The lumens of these cysts were filled with a mildly basophilic precipitate which was much less dense than the adjacent thyroid colloid and, unlike in the latter, gave no PAS reaction. Occasionally, disintegrating cells could be seen within the cyst cavities, but usually most of the contents were lost during manipulation for staining (Fig. 1, 2). The skeletal musculature of this group showed widespread patches of degeneration with moderate calcium deposition, especially around the sarcolemma sheath, and intense Mönckeberg type of calcification in the muscular arteries (Fig. 3, 4).

Discussion. It appears that combined treatment with DHT and calcium acetate causes a highly specific change in the parathyroids which is primarily characterized by cyst formation. The functional significance of this lesion is not clear but it is tempting to assume, as a working hypothesis, that our treatment somehow interfered with the release of parathyroid secretion and that the newly formed cavities represent "retention cysts." This parathyroid response is associated with widespread functional and structural derangements in the skeletal musculature. The observation is reported in the hope that a technique permitting consistent production of such parathyroid cysts may be useful in studying the factors that regulate parathyroid function and in clarifying the effect of these glands upon the skeletal musculature in conditions other than parathyroprival tetany.

Summary. Experiments on rats indicate that oral administration of dihydrotachysterol (DHT) plus calcium acetate, regularly induces extensive cyst formation in the parathyroids, associated with widespread degenerative changes in the skeletal musculature. Under the conditions of these experiments, neither DHT nor calcium acetate alone produced such changes.

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The Absence of Anticonvulsant Properties of Quinacrine and Chloroquine in Mice.* (29187)

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Méndez and Hartley(1) reported the disappearance of petit mal seizures in a patient receiving quinacrine for a Giardia lamblia intestinal infestation. Since then, there have been several reports concerning the efficacy of quinacrine and/or chloroquine in the treatment of petit mal refractory to other drugs (2,3,4,5,6,7,8,9). In view of these reports, it seemed of interest to compare these compounds with phenobarbital and trimethadione as to their efficacy in modifying seizures produced in mice by electroshock and pentylenetetrazol (Metrazol).

Materials and methods. Adult male albino mice obtained from the Arthur Sutter Farms (Rockland strain), weighing 20 to 25 g were

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maintained on Purina laboratory chow and allowed free access to food and water except during the test period. Each animal was used for one experiment only. The test procedures employed were: a) the supramaximal electroshock seizure technique (M.E.S.) of Toman *et al*(10), in which alternating current, 50 ma, of 0.2 second duration was delivered through Spiegel corneal electrodes(11) from an electroshock apparatus constructed according to the design of Woodbury and Davenport(12); and b) the Metrazol seizure threshold test (Met.) of Swinyard *et al*(13), in which Metrazol (85 mg/kg) was injected subcutaneously. The end point for the M.E.S. test was abolition of the tonic extensor component of the seizure pattern; the end point for the Met. test was abolition of clonic spasms.

Quinacrine hydrochloride and chloroquine phosphate, in 10% acacia, were administered orally. The mice (10 per compound) were observed for signs of toxicity following administration of 1 g/kg of the drug. The mice were examined at 15-minute intervals for at least 1 hour and thereafter until 2 successive examinations indicated no change, or until a decrease in the number of mice exhibiting toxic signs was seen. In addition, the dose lethal to 50% of the animals within 24 hours after drug administration (LD_{50}) was also determined for each agent.

The compounds were tested in groups of 10 mice for their efficacy in modifying the seizure patterns elicited by the test procedures *(vide supra)*. Each drug was administered to 6 groups of 10 animals. The respective groups of mice were then subjected to the test procedure at 30 minutes, 1, 2, 3, 4, and 6 hours after administration of 250 and 500 mg/kg of the drug. For comparative purposes, the 50% effective dose (ED_{50}) for trimethadione and phenobarbital was determined. The mice were tested 1½ hours following trimethadione administration and 2 hours following administration of phenobarbital sodium. These time intervals represent the approximate time of peak effectiveness for each drug, as determined in our laboratories utilizing the M.E.S. technique. The time of peak effect for these agents is in agreement with that reported by Swinyard *et al*(13) and Chen *et al*(14).

In another experiment, quinacrine hydrochloride and chloroquine phosphate were administered in a dose of 250 mg/kg every 6 hours for a period of 24 hours. The test procedures were performed 2 hours later.

In a subsequent experiment, the effect of the antimalarials on the ED_{50} for trimethadione in the Met. test was determined. The antimalarials were administered twice daily (at approximately 8 AM and 5 PM) for a period of 4 days. On the fifth day, another dose of the antimalarial was given at 8 AM and trimethadione was given 1½ hours later. Three hours after the last dose of the antimalarial, Metrazol, 85 mg/kg, was injected subcutaneously. The ED_{50} for trimethadione in this group of animals was compared to the ED_{50} for trimethadione in a group of mice which had received only the acacia vehicle twice daily for 4½ days.

The computations for fitting the probit-log dose regression line, the determination of the LD_{50}, ED_{50}, and the 95% confidence interval were done according to methods described by Finney(15). In determining the ED_{50}'s and LD_{50}'s at least 3 dose levels, yielding between 10% and 90% effect, were used. At least 10 mice were utilized in determining each point.

Results. The anticonvulsant activities for phenobarbital and trimethadione are detailed in Table I. These data are in general agreement with those of Swinyard *et al*(13), Goodman *et al*(16), and Chen *et al*(14) as well as with those which have been previously reported from this laboratory(17).

TABLE I. ED_{50} Values for Phenobarbital Sodium and Trimethadione.*

Drug	ED_{50}, mg/kg	
	Met	M.E.S.
Phenobarbital sodium	13 (7–22)†	17 (10–24)
Trimethadione	437 (299–585)	1377 (1125–1766)

* Test procedures were performed 2 hr after phenobarbital and 1½ hr after trimethadione administration.

