the procedure described above, were given doses of 10 mg per kg. The rectal temperatures at which respiratory rates of 200 per min. were attained before and after DNP respectively were: 39.8 and 40.2; 39.8 and 40.0, and 39.6 and 39.8°C, the threshold being increased by an average of 0.3°C. This difference is smaller than but in the same direction as the difference obtained with the larger dose of DNP.

Conclusion. We may conclude that DNP in doses of 10 and 20 mg per kg, although it does not prevent the occurrence of thermal polypnea, does significantly increase the rectal temperature level at which such polypnea appears. It accordingly appears that DNP does not sensitize the heat defense mechanism as would be required by the second hypothesis stated above. Rather it suggests that DNP depresses both heat and cold defense mechanisms by a nonspecific toxic action.

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Effect of Insulin on Rate of Metabolism of Ethyl Alcohol.

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A review of the literature shows that the great majority of workers who have investigated the problem found that insulin in adequate dosage was effective in accelerating the rate of metabolism of alcohol. Thus Supniewski[1] showed that 1 unit of insulin per kg administered to rabbits about doubled the rate at which alcohol disappeared from the blood. Newman and Cutting[2] gave the same dose of insulin to 2 human subjects after administration of alcohol intravenously and found a 50% increase in rate of metabolism. Serianni[3] found a similar increase in man after a dose of 20 units of insulin per individual. Widmark[4] showed that 0.85 unit per kg in the dog accelerated the rate of alcohol metabolism, particularly in dogs with an initially low rate of metabolism of alcohol, but that the effect varied in intensity from dog to dog and in the same dog from day to day. Clark and his associates[5,6] gave doses of 1 and 2 units per kg to dogs and found a significant increase in rate of disappearance of alcohol from the blood.

Gregory, Ewing and Duff-White,[7] on the contrary, reported that "there is no evidence from 24 experiments in 6 dogs that insulin, glucose, or insulin plus glucose increases the rate of metabolism of ethyl alcohol." They refer to certain reports in the literature in support of this finding. Thus Herschfelder and Maxwell[8] concluded that insulin in doses up to 3 units per kg did not expedite the disappearance of symptoms of intoxication in the rabbit. When one considers that such doses of insulin might well in themselves induce a state similar to alcoholic intoxication in its symptomatology, one is not justified in drawing any conclusions from these experiments regarding the effect of insulin on rate of alcohol metabolism. Fleming and Rey-

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2 Newman, H. W., and Cutting, W. C., *J. Clin. Invest.*, 1935, **14**, 945.

3 Serianni, E., *R. C. Accad. Lincei*, 1935, **21**, 394.

4 Widmark, E. M. P., *Biochem. Z.*, 1935, **282**, 79.

5 Clark, B., and Morrissey, R., *Am. J. Physiol.*, 1938, **123**, 37.

6 Clark, B., Morrissey, R., Fazekas, J., and Welch, C., *Quart. J. Studies Alc.*, 1941, **1**, 663.

7 Gregory, R., Ewing, P., and Duff-White, V., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 206.

8 Hirschfelder, A. D., and Maxwell, H. C., *Am. J. Physiol.*, 1924, **70**, 520.

nolds[9] gave one human subject a dose of 10 units of insulin and found no effect on the rate of disappearance of alcohol injected intravenously. Here the dosage is conspicuously lower than that employed by those workers cited above who found an effect from insulin. The work of Goldfarb, Bowman and Parker[10] can hardly be classed as supportive, since they found that while neither insulin nor glucose alone expedited the removal of alcohol from moderately intoxicated patients, a combination of the two was effective. Neither can the unelaborated statement of Mirsky and Nelson[11] that in dogs "treatment with insulin and glucose" had little effect on the rate of alcohol metabolism be very heavily weighted as evidence. Thus it is seen that the evidence in the literature referred to by Gregory and coworkers is not impressive. However, a short communication by Harger and Hulpieu[12] is less easily disposed of. These workers found that the rate of fall of alcohol concentration in dogs after gastric administration of doses from 1.5 to 3.0 g per kg was not changed by the administration of 1 unit of insulin per kg, alone or with glucose. Gregory and coworkers would, however, object to this work on the basis that the alcohol was given by mouth, since they reported that after gastric administration the blood alcohol levels were so variable, and disappearance curves so irregular, that this was an unsatisfactory method of giving alcohol for this type of investigation.

For this reason, they[7] administered the alcohol intravenously, and followed the concentration in the blood until it approached zero. They published one graph which shows the curves of blood alcohol concentration in one dog after a control dose of 2.0 cc per kg of alcohol alone, alcohol and glucose, alcohol and insulin 1 unit per kg, and finally alcohol and combination of insulin and glucose. All of the curves reached the base line in from 11 to 12 hours, so that there is no evidence in this dog of acceleration by insulin. The authors stated that the results in the other 5 dogs were "practically identical", but did not publish the data on which they based this statement.

In view of the conflict of these results with most of the reported work, including our own work in man where the method of procedure was practically identical, it was felt that further investigation of the problem, adhering closely to the methodology of Gregory and coworkers, was indicated.

