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Dose Level and Degree of Ketonemia Produced by Growth Hormone and Adrenocorticotropic Hormone.*

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Previous work[1] from this laboratory has shown that both pure growth hormone and pure adrenocorticotropic hormone will increase the ketonemia and ketonuria of fasted normal rats. In these previous experiments only one dose level of hormone was used. The present experiments have been undertaken to establish whether there was a relationship between the amount of hormone injected and the degree of ketonemia produced.

All animals used were male rats of the Long-Evans strain between 70-76 days of age, weighing between 154-275 g. They were maintained on a stock diet† and were fasted 24 hours prior to the experiment. An initial 0.5 ml of tail blood was obtained under evipal anesthesia. Following this ⅓ of the total dose of hormone was injected intraperitoneally. At 1 and 2 hours later, identical injections of hormone were given and the final 0.5 ml sample of tail blood was taken under nembutal anesthesia 1 hour after the last injection. Blood ketone bodies were determined by the method of Weichselbaum and Somogyi.[2]

The controls consisted of 12 animals which received no injection and of 5 animals which were injected with 3 mg of serum albumin. The hormones used were prepared according to the previously published methods[3,4] and the total doses given were ½ mg, 1½ mg, and 3 mg per rat. There were from 6-9 animals in each experimental group.

Results. The data from the experiments are summarized in Table I. It will be seen that with both hormones there was a significant increase in ketonemia with all dose levels and that there was a graded response with increasing amounts of hormone. When the 2 hormones were given simultaneously at the 1½ mg level the mean effect produced was essentially a summation of the effects of the 2 hormones separately administered. Statistical analysis showed that the increased ketonemia produced by the combination of hormones was significantly greater than that produced by the growth hormone alone, but not greater than that produced by the adrenocorticotropic hormone alone. When the 2 hormones were given simultaneously at the 3 mg level no summation of effects could be demonstrated. This failure to demonstrate summation of effects at the 3 mg level could have been due to the fact that under these conditions the effect of 3 mg of adrenocorticotropic hormone was maximal.

Conclusions. 1. The production of increased ketonemia by either growth hormone or adrenocorticotropic hormone in fasted nor-

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1 Bennett, L. L., Kreiss, R. E., Li, C. H., and Evans, H. M., *Am. J. Physiol.*, 1948, **152**, 210.

† The diet fed consisted of ground whole wheat 67.5%, casein 15.0%, whole milk powder 10.0%, NaCl 0.75%, $CaCO_3$ 1.5%, hydrogenated vegetable oil (Crisco or primex) 5.25%. To each kg of diet were added 3.5 g of sardilene (fish oil concentrate containing 3000 USP units of vitamin A and 400 chick units of vitamin D per g).

2 Weichselbaum, T. E., and Somogyi, M., *J. Biol. Chem.*, 1941, **140**, 5.

3 Li, C. H., Evans, H. M., and Simpson, M. E., *J. Biol. Chem.*, 1945, **159**, 355.

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TABLE I.
Effect of GH and ACTH on Blood Ketone Bodies of Fasted Normal Rats.

Injection	Initial blood	3-hr blood	Change	P‖
Controls, no inj. (12)†	7.9 ± 0.94‡	8.0 ± 1.06	+ 0.1 ± 0.85	
3 mg Albumin (5)	6.8 ± 1.45	6.1 ± 1.54	— 0.7 ± 0.18	.55
½ '' ACTH (7)	7.8 ± 1.41	13.0 ± 2.18	+ 5.2 ± 1.83	.01
1½ '' '' (6)	6.9 ± 0.79	16.3 ± 2.52	+ 9.3 ± 2.25	.01
3 '' '' (9)	7.9 ± 1.52	25.6 ± 1.97	+17.7 ± 2.65	.01
½ '' GH (8)	6.4 ± 0.85	10.1 ± 1.25	+ 3.7 ± 0.57	.01
1½ '' '' (7)	7.0 ± 0.84	11.4 ± 1.32	+ 4.4 ± 0.80	.01
3 '' '' (8)	7.4 ± 1.48	16.2 ± 2.00	+ 8.8 ± 1.70	.01
1½ '' ACTH + 1½ mg GH (6)	7.5 ± 0.87	21.5 ± 1.25	+14.0 ± 1.27	.01 .01§ .06*
3 '' '' + 3 '' '' (6)	9.8 ± 1.27	21.5 ± 0.86	+11.8 ± 1.21	.01 .20§ .09*

* Compared with the same dose of ACTH alone.
† Figure in parentheses indicates number of animals.
‡ Standard deviation of the mean.
§ Compared with the same dose of GH alone.
‖ From Fisher's[5] table of t. A value of 0.05 or less is considered significant.

mal rats is confirmed. 2. Under the experimental conditions used, the degree of ketonemia produced is correlated with the amount of hormone administered.

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Effect of Age upon Toxicity of Methadon.*

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It has been mentioned that infants are highly susceptible to morphine as compared with adults.[1-3] This statement has been substantiated in animals by Döbeli,[4] Sollmann,[5] Gibbs and Bobb,[6] and Chester and associates.[7] Further, Eddy[8] and Chen and Robbins[9] showed that morphine was more toxic to both very young and aged rabbits, and rats, respectively, as compared with adults. The ages of their animals were accurately recorded.

Methadon is a drug of German origin, picked up by the Technical Industrial Committee[10] of the U. S. Government. Pharmacologic studies by Scott and Chen,[11,12] and

* The material used in this investigation was 'Dolophine' (Methadon, Lilly).

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