† Values in parentheses represent 95% confidence interval.

TABLE II. Twenty-four Hour LD_{50} for Quinacrine Hydrochloride and Chloroquine Phosphate.

Drug	LD_{50} (mg/kg)
Quinacrine hydrochloride	1837 (1002-2931)*
Chloroquine phosphate	1189 (873-1618)

* Values in parentheses represent 95% confidence interval.

The LD_{50}'s for quinacrine hydrochloride and chloroquine phosphate are presented in Table II. The toxic signs consisted of hyperactivity followed by clonic spasms and death. Death occurred within one hour following drug administration. The heart was still beating following cessation of respiration.

Neither quinacrine or chloroquine, in single doses of 250-500 mg/kg afforded protection from electroshock or Metrazol at any of the time intervals investigated (30 minutes, 1, 2, 3, 4 and 6 hours). In addition, administration of 250 mg/kg of these agents every 6 hours for a period of 24 hours did not alter the response to electroshock or Metrazol. Furthermore, chronic administration of these agents (quinacrine hydrochloride, 100 mg/kg twice daily for 4½ days, and chloroquine phosphate, 50 and 100 mg/kg, twice daily for 4½ days) did not reduce the ED_{50} for trimethadione in the Met. test (Table III). Higher doses of these agents (250 mg/kg) administered over the same time period produced marked hyperactivity and a failure to gain weight.

Discussion. The data presented indicate that quinacrine and chloroquine do not prevent the hindleg tonic-extensor component evoked by the M.E.S. test, nor do they afford protection against seizures induced by subcutaneous injection of Metrazol.

TABLE III. Effect of Chronic Administration of Quinacrine and Chloroquine on ED_{50} for Trimethadione in the Met Test.*

Drug	Trimethadione ED_{50} (mg/kg)
Quinacrine, 100 mg/kg	610 (318-1094)†
Chloroquine, 50 "	423 (256- 566)
" 100 "	498 (338- 656)
Acacia, 10%	419 (288- 535)

* The antimalarials and/or acacia were administered twice daily for 4½ days. The Met. test was performed 1½ hr after administration of trimethadione (see Methods).

† Values in parentheses represent 95% confidence interval.

Both quinacrine and chloroquine, in high doses, produced hyperactivity and/or clonic seizures. Quinacrine has been reported by Engle *et al*(18) to be a stimulant in man. That is, it produced restlessness, sleeplessness and an acceleration of the electroencephalogram similar to that produced by amphetamine. Many agents which have been employed in treatment of petit mal epilepsy are capable of producing excitement in man and/or convulsions in experimental animals (*e.g.*, amphetamine, caffeine and diphenhydramine). Whether the salutary effect (if any) of quinacrine and chloroquine in certain cases of petit mal is due to a central stimulatory effect is a matter for conjecture. In any event, it seems clear from the data presented here that an anticonvulsant effect of these agents in mice cannot be demonstrated using 2 standard anticonvulsant laboratory procedures.

Summary. Quinacrine and chloroquine were tested in mice for their ability to modify maximal electroshock seizure pattern and to prevent Metrazol convulsions. In addition, the effect of chronic administration of these agents on the ED_{50} for trimethadione in the Metrazol seizure threshold test was determined. The data indicate that these drugs do not modify seizure patterns elicited by electroshock or Metrazol.

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Influence of Reduced Glutathione on Oxygen Consumption.* (29188)

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A marked reduction in basal oxygen consumption levels is associated with the obese hyperglycemic syndrome in mice(1). In addition, these animals are particularly sensitive to a variety of traumata(2,3). They are also more susceptible to decompression sickness following pressure-decompression treatment than thin littermate controls(4). Observations in our laboratory indicate occasional symptomatic improvement when reduced glutathione (GSH) is administered to obese mice exhibiting decompression sickness. The present series of investigations were carried out to explore the role of possible metabolic mechanisms in the protective effects of GSH in the obese mouse. Determination of the effects of GSH administration on total oxygen consumption levels in obese hyperglycemic mice and their thin siblings were performed. Effects of GSH on respiration of salamanders were also investigated in order to provide broader characterization of the effects of GSH on metabolic rate.

Materials and methods. Obese mice and their thin siblings of both sexes were obtained from the Roscoe B. Jackson Memorial Laboratory and housed in standard laboratory cages in a thermostatically controlled animal room (25°-27°). Purina laboratory chow and water were given *ad libitum*. Oxygen consumption measurements were carried out in the Warburg apparatus utilizing standard Machlett manometers and specially designed flasks which could accommodate a single mouse (Fig. 1). Flasks were placed in a 20°C water bath for 5 minutes with stopcocks open to the outside atmosphere, and oxygen consumptions were then determined during a 2nd 5-minute period following closing of the stopcocks. Values were expressed as μl O_2/g/hr. The gas phase was air. GSH dissolved in saline was administered subcutaneously in doses ranging from 30-180 mg.

Salamanders were injected weekly with GSH and/or various nutrient supplements (5). Body weights and O_2 consumptions were determined on groups of 3-5 animals placed in the Warburg flask. Since considerable day-to-day variations were encountered in the O_2 consumption levels of salamanders (Fig. 2), values in the experimental groups were treated as absolute deviations from control groups which were run simultaneously. The low oxygen consumption levels of the salamander necessitated group measurements. In chronic experiments with GSH in mice and in salamanders, O_2 consumptions were carried out at least biweekly.

Results and discussion. Experiments were carried out with an initial group of 43 obese mice averaging 39 g in weight and a second group of 43 thin mice averaging 19 g in weight. Fasting oxygen consumption levels

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