dicative of abnormal adrenal cortical function. No evidence was presented to implicate abnormal adrenal function as the cause of hypoglycemia which developed in pertussis-vaccine treated mice(2). Other evidence exists which suggests the possibility that pertussis vaccine causes dysfunction of the adrenal glands. The sensitivity to histamine (injected I.P.) in pertussis-treated and adrenalectomized mice is partially or completely restored by proper treatment with cortisone (5) or a combination of cortisone and epinephrine(14). Nevertheless, the effects of these substances may be pharmacological in nature rather than specific physiological effects of replacement therapy after adrenal inactivation.

The authors are not aware of published data which prove that pertussis-vaccine alters the adrenal cortex as indicated by cholesterol content, ascorbic acid depletion, or other tests of adrenal function.

Summary. In a Swiss-Webster strain of mice, pertussis vaccine treatment increased the sensitivity to intravenously injected histamine 33 times, whereas surgical adrenalectomy had no significant effect on sensitivity to histamine. This finding, in addition to lack of direct evidence to the contrary, warrants the conclusion that *Hemophilus pertussis* vaccine enhances sensitivity of mice to histamine through some mechanism other than impairment of adrenal function.

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Diet and TEPA Therapy in Sarcoma-Bearing Rats.* (22151)

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Data have been presented to demonstrate that N, N', N'' triethylenephosphoramide (TEPA) reduced food efficiency and growth of normal as well as tumor tissue in tumor-bearing rats(1). Given an optimum dosage and a susceptible tumor, however, reduction in growth of the tumor was greater than reduction in weight of normal tissues(2). These data also demonstrated that a high protein diet, or a low casein diet supplemented with methionine, reduced the depleting effect of TEPA on normal tissue without altering the deleterious effect on the tumor(1,2). Other experiments have demonstrated that supplementing a low casein diet with a mixture of methionine and guanidoacetic acid or methionine and glycine resulted in increased protection of normal tissues to the depleting effects of the tumor(3). Further work has been done to determine the effect of these mixed supplementations upon chemotherapy of TEPA in tumor-bearing rats.

* Some of these results were read before the Am. Chem. Soc. Meeting in New York, Sept. 1954. These studies were supported by an Institutional Grant from the American Cancer Society.

TABLE I. Effect of Various Supplementations in Diet Containing 12% Casein upon TEPA Therapy (1 mg/Day/kg Body Wt). Food efficiencies were calculated as grams gain in body wt (tumor wt subtracted) per 100 g of food intake.

Diet	Food efficiency	Tumor wt, g	Gain in body wt/tumor
	Avg data using 10 animals/group		
Casein 12% (no TEPA)	8.6	36.7	1.41 ± .26*
Casein 12% + TEPA	4.1	10.9	1.97 ± .39
+ glycine (Gl) + TEPA	4.4	9.7	2.29 ± .24
+ alanine (Al) + TEPA	4.2	10.7	2.02 ± .44
+ NH_4 citrate (NH_4) + TEPA	4.2	8.4	1.50 ± .86
+ methionine (M) + TEPA	5.4	8.4	3.24 ± .67
+ M + NH_4 + TEPA	4.0	8.2	2.76 ± .80
+ M + Al + TEPA	5.7	13.3	3.00 ± .50
+ M + Gl + TEPA	5.4	7.2	3.61 ± .30
+ M + guanidoacetic acid + TEPA	8.1	7.2	5.64 ± 1.22
Casein 12% + TEPA	4.2	6.9	1.95 ± .67
+ M + TEPA	5.9	5.4	3.10 ± .96
+ M + NH_4 + TEPA	6.2	7.1	3.37 ± .95
+ M + Gl + TEPA	6.0	7.1	3.15 ± .98
+ M + casein 1.5% + TEPA	6.1	7.5	3.04 ± .78
+ M + guanidoacetic acid + TEPA	9.6	4.6	6.57 ± 1.12
	Avg data using 58 animals/group		
Casein 12% + TEPA	4.0	7.7	2.47 ± .59
+ M + TEPA	7.9	7.3	4.37 ± .74
+ M + guanidoacetic acid + TEPA	10.31	5.5	7.62 ± 1.00

* Stand. error.

