Henry Ford Hospital Medical Journal

Volume 9 | Number 1 Article 1

3-1961

Intra-Arterial Chemotherapy of Malignant Diseases

R. W. Talley

V. K. Vaitkevicius

M. J. Brennan

J. E. Kelly

INTRA-ARTERIAL CHEMOTHERAPY OF MALIGNANT DISEASES*

R. W. Talley, M.D., V. K. Vaitkevicius, M.D.,
M. J. Brennan, M.D., and J. E. Kelly, M.D.**

During the past two decades the interest in the application of chemicals to the patient with inoperable, radiation-resistant, malignant disease has markedly increased. Many compounds have been evaluated and those which have shown efficacy have been limited in usefulness by their general systemic toxicity. Even though the quest for new, relatively non-toxic chemicals is progressing at a rapid rate, there is no evidence of which we are aware that such an agent is out of the test tube.

However, by the administration of these agents intra-arterially their systemic toxicity may be decreased. Several methods have been employed and, for sake of simplicity, we have divided these into the following three categories: (1) acute infusion, (2) acute perfusion, and (3) chronic infusion with antidote. The technique of acute infusion was first described by Klopp[1] and results will not be discussed here but in a subsequent publication.

RESULTS

The acute perfusion technique as first described by Creech and co-workers[2] has been most applicable in tumors localized in an extremity in which amputation or other surgical technique could not be employed. However, perfusion of the pelvis, lungs, brain, and other vascular isolatable organs are under evaluation. In a recent Perfusion Conference held at Tulane University in New Orleans, the results of many investigators were presented and, for a comprehensive survey, the reader is referred to the publication[3] of this conference.

In perfusion of an extremity the vascular supply of the area is isolated surgically with cannulization of the major artery and vein and tourniquet applied proximal to these. The chemotherapeutic agent, usually an alkylating agent, is administered by a sigmamotor pump extracorporeal system with bubble oxygenator. The drug employed in all of our cases except two has been nitrogen mustard at a dose of 0.6 to 1.0 mg./kg. We have found that, by careful monitoring of the perfusion system and the patient's blood from a distant sight with chromate labeled red cells, as well as keeping the perfusion system pressure (Austen and co-workers)[5] below the patient's average blood pressure, systemic toxicity may be kept to a minimum.

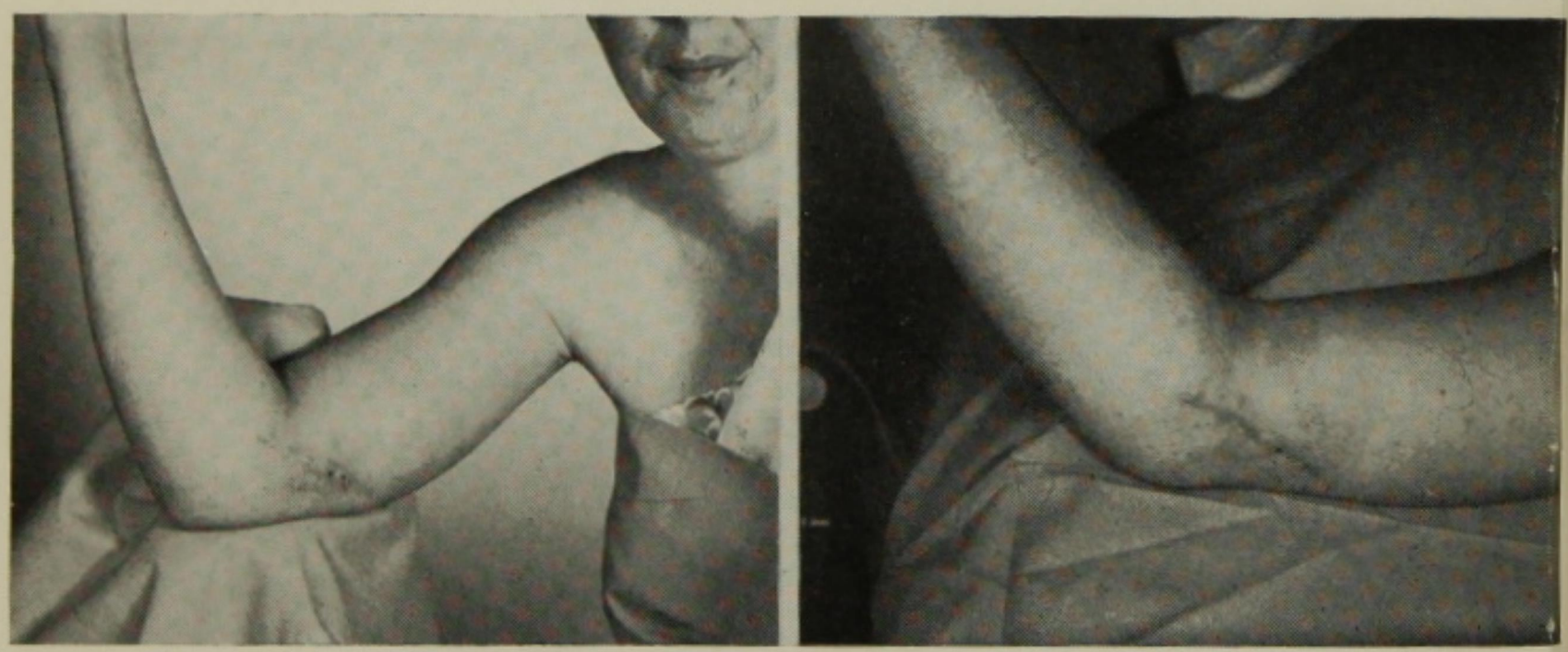
The seven patients undergoing such procedure are listed in Table I. Two of these patients (#3 and 7) can be classified as prophylactic perfusions; the rationale for such prophylactic perfusion has been convincingly put forth by Stehlin.[6] Patients #2 and #5 had worthwhile responses. Patient #5 is a 31-year-old, white female with recurrent melanoma (Fig. 1) in right epitrochlear node and right axillary nodes. Axillary node dissection followed by perfusion with nitrogen mustard at 1.0 mg./kg. resulted in 7 cm. decrease in circumference of arm. There has been no evidence of regrowth of the tumor five months after the perfusion.

