STUDIES OF THE EXCRETION OF POLYVINYLPIRROLIDONE BY THE NORMAL HUMAN KIDNEY*

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In developing any plasma substitute the problem of finding a high molecular weight compound which can temporarily take the place of the plasma proteins is the major one, since the electrolyte composition involves no fundamental difficulties. The function of this high molecular weight compound is to exert an osmotic pressure across the blood capillary walls and, hence, assist in controlling the fluid balance in patients in whom there has been a loss of plasma protein. Provided any given polymer is pharmacologically inert and shows no toxicity either immediate, due to allergic reactions, or long-term, due to permanent storage of the foreign body in the tissue, its value in a plasma substitute will depend largely upon the persistence of the osmotic pressure which it exerts across the capillary wall. This will depend upon the rate of elimination of the polymer from the body and the rate at which it passes through the capillary walls into the tissue fluid. The elimination mechanisms will, in general, involve excretion of unchanged polymer by the kidney or by other means, and its degradation to smaller molecules. The passage of polymer molecules through both the kidney and the capillary wall will depend upon the shape, structure, charge, and molecular weight of the molecules present. The importance of molecular weight in selecting a polymer for use in a plasma substitute has recently been emphasized by Boyd, Fletcher, and Ratcliffe (1953), but not enough attention appears to be given to the effect that the shape and structure of a molecule can have on its passage through a membrane. Consequently, the molecular weight most suitable for use in a plasma substitute will vary with the type of polymer. The molecular weight distribution of a polymer does not necessarily remain constant after its infusion into the body, since it is unlikely that all the elimination

mechanisms will be independent of molecular weight. For a complete understanding of the behaviour in the body of any polymer, knowledge of the variation of its molecular weight distribution with time is important. In all published work on the fate in the body of polymers, which are normally foreign to the body, no attempts appear to have been made to determine such changes in molecular weight distribution. In the present paper some of the changes in molecular weight distribution which occur in the case of the particular synthetic polymer, polyvinylpyrrolidone (P.V.P.), used in these studies are described.

Ideally, after an infusion of a plasma substitute, the polymer would be eliminated from the body at such a rate that the osmotic pressure due to the polymeric component decreased as the osmotic pressure due to the plasma proteins returned to normal as the deficiency in these was made good. An exact balance would, in practice, be impossible to achieve, but a rational approach to the problem of selecting the most suitable molecular weight range of any particular polymer is based on a knowledge of the time taken for the restoration to normal, after sudden depletion, of the plasma proteins in human subjects. Unfortunately, there appears to be insufficient data available at present on the rate of regeneration of plasma proteins under conditions similar to those when an infusion of a plasma substitute might be given. Most information on the regeneration of plasma proteins in human subjects is for cases of malnutrition. Wallace and Sharpey-Schafer (1941) have shown in human subjects not suffering from shock that regeneration of the plasma proteins was virtually complete in three to 90 hours, but no similar studies have been made on human subjects who are in a severely shocked condition due to loss of blood. Ebert, Stead, Warren, and Watts (1942) have shown that in dogs, severely shocked after considerable loss of blood which was replaced by an equal volume of isotonic saline, regeneration of proteins

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was extremely slow. No reason was given for this slow regeneration. It is not known whether the presence of a synthetic colloid can affect the regeneration of the plasma proteins through its property of maintaining the circulating volume.

In the absence of such information as would allow a theoretical approach to the development of a plasma substitute, it is of value to determine the behaviour in the body of those plasma substitutes which are clinically acceptable. Such a plasma substitute is "plasmosan," which was first described by Thrower and Campbell (1951). The clinical value of this material has been shown by Arden, Mandow, and Stoneham (1951), by Haler, Clift, Jameson, and Swinton (1953), and by Russell-Stoneham (1953). The present paper describes renal excretion studies of the colloidal component, P.V.P., from human subjects after infusion of "plasmosan." This polymer, originally examined for use in a plasma substitute by Hecht and Weese (1943), has since been further developed in France and in this country. Since much of the published work on this type of plasma substitute relates to P.V.P. of inadequately defined molecular weight range, conflicting results have been reported, and it must be emphasized that the results described in this paper apply to only one grade of P.V.P. of definite molecular weight distribution. A preliminary account of the present studies has already been given by Campbell (1953).

