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INTRA-ARTERIAL 5-BROMODEOXYURIDINE AND X-RAY THERAPY*

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IN SPITE of the substantial radiobiologic evidence for the efficacy of some halogenated pyrimidines as radiosensitizing agents, rigorous clinical confirmation of radiosensitization has not been achieved. Greer and Zamenhof[11,12] first demonstrated an increase in the sensitivity of *E. coli* to ultraviolet radiation following the incorporation of 5-bromouracil (BU) into the DNA of the organism. Djordjevic and Szybalski[5] observed an increase in sensitivity to both x-ray and ultraviolet irradiation when mammalian cells were pretreated *in vitro* with 5-bromo-2′-deoxyuridine (BUdR). Kaplan, Smith, and Tomlin[13] observed sensitization of bacteria to x-rays after BU incorporation. Increase in radiosensitivity of cells grown *in vitro* has also now been produced with 5-chlorodeoxyuridine (CUdR),[8] 5-bromodeoxycytidine (BCdR),[1,21] 5-iododeoxyuridine (IUdR) and 5-iododeoxycytidine (ICdR).[9] In all instances of radiosensitization by halogenated pyrimidines, the degree of radiosensitivity has been shown to be a function of the degree of replacement of the normal base, thymine in the DNA of the cells of the sensitized tissue by the halogenated analogue. Maruyama *et al.*[18] and Berry and Andrews[2] demonstrated radiosensitization *in vivo* when ascites tumor cells were pretreated with the halogenated nucleosides. A more comprehensive review has recently been prepared by Doggett *et al.*[6]

Limited clinical trials with BUdR and IUdR in combination with radiation have been reported. In an uncontrolled study, Krant *et al.*[14] treated 14 patients with intravenous BUdR and irradiation and thought that they observed some increase in radiation response, although Kriss and co-workers[15,16] observed rapid debromidation of BUdR after intravenous injection both in rats and in man. Kriss *et al.* have shown more recently mean body retention of 24 per cent and 31 per cent of 2-C^{14}-BUdR and 2-C^{14}-BCdR by monitoring the $C^{14}O_2$ expired by patients given 30 minute intravenous infusions of BUdR or BCdR with the C^{14} labeled tracer. It is reasonable to assume that the retained labeled thymidine analogue is incorporated into the DNA of any tissue actively synthesizing DNA at the time. This suggests that the enzymatic process by which the analogues are catabolized, leading to debromidation, is less capable of handling larger doses, thus permitting analogue incorporation into DNA.[17] Fletcher *et al.*[10] treated 4 patients with advanced head and neck cancer and intra-arterial infusions of BUdR (40–48 mg./kg.) for 4 days prior to the administration of irradiation by cobalt 60 teletherapy (2,000 rads total in two 1,000 rad doses 7 days apart). In 2 patients, DNA extracted from tumor biopsies was subjected to centrifugation in a cesium chloride gradient. No incorporation of the BUdR into tumor DNA could be demonstrated.

Since 1961, we have been investigating

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combination therapy using various chemotherapeutic agents intra-arterially for advanced cancer of the head and neck and pelvis.[7] In 1964, BUdR for human use was supplied to us by the Cancer Chemotherapy National Service Center. Five patients were treated in a pilot study to determine the feasibility of using this drug. The first 3 patients received intra-arterial BUdR (250–500 mg./catheter) in 30 minute pulses b.i.d. the 48 hours preceding each x-ray treatment (500 rads every 3–4 days for 5–6 weeks). This plan allowed at least 1 day post irradiation for recovery of DNA synthesis and mitotic activity. The 2 other patients were given BUdR continuously throughout their course of irradiation after an initial loading dose of BUdR for 4 days. There were no serious untoward reactions encountered in these 5 patients, although the 3 who received 30 minute pulses of up to 500 mg. complained of facial pain during the drug infusion. Because methotrexate blocks the *de novo* synthesis of thymidine, it was decided to administer methotrexate prior to the BUdR in an effort to enhance its incorporation into tumor cells. The final experimental protocol is presented below.

