[CANCER RESEARCH 36, 216–221, January 1976]

Clinical Effects and Pharmacokinetics of Different Dosage Schedules of Adriamycin[1]

William A. Creasey,[2] L. Sue McIntosh, Thomas Brescia, Oluwole Odujinrin, Gregg T. Aspnes, Ethelann Murray, and John C. Marsh[3]

Departments of Internal Medicine and Pharmacology [W. A. C., T. B., O. O., E. M., J. C. M.] and Pediatrics [L. S. M., G. T. A.], Yale University School of Medicine, New Haven, Connecticut 06510

SUMMARY

Adriamycin was administered to 60 adults and 21 children by 3 different dosage schedules: 22.5 mg/sq m (0.6 mg/kg) daily for 4 days, 15 mg/sq m (0.4 mg/kg) every 8 hr for a total of 6 doses, and 50 to 120 mg/sq m as a single dose every 3 to 4 weeks. Objective responses lasting more than 1 month occurred in 5 subjects with acute leukemias or lymphoma, 3 with transitional cell carcinomas, 2 with sarcomas, 2 with Ewing's sarcoma and 1 each with bronchogenic carcinoma, orchidoblastoma, and thymoma. Toxic reactions included nausea, vomiting, stomatitis, alopecia, and hematopoietic depression, but significant cardiac toxicity occurred in only 1 patient. Pharmacokinetic data, collected in 25 patients by fluorometric and chromatographic assay, suggested a biphasic plasma clearance of drug with initial and secondary half-lives of about 1.5 and 14 to 21 hr, respectively. When drug was given every 8 hr there was evidence of loss of an initial very rapid phase of distribution of adriamycin and its metabolites. Urinary excretion accounted for 3.4 to 38.1% of administered fluorescence over a 72-hr period; in the first 24 hr, between 48.2 and 100% of this urinary material was in the form of adriamycin; later, this fraction declined. No adriamycin or its fluorescent metabolites could be extracted from the stools.

INTRODUCTION

Adriamycin is a glycosidic antibiotic of the anthracycline group isolated from cultures of *Streptomyces peucetius* var. *caesius*. It is closely related to daunorubicin from which it differs only in having a hydroxyl substituent on C-14. The therapeutic index of adriamycin is superior to that of daunorubicin (12, 23), however, and this finding has led to extensive clinical trials with the resulting demonstration of a wide spectrum of anticancer activity (10, 18, 25). Much of the available clinical data has been summarized recently (9), and a clinicopathological analysis of the cardiotoxicity has appeared (15).

In view of the clinical importance of this new agent with broad activity against solid tumors and the desirability of using pharmacological data in devising dosage schedules, more knowledge of the clinical pharmacology of adriamycin is needed. This study was undertaken to provide more data on both the clinical effects and the human pharmacokinetics of several different dosage schedules. A preliminary account of our clinical findings has been published (20).

MATERIALS AND METHODS

Patient Selection and Evaluation. These studies were undertaken in 60 adult and 21 pediatric patients with advanced neoplastic disease (Table 1). Patients were hospitalized for study and treatment in the Clinical Pharmacology and Oncology and Pediatric Research Units of the Yale-New Haven Medical Center, and written informed consent was obtained. Three major dosage schedules were used: single doses, 22.5 mg/sq m daily for 4 days, and 15 mg/sq m every 8 hr for a total of 6 doses. These courses were repeated as shown in Table 1. In no case did the maximal cumulative dose of drug given to an adult exceed 450 mg/sq m. One of the pediatric patients received 715 mg/sq m. Pretreatment assessments of the extent of disease were made by physical examination, X-ray, peripheral blood and bone marrow findings, and multiple studies of liver and renal function. Careful observations were made for symptoms and signs of drug toxicity as well as for antineoplastic effects. Serial hematological, hepatic and renal function studies, and electrocardiograms were performed as indicated, and routine blood and urine chemistries were determined. Blood samples obtained for drug assay by venipuncture were collected in heparinized Vacutainers.

