

facts suggest that alkali-treated bovine serum albumin may prove useful as a substitute for blood in man.

*Note.* Since submission of this paper for publication whole bovine serum, horse serum, and horse serum albumin have been treated with sodium hydroxide solutions. Such sera are not toxic and possess little or no antigenicity. Studies on the use of such alkali-treated sera for blood replacement in man and lower animals will be reported in later communications.

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**Nitrites. X. Effect of Sodium Nitrite Upon the Blood Pressure of Unanesthetized Hypertensive Rats.\***

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According to Grollman and his associates<sup>1</sup> nitrites and nitrates do not appreciably lower arterial blood pressure. An increase in cardiac output, they state compensates for the dilatation in the peripheral circulation and it is only when this stimulation of cardiac action fails that a fall in blood pressure ensues. It is maintained that in the case of the anesthetized animal the blood pressure decline is probably conditioned by this failure of the heart to respond owing to the disordered state of circulation induced by the anesthetic. In order to obviate any possible influence upon blood pressure, the experiments to be described presently were performed on the unanesthetized animal.

*Measurement of Blood Pressure.* The systolic blood pressures in the tails of rats were determined by the plethysmographic method of Williams, Harrison and Grollman.<sup>2</sup> The drug was not administered until a fairly constant level of blood pressure from day to day was established. The blood pressure of normal unoperated rats ranged

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<sup>1</sup> Grollman, A., Harrison, T. B., and Williams, J. R., Jr., *J. Pharm. and Exp. Therap.*, 1940, **64**, 76.

<sup>2</sup> Williams, J. R., Harrison, T. R., and Grollman, A., *J. Clin. Invest.*, 1939, **18**, 373.

between 75 and 110 mm of mercury, the mode was approximately 100. The variation from day to day for each rat, after sufficient training, was not more than 5 to 10 mm. In this experiment, each recording represents the average of 2 successive blood pressure readings varying in most cases not more than 0 to 5 mm.

*Operative Technic.* Rats were rendered hypertensive by (a) subtotal nephrectomy (Chanutin and Ferris<sup>3</sup>) or (b) bilateral wrapping of cellophane on the kidneys or (c) unilateral nephrectomy combined with unilateral cellophane wrapping, according to the method of Page.<sup>4</sup> The last two procedures were found superior because the operation can be performed in 1 stage and a lower mortality rate results than with subtotal nephrectomy.

Only about one-half of the animals became hypertensive and it took from 2 to 6 months for hyperpiesis to develop. In the majority of hypertensive rats the duration of the elevated arterial tension

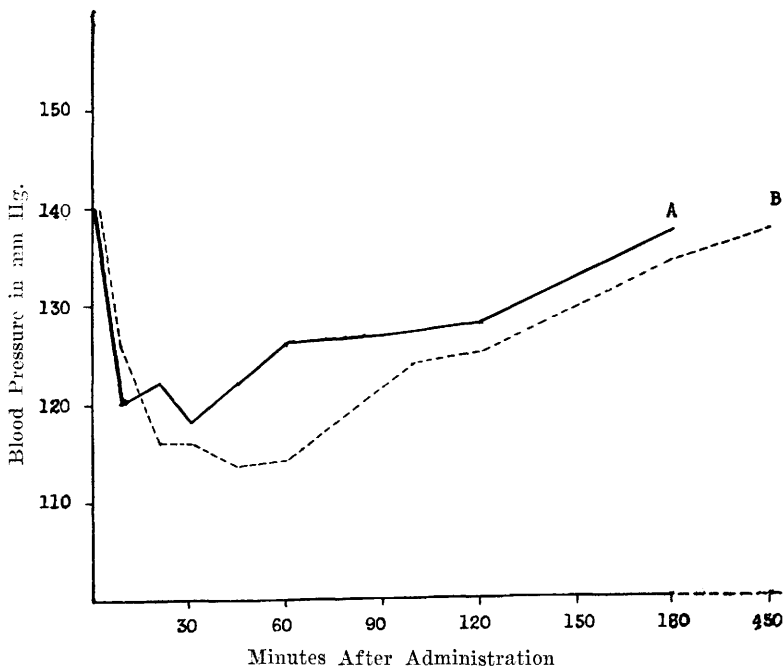


FIG. 1.

The Effect of Oral and Intraperitoneal Administration of Sodium Nitrite upon the Blood Pressure in Unanesthetized Hypertensive Rats.

Curves A and B show, respectively, the average fall in blood pressure after oral administration of 4 mg of sodium nitrite per 100 g and intraperitoneal injection of 2.5 mg of the same drug per 100 g body weight.

<sup>3</sup> Chanutin, A., and Ferris, E. B., *Arch. Int. Med.*, 1932, **49**, 767.

<sup>4</sup> Page, I. H., *J. Am. Med. Assn.*, 1939, **113**, 2046.

was limited; *i. e.*, about 6 months after the peak had been reached the blood pressure had fallen considerably.

*Results of Administering Sodium Nitrite.* Inspection of Fig. 1, which presents the results with a non-toxic, oral dose of 4 mg of sodium nitrite per 100 g of body weight, reveals that the blood pressure can be reduced by this drug. Twelve experiments were performed on 4 rats. The difference between the average blood pressure before oral administration (140 mm) and the lowest average blood pressure (118 mm, 30 minutes after feeding) was 22 mm of mercury. With the standard error of the difference equal to 3.1 mm, this difference is statistically significant.

Fig. 1 shows also the results of 12 experiments on the intraperitoneal injection of sodium nitrite (2.5 mg per 100 g of body weight) into 4 rats. An average reduction of 24 mm about 20 minutes after injection was observed. Statistical analysis shows that the standard error of the difference between the original blood pressure (140 mm) and the average blood pressure 20 minutes after injection (116 mm) is 6.4 mm.

No symptoms of nitrite poisoning were observed throughout the experiments. By oral administration, a dosage as high as 15 mg per 100 g was apparently not sufficient to evoke abnormal signs but 20 or more mg per 100 g was either toxic or lethal. Intraperitoneal doses of 10 mg or more were followed by toxic symptoms or death.

Grollman and coworkers<sup>1</sup> reported that inappreciable reductions in blood pressure were induced in hypertensive rats when sodium nitrite was given in a dosage of 0.1 g per rat per day mixed with the animal's food. Although this method of administration may effect a rather uniform and constant supply of the drug, it is conceivable that so little of the nitrite was ingested or available for absorption into the blood stream at any given time that a hypotensive action was not observed.

*Summary.* Sodium nitrite, when administered orally 4 mg per 100 g or intraperitoneally 2.5 mg per 100 g, reduces the arterial pressure of unanesthetized hypertensive rats.