

MEDICAL LIBRARY
University of Wisconsin, S.M.I. Bldg.
N. Charter St., Madison, Wis.

cancer chemotherapy

reports

JANUARY-FEBRUARY 1966
vol. 50, nos. 1 and 2

U. S. DEPOSITORY COPY
DO NOT DISCARD

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service

QUANTITATIVE COMPARISON OF TOXICITY OF ANTICANCER AGENTS IN MOUSE, RAT, HAMSTER, DOG, MONKEY, AND MAN^{1,2}

Emil J Freireich,³ Edmund A. Gehan,⁴ David P. Rall,⁵ Leon H. Schmidt,⁶ and Howard E. Skipper⁷

SUMMARY

Toxicity data from small animals (mouse, rat, and hamster), large animals (dog and monkey), and humans were gathered, placed on a reasonably similar basis, and compared quantitatively. Each animal species and all species combined were used to predict the toxic doses in man (based on mg/m² of surface area). Two models were assumed for the relationship between the maximum tolerated dose (MTD) in man and the approximate LD10 in each animal system:

$$(\text{dose in man}) = (\text{dose in animal system } i) \quad (1)$$

and

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i), \quad (i = 1, \dots, 6) \quad (2)$$

where A_i is the fraction of the dose in animals used to predict the dose in humans (assumed different for each animal system, ie, $i = 1, \dots, 6$). It was found that when animal systems other than the rat were used the very simple model (1) was remarkably good for predicting the MTD in humans, though model (2) leads to slightly better predictions. Based on model (2), the animal systems are ranked in order of predictive ability: rhesus monkey, Swiss mouse, rat, BDF₁ mouse, dog, and hamster. The best estimate of the MTD in man is made by weighting the estimates from the various animal species. Dose on an mg/m² basis is approximately related to dose on an mg/kg basis by the formula

$$(\text{dose in mg/m}^2) = (km)_i \times (\text{dose in mg/kg}), \quad (i = 1, \dots, 7)$$

where $(km)_i$ is the appropriate factor for converting doses from mg/kg to mg/m² surface area for each species. When the $(km)_i$ factors are known, equally good predictions of MTD in man can be made by either dose unit. On an mg/m² basis, the MTD in man is about the same as that in each animal species. On an mg/kg basis, the MTD in man is about $\frac{1}{12}$ the LD10 in mice, $\frac{1}{9}$ the LD10 in hamsters, $\frac{1}{7}$ the LD10 in rats, $\frac{1}{3}$ the MTD in rhesus monkeys, and $\frac{1}{2}$ the MTD in dogs. In each case the ratio is the (km) factor in the animal system to that in man. Hence relationships among the various animal species and man are somewhat simpler and more direct on an mg/m² basis. These results support the conclusion that the experimental test systems used to evaluate the toxicities of potential anticancer drugs correlate remarkably closely with the results in man.

¹ Received Dec 29, 1965; revised Jan 17, 1966.

² Study done under the auspices of the Acute Leukemia Task Force of the National Cancer Institute by the Subhuman Subcommittee.

³ M. D. Anderson Hospital, Houston, Tex.

⁴ Biometry Branch, National Cancer Inst, Public Health Service, Bethesda, Md.

⁵ Laboratory of Chemical Pharmacology, National Cancer Inst, Public Health Service, Bethesda, Md. Please address requests for reprints to Dr. Rall.

⁶ National Center for Primate Biology, Univ of California at Davis.

⁷ Kettering-Meyer Laboratory of Southern Research Inst, Birmingham, Ala.

The biologic aspect of a drug development program to discover compounds effective against any clinical disease is generally an exercise in comparative pharmacology. In the typical program, compounds are screened in small animals against some easily produced and reproduced pathologic condition. A close relationship must exist between the screening system and the ultimate clinical condition for the program to have the potential for success. Thus examination of this relationship is highly important. In cancer chemotherapy the similarities and differences have often been considered among transplantable tumors, virus-induced tumors, carcinogen-induced tumors, and spontaneous tumors in animals, and between animal tumors and the various cancers and leukemias in man. However the similarities and differences between mice, rats, hamsters, dogs, monkeys, and man have been considered less often in terms of quantitative and qualitative aspects of the toxic effects of drugs. The consistency of the action of therapeutic agents among various mammalian species is a keystone of most drug development programs, yet only rarely has this been studied in a quantitative manner.

Classically comparative pharmacology and physiology have been concerned with differences which permit analytic studies of specific biologic systems, and these studies have yielded valuable information. But it is equally important to consider the much more frequent similarities; we have tried to do this in the present analysis.

Of all the toxicologic end points, lethal toxicity is the easiest to measure with reasonable precision. Therefore we considered the lethal dose of certain cancer chemotherapeutic agents in various laboratory animals. For man the end point was the maximum tolerated dose (MTD). Hopefully two benefits might accrue from this evaluation: (1) If there is reasonable consistency in the reactions of various mammalian species, the toxicologic component of cancer chemotherapy screening will be shown to have a rational basis. (2) If such consistency is found, the problems of introducing highly toxic therapeutic agents into man might be approached more confidently. If major inconsistencies are discovered frequently, this would highlight the deficiencies in present screening systems and raise serious questions about the utility of these schemes for safe introduction of new drugs into man.

No attempt was made to relate therapeutic doses in the various mammalian species. In the future this correlation should be attempted since the therapeutic target in the host is not the same as the toxicity target. However if an agent has therapeutic properties in an experimental system, it is well to know the dose level for patients. Since there is some justification for using MTD's in cancer therapy, these dose levels were studied.

The plan of this retrospective study was to examine considerable toxicologic data obtained in (a) small animals, used in primary screening and quantitative secondary drug evaluation; (b) larger animals, dogs and monkeys, for the quantitative and qualitative aspects of toxicity at sublethal and lethal levels; and (c) man, the target species. The goal was to determine what relationship exists, if any, between certain commonly used toxicologic end points in the various animal species and man for a number of anticancer agents.

Nothing in this report is intended to suggest or imply that short cuts are allowable in pre-clinical or clinical toxicologic studies. Dose-limiting and serious toxic effects in man are not always apparent from even the most carefully done toxicologic investigations in animals (1). *It is emphasized and should be clearly understood that it is dangerous to attempt to extrapolate directly from animal toxicity data to maximum tolerated doses in man!* New drugs can be introduced safely into clinical trial only through careful toxicologic and pharmacologic study in animals and then very cautious study in man, starting with much lower dosages than those which appear to be tolerated by the animals.

APPROACHES AND ASSUMPTIONS IN THIS STUDY

The published and unpublished data which form the basis for this analysis were obtained by numerous investigators using different protocols and end points. We used consistent and reasonable general assumptions so that the data were comparable. The biologic end points, protocols, assumptions, and corrections necessary to make the results more comparable are described briefly.

Toxicologic End Points (See Appendix I)

Mouse, rat, or hamster: Lethality—the dose which when administered by a certain route and schedule killed a selected percentage (10%, ie, the LD10) during a specified observation period; 50 to more than 100 animals were used in a typical determination.

Dog or monkey: (a) MTD; typically 2-4 animals were used at each dose level, spaced by 2-fold increments. In all instances individual doses which killed 0 and 100% were used. The highest dose killing 0% was considered the MTD. (b) Dose-related, hematopoietic effects; localized hemorrhages of the gastrointestinal tract; generalized hemorrhagic lesions (abdominal and thoracic viscera); stimulation of the central nervous system (CNS); others.

Man: (a) MTD for a fixed schedule (dose causing mild to moderate sublethal toxic effects in a significant percent of patients); (b) MTD for a variable schedule, calculated from the daily dose and median period to toxic effects requiring cessation of drug; the judgment of many clinical investigators was necessarily accepted in making this estimation.

Because of the nature of the available data, the toxicologic end points in the various animal species were related to the MTD in man. Although it was necessary to assume that the dosages resulted in the same percentage of toxicity in each species, the results do not depend, in a major way, on this assumption. For the drugs in this study, the dose-toxicity curves were relatively steep so that if the true percentage of toxicity for a given dosage was, say, between 5% and 15%, the actual dosage used would not differ very much from the dosage that should have been used.

It was necessary to use toxicologic data obtained by various routes of drug administration, ie, intraperitoneal (ip) for small animals, oral for small animals and man, and intravenous (iv) for large animals and man. In mice and rats the LD10's obtained by the ip and iv routes are usually comparable.

Another variable for which some reasonable correction must be made is the dosage schedule including the total dose. We assumed that the toxicity of anticancer agents is cumulative. Griswold et al. (3) reported that when the LD10's in BDF₁ mice of 70 agents, including the major classes of anticancer agents, were compared for two schedules, qd 1-7 days and qd 1-11 days,^{*} the mean ratio (qd 1-7 days/qd 1-11 days) was 1.56. This is very close to that which might be expected from direct cumulative drug toxicity (11 days/7 days = 1.57).

Pinkel (2) and other investigators pointed out that the usual doses of certain drugs in various animal species and man were comparable when the dose was measured on the basis of mg/m² of surface area. Consequently most of the results are presented in mg/m². However since mg/kg is a commonly used unit of drug dosage, some results are also presented in this

unit. Only a simple transformation is required to change mg/kg to mg/m²; therefore the relationships developed are equivalent whichever unit is used. The quantitative relationships were simpler when expressed in mg/m².

A conversion factor (*km*) was used to transform mg/kg to mg/m² by the equation $\text{mg/kg} \times (km) = \text{mg/m}^2$; (*km*) factors for animals, given their weight, are presented in table 1 (Appendix II), and table 2 (Appendix II) presents a way of transforming doses in mg/kg to mg/m² for man, given height and body weight. Chart 1 (Appendix II) is a diagram for determining surface area in man, given height and weight.

Calculations based on units of body surface area have no intrinsic merit per se. Very likely some other basis such as surface area of the site of action of the drug, lean body mass, or some fractional power of body weight, possibly related to length or some organ-membrane surface area, would be as appropriate or more appropriate. However the body surface area has been used to relate many physiologic parameters among species and means of transforming the data are readily available. Further, in our clinical studies we routinely use body surface area to adjust drug dose for patients of different size and weight.

RESULTS

The first step in analyzing the data was to correct the daily dosage schedules for man and for animals, when necessary, to a uniform schedule of qd 1-5 days. Thus if an LD10 for mice, or MTD for man, was obtained by a schedule of qd 1-10 days, we calculated that the LD10 (or MTD) for a schedule of qd 1-5 days was twice that value. The next step was to convert doses (LD10's or MTD's) from mg/kg to mg/m². This was accomplished by the approximate formula

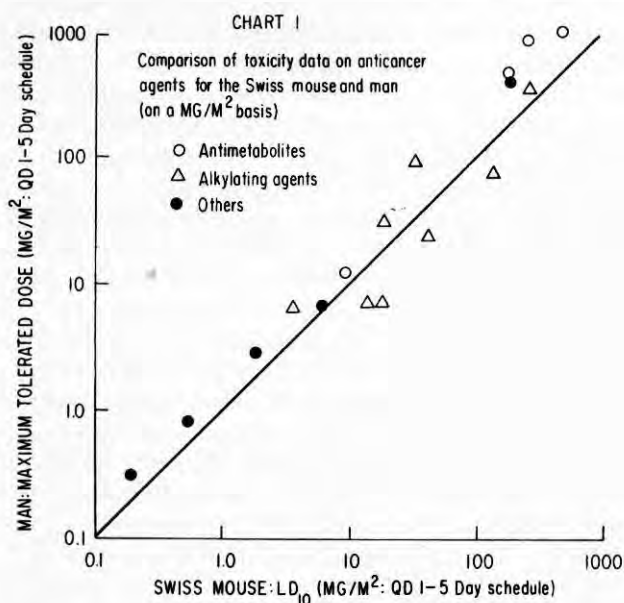
$$(\text{mg/m}^2) = (km)_i \times (\text{mg/kg}), (i=1, \dots, 7)$$

where the (*km*)_i factor differs according to the species and also according to body weight within each species. In the analysis an average (*km*)_i factor was used, assuming that individuals in each species were of average height-to-body-weight ratios. The (*km*)_i factors were derived from standard relationships between weight and surface area as given in Spector (40) and Sendroy and Cecchini (39). Details and other information on relating drug doses in mg/kg to doses in mg/m² are given in Appendix II.