*Presented at Regional Meeting, American College of Physicians, Flint, Mich., December 3, 1960.
**Department of Medicine, Division of Oncology.

TABLE I

PERFUSION RESULTS WITH ALKYLATING AGENTS

Patient	Diagnosis	Perfusion Site	Drug and Dose	Toxicity	Other RX	Results
1. M.L.	Ca. Bladder	Pelvis	TESPA 60 mg.	WBC ↓ 500	—	Subj., 4 wk
2. R.W.	Ewing's Sarcoma	Left leg	HN_2, 0.6 mg./kg.	WBC 2,000	Radiation 6,000 r	No recur in 9 months
3. K.S.	Melanoma	Left leg	HN_2, 0.8 mg./kg.	N & V	Radical groin dissection	No recur in 9 months
4. H.Z.	Squamous cell ca.	Right leg	TESPA 60 mg.	—	Radical groin dissection	No effect
5. M.L.	Melanoma	Right arm	HN_2, 1.0 mg./kg.	N & V	Axillary dissection	Obj. rem. 5 months
6. H.P.	Melanoma	Right leg	HN_2, 0.8 mg./kg.	Sciatic nerve paresthesias	Inguinal dissection	No effect
7. M.S.	Melanoma	Right leg	HN_2, 0.8 mg./kg.	Vesicular dermatitis, Peroneal nerve palsy	Inguinal dissection	Prophylac. only — no recur in 5 months



9-13-60 10-5-60

Figure 1

Patient #5, M. L., showing site of epitrochlear metastases of a recurrent melanoma. The circumference of upper arm on September 13, 1960, was 35 cm. and on October 5, 1960, it measured 27 cm.

Patient #2 is a 16-year-old boy with Ewing's sarcoma of the left femur (Fig. 2). Local acute perfusion with nitrogen mustard at 0.6 mg./kg. resulted in decrease in pain and swelling of leg. This was followed by 6,000 r delivered by a cobalt teletherapy unit. There has been no recurrence of disease eleven months later. It is impossible to say whether such combined therapy has been or will be any more efficacious than radiation therapy alone, but it is planned to treat additional patients in such a manner if the opportunity arises.