Processing of Blood and Urine Samples. Blood samples (10 to 30 ml) and total urine outputs were obtained; plasma was separated by centrifugation for 10 min at 1600 × *g*. Samples of the plasma were brought to pH 9 with NaOH and shaken with 0.7 volume of water-saturated 1-butanol, which produced an emulsion; this was broken by freezing, thawing, and centrifuging the mixture, after which the 1-butanol layer was taken for assay. Urine was treated similarly, except that 0.3 volume of 1-butanol was used for samples to be subjected to thin-layer chromatography, and 2 volumes of the alcohol were used for those in which total fluores-

[1] Supported by Grants CA 5138, CA 08341, and CA 12317 of the USPHS and Grant ACS DI 10 H of the American Cancer Society.

[2] To whom requests for reprints should be addressed, at the Yale University School of Medicine, 333 Cedar St., New Haven, Conn. 06510.

[3] Faculty Research Associate of the American Cancer Society.

Received January 17, 1975; accepted October 7, 1975.

Table 1
Disease categories and therapeutic responses in patients treated with adriamycin

Tumor types	No. of patients treated	No. of patients evaluable	No. of courses: Daily for 4 days	No. of courses: Every 8 hr for 6 doses	No. of courses: Single dose	Response category[a]: 0-0	0-A	0-C	I-A	I-C	II
Adults											
Acute lymphoblastic leukemia	4	4	8	1		2			2 (3, 2)[b]		
Acute nonlymphoblastic leukemia	2	2	1	3		2					
Hodgkin's disease	2	2	2		1			1	1 (2)		
Non-Hodgkin's lymphoma	2	1	1	3	1						
Transitional cell carcinoma of urinary tract	13	12	25	3	19	4	5		2 (9, 1+)	1 (24+)	
Osteogenic sarcoma	2	2	4		1		1	1			
Ewing's sarcoma	2	2	8			1			1 (9)		
Fibrosarcoma	2	2	8		2		1		1 (6)		
Liposarcoma	2	1		2	3	1					
Leiomyosarcoma	5	3	1		12	3					
Rhabdomyosarcoma	1	1			1	1					
Myxosarcoma	1				6						
Chondrosarcoma	1	1			2	1					
Breast carcinoma	5	5			14	4	1				
Hepatoma	1	1			4		1				
Thyroid carcinoma	1	1			1	1					
Epidermoid carcinoma of head and neck	2	1			4	1					
Bronchogenic carcinoma	4	4			15	2			1 (2)		1
Alveolar cell carcinoma	1	1	3				1				
Ovarian carcinoma	1	1			1	1					
Thymoma	1	1		2					1 (1.5)		
Testicular carcinoma (mixed)	1		1								
Melanoma	1	1		2		1					
Unknown primary	2	2	4			2					
Liver "spindle cell" sarcoma	1	1		6					1 (7)		
Adult total	60	52	66	22	87	27	10	2	10	1	1
Children											
Acute leukemia	16	11		1	16	7			4 (1.5, 1.5, 1+, 1+)		
Non-Hodgkin's lymphoma	2	2		1	1	2					
Orchidoblastoma	1	1		2	10				1 (3)		
Ewing's sarcoma	1	1		2	2				1 (6)		
Neuroblastoma	1	1			2		1				
Children total	21	16		6	31	9	1		6		

[a] From Karnofsky (13): 0-0, disease progresses without subjective or objective benefit; 0-A, subjective benefit without favorable objective changes; 0-C, subjective benefit and favorable objective changes of less than 1 month duration; I-A, subjective benefit and favorable objective changes for more than 1 month; I-C, subjective benefit and favorable objective changes for more than 12 months; II, interruption or slowing in the progression of the disease without definite evidence of subjective or objective improvement.
[b] Numbers in parentheses, duration of response in months.

cence was to be measured. In this case the butanol layer was dried over anhydrous sodium sulfate. In our hands, extraction at pH 8 to 9 gave better recovery of adriamycin (range of 5 experiments, 84.5 to 94.4%) than when the aqueous phase was neutral, as in earlier studies with this drug (22) and daunorubicin (5). Extraction under mild alkaline conditions has also been used for daunorubicin (3). In all procedures subdued lighting (or darkness) was used where possible because of the photosensitivity of the drug in solution.

