

TABLE II.
Quellung Reactions with Unconcentrated Rabbit Sera Prepared by Authors.

Rabbit serum No.	Vaccine used in preparation of serum	Culture used in quellung test		
		Type 6 pneumo.	Type 29 pneumo.	Type B <i>H. influenzae</i>
1316	Living type B <i>H. infl.</i> (62B)	Neg.	2+ quellung	4+ quellung
1317	" " " " " "	"	2+ "	4+ "
1318	" " " " " " (191)	"	± "	4+ "
1319	" " " " " "	"	Neg.	4+ "
1386	" " 6 pneumococci	4+ quellung	"	+ "
1387	Heat killed type 6 pneumococci	4+ "	"	Neg.
1388	Living type 29 pneumococci	Neg.	4+ quellung	4+ quellung
1389	" " " " " "	"	4+ "	4+ "
1390	Heat killed type 29 pneumococci	"	4+ "	+ "

in the latter instance this relationship is much less clear cut. This and other evidence thus far accumulated indicates that the antigenic components involved in these cross reactions are not identical. The clarification of the relationship involved must await absorption experiments. Types of *H. influenzae* other than type B are being investigated. It is very probable that other relationships between *H. influenzae* and the pneumococcus group will be uncovered as they are sought. In fact, while this article was being prepared for pub-

lication, Chapman and Osborne¹ stated that they had discovered a mutual quellung reaction between pneumococcus type 6B and *H. influenzae* type A. These authors also described the quellung of *H. influenzae* type C in type 21 anti-pneumococcus rabbit serum.

Conclusion. Four strains of type 6 pneumococci and 4 strains of type 29 pneumococci have been encountered which appear to have one or more capsular antigens in common with 7 strains of type B *H. influenzae* which have recently been recovered from the spinal fluid or blood of infants. This relationship has been demonstrated by the capsular quellung method.

¹ Chapman, O. D., and Osborne, W., *J. Bact.*, 1942, **44**, 620.

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Effect of Thymoxyethyldiethylamine on Various Pain Thresholds with Special Reference to Referred Pain.*

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Observations that the phenol ether, thymoxyethyldiethylamine, administered to unanesthetized dogs produced a generalized elevation of the cutaneous threshold for pain stimuli without evident signs of central narcosis¹ suggested to the authors its possible

utility in the experimental study of visceral pain.

Method. Adult untrained dogs were used. The threshold for pain was determined by electrical stimuli supplied from a Harvard inductorium with 4.5 v on the primary circuit. Faradic stimuli of graded intensity were applied by means of bipolar electrodes in contact with the shaved abdominal skin, the parietal and visceral peritoneum of the abdomen, me-

* Aided partially by a grant from Abbott Laboratories.

¹ Rosenthal, S. R., and Minard D., *J. Exp. Med.*, 1939, **70**, 415.

senteric nerve trunks, and the exposed saphenous nerve. The pupillodilator reflex served as a reliable index of pain responses. The electrical threshold for eliciting this reflex was expressed as the distance in centimeters of the secondary from the primary coil, this distance being inversely related to the intensity of the stimulus.

The drug was administered in 1 or 2% solution of the hydrochloride in doses ranging from 30 to 50 mg per kg expressed as the base either parenterally by subcutaneous injection or enterally by rectum or by mouth. In the latter case atropin sulfate (.05 mg per kg) was injected 15 minutes before giving the drug to allay drug loss from vomiting.

To insure more uniform results all extraneous stimuli tending to disturb the animal, such as loud talking, barking of other dogs, and rough handling must be strictly avoided during the initial stages of the drug action. Later, such precautions are less essential.

In the first experiment (dog No. 1) control values for the various thresholds were obtained before administering the drug, the abdomen being opened under local (procaine) anesthesia. In subsequent experiments opening of the abdomen and visceral stimulation was postponed until the drug had taken maximal effect as indicated by the elevation of the skin threshold. In some experiments readings were then taken periodically until the pain thresholds of viscera and skin had again approached normal. In 5 of the 27 experiments in which the edges of the abdominal wound were infiltrated with solutions of procaine or of the drug to eliminate a possible decrease in sensory threshold at these sites, a further elevation of skin and visceral thresholds was noted.