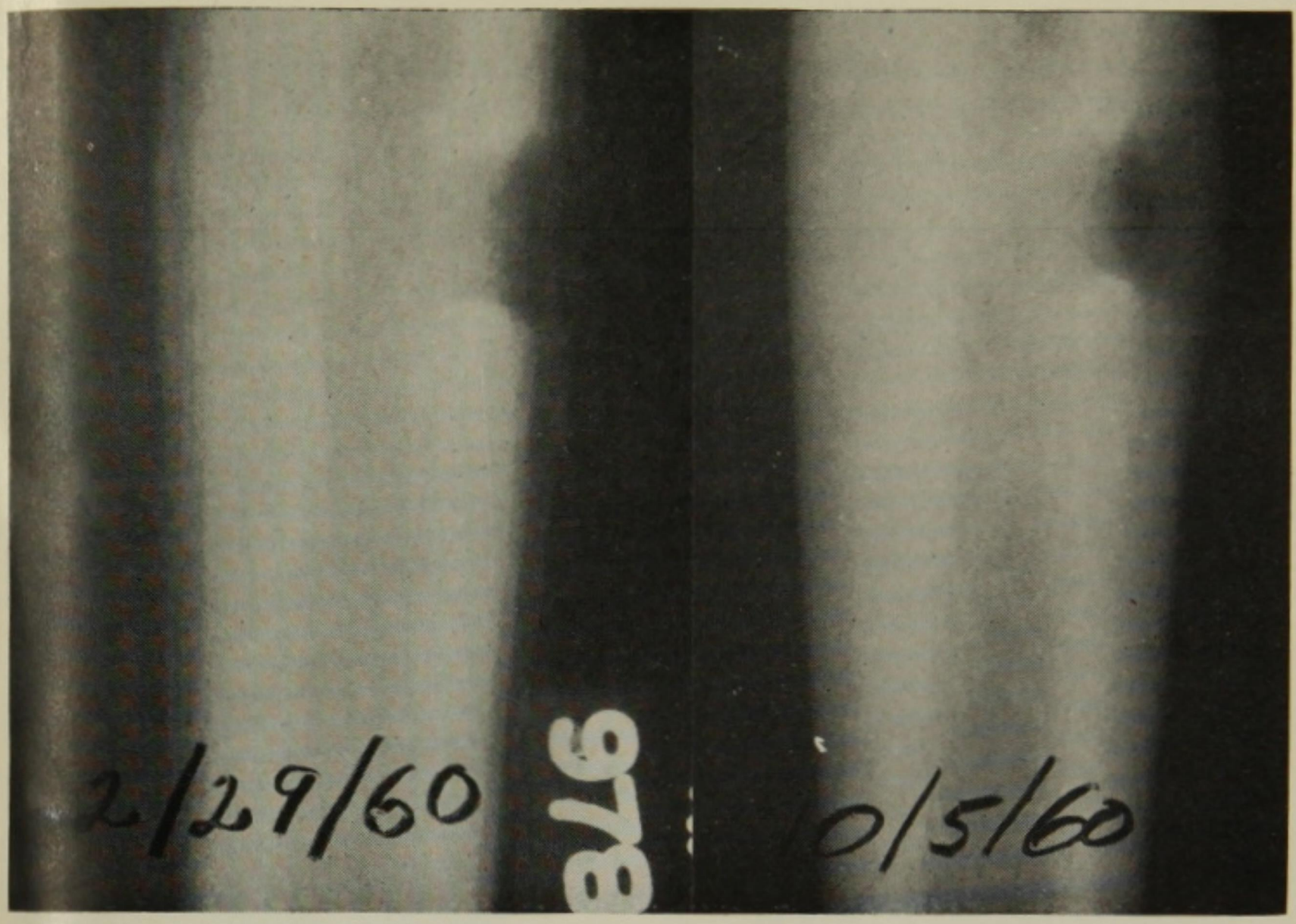


Figure 2

Roentgenograms of left femur in patient #2, R. W., reveal typical "onion peel" appearance of left femur. Large defect is the biopsy site. There has been complete disappearance of the "onion skin" appearance in the film of 10/5/60 and, expect for thickening of cortex, the bone appears normal. This film was taken 8 months after nitrogen mustard perfusion and radiation therapy.

The third technique being discussed, chronic arterial infusion of antimetabolite with systemic metabolite therapy and the rationale for such, was recently described by Sullivan.[4] In this technique, an antimetabolite such as amethopterin is administered via a constant arterial infusion to a localized area by a Barron pump.[7] Simultaneously, the patient is given relatively large doses of the normal metabolite such as folinic acid to prevent or delay systemic toxicity. Amethopterin is administered in a dose of 50 mg./day via arterial infusion for at least four days and folinic acid is given in intermittent daily doses of 9-36 mg. intramuscularly. Fifteen patients have been treated by this technique and are presented in Tables II, III, and IV according to the area infused.

TABLE II

ARTERIAL INFUSION WITH AMETHOPTERIN

A. Pelvic Infusion via Hypogastric Arteries

Patient	Diagnosis	Total Dose (Milligrams)	Response Subj.	Response Obj.	Minimal WBC	Other Toxicity
1. G.S.	Ca. Cervix	310 mg.	††† 5 mo.	† 2 mo.	950	Diarrhea, stomatitis
2. M.K.	Ca. Cervix	200 mg.	† 1 mo.	†† 1 mo.	700	Staph-entero colitis
3. R.C. (a)	Ca. Colon	175 mg.	0	†	5450	Diarrhea
(b)	Ca. Colon	125 mg.	0	0	2000	Diarrhea

TABLE III
ARTERIAL INFUSION WITH AMETHOPTERIN

B. Via Internal Carotid

Patient	Diagnosis	Total Dose (Milligrams)	Response Subj.	Response Obj.	Minimal WBC	Other Toxicity
4. H.R.	Glioblastoma	350 mg.	0	†	3500	—
5. R.M.	Glioblastoma	525 mg.	† 1 mo.	†† 1 mo.	1450	Diarrhea
6. P.D. (a)	Meningiosarc.	100 mg.	—	—	6000	—
(b)	Meningiosarc.	250 mg.	—	—	750	Dead on 7th post-inf. day
7. H.G.	Astrocytoma	250 mg.	—	—	8200	Death 1 day post-infusion

TABLE IV
ARTERIAL INFUSION WITH AMETHOPTERIN

C. Via External Carotid

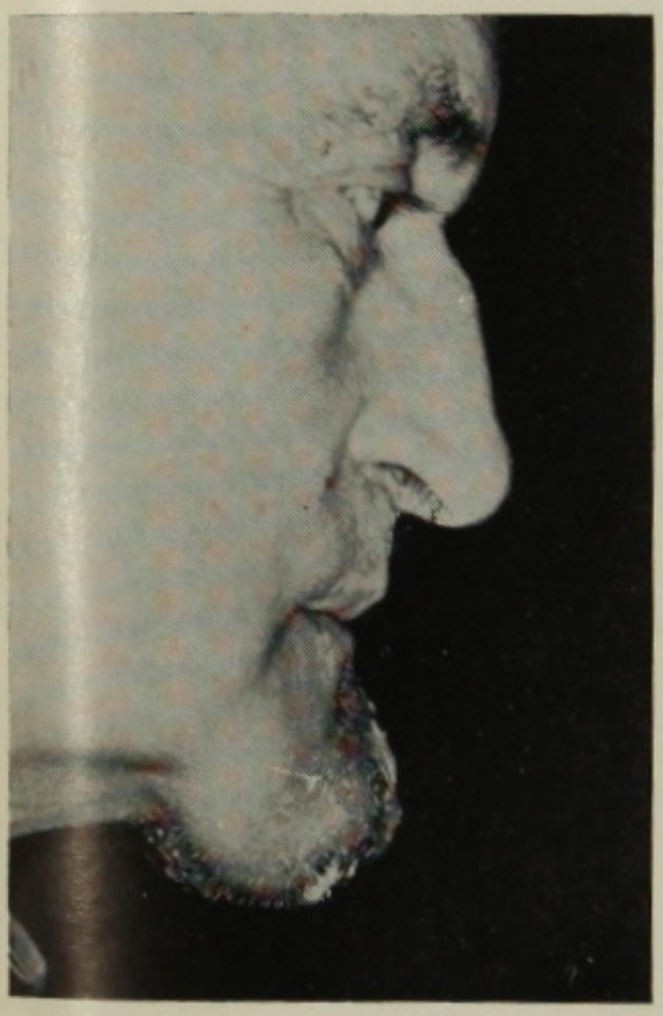
Patient	Diagnosis	Total Dose (Milligrams)	Response Subj.	Response Obj.	Minimal WBC	Other Toxicity
8. D.R. (a)	Ca. Floor of Mouth	490 mg.	†††† 1 mo.	††† 1 mo.	4200	Stomatitis
(b)	Ca. Floor of Mouth	412.5 mg.	††	†††	1450	Stomatitis
9. H.H.	Ca. Tonsil	350 mg.	—	—	50	Death- Leukopenia, acute pulm. edema
10. L.A.	Ca. Pharynx	350 mg.	†	—	2600	Stomatitis & severe anx'y
11. R.K.	Ca. Tongue	350 mg.	†	† 3 wks	4800	CVA ?
12. S.M. (a)	Ca. Tongue	335 mg.	†† 3 wks	† 3 wks	3100	Stomatitis,
(b)	Ca. Tongue	290 mg.	†† 7 wks	†† 7 wks	1250	diarrhea, & bronchopneu
13. J.K. (a)	Osteogenic Sarcoma	300 mg.	††	†	3800	Stomatitis
(b)	Zygoma.	300 mg.	†	†	2800	Stomatitis
(c)		200 mg.	††† 5 wks	†† 4 wks	4350	—
14. J.E.	Melanoma	200 mg.	—	—	4200	Inf. D/C'd at patient req.
15. V.D.	Ca. Breast, scalp metast.	240 mg.	†	†	3300	Stomatitis Hemorrhage

