The SLE virus appears to be one which parasitizes the tumor cells and proliferates readily while exerting no more than a slight oncolytic effect at best on the malignant cells in the process.

Summary. The virus of St. Louis encephalitis has been propagated in serial passage in the Ehrlich carcinoma of mice. The optimal conditions for the multiplication of the agent have been determined and relatively high viral titers have been obtained in the ascitic fluid. Some evidence suggesting a slight oncolytic effect has been obtained.

† Preliminary comparative Warburg studies carried out by Dr. Robert E. Olson on normal and viral infected tumor cells have shown no significant differences in endogenous metabolism, or in exogenous metabolism when the following substrates were added: pyruvate, lactate, succinate or glucose.

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Consideration of Dose-Weight Relationships. (20505)

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Susceptibility of individual animals to the action of a drug is frequently expressed in terms of the dose required to produce a given effect. With some drugs this dose varies in a systematic fashion with the weight of the animal. It has become common practice to express dose as a linear function of body weight (mg/kg) in an effort to remove this source of systematic variation. That such a correction implies a direct proportionality between dose and weight of animal is not generally recognized, in spite of the fact that the inadequacies of this correction have been emphasized(1-5). Moreover, application of this correction to relationships other than a direct proportionality serves only to trade one type of systematic variation for another. Occasionally, this correction term has been applied when none was indicated, and erroneous interpretations of the influence of weight on susceptibility have resulted.

An example of the inappropriate use of the linear correction factor may be found in the susceptibility of wild Norway rats to alpha-naphthyl-thiourea (ANTU). Adequate data have been presented on this(6) to allow investigation of the dose/weight relationships.

On examining these data (Table I) it is apparent that the LD_{50} in mg/kg varies with weight, and in a systematic fashion. In the last column is found the LD_{50} in mg/animal for each weight group which we have calculated as the product of mean weight and LD_{50} in mg/kg. These values, in contrast to the LD_{50}'s in mg/kg, are relatively constant and show no systematic variation related to body weight. The mean LD_{50} is 2.63 mg/animal with a coefficient of variation of 15.6%. The comparable index of variation for the LD_{50}'s in mg/kg is 83.3%. The slope constant of the regression of LD_{50} in mg/animal on body

TABLE I.
Toxicity of ANTU for Wild Norway Rats.

No. rats*	Mean wt* (kg)	$LD_{50} \pm$ S.E.* (mg/kg)	LD_{50}† (mg/animal)
24	.039	58 ± 4.4	2.3
40	.081	43 ± 5.7	3.5
35	.112	22 ± 3.2	2.5
22	.140	18 ± 2.7	2.5
29	.170	16 ± .9	2.7
36	.263	8.1 ± .9	2.1
82	.348	7.7 ± 1.0	2.7
56	.448	6.2 ± .6	2.8

* From Dieke and Richter.
† Calculated as product of mean wt and LD_{50} in mg/kg.

weight is not significantly different from zero; and the line may be regarded as horizontal with the intercept (2.63 mg), representing an estimate of the LD_{50} in mg/animal for all weight groups. Thus, it is evident that the toxicity of ANTU for wild Norway rats is expressed with less variation as dose/animal than dose/unit weight of animal, and the use of the customary correction for body weight (mg/kg) in expressing the LD_{50} introduces systematic variation between weight groups.

These data, presenting only mean body weight and LD_{50} in mg/kg with its standard error, allow no estimation of the intra-group variation of the LD_{50} in mg/rat as obtained by calculation. It seemed of interest, therefore, to determine the resistance of rats of differing weight to ANTU and to administer the drug on a dose per animal basis. This permits estimation of variation within weight groups and also obviates any inaccuracies in converting an LD_{50} in mg/kg to LD_{50} in mg/animal.

Adult male Sprague-Dawley albino rats were placed according to body weight into 8 groups with a range of about 40 g in each group. The dose of ANTU, dissolved in 1 cc of propylene glycol, was injected intraperitoneally, 5 doses for each group. All animals not dead by 24 hours were classified as survivors. The LD_{50} in mg/animal and the 95% confidence limits were determined for each weight group by the method of Litchfield and Wilcoxon(7). In addition, the LD_{50}'s in mg/kg were obtained by the same method. The mean weight for each group was used to determine each of the 5 mg/kg doses.

