in the absence of the thyroid, a lowering of the environmental temperature did not modify the deuterium content of the liver cholesterol under the conditions of this experiment. These data were interpreted to indicate that an increase in the metabolic rate alone did not influence the incorporation of deuterium into cholesterol in the liver. It was concluded, therefore, that the phenomenon observed in the hyperthyroid rats as reported above was similarly not mediated primarily by an increase in the metabolic rate, but that it was very likely a direct consequence of the increased thyroid activity.

Summary. 1. The incorporation of deuterium into cholesterol was studied in rats injected with thyroxine, in normal rats and in thyroidectomized rats. 2. It was observed that thyroxine stimulated, and thyroidectomy depressed, the incorporation of deuterium into cholesterol in the liver, intestine, kidneys and spleen, but not in the lungs. 3. In thyroidectomized rats, a lowering of the environmental temperature by approximately 20-28°C did not alter the rate of incorporation of deuterium into cholesterol in the liver.

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Response of Dogs to Intravenous Administration of Polyvinylpyrrolidone and Its Monomer.* (20291)

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Hecht and Weese(1) first reported the effective use of polyvinylpyrrolidone (PVP), a fractionated polymer of N-vinylpyrrolidone synthesized from acetylene and formaldehyde, as a plasma volume expander in clinical shock. At that time they also showed that the dog exhibits a sensitivity to PVP; this observation has been confirmed by several other investigators(2,3,4). Untoward reactions to PVP, used as a therapeutic agent in shock, have not been encountered either in man or other species of laboratory animals(1,4-8). During a survey of the more recent colloidal solutions recommended for use in clinical shock, the authors found that PVP was inferior to certain other colloids tested in dogs subjected to hemorrhagic shock; undoubtedly the peculiar canine reaction, in which hypotension and hemoconcentration are the primary manifestations, contributed to these results. Attempts to render the dog less sensitive to infusions of PVP by prior small injections(1,2) failed in our hands.

It was considered of interest to attempt to delineate the cause of the "canine reaction". In view of the use of cortisone in certain hypersensitive conditions and its positive effect in the rat after injection of dextran(9, 10) and human globin(10), this steroid was used to determine its effects on the reaction of the dog to PVP. Thus, the purpose of this investigation was two-fold: 1) to trace down the component of PVP solutions responsible

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TABLE I. Blood Pressure and Hematocrit Data after Injection of PVP (3 cc/kg) of Various Molecular Sizes and Its Monomer.

Treatment	No. of cases	Avg values after inj.—% of init. Blood pressure 1-3 min.	Blood pressure 5 min.	Blood pressure 30 min.	Hematocrit 5 min.	Hematocrit 30 min.
PVP (clinical)	6	41	45	52	117	138
" (K-21)	3	33	41	41	122	129
" (K-62)	6	108	96	99	98	103
Monomer (170 ×)						
45 sec. inj.	3	61	94	99	108	108
Rapid inj.	4	52	79	90	105	102
Cortisone + PVP	5	58	75	89	106	104

for the untoward reaction, and 2) to determine to what extent the adverse hemodynamic responses detract from the colloid oncotic properties of PVP in "shocked" dogs.

Procedure and methods. Mongrel dogs were anesthetized with pentobarbital sodium and a femoral artery was cannulated when needed for recording blood pressure and for bleeding. Some unanesthetized dogs were also used in which case blood pressure was determined by arterial puncture. Blood samples were collected in heparinized tubes at various intervals and hematocrits were determined in Wintrobe tubes centrifuged for 30 minutes at 3200 rpm, radius 14 cm (to end of tube). For the experiments on bled dogs, 2 hemorrhage procedures previously reported(11) were employed: Procedure I—acute hemorrhage to a blood pressure end point of 20 mm Hg followed by immediate infusion of a volume of replacement fluid equal to the volume of hemorrhage; Procedure II—acute hemorrhage to 30 mm Hg with one hour of hypotension at this pressure intervening before infusion of an equal volume of substitute.