Estimation of Urinary Fluorescence. This was carried out with an Aminco-Bowman spectrofluorometer. The activation wavelength was 485 nm, and readings of the emission were made at 500 and 570 nm. Adriamycin does not fluoresce at 500 nm, but this reading was used to help correct for endogenous fluorescent material in the urines, where the ratio of emissions at 570 and 500 nm was relatively constant in any given subject. The lower limit of detection was 0.002 μg of adriamycin equivalents per ml. In some cases plasma fluorescence was also estimated in the same manner, but for most samples the following method was used.

Estimation of Plasma Fluorescence. Samples of the 1-butanol extracts were applied to 0.5-mm layers of Silica Gel

H (Merck & Co., Rahway, N. J.) on 20- x 20-cm glass plates. Extracts of control plasma to which various levels of adriamycin had been added were used as standards. The plates were scanned with the Camag TLC scanning accessory attached to a Turner Model 111 fluorometer provided with a Beckman 10-inch recorder. A sharp-cut No. 16 filter was used for the emission and a No. 48 filter was used for activation of the sample. Peak sizes were measured by cutting and weighing the areas under the curves traced on the paper. The lower limit of detection was 0.03 μg/ml by this method.

Chromatography. Urinary extracts in 1-butanol were applied to thin-layer plates coated with Silica Gel H (0.5 mm). These plates, and those previously scanned for plasma fluorescence, were then subjected to ascending chromatography with chloroform:methanol:acetic acid (80:20:4, v/v) as the solvent system. The major spot, ascribable to adriamycin, had an R_F value of 0.19 under these conditions. Two other materials with the same characteristic fluorescence as adriamycin were found in essentially all chromatograms; 1 remained at the origin while the other had an R_F value of 0.08. In addition, a further fluorescent area (R_F 0.30) was present on a significant proportion of the plates. This represents inadequately extracted nonpolar material. No attempt was made to identify these metabolites. The amounts of adriamycin and its metabolites were measured by scanning, as described for plasma fluorescence. However, in samples where greater amounts of fluorescent material were present, spots were also scraped off and eluted with butanol. Results obtained by reading the fluorescence of these extracts were in agreement with those obtained by direct scanning. When pure adriamycin samples were run through this procedure, there appeared to be no significant breakdown, since a mean of 98% was recovered as 1 spot.

RESULTS

Clinical Response. During a 3-year period, 60 adults were treated with 174 courses of adriamycin in 3 different dose schedules: 0.6 mg/kg (22.5 mg/sq m) daily for 4 days (66 courses), 0.4 mg/kg (15 mg/sq m) every 8 hr for 6 doses (22 courses), and 60 to 75 mg/sq m as a single dose every 3 to 4 weeks (87 courses). Doses were modified in the presence of preexisting marrow depression by disease or prior treatment or because of severe toxicity from a previous dose. During the latter part of the study, virtually all patients were treated with the single-dose regimen because of its convenience for outpatient therapy and reports of the effectiveness of this schedule (8, 14, 19).

Of the 60 adults treated, 52 (87%) were evaluable for therapeutic response (Table 1). Twenty-six received the single-dose schedule, 19 the daily dose, and 7 received the every 8-hr treatment. Five of the nonevaluable patients died within 2 weeks; 3 others had no measurable disease when therapy was started, 1 of whom had known disease after partial surgical excision. Virtually all patients had had prior chemotherapy except those with sarcomas and transitional cell carcinomas of the urinary tract.