To this end, alcohol was administered intravenously to each of three dogs in a dose approximating 2 cc per kg, and the blood alcohol concentration followed with serial samples until it approached zero. Analyses for alcohol were carried out according to the method of Newman.[13] Extrapolation of the best-fitting line between these points to the base line was used to estimate the time required for disappearance of alcohol, and from this it was a simple matter to calculate the average rate of metabolism in mg per kg per hour. In order to establish fully the range of variation in this rate in a given dog from day to day, 3 controls with alcohol alone were run

TABLE I.
Rate of Metabolism of Alcohol With and Without Insulin in Dosage of 1 Unit per Kg Body Weight.

Dog	Wt kg	Dose alcohol g/kg	Rate of metabolism mg/kg/hr Control	Insulin
1	23	1.5	102	
		1.5	98	
		1.5	103	
		1.5		143
2	21	1.5	123	
		1.5	102	
		1.5	107	
		1.5		158
		1.5		164
5	10.5	1.43	102	
		1.43	104	
		1.43	106	
		1.43		112

9 Fleming, R., and Reynolds, D., *J. Pharmacol. and Exp. Therap.*, 1935, **54**, 236.

10 Goldfarb, W., Bowman, K. M., and Parker, S., *J. Clin. Invest.*, 1939, **18**, 581.

11 Mirsky, I. A., and Nelson, N., *Am. J. Physiol.*, 1939, **127**, 308.

12 Harger, R. N., and Hulpieu, H. R., *J. Pharmacol. and Exp. Therap.*, 1935, **54**, 145.

13 Newman, H. W., *J. Pharmacol. and Exp. Therap.*, 1936, **56**, 278.

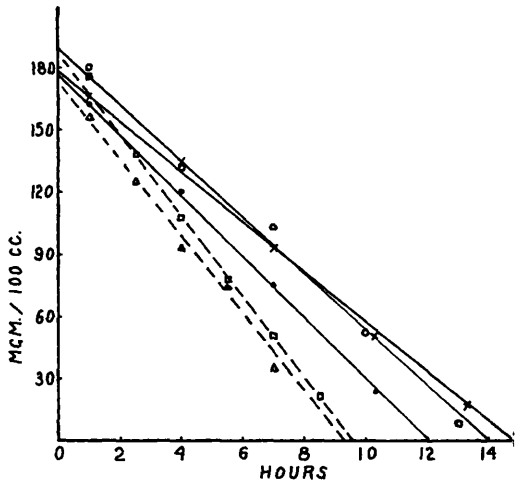

FIG. 1.

Blood alcohol concentrations after intravenous injection of 1.5 g of alcohol per kg in a dog. Three control injections are represented by crosses, open circles, and dots. Two injections with insulin 1 unit per kg are shown with open squares and open triangles. The best fitting lines between these points are extrapolated to the base line to estimate the time of disappearance of alcohol from the blood stream.

on each dog. Then the same procedure was repeated after administration of a single dose of 1 unit of regular insulin per kg, and in the animal which showed the greatest acceleration the insulin run was repeated so that we could be doubly sure of the results. The results are presented in Table I, and those in the dog which had the 2 trials with insulin are shown graphically in Fig. 1. It is seen that 2 of the 3 animals responded to this dose of insulin by an increase in rate of alcohol metabolism of approximately 50%, while the slight increase in the third animal, although deviating from the average of the control values by a considerable margin over the range of these values, was far less striking. The same procedure was repeated with two other dogs, with the exception that the dose of insulin was reduced to 0.5 unit per kg. In neither animal did this smaller dosage of insulin produce any acceleration of alcohol metabolism.

Summary. Insulin in a dose of 1 unit per kg was found to be variably effective in accelerating the rate of alcohol metabolism, the effect being striking in 2 dogs, much less in another. This is in accord with the variable results reported by Widmark.[4] Half this dose was entirely ineffective in 2 dogs. The failure of Gregory and coworkers[7] to demonstrate this accelerating action of insulin in adequate dosage must be due to the possibility that their 6 dogs fell, by chance, into the group of animals which does not show a striking acceleration with insulin.

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Prolongation of Pseudopregnancy by Deciduomata in the Rat.*

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Astwood and Greep[1] have stated that the presence of deciduomata in the rat does not prolong the diestrus of pseudopregnancy. Ershoff and Deuel,[2] however, have presented data showing pseudopregnancy in the rat to be prolonged as much as 7 days by production of deciduomata. More recently Kamell and Atkinson[3] reported that deciduomata do not prolong pseudopregnancy in the mouse. The following data confirm those of Ershoff and Deuel.

* Supported in part by a grant from Ciba Pharmaceutical Products, Inc.

1 Astwood, E. B., and Greep, R. O., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 713.

2 Ershoff, B. H., and Deuel, H. J., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 167.

3 Kamell, S. A., and Atkinson, W. B., PROC. SOC. EXP. BIOL. AND MED., 1948, **67**, 415.