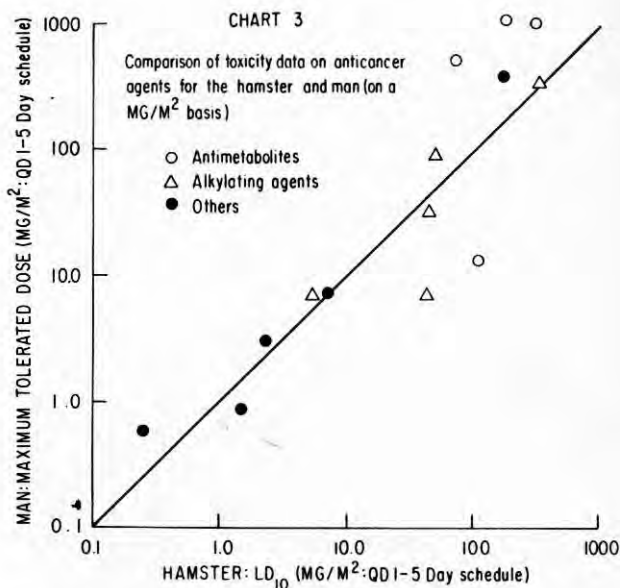
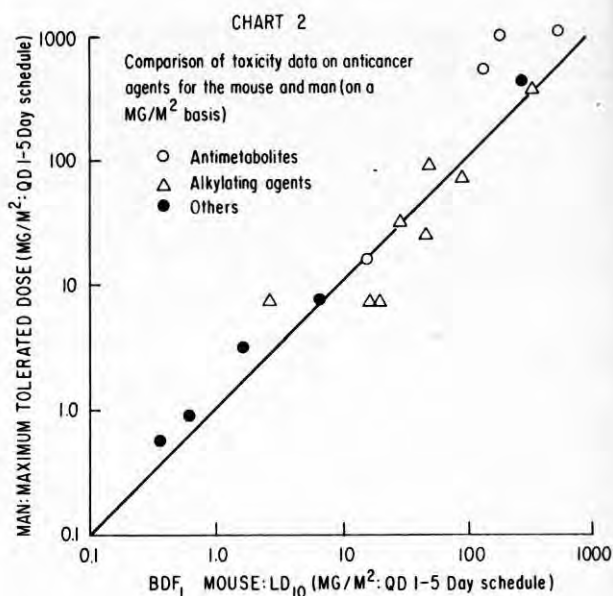
^{*} qd = drug given once daily for as many days as indicated.

The basic data used in this study are given in table 1. Doses of 18 drugs⁹ are presented in mg/kg and mg/m² for the 6 species, along with source information and other pertinent data. An average dose (LD10 or MTD) of each drug was calculated from the multiple studies, if done, on each species. The average doses for the 6 animal systems and man are given in mg/kg in table 2, and in mg/m² in table 3. Charts 1-6 indicate the closeness of the relationship between the logarithm of the LD10, or MTD, in the various animal systems and in man when the dose is measured in mg/m². Chart 7 indicates the close relationship between 12 times the LD10 in the BDF₁ mouse and the MTD in man when the dose is measured in mg/kg. The ratio of the (*km*) factors for an average man and a mouse is $37/3 = 12.3$. It will be shown later that relationships between systems on an mg/kg basis are the same as those on an mg/m² basis if the ratio of (*km*) factors is considered.

To examine further the relationship of dosage, in mg/m², between the animal systems and man, consider the following: For each animal system and man, there is a dose-toxicity curve. The basic data for each drug consist of estimates of a single point, the approximate LD10, on the dose-toxicity curves for man and the 6



⁹Chemical Abstracts' nomenclature and NSC numbers for the agents are given on page 243.



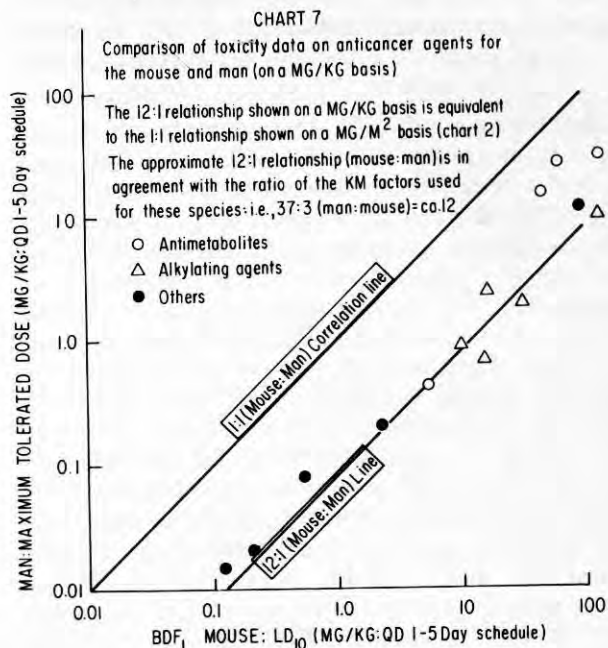
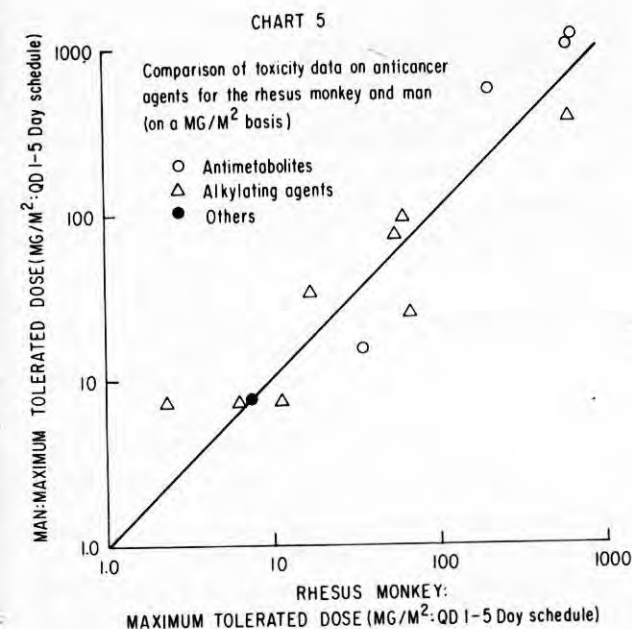
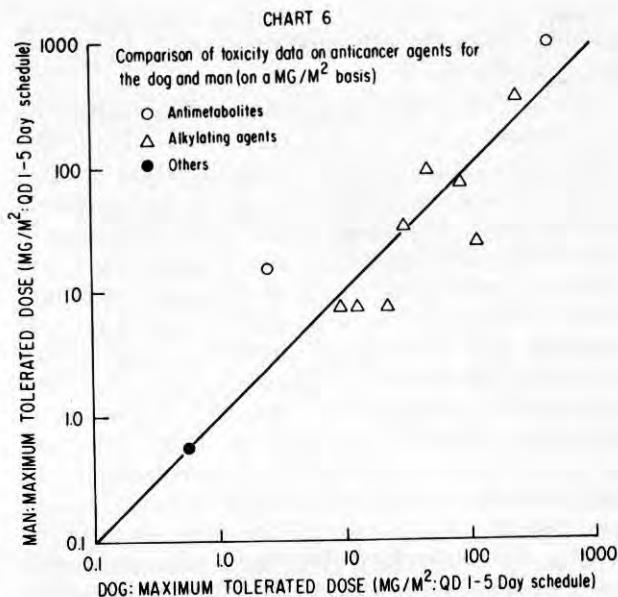
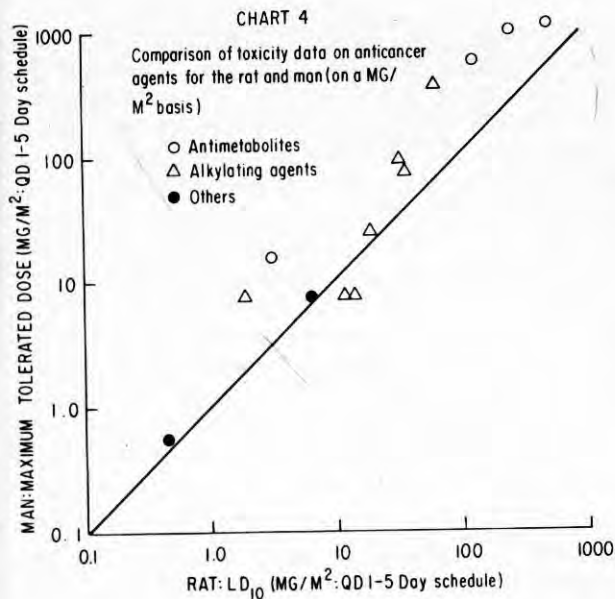
animal systems. We wish to describe the relationship between the dose-toxicity curve for man and that for each of the animal systems. Two models are considered:

$$(\text{dose in man}) = (\text{dose in animal system } i) \quad (i = 1, \dots, 6) \quad (1)$$

and

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i), \quad (i = 1, \dots, 6). \quad (2)$$

Model (1) is a special case of model (2) since they are the same when $A_i = 1$. Model



(1) assumes that the dose in each animal system gives a direct prediction of the dose in man. Model (2) assumes that the dose in man is a fraction (A_i) of the dose in the animal system and the fraction remains constant for the sample of drugs.

A third model was considered:

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i)^{B_i}, \quad (i = 1, \dots, 6)$$

where B_i is the power to which the dose is

raised, assumed to be 1 in models (1) and (2). This model is a natural generalization of (2). However, since the estimates of B_i were near 1 for all animal systems, in fact within 1 standard error (SE) limit, there is no advantage to using a more general model than (2).

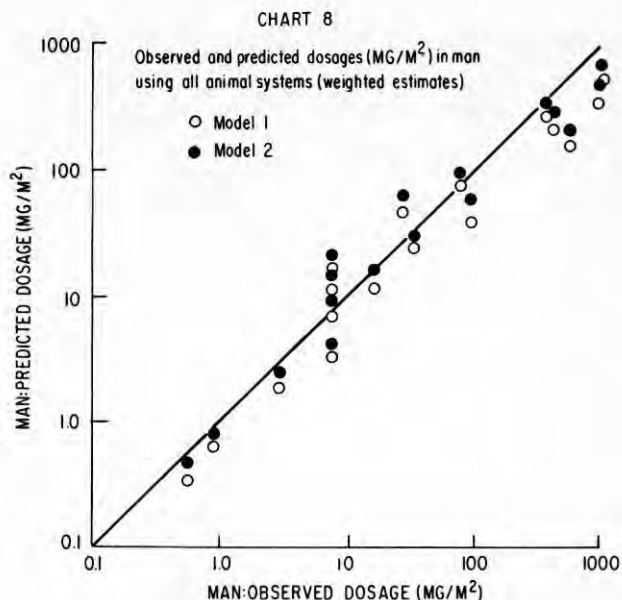
By these models, we wish to predict the dose in man from the dose in each animal system when both determinations are subject to sampling variation (and other assumptions as men-

tioned) in the sample of drugs. The statistical considerations in fitting these models are given in Appendix III.

Model (1) is the simplest possible model; no parameters need to be estimated. Thus the doses in table 3 for each animal system are the predicted values of the dose in man and charts 1-6 indicate that these predictions are reasonably good. The standard deviations, on a log scale, of a predicted value of log (dose in man) were calculated for each animal system. The systems are ranked in order of predictive ability in the top half of table 4: monkey, Swiss mice, BDF₁ mouse, dog, rat, and hamster. A predicted value of the dose in man has been calculated by weighting the estimates from each animal system (see Appendix III) and the results are given in the last column of table 3. The standard deviation of a predicted value of log (dose in man) is 0.299, with multipliers of 0.50 and 2.0 for lower and upper standard deviation limits respectively. Thus the weighted estimate based on all systems is better than the estimate from any single system.

Assuming model (2), the estimates of A_i and $A_i \pm 2$ SE are given in the bottom half of table 4. Note that the approximate 95% confidence limits for the multiplying factor, A_i , include 1 for all animals systems except the rat. Thus for the other animal systems it is reasonable to accept the very simple model (1) as providing an adequate prediction of the dose in man. However when all systems are combined to obtain an overall estimate of A_i (see Appendix III), the approximate 95% confidence limits do not include 1. Also, note from the bottom half of table 4 that the standard deviation of a predicted value of log (dose in man) is 0.275, almost a 10% reduction from that of model (1). Therefore model (2) is preferred for fitting these data; however for future studies in which more precise estimates of LD10 are available, it may be that model (1) will be adequate.