Experimental

At the hospital each patient, selected by the medical staff as being free from any kidney disease, was infused with up to one bottle (540 ml.) of "plasmosan." The time of beginning and ending the infusion was recorded, together with the volume of "plasmosan" unused. One 24-hour sample of urine was collected up to the time of the infusion. After the infusion individual samples of

urine were collected during an initial period of about two days and then 24-hour samples for at least another nine days. In some surgical cases dressings which might contain P.V.P. from the open wounds were retained. In our laboratories all samples of urine were initially examined by the tests given below and then the P.V.P. was extracted. The molecular weight distributions of the extracted samples were determined. The wound dressings were also examined.

Details of Patients and Treatment.—Table I gives details of each patient together with notes on the loss of P.V.P. by various means. Mr. G. P. Arden, in charge of all the surgical cases, stated that there was no excessive bleeding in any case. The actual quantity of blood lost in the operation cannot, however, be stated.

Plasmosan from the same batch was used in all infusions. The composition of "plasmosan" has previously been given by Thrower and Campbell (1951). The molecular weight distribution curve for the P.V.P. used in this batch is given in Figs. 4 and 5, and had not changed during storage since the preparation of the "plasmosan."

Experimental Methods.—The clarity, specific gravity (by hydrometer), and pH (by glass electrode) of each sample of urine were noted. Albumin was tested for qualitatively by the sulphosalicylic acid test and for reducing sugar by Benedict's test. Creatinine was determined by the Jaffe method, the resulting intensity of colour being measured on an EEL colorimeter using a No. 624 filter. Details of the latter three tests have been given by Hawk, Oser, and Summerson (1947). The P.V.P. concentration was determined colorimetrically by the iodine method as described by Campbell and Hunter (1953) and by Campbell, Kane, and Ottewill (1954a). An EEL colorimeter with No. 623 filter was used to measure the intensity of colour. From the P.V.P. concentration, and the volume of the urine sample, the weight of P.V.P. present was obtained.

A representative quantity of the P.V.P. in each sample of urine was extracted by the following method. To the urine was added 22% by weight of exsiccated sodium

TABLE I
DETAILS OF PATIENTS

Patient Serial No.	Sex	Type of Case	Age	Diagnosis or Operation	Kidney Function from Clinical Evidence	Known Loss of P.V.P.
3	M	Medical	23	Suspected mildly active tuberculous pleural effusion	Normal	None
13	F	"	58	Duodenal ulcer	"	"
16	M	"	26	Pneumonia resolved before P.V.P. infused	"	"
17	M	"	31	Abdominal investigation—N.A.D.	"	D
18	M	"	61	Gastric ulcer	"	None
4	F	Surgical	73	Fractured left femur (Smith-Petersen pin)	"	B, C, E
5	F	"	54	Bilateral hallux valgus (Keller's)	"	E
6	M	"	18	Removal of exostosis of first metatarsal	"	B, E
7	F	"	46	Bilateral hallux valgus (Keller's)	"	E
8	F	"	53	" " " "	"	C, E
9	F	"	50	" " " "	"	B, C, E
10	F	"	39	" " " "	"	B, E, A
11	F	"	33	" " " "	"	B, E
12	F	"	21	Bilateral Keller's operation and spike arthrodesis	"	C, E, A
15	F	"	47	Right hallux valgus (Keller's)	"	E

A=loss by menstruation, B=loss of urine by hospital, C=incontinence and/or bowels opening, D=loss of urine in laboratory, E=loss by bleeding into wound dressing.