Results. As may be seen from the data in Table II, the LD_{50}'s in mg/animal show no systematic variation and they all lie within the 95% confidence limits of each other. The mean value is 0.98 mg/rat and the coefficient of variation is 5%. The LD_{50} in mg/kg varies from 6.80-2.15, consistent with data presented in other reports(6,8), and coefficient of variation of these values is 60%. The slope constant of the regression of LD_{50} in mg/rat on body weight (0.00011) is not significantly different from zero, and again the regression line may be considered horizontal with the intercept (0.98) providing an estimation of the LD_{50}. Thus, for the albino, as well as the wild Norway rat, the dose of ANTU necessary to kill 50% of the animals is independent of body weight and may be properly expressed as mg ANTU/animal.

TABLE II. Toxicity of ANTU for Albino Rats.

No. rats	Mean wt (kg)	LD_{50} in mg/animal	LD_{50} in mg/kg
42	.154	1.02 (.79–1.31)*	6.80 (5.40–8.57)*
64	.207	.90 (.76–1.06)	4.33 (3.80–4.94)
123	.246	.91 (.74–1.12)	3.73 (3.11–4.48)
92	.282	.98 (.84–1.14)	3.50 (2.97–4.13)
52	.324	1.04 (.85–1.24)	3.48 (2.78–4.35)
49	.363	.99 (.79–1.25)	2.78 (2.06–3.75)
58	.407	1.00 (.86–1.16)	2.60 (2.18–3.09)
28	.443	.97 (.80–1.18)	2.15 (1.79–2.58)

* 95% confidence limits.

Discussion. The use of an improper weight correction factor has in this instance led to the erroneous conclusion that there is marked age and weight variation in the susceptibility of wild Norway rats to ANTU. Instead of removing body weight as a source of systematic variation, this correction has actually added it. It seems appropriate, therefore, to consider what constitutes a proper correction of dose for body weight. The first requirement for this correction is that it should minimize variation in effective dose between animals grouped according to weight as compared to variation within these weight groups. Further, variation in effective dose between weight groups must be random and not related to body weight. This obtains if there is no significant regression of corrected effective dose on body weight.

The correction factor may be determined from experimental data by deriving an equation that satisfactorily relates amount of drug necessary to produce a given effect to weight of animals. In general, if LD_{50}'s are plotted against mean weight of the animal groups, a smooth curve will be obtained. Since this relationship usually is curvilinear, rectification is necessary. For many drugs, the empirical procedure of plotting log dose against log weight will adequately rectify the data. This relationship may be expressed by the equation: dose $=$ (a) weight$^{(b)}$. The value of the exponent (b) represents the slope of the line from the double log transformation, and (a) represents the intercept constant by which the

dose is multiplied to remove the variation due to weight. The correction factor, therefore, is 1/a weight^b. There are numerous instances in which dose of drug is proportional to a power of body weight(2,3,9-11). If the value of (b) is unity, then a direct proportionality exists and the customary mg/kg correction is proper(12,13). If (b) is zero, then the correction factor becomes unity and dose is independent of body weight. This is illustrated by the data of ANTU in albino rats for which it can be shown that $Y = 0.98 \text{ weight}^{0.03 \pm 0.06}$.

Summary. The toxicity of alpha-naphthyl thiourea for both wild pigmented and laboratory albino rats, when expressed as a dose per animal, appears to be constant over a wide age and weight range. The use of the customary mg/kg correction for body weight introduces marked systemic variation. The requirements for a proper correction factor of dose for weight of animal are considered and it is suggested that this factor should minimize variation in effective dose between groups of animals of different weights and make corrected dose independent of body weight.

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Effect of Phenylbutazone (Butazolidin) on Renal Excretion of P-Aminohippurate and Thiosulfate in the Dog.* (20506)

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This study of the effect of phenylbutazone‡ on the renal tubular transport of p-aminohippurate (PAH) and thiosulfate was prompted by a report that the drug produced a striking diminution in the serum uric acid of patients with gout(1). It seemed possible, therefore, that the drug might be a uricosuric agent. If so, it would be of interest to determine whether it resembles p-(di-n-propylsulfamyl)-benzoic acid (Benemid), which blocks PAH but not thiosulfate transport, or 4'Carboxyphenylmethanesulfonanilide (Caronamide) which blocks both PAH and thiosulfate(2). Subsequent reports as to the uricosuric activity of phenylbutazone are conflicting. One group of investigators states that there is "no marked increase in urinary excretion of urates"(3) while another believes that the drug "usually increases urinary excretion of urates"(4). Phenylbutazone has also been said to inhibit

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