PROTOCOL

Patients with advanced untreated epidermoid carcinoma of the head and neck (T_3-N_1, N_2,-N_3,-M_0 or T_4, -N_0, -N_1, -N_2, -N_3, -M_0) or patients with either Stage III or IV carcinoma of the cervix are admitted to the radiotherapy cancer research unit. A pretreatment evaluation is initiated and includes a routine admission work-up, evaluation of hepatic function, extensive roentgen examination of the primary region and likely metastatic sites, electrocardiogram, electroencephalogram and bacterial cultures of the mouth, nose and throat. Each patient is then assigned to one of three treatment plans by the cast of a die. The three possibilities include:

(A) Intensive radiation therapy alone (6,000 rads in 6 weeks at 200 rads daily to the primary and all positive lymph node regions);

(B) Arterial infusion of methotrexate (25 mg./catheter/day, and citrovorum factor, 6 mg. intramuscular g 6 hr. for 2 weeks followed by irradiation as in option A);

(C) Pre-irradiation arterial infusion with methotrexate as in option B, followed by pre-irradiation arterial infusion of BUdR (500 mg./catheter/day plus 25 microcuries 2-C^{14}-BUdR per catheter/day) administered for 4 days at the conclusion of the methotrexate infusion (loading dose).

In group (C) after the loading dose of BUdR, the drug is continued at 250 mg./catheter/day throughout the course of x-ray therapy or until excessive local reaction or a significant catheter complication dictates its discontinuation. In each patient the position of the catheter is frequently verified by fluorescein injection and ultraviolet illumination. Biopsies are obtained of both the neoplastic and regionally infused normal tissues after the 4 day loading dose with tagged BUdR. The tissue is submitted for biochemical determination of the 2-C^{14}-BUdR incorporation in the DNA of the biopsy specimen. Additional biopsies are obtained for bromine activation analysis and for radioautography. Frequent clinical examination of the patient, serial blood counts, hepatic function tests, and serum bromide levels are carried out.

CLINICAL OBSERVATIONS

All patients treated with BUdR and x-ray, irrespective of the methotrexate pretreatment, displayed intense local reactions both in the tumor and in the normal mucosa sharply restricted to the infusion bed. The earliest changes are manifest by erythema of the infused tissue within the same field of irradiation. The erythema was most easily detected on the dorsal surface of the tongue by an early effacement of the hypertrophied papillae of the tongue (furry tongue) often seen in patients with

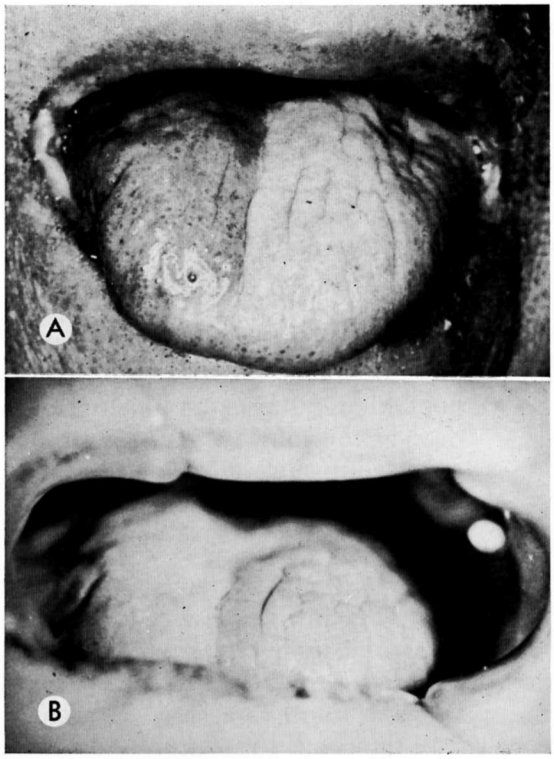

Fig. 1. (*A*) Early erythematous radiation reaction limited to right side of tongue after BUdR infusion into right carotid artery. Both sides of tongue received 1,000 rads. (*B*) Photograph exposed with ultraviolet light after fluorescein injection of right external carotid artery. Note limitation of fluorescence to right side of tongue.