Results. The thymoxyethyldiethylamine preparations used in these experiments were effective in producing an elevation of the cutaneous threshold in approximately 80% of the dogs tested. Its failure to act in some animals has not been investigated.

The experimental results in a series of 27 dogs in which definite cutaneous analgesia was obtained are given in the accompanying tables. The values given represent the setting of the secondary coil at threshold intensity.

For consideration the experiments are

divided into two groups, the first (Table I) including dogs in which the skin threshold following administration of the drug increased 3.5 cm or more, and the second group (Table II) those in which the increase was 3 cm or less. Stimuli with a secondary coil setting of less than 2 cm from the primary were avoided to prevent tissue damage.

In 7 of 9 dogs in the first group the threshold obtained for the visceral peritoneum covering the free border of the small intestine was found to be 2 cm or higher during the maximal drug effect. In the second group this degree of threshold elevation was found in only 6 of 15 animals. In all experiments in which readings were taken repeatedly, the threshold values for both skin and viscera decreased gradually as the drug action diminished. In general, values obtained for parietal and for visceral peritoneum varied in the same direction.

Similarly the mesenteric nerve threshold was found to be elevated to a greater extent in the first group than in the second; in general, the changes in threshold of the mesenteric nerve approximately paralleled the threshold changes in skin and peritoneum.

In 9 experiments in which the threshold values for the saphenous nerve were determined both before and after drug administration, little or no change was evident. However, determinations with an instrument giving absolute values of current intensity would be desirable since intensities in the range used in these experiments were not comparable on an absolute scale.

In one experiment (dog No. 12) sodium pentobarbital (20 mg per kg) was given with the thymoxyethyldiethylamine. The saphenous nerve threshold, taken during the light general anesthesia which ensued, was elevated to 3 cm.

Discussion. Thymoxyethyldiethylamine administered enterally or parenterally induces a reversible generalized cutaneous analgesia in the majority of the dogs tested. Although not definitely established the site of this action of the drug is believed to be peripheral since little or no change in electrical threshold of the saphenous nerve, a somatic sensory trunk, could be detected by the method employed.

TABLE I.

Various Electrical Thresholds, as Determined by the Harvard Inductorium, Before and After the Administration of Thymoxyethyldiethylamine. (Elevation of skin threshold of 3.5 cm or more.)

Dog No.	Skin threshold, cm		Serosa intestine, cm		Mesenteric nerves, cm		Saphenous nerve trunk, cm	
	Before	After	Highest Reading	Lowest Reading	Highest Reading	Lowest Reading	Before	After
1	6	2.5	8.5†	2‡	10‡	4.5	13 -80°	13 -80°
2	6.5	2		2		2	12 -30	12 -30
3	6.75	2.5		2.5	10	4	12.5-70	12.5-60
4	6.25	2	5	2	5.5	2.9	12.5-30	12.5-30
5	6.25	2		2	6	2	12.5-60	12.5-60
6	6.25	2		2	7	5		
7	6.25	2		6.5		8		
8	5	1	8	6			12 -80	12 -80
9	6	2				3		
10	6.75	2		2		5.5		
11	7	2					12 -85†	
12	6.5						3*	

*Pentobarbital sodium and thymoxyethyldiethylamine injected.

†Abdomen not opened.

‡Readings taken before injection of thymoxyethyldiethylamine.

§Abdominal incision injected.

TABLE II.

Various Electrical Thresholds, as Determined by the Harvard Inductorium Before and After the Administration of Thymoxyethyldiethylamine. (Elevation of skin threshold of 3 cm or less.)

Dog No.	Skin threshold, cm		Serosa intestine, cm		Mesenteric nerves, cm		Saphenous nerve trunk, cm	
	Before	After	Highest Reading	Lowest Reading	Highest Reading	Lowest Reading	Before	After
13	5.75	4.5	8	2	10.5	6	12 -80°	12 -80°
14	6.75	4		2		5		12 -45
15	6.75	5.5		7.5		10		
16	6.5	4.75		1*		5.5	13 -70	
17	6.25	5	10	3*	10	6	13 -60	13 -60
18	6.5	4	8	3*	10	3	12.5-30	
19	5.75	3.25		2.5	6	4.25	12 -70	12 -40
20	6.25	3.5	7	3*	8	3		12 -30
21	6.5	4	6	3		6.5		13 -30
22	7	5		2		2		11 -65
23	6.75	3		3		3		12.5-30
24	6	4		6.75		6.75		11 -60
25	6.5	3		1		1		12 -85
26	6.25	3.5	6	2	7	5		
27	6	3.25		2		2		

*Abdominal incision injected.