Objective responses lasting more than 1 month were observed in 11 patients: 3 with acute leukemias or lymphoma; 3 with transitional cell carcinomas; 2 with sarcomas; and 1 each with Ewing's sarcoma, bronchogenic carcinoma, and thymoma. Brief objective remissions were seen in 1 patient each with Hodgkin's disease and osteogenic sarcoma. Of the 11 patients responding for more than 1 month, 8 were treated with the 4-day schedule, 1 was treated with the every-8-hr schedule, and 2 were treated with single-dose schedule. The best response was in a patient with transitional cell carcinoma of the renal pelvis who continues to be in remission 2 years after cessation of 10 courses of adriamycin; this patient has been reported elsewhere in detail (16). Twenty patients received only 1 course of adriamycin; 9 of these died within 1 month after administration of the drug.

Among children with acute lymphoblastic or acute undifferentiated leukemia, 16 were given adriamycin, 50 to 120 mg/sq m, in a single dose. Two children receiving 90 to 120 mg/sq m achieved complete hematological remission that lasted 6 weeks. Of 9 receiving 50 to 80 mg/sq m who were evaluable, 2 obtained a I-A Karnofsky response, and 7 failed to show improvement. Five additional patients developed fatal septicemia within 2 weeks without dramatic hematological improvement and were classed as nonevaluable.

Nonhematological Toxicity. Nonhematological effects of the drug in adults included nausea, vomiting, stomatitis, alopecia, and passage of "red urine" (due to coloration by drug and metabolites). No definite renal or hepatic toxicity due to the drug was observed. No episodes of congestive heart failure occurred. Administration of the drug was stopped after 10 courses in the patient with the best response because of frequent premature contractions and subsequent chest pain when a total dose of 450 mg/sq m had been reached.

As in adults, clinical toxicity among pediatric patients was manifested by alopecia, nausea, vomiting, and nasal and oral mucosal ulceration. No clinical or laboratory evidence was found for renal or hepatic toxicity, but 1 boy developed acute angioneurotic edema after a total dose of 715 mg/sq m.

Hematological Toxicity. In nonleukemic adults, 112 courses were evaluable totally or in part for hematological effects, in that blood counts were obtained 9 to 15 days after drug administration (Table 2). No differences between courses were evident for erythroid toxicity. The daily and single-dose schedule appeared to be more toxic for platelets than the every-8-hr schedule. There were no known deaths from drug-induced thrombocytopenia and hemorrhage. Granulocyte toxicity was more severe with the 2 multiple-dose schedules, perhaps reflecting either the higher total dose (90 mg/sq m) in most of the multiple courses, as compared to the single-dose regimen, or possible buildup in blood and tissue levels of drug. However, since most subjects did not receive drug by all the schedules, adequate internal controls were lacking. Seven patients received the drug in different dose schedules at different times. Comparable granulocyte toxicity was seen in 1 patient who received 50 mg/day for 4 days or 150 mg as a single dose. Another patient received 25 mg/day for 4 days for 2 courses and 100 mg as a single dose; the neutropenia was slightly more pronounced in the latter instance. At least 1 patient died of sepsis in association with drug-induced

Table 2
Hematological toxicity from adriamycin manifested in 50 adult patients with solid tumors

Dose schedule	Toxicity expressed as % of total courses evaluable				
	Hematocrit drop more than 5 vol % below initial value	Granulocyte nadir (cu mm)		Platelet nadir (cu mm)	
		<1000	<500	<100,000	<50,000
Daily for 4 days (41 courses; 90 mg/sq m)	28	53	33	23	15
Every 8 hr for 6 doses (9 courses; 90 mg/sq m)	33	55	22	11	0
Single dose (62 courses; 60–75 mg/sq m)	28	25	13	23	10

