

Intravenous and Subcutaneous Administration of Alkali-Treated Bovine Serum Albumin to Man and Lower Animals.

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In previous papers we have recorded the results of the administration of bovine serum albumin to human beings¹ and to lower animals.² The present report is concerned with the use of alkali-treated bovine serum albumin in man and other animals.

Materials. Bovine serum albumin prepared by the method already described¹ was treated with sodium hydroxide solutions. The details of the method will be described in a later communication. The sterility of the solutions was ascertained before they were used for injection. The albumin content of the untreated serum was 4 g % and of the alkali-treated serum 3 g %.

Antigenicity. Male guinea pigs were given 3 subcutaneous injections of alkali-treated albumin at suitable intervals. Three weeks later, a shocking dose of 1 cc was given by the intracardiac route. None of the animals died. Only very mild symptoms of anaphylaxis such as excitement and rubbing of the nose were noted. Control guinea pigs sensitized to untreated albumin revealed typical evidences of anaphylactic shock when the final intracardiac injection was given. Several animals died. The surviving animals displayed severe spasms of the abdominal muscles and dyspnea and were noticeably sick and listless for several days. Male white mice (hybrid strains) were sensitized by subcutaneous injections to untreated albumin. When the final injection was given through the dorsal tail vein, typical anaphylactic phenomena occurred. A parallel series of male white mice (hybrid strains) which received subcutaneous injections of treated albumin displayed few or no evidences of anaphylaxis when the final intravenous injection was made. Two dogs which had received treated albumin by vein 2 weeks previously, when given a second intravenous injection without anesthesia exhibited only mild transitory excitement and no typical anaphylaxis.

Toxicity. Twelve white mice given intraperitoneal injections of

¹ Davis, H. A., Eaton, A. G., and Williamson, J., *PROC. SOC. EXP. BIOL. AND MED.*, 1942, **49**, 96.

² Davis, H. A., and Eaton, A. G., *PROC. SOC. EXP. BIOL. AND MED.*, 1942, **49**, 20.

treated albumin in relatively large amounts (1 cc per 30 g of body weight) and 6 rabbits given intravenous injections (1 cc) showed no toxic symptoms.

Effectiveness for Blood Replacement. To determine the effectiveness of alkali-treated albumin as a blood substitute, 3 dogs weighing from 3.2 kg to 4.8 kg were used. Under ether anesthesia the right carotid artery was cannulated to record the blood pressure. Amounts of blood were removed equivalent to one-third to one-half of the calculated blood volume of each animal. When the lowered blood pressure showed no tendency to rise, alkali-treated albumin in solution was administered by vein in amounts sufficient to replace the blood which had been removed. The blood pressures rose almost to the initial level, where they were maintained. All of the animals recovered without any untoward effects and are alive at the time of writing.

Administration to Human Beings. Alkali-treated serum albumin which had been subjected to preliminary tests for sterility and toxicity was administered to human beings. In 67 male and female subjects, skin tests for sensitivity were carried out by the subcutaneous and intracutaneous injection of 0.5 cc of the albumin solution. Control injections of 0.5 cc of sterile distilled water were given. The skin tests were negative in all cases. Three men (H.C., J.J., and H.S.) were each given 50 cc of alkali-treated bovine serum albumin by vein at a rate of 5 cc per minute. In 2 of the individuals the blood pressure (systolic and diastolic) rose 6 to 14 mm Hg above the initial level during the injection and slowly returned to this level after the completion of the injection. In the third subject the blood pressure (systolic and diastolic) did not change during or after the injection. The pulse rates were not significantly affected by the injections. Urine collected from each subject after administration of the alkali-treated albumin showed no albuminuria. One individual (H.S.) had received an intravenous injection of untreated bovine serum albumin (100 cc) 3 months previously. In this subject, as in the others, no evidences of anaphylaxis or toxicity could be observed. Preliminary cross-matching tests were not performed.

Summary and Conclusion. Alkali-treated bovine serum albumin when administered by vein or by other parenteral routes is not toxic to human beings, dogs, rabbits, guinea pigs, or mice. It possesses little or no antigenicity. It is capable of raising and maintaining the blood pressure of dogs subjected to severe hemorrhage. These

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.

13760

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

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According to Grollman and his associates¹ 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.² 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

* The expense of this investigation has been defrayed in part by a grant from the Bressler Research Alumni Fund of the University of Maryland.

† The material contained in this paper is part of a thesis submitted by Maurice M. Rath to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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

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