Climenko, Homburger and Messer² in a recent study of the pharmacology of this drug noted a local anesthetic action at the site of injection which they ascribe to local tissue injury but these authors fail to discuss the generalized sensory effect previously noted by two of us.¹

² Climenko, D. R., Homburger, E., and Messer, F. H., *J. Lab. and Clin. Med.*, 1941, **27**, 289.

Burchell and Varco,³ in a study of the effect of the drug on gastric secretion in dogs, report a lowered sensitivity to pain in 4 animals but only when the drug was given in doses of 75 mg per kg. The discrepancy in dosage and degree of action between these findings and

³ Burchell, H. B., and Varco, R. L., *J. Pharm. and Exp. Therap.*, 1942, **75**, 1.

our own requires further investigation. More recent experiments in which the variability in action of newer preparations of the drug was more marked than in the earlier experiments reported here suggest that the potency of different preparations may vary.

In contrast to its lack of effect on the threshold of somatic nerve, the drug produces an elevation of the sensory threshold of viscera

and visceral nerve which is roughly proportional to the change in skin threshold. Unless one postulates an action of the drug on visceral sensory nerve differing in effect from that on somatic sensory nerve, the findings reported here support the view that in the dog visceral pain is referred wholly or in part to the skin.⁴

⁴ Rosenthal, S. R., and Lambert, E. H., in publication.

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Physiological Effects at Low Oxygen Tensions of Replacing Oxygen with Carbon dioxide.*

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The following experiments were designed to determine if, on the basis of increased respiratory minute volume, an increased alveolar oxygen tension may be obtained at low oxygen tensions by replacing some of the oxygen with an equal amount of carbon dioxide. Johnson, Eckman, Ramsay and Barach,¹ in experiments on nembutalized dogs in a low pressure chamber, found that addition of 14.3 mm Hg of CO₂ produced no beneficial effect on the oxygen tension of mixed venous blood. The value of these results is limited by the fact that nembutalized dogs are not normally sensitive to the stimulatory effects of carbon dioxide on respiration. However, in a subsequent study which included 4 human subjects, Himwich, Fazekas, Herrlich, Johnson and Barach² found that the oxygen content of the arterial and cerebral venous blood was approximately the same whether a 10% CO₂-90% O₂ mixture or 100% O₂ was breathed at a simulated altitude of about 35,000 feet. Numerous studies have demonstrated that

addition of CO₂, without proportionate removal of oxygen, has a beneficial effect when the original alveolar oxygen tension is below that required for normal oxygenation of hemoglobin. However, the problem in the latter case is quite different than when the sum of the oxygen tension plus the carbon dioxide tension is kept constant.

Procedures. Eighteen men between the ages of 23 and 35 were used as subjects. These subjects had no known respiratory or cardiovascular abnormalities. The procedure for performing an experiment was as follows. The subject lay on a cot in the supine position for 10 minutes. Then a sample of alveolar air was obtained by collecting the last 200 cc of a forced expiration begun at the end of a normal expiration, and the oxygen and carbon dioxide content of the sample was determined immediately by the use of the Haldane gas analysis apparatus. After allowing the subject a few minutes to equilibrate, following collection of the alveolar sample, he was connected by means of a mouthpiece with a spirometer containing air at 23 to 25°C and saturated with water vapor and at a pressure of 743 to 755 mm Hg. Two one-way valves placed close to the mouthpiece were so arranged that the subject inhaled from the spirometer and exhaled through a gas meter offering a

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¹ Johnson, A. E., Eckman, M., Ramsey, C., Jr., and Barach, A. L., *J. Aviation Med.*, 1942, **13**, 130.

² Himwich, H., Fazekas, J., Herrlich, H., Johnson, A. E., Barach, A. L., *J. Aviation Med.*, 1942, **13**, 177.