sulphate, which was dissolved by heating. The solution was cooled to 25–30° C. and the P.V.P. was thrown out of solution as an insoluble gel. The solution was extracted three times with one-quarter its volume of chloroform. The separating funnel was shaken vigorously for five minutes for each extraction. Any gel formed was cleared on a centrifuge, and the "skin" formed at the interface was extracted with a little more chloroform to remove any adsorbed P.V.P. The chloroform extracts were combined and, if opalescent, were cleared by the addition of a small quantity of methanol. This had the effect of converting the two-phase system chloroform-water into a single phase, and sodium sulphate dissolved in the aqueous phase was precipitated. The clear liquid was then filtered and evaporated to dryness on a steam bath. The solid residue was freed from traces of chloroform by heating on a steam bath at reduced pressure (filter pump) and dissolved in an appropriate volume of water to give an aqueous solution which was then suitable for the determination of the molecular weight distribution. Experiments, in which P.V.P. of known molecular weight distribution was added to urine, have shown that there was no detectable difference between the dissolved and the extracted P.V.P. Distributions of molecular weight were determined by the turbidimetric method as described by Campbell, Kane, and Ottewill (1953).

Each wound dressing was extracted with boiling water. After filtering, the aqueous solutions were concentrated by vacuum distillation and clarified in a centrifuge. The solutions were then examined by the iodine method for the presence of P.V.P. Attempts were made to determine molecular weight distribution curves. A wound dressing from a patient who had not received "plasmosan" was similarly examined.

Methods of Calculation.—Since the actual period of the infusion was at least one hour, zero time for calculating the rate of excretion of P.V.P. has been taken as the

arithmetic mean of the beginning and end of this period. This introduces an indeterminate error when a comparison is made of the excretion by different patients at times less than 10 hours after infusion, but this error is negligible for longer periods.

The uncorrected weight of P.V.P. present in any sample of urine was obtained from the iodine estimation without allowance for variations in sensitivity of the method with molecular weight. When a correction was made for this, using the peak molecular weight of the distribution curve, the weight of P.V.P. present is referred to as the corrected weight. The correction factors used are given by Campbell, Kane, and Ottewill (1954a). This may introduce a small error, since the true correction factor, which cannot at present be determined, will depend upon the distribution of molecular weights rather than on the peak molecular weight.

In comparing the molecular weight distributions of the infused and total excreted P.V.P., it is convenient to consider the fate in each patient of 1 g. of P.V.P. which is completely characteristic of all the P.V.P. infused. Of each gramme infused, the fate of R/100 g. is known where R is the percentage total weight excreted. Therefore, molecular weight distribution curves for 1 g. of infused and R/100 g. of total excreted P.V.P. are compared. This latter is obtained by summing the molecular weight distribution curves for r/100 g. of each successive sample of excreted P.V.P. (of known percentage weight r) where $\Sigma r = R$.

Experimental Results

A complete picture of the renal excretion of P.V.P. can be obtained only from those cases in which there was negligible loss of P.V.P. (see Table I). The data from those patients in which indeterminate losses of P.V.P. did occur can, how-

TABLE II
EXPERIMENTAL DATA FOR PATIENT NO. 16 AFTER INFUSION OF 16.5 G. P.V.P.

