500 mg/kg are similar in some aspects to the clinical phenomena of epilepsy, the effects in dogs are dealt with in some detail.

Early effects were alike in all the dogs, regardless of dose or route of administration. All appeared irritable and all urinated, defecated, and vomited, and some became restless. Three dogs that were passing into the second stage of action seemed dazed, panted a great deal, and salivated to some extent. Panting and salivation became more marked as the second stage progressed. Walking was associated with head held low, attempts to lie down, and finally a collapse. Feces were mixed with considerable mucus. The remarkable thing about these second-stage dogs was that they recovered several times and seemed to behave normally for intervals of 5 to 10 minutes, after which they again relapsed. In every instance where coma did not develop, symptoms disappeared within 3 hours.

Late stages of toxicity were always ushered in with considerable excitability. Barking, panting, and salivation were very marked. Convulsions of the clonic-tonic type occurred at intervals, between which the dogs seemed stuporous. Continuous salivation and occasional twitching, particularly of the extremities, were observed between the seizures.

Dogs given kojic acid intravenously exhibited a more severe degree of toxicity than those given the acid by another route. None of the dogs died, although the canine that received 500 mg/kg of kojic acid intravenously exhibited a very stormy convulsive stage. All of the dogs given kojic acid intravenously developed third-stage toxicity, and the two dogs given the higher doses of kojic acid had convulsions of the clonic-tonic type. Effects, regardless of the dose, occurred within 15 minutes and, with the largest dose, within 5 minutes. None of the dogs recovered completely until approximately 24 hours after injection, and the dog given the largest dose, 500 mg/kg, was not well for about 48 hours. The dog given the smallest dose of kojic acid intravenously, 200 mg/kg, recovered sufficiently in about 8 hours to drink small quantities of water.

The reaction patterns observed in the dogs given kojic acid subcutaneously and peritoneally were similar to those observed after intravenous administration. What differences were noted could be ascribed mainly to the route.

If the response of the dogs differs in any manner from the manifestations of the other animal species, it is in the retching and vomiting observed early, and in what may be described as intervals of relative normalcy between periods of seizure and later effects. Since deaths, with the doses used, occurred in the other animals and not among the dogs, it is possible that the latter are better able to detoxify kojic acid.

In the evaluation of the protective ratio (PR) of barbital and phenobarbital (50 mg/kg each) by the Orloff method (*4*), kojic acid was substituted for, and compared with, Metrazol. The average dose of Metrazol for a single twitch was 50 mg/kg and for a persistent convulsion, 150 mg/kg. To produce comparable effects with kojic acid took 135 and 400 mg/kg, respectively. Average dosages were obtained from 20 mice weighing 18 to 20 g. The protective ratios are tabulated in Table 1. The ratios for barbital-Metrazol and for barbital-kojic acid are very much alike.

Metrazol is a much more toxic substance per unit weight than kojic acid, for the latter required approximately 400 mg/kg of body weight to produce a persistent convulsion, whereas Metrazol required approximately one-third of this amount. It is of interest to note that when kojic acid was administered to mice in the dose of 400 mg/kg of body weight by way of the rapid infusion technique (effective convulsive dose studies), two out of ten mice died, whereas all recovered from an equal amount of kojic acid administered by the divided-infusion method. The detoxification mechanism probably is given a longer opportunity to act in the divided-infusion method.

Table 1. Evaluation of the anticonvulsive properties of barbital and phenobarbital—comparison of kojic acid and Metrazol. Twenty mice were used in each experiment.

Group	Time (min)	Dose (avg.) for one twitch (mg/kg)	PR for one twitch	Dose (avg.) persistent convulsions	PR for persistent convulsions
Phenobarbital-Metrazol	5	83.00	1.66	240.00	1.60
	60	116.50	2.33	180.00	1.20
	120	100.00	2.00	255.00	1.70
Phenobarbital-kojic acid	5	236.25	1.75	664.00	1.66
	60	337.50	2.5	415.00	1.00+
	120	286.20	2.12	580.00	1.45
Barbital-Metrazol	5	83.00	1.66	195.00	1.30
	60	100.00	2.00	225.00	1.50
	120	66.50	1.33	180.00	1.20
Barbital-kojic acid	5	218.70	1.62	440.00	1.10
	60	270.00	2.00	600.00	1.50
	120	236.25	1.75	420.00	1.00+

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Detection of Rare-Earth Ions as Oxalates and Cupferrates

Although a great amount of work has been published on the rare-earth oxalates, little is known about the sensitivity of the reaction between the metal ions and oxalic acid. In 0.5*N* mineral acid medium at 60°C, the sensitivity limit has been set as 700 ppm (*1*). This, however, is for the rare-earth group and not for the individual rare-earth metal ions.

Cupferron (ammonium nitrosophenylhydroxylamine) also forms insoluble precipitates with the rare-earth metal ions (*2, 3*). However, nothing is known concerning the sensitivity of the precipitation reaction.

A modification of the method of Irving, Butler, and Ring (*4*) was used to determine the reaction sensitivity. Tests were conducted in 1- by 6-in. test tubes containing a known amount of the 0.01*M* or 0.001*M* rare-earth metal chloride solution and 0.2 ml of 0.1*M* precipitating agent solution in a total volume of 7.0 ml. The test solutions were heated for 10 minutes at 80°C, allowed to cool to room temperature, and then observed visually for the presence of a precipitate.

Table 1. Results of sensitivity tests.