Results. I. *Reaction of intact dogs to injections of PVP and vinylpyrrolidone* (monomer of PVP). Table I lists the various materials used and shows their effect on blood pressure and hematocrit at intervals up to 30 minutes. Unanesthetized and anaesthetized animals did not differ significantly in their blood pressure and hematocrit responses to PVP; consequently, anaesthetized dogs were used primarily.

a) *Clinical PVP.*† Animals were variable in their reaction to very small injections. Of 2 dogs injected with as little as 0.03 cc/kg, one showed an immediate fall in blood pressure from 135 to 55 mm Hg and returned to normal within 10 minutes, while the other was not affected. Doses of 0.37 cc/kg and 0.5 cc/kg failed to produce severe reactions in all dogs tested; an unanesthetized animal receiving the larger dose exhibited marked flushing of the skin, labored respiration, cyanotic tongue, feeble pulse, unsteady gait, and shaking and scratching of the head, whereas a second dog showed only mild symptoms. Consistently severe reactions occurred in all 6 dogs receiving 3 cc/kg injected in 45 seconds (equivalent to a rate of 4 cc/kg/min). Even by 90 minutes after this dose, the average blood pressure was only 67% of initial and the average hematocrit remained elevated to 134% of the initial value. After one to 5 hours in those animals receiving 3 cc/kg, the blood pressure rose slowly and was maintained at a lower level than the initial. If a second injection was now administered, then the severity of the accompanying reaction was considerably reduced, and in some instances, no apparent effect was noted. Twenty-four hours after the first injection, however, a third injection of the same magnitude elicited a marked reaction.

b) *K-21 PVP, K-62 PVP and monomer of PVP.*‡ Since the clinical preparation of PVP,

† 3.5% Solution, Schering Corp. Lot GA-PVP-111; K-value 33.5, Weight average molecular weight 81000(12). Allocated by the National Research Council.

‡ Powdered PVP (K-21 and K-62) and pure liquid vinylpyrrolidone were supplied through the courtesy of Dr. J. C. Howard, Jr., Schenley Laboratories. K-21 and K-62 PVP were compounded in sterile 0.9% saline as 3.5% solutions; the reported average weight molecular weights are 20500 and 560000 respectively(14).

as well as other colloidal solutions used as plasma volume expanders, consists of a material with a wide range of molecular sizes, it was considered pertinent to use "narrow cuts" at both ends of the range to ascertain the relative effects of small and large molecules of the polymer. Also present in the clinical PVP solution is approximately 17.5 mg % vinylpyrrolidone(13); this material was injected intravenously in amounts varying from 1 to 170 times that present in the clinical solution, both undiluted and diluted in saline to a volume of 3 cc/kg. Data presented in Table I show that K-21 PVP produced practically the same profound reaction as the clinical preparation, whereas the K-62 material caused only insignificant effects. With the smaller molecular weight material even at 90 minutes after injection, the blood pressure remained depressed at 59% of initial and hematocrit was elevated to 125% of initial; with the larger, there was a slight hypertensive effect immediately after injection followed by a slight decline in blood pressure and then a return to normal levels (slight flushing did occur in an occasional animal with K-62 PVP). Quantities of pure liquid vinylpyrrolidone up to 170 times that found in clinical PVP, diluted in saline and injected in volumes of 3 cc/kg, produced no significant changes. Injected undiluted in the largest amount, the monomer caused transitory hypotension, which was more protracted with the rapid rate of injection (Table I).

c) *Prophylactic treatment with cortisone before injection of clinical PVP.* Five dogs were injected with cortisone intramuscularly for five days prior to an intravenous injection of 3 cc/kg of clinical PVP. One animal received 5 mg per day, one 10 mg, and three 50 mg per day. The steroid was injected once daily, half of the dose in each hind quarter. On the morning of the sixth day these animals were injected with 3 cc/kg of clinical PVP. Prophylactic treatment with cortisone did not completely nullify the "canine reaction" to PVP, but did decrease its severity and duration. By 30 minutes after the PVP injection (Table I), average blood pressure and hematocrit values for the cortisone-treated groups were approaching the initial values, whereas by 90 minutes the average hematocrit for the PVP group not receiving cortisone remained significantly elevated (134% of initial) and hypotension still persisted (B.P.: 67% of initial). Among the cortisone-treated animals only the one receiving the smallest dose exhibited marked flushing of the skin, 2 showed mild flushing, and 2 showed no flushing.