Sample Number	Determination of P.V.P. in Urine						Laboratory Tests on Urine					
	Time from Infusion (hours)	Sample Volume (ml.)	Peak Molecular Weight $\times 10^{-3}$	Weight Factor	Uncorrected Weight of P.V.P. (g.)	Corrected Weight of P.V.P. (g.)	Clarity	Specific Gravity 15° C.	pH	Albumin	Sugar	Creatinine (g.)
16 1	Pre-infusion	1,090			0	0	Normal	1.013	6.1	—	—	1.31
16 2	0.5	475	10.5	1.48	4.89	7.24	"	1.014	7.0	—	—	0.22
16 3	9	435	20	1.08	4.35	4.70	"	1.015	6.0	—	—	0.64
16 4	18.5	330	21	1.08	0.99	1.07	"	1.024	5.8	—	—	0.71
16 5	20.5	220	21.5	1.07	0.20	0.21	"	1.012	6.6	—	—	0.10
16 6	21.5	360	25	1.05	0.19	0.20	"	1.007	6.9	—	—	0.12
16 7	23.5	540	26	1.04	0.21	0.22	"	1.015	7.0	—	—	0.15
16 8	45	1,800	25.5	1.04	1.14	1.19	"	1.007	5.9	—	—	1.39
16 9	69	2,250	30.5	1.00	0.93	0.93	"	1.011	6.5	—	—	1.91
16 10	93	2,034	33.5	1.00	0.51	0.51	"	1.012	6.1	—	—	1.77
16 11	117	750	37	1.00	0.33	0.33	Highly turbid	1.023	5.8	—	++	1.77
16 12	141	1,935	34	1.00	0.23	0.23	Normal	1.012	6.1	—	—	1.82
16 13	165	1,660	36	1.00	0.14	0.14	"	1.012	6.4	—	—	1.68
16 14	189	2,040	39	1.00	0.13	0.13	"	1.015	6.0	—	—	1.77
16 15	213	2,710	40.5	1.00	0.11	0.11	"	1.008	6.5	—	—	1.71
16 16	237	1,770	39	1.00	0.08	0.08	"	1.008	6.5	—	—	1.50
16 17	261	1,340	47	1.00	0.02	0.02	"	1.017	5.9	—	—	1.77
16 18	285	2,420	38	1.00	0.03	0.03	"	1.009	6.3	—	—	1.79
16 19	309	2,605	49	1.00	0.02	0.02	"	1.009	6.4	—	—	1.80
16 20	333	1,270	59	1.00	0.02	0.02	"	1.013	6.2	—	—	1.46

ever, be used to support some of the main conclusions. A set of data for one typical medical patient is given in Table II.

Pattern of Excretion.—A typical set of molecular weight distribution curves for P.V.P. recovered from successive samples of urine passed by patient 16 is given in Fig. 1. The molecular weight distribution curves for all the samples of recovered P.V.P. showed the characteristics typical of fractionated material, a narrower molecular weight range and sharper peak than with the original unfractionated polymer. The curves, very sharp and narrow on the first day, gradually broadened as the post-infusion period extended. The increase in peak molecular weight with time after the infusion is illustrated in Fig. 2. Towards the end of the excretion study on any particular patient, about 150 hours after infusion, the difference between

successive molecular weight distribution curves was less than the experimental error, which became large in this period due to the extremely small amount of P.V.P. present in the urine. The data for the cases which were incomplete through loss of urine or other causes were not in disagreement with this general picture.

Rate of Excretion.—Fig. 3 shows the variation of percentage weight excreted, with time after the infusion, for four medical and three surgical cases. The excretion rate, high during the first 24 hours after infusion, decreased to a small value after about 100 hours. Excretion did continue at this small, but measurable, rate for 300 to 600 hours for different patients. The rapid excretion immediately after infusion is illustrated by Table III, which includes data for all patients. The variation between different patients due to errors already dis-

FIG. 1.—Molecular weight distribution curves for P.V.P. recovered from successive samples of urine from patient 16 (see Table II). These curves are not normalized.

FIG. 2.—Increase in peak molecular weight with time after infusion. A is patient No. 9 (surgical), B is patient No. 12 (surgical), C is patient No. 3 (medical), D is patient No. 16 (medical), E is patient No. 13 (medical).

TABLE III
PERCENTAGE WEIGHT OF P.V.P. EXCRETED DURING
FIRST 48 HOURS AFTER INFUSION

Type of Case	Patient No.	% Weight Excreted at 12 Hours		% Weight Excreted at 24 Hours		% Weight Excreted at 48 Hours	
		Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected	Corrected
Medical	3	44	56	55	66	64	75
	13	62	75	70	83	75	84
	16	58	75	66	83	73	92
	17 (a)	66	—	73	—	81	—
	18	58	81	65	89	73	96
Surgical	4 (b)	—	—	—	—	—	—
	5	50	56	56	73	75	79
	6	12	14	22	25	35	40
	7 (c)	1	1	13	17	48	52
	8	12	15	22	27	32	38
	9	17	19	20	22	23	25
	10 (b)	—	—	—	—	—	—
	11	68	88	76	92	82	98
	12	32	40	39	47	44	52
	15	34	49	53	62	69	75

(a) Corrected weights are not available. (b) Data have not been calculated due to considerable loss of urine in this period. (c) The low values at 12 and 24 hours are probably due to retention of urine over this period.

cussed on page 254, in the times calculated for each sample of urine is small at 12, 24, and 48 hours after infusion.

