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 CO_2 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 Barach[2] found that the oxygen content of the arterial and cerebral venous blood was approximately the same whether a 10% CO_2-90% O_2 mixture or 100% O_2 was breathed at a simulated altitude of about 35,000 feet. Numerous studies have demonstrated that addition of CO_2, 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.

TABLE I.
Comparison of Respiratory and Cardiovascular Effects of Oxygen-Carbon-dioxide-Nitrogen Mixtures.

Composition of gas mixtures	Avg alveolar CO_2 after breathing mixture for 8 minutes	Alveolar O_2 after breathing mixture for 8 minutes*	Blood pressure changes	Heart rate incr., beats/min.*	% incr., R.M.V.*	Alveolar O_2 tension (calc.) % sat. of Hb. (calc.)	
						mm Hg	% sat.
10-2-88	5.6	5.5-6.7	No change 6; remainder, systolic 4-12 mm rise; diastolic no rise.	10-22	20-100	45	80
12-0-88	5.5	5.6-6.8	No change 9; remainder, systolic 4-10 mm rise; diastolic no rise.	10-18	2-29	46.5	81
12-2-86	5.8	6.8-7.8	No change 4; remainder, systolic 4-10 mm rise; diastolic 4-10 mm rise one-half of cases.	4-13	29-65	54.8	87.5
12-3-85	5.9	7.9-9.5	No change 2; in 16 cases 4-10 mm rise systolic; milder rise diastolic.	4-15	53-101	65.25	90

* Range includes middle 16 of 18 experiments.

resistance of less than 5 mm of water. Rebreathing was negligible as indicated by the fact that the same reading for respiratory minute volume was obtained when the subject inhaled from the spirometer and exhaled through the gas meter as when he inhaled room air through the nose and exhaled from the mouth through the gas meter. Moreover, the dead space remained constant throughout the experiments. A mask was not used because the best fitting masks contained sufficient dead space to cause a significant increase in respiratory minute volume over that obtained when a mouthpiece was used. After the subject was connected to the apparatus for 3 or 4 minutes, recording of blood pressure, heart rate, and respiratory minute volume was begun. Within 4 to 8 minutes after constant figures for these determinations were obtained one of 4 gas mixtures contained in cylinders was fed through a humidifier and temperature regulator into the spirometer instead of air. Recording of respiratory minute volume and heart rate and blood pressure was continued until a few minutes after they became constant. This occurred in all cases within 8 minutes. Another alveolar air sample was obtained at the end of the period of breathing the gas mixture.

Results. The effects of each of the four gas mixtures on the 18 subjects are summarized in Table I. It may be noted that there is no significant difference in the alveolar oxygen tension after breathing the 12-0-88 mixture as compared with that after breathing the 10-2-88 mixture. The increased respiratory minute volume produced by the later is barely sufficient to compensate for its lower oxygen tension. The heart rate and blood pressure increase similarly with the two mixtures. The rise in heart rate with no decrease in pulse pressure is compatible with Grollman's[3] finding that an increased cardiac output occurs when the percent saturation of hemoglobin of arterial blood falls below 85. It is possible that the fraction of the total cardiac output reaching the brain is not the same when breathing the two different mixtures; however, the experiments of Himwich *et al.*[2] indicated no increase in the oxygen tension of the cerebral venous blood.

The wide individual differences in sensitivity of the respiratory mechanism to the stimulatory action of oxygen-lack and carbon dioxide excess is shown by the figures indicating the percentage increase in respiratory minute volume. There is also a considerable variation in the cardio-accelerator response to oxygen lack, but the 12-0-88 mixture produced a significant increase in heart rate in all cases while a significant increase in respiratory minute volume (greater than 6%) occurred in only 14 of the 18 cases.

[3] Grollman, A., *Cardiac Output in Man in Health and Disease*, Springfield, Ill., Chas. C. Thomas, 1932.

The only significant difference in response to the 10-2-88 mixture as compared with the response to the 12-0-88 mixture was the greater respiratory activity produced by the former. Therefore, the results indicate that no beneficial effects would be obtained by substituting carbon dioxide for oxygen when the original oxygen tension is insufficient for normal saturation of the hemoglobin of arterial blood. On the other hand, it is apparent that a considerable part of the oxygen in inspired air may be replaced with carbon dioxide without a reduction in alveolar oxygen tension.

Comparison of the effects of the last 3 mixtures listed in Table I indicates that increasing the carbon dioxide in the inspired air, when the oxygen tension of the inspired air is deficient but is kept constant, results in an increase in the alveolar oxygen tension on the basis of increased respiratory minute volume. This result is in accord with a number of observations reported in the literature of relief of hypoxia obtained by increasing the carbon dioxide tension of inspired air without a corresponding reduction of oxygen tension. However, the alveolar oxygen tension when breathing the 12-2-86 and 12-3-85 mixtures is not significantly higher in the average case than the alveolar oxygen tension that would be expected to result from breathing 14% and 15% oxygen respectively even if no respiratory stimulation occurred. This does not necessarily mean that the oxygen tension in tissues would be the same in each case.

Comment. In view of the above results, in the presence of a degree of hypoxia that will allow a "leveling off" of the blood pressure and heart rate and respiratory minute volume within a few minutes after the onset of the hypoxia, it appears unlikely that increasing the carbon dioxide tension of the inspired air will produce any beneficial results beyond that produced by addition of an equivalent oxygen tension. It is possible that a different result would be obtained in the presence of more severe hypoxia, but such a degree of hypoxia would be tolerable for only a brief time.

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The Vasodilator Properties of a Pancreatic Extract.*

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Since the demonstration by Frey and Kraut[1] of the presence of a depressor substance in urine and blood and the subsequent preparation of extracts of pancreas with similar effects upon blood pressure, many clinical trials have been made with pancreatic extracts. Most of the reports deal with the so-called circulatory hormone of the pancreas, kallikrein or "Padutin" (see Rigler[2] for review of literature). A deproteinated extract of pancreas,* free of insulin, choline esters, and histamine, has been tried with reported success in various clinical conditions. In many of the clinical studies, however, no convincing control observations were made, and the subjective response of the patient was often the accepted criterion.

* The pancreatic extract used is manufactured and supplied by Sharp & Dohme, Inc., under their trade name, "Depropanex" deproteinated pancreatic extract. It is stated to contain not more than 2.5% solids, including not more than 0.5% nitrogen, 0.9% sodium chloride, and 0.25% phenol as a preservative. This investigation was aided by a grant from Sharp & Dohme, through the courtesy of Dr. L. Earle Arnow.

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1 Frey, E. K., and Kraut, H., *Z. physiol. Chem.*, 1926, **157**, 32.

2 Rigler, R., *Heffter's Handb. exp. Pharmakol.*, 1938, **7**, 63.