advanced oral cancer. The hypertrophied papillae apparently desquamate, resulting in an atrophic, erythematous and somewhat painful mucosa (Fig. 1, *A* and *B*). Depapillation has also been observed with 6-mercaptopurine and seems distinctly different from the rather rapid development of the patchy membranous mucositis observed after intra-arterial methotrexate. Table 1 depicts the time course of the development of mucositis in the BUdR patients as compared to our previously reported series of patients treated with either methotrexate or 6-mercaptopurine administered concomitantly with x-ray. It is particularly notable that in the BUdR patients once mucositis developed it progressed rapidly through the patchy to the confluent stage. Asymmetric skin reactions were observed in 3 patients. In 2 a minimal increase in cutaneous erythema was noted within the radiation field on the infused side as compared to the contralateral skin which had received the same radiation dose. In 1 patient, however, this asymmetry of cutaneous reaction was particularly striking (Fig. 2, *A* and *B*). This patient received periodic irradiation at the rate of 500 rads skin dose every fourth day administered by opposed facial fields. At a skin dose of 5,500 rads, a

Table I

LOCAL MUCOSAL EFFECTS AND DOSE/TIME FACTORS IN PATIENTS RECEIVING CHEMICAL INFUSION AND X-RAY THERAPY FOR ADVANCED HEAD AND NECK TUMORS

Group	Pre 1964 MTX with X-ray (22 pt.)		Pre 1964 6-MP with X-ray (9 pt.)		A X-ray Alone (9 pt.)		Pilot BUdR with X-ray (5 pt.)		B MTX before X-ray*	C MTX before BUdR with X-ray (8 pt.)	
	Rads	Days	Rads	Days	Rads	Days	Rads	Days		Rads	Days
Onset Patchy Mucositis	1,700	13	2,430	20	3,200	23	2,320	18		2,230	17
Onset Confluent Mucositis	2,850	21	3,800	29	4,500	32	2,575	19		2,980	23
Average Total X-ray Dose and Treatment Time	6,310	46	6,510	43	6,360	45	5,900	47		6,340	57

* By chance, the number of patients allotted to Group B is as yet insufficient to be reported.