Three hypogastric artery infusions for pelvic carcinoma (Table III), resulted in production of significant subjective and objective improvement in one patient with carcinoma of the cervix, definite but limited benefit in another patient with carcinoma of the cervix, and no help in a patient with carcinoma of the rectum.

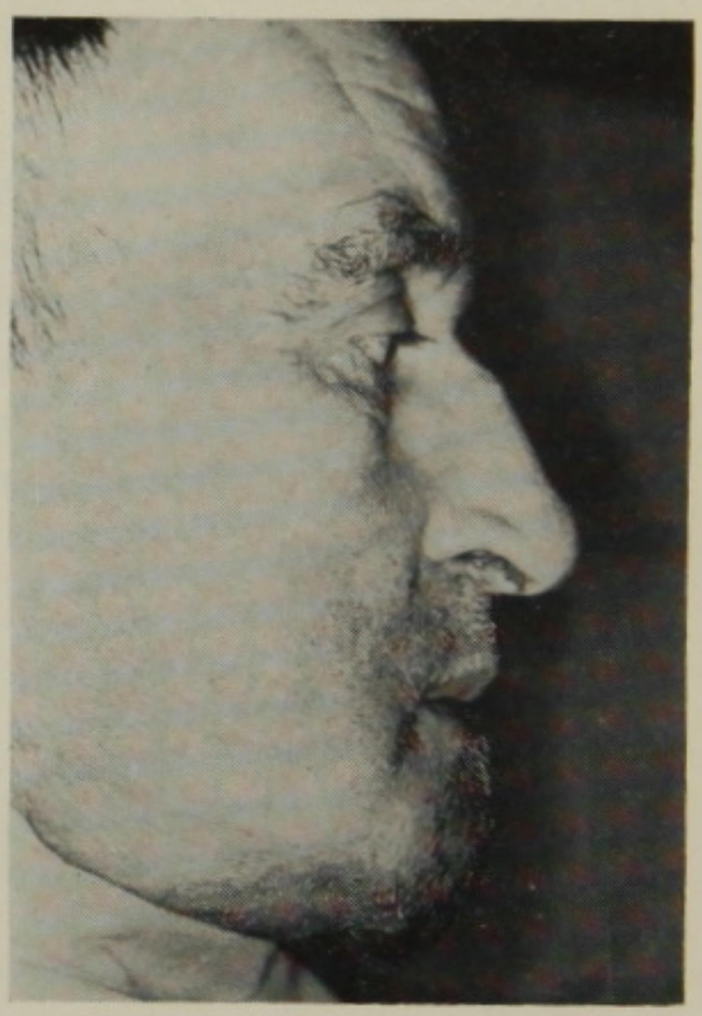
Four patients with various brain tumors were infused via the internal carotid artery as shown in Table IV. Only one patient (H.R.) obtained objective benefit with decrease of intracranial pressure to normal and disappearance of pain, but because

of pre-existing brain damage, this response was considered to be of limited value.

Eight patients have been infused via the external carotid artery and objective and subjective benefits have been noted in six, but of short duration in all (Table IV). Sullivan[4] reported significant prolonged regressions in three of eighteen patients treated similarly. Prolonged regressions were not noted in our series, but worthwhile palliation was obtained in four patients. The most gratifying result was obtained in patient #8, a 50-year-old man with recurrent radiation-resistant carcinoma of the floor of the mouth with direct extension through the mandible, in whom the infusion was carried out on two occasions. After both infusions there was dramatic diminution of the tumor mass (Fig. 3), but after the first infusion there was rapid regrowth of the



12-9-59



2-2-60

Figure 3

Patient #8, D. R. (Table III), with carcinoma of floor of the mouth with direct extension through the mandible. Photograph prior to Amethopterin infusion and appearance of lesion 4 days after completion of second infusion.

tumor. Because of the rapid growth of the tumor after the first infusion and the obvious fact that not all of the tumor had responded after the second infusion, a radical excision of the anterior half of the mandible and tongue was performed. The pathologic specimen did not reveal any recognizable viable malignant cells in the marginal lymph nodes and edges of the excised specimen. There has been no recurrence in eleven months and the patient is now undergoing plastic reconstruction of the face. It is impossible to say whether or not such a surgical procedure would have been possible without chemotherapy, however, this patient had been considered inoperable by several examiners.

