Other studies in this laboratory[5] have shown that skin tissue prepared for the Shwartzman phenomenon exhibits an abnormal degree of aerobic glycolysis and lactic acid accumulation. Whether this alteration is related to an impairment in the permeability of vessels in prepared skin is a subject for further investigation. It is of interest to note that the application of bromobenzene to prepared skin had no demonstrable effect on the degree of aerobic glycolysis exhibited by such tissue.[8]

*Summary.* Complete inhibition of the Shwartzman phenomenon was produced by a single application of bromobenzene to the surface of prepared skin areas at any time during the 20 hours after the intradermal injection of bacterial toxin. Similar results were obtained with other benzene derivatives, and, less constantly, with chloroform and methyl salicylate.

Areas of rabbit skin which were prepared by the intradermal injection of meningococcal toxin showed no increase in permeability to Evans Blue dye, when the dye was injected intravenously.

A single application of bromobenzene to the surface of normal rabbit skin resulted in the prompt appearance of intravenously injected Evans Blue dye in the painted area. In contrast, little or no dye appeared in painted areas which had previously been injected with meningococcal toxin. Similar results were obtained when skin was painted with other benzene derivatives, chloroform and methyl salicylate.

The possible bearing of these observations on the problem of the mechanism of the Shwartzman phenomenon is discussed.

8 Unpublished observation.

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## Influence of Dinitrophenol on Body Temperature Threshold for Thermal Polypnea.*

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The capacity of dinitrophenol (DNP) to cause hyperthermia in animals through accelerating heat production is well known. In animals at low environmental temperatures, however, it reduces body temperature and total heat production,[1] apparently through reducing the activity of the cold defense mechanism, as shown by depression of shivering.[2] In discussing the mechanism of this inactivation of cold defense, Hall, Crismon and Chamberlin[2] suggested two possibilities: (a) DNP might depress the centers involved in cold defense by a nonspecific toxic action similar to that by which it depresses other nervous processes such as spontaneous running activity;[3] (b) DNP, which increases the oxygen consumption of cerebral cortical tissue in concentrations likely to be attained when ordinary doses are injected,[4] might accelerate the metabolic activity of the temperature regulating centers, so causing the centers to behave as if heated which would reduce or abolish shivering. If the latter were the case, one would expect from the known reciprocal relationship of the cold and heat defense mechanisms that, when the body temperature

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TABLE I.
Effect of Dinitrophenol and of Salt Solution on Threshold for Thermal Polypnea of Rabbits.

| Rabbit No. | Normal threshold °C | DNP threshold °C | Change in threshold °C |
|---|---|---|---|
| | A. Dinitrophenol (20 mg per kg) | | |
| 1A | 39.4 | 41.0 | +1.6 |
| 1B | 40.1 | 41.0 | +0.9 |
| 2A | 40.4 | 41.9 | +1.5 |
| 2B | 40.9 | 40.7 | —0.2 |
| 2C | 40.9 | 41.4 | +0.5 |
| 3A | 40.0 | 40.9 | +0.9 |
| 3B | 39.5 | 40.2 | +0.7 |
| 4A | 40.3 | 41.7 | +1.4 |
| 4B | 40.1 | 41.6 | +1.5 |
| 4C | 40.1 | 41.0 | +0.9 |
| Avg | 40.2 | 41.1 | +0.9 |
| | B. Controls with physiological salt solution | | |
| Rabbit No. | Normal threshold | Threshold after saline | Change in threshold |
| 5A | 39.5 | 39.1 | —0.4 |
| 5B | 39.0 | 39.0 | 0.0 |
| 5C | 39.1 | 39.6 | +0.5 |
| 6A | 39.0 | 38.1 | —0.9 |
| 6B | 38.4 | 38.3 | —0.1 |
| Avg | 39.0 | 38.8 | —0.2 |

is raised, processes accomplishing heat loss should be more readily activated under the influence of DNP than in its absence. Among other effects, DNP should (at constant environmental temperature) reduce the body temperature level at which thermal polypnea appears. The experiments described here were designed to test this possibility.

Albino rabbits weighing between 2 and 3 kg were placed in a box in which the air temperature was maintained at 30°C ± 2°). This environmental temperature is higher than that at which the rabbit can maintain a constant body temperature. Accordingly a progressive rise in body temperature occurred, and with it a rise in respiratory rate. When the latter reached 300 per min., the rectal temperature was measured with a mercury thermometer. This value was designated as the normal threshold for thermal polypnea.

The rabbits were then placed in a refrigerator at about 10°C per 45 to 60 min. Their rectal temperatures were reduced by this procedure to values well below the normal threshold for thermal polypnea. A dose of 20 mg per kg of the sodium salt of 2,4-dinitrophenol was then injected intramuscularly and the rabbits returned to the box at 30°C. As their rectal temperatures rose under the combined action of the high environmental temperature and the calorigenic action of the drug, the respiratory rate accelerated. The rectal temperature at which it again reached 300 per min. was determined and designated as the DNP threshold for thermal polypnea.

The results of 10 such experiments are shown in Table I. With one exception, the DNP thresholds for thermal polypnea are greater than the corresponding normal thresholds. The average change in threshold after DNP was +0.9°C. The chances that these results could have occurred by chance have been calculated to be less than one in one thousand.

A second series of 5 rabbits was treated in the same manner except that a volume of physiological salt solution equal to the volume of DNP solution was injected. The results, also given in Table I, show an average reduction of the threshold determined after saline injection amounting to 0.2°C. This finding rules out the possibility that, in the DNP series, the elevated threshold might be due to factors other than those attributable to DNP itself.

In view of the possibility that the dose of 20 mg per kg might have toxic effects not shown by lower doses, 3 rabbits subjected to

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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