Using model (2), we can rank the animal systems in order of their predictive ability by considering the deviations of observed from predicted values of dose in man. These standard deviations are given in table 4. Thus the order is monkey, Swiss mouse, rat, BDF₁ mouse, dog, and hamster. The best predictions with model (2) are obtained by weighting the estimates of the dose in man from all 6 animal systems (the method is explained in Appendix III). The predictions for the drugs in this study are given



in table 5 and the weighted estimates based on all animal systems combined are plotted in chart 8. The best estimates of dose in man, as indicated by the standard deviations in table 4, are given by weighting the individual estimates from each animal system.

Another model was considered in which the dose in man (mg/m²) was related to doses in the animal species in a single equation:

$$\begin{aligned} \log (\text{dose in man}) = & 0.284 + 0.847 \log (\text{dose in Swiss mouse}) \\ & - 1.064 \log (\text{dose in BDF}_1 \text{ mouse}) \\ & + 0.539 \log (\text{dose in rat}) \\ & + 0.801 \log (\text{dose in monkey}) \\ & - 0.175 \log (\text{dose in dog}). \end{aligned}$$

This predicting equation leads to a slight improvement in the prediction of the dose in man; the deviations of observed from predicted dosages were less (standard deviation of 0.249 on log scale compared to 0.275 by using weighted, combined estimates). However a prediction of dosage in man cannot be made unless estimates of LD10 are available from all the animal systems mentioned; also the model does not provide any real insight into the relationship between the dose-toxicity curve in each animal system and that in man.

From considering charts 1-6, this question arose: Do the differences between the dose-

toxicity curves for man and for each animal system differ depending on whether an antimetabolite or an alkylating agent was given? Usually the animal species, except the rat and monkey, underpredict the doses of antimetabolites and overpredict the doses of alkylating agents for man. By a statistical test (t test), there was some suggestion ($P < 0.10$) that in Swiss mice and BDF₁ mice the predictions of dosage in man were lower for antimetabolites than for alkylating agents. There was no evidence of a difference in the other species. Only 4 antimetabolites and 8 alkylating agents were tested in all animal species. Consequently further study is needed to determine whether the difference between dose-toxicity curves really depends on the type of agent.

There is some value in comparing the relationships found on an mg/m² basis with what would have been found on an mg/kg basis. Some indication of this has already been given in chart 7 which shows that there is a close relationship between 12 times the LD₁₀ in the BDF₁ mouse and the MTD in man. Since the relationship between mg/kg and mg/m² used is

$$(mg/m^2) = (km)_i \times (mg/kg), \quad (i = 1, \dots, 7),$$

models (1) and (2) become, in terms of mg/kg,

$$(\text{dose in man}) = \frac{(km)_a}{(km)_m} \times (\text{dose in animal system}) \quad (1)$$

and

$$(\text{dose in man}) = \frac{(km)_a}{(km)_m} A_i \times (\text{dose in animal system}) \quad (2)$$

where $(km)_a$ and $(km)_m$ refer to the (km) factor in the particular animal system and man respectively, and A_i is exactly the same as stated before. Hence it should be clear that dose in man can be predicted equally well either on an mg/kg basis or on an mg/m² basis. Thus by using the km factors and model (1), the dose in man (mg/kg) is approximately $\frac{1}{12}$ the dose in mice, $\frac{1}{9}$ the dose in hamsters, $\frac{1}{7}$ the dose in rats, $\frac{1}{3}$ the dose in rhesus monkeys, and $\frac{1}{2}$ the dose in dogs.

DISCUSSION

Originality is not claimed or implied for this analysis. We have confirmed and extended the general observations and conclusions of

Pinkel (2) who confirmed and extended specific aspects of the basic observation of Rubner (36), made 80 years ago, and many other investigators later.

The availability of much more extensive toxicity data from the Cancer Chemotherapy National Service Center program, from certain other published sources, and from our own laboratories seemed to make this present analysis timely. Also we believe it is important to use more definitive biologic end points of toxicity. This analysis and study of data on toxicity to animals and humans of several types of anticancer agents (tables 1, 3, and 5) lead us to conclude that the toxic dose of an agent is similar among species when the dose is measured on the basis of surface area. The skin surface area was used here though it is unlikely that the skin is the target area of action of any particular drug. More likely the skin surface is more or less proportional to the true target surface.

To the extent that mammalian species are broadly similar and have corresponding organs and tissues, it is true that any surface area will increase approximately with the two-thirds power of weight (38). Thus the two-thirds power of body weight would have been a convenient unit of surface area to use and the results of the analysis would have been almost the same (see Appendix II).

Pinkel (2) suggested that "cancer chemotherapists consider the applicability of body surface area as a criterion of drug dosages in their laboratory and clinical studies." We suggest that a unit proportional to body surface area is sufficient and an appropriate unit is (weight)^{2/3}.

We have been concerned only with comparisons among species, not within species, and with adult animals, not immature and adult animals. Also we have been concerned solely with anticancer drugs.

Some of the toxicologic data tabulated may disagree with unpublished and published observations of some experimentalists and clinicians. The Acute Leukemia Task Force of the National Cancer Institute wishes to correct, update, and extend this analysis at some future time. Those interested in seeing such correlation efforts extended can help by providing ad-

ditional data, both clinical and experimental, in a form similar to that in table 1.

The present study has emphasized the quantitative aspects of toxicity of anticancer drugs to animals and man. Regarding the prediction of the qualitative effects of anticancer drugs in man from laboratory animal studies, Owens (1) suggested:

<i>Predictive value</i>	<i>Preclinical toxicity studies</i>
Good	Bone marrow, gastrointestinal tract, liver, kidney
Questionable	Nervous system, including peripheral neuropathy, extraocular palsies, and CNS toxicity
None	Skin and appendages, including skin rashes, dermatitis, and alopecia

Of the 18 agents in this study, 17 produced limiting toxicity to the bone marrow (marrow depression: MD) and to the gastrointestinal (GI) tract. If the mg/m^2 doses in man that are predicted by using the weighted combined estimate are compared to the observed doses, then the largest ratio of predicted dose/observed dose is 3, for thioTEPA. Consequently it would be reasonable to study preclinical toxic effects in the mouse, rat, dog, monkey, and hamster, to estimate the MTD (mg/m^2) in man, and to start clinical cancer chemotherapy trials at about one-third the predicted dose. This would have been a safe procedure for all 18 drugs mentioned. Owens (1) suggested that it might be reasonable "to begin a human trial at one-tenth of the maximum tolerated dose in the most susceptible animal" (on an mg/kg basis). Since the most susceptible animal will ordinarily be the dog or rhesus monkey, Owens' rule of thumb on an mg/m^2 basis becomes: begin trial in man at about one-third the dose for monkeys or one-fifth the dose for dogs. Thus there is reasonable agreement between the two recommendations. However if the ani-

mal data are not placed on the mg/m^2 basis before using Owens' rule of thumb, any additional knowledge which the small animals (mouse and rat) might contribute will be overlooked. Remember also that the toxicity values (LD_{10} 's) for such small animals are often more reliable statistically because more animals are generally used.

The ratios of animal/human toxicity (mg/m^2 basis) for the mouse, hamster, dog, and monkey are remarkably close to unity. Thus each species generally predicts for man. That this is true for the mouse is particularly pertinent to cancer chemotherapy. Extensive drug development programs which use mouse tumors seem to be on firmer ground than we had previously thought. In general the rat is more susceptible to these agents than the other species. The hamster is unusually resistant to amethopterin and sensitive to the fluorinated pyrimidines. The dog and monkey, long known to be reasonably good predictors of toxicity to humans, have shown up well in this analysis.

We are not suggesting that it is wise to take mouse or rat LD_{10} 's, convert the doses to mg/m^2 , and then start clinical trials at one-third this level (in mg/m^2 for man). The additional safety provided by toxicity data from multiple species is well established, *as is the value of specific qualitative knowledge on dose-related sublethal toxicity and its reversibility.*

Finally it is suggested that the quantitative relationships between toxicity to animals and to humans are simpler when compared on an mg/m^2 basis than on an mg/kg basis. Broader use of a surface area unit, either mg/m^2 or (weight)^{2/3}, by experimental and clinical cancer chemotherapists, as well as biochemists and pharmacologists concerned with mechanism studies, might prove helpful in many types of experimental planning and data analysis.

Table 1

Comparison of Approximate Maximum Human Dosages of Certain Anticancer Agents with LD₅₀'s for the Mouse, Rat, and Hamster and Approximate Maximum Nontoxic Doses for the Dog and Monkey

Agent	Species ^(a)	No. of Patients or Animals	Drug Administration Route	Period of Obs. Toxicity in Days; or Median Days to Max. Toxicity in Man	Toxicologic End Point for Species Indicated	Brief Toxicity "Rating" in Man:			Limiting Toxicologic Symptoms or Reactions	Daily Dose to Schedule (mg/kg)	Daily Dose to Surface Area (mg/m ²)	Ratio (mg/m ²) (Animal/Man)	Reference
						Reactions to Dose							
						0	Mild	Severe					
1. Amethopterin	Man	63	I.V. or I.M.	11 ⁺	MTD				MD; GI	0.42	37.0	16.0	Hertz, Lewis, and Lipsett (4)
		22	I.V.	9	MTD				MD; GI	0.41	37.0	15.0*	"Bike" program, NCI (5)
	Swiss mouse	50-100	Oral	qd 1-20	Usual dose				MD; GI	0.10	0.40	37.0	Karnofsky (6)
		50-100	I.P.	qd 1-5	LD ₅₀					3.5	3.0	10.5	Schmidt (7)
		50-100	I.P.	qd 1-5	LD ₅₀					4.7	4.0	14.1	Schmidt (7)
		50-100	I.P.	qd 1-7	LD ₅₀					2.0	2.8	8.4	Griswold (3)
	BDF ₁ mouse	50-100	I.P.	qd 1-7	LD ₅₀					4.6	6.4	3.0	Griswold (3)
		50-100	I.P.	qd 1-11	LD ₅₀					2.1	4.6	3.0	Griswold (3)
	Hamster	50-100	I.P.	qd 1-7	LD ₅₀					18.0	25.2	4.1	Griswold (8)
		50-100	I.P.	qd 1-5	LD ₅₀					0.84	0.64	5.2	Schmidt (7)
	H. Rat ^(d) S. D. Rat (250 g) S. D. Rat (68 g)	50-100	I.P.	qd 1-5	LD ₅₀					0.85	0.85	5.2	Schmidt (7)
		50-100	I.P.	qd 1-15	LD ₅₀					0.13	0.40	7.0	Rail (9)
2. 6-Mercaptopurine	Dog	18	I.V.	qd 1-15	MTD				MD	0.04	0.12	19.8	Rail (9)
		7	I.V.	qd 1-15	MTD				GI	1.0	3.0	35.0	Rail (9)
	Monkey	18	I.V.	qd 1-5	MTD				MD	27.0	27.0	37.0	1000 ^a
		16	I.V.	qd 1-5	MTD				MD	12.0	12.0	37.0	450
	Swiss mouse	50-100	Oral	qd 1-20	Usual dose				MD	2.5	10.0	37.0	Karnofsky (6)
		50-100	I.P.	qd 1-5	LD ₅₀					90.0	90.0	3.0	Schmidt (7)
		50-100	I.P.	qd 1-5	LD ₅₀					82.0	82.0	3.0	Schmidt (7)
		50-100	I.P.	qd 1-7	LD ₅₀					58.0	81.0	3.0	Griswold (3)
	BDF ₁ mouse	50-100	I.P.	qd 1-7	LD ₅₀					44.0	82.0	3.0	Griswold (3)
		50-100	I.P.	qd 1-11	LD ₅₀					28.0	82.0	3.0	Griswold (3)
	Hamster	50-100	I.P.	qd 1-7	LD ₅₀					56.0	78.0	4.1	Griswold (8)
		50-100	I.P.	qd 1-5	LD ₅₀					54.0	54.0	5.2	Schmidt (7)
	H. Rat F. Rat	50-100	I.P.	qd 1-5	LD ₅₀					48.0	48.0	5.2	Schmidt (7)
50-100		I.P.	qd 1-5	LD ₅₀					48.0	48.0	5.2	Schmidt (7)	
3. 5-Fluorouracil	Dog	10	I.V.	qd 1-4	MTD				MD; GI	17.5	21.9	19.8	Philips et al. (10)
		4	I.V.	qd 1-7	MTD				MD; GI	40.0	56.0	37.0	Rail (9)
	Monkey	1300	I.V.	qd 1-5(e)	MTD				2.5% GI; MD	15.0	15.0	37.0	555 ^a
		200	I.V.	qd 1-5(f)	<MTD				0% GI; MD	12.0	12.0	37.0	444.0
		223	I.V.	qd 1-5(g)	MTD				3% GI; MD	15.0	15.0	37.0	555.0
			I.V.	qd 1-5	Usual dose				GI; MD	15.0	15.0	37.0	555.0
	Swiss mouse	50-100	I.P.	qd 1-5	LD ₅₀					31.0	31.0	3.0	Schmidt (7)
		50-100	I.P.	qd 1-5	LD ₅₀					30.0	30.0	3.0	Schmidt (7)
		50-100	I.P.	qd 1-7	LD ₅₀					38.0	33.0	3.0	Griswold (3)
		50-100	I.P.	qd 1-7	LD ₅₀					30.0	30.0	3.0	Griswold (3)
	BDF ₁ mouse	50-100	I.P.	qd 1-7	LD ₅₀					37.0	46.0	3.0	Griswold (3)
		50-100	I.P.	qd 1-11	LD ₅₀					27.0	59.0	3.0	Griswold (3)
	Hamster	50-100	I.P.	qd 1-7	LD ₅₀					12.0	17.0	4.1	Griswold (8)
		50-100	I.P.	qd 1-5	LD ₅₀					25.0	25.0	5.2	Schmidt (7)
H. Rat F. Rat	50-100	I.P.	qd 1-5	LD ₅₀					25.0	25.0	5.2	Schmidt (7)	
	50-100	I.P.	qd 1-10	MTD					5.0	10.0	19.0	Philips (37)	
4. 5-FUDR	Monkey	6	I.V.	qd 1-5	MTD				MD; GI	13.0	18.0	11.5	207.0
		51	I.V.	qd 1-5(h)	<MTD				2% GI; MD	30.0	30.0	37.0	1110.0*
	Man	200	I.V.	qd 1-5(i)	MTD				3% GI; MD	40.0	40.0	37.0	1480.0
		51	I.V.	qd 1-5(j)	MTD				4% GI; MD	40.0	40.0	37.0	1480.0
			I.V.	qd 1-5	Usual dose				GI; MD	30.0	30.0	37.0	1110.0
			I.V.	qd 1-5	Usual dose				GI; MD	30.0	30.0	37.0	1110.0
	Swiss mouse	50-100	I.P.	qd 1-5	LD ₅₀					31.0	31.0	3.0	Schmidt (7)
		50-100	I.P.	qd 1-5	LD ₅₀					30.0	30.0	3.0	Schmidt (7)
		50-100	I.P.	qd 1-7	LD ₅₀					38.0	33.0	3.0	Griswold (3)
		50-100	I.P.	qd 1-7	LD ₅₀					30.0	30.0	3.0	Griswold (3)
	BDF ₁ mouse	50-100	I.P.	qd 1-7	LD ₅₀					37.0	46.0	3.0	Griswold (3)
		50-100	I.P.	qd 1-11	LD ₅₀					27.0	59.0	3.0	Griswold (3)
Hamster	50-100	I.P.	qd 1-7	LD ₅₀					12.0	17.0	4.1	Griswold (8)	
	50-100	I.P.	qd 1-5	LD ₅₀					25.0	25.0	5.2	Schmidt (7)	
H. Rat F. Rat	50-100	I.P.	qd 1-5	LD ₅₀					25.0	25.0	5.2	Schmidt (7)	
	50-100	I.P.	qd 1-10	MTD					5.0	10.0	19.0	Philips (37)	