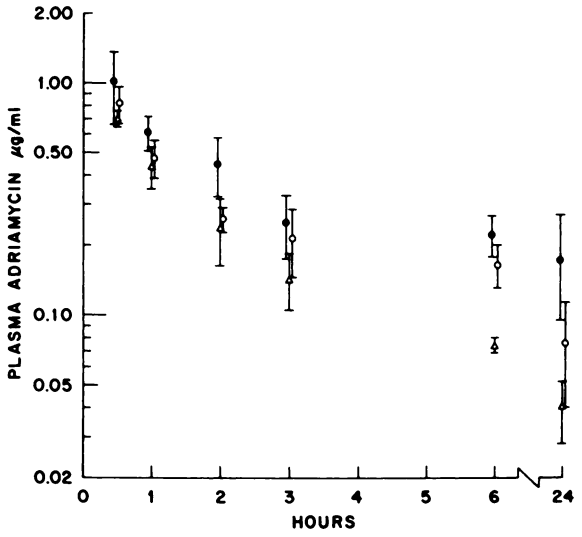

Chart 1. Plasma concentrations of adriamycin after 1 dose of drug at 90 mg/sq m (●, 7 patients), 50 and 60 mg/sq m (○, 6 patients), and 22.5 mg/sq m in the daily schedule (△, 5 patients). Data are expressed as means ± S.E. (*bars*).

neutropenia. Eight patients died 9 to 17 days after drug administration, and some of these may well have had fatal infection secondary to drug-induced granulocytopenia.

Metabolism of Adriamycin. For metabolic studies, the drug was administered to adults and children by 3 major dosage schedules, that is, 90 and 50 or 60 mg/sq m as single doses, 90 mg/sq m in 4 divided daily doses (22.5-mg/sq m/dose), and 90 mg/sq m in 6 individual doses at 8-hr intervals (15-mg/sq m/dose). Data for the first 2 schedules are collected and summarized in Chart 1, which gives the mean plasma adriamycin levels with their standard errors. Too few points were collected for detailed pharmacokinetic analysis, but the decline between 0.5 and 2 hr was suggestive of an initial rapid clearance with a half-life of about 1.5 hr, close to the value of 1.1 obtained by Benjamin *et al.* (7). The secondary half-life from Chart 1 was estimated to be in the range of 14 to 21 hr, compared with 16.7 hr for the study mentioned above (7). One major purpose of studying blood levels during the 6-divided-dose schedule was to see whether drug accumulated over the course of treatment. Accordingly, levels of adriamycin plus metabolites were compared after the 1st and 6th doses. It is evident from Chart 2 that concentrations of total fluorescent material were generally higher after the last dose. This apparently results from the absence from the 6th-dose curve of the initial very rapid phase of distribution seen after the 1st dose, presumably because the preceding 5 doses served to saturate the tissues responsible for this uptake phase.

Urinary excretion was studied for periods of up to 120 hr, and in several patients stools were collected for 6 days. The data for urinary excretion indicate that 3.4 to 38.1% of the administered fluorescent drug was found in the urine over a 72-hr period, with most values falling in the lower portion of the range. The mean values with respect to dosage regimen were: single doses, 12.0%; every 24 hr, 10.7%; every 8 hr, 13.9%. In all the patients except 1, adriamycin was the major urinary excretion product, in contrast to the situation seen with the related daunorubicin (2). However, adriamycin is extensively metabolized. The percentage of urinary fluorescence in the form of adriamycin varied from 48.2 to 100 in the 0- to 24-hr fraction, 21.6 to 99.6 in the 24- to 48-hr sample, and 12.2 to 81.8 in the 48- to 72-hr collection. Our attempts to assay adriamycin fluorescence in the stools were unsuccessful. Neither by extraction and fluorescence assay

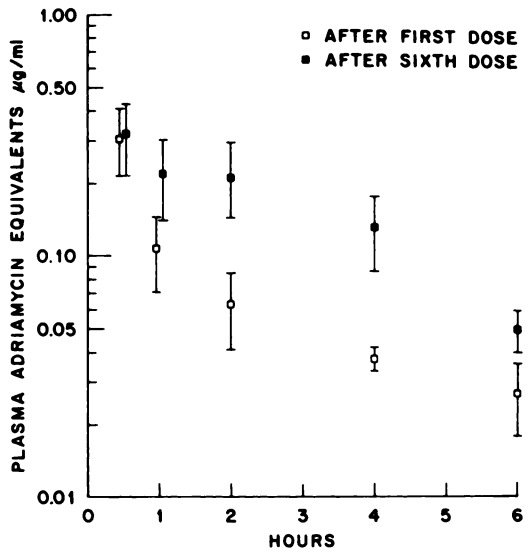

Chart 2. Plasma concentrations of adriamycin and its metabolites after the 1st (□) and 6th (■) doses of an every-8-hr schedule (6 patients, 15 mg/sq m). Data are expressed as means ± S.E. (*bars*).