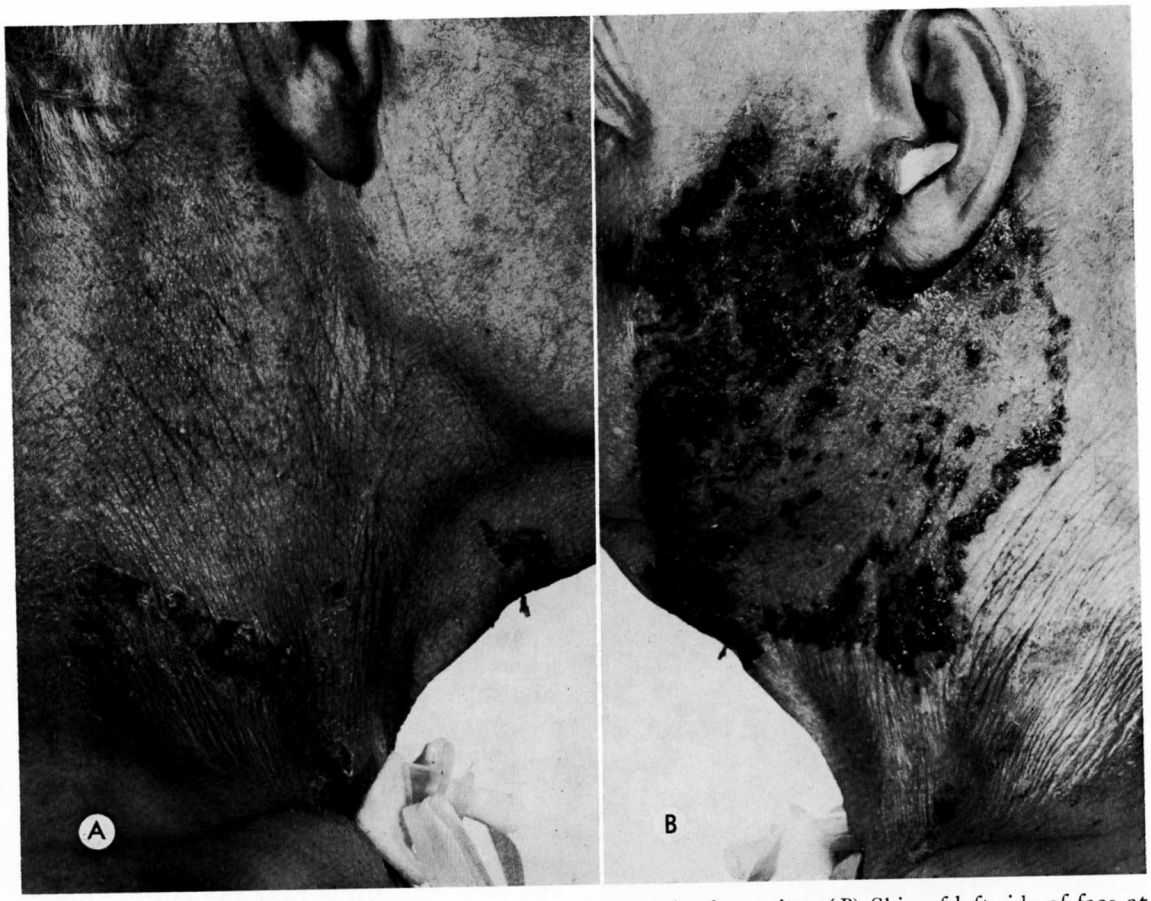

Fig. 2. (*A*) Skin of right side of face at 5,500 rads. Note minimal reaction. (*B*) Skin of left side of face at same radiation dose but with concomitant BUdR infusion. Note moist radioepidermatitis.

confluent moist radioepidermatitis appeared on the infused side whereas only minimal erythema of the contralateral skin was observed. Figure 3 demonstrates complete healing of the radioepidermatitis after 1 month. Epilation occurs consistently in the anatomic area of distribution of the infused external carotid artery. It was noted after about 3 weeks of BUdR infusion and is only temporary. Fletcher *et al.* observed alopecia in 1 of the 4 patients treated with intra-arterial BUdR and it was a consistent finding in the patients who received intravenous IUdR reported by Calabresi *et al.*[4]

A finding which we have not seen reported is the development of transverse furrows in the fingernails (Beau's lines). In contrast to the intravenous IUdR, we have not observed significant bone marrow depression (Table II). Peripheral white blood cell depression (as low as 3,000 white blood cells/cubic millimeter) occurred but this has been observed frequently in patients treated with x-ray alone. Similarly, the incidence of hepatic toxicity as manifest by at least two abnormal liver function tests other than bromsulphalein has been observed infrequently in contrast to our previous observations with methotrexate.

BIOCHEMICAL STUDIES

Biopsies of normal and neoplastic tissue were obtained from patients who had received BUdR labeled with C^{14} in the two position of the pyrimidine ring. One-hundred microcuries were mixed with the cold BUdR during the 4 day period of drug administration prior to the initiation of