(Continued)

Table 1 (Cont'd)

Agent	Species(a)	No. of Patients or Animals	Drug Administration Route	Period of Obs. Toxicity in Days; or Median Days to Max. Toxicity in Man	Toxicologic End Point for Species Indicated	Brief Toxicity "Rating" in Man: Reactions in Large Animals				Limiting Toxicologic Symptoms or Reactions	Daily Dose (mg/kg)	Daily Dose "Corrected" qd 1-5 day Schedule (mg/kg)	Area Under Curve (mg/m ²)	Ratio (mg/m ²) (Animal/Man)	Reference	
						Reactions in Large Animals										
						0	Mild	Mod.	Severe							
4. 5-FUDR (Cont'd)	Swiss mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	15	0	MD; GI	0.2	0.2	37.0	7.4*	Clifford et al. (13)	
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	1.0	0.2	37.0	7.4	Krethmar et al. (14)	
	Swiss mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.4	0.08	37.0	3.0	Karnofsky (6)	
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	1.5	1.5	3.0	4.5	0.61	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.66	1.0	3.0	3.0	0.41	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.33	0.46	3.0	1.4	0.19	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀	0	0	8	0	MD; GI	0.30	0.66	3.0	2.0	0.27	Griswold (3)
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.90	1.3	4.1	5.3	0.72	Griswold (8)
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	0.88	88.0	5.2	458.0	0.41	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	90.0	90.0	5.2	468.0	0.42	Schmidt (7)
5. Nitrogen mustard (HN2)	Dog	6	I.V. qd 1-10	1-40	MTD	0	0	8	0	MD; GI	20.0	40.0	19.0	760.0	0.68	Phillips (37)
	Monkey	8	I.V. qd 1-6	1-60	MTD	0	0	8	0	MD; GI	50.0	60.0	11.5	890.0	0.62	Rail (9)
	Man	15	I.V. qd 1-5	15	MTD	0	0	15	0	MD; GI	0.2	0.2	37.0	7.4*	Clifford et al. (13)	
	Man	8	I.V. Day 1 only	7	MTD	0	0	8	0	MD; GI	1.0	0.2	37.0	7.4	Krethmar et al. (14)	
	Swiss mouse	Large no.	I.V. Day 1 only	1-21	Usual dose	0	0	8	0	MD; GI	0.4	0.08	37.0	3.0	Karnofsky (6)	
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	1.5	1.5	3.0	4.5	0.61	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	1.5	1.5	3.0	4.5	0.61	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.66	1.0	3.0	3.0	0.41	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.33	0.46	3.0	1.4	0.19	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀	0	0	8	0	MD; GI	0.30	0.66	3.0	2.0	0.27	Griswold (3)
6. Nitrovin	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; GI	0.90	1.3	4.1	5.3	0.72	Griswold (8)
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	0.48	0.48	5.2	2.5	0.34	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; GI	0.25	0.25	5.2	1.3	0.18	Schmidt (7)
	Dog	4	I.V. qd 1-12 to 16	1-17	MTD	0	0	8	0	MD; GI	0.17	0.43	19.0	9.1	1.2	Schmidt (15)
	Monkey	15	I.V. qd 1-6 to 18	1-19	MTD	0	0	8	0	MD; GI	0.084	0.20	11.5	2.3	0.31	Schmidt (15)
	Man	71	I.V. qd 1-5	21	MTD	0	0	8	0	MD; CNS	2.0	2.0	37.0	74.0*	Close (16)	
	Swiss mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	52.0	52.0	3.0	156.0	2.1	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	46.0	46.0	3.0	138.0	1.9	Schmidt (7)
	Swiss mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; CNS	27.0	38.0	3.0	114.0	1.5	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; CNS	20.0	28.0	3.0	84.0	1.1	Griswold (3)
BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀	0	0	8	0	MD; CNS	9.0	20.0	3.0	60.0	0.81	Griswold (3)	
7. L-Phenylalanine mustard	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	8.6	8.6	5.2	45.0	0.61	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	5.4	5.4	5.2	28.0	0.38	Schmidt (7)
	Dog	4	I.V. qd 1-6 to 15	1-16	MTD	0	0	8	0	MD; CNS	2.1	4.4	19.0	84.0	1.1	Schmidt (15)
	Monkey	8	I.V. qd 1-8 to 15	1-16	MTD	0	0	8	0	MD; CNS	2.1	4.8	11.5	55.0	0.74	Schmidt (15)
	Man	210	I.V. Single dose	10-12	MTD	0	0	8	0	MD; CNS	1.0	0.2	37.0	7.4*	Burns et al. (17, 18)	
	Man	70	F.O. qd 1-4	10-12	MTD	0	0	8	0	MD; CNS	0.2	0.16	37.0	5.9	Burns et al. (17, 18)	
	Swiss mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	5.1	5.1	3.0	15.3	2.1	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	5.5	5.5	3.0	16.5	2.2	Schmidt (7)
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	2.8	2.8	5.2	14.6	2.0	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀	0	0	8	0	MD; CNS	1.7	1.7	5.2	8.8	1.2	Schmidt (7)
8. Alanine mustard	Dog	10	I.V. qd 1-12 to 18	1-19	MTD	0	0	8	0	MD; CNS	0.21	0.63	19.0	12.0	1.6	Schmidt (15)
	Monkey	9	I.V. qd 1-9 to 17	1-18	MTD	0	0	8	0	MD; CNS	0.21	0.55	11.5	6.3	0.85	Schmidt (15)
	Man	34	I.V. qd 1-5	14-21	MTD	0	0	8	0	MD; CNS	0.9	0.9	37.0	33.0	Dietrich et al. (19)	
	Swiss mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; CNS	4.5	6.3	3.0	18.9	0.57	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; CNS	7.2	10.0	3.0	30.0	0.91	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀	0	0	8	0	MD; CNS	4.2	9.3	3.0	27.9	0.85	Griswold (3)
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀	0	0	8	0	MD; CNS	8.0	11.2	4.1	46.0	1.4	Griswold (8)
	Dog	4	I.V. qd 1-8 to 15	1-16	MTD	0	0	8	0	MD; CNS	0.63	1.5	19.0	29.0	0.88	Schmidt (15)
	Monkey	5	I.V. qd 1-8 to 16	1-17	MTD	0	0	8	0	MD; CNS	0.63	1.5	11.5	17.0	0.52	Schmidt (15)

(Continued)