TABLE II. Blood Pressure Response to Infusions of Clinical PVP (13 Dogs).

PVP, cc/kg	Blood pressure—mm Hg			
	Init.	Min. after inf. 2–3	30	90
	Intact—4 cc/kg/min.			
40	90	40	30	55
40	140	65	120	130
40	100	60	65	85
	Bled—4 cc/kg/min.			
42.5	115	30	35	45
54.5	145	Died during infusion		
	Bled—2 cc/kg/min.			
50	155	60	95	90
28	150	45	60	90
35	160	55	80	100
43.5	130	60	95	110
37.5	120	40	75	100
	"Primed"—bled—4 cc/kg/min.			
24.3	95	50	50	75
40.4	90	75	95	110
21.1	80	40	40	80

II. *Response of intact and bled dogs to infusions of clinical PVP.* a. Effect of rate of infusion. The pertinent blood pressure data are presented in Table II. Three intact anaesthetized dogs were infused with 40 cc/kg at the rate of 4 cc/kg/min; no deaths occurred, but the typical reaction ensued (the magnitude of the infusion masked the hemoconcentrating effects produced by small injections). Two dogs were subjected to a controlled hemorrhage to a blood pressure end point of 20 mm Hg and were immediately infused at 4 cc/kg/min with a volume of PVP equal to the volume of blood removed; the blood pressure response of one of these dogs was extremely sluggish (39% of initial 90 minutes after infusion), and the other died before the end of infusion. No fatalities resulted in bled dogs infused at the rate of 2 cc/kg/min and blood pressure increased significantly over the immediate post-infusion

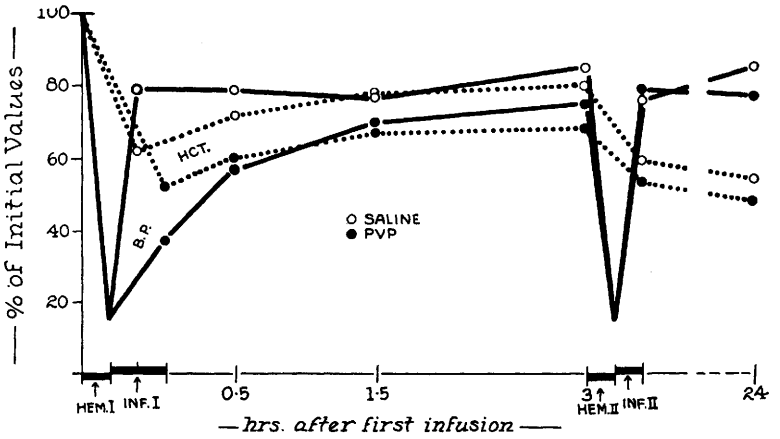

FIG. 1. Avg curves for blood pressure (solid lines) and hematocrit (dotted lines) for bled dogs on Procedure I.

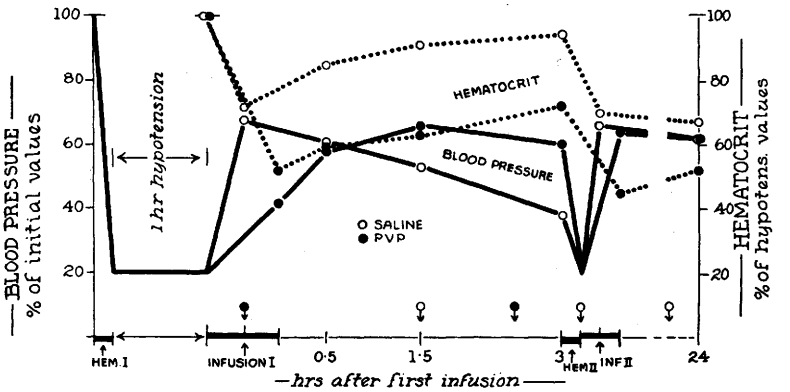

FIG. 2. Avg curves for blood pressure (solid lines) and hematocrit (dotted lines) for surviving bled dogs on Procedure II. Symbols with arrows represent time of death for each animal on indicated therapy.