TOXICITY

Toxicity associated with alkylating agent perfusion has been summarized recently by Reemstra.[8] Gastrointestinal reactions, leukopenia, nerve injuries, skin erythema,

and skin ulceration were the most common complications noted in a series of 231 perfusions. All of these were noted in our small series of seven patients. The most marked leukopenia was noted in patient #1, in whom pelvic perfusion was undertaken, and had an approximate 70% leak as calculated by chromium$_{35}$-tagged red cells. The toxicities are summarized in Table I. Our series is too small to give any true incidence of these complications.

The major toxicity associated with the chronic infusion of amethopterin was that of bone marrow depression with leukopenia and thrombocytopenia. Ulceration of the buccal mucosa in external carotid infusions and of diarrhea in hypogastric infusions were a problem in about one-half of each group. There were two deaths in association with severe leukopenia.

The dose relationship of folinic acid to leukopenia in the amethopterin treated patient is of great importance and leukopenic responses in relation to three dose levels of folinic acid is demonstrated in Fig. 4, 5, and 6. The maximal leukopenia in patients receiving less than 35 milligrams of folinic acid a day occurred by the 8th day, in the majority of patients. Recovery to normal levels in all of these patients was about the same. Patients receiving 36 or more milligrams a day did not drop to as low a level and recovered more rapidly, however, the differences were not great. Two fatal