Rare-earth ion	$H_2C_2O_4$ (M^{+3} μg/ml)	Cupferron (M^{+3} μg/ml)
Lanthanum	6.3	2.4
Cerium (III)	6.4	1.6
Praseodymium	6.4	1.6
Neodymium	6.6	2.5
Samarium	6.9	5.1
Gadolinium	17.8	17.8
Yttrium	10.2	10.2

The results of the sensitivity tests are given in Table 1. In general, cupferron appears to be a more sensitive reagent for the detection of the metal ions than oxalic acid. The sensitivity of the oxalic acid tests are greater than those previously found (*1*) but this is perhaps attributable to the absence of a mineral acid. The sensitivity of both reagents decreases with an increase in metal ion atomic number.

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Blood Groups in Pituitary Adenoma—"Suspected Correlation" Reexamined

Mayr, Diamond, Levine, and Mayr (*1*) have recently presented data on ABO blood groups in 123 patients with chromophobe adenoma of the pituitary gland. Of these patients, 57 were from three Boston hospitals and 66 from two hospitals in New York City—23 from the New York Hospital and 43 from the Presbyterian Hospital. Boston and New York patients alike showed marked deviations—more group O, less group A—from the distributions (i) estimated for the total Boston population and (ii) found among 637 Boston patients with brain tumors other than chromophobe adenoma. Distributions i and ii were virtually identical. When the Boston brain-tumor patients were compared with all 123 patients with chromophobe adenoma, the χ^2 test gave a p value < 0.001, but when they were compared with the 57 Boston adenoma patients, $0.02 > p > 0.01$ (my calculation).

Mayr *et al.* wisely considered their findings as tentative, in view of the smallness of their pituitary adenoma sample, despite the statistical significance of the deviation and the concordance of data from four of the five hospitals.

Their investigation has been extended for two reasons. A previous compilation (*2*) on a larger sample of Presbyterian Hospital patients with chromophobe adenoma of the pituitary had shown a blood group distribution unlike that of Mayr *et al.* from the same hospital and one which, in fact, did not differ from that of the Presbyterian Hospital as a whole (*3*). Moreover, the adequacy of a Boston population as a control can be questioned, in view of the high proportion, in certain New York hospitals, of Negroes, with a greater than 2 to 1 preponderance of blood group O over A (*4*), and in view of the different ancestry of the Boston and New York white populations. Not only cities but hospitals within a city and even services within the same hospital may vary widely in genetic composition. It was therefore decided to review (*5*) all cases of chromophobe adenoma at the Presbyterian Hospital for the past 20 years, as far back as records are readily available, and to compare their ABO incidence with that for the Presbyterian Hospital as a whole. This was based on all persons (2259 in number) who received blood transfusions during a 6-month period in 1953. Although the hospital population may have changed over the 20-year period, the transfusion series was deemed an adequate control group for the purpose.

After exclusion of mixed chromophobe and eosinophilic adenomas and of cases where the diagnosis was doubtful or where a microscopic tumor was encountered incidentally at autopsy, 321 cases of adenoma were found. The diagnosis rested on tissue examination or on firm clinical grounds (including enlarged sella turcica, encephalograms, endocrinological and visual abnormalities, and response to x-ray therapy), or on a combination of the two. Of the 321 patients, blood had been typed in 203. There was no difference in ancestry between those who had and those who had not blood-group determinations ($p = 0.60$) or in blood-group frequencies between the 132 with and the 71 without tissue diagnosis ($0.05 > p > 0.02$). The patients with blood-group determinations included 18.2 percent Jews, 7.4 percent Italians, 46.4 percent other whites, and 17.2 percent Negroes. Corresponding figures for the "transfusion group" were quite comparable—16.1 percent, 5.7 percent, 60.0 percent, and 16.4 percent.

In ABO frequency (Table 1), neither whites, Negroes, nor the adenoma series as a whole, which also included eight Puerto Ricans, ten other Latin Americans, and one Chinese, differed from the corresponding "transfusion" group. Chi-square tests gave the respective p values of 0.40, 0.40, and 0.60. While there was a slight percentage preponderance of group O and deficit of A, it is not permissible statistically to compare such subtotals when the complete distributions do not differ (*6*). Neither the total Presbyterian Hospital adenoma series nor the white subgroup within it differed from the Boston brain-tumor series of Mayr *et al.*—p values are 0.25 and 0.40, respectively. Thus, a sizable Presbyterian Hospital series affords no basis for the "suspected correlation" between blood-group frequency and pituitary adenoma.

Should a comparable anlysis of the New York Hospital data yield similar results—a not unreasonable supposition—the "suspected correlation" would rest solely on a probability, based on 57 Boston patients, between the 1-percent and 2-percent significance levels—far from the 0.001 level recommended by Fraser Roberts (*7*) for blood-group correlations.

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Table 1. ABO blood groups in Presbyterian Hospital patients receiving blood transfusion and those with chromophobe adenoma of the pituitary.

	Blood group								
	O		A		B		AB		Total
	No.	%	No.	%	No.	%	No.	%	No.
Whites									
"Transfusion group"	802	43.4	751	40.6	213	11.5	82	4.4	1848
Adenomas	71	47.3	50	33.3	21	14.0	8	5.3	150
Negroes									
"Transfusion group"	187	50.5	101	27.3	67	18.1	15	4.0	370
Adenomas	20	58.8	8	23.5	6	17.6	0	0	34
Total series									
"Transfusion group"	1011	44.5	865	38.3	286	12.6	97	4.6	2259
Adenomas	101	49.8	66	32.5	28	13.8	8	3.9	203