Table 1 (Cont'd)															
Agent	Species(s)	No. of Patients or Animals	Drug Administration Route (days)	Period of Obs. Toxicity in Days; or Median Days to Max. Toxicity in Man	Toxicologic End Point for Species Indicated	Brief Toxicity "Rating" in Man: and Intensity of Major Reactions in Laboratory Animals				Limiting Toxicologic Symptoms or Reactions	Daily Dose (mg/kg)	Daily Schedule	Daily Dose (mg/m ²) to Surface Area Basis (c)	Ratio (mg/m ²) (Animal)	Reference
						Reactions in Laboratory Animals									
						0	Mild	Mod.	Severe						
9. Cytosin	Man	30	I.V. Single dose	7-10	MTD	0%	50%	35%	15%	MD; GI	50.0	10.0	37.0	370.0*	Coggins et al. (20)
		27	I.V. qd 1-6	7-10	<MTD	20%	55%	20%	5%		7.5	9.0	37.0	333.0	Coggins et al. (20)
	Swiss mouse	50-100	I.V. qd 1-5	1-21	Usual dose						10.0	10.0	37.0	370.0	Karnofsky (6)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						160.0	160.0	3.0	480.0	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						130.0	130.0	3.0	390.0	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						50.0	70.0	3.0	210.0	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						81.0	85.0	3.0	255.0	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						57.0	125.0	3.0	375.0	Griswold (3)
	Swiss mouse	50-100	I.P. Single dose	1-30	LD ₅₀						252.0	50.0	3.0	150.0	Schabel (21)
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						56.0	78.0	4.1	320.0	Griswold (8)
10. ThiotePA	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						14.0	14.0	5.2	73.0	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						10.3	10.3	5.2	54.0	Schmidt (7)
	Dog	7	I.V. qd 1-7 to 15	1-16	MTD	GI	MD	MD	MD		5.6	12.3	19.0	234.0	Schmidt (15)
	Monkey	12	I.V. qd 1-8 to 15	1-16	MTD						22.4	54.0	11.5	621.0	Schmidt (15)
	Man	87	I.V. qd 1-5	15	Usual dose	30%	30%	25%	15%	MD	0.2	0.2	37.0	7.4*	Moore (22)
	Swiss mouse	50-100	I.V. qd 1-5	1-21	Usual dose						0.2	0.2	37.0	7.4	Karnofsky (6)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						6.2	6.2	3.0	18.6	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						6.2	6.2	3.0	18.6	Schmidt (7)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						3.7	5.2	3.0	15.6	Griswold (3)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						5.8	8.1	3.0	24.3	Griswold (3)
11. Myleran	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						2.4	5.3	3.0	15.9	Griswold (3)
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						7.3	10.2	4.1	41.8	Griswold (8)
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						3.0	3.0	5.2	15.6	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						2.3	2.3	5.2	12.0	Schmidt (7)
	Dog	5	I.V. qd 1-10 to 17	1-18	MTD	GI	MD	MD	MD		0.38	1.1	19.0	20.9	Schmidt (15)
	Monkey	8	I.V. qd 1-8 to 17	1-18	MTD	GI	MD	MD	MD		0.38	1.0	11.5	11.5	Schmidt (15)
	Man	13	Oral qd 1-4(h)	16	Usual dose	0%	40%	30%	30%	MD	0.8	0.7	37.0	25.0*	Sullivan (31)
	Swiss mouse	50-100	Oral qd 1-30	1-21	Usual dose						0.1	0.5	37.0	22.2	Karnofsky (6)
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						15.0	15.0	3.0	45.0	Schmidt (7)
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						15.0	15.0	3.0	45.0	Schmidt (7)
12. BCNU	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						4.1	4.1	5.2	21.0	Schmidt (7)
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						3.2	3.2	5.2	17.0	Schmidt (7)
	Dog	7	I.V. qd 1-14 to 15	1-16	MTD	GI	MD	MD	MD		2.0	6.0	19.0	114.0	Schmidt (15)
	Monkey	14	I.V. qd 1-14 to 16	1-17	MTD	GI	MD	MD	MD		2.0	6.0	11.5	69.0	Schmidt (15)
	Man	7	I.V. qd 1-3	42	MTD	0	4	2	1	MD	4.1	2.5	37.0	93.0*	De Vita et al. (23)
	Swiss and BDF ₁ mouse	50-100	I.V. Single dose	44	MTD	0	4	4	0	MD	8.1	1.6	37.0	39.0*	De Vita et al. (23)
	Swiss mouse	50-100	I.P. qd 1-5	1-24	LD ₅₀						13.0	13.0	3.0	39.0	Schmidt (15)
	BDF ₁ mouse	50-100	Oral qd 1-5	1-24	LD ₅₀						11.0	11.0	3.0	33.0	Schmidt (15)
	Swiss mouse	50-100	I.P. Day 1 only	1-30	LD ₅₀						19.0	3.8	3.0	11.4*	Schabel (21)
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						12.0	16.8	3.0	50.4	Schabel (21)
Note: BCNU possesses an unusual propensity to cause delayed toxicity even at extended periods after cessation of drug administration (in small animals, large animals, and man).															
(Continued)	BDF ₁ mouse	50-100	Oral qd 1-7	1-14	LD ₅₀						14.0	19.6	3.0	38.5	Schabel (21)
	BDF ₁ mouse	50-100	Oral qd 1-7	1-14	LD ₅₀						8.4	11.8	3.0	35.4	Schabel (21)
	BDF ₁ mouse	50-100	Oral qd 1-7	1-14	LD ₅₀						12.0	16.8	3.0	50.4	Schabel (21)
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						8.1	17.8	3.0	53.4	Schabel (21)
	BDF ₁ mouse	50-100	Oral qd 1-11	1-21	LD ₅₀						7.5	16.5	3.0	49.5	Schabel (21)
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						8.3	11.6	4.1	47.6	Schabel (21)
	Rat	50-100	I.P. qd 1-5	1-25	LD ₅₀						6.6	6.6	5.2	34.3	Schmidt (15)
	Dog	15	I.V. qd 1-4 to 17	1-18	>MTD (3/6 deaths)	GI	MD	MD	MD		<1.25	<2.75	19.0	<52.3	Schmidt (15)
	Monkey	13	Oral qd 1-6 to 10	1-50	ca MTD (1/5 deaths)	GI	MD	MD	MD		1.25	2.0	19.0	38.0	Schmidt (15)
	Monkey	15	I.V. qd 1-5 to 16	1-17	MTD	GI	MD	MD	MD		2.5	3.0	11.5	58.0	Schmidt (15)
Monkey	15	Oral qd 1-7 to 15	1-29	MTD	GI	MD	MD	MD		2.5	3.0	11.5	63.3	Schmidt (15)	

(Continued)

Table 1 (Cont'd)

Agent	Species(a)	No. of Patients or Animals	Drug Administration Route	Period of Obs. Toxicity in Days; or Median Days to Max. Toxicity in Man	Toxicologic End Point for Species Indicated	Brief Toxicity "Rating" in Man; and Intensity of Major Reactions in Large Animals					Limiting Toxicologic Symptoms or Reactions	Daily Dose (mg/kg)	Daily Schedule (mg/kg)	Daily Dose to Surface Area Basis (c) (mg/m ²)	Ratio (mg/m ²) (Animal/Man)	Reference
						Reactions in Large Animals										
						0	Mild	Mod.	Severe	Rating						
13. Actinomycin D	Man	25	I.V. qd 1-5	12	MTD	0%	55%	30%	15%	GI; MD	0.015	0.015	37.0	0.55*	Moore et al. (24)	
	Swiss mouse	50-100	I.V. qd 1-5	1-21	Usual dose					GI; MD	0.015	0.015	37.0	0.55	Karnofsky (6)	
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						ca 0.06	ca 0.06	3.0	ca 0.18	Schmidt (7)	
	Swiss mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						0.11	0.11	3.0	0.33	Schmidt (7)	
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.06	0.06	3.0	0.24	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.095	0.13	3.0	0.39	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						0.05	0.11	3.0	0.33	Griswold (3)	
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.044	0.06	4.1	0.25	Griswold (8)	
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						0.08	0.08	5.2	0.42	Schmidt (7)	
	F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						0.08	0.09	5.2	0.47	Schmidt (7)	
Dog			I.V. qd 1-15		MTD					0.01	0.03	19.0	0.57	1.0 Philips et al. (25)		
14. Mitomycin C	Man	12	I.V. qd 1-4	21	MTD	1	1	7	3	MD	0.25	0.20	37.0	7.4*	Miller et al. (26)	
	Swiss mouse	50	I.V. qd 1-10(h)	15	MTD	10%	40%	45%	5%	MD	0.10	0.20	37.0	7.4	Evas (27)	
	BDF ₁ mouse	50-100	I.V. qd 1-10		Usual dose						0.10	0.20	37.0	7.4	Karnofsky (6)	
	Swiss mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						1.7	1.7	3.0	3.1	Schmidt (7)	
	BDF ₁ mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						1.8	1.8	3.0	3.4	Schmidt (7)	
	Swiss mouse	50-100	I.P. qd 1-5	1-21	LD ₅₀						2.1	2.9	3.0	8.7	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						2.1	2.9	3.0	8.7	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						0.8	1.8	3.0	5.4	Griswold (3)	
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						1.2	1.7	4.1	7.0	Griswold (8)	
	H. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						1.3	1.3	5.2	6.8	Schmidt (7)	
F. Rat	50-100	I.P. qd 1-5	1-21	LD ₅₀						ca 1.2	ca 1.2	5.2	ca 6.2	Schmidt (7)		
Monkey	6	I.V. qd 1-2	1-30	MTD		GI	MD			1.6	0.64	11.5	7.4	1.0 Rall (9)		
15. Vinblastin	Man	20	I.V. qd 1-3	10-14	MTD	0%	10%	40%	50%	MD	0.13	0.08	37.0	3.0*	Hertz et al. (28)	
	Swiss mouse	10	I.V. qd 1-3	10-14	>MTD	0	4	2	4	MD	0.10	0.06	37.0	2.2	Goldenberg (29)	
	BDF ₁ mouse	21	I.V. qd 1-5	10-14	>MTD	0	6	7	8 (deaths)	MD	0.10	0.10	37.0	3.7	Smart et al. (30)	
	Swiss mouse	50-100	I.V. once wk x 5 (2-7)		Usual dose						0.15	(0.03)	37.0	(1.1)	Karnofsky (6)	
	BDF ₁ mouse	50-100	I.P. Single dose	1-30	LD ₅₀						2.7	0.54	3.0	1.6	Schabel (21)	
	Swiss mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.48	0.87	3.0	2.0	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						0.24	0.53	3.0	1.6	Griswold (3)	
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.38	0.53	4.1	2.2	Griswold (8)	
	Man	28	I.V. Single dose	14-21	MTD	0%	10%	50%	40%	Periph. nerve and GI	0.1	0.02	37.0	0.74	Carbone et al. (32)	
	Man	10	I.V. qd 1-4(h)	14-21	MTD		50%	40%	10%	Periph. nerve and GI	0.03	0.024	37.0	0.89*	Carey et al. (33)	
16. Vincristine	Swiss mouse	50-100	I.V. once/wk x 4	1-30	Usual dose						0.05	(0.01)	37.0	(0.37)	Karnofsky (6)	
	BDF ₁ mouse	50-100	I.P. Single dose	1-14	LD ₅₀						1.1	0.22	3.0	0.66	Schabel (21)	
	Swiss mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.1	0.14	3.0	0.42	Schabel (21)	
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						0.09	0.20	3.0	0.60	Schabel (21)	
	Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						0.24	0.34	4.1	1.4	Schabel (21)	
	Man	36	I.V. qd 1-14(h)	10-21	MTD	(5%)	(20%)	(45%)	(30%)	GI; skin	4.1	11.4	37.0	420.0*	Levin et al. (34)	
	Man	12	I.V. qd 1-11(h)	10-14	MTD	(5%)	(20%)	(45%)	(30%)	GI; skin	5.0	11.0	37.0	410.0	Levin et al. (34)	
	Swiss mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						42.0	58.8	3.0	176.0	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-7	1-14	LD ₅₀						61.0	85.4	3.0	256.0	Griswold (3)	
	BDF ₁ mouse	50-100	I.P. qd 1-11	1-21	LD ₅₀						46.0	101.2	3.0	304.0	Griswold (3)	
Hamster	50-100	I.P. qd 1-7	1-14	LD ₅₀						29.0	41.0	4.1	168.0	Griswold (8)		
17. Methyl GAG	Man	36	I.V. qd 1-11(h)	3-28	<MTD	0%	(10%)	(80%)	(10%)	MD	60.0	132.0	37.0	4900.0	Thurman et al. (35)	
	Man	19	Oral qd 1-10(h)	3-28	MTD	0%	0%	(50%)	(50%)	MD	80.0	160.0	37.0	5900.0*	Thurman et al. (35)	
	Dog	12	I.V. qd 1-28	1-56	MTD						100.0	560.0	19.0	10640.0	1.8 Rall (9)	
	18. Hydroxyurea	Man	36	Oral qd 1-11(h)	3-28	<MTD	0%	(10%)	(80%)	(10%)	MD	60.0	132.0	37.0	4900.0	Thurman et al. (35)
		Man	19	Oral qd 1-10(h)	3-28	MTD	0%	0%	(50%)	(50%)	MD	80.0	160.0	37.0	5900.0*	Thurman et al. (35)
		Dog	12	I.V. qd 1-28	1-56	MTD						100.0	560.0	19.0	10640.0	1.8 Rall (9)

(Continued)

Table 1 (Cont'd)

Note. (a) All of the human toxicity data are calculated on the basis of a 60-kg man (km factor = 37); approximately 20-gram mice were employed; 50-gram hamsters; 100-gram rats (except where otherwise indicated); 2.5-kg Rhesus monkeys; 7 to 8-kg young Beagle dogs (7-12 months of age).
 (b) Numbers of patients exhibiting the indicated degree of "toxicity" are given unless the value is indicated as per cent. The intensity of marrow depression and gastrointestinal toxicity listed is the average or most frequent observed for dogs or monkeys receiving the dosage indicated.
 (c) The human dosage (qd 1-5 day, mg/m²) indicated by an asterisk was used to obtain the animal : man ratios. Underlined values represent studies in which mg/m² was the original basis for dosage.

(d) H. rat is the Holtzman line of Sprague-Dawley rat; F. rat is Fischer rat; S. D. is Sprague-Dawley rat.

(e) Average patient received one additional half dose on day 7. Maximum of 11 half doses given q. o. d.

(f) Average patient received four additional half doses q. o. d. Maximum of 11 half doses given q. o. d.

(g) Average patient received no additional therapy.

(h) Median duration of therapy to toxicity for daily treatment.

(i) Four additional half doses on days 7, 9, 11, and 13.