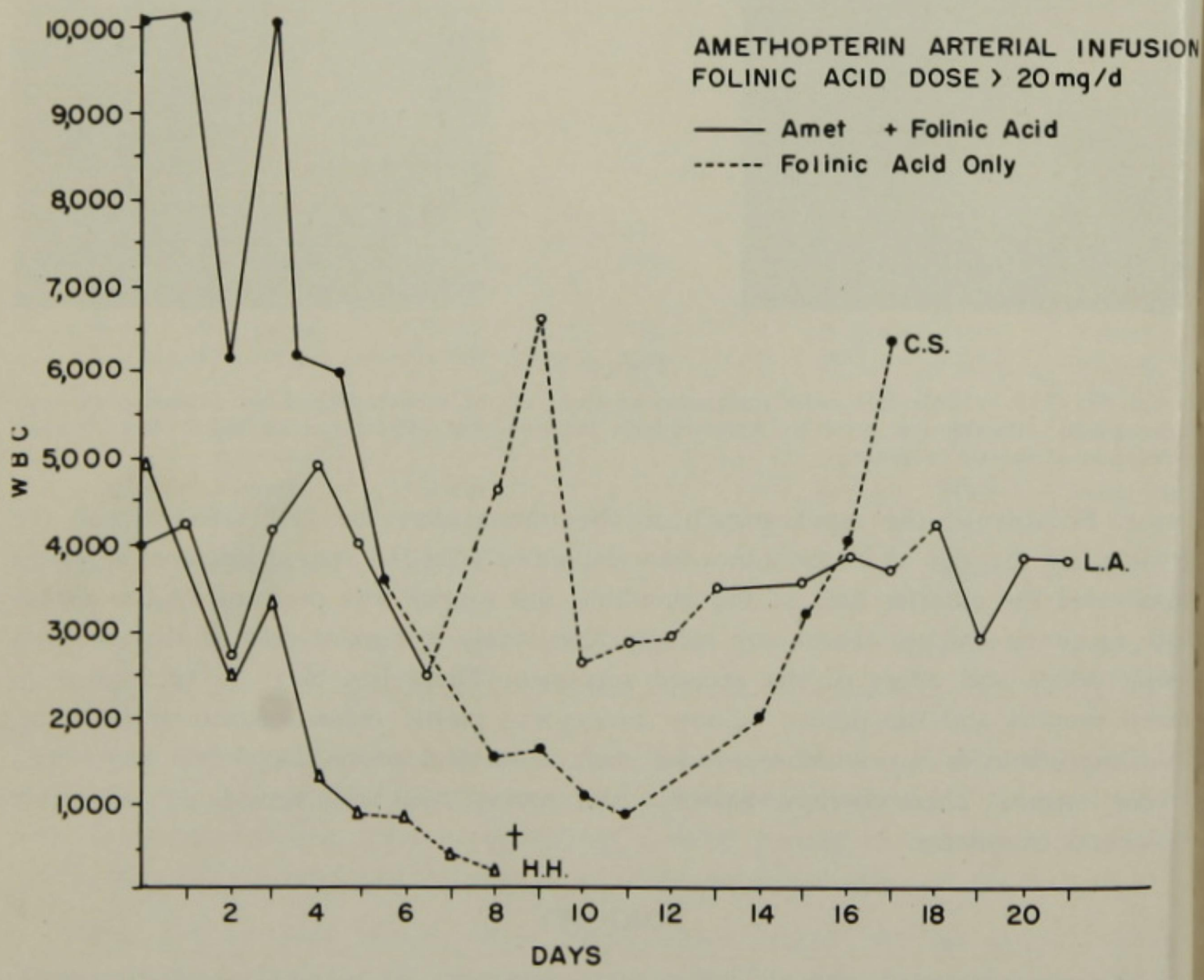


Figure 4

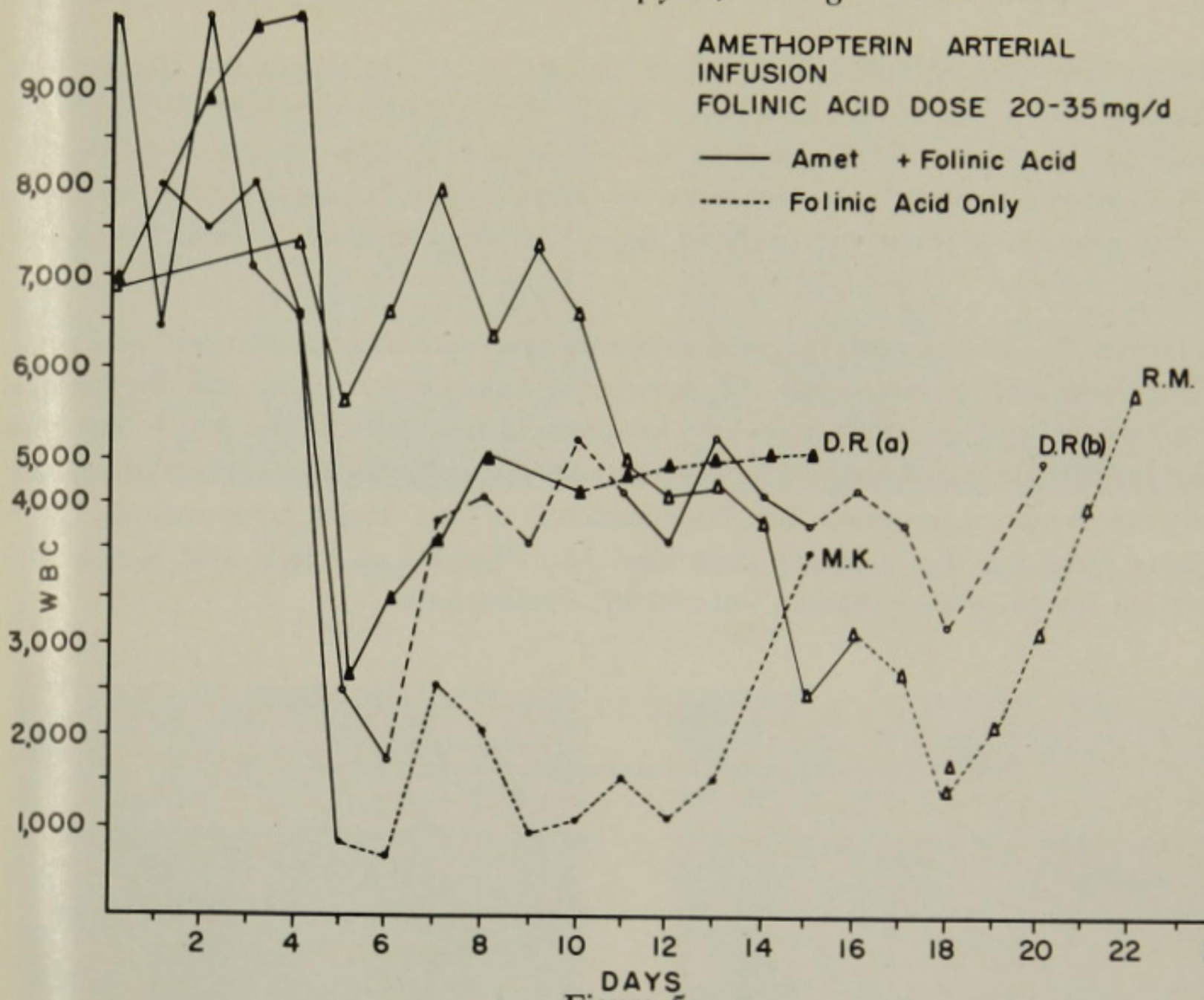


Figure 5

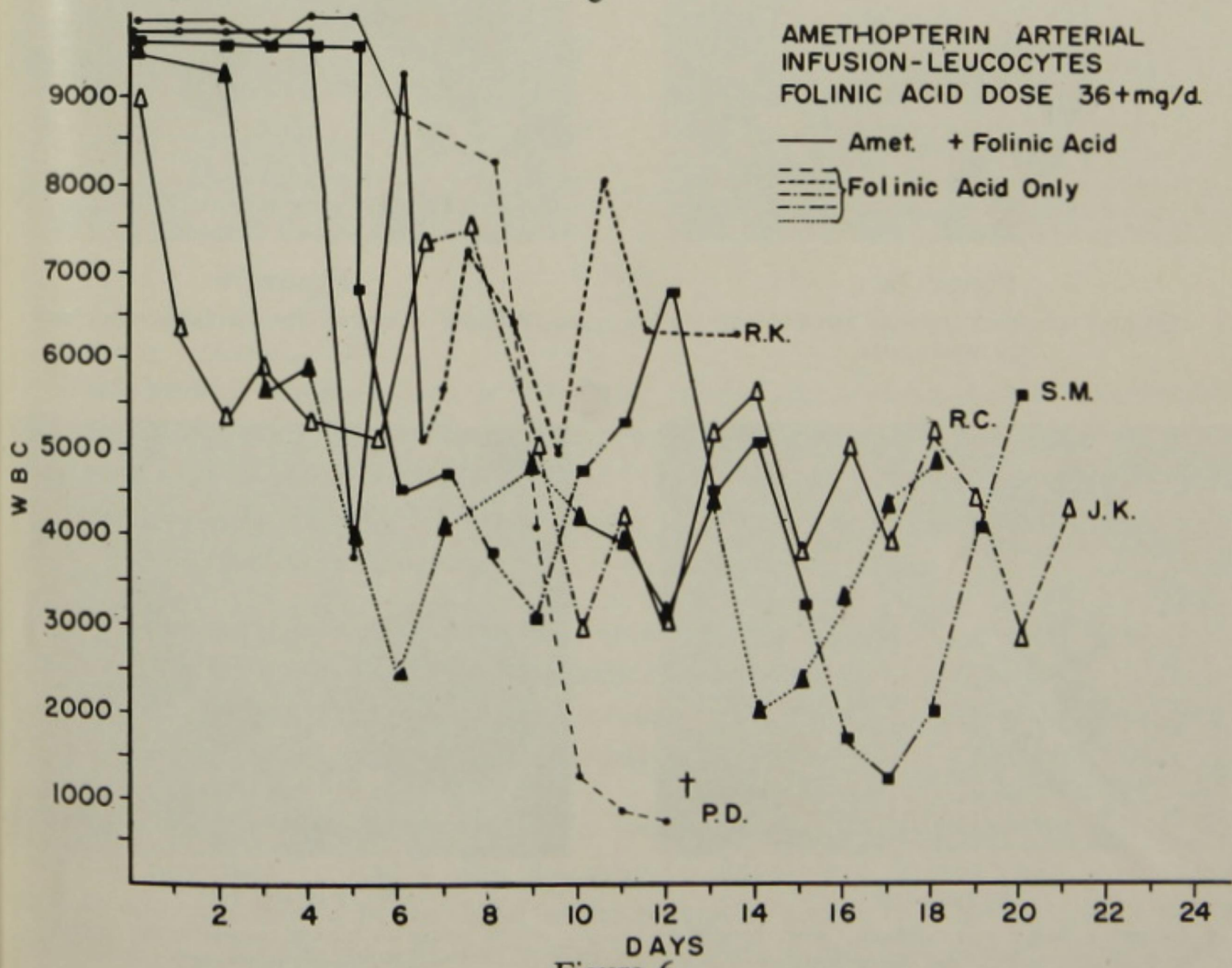


Figure 6

leukopenic reactions occurred and, in one patient, P. D., in whom the amethopterin was discontinued when the peripheral white blood count was still 8,400. Partly because of this, we now rely heavily on cytological changes in the bone marrow which demonstrate progressive evidence of megaloblastic changes in the erythroid series, increase in granulocytic-erythroid ratio, and disappearance of immature granulocytes.

In Fig. 7 (a-h.) we see atypical erythroid and granulocytic elements developing in patient #4 (H.R.), receiving 50 milligrams amethopterin daily via the internal carotid artery and 36 milligrams of folinic acid intramuscularly daily. The first typical megaloblastic cell suggesting a thymine deficiency[9] is seen at 28 