levels. The bled dog could indeed tolerate the faster rate, if hemorrhage and infusion were performed two to three hours after a second (or third) small injection had been administered, *i.e.*, after the blood pressure had reached a plateau (*vide supra*). In view of the existing hypotension, however, it is highly questionable if such animals could be considered as fully recovered from the effect of the "priming" injections.

b) Evaluation as a Plasma Expander in the Bled Dog. Ten dogs were subjected to a controlled hemorrhage in accordance with Procedure I, infused immediately with PVP and 5 with physiological saline. Nine dogs were bled in accordance with Procedure II; 4 being infused with PVP after the delay of one hour and 5 with saline. Fig. 1 and 2 show average mean blood pressure and average hematocrit responses for the 2 procedures. In each instance the infusion rate for PVP was one-half that for saline—2 cc/kg/min in Procedure I, and 1 cc/kg/min in Procedure II for the initial infusion. The figures show clearly the delay in blood pressure response to PVP infusions. They also demonstrate that the PVP infusions caused a greater hemodilution as measured by hematocrit change than did saline, particularly in the more severely shocked animals. All animals survived on Procedure I, while several animals in each group succumbed before 24 hours on Procedure II (indicated by symbols with arrows in Fig. 2). To estimate the relative overall effectiveness of various infusion fluids, the ratio of subsequent bleeding volumes to the

initial, termed the Bleeding Volume Index (BVI), has been employed. For Procedure I at 3 hours after infusion, the BVI's for PVP and saline were 64 and 54 respectively; for Procedure II, 23 and 12 respectively.

Comments. The foregoing data indicate that the smaller molecular weight portions of PVP produce the prolonged hypotensive effect observed in intact and bled dogs. Since amounts of vinylpyrrolidone equivalent to those encountered in clinical PVP produce insignificant changes, and only in excessive amounts does a transitory effect ensue, this substance may be ruled out as the causative agent of the "canine reaction." Whether the smaller molecules themselves act as a vasodilator component or whether they elicit the release of a vasodilator substance into the circulation remains for further investigation. In view of its hemoconcentrating effect and the partial benefits of cortisone, the possible influence of this material on capillary permeability is also indicated for additional study.

Polyvinylpyrrolidone is not recommended as a suitable therapeutic agent for shocked dogs. Although apparently superior to crystalloidal solutions in certain respects(15), PVP has not proven to be as effective in the dog as dextran, oxypolygelatin, or modified fluid gelatin under the same experimental conditions(16).

Summary. 1. Due to a species sensitivity, whose nature is as yet unknown, PVP cannot be considered as a suitable colloid replacement fluid for the treatment of "shocked" dogs. 2. Intact dogs were variable in their response to small intravenous doses, 0.03 to 0.5 cc/kg of clinical PVP, but reacted severely to intravenous injections of 3 cc/kg exhibiting hypotension, hemoconcentration, and flushing of the skin of several hours' duration. 3. A small molecular weight fraction of PVP (K-21) produced severe reactions, while with a larger molecular weight fraction (K-62) only insignificant changes occurred. 4. Monomeric vinylpyrrolidone, in quantities far in excess of those found in clinical PVP solutions, caused only transitory hypotension when injected undiluted. 5. Cortisone, used prophylactically over a period of 5 days prior to an injection of 3 cc/kg of PVP, decreased the severity and duration of the "canine reaction." 6. Bled dogs did not tolerate well an infusion rate of 4 cc/kg/min; no fatalities resulted from infusions at half this rate.

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