natural 5-HT or, perhaps, of other venopressor agents. Protein solutions from platelets incubated with 5-HT, however, proved to possess higher venopressor effect than from platelets alone, all experimental conditions being equal. Presumably, some 5-HT had been absorbed or bound by platelets.

Summary. 1. 5-hydroxytryptamine creatinine sulfate (5-HT) administered intravenously causes significant elevation of the local venous pressure at doses as small as 0.3 γ/min. This effect is not affected by short-time incubation with fresh serum, platelet-rich and platelet-poor plasma. Incubation for 16 hours causes destruction of 5-HT activity. 2. Activity of 5-HT also disappears after incubation for 16 hours with suspensions of washed platelets. Some of the activity, however, can be recovered after total disruption of thrombocytes. Also a protein solution from human platelets exhibits significant venopressor activity, while intact platelets are inactive. 3. These findings suggest: (a) presence of natural 5-HT or of substances with venopressor effect in human platelets; (b) absorption of 5-HT by platelets upon incubation; (c) strong bondage between 5-HT and platelet constituents.

1. Zucker, F. T., and Stewart, G. N., *Zbl. Physiol.*, 1913, v27, 85.

2. Bracco, M., and Curti, P., *Haematologica*, 1953, v37, 721.

3. Stefanini, M., and Murphy, I. S., *J. Clin. Invest.*, 1956, v35, 355.

4. Humphrey, J. H., and Toh, C. C., *J. Physiol.*, 1952, v124, 300.

5. Magalini, S. I., Stefanini, M., and Smith, F. E., PROC. SOC. EXP. BIOL. AND MED., 1956, v92, 433.

6. Stefanini, M., and Silverberg, J. H., *Am. J. Clin. Path.*, 1951, v21, 1030.

7. Magalini, S. I., and Stefanini, M., *Science*, 1956, v123, 796.

8. Udenfriend, S., and Weissbach, H., *Fed. Proc.*, 1954, v13, 412.

9. Erspamer, V., *Rendiconti Scientifici Farmitalia*, 1954, v1, 1.

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Action of Sodium Salicylate on Tissue Gas Tensions.* (22616)

R. H. MILLER† AND S. M. TENNEY.† (Introduced by W. S. McCann.)

Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

It is known that after intravenous administration of sodium salicylate (100 mg/kg body weight) ventilation increases secondary to both direct respiratory center stimulation and elevation in metabolic production of CO_2; alveolar CO_2 tension decreases 10%; oxygen consumption increases approximately 70%; arterio-venous oxygen content difference increases by 50%; and cardiac output is elevated by 20%(1).

With the above actions in mind, the question arises as to how tissue gas tensions are altered. Tissue carbon dioxide may be expected to follow alveolar air, but the oxygen tension in tissues is determined by an exacting relationship between the tissue metabolic demand and its blood supply. The problem of measuring gas tensions in tissue was approached through construction and analysis of subcutaneous depots of gas, a technic developed by Campbell(2) and shown to provide an adequate estimate of extracellular, if not intracellular fluid gas tensions.

Methods. Gas depots were formed in the interscapular region of non-fasting albino rats by subcutaneous injection of 20 cc of sulphur hexafluoride, an inert gas of high molecular weight and low blood solubility. Its prolonged disappearance time facilitated sampling and in no way interfered with the equilibrium tensions of CO_2 and O_2(3). Twenty-four hours after depot construction, 2 groups

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† Present address: Department of Physiology, Dartmouth Medical School, Hanover, New Hampshire.

TABLE I. Tissue Tensions Albino Rats.*

Category	No.	CO_2 tension, mm Hg	O_2 tension, mm Hg	Stand. error of difference between means	
				CO_2 tension	O_2 tension
Control	12	45.4 ± .7 (41.3–49.2)	49.2 ± .8 (44.0–54.0)		
Sodium salicylate, 200 mg/kg/24 hr	11	34.6 ± .6 (37.9–49.5)	43.8 ± 1.2 (37.9–49.5)	.9	1.5
" " ,300 "	10	38.2 ± .6 (34.8–40.5)	49.3 ± 1.6 (41.2–57.1)	.9	—

* Mean values ± 1 stand. dev., (range in parentheses).

of rats received sodium salicylate intraperitoneally in divided doses over the next 18 hours. The third group, controls, received no drug. Gas depots were aspirated in all groups 48 hours subsequent to construction and analysed for CO_2 and O_2 by the Scholander-Roughton technic(4). At the time chosen for analysis, though arbitrary, one could anticipate that an equilibrium had been achieved between gas tensions in the subcutaneous depot and tissue fluids, but development of fibrous changes in the tissue had not occurred(2). No evidence of subcutaneous infection was noted in any of the rats employed.