nor by chromatography was any evidence of the drug or its metabolites obtained. The high background fluorescence and relatively low recovery of adriamycin from stool homogenates (around 60%) may contribute to this negative finding.

DISCUSSION

The clinical data obtained in this project serve to expand upon the already large body of results showing favorable responses in a wide range of neoplastic diseases. Acute lymphoblastic leukemias, transitional cell carcinomas of the urinary tract, and Ewing's sarcoma were the most sensitive tumors, with responses also occurring in patients with sarcomas, orchidoblastoma, and thymoma. Such a spectrum of activity is similar to that reported by other investigators (9, 10, 18, 21, 25, 26). In adults, responses of the I-A or I-C category of Karnofsky were seen more frequently during treatment by the 4-daily-dose schedule. This could reflect the higher total doses often given by this schedule as compared to single dosage, some selectivity in the sensitivity of the tumors treated, or possible accumulation of drug. Most of the children received single-dose therapy so that comparison of efficacy of regimens is not possible.Toxicity was of the type described previously, but significant cardiotoxicity occurred in only 1 subject with transitional cell carcinoma of the renal pelvis, who received a large total dose (450 mg/sq m).

This study presents additional pharmacological data for several dosage schedules. Benjamin *et al.* (7) used single doses of 60 mg/sq m, and Rosso *et al.* (22) used 0.4 mg/kg, which is approximately equivalent to 15 mg/sq m. We have studied single doses at 50 to 90 mg/sq m, 15 mg/sq m every 8 hr for 6 doses, and 22.5 mg/sq m daily for 4 days. Points of agreement emerge with the study of Benjamin *et al.* (7). Notably, these are the similar estimates of plasma half-lives, and the finding that there is very significant metabolism of adriamycin in man, in clear disagreement with the earlier report that metabolism of adriamycin does not occur (22). The explanation for this discrepancy may be the relatively poor extraction of adriamycin and its metabolites by 1-butanol at acidic or neutral pH, compared with our alkaline extraction and with the ethanol-HCl procedures of Benjamin (7) and Chan and Harris (11) and the method of Schwartz (24). However, the rather erratic presence of nonpolar metabolite in our samples compared with the findings of Chan and Harris (11) suggests that extraction of metabolites may be incomplete.

Several new findings have also emerged from this study. It would appear that closely spaced schedules such as the 8-hr treatments might have the potential for causing greater toxicity than widely spaced doses. This follows from the saturation of tissue-binding or distribution processes leading to somewhat higher plasma drug levels over the course of the 6 doses. Certainly, the overall granulocyte toxicity was greater with the 2 multiple-dose schedules, which would be expected if such a buildup were to occur. In addition, objective responses classified as I-A or I-C by Karnofsky (Ref. 13; Table 1) were seen more frequently during treatment by the 4-daily-dose schedule. It is unlikely that these findings result only from the somewhat lower total dosages sometimes given on the single-dose schedule. Whether the every-8-hr type of divided-dose schedule would also modify toxicity through an effect on metabolism cannot be decided on the basis of this work. In 1 of the 2 patients who received both single and multiple doses, the urinary excretion data did not indicate any greater metabolism of drug by the divided-dose schedule except at very late times (6.9% *versus* 51.4% unchanged drug in 48- to 72-hr urine). On the other hand, there were clearly greater amounts of metabolites in the urine of another subject while on this schedule (27.4 to 54.2% compared with 57.9 to 88.2% adriamycin on single dosage). It has been claimed that metabolites of daunorubicin and adriamycin, notably aglycones, may exert greater cardiotoxicity than the parent drugs (17). Conversely, toxicity has been ascribed to the daunosamine moiety by analogy with the greater effectiveness of the digitalis glycosides as compared with their aglycones (1). If either of these hypotheses is true, modification of the metabolic pattern by changes in the schedule of administration could be a major factor in determining the amount of toxicity produced.