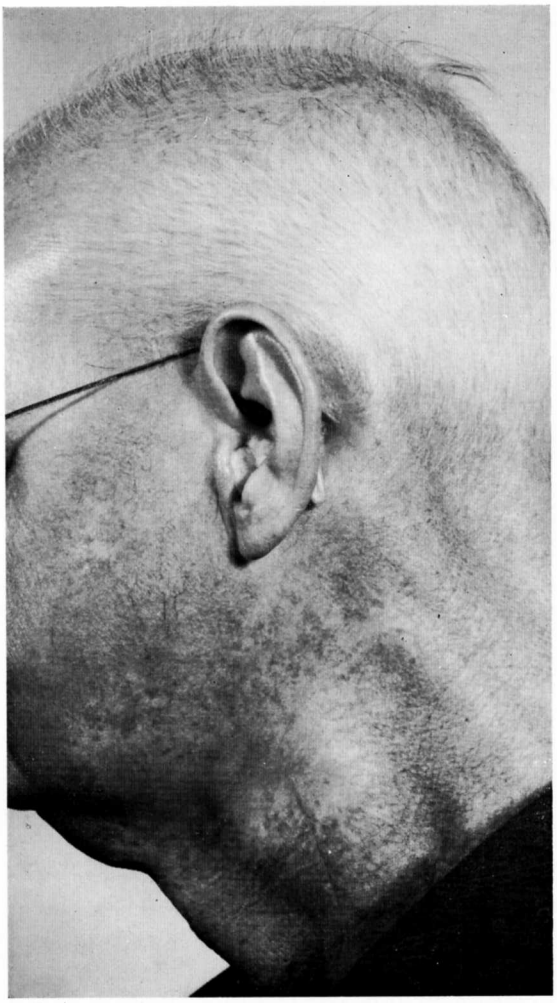

FIG. 3. Same patient as illustrated in Figure 2*B* but 1 month later, showing complete healing of the radioepidermatitis.

radiation therapy (loading dose). The biopsies were obtained at the conclusion of the loading dose and in 1 instance a second tracer dose of C^{14}-BUdR was administered after 1 month of therapy. In 5 patients, it was possible to determine the total radioactivity in the DNA of the specimen by the following method:

Total Radioactivity of Biopsy. Approximately 0.1 gm. of weighed tissue was extracted in 1 ml. of 0.5 *N* perchloric acid at 80°C. for 60 minutes. The solution was cooled, centrifuged to remove protein and a 0.5 ml. aliquot of the supernatant (containing the hydrolyzed nucleic acids) was counted in a liquid scintillation counter. A value for the μM of BUdR incorporated per gram of tissue was calculated (Table III) from the counts per gram of tissue and the specific activity of injected BUdR.

This determination indicates only the presence of C^{14} in the DNA of the biopsy and does not prove that the label is incorporated as BU. In general, sample sizes were too small to permit separation of the bases and positive identification of bro-

TABLE II

SYSTEMIC TOXICITY OF INTRA-ARTERIAL CHEMICAL AND X-RAY THERAPY OF PATIENTS WITH ADVANCED HEAD AND NECK CANCER

	MTX and X-ray (22 pt.)	X-ray Alone (9 pt.)	BUdR and X-ray (5 pt.)	MTX before BUdR and X-ray (8 pt.)
White Blood Cell Count				
3,000–4,000	12	4	4	4
2,000–3,000	8	—	2	2
under 2,000	—	—	—	—
Platelet Count				
100,000–150,000	7	1	1	—
50,000–100,000	2	1	—	—
under 50,000	—	—	—	—
Hematocrit				
under 30%	9	1	3	3
Hepatic Toxicity	11	—	2	4

Table III

Patient	Source of Sample	μM BUdR/gm. Tissue	Per Cent Thymine Replacement
B.S.	Tumor	0.145	4.9
A.C.	Tumor after BUdR alone	0.084	
	After FUdR+BUdR	0.129	
	A. Tumor after four 30 minute pulses of BUdR 12 hours apart (5 different samples from biopsy)	0.046	
P.C.	B. Tumor (second specimen obtained 96 hours after A)	0.032	
	C. Tumor (third specimen 1 month after continuous BUdR and X-ray therapy)	0.013	
E.S.	Tumor (multiple biopsies)		
	anterior	0.028	
	posterior	0.045	
	superior	0.025	
	inferior	0.024	
	center	0.034	
		0.031 Average	
L.L.	Normal tissue in infusion bed (histologically this proved to be mostly scar)	0.037	
	Tumor (multiple biopsies)	1. 0.134	
		2. 0.108	
		3. 0.131	
		0.124 Average	
H.S.	Tumor	*0.25	
J.L.	Tumor	*1.0	