An indication of the quantity of P.V.P. excreted over shorter post-infusion periods can be obtained (Table IV). Samples of urine, collected from two patients (Nos. 13 and 16) within 15 minutes of the end of the infusion, contain the P.V.P. actually

TABLE IV
EXCRETION OF P.V.P. DURING AND IMMEDIATELY
AFTER INFUSION

Patient No.	Infusion		Time of Collection of Urine Samples	% Weight of P.V.P. Recovered	
	Time	Duration (hours)		Uncorrected	Corrected
13	10-45 to 11-45	1-00	11-50	3.5	5.2
16	10-05 to 12-20	2-25	12-34	29.8	44.1

excreted by the kidney during the infusion and for a short period afterwards. These data also indicate an immediate and rapid excretion of P.V.P.

Total Recovery of P.V.P.—The total recoveries of P.V.P. from all patients are given in Table V.

Renal Threshold Molecular Weight.—In all the patients studied, P.V.P. with molecular weights over the whole range 0 to more than 100,000 was recovered from the urine. If there is a threshold

FIG. 3.—The variation, with time, of percentage weight of P.V.P. recovered from urine.

A + Patient No. 11 (surgical)
 ● Patient No. 5 (surgical)
 × Patient No. 15 (surgical)

B + Patient No. 18 (medical)
 ● Patient No. 16 (medical)
 × Patient No. 13 (medical)
 ▲ Patient No. 3 (medical)

TABLE V

TOTAL RECOVERY OF P.V.P. FROM URINE OF PATIENTS

Type of Case	Patient Number	Known Loss of P.V.P. other than by Bleeding from Wound	% Weight Recovered from Urine	
			Uncorrected	Corrected
Medical	3	None	70.3	88.0
	13	"	92.8	106.2
	16	"	87.9	105.3
	17	"	91.3	—*
	18	"	86.0	107.4
Surgical	4	Some	13.8	14.1
	5	None	81.5	89.8
	6	Some	42.4	46.6
	7	None	53.9	59.0
	8	Some	38.7	44.3
	9	"	27.1	29.2
	10	"	48.2	57.1
	11	"	90.5	107.3
	12	"	56.7	64.9
	15	None	76.1	84.4

*Molecular weight distribution data not available to allow correction to be made.

molecular weight above which molecules of P.V.P. cannot pass through a normal kidney, this threshold must, therefore, be considerably greater than 100,000.

Degradation of P.V.P. in the Body.—When more than about 80% of the infused P.V.P. was recovered a comparison could be made between the molecular weight distribution for the infused P.V.P. and for the sum of all the samples of P.V.P. excreted by any one patient. No allowance has been made for the departure of the recovered P.V.P. from 100%. Fig. 4 shows molecular weight distribution curves for four medical patients and Fig. 5 for two surgical patients. The distribution curves are presented as histograms, since this simplified the calculations. Owing to the very small quantity of P.V.P. of molecular weight above 100,000, the histograms in this region cannot be drawn so that they are distinguishable from the base line.

Wound Dressings.—The presence of P.V.P. in the wound dressing was demonstrated by the iodine method of estimation and the turbidimetric method for the determination of molecular weight distribution, but no quantitative results were obtained owing to the presence of interfering substances.

FIG. 4.—A comparison of the molecular weight distribution curves of infused (—) and recovered (.....) P.V.P. for four medical cases. A is patient No. 3, B is patient No. 13, C is patient No. 16, and D is patient No. 18.

FIG. 5.—A comparison of the molecular weight distribution curves of infused (—) and recovered (.....) P.V.P. for two surgical cases. A is patient No. 11 and B is patient No. 15.

These were also found in dressings from patients not receiving "plasmosan."