Although it has been reported that biliary excretion of adriamycin occurs (4, 6), we have been unable to detect fluorescence of the type ascribable to adriamycin or its metabolites in the stools. This could result from extensive metabolism of the molecule by the intestinal flora, poor recovery of drug and metabolites from the stools, or efficient reabsorption from the intestine during a process of enterohepatic circulation. Although it cannot be ruled out that major changes in the ring structure of the antibiotic may occur, thus eliminating the characteristic fluorescence, it would seem unlikely that this process would be so complete that other metabolites would not be found. Reabsorption, with some contribution from degradation, appears most likely, leading to a very low concentration of metabolites that might be difficult to detect against the high and variable fluorescent background of the stools.

In view of the long-term retention of this agent in the body and the failure to account for the total administered drug, it is obviously important to undertake further more intensive studies on the clinical pharmacology of this widely used agent. Radiolabeled antibiotic should be used in an attempt to define the uptake by normal and malignant tissues and the fate of material that is excreted by the biliary route.

ACKNOWLEDGMENTS

The authors wish to thank Bartlett R. Toftness and Carolyn Angelicola for their skilled technical assistance. The following doctors, J. R. Bertino, R. L. Capizzi, R. C. DeConti, M. S. Mitchell, R. T. Skeel, H. M. Kaetz, J. F. Pezzimenti, R. P. Zanes, M. Mosher, H. L. Bruckner, B. Boston, L. R. Farber, D. Berd, M. Rosman, and S. Bobrow, participated in the care of many of these patients.

REFERENCES

1. Adamson, R. H. Daunomycin (NSC-82151) and Adriamycin (NSC-123127): A Hypothesis Concerning Antitumor Activity and Cardiotoxicity. Cancer Chemotherapy Rept., *58:* 293–294, 1974.
2. Alberts, D. C., Bachur, N. R., and Holtzman, J. L. The Pharmacokinetics of Daunomycin in Man. Clin. Pharmacol. Therap., *12:* 96–104, 1971.
3. Bachur, N. R. Daunorubicinol, a Major Metabolite of Daunorubicin:

Isolation from Human Urine and Enzymatic Reactions. J. Pharmacol. Exptl. Therap., *177:* 573–578, 1971.
4. Bachur, N. R., Egorin, M. J., Hildebrand, R. C., and Takanashi, S. Human Biliary Metabolites of Adriamycin (A) and Daunorubicin (D). Proc. Am. Assoc. Cancer Res., *14:* 14, 1971.
5. Bachur, N. R., and Gee, M. Daunorubicin Metabolism by Rat Liver Preparations. J. Pharmacol. Exptl. Therap., *177:* 567–572, 1971.
6. Benjamin, R. S. Pharmacokinetics of Adriamycin (NSC-123127) in Patients with Sarcomas. Cancer Chemotherapy Rept., *58:* 271–273, 1974.
7. Benjamin, R. S., Riggs, C. E., Jr., and Bachur, N. R. Pharmacokinetics and Metabolism of Adriamycin in Man. Clin. Pharmacol. Therap., *14:* 592–600, 1973.
8. Benjamin, R. S., Wiernik, P. H., and Bachur, N. R. Adriamycin Chemotherapy—Efficacy, Safety, and Pharmacologic Basis of an Intermittent Single High Dosage Schedule. Cancer, *33:* 19–27, 1974.
9. Blum, R. H., and Carter, S. K. Adriamycin, a New Anticancer Drug with Significant Clinical Activity. Ann. Internal. Med., *80:* 249–259, 1974.
10. Bonadonna, G., Monfardini, S., DeLena, M., Fossati-Bellani, F., and Beretta, G. Phase I and Preliminary Phase II Evaluation of Adriamycin (NSC-123127). Cancer Res., *30:* 2572–2582, 1970.
11. Chan, K. K., and Harris, P. A. A Fluorometric Determination of Adriamycin and Its Metabolites in Biological Tissues. Res. Commun. Chem. Pathol. Pharmacol., *6:* 447–463, 1973.
12. DiMarco, A., Gaetani, M., and Scarpinato, B. Adriamycin (NSC-123127), a New Antibiotic with Antitumor Activity. Cancer Chemotherapy Rept., *53:* 33–37, 1969.
13. Karnofsky, D. A. Editorial: Meaningful Clinical Classification of Therapeutic Responses to Anti-Cancer Drugs. Clin. Pharmacol. Therap., *2:* 709–712, 1961.
14. Kenis, Y., and Michel, J. Preliminary Results of a Clinical Trial with Intermittent Doses of Adriamycin in Lung Cancer. *In:* S. K. Carter, A. DiMarco, M. Ghione, *et al.* (eds.), International Symposium on Adriamycin, pp. 161–164. New York: Springer-Verlag, Inc., 1972.
15. Lefrak, E. A., Pitha, J., Rosenheim, S., and Gottleib, J. A. A Clinicopathologic Analysis of Adriamycin Cardiotoxicity. Cancer, *32:* 302–314, 1973.
16. McGuire, E. J., Lytton, B., and Mitchell, M. S. Treatment of Metastatic Transitional Cell Carcinoma with Adriamycin: A Case Report. J. Urol., *110:* 384–386, 1973.
17. Mhatre, R., Herman, E., Huidobro, A., and Waravedekar, V. The Possible Relationship between Metabolism and Cardiac Toxicity of Daunomycin and Related Compounds. J. Pharmacol. Exptl. Therap., *178:* 216–222, 1971.
18. Middleman, E., Luce, J., and Frei, E., III. Clinical Trials with Adriamycin. Cancer, *28:* 844–850, 1971.
19. O'Bryan, R. M., Luce, J. K., Talley, R. W., Gottlieb, J. A., Baker, L. H., and Bonnadonna, G. Phase II Evaluation of Adriamycin in Human Neoplasia. Cancer, *32:* 1–8, 1973.
20. Odujinrin, O., McIntosh, S., Murray, E., and Marsh, J. Clinical Experience with Adriamycin. Am. Soc. Clin. Oncol. Abstr., *9:* 26, 1973.
21. Oldham, R. K., and Pomeroy, T. C. Treatment of Ewing's Sarcoma with Adriamycin (NSC-123127). Cancer Chemotherapy Rept., *56:* 635–639, 1972.
22. Rosso, R., Ravazzoni, C., Esposito, M., Sala, R., and Santi, L. Plasma and Urinary Levels of Adriamycin in Man. European J. Cancer, *8:* 455–459, 1972.
23. Sandberg, J. S., Howsden, L., DiMarco, A., and Goldin, A. Comparison of the Anti-leukemic Effect in Mice of Adriamycin (NSC-123127) with Daunomycin (NSC-82151). Cancer Chemotherapy Rept., *54:* 1–7, 1970.
24. Schwarz, H. S. A Fluorometric Assay for Daunomycin and Adriamycin in Animal Tissues. Biochem. Med., *7:* 396–404, 1973.
25. Wang, J., Cortes, E., Sinks, L., and Holland, J. Therapeutic Effect and Toxicity of Adriamycin in Patients with Neoplastic Disease. Cancer, *28:* 837–843, 1971.
26. Whitehouse, J. M. A., Crowther, D., Bateman, C. J. T., Beard, M. E. J., and Malpas, J. S. Adriamycin in the Treatment of Acute Leukemia. Brit. Med. J., *1:* 482–483, 1972.