (Table 21).

Arteritis resulting from the irritative effect of the chemotherapeutic agent occurred in two patients and produced gangrene necessitating amputation in both. Histologic examination in one instance revealed a severe inflammatory reaction involving the media and producing occlusion of the popliteal artery.

Discussion

When this investigation was begun it was assumed that increasing the local concentration of an antitumor agent would increase its tumor-inhibiting effect. The results observed in 350 patients support this assumption. Thus, the rate of objective response following regional chemotherapy by perfusion is significantly greater than that following systemic chemotherapy with the same agents.

The assumption that regional perfusion would decrease the incidence and severity of systemic toxicity from the antitumor agents has also proved correct although isolation of the effects of the drug to the area perfused seems impossible to achieve completely. Further, increasing the dose of an agent administered by perfusion is not accompanied by an increasing tumoricidal effect beyond the point where severe damage to normal tissues occurs. Thus, in regional chemotherapy, as in systemic chemotherapy, the toxic side effects of an agent remain the limiting factor to therapy.

The results obtained in carcinoma and glioblastoma are not good in terms of control of tumor growth and the frequency of palliation is offset by its short duration. In addition, the operative morbidity and mortality among patients with carcinoma have been high. Thus, chemotherapy by perfusion probably is not indicated in the treatment of carcinoma involving the pelvis and lung, and in most instances infusional therapy is preferred for carcinoma of the head and neck and glioblastoma. It is true that some inoperable tumors apparently were made operable by regional perfusion, particularly in cases of cancer of the breast. However, the same result might have been achieved with radiation.

The results obtained in the treatment of sarcoma are encouraging since they are considerably better than our results with excisional therapy alone. As indicated earlier, in a majority of patients in whom growth of tumor was controlled excision was carried out at or subsequent to perfusion. In several instances regional perfusion produced regression of a large strategically located sarcoma to the extent that local excision was possible and usefulness of the limb preserved. Some of the lesions controlled by a combination of regional chemotherapy and excision were slow growing and might have been controlled by excision alone. On the other hand, in two of the cases of liposarcoma and in cases of rhabdomyosarcoma and fibrosarcoma, the lesions were recurrent or rapidly growing and there is reason to believe that regional perfusion was at least partially responsible for control of growth.

The results observed with malignant melanoma have been gratifying although the number of patients followed three or four years is small. Melanoma responds poorly to systemic chemotherapy, yet a significant response has occurred in 70 to 80 per cent of patients treated by regional perfusion. Perfusion was used as an adjunct to excision of the primary lesion in only a few patients and the results are not significant at this time. However, within the past year and one-half an increasing number of perfusions were for primary treatment of melanoma. In one instance a large primary melanoma of the palm was treated by perfusion alone and has been completely controlled for one and one-half years. In another instance, the primary lesion was not excised until six weeks after

perfusion, at which time there was no evidence of active tumor.

Several patients with disseminated regional metatasis have been controlled for relatively long periods following treatment by perfusion alone. In a number of others melanoma has been so affected that excision was possible and effective palliation achieved. It is of particular significance that among those with regional metastasis it was possible to control the growth of the lesions and preserve usefulness of the limb although death eventually occurred from systemic spread. This represents genuine palliation and to date is the most gratifying result of regional perfusion. There is little doubt that regional perfusion will produce as good results as major amputation in advanced melanoma of the extremities and may prove to be more effective.

Further, the results observed in the treatment of advanced melanoma and sarcoma of the extremities suggest that the adjunct use of regional perfusion in the primary treatment of these tumors appears warranted.

It has been emphasized that the addition of cancer chemotherapy to a major operative procedure increases the hazards of both. This is clearly demonstrated by the morbidity and mortality observed in this series. Wound complications were common when regional node dissections were performed in conjunction with perfusion and relatively uncommon in other cases. Injury to normal tissues was largely a result of administration of an excessive amount of drug and as experience has accumulated these changes have become less frequent. Neurotoxicity can be avoided by fractionating the total dose of the alkylating agents, particularly nitrogen mustard, so that no more than three or four milligrams are administered at any one time.

In about 60 per cent of the cases it was possible to confine the cytotoxic effects of the agents to the area perfused. On the other hand, when isolation was inadequate, when the amount of agent administered was large and when necrosis of bulky tumors occurred, the incidence of serious hematopoietic depression was high. With experience it is possible to recognize circumstances under which isolation is inadequate and to reduce the dose of a chemotherapeutic agent accordingly. Further, if systemic escape of the agent is monitored continuously the amount of agent administered can be kept within a safe range.

Ten per cent of patients in this series died from operation or chemotherapy. A majority of these deaths might have been avoided by more careful case selection and a reduction in the amount of chemotherapeutic agent used. On the other hand, the hazards of a general anesthetic, the use of whole blood transfusions and the unpredictable response of the individual patient to cancer chemotherapy irrespective of the dose, contribute to the risk of regional perfusion. Thus, greater care must be exercised during conduct of the operation and in the postoperative period than is necessary in many other types of operative procedures. For this reason, use of chemotherapy by regional perfusion should be confined to institutions where specially trained personnel and adequate facilities are available.

Summary

1. Experience with cancer chemotherapy by regional perfusion in the treatment of 350 patients has been reviewed.

2. Melanoma was treated most frequently and glioblastoma least frequently. Lesions of the lower extremities were perfused most often.

3. Among a variety of carcinoma, lesions of the pelvis were most common. Sarcoma and melanoma were predominantly on the extremities.

4. Alkylating agents were used in a majority of instances although many others were given limited trial.

5. Three hundred and three patients were followed six months or longer after treatment. Of these, 50 per cent showed an objective response.

6. Analysis of follow up data according to control of tumor growth for one or more years indicates the following: At the end of three years growth of tumor was controlled in 10 per cent of patients with carcinoma, 39 per cent of patients with sarcoma and 30 per cent of those with melanoma.

7. Thirty-four patients died as a result of operation or chemotherapy and 161 died of progression of neoplastic disease.

8. Wound complications were frequent especially when regional node dissection was combined with perfusion. Nerve injury was common when large amounts of the alkylating agents were administered. In 69 per cent of patients no significant depression of hematopoiesis occurred.

9. Cancer chemotherapy by perfusion is indicated in the treatment of sarcoma and melanoma of the extremities 1) as an adjunct to surgical excision of primary lesions; and 2) for palliation of advanced lesions.

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