hours. Approximately 48 hours is required for disappearance of the major abnormalities. It is suggested from this that a greater dose than 36 milligrams of folinic acid is necessary to prevent hematopoietic changes induced by amethopterin.

Figure 7a - 7b

Series microphotographs of marrow elements from patient H. R.

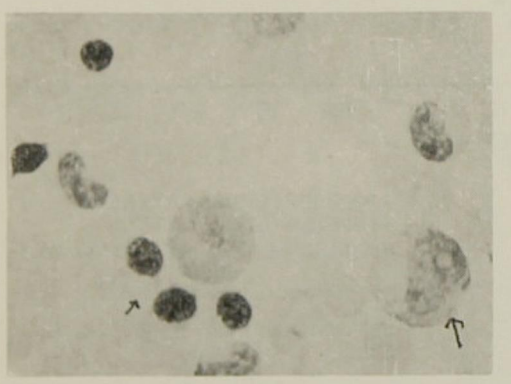


Figure 7a

Control specimen showing normoblasts and myelocytes.

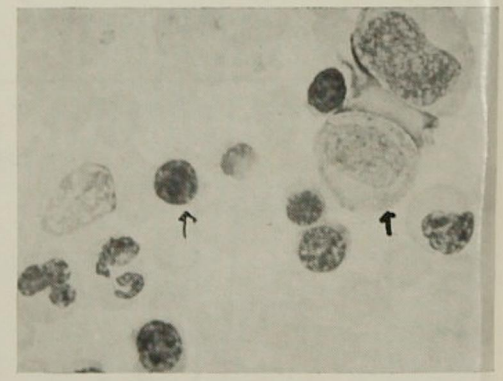


Figure 7b

4-hours — essentially normal normoblasts and myelocytes.

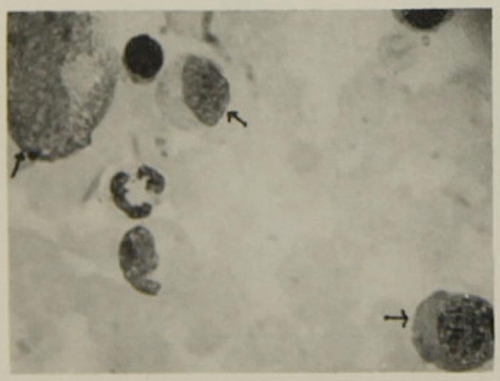


Figure 7c

16 hours — large normoblasts, with loosening of nuclear chromatin, and giant metamyelocytes.

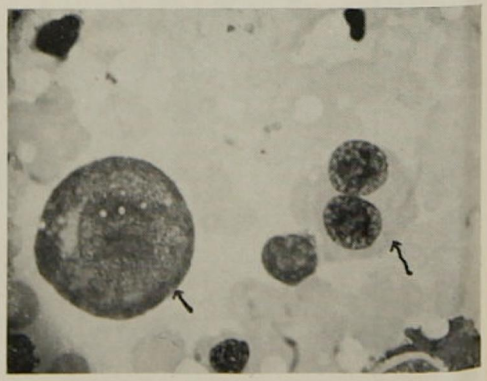


Figure 7d

28 hours — typical megaloblast, double nucleated normoblast.

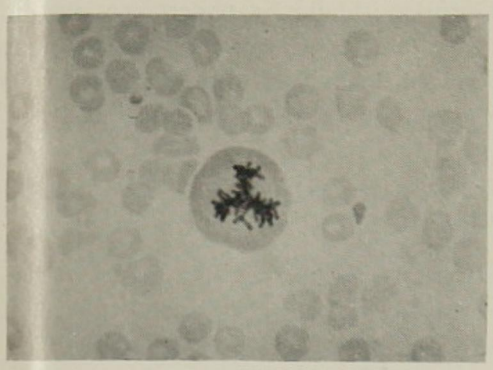


Figure 7e
36 hours — tripolar mitotic figure.

