Summary. Two hydroquinone derivatives, 2,5-di-*tert*-butylhydroquinone and 2,5-di-*tert*-amylhydroquinone, have been suggested as antioxidants to protect carotene of dehydrated alfalfa meal. Neither compound modified growth, appearance, organ weights or histological structure of rats eating diets containing as much as 0.2% of antioxidants for 500 days. No symptoms of intoxication developed in exploratory tests on rats when single doses of 1500 mg/kg of compounds were given by stomach tube. These materials did not sensitize the skin of guinea pigs but did produce a reversible lesion on rabbit and guinea pig skin when applied daily to the skin as 10% solutions in cottonseed oil.

Histopathological examination of tissues was made by Dr. Lelland J. Rather, Stanford Univ. School of Med.

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Effect of Cortisone on Survival of Morphine Treated Guinea Pigs under Decompression Hypoxia.* (25716)

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It is well known clinically that morphine constitutes a hazard in respiratory impairment. It is generally stated that this is due to depression of the respiratory center. Morphine is known to inhibit release of ACTH following exposure to stressors(1,2) by actions on some site(s) in the central nervous system. Although the purpose served by increase in production of adrenal steroids following such exposure is not clear, it seems possible that this action of morphine may contribute to some of its adverse effects. The effect of simulated altitude upon mortality of guinea pigs with and without concurrent administration of morphine was investigated. Morphine increased mortality under these circumstances. Administration of cortisone and ACTH reduced mortality.

Methods. Guinea pigs weighing 300-350 g of either sex were employed. All animals received 5 ml of saline intraperitoneally at start of observation. Animals receiving morphine were injected with 2.5 mg (or 5 mg) of morphine sulphate/100 g body weight 10 minutes earlier. Those which received cortisone were injected subcutaneously with 60 mg/kg of cortisone acetate twice daily on 3 preceding days and ½ hour prior to injection of morphine. This seemingly large dose of cortisone acetate has been used routinely for experiments with guinea pigs in our laboratory since this species is relatively resistant to its anti-anabolic action(3). ACTH was administered in single dose of 8 U of corticotrophin gel (Organon) subcutaneously and 8 U of corticotrophin powder (Armour) intraperitoneally, 30 minutes prior to morphine injection. When administered in multiple doses, 8 U of gel was injected subcutaneously twice daily for 3 days prior to experiments. On day of experiment, gel and powder were administered 30 minutes prior to morphine injection as indicated above. Two types of evacuation chambers were used, one employing jars with a single animal and the other vacuum ovens with 4 animals at a

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TABLE I. Mortality of Guinea Pigs after 6 Hours at 25,000 Feet Simulated Altitude.

Group	n	Died	%
Control	70	26	37
Morphine, 2.5 mg/100 g	123	62	50
" .5 "	24	18	75
" 2.5 " & cortisone	76	17	22
" .5 " " "	24	7	29
" 2.5 " & ACTH (S)*	13	7	54
" 2.5 " & ACTH (M)*	43	8	19

* S = Single dose; M = Multiple dose.

time. Average air space animal was approximately 3200 cc. Air pressure was maintained by vacuum pump. It was observed that mortality was greatly affected by air temperature, humidity and rate of admittance of air. To assure constancy in the latter, the same pump was used throughout experiment. Air seeped into the chamber in uniform manner. The experiment was carried out in a small room where temperature could be set to approximately 85°F. A vaporizer was kept in operation constantly to humidify the air. A simulated altitude of 25,000 feet was employed. This was achieved within 30 seconds. Duration of decompression was 6 hours.

Results. Mortality of 37% occurred in guinea pigs placed in evacuation chamber at 25,000 feet simulated altitude (Table I). This included all animals found dead at end of 6 hour period. It cannot be stated which animals died from sudden decompression and which died during ensuing period. However, deaths occurred from both causes. Among animals which had received morphine, mortality was 50% when dose was 2.5 mg/100 g and 75% when dose was 5 mg/100 g. Morphine-treated animals which had received cortisone as well exhibited marked reduction in mortality to 22% in those receiving a dose of 2.5 mg/100 g and 29% in those receiving 5 mg/100 g. Repeated priming with ACTH appeared to be even more effective in reducing mortality (19%).

Corticoids were determined in urine from survivors at completion of 6 hour decompression period. The hypoxic animals exhibited 65% increase in excretion of corticoids/mg creatinine over that of controls. Morphine-treated hypoxic animals exhibited 20% decrease in excretion over that of morphine-treated controls. However, in view of disturbance in cardio-renal hemodynamics which must be marked under such conditions, these findings cannot be considered reliable.

Discussion. Cortisone and ACTH reduced mortality of guinea pigs subjected to decompression hypoxia and morphine. These findings suggest increased requirement for adrenal cortical steroids under these conditions. Other conditions investigated(2,4) induced a large increase in corticoid excretion which was virtually abolished by morphine, but fatalities did not occur. It is possible therefore that corticoids played a particular role in hypoxic animals, for example by reducing oxygen requirements. This suggestion is not too unreasonable in view of the findings of Henneman and Bunker(5) that cortisone induced an increased excretion in lactic acid. Possibly cortisone increased availability and utilization of energy derived from glycolysis. This might be a fundamental purpose for activation of the hypothalamus, anterior pituitary, adrenal complex by stressors.

Summary. Mortality of 37% was induced in guinea pigs under decompression to a simulated altitude of 25,000 feet for 6 hours. Morphine sulfate increased mortality to 50%, and 75% if administered at dose of 2.5 mg or 5 mg/100 g body weight respectively. Prior treatment with cortisone for 3 days reduced mortality to 22% and 29% respectively. Multiple injections with ACTH reduced mortality to 19%.

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