Results. Results are tabulated in Table I. The fall in CO_2 tension finds a ready explanation in the action of salicylate as a primary respiratory stimulant. The resultant decrease in alveolar (arterial) CO_2 tension will be promptly reflected as an almost equivalent decrease in venous blood and tissue CO_2 tension. The absolute decrease in both alveolar and tissue tensions will depend on relative excess of ventilatory drive initiated by salicylate over the action of this drug to increase metabolic production of CO_2. The significant decrease in tissue O_2 tension caused by 200 mg/kg, 24 hr of sodium salicylate can be explained on the basis of several mechanisms acting simultaneously. Of primary importance is relationship of regional blood flow to tissue metabolism. By the Fick principle, blood flow is directly proportional to oxygen consumption and inversely proportional to the arterio-venous oxygen content difference. If tissue oxygen tensions were to remain constant in the presence of an increased oxygen consumption initiated by salicylate, increase in blood supply must be equivalent to increase in oxygen consumption. Any failure of the blood supply to meet this demand would necessitate an increase in the arterio-venous oxygen content difference and thus a fall in venous oxygen tension. Since gas in tissues and regional venous blood are in equilibrium(5), a fall in tissue oxygen tension to at least the same degree will result in each. The fall in tissue O_2 tensions produced by salicylate can only mean that there has been a relatively greater increase in O_2 consumption by this drug than in regional blood flow.

The rise in alveolar ventilation responsible for the decrease in alveolar CO_2 tension will result in a simultaneous rise in alveolar oxygen tension. If the alveolar-arterial O_2 tension gradient remains unchanged, this will raise directly the arterial O_2 tension and arterial O_2 content. However, if there were a constant arterio-venous O_2 content difference, the venous oxygen tension would fall slightly because of the effect of CO_2 on the oxygen dissociation curve of hemoglobin (Bohr effect). This mechanism could however, account for only about 3 mm. Hg fall in O_2 tension.

In the dog, the increase in oxygen consumption following large doses of salicylate may be less pronounced than with smaller doses(1) and metabolic depression with high concentrations *in vitro* has been amply confirmed(6,7,8). The difference in tissue oxygen tension response to 200 and 300 mg doses suggests that the metabolic dose-response pattern may be similar in the rat. The CO_2 tension differences between the 200 mg and 300 mg doses similarly implies that a dose-response relationship exists for direct stimulation of the respiratory center.

Summary. In the rat, sodium salicylate in

doses of 200 mg/kg/24 hr produced a fall in tissue CO_2 and O_2 tensions, effects due to the increased alveolar ventilation and relatively greater increase of tissue oxygen consumption than tissue perfusion.

1. Tenney, S. M., and Miller, R. M., *Am. J. Med.*, 1955, v19, 498.
2. Campbell, J. A., *Physiol. Rev.*, 1931, v11, 1.
3. Tenney, S. M., Carpenter, F. G., and Rahn, H., *J. Appl. Physiol.*, 1953, v6, 201.
4. Scholander, P. F., and Roughton, F. J. W., *J. Biol. Chem.*, 1947, v167, 235.
5. Van Liew, H. D., *Fed. Proc.*, 1956, v15, 192.
6. Lutwak-Mann, C., *Biochem. J.*, 1942, v36, 706.
7. Fishgold, J. T., Field, J., and Hall, V. E., *Am. J. Physiol.*, 1951, v164, 727.
8. Sproull, D. H., *Brit. J. Pharmacol.*, 1954, v9, 262.

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A Study of the Mechanism of the Schultz-Dale Reaction.* (22617)

WALTON B. GEIGER,† ELIZABETH M. HILL,‡ AND MABELLE THOMPSON.
(Introduced by Ann G. Kuttner.)

Irvington House, Irvington-on-Hudson, N. Y., and the Southwest Foundation for Research and Education, and Trinity University, San Antonio, Texas.

The Schultz-Dale reaction(1,2), which consists of the contraction of smooth muscle from an antigenically sensitized animal on re-exposure *in vitro* to the antigen, has a manipulative simplicity that makes studies of mechanism particularly inviting. The mechanisms that have been proposed fall into 2 overlapping groups: (1) liberation of a stimulant such as histamine or acetylcholine as a result of the antigen-antibody(3,4,5) and (2) involvement of nerve, a possibility that has been considered both favorably(6) and unfavorably(7,8,9), without very final evidence either way. The literature concerning the effects of pharmacodynamic agents and enzyme inhibitors on this reaction gives useful preliminary information bearing upon questions of mechanism, but the data are scattered and were obtained under a wide variety of experimental conditions. Therefore a preliminary study was made of the effects of a selected group of drugs and enzyme inhibitors upon the reaction, since it seemed likely that indications might be obtained as to which physiological or enzymological systems were involved in the reaction.

Gray, Pedrick and Winne(10), using guinea-pig ileum, found that 0.8% ethyl alcohol blocked the Schultz-Dale reaction, which suggested to us that nerve might be involved, and further experiments to test this possibility were performed. Results that support the hypothesis that nerve is involved are presented below.

Materials and methods. Guinea pigs weighing about 500 g received intraperitoneally 2.0 mg of crystalline egg albumin on 2 successive days. After 21 to 24 days, the animals were killed, and the ileum was removed and washed with Tyrode's solution. Portions of the ileum about 15 mm long were set up in a muscle bath stirred by aeration and arranged for washing by overflow. It was found important to keep the lumen open at both ends. The bath and all solutions were kept at 37.5°C. Contractions were recorded with an ink-writing lever that exerted a tension of about 0.5 g, and gave an amplification of 1:4.5. The usual method of testing the effect of a substance of interest upon the action of antigen and other stimulants was to add the substance to the bath containing the ileum, and after 15 minutes, to add the stim-

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† Mailing address: Southwest Foundation for Research and Education, 8500 Culebra Road, San Antonio, Texas.

‡ Present address: Charing Cross Hospital, London, England.