Methods. Transplanting the sarcoma in the rat and measuring growth of the tumor have been described previously(1). The tumor developed most rapidly in rats fed a semi-synthetic diet containing 12% casein, a diet that has been reported in detail(1). The effect of various types of supplementation of the diet on growth of the body and the sarcoma in the presence of TEPA is reported in this paper. These supplements were 0.67% DL methionine and 0.67% DL methionine plus 0.67% guanidoacetic acid. These percentages and mixtures had been demonstrated to be optimum for growth of normal tissue in tumor-bearing rats(3,4) and for growth in weanling rats(5) fed 12% casein diet. Glycine (1.28%), alanine (1.53%), ammonium citrate (1.95%) and casein (1.5%) which contain nitrogen in amounts equivalent to that found in guanidoacetic acid (0.67%) were studied also as single supplements and combined with methionine. Food efficiencies were calculated as grams gained in body weight (tumor weight subtracted) per 100 g of food intake. TEPA was injected intraperitoneally as 1 mg/day/kg of body weight after tumor had reached approximately one g in weight and was well established. Ten rats were used to determine the effect of each supplement on TEPA therapy.

Results. Data recorded in Table I illustrate food efficiencies, tumor weights and Δ body weight/tumor ratios approximately 3 weeks after transplantation of the sarcoma. The rate of increase in body with respect to the tumor is taken as one measure of the effect of the tumor on the body. At the end of 3 weeks the tumor had reached lethal proportions (36.7 g) in rats not given TEPA. The Δ body/tumor ratio was low (1.41) indicating a depleted body. The TEPA therapy (1 mg/day/kg body weight) was started in other groups of rats after the tumor had reached about one g in size and was well established. This therapy reduced growth of tumor to 10.9 g in rats fed 12% casein diet over this 3-week period but also reduced food efficiency and growth of the body of the animal. Supplementing the 12% casein diet with glycine, alanine or ammonium citrate did not alter results significantly. Supplementing with methionine, however, did increase food efficiency and rate of growth of the body with respect to the tumor in the

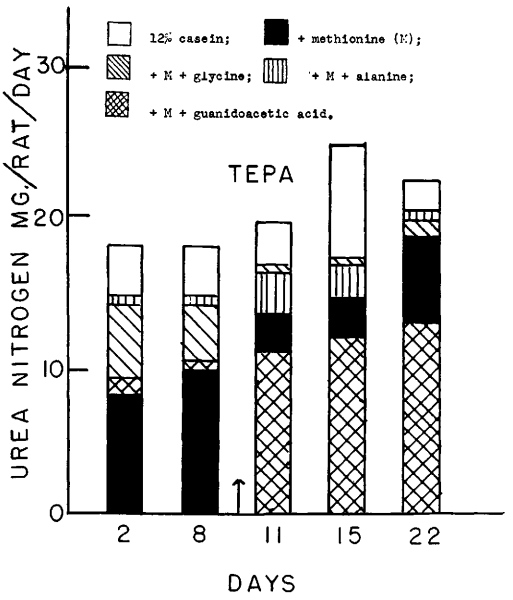

FIG. 1. Effect of different diets on excretion of urea nitrogen in sarcoma-bearing rats. All values start from base. TEPA therapy was instituted at time indicated by arrow.

presence of TEPA. Supplementing with methionine plus guanidoacetic acid increased food efficiency and rate of growth of the body still further. Adding an equivalent amount of nitrogen to guanidoacetic acid in the form of glycine, alanine, ammonium citrate or casein with the methionine did not have the marked effect noted with guanidoacetic acid. results which suggest a specific role for this acid.

The possibility that supplementation with a mixture of methionine and guanidoacetic acid could reduce catabolic activity of tissue proteins was suggested. The white bars in Fig. 1 record excretion of urea nitrogen in tumor-bearing rats fed 12% casein, data that illustrate the high excretion of urea nitrogen associated with a nutritionally malignant tumor. The black bars illustrate reduction in excretion of urea nitrogen in rats fed the casein diet supplemented with methionine. The bars with slanted lines record excretion in the presence of methionine plus glycine while bars with vertical lines record excretion of urea nitrogen in the presence of methionine plus alanine. Adding glycine or alanine increased excretion of urea, probably reflecting the catabolism of these amino acids. The bars with crossed lines illustrate excretion of urea nitrogen in tumor-bearing animals fed the casein diet supplemented with both methionine and guanidoacetic acid. Thus methionine plus guanidoacetic acid reduced excretion of urea nitrogen markedly during TEPA therapy, a reduction that may be correlated with better gain in body weight. These results emphasize the importance of combining nutritional therapy with chemotherapy.

Summary. Data have been presented to demonstrate that TEPA reduced food efficiency and growth of body weight as well as tumor weight in sarcoma-bearing rats fed a 12% casein diet. Supplementing with methionine and guanidoacetic acid increased food efficiency and growth of the body without increasing the growth of the tumor. This increase in growth of the body is correlated with reduction in excretion of urea.

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