Table 2

A Comparison of Small-Animal LD₁₀'s, Large-Animal Maximum Tolerated Doses, and Human

Maximum Tolerated Doses on a Mg/Kg Basis

Mg/Kg (qd 1-5 Day Schedule)

Agent	LD ₁₀ :		LD ₁₀ :		LD ₁₀ :		MTD:		MTD:	
	Swiss Mouse	BDF ₁ Mouse	BDF ₁ Mouse	Rat	Rhesus Monkey	Dog	Man	Dog	Man	
1. Amethopterin	3.2	5.2	0.58	0.12	3.0	0.41	0.41	0.12	0.41	
2. 6-Mercaptopurine	86.0	62.0	51.0	22.0	56.0	27.0	27.0	22.0	27.0	
3. 5-Fluorouracil	42.0	45.0	25.0	18.0	18.0	15.0	15.0	10.0	15.0	
4. 5-FUDR	160.0	190.0	89.0	40.0	59.0	30.0	30.0	40.0	30.0	
5. Nitrogen Mustard	1.3	0.90	0.37	0.2	0.2	0.48	0.2	0.48	0.2	
6. Nitromin	45.0	31.0	7.10	4.8	4.8	2.0	2.0	4.4	2.0	
7. L-Phenylalanine	5.1	5.5	2.3	0.55	0.55	0.63	0.2	0.63	0.2	
8. Alanine Mustard	6.3	9.7	-	1.5	1.5	1.5	0.9	1.5	0.9	
9. Cytosoxan	93.0	110.0	12.0	54.0	54.0	10.0	10.0	12.0	10.0	
10. ThioTEPA	5.7	6.5	2.7	1.0	1.0	0.2	0.2	1.1	0.2	
11. Myleran	15.0	15.0	3.7	6.0	6.0	0.7	0.7	6.0	0.7	
12. BCNU	11.0	16.0	6.6	5.3	5.3	2.5	2.5	2.4	2.5	
13. Actinomycin D	0.07	0.12	0.09	-	-	0.03	0.015	0.03	0.015	
14. Mitomycin C	2.3	2.2	1.3	0.64	0.64	0.2	0.2	-	0.2	
15. Vinblastin	0.60	0.53	-	-	-	0.08	0.08	-	0.08	
16. Vincristine	0.18	0.20	-	-	-	0.024	0.024	-	0.024	
17. Methyl GAG	59.0	93.0	-	-	-	11.0	11.0	-	11.0	
18. Hydroxyurea	-	-	-	-	-	560.0	160.0	-	160.0	

Note: Average animal doses have been compared with human doses indicated by an asterisk in Table 1, and have been rounded to two significant figures.

A Comparison of Small-Animal LD₁₀'s, Large-Animal Maximum Tolerated

Agent	Doses and Human Maximum Tolerated Doses on a mg/m ² Basis							Estimated MTD Man (All Systems)
	LD ₁₀ Swiss Mouse (km=3)	LD ₁₀ BDF ₁ Mouse (km=3)	LD ₁₀ Hamster (km=4.1)	LD ₁₀ Rat (km=5.2)	Rhesus Monkey (km=11.5)	MTD Dog (km=19)	MTD Man (km=37)	
1. Amethopterin	9.5	16.0	103.0	3.1	35.0	2.0	15.0	11.6
2. 6-Mercaptopurine	257.0	186.0	320.0	266.0	644.0	434.0	1000.0	327.0
3. 5-Fluorouracil	126.0	135.0	70.0	130.0	207.0	190.0	555.0	154.0
4. 5-FUDR	494.0	574.0	165.0	463.0	690.0	760.0	1110.0	514.0
5. Nitrogen Mustard	3.8	2.6	5.3	1.9	2.3	9.1	7.4	3.1
6. Nitromin	135.0	94.0		37.0	55.0	84.0	74.0	73.0
7. L-Phenylalanine Mustard	15.0	17.0		12.0	6.3	12.0	7.4	11.5
8. Alanine Mustard	19.0	29.0	46.0		17.0	29.0	33.0	22.8
9. Cytoxan	280.0	340.0	320.0	64.0	621.0	234.0	370.0	266.0
10. ThioTEPA	17.0	20.0	42.0	14.0	11.5	21.0	7.4	16.5
11. Myleran	45.0	45.0		19.0	69.0	114.0	25.0	47.4
12. BCNU	34.0	47.0	48.0	34.0	61.0	45.0	93.0	43.8
13. Actinomycin D	0.21	0.35	0.25	0.45		0.57	0.55	0.34
14. Mitomycin C	6.9	6.5	7.0	6.5	7.4		7.4	6.9
15. Vinblastin	1.8	1.6	2.2				3.0	1.8
16. Vincristine	0.54	0.60	1.4				0.89	0.63
17. Methyl GAG	176.0	280.0	168.0				420.0	211.0
18. Hydroxyurea						10,640.0	5900.0	-

Note: Average animal doses have been compared with human doses indicated by an asterisk in Table 1.
The last column is the weighed estimate from the animal results (See Appendix III).

Table 4. Various Estimated Values Assuming Model (1) and Model (2).

Model (1) (Dose in man mg/m^2) = 1 (Dose in animal system [mg/m^2])			
Animal System	St. Deviation (log scale)	Multipliers for dose in animal system giving lower and upper standard deviation limits (mg/m^2 scale)	
		lower*	upper*
1. monkey	.312	.49	2.1
2. Swiss mouse	.369	.43	2.3
3. BDF ₁ mouse	.379	.42	2.4
4. dog	.422	.38	2.6
5. rat	.495	.32	3.1
6. hamster	.601	.25	4.0
all combined (weighted)	.299	.50	2.0

Model (2) (Dose in man mg/m^2) = A_i (Dose in animal system [mg/m^2]).					
Animal System	Estimate of A_i	$A_i \pm 2 \text{ S.E.}$	St. Deviation (log scale)	Multipliers for dose in animal system giving lower and upper st. deviation limits (mg/m^2 scale)	
				lower	upper
1. monkey	1.15	.79 - 1.67	.293	.51	2.0
2. Swiss mouse	1.39	.93 - 2.06	.323	.48	2.1
3. rat	2.08	1.35 - 3.21	.339	.46	2.2
4. BDF ₁ mouse	1.29	.84 - 1.97	.346	.45	2.2
5. dog	1.05	.60 - 1.83	.400	.40	2.5
6. hamster	1.32	.61 - 2.86	.556	.28	3.6
all combined (weighted)	1.36	1.13 - 1.60	.275	.53	1.9

*As an example, the toxic dosage of amethopterin in the monkey is $40.2 \text{ mg}/\text{m}^2$. Thus, the predicted MTD in man is $40.2 \text{ mg}/\text{m}^2$ with one st. deviation limits $40.2 \times .49 = 19.7 \text{ mg}/\text{m}^2$ to $40.2 \times 2.1 = 84.4 \text{ mg}/\text{m}^2$.

Predicted Dosages (mg/m²) in Man Using Each Animal System
and All Systems Combined

Agent	Swiss Mice	BDF		Hamster	Rat	Monkey	Dog	Overall	
		Mice	Mice					Unweighted	Weighted
1. Amethopterin	13.2	20.6	116.0	6.4	40.2	2.5	17.0	15.7	15.0
2. 6-Mercaptopurine	357.0	240.0	424.0	554.0	740.0	457.0	435.0	444.0	1000.0
3. 5-Fluorouracil	244.0	174.0	92.7	271.0	238.0	200.0	182.0	210.0	555.0
4. 5-FUDR	686.0	740.0	219.0	964.0	793.0	800.0	581.0	699.0	1110.0
5. Nitrogen Mustard	5.3	3.4	7.0	4.0	2.6	9.6	4.8	4.2	7.4
6. Nitromin	187.0	121.0		77.0	63.1	88.3	99.1	99.6	74.0
7. L-Phenylalanine Mustard	20.8	21.9		25.0	7.2	12.6	16.0	15.6	7.4
8. Alanine Mustard	26.4	37.3	61.0		19.5	30.5	35.3	31.0	33.0
9. Cytoxin	388.0	439.0	424.0	133.0	711.0	246.0	345.0	362.0	370.0
10. ThioTEPA	23.6	25.8	55.6	29.1	13.2	22.1	25.7	22.5	7.4
11. Myleran	62.4	58.0		39.5	79.3	120.0	66.8	64.6	25.0
12. BCNU	47.2	60.5	63.5	70.8	68.4	47.3	59.1	59.6	93.0
13. Actinomycin D	0.29	0.27	0.33	0.44		0.54	0.46	0.46	0.55
14. Mitomycin C	9.6	8.4	9.3	13.5	8.5		9.2	9.3	7.4
15. Vinblastin	2.5	2.1	2.9					2.4	3.0
16. Vincristine	0.75	0.77	1.9					0.85	0.89
17. Methyl GAG	244.0	361.0	222.0					287.0	420.0
18. Hydroxyurea						11,190.0			5900.0

More Detailed Description of the Toxicologic Data Used

Small animals (mouse, rat, and hamster).—The classic end point for assessing drug toxicity to small animals is death (LD10, LD50, LD90). A reliable method of determining the lethality of a drug is to give an appropriately spaced series of doses to groups of about 10 animals each; to record percent deaths at each drug level; and then to plot the dose-mortality data on log-probit paper (7), draw a line of best fit, and read the lethal dose for 10, 50, or 90%, or any other fraction of the animals. The reliability of such end points depends on the number of animals, and the LD10, LD50, or LD90 (in mg/kg or mg/m²) for a given animal species is incomplete unless it is accompanied by information on the route of administration, the dosage schedule, and the period of observation for delayed death after cessation of drug administration. Useful information may be gained from the median day of death, during and after administration of various dose levels, and the slope of the dose-mortality curve.

Most of the mouse toxicity data in this analysis were obtained by Schmidt (7) and Griswold et al. (3); the rat toxicity data by Schmidt (7); and the hamster toxicity data by Griswold et al. (8). All toxicity data were plotted as indicated previously and values were read from lines of best fit. About 50 to more than 100 animals were used in each toxicity determination. The ip route was used in most instances, and all animals were kept for 1–3 weeks after the end of treatment for observation of delayed death. The schedules used most frequently were qd 1–5, qd 1–7, qd 1–11, and qd 1–15 days.

We are aware that the LD10 is not as reliable statistically as the LD50; however the LD10 is closer to the maximum doses accepted in typical experimental cancer chemotherapy trials and to the maximum doses reached in clinical drug evaluation.

Some indication of the overall reproducibility and reliability of LD10's obtained by the general procedure described may be found in calculations by Griswold et al. (3): "among the 219 LD10's determined (Swiss mice, qd 1–7; BDF₁ mice, qd 1–7 and qd 1–11 days), the median range between the lower and upper 95% confidence limits was 0.35 logs." No con-

sistent difference was observed in the toxicity of a wide variety of agents to randombred Swiss mice and inbred BDF₁ mice (3).

The procedures for obtaining and interpreting toxicity data for the rat and hamster were essentially the same as those described for the mouse.

Large animals (dog and monkey).—Since it is rarely feasible to obtain extensive dose mortality data for dogs and monkeys, accurate LD10's, LD50's, or LD90's usually are not available. However the lethal dose range in such species is determined for anticancer agents being considered for clinical trial. In general the dose-mortality data for dogs and monkeys consisted of daily dose levels (2-fold increases) given to groups of 2–4 animals up to 100% mortality. The approximate toxicologic end point selected for this analysis was the highest dose which killed 0% of 2–4 animals. Usually, doubling this dose killed all the animals. As with other species, the dose levels given to dogs and monkeys were corrected to a schedule of qd 1–5 days.

The major limiting toxic effects of the classes of agents considered in this analysis were marrow depression and gastrointestinal lesions. Table 1 (Appendix I) presents the basis for rating the intensity of these dose-related hematopoietic effects and gastrointestinal and soft tissue lesions.