* The BUdR concentrations were calculated from the amount of tissue bromine which was determined by neutron activation analysis. The neutron activation analyses were performed through the courtesy of W. F. Bethard, M.D., General Atomic, San Diego, California. The unfixed biopsy specimens were irradiated in a Triga reactor. They were allowed to set for 6 days to permit decay of Na^{24} and Cl^{38} and then counted in a gamma-ray spectrometer.

mouracil. In 1 patient, however, sufficient DNA was recovered to permit base analysis by the following procedure:

Per Cent Replacement of Thymine by Bromouracil. DNA was isolated from about 0.5 gm. of tissue using a detergent extraction procedure. The DNA was hydrolyzed in trifluoroacetic acid and the resultant bases separated by two-dimensional paper chromatography. The amount of thymine present was determined by optical density measurements. The amount of bromouracil was determined by the amount of radioactivity in the bromouracil spot. From these data the per cent replacement of thymine by bromouracil was calculated.

The results are tabulated in Table III. In the patient, B. S. in whom BUdR was identified, 0.145 micromoles of BUdR per gram of tissue represented 4.9 per cent thymidine replacement. In this patient, rapid regression of neoplasm was noted as well as the striking depapillation of the infused half of the tongue (Fig. 1*B*). The neoplasm recurred within 2 months and a subsequent radium implantation failed to control its progress. The patient died with persistent tumor. If one assumes that the micromoles of BUdR per gram of tissue represent thymidine replacement as was

proven for B. S., then several pertinent observations are possible. For example, in patient A. C., 0.084 micrograms BUdR per gram of tissue was recovered after the initial BUdR (20 mg. over 8 hours) loading dose. A second loading dose of BUdR was administered following 5-fluorodeoxyuridine (FUdR). The FUdR was added in order to enhance the BUdR uptake. The total uptake increased to 0.129 micrograms BUdR per gram of tissue, 0.045 micrograms more than noted after the administration of BUdR alone. The net increase in incorporation, however, was less than the initial incorporation of BUdR without FUdR. In patient P. C., a relative decrease in the uptake of BUdR was noted as the patient progressed through the course of therapy. In patient E. S., multiple biopsies were analyzed in order to determine the homogeneity of uptake in the tumor. The values ranged from 0.028 to 0.045. This variation probably reflects inhomogeneities within the vascular bed of the neoplasm. In one patient (L. L.) there was 0.037 micrograms BUdR per gram of mucosa, whereas 3 biopsies from the adjacent neoplasm showed an average of 0.124 micrograms of BUdR per gram, suggesting that the neoplasm incorporated at least twice as much BUdR as the normal mucosa. The limited incorporation of BUdR in the mucosa, however, may have reflected only the large amount of fibrosis which is seen histologically rather than true epithelial incorporation.

In 2 patients, the actual bromine concentration in the tumor was determined by neutron activation analysis and the values were substantially higher than obtained by the tracer technique in other tumors. The activation analysis, however, was performed on raw tissue and the value for bromine represents bromine not only present in the DNA but also present in intra- and extra-cellular fluid compartments. We are now preparing specimens of DNA extracted from the neoplastic and normal tissue for activation analysis.

Although autoradiograms were prepared in each patient, detection of incorporation by this method was uniformly unsuccessful even after many weeks of exposure.