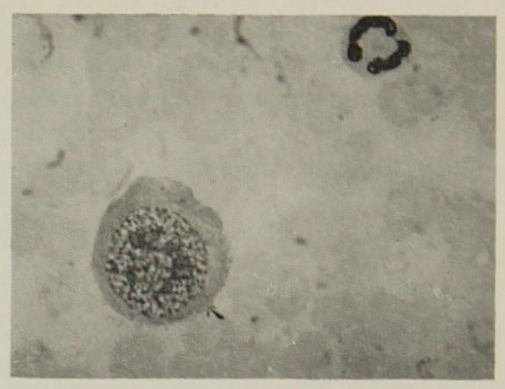


Figure 7f
48 hours — typical megaloblast, sparseness of myelocytes.

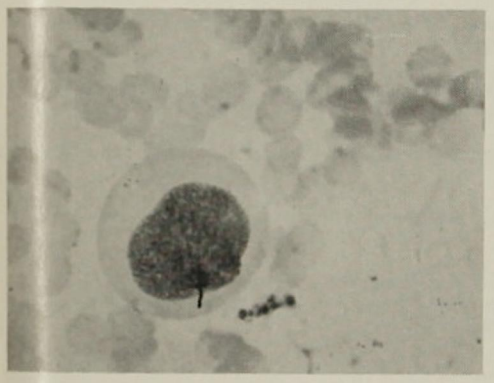


Figure 7g
24 hours after discontinuance of Amethopterin — megaloblast with increasing condensation of nuclear chromatin.

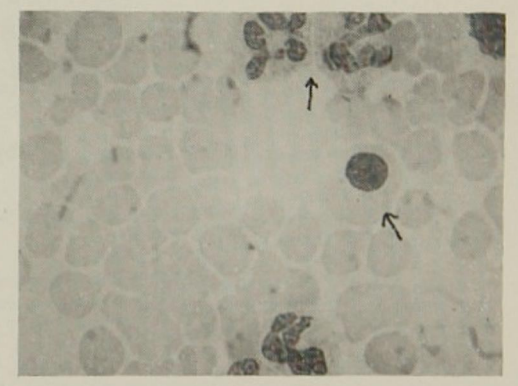


Figure 7h
48 hours after completion — macrocytic normoblast and hypersegmented granulocytes.

SUMMARY

Intra-arterial administration of alkylating agents and antimetabolites have become more practicable with the development of newer techniques and, in occasional instances, have produced effective palliative results. However, the toxicity from any of our currently available chemotherapeutic agents is still a significant hazard even from arterial administration techniques.

Perfusion of an isolated vascular area appears to be beneficial primarily in tumors in an extremity, though development of techniques for perfusion of other areas are in progress. However, this is primarily a surgical problem and we depend on our surgical colleagues for developments in this area.

The administration of amethopterin intra-arterially to 15 patients while simultaneously administering folinic acid has been of definite but limited value in 6 of 12 patients with carcinoma in the head or neck region, and 1 of 3 patients with pelvic carcinoma. No definite benefit was noted in patients with brain tumors. The toxicity

of such therapy is significant. Amethopterin infusion should be undertaken only in patients willing to accept a definite hazard. It must be stressed, however, that in many patients there is no other therapy available. If procedures such as those described here are undertaken with caution, some patients will obtain a degree of palliation not previously available to them.

ACKNOWLEDGMENTS

We wish to acknowledge and thank our surgical colleagues for the assistance and advice in the treatment of these patients, and especially for their skill in placement of catheters in the proper arteries. They are: Dr. E. Szilagyi, Dr. J. G. Whitcomb, Dr. R. F. Smith of Vascular Surgery, Dr. R. S. Knighton, Dr. A. B. Eisenbrey of Neuro-Surgery, and Dr. Paul Hodgkinson of Gynecology.

REFERENCES

1. Klopp, C. T.: Fractionated intra-arterial cancer chemotherapy with methyl bis amine hydrochloride; preliminary report, Ann. Surg. 132:811, 1950.

2. Creech, O., Jr.: Experience with isolation-perfusion techniques in the treatment of cancer, Ann. Surg. 149:627, 1959.

3. Conference on Cancer Chemotherapy by Regional Perfusion, Cancer Chemotherapy Reports, 10, Dec. 1960.

4. Sullivan, R. D., Miller, E., and Sikes, M. P.: Antimetabolite-metabolite combination cancer chemotherapy, Cancer 12:1248, 1959.

5. Austen, W. G., Monaco, A. P., Richards, G. S., Baker, W. H., Shaw, R. S., and Raker, J. W.: Treatment of malignant pelvic tumors by extracorporeal perfusion with chemotherapeutic agents, New England J. New England J. Med. 261:1037, 1959.

6. Stehlin, J. S., Jr., Clark, R. L., White, E. C., Smith, J. L., Jr., Griffin, A. C., Jesse, R. H., Jr., and Healey, J. E., Jr.: Regional chemotherapy for cancer; experiences with 116 perfusions, Ann. Surg. 151:605, 1960.

7. Tucker, J. L., and Talley, R. W.: Prolonged intra-arterial chemotherapy for inoperable cancer; a technique, Cancer (In press).

8. Reemstra, K.: Complications of perfusion, Cancer Chemotherapy Reports, 10, p. 75, Dec. 1960.

9. Vilter, R. W., Harrigan, D., Mueller, J. F., Jarrold, T., Vilter, C. F., Hawkins, V., and Seaman, A.: Studies on the relationships of vitamin B_{12}, folic acid, thymine, uracil, and methyl-group donors in pernicious anemia and related megaloblastic anemias, Blood 5:695, 1950.