Man.—Most clinical cancer chemotherapy studies use an experimental design in which the drug dose and schedule are varied so that each patient receives the optimum dose of the agent and therefore each patient becomes a unit of study. For this type of study, any analysis of the toxic effect of a certain dose, schedule, and route of administration becomes very difficult. For this reason the published literature and unpublished data available were searched for studies using a fixed-dose schedule and fixed route of administration for a series of patients, followed by a period of observation without chemotherapy. In such circumstances it was possible to assess the effects of treatment on the individual. When possible, studies were chosen of patients who had normal peripheral blood and bone marrow and who had not received marrow-suppressive therapy for the 6 weeks preceding the study. Another criterion for selecting data was that objective toxic effects were observed in a significant

Rating of the Intensity of the Major Toxicologic Reactions as Observed in Dogs and Monkeys

Classification	Reaction	Determined By	Basis for Rating as:			
			0	Mild (or +)	Moderate (or ++)	Severe (or +++)
Anemia*		Decrease in RBC count	Essentially none	1.0-1.5 x 10 ⁹ /cmm < control	<4.5 to >3.5 x 10 ⁹ /cmm	<3.5 x 10 ⁹ /cmm
Reticulocytopenia**		Decrease in retic-% RBC	Essentially none	>0.5%; <1/2 control	>0.01%; <0.05%	<0.01%
Hemoconcentration*		Increase in hematocrit	Essentially none	>10%; <20% control	>20%; <30% control	>30% control
Leucopenia*		Decrease in WBC count	Essentially none	<1/2 control	>2.5 x 10 ³ /cmm; <5 x 10 ³ /cmm	<2.5 x 10 ³ /cmm
Thrombocytopenia*		Decrease in platelet count	Essentially none	>10 ⁵ /cmm; <1/2 control	>10 ⁵ /cmm; <10 ⁵ /cmm	<10 ⁴ /cmm
Marrow depression*		Decrease in absolute count	Essentially none	>10 ⁵ /cmm; <5 x 10 ⁵ /cmm	>5 x 10 ⁴ /cmm; <10 ⁵ /cmm	<5 x 10 ⁴ /cmm
Hemorrhagic lesions**		GI tract	Essentially none	Isolated, punctate	Gross - limited area	Gross - widespread
Hemorrhagic lesions**		Generalized, soft tissue	Essentially none	Isolated, punctate	Gross - limited area	Gross - widespread
CNS stimulation		Convulsions	Essentially none		Described as observed	
Other		--	Essentially none		Described as observed	

Note: *Grouped under the term "marrow depression" (MD) in this general paper.

**Grouped under the term "gastrointestinal tract damage" (GI) in this paper.

Detailed data regarding specific hematologic and tissue and organ damage are available but are not included herein. In Table 1 of the text, only the average degree of marrow depression and gastrointestinal damage are presented under 0, mild, moderate, or severe.

number of patients treated with a certain dose and schedule. The most commonly used parameter was white blood cell count (WBC). The toxic manifestations were then graded on a 0 to 3+ scale, ie, none, mild, moderate, or severe (when possible). Chemotherapy experiments which used very small doses of drug given in periods of 6-8 weeks were not included because of the lack of an appropriate counterpart in experimental systems. Therefore we tried to find tests in which maximum tolerated doses were given in minimum time intervals by fixed-dose schedules (and fixed routes).

APPENDIX II

Relationship Between Drug Doses in Milligram Per Kilogram and in Milligram Per Square Meter of Surface Area for Man and for Small and Large Animals

In table 1 (Appendix II) the estimated square meters of surface area are given for several body weights (kg) within each mammalian species. The surface area in square meters was estimated by the formula

$$(\text{body surface area}) = \frac{K \times w^{.75}}{10^4}$$

The K values are given for each species by Spector (ref. 40, p 175) and w is body weight in grams. The K values differ among species

and also within species; however a single K factor was chosen for each species except man. The conversion factors (km) were obtained simply by dividing the body weight by the surface area. Thus to convert a dose in mg/kg to a dose in mg/m², we use the approximate formula

$$(\text{dose in mg/m}^2) = (km) \times (\text{dose in mg/kg})$$

where the (km) factor is selected according to the species and body weight. For example, a dose of 20 mg/kg/day given to a 20-g mouse is approximately equal to $20 \times 3 = 60 \text{ mg/m}^2/\text{day}$.

Note that the (km) factor is simply

$$(km) = \frac{10^2 \times (kg)^{.75}}{K}$$

where kg is weight in kilograms. The (km) factors used in this study were

Species	Approx. wt. (kg)	(km) factor
Man	60	37
Mouse	.020	3.0
Rat	.100	5.2*
Hamster	.050	4.1
Monkey	2.5	11.5
Dog	7.0-8.0	19.0-19.8

* Except as otherwise indicated in table 1 of text.

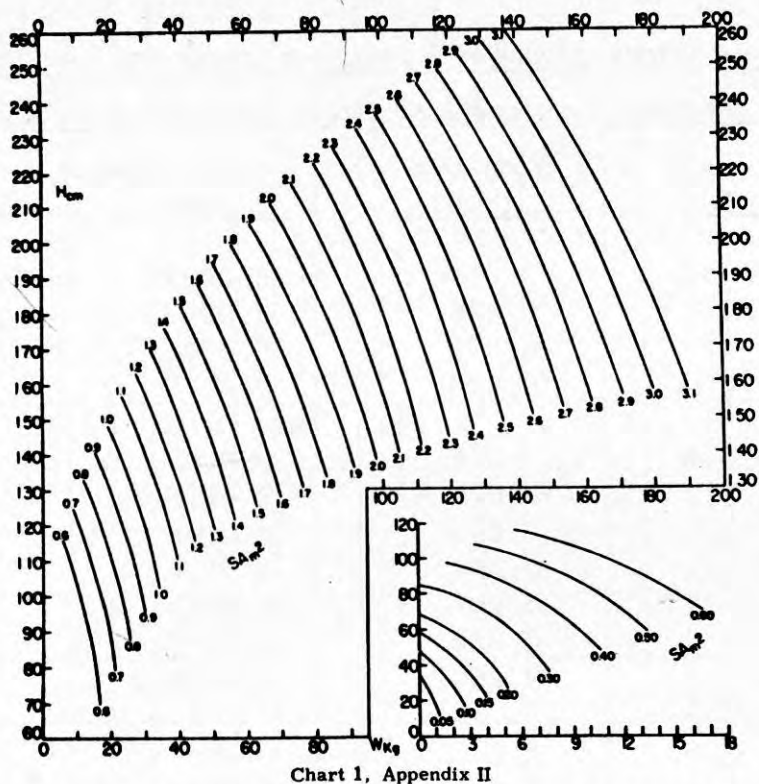


Chart 1, Appendix II

Diagram for Determination of Human Surface Area from Height and Weight. (Insert is Used for Low Range of SAm^2 from 0.05 to 0.60). Taken from Sendroy and Cecchini, J. Applied Physiol. 7: 1-12 (1954). H_{cm} = height in centimeters; W_{kg} = weight in kilograms; SAm^2 = surface area in sq. meters.

(Reprinted by permission of J Appl Physiol)

Conversion Factors (Dosages in mg./kg to mg./m²) for the Mouse,
Rat, Monkey, Dog and Man Given Body Weight Only.

<u>Species</u>	<u>K</u>	<u>Body Wt. (kg)</u>	<u>Square Meters Area</u>	<u>Conversion Factor (km)</u>
Mouse	9.0	0.018	0.0062	2.9
		0.020	0.0066	3.0
		0.022	0.0071	3.1
		0.024	0.0075	3.2
Rat	9.0	.050	0.0122	4.1
		.070	0.0153	4.6
		.080	0.0167	4.8
		0.100	0.0194	5.2
		0.150	0.0254	5.9
		0.200	0.0308	6.5
		0.250	0.0357	7.0
Monkey	11.8	2.0	0.188	10.6
		2.5	0.217	11.5
		3.0	0.244	12.3
Dog	10.1	6.0	0.334	18.0
		7.0	0.369	19.0
		8.0	0.404	19.8
		9.0	0.437	20.6
Man (avg.)		5.0	0.26	19.0
		10.0	0.44	23.0
		20.0	0.80	25.0
		40.0	1.30	31.0
		60.0	1.62	37.0
		70.0	1.80	39.0
		80.0	1.96	41.0

Conversion Factors (Dosages in Mg/Kg to Mg/M² Body Surface Area) for Man Given Height and Body Weight

Body Wt. Kg	Feet: Inches: Cm:	Height																		
		1.3 16 40	1.7 20 50	2.0 24 60	2.3 28 70	2.7 32 80	2.9 35 90	3.3 39 100	3.6 43 110	3.9 47 120	4.3 51 130	4.6 55 140	4.9 59 150	5.3 63 160	5.6 67 170	5.9 71 180	6.3 75 190	6.6 79 200	6.9 83 210	7.3 87 220
5	11	22	19	17	15	14														
10	22	28	26	24	23	21	19	18												
15	33				26	25	24	22	21											
20	44					29	28	26	25	24	22	21								
25	55							30	28	27	26	24	23	22						
30	66							33	31	30	29	27	26	25						
35	77								34	32	31	30	28	27	26					
40	88									35	33	32	31	30	28	27				
45	99									37	35	34	33	31	30	29	28			
50	110									38	37	36	35	34	32	31	30	29		
55	121										39	38	37	35	34	33	32	31		
60	132										41	39	38	37	36	35	34	32	31	
65	143											41	40	39	38	36	35	34	33	
70	154											42	41	40	39	39	37	36	35	
75	165											44	43	41	40	39	38	37	36	
80	176											45	44	43	42	41	40	39	38	
85	187												45	44	43	42	41	40	39	
90	198													45	44	43	42	41	40	
95	209													46	45	44	43	42	41	
100	220														46	45	44	43	42	
105	231															47	46	45	44	
110	242																47	46	45	

Note: The underlined conversion factors are for individuals of approximately average height to body weight ratios.

The above km factors were calculated from data presented in: Spector, W. S., Handbook of Biological Data, W. B. Saunders Company, Philadelphia and London (1956). The basic data (Spector) were derived according to the method of Sendroy and Cecchini, 1954 (Sendroy, J., Jr., and Cecchini, L. P., J. Applied Physiology 7: 1-12, 1954).

Example: A dosage of 2.5 mg/kg/day of 6-MP (to a 20-kilo child of 110-cm height) is equal to 2.5 x 25 (km factor) = 62.5 mg/m²/day.

Table 2 (Appendix II) presents the (km) factors for man. Chart 1 (Appendix II) is a diagram for determining the surface area of humans from height and weight (taken from Sendroy and Cecchini [39]).

It may be of some interest to indicate how the results of the analysis would have changed if surface area had been estimated as

$$(\text{surface area}) = (\text{kg})^{2/3}.$$

The rationale is that since body surface area is clearly not the target area of action of the drug but presumably is proportional to the true target area, it is sufficient to measure surface area in units proportional to the true target area. The surface area unit is simply the two-thirds power of weight, though it is not easy to visualize this quantity. This leads to the formula

$$(\text{dose in mg/surface area}) = (km) \times (\text{dose in mg/kg})$$

where (km) = (kg)^{2/3} instead of [$(\text{kg})^{2/3} \times 10^2$]/ K as before. If the K factors were the same for each species, the analysis in the new surface area unit would be exactly the same as that given. Since the K factors do differ among species, ranging from 9.0–11.8, the results of a re-analysis would differ slightly from those given here but certainly not substantially. The most appropriate K factor for any drug would be that which makes the two-thirds power of weight for each species equal to the surface area where the drug acts. Since this information is not generally known, it matters little whether the K factors among species are assumed to be the same or to differ slightly.

APPENDIX III

Statistical Considerations

The notation used is as follows:

y = true log (dose in mg/m^2) in man

x_i = true log (dose in mg/m^2) in animal system i , ($i = 1, \dots, 6$).

The doses are the MTD in man and the LD10 in each animal system. Now, y and x_i are variables that have particular values when a drug is given according to a certain schedule and route of administration (assumed here to be qd 1–5 days and the ip or iv route with a

few exceptions). Because of random error, and other factors, we do not observe y and x_i , but

$$y' = y + d_i \quad (\text{A1})$$

$$x' = x_i + e_i \quad (\text{A2})$$

where d_i and e_i are random variables. We assume that d_i and e_i are independently distributed with zero means and are independent of y and x_i . The primes indicate observed values of y and x_i .

We postulate that the underlying structural relationship (model) is

$$y = \alpha_i + x_i, \quad (i = 1, \dots, 6) \quad (\text{A3})$$

where $\alpha_i = \log A_i$ according to the notation in the text. In model (1), α_i is zero and in model (2) it is a parameter to be estimated. These are the simplest models that could be considered. Actually the more general relationship $y = \alpha_i + \beta_i x_i$ was also considered but since the estimates of β_i ($i = 1, \dots, 6$) were all near 1, only the simpler models given will be investigated further.

Substituting (A1) and (A2) into (A3), we have

$$\begin{aligned} y' - d_i &= \alpha_i + x_i - e_i \\ y' &= \alpha_i + x'_i + (d_i - e_i) \end{aligned}$$

where $(d_i - e_i)$ is a random variable with zero mean. We have n_i pairs (usually 17) of observations, (y'_j, x'_{ij}) , $j = 1, \dots, n_i$, and we wish to estimate the parameter α_i in model (2). Since each animal system provides an estimate of y , we will also be interested in a combined estimate of y .