BLOOD BROMIDE LEVELS

Weekly determinations of the serum bromide were performed in all patients. The results were so variable that a clear relationship between BUdR dosage and serum bromide levels was not demonstrated. In some patients, the level rose to between 20 and 32 mg. per cent by about the twelfth day of the infusion and seemed to plateau. In 1 patient, a maximum of 48 mg. per cent was noted. Clinical evidence of toxicity was difficult to assess. In 3 patients, a definite daytime somnolence was observed, however, in each instance the patients were in the midst of distressing mucosal reactions which interfered with their nutrition and their normal sleep cycle and required the administration of anodynes. In several patients, serial electroencephalograms were characterized by diffuse slow wave activity which occurred after the BUdR administration.

TUMOR CONTROL

Although early regression of the neoplasm was observed, the intense mucosal reaction tended to interfere with the planned therapy to the extent that irradiation of the neoplasm might have been compromised. The clinical status of the patients is presented in Table IV. It is impossible to detect a significant difference in survival between the control and experimental groups.

DISCUSSION AND CONCLUSIONS

In the patients who received intra-arterial BUdR, early reaction in both the neoplasm and the mucosa was consistent with the results of combined radiation and BUdR treatment reported by Fletcher *et al.*[10] Contrary to their experience, we were able to demonstrate 4.9 per cent thymidine replacement by BUdR in the DNA extracted from infused neoplastic tissue in 1 instance. Early tumor response was some-

Table IV

RESULTS OF LINEAR ACCELERATOR IRRADIATION OF PATIENTS WITH ADVANCED HEAD AND NECK CANCER WITH AND WITHOUT INTRA-ARTERIAL CHEMICAL INFUSION

	X-ray Alone (9 pt.)			BUdR and MTX-BUdR (12 pt.)		
			Total			Total
Interval Since Treatment Began (mo.)	less than 12	12–24		less than 12	12–24	
Alive without Disease	1*	4	5	4		4
Alive with Disease		1	1	5		5
Dead with Disease		3	3		3	3

* Recurrence excised.

times evident along with increased cutaneous reaction, as observed by Calabresi[3] in patients receiving intravenous IUdR plus irradiation.

Clinically, useful radiosensitization with a pyrimidine analogue appears to depend upon (1) the achievement of preferential uptake of the BUdR into the DNA of the neoplastic cells, and (2) incorporation of the analogue into all of the cells of the neoplasm. Reliance upon a supposed difference in mitotic activities between normal and neoplastic tissue for achieving a differential uptake appears inadequate. In fact, the relative rates of cellular proliferation between normal and neoplastic tissue are not clearly defined. Mendelsohn,[19,20] for example, has shown that a substantial proportion of cells in murine mammary tumors are not proliferating rapidly. In normal mucosa, proliferation of the cells of the basal layer may be more orderly and occur at a more rapid rate than cells of the neoplastic counterpart. This relationship might favor analogue incorporation into normal epithelium, accounting for the intense mucosal reactions observed in this series.

Woodman[23] has recently reported achieving a favorable differential uptake of iodine in neoplastic versus normal tissues exposed to IUdR which has been complexed with the polycation, polyethylene imine. He suggests that if tumor cells have a higher anionic surface charge or the duration of the hyperanionic state is longer, then polycation complexing of the analogues might permit a preferential absorption of the pyrimidine radiosensitizers into neoplastic cells.

Suit[22] has pointed out that the ultimate radiosensitivity of a sensitized neoplasm is largely determined by that fraction of cells which does not incorporate the radiosensitizers. Methods of achieving incorporation which rely solely upon semi-conservative DNA synthesis in the normal course of cell division may never achieve sensitization of all of the cells. Other routes for the introduction of pyrimidine analogues into the DNA of neoplastic cells such as incorporation during repair of DNA injury or the use of polycation complexes as mentioned above should be investigated.

Thus despite the clinical evidence for radiosensitization of neoplastic and normal tissues alike noted in this small series, a method for achievement of differential radiosensitization of carcinoma in man with the pyrimidine analogues remains elusive.

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