The aim in estimating the parameter of the model is to predict a value of y (denoted by $\hat{y}$), for a given value of x' . The prediction equation is

$$\hat{y} = \hat{\alpha}_i + x'_i \quad (\text{A4})$$

As Lindley (38) noted, x'_i is measured without error and standard least squares may be used for estimating α_i . Thus the estimate of α_i , denoted by $\hat{\alpha}_i$, is simply

$$\hat{\alpha}_i = \frac{\sum_j (y'_j - x'_{ij})}{n_i}, \quad (i = 1, 2, \dots, 6).$$

The values of A_i given in the text are the antilogs of $\hat{\alpha}_i$.

To obtain an estimate based on results from all animal systems, we can simply average the values of $\hat{y}$ from the six animal systems or calculate a weighted average where the weight for each y is inversely proportional to its variance. The weighted combined estimate is

$$\hat{y}_{wc} = \frac{\sum_{i=1}^6 w_i (\hat{\alpha}_i + x_i)}{\sum_{i=1}^6 w_i}$$

where

$$w_i = \frac{1/s_i^2}{\sum_{i=1}^6 1/s_i^2}$$

and s_i^2 is the variability about $\hat{y}$. That is,

$$s_i^2 = \frac{\sum_{j=1}^{n_i} (\hat{y}_j - y_j)^2}{n_i - 1}, \quad (i = 1, \dots, 6)$$

for model (2). For model (1) the divisor is n_i .

A sample of the calculations required is given for illustrative purposes, assuming that only two drugs, amethopterin and 6-mercaptopurine (6-MP), have been studied in Swiss mice and man. The data are in log (dose in mg/m²):

Drug	Man ($\hat{y}_i$)	Swiss mice (x_i)
Amethopterin	1.176	0.978
6-MP	3.000	2.410

For model (1) the predicted values of the dose in man are simply the doses observed in Swiss mice, namely, 9.5 mg/m² for amethopterin and 257.0 mg/m² for 6-MP. The standard deviation is

$$s_i = \sqrt{\frac{(1.176 - .978)^2 + (3.00 - 2.410)^2}{2}} = 0.440.$$

For model (2) we have

$$\hat{\alpha}_i = \frac{\sum y_j' - \sum x_j}{2} = \frac{4.176 - 3.388}{2} = 0.394$$

and so $\hat{A}_i = 2.48$. The predicted values of $\hat{y}$ in man are

Drug	Equation	Dose (mg/m ²)
Amethopterin	$\hat{y}_1 = 0.394 + .978 = 1.372$	23.6
6-MP	$\hat{y}_2 = 0.394 + 2.410 = 2.804$	636.8

The standard deviation for model (2) is:

$$s_i = \sqrt{\frac{(1.372 - 1.176)^2 + (3.000 - 2.804)^2}{1}} = 0.277$$

and $1/s_i^2$ is the term in the numerator and the first term in the denominator of w_i . The standard error of α_i is

$$\text{SE of } \alpha_i = \frac{0.277}{\sqrt{2}} = 0.196.$$

LIST OF COMPOUNDS

Actinomycin D: NSC-3053.
 Alanine mustard: NSC-17663; DL-alanine, *N,N*-bis(2-chloroethyl)-, hydrochloride.
 Amethopterin: NSC-740; glutamic acid, *N*-[*p*-[(2,4-diamino-6-pteridiny)l)methyl]methylamino]benzoyl]-.
 BCNU: NSC-409962; urea, 1,3-bis(2-chloroethyl)-1-nitroso-.
 Cytoxan: NSC-26271; 2*H*-1,3,2-oxazaphosphorine, 2-[bis(2-chloroethyl)amino]tetrahydro-, 2-oxide, hydrate.
 5-Fluorouracil: NSC-19893.
 5-FUDR: NSC-27640; uridine, 2'-deoxy-5-fluoro-.
 Hydroxyurea: NSC-32065.
 6-Mercaptopurine: NSC-755; purine-6-thiol, hydrate.
 Methyl-GAG: NSC-32946; guanidine, 1,1'-[(methylethanediyldine)dinitrilo]di-, dihydrochloride, hydrate.
 Mitomycin C: NSC-26980; carbamic acid, ester with 6-amino-1,1a,2,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3':3,4]pyrrolo[1,2-*a*]indole-4,7-dione.
 Myleran: NSC-750; 1,4-butanediol, dimethanesulfonate.
 Nitrogen mustard (HN2): NSC-762; diethylamine, 2,2'-dichloro-*N*-methyl-, hydrochloride.
 Nitromin: NSC-10107; diethylamine, 2,2'-dichloro-*N*-methyl-, *N*-oxide, compd. with hydrochloride (1:1).
 L-Phenylalanine mustard: NSC-8806; L-alanine, 3-[*p*-[bis(2-chloroethyl)amino]phenyl]-, hydrochloride.
 ThioTEPA: NSC-6396; phosphine sulfide, tris(1-aziridiny)-.
 Vinblastine: NSC-49842; vincalkebostine, sulfate, hydrate.
 Vincristine: NSC-67574; leurocristine, sulfate.

REFERENCES

1. OWENS, A. H. Predicting anticancer drug effects in man from laboratory animal studies. *J Chronic Dis* 15:223-228, 1963.
2. PINKEL, D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. *Cancer Res* 18:853-856, 1958.
3. GRISWOLD, D. P., LASTER, W. R., JR., SNOW, M. Y., SCHABEL, F. M., JR., and SKIPPER, H. E. Experimental evaluation of potential anticancer agents. XII. Quantitative drug response of Sa180, Ca755, and leukemia L1210 systems to a "standard list" of "active" and "inactive" agents. *Cancer Res (supp)* 23(No. 4, part 2):271-520, 1963.
4. HERTZ, R., LEWIS, J., JR., and LIPSETT, M. B. Five years experience with chemotherapy of metastatic choriocarcinoma and related trophoblastic tumors in women. *Amer J Obstet Gynec* 82:631-640, 1961.
5. FREIREICH, E. J., KARON, M., FLATOW, F. and FREI, E. III. Effect of intensive cyclic chemotherapy (BIKE) on remission duration in acute lymphocytic leukemia. (Abstr). *Proc Amer Ass Cancer Res* 6:20, 1965.
6. KARNOFSKY, D. A. Cancer chemotherapeutic agents. *CA* 14:67-72, 1964. Also personal communication: "these doses are approximate, and some patients may tolerate 2 to 3 times as much or less than noted." These values represent best estimates of the "usual dose" and "usual number of doses/course" for adults.
7. SKIPPER, H. E., and SCHMIDT, L. H. Quantitative assessment of various classes of agents employing advanced leukemia L1210 in mice. *Cancer Chemother Rep* 17:1-178, 1962.
8. GRISWOLD, D. P. Unpublished data.
9. RALL, D. P. Unpublished data obtained under NCI, CCNSC contract at Hazleton Laboratories.
10. PHILIPS, F. S., STERNBERG, S. S., HAMILTON, L., and CLARKE, D. A. The toxic effect of 6-mercaptopurine and related compounds. *Ann NY Acad Sci* 60:283-296, 1954.
11. ANSFIELD, F. J. Personal communication; manuscript in preparation.
12. MOERTEL, C. G., REITEMEIER, R. J., and HAHN, R. G. Fluorinated pyrimidine therapy of advanced gastrointestinal cancer. *Gastroenterology* 46:371-378, 1964.
13. CLIFFORD, P., CLIFT, R. A., and DUFF, J. K. Nitrogen mustard therapy combined with autologous marrow transfusion. *Lancet* 1:687-690, 1961.
14. KRETCHMAR, A. L., ANDREWS, G. A., and SITTERSON, B. W. Attempted bone marrow autografts after large doses of nitrogen mustard. *New Eng J Med* 268:427-428, 1963.
15. SCHMIDT, L. H. Unpublished data.
16. CLOSE, H. P. Unpublished data. VA Chemotherapy Group.
17. BURNS, B. C., RUTLEDGE, F., and GALLAGER, H. S. Phenylalanine mustard in the palliative management of carcinoma of the ovary. *Obstet Gynec* 22:30-37, 1963.
18. BURNS, B. C. Personal communication; manuscript in preparation.
19. DIETRICH, F. S., COPE, C., RIVERS, S., KRANTZ, S., BAUM, G., BECK, H. J., and RODENSKY, P. Clinical trial with alanine mustard. *Cancer Chemother Rep* 23:31-38, 1962.
20. COGGINS, P. R., EISMAN, S. H., ELKINS, W. L., and RAYDIN, R. G. Cyclophosphamide therapy in carcinoma of the breast and ovary—a comparative study of intermittent massive versus continuous maintenance dosage regimens. *Cancer Chemother Rep* 15:3-8, 1961.
21. SCHABEL, F. M., JR. Unpublished data.
22. MOORE, G. E. Clinical experience with triethylthiophosphoramide with special reference to carcinoma of the breast. *Ann NY Acad Sci* 68:1074-1080, 1958.
23. DeVITA, V. T., GOLD, G. L., OWENS, A. H., and MILLER, J. M. Preliminary studies with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). (Abstr). *Proc Amer Ass Cancer Res* 5:15, 1964.
24. MOORE, G. E., DiPAOLO, J. A., and KONDO, T. The chemotherapeutic effects and complications of actinomycin D in patients with advanced cancer. *Cancer* 11:1204-1214, 1958.
25. PHILIPS, F., SCHWARTZ, H. S., STERNBERG, S. S., and TAN, C. Toxicity of actinomycin D. *Ann NY Acad Sci* 89:348-360, 1960.
26. MILLER, E., SULLIVAN, R. D., and CHRYSOCHOOS, T. The clinical effects of mitomycin C by continuous intravenous administration. *Cancer Chemother Rep* 21:129-135, 1962. Amplified by personal communication from R. D. Sullivan.
27. EVANS, A. E. Mitomycin C. *Cancer Chemother Rep* 14:1-9, 1961.
28. HERTZ, R., LIPSETT, M. B., and MAY, R. H. Effect of vincalkebostine on metastatic choriocarcinoma and related trophoblastic tumors in women. *Cancer Res* 20:1050-1053, 1960. Amplified by personal communication from G. T. Ross.
29. GOLDENBERG, I. S. Vinblastine sulfate (VBL) therapy of women with advanced breast cancer. *Cancer Chemother Rep* 29:111-113, 1963.
30. SMART, C. R., ROCHLIN, D. B., NAHUM, A. M., SILVA, A., and WAGNER, D. Clinical experience with vinblastine sulfate (NSC-49842) in squamous cell carcinoma and other malignancies. *Cancer Chemother Rep* 34:31-45, 1964.
31. SULLIVAN, R. D. Myleran therapy in bronchogenic carcinoma. *Ann NY Acad Sci* 68:1038-1045, 1958.
32. CARBONE, P. P., BONO, V., FREI, E. III, and BRINDLEY, C. O. Clinical studies with vincristine. *Blood* 21:640-647, 1963.
33. CAREY, R. W., HALL, T. C., and FINKEL, H. E. A comparison of two dosage regimens for vincristine. *Cancer Chemother Rep* 27:91-96, 1963.
34. LEVIN, R. H., HENDERSON, E., KARON, M., and FREIREICH, E. J. Treatment of acute leukemia with methylglyoxal bis(guanylhydrazone). *Clin Pharmacol Ther* 6:31-42, 1965.
35. THURMAN, W. G., BLOEDOW, C., HOWE, C. D., LEVIN, W. C., DAVIS, P., LANE, M., SULLIVAN, M. P., and GRIFFITH, K. M. A Phase I study of hydroxyurea. *Cancer Chemother Rep* 29:103-07, 1963.
36. RUBNER, M. Ueber den Einfluss der Körpergrösse Stoff- und Kraftwechsel. *Z Biol* 19:535-562, 1883.
37. PHILIPS, F. Personal communication.
38. LINDLEY, D. V. Regression lines and the linear functional relationship. *J Roy Statist Soc Supp* 9:218, 1947.
39. SENDROY, J., and CECCHINI, L. Determination of human body surface area from height and weight. *J Appl Physiol* 7:1-12, 1954.
40. SPECTOR, W. S. *Handbook of Biological Data*. Philadelphia, W. B. Saunders Co., 1956.