Discussion

Although all patients had been selected by the medical staff of the hospitals concerned as free from any kidney disease, some properties of the

urine samples, which are listed above in the experimental section, were recorded as supplementary evidence. Apart from the 24-hour volume and creatinine content, there appeared to be no marked departures from normality. Surgical cases differed from medical in that both urine volume and creatinine excretion fluctuated considerably and, on the whole, were appreciably lower than what are regarded as normal values. Such variations, particularly in the immediate post-operative period, might well be due to variations in the patient's fluid intake and disturbance of his nitrogen metabolism. The administration of P.V.P. itself has already been shown by Thrower and Campbell (1951) to exert no ill effect on kidney function.

Low recoveries of P.V.P. in some of the patients studied may have been due to one or more of the following: (1) Loss of urine due to (a) incontinence of urine or its contamination by faeces, or (b) failure to preserve the urine samples or their loss during examination. (2) Loss of blood into wound dressings and due to menstruation. Such losses were of most significance when they occurred in the first 48 hours after infusion when the concentrations of P.V.P. in blood and urine were greatest. The actual quantity of P.V.P. lost cannot be determined. In all the medical cases the constancy of the 24-hour volume and creatinine content of the

urine indicated that losses were negligible. In the surgical cases, however, no such simple interpretation was possible, since the effect of surgery on the urine volume and creatinine excretion was not known. In all surgical cases loss of P.V.P. due to bleeding occurred. For reasons discussed above, such losses could not be assessed and, hence, the

amount of P.V.P. recovered must be regarded as minimal.

In all the cases studied, no differences between the experimental results for male and female patients have been found. It is impossible to say whether the experimental differences between surgical and medical cases, such as the total P.V.P. recovery (Table V), are due to any other causes than the losses of P.V.P. known to occur in the surgical cases.

Apart from its dependence upon blood concentration, the rate at which P.V.P. passes through the kidney must depend inversely upon its molecular weight in order to explain the general shape of the curves in Fig. 2 which give the increase in peak molecular weight with time after infusion. A more detailed analysis of the kinetics of excretion is impossible at present owing to the complicating factor of degradation of P.V.P. Although P.V.P. passes through the kidney very slowly at high molecular weights, evidence has been obtained that P.V.P. of all the molecular weights present in the polymer infused can pass through the kidney. If a threshold molecular weight exists, above which P.V.P. molecules will not pass through the kidney, this is in excess of 100,000. The value of this threshold molecular weight cannot be stated at present with greater accuracy, since the actual weight of P.V.P. of molecular weight greater than 100,000 in "plasmosan" is too small to allow precise measurements to be made. An accurate determination would require excretion studies using P.V.P. of a much higher molecular weight. The excretion of P.V.P. of all the molecular weights present in "plasmosan" is confirmed by the complete recovery of P.V.P. in the urine of those patients in whom loss of P.V.P. may be regarded as negligible (Table V). This complete recovery indicates that disposal of P.V.P. in the body other than by renal excretion is insignificant and that it is not permanently stored in the body. Histological evidence that the grade of P.V.P. used in "plasmosan" is not permanently stored has been found by Whitelaw (see Thrower and Campbell, 1951) in rabbits, and by Haler and co-workers (1953) in a human subject. These experiments refer to plasma concentrations of P.V.P. not grossly in excess of those likely to be found in normal clinical practice. Conflicting evidence concerning storage of other grades of P.V.P. in various animals has been reported by Korth and Heinlein (1943), by Bargmann (1947), by Schoen (1949), by Fresen (1949a), and by Steele, Van Slyke, and Plazin (1952). This lack of agreement between different workers may partly be due to the use of different grades of P.V.P., the

molecular weight ranges of which have never been specified, since Fresen (1949b) has shown that the possibility of storage will certainly increase with increasing molecular weight. Other relevant factors may be the weight of P.V.P. per kilogram of body weight infused, and the possibility of differences in the renal excretion between different species of animals.

The threshold molecular weight of excretion for proteins as found by Bayliss, Kerridge, and Russell (1933) is about 68,000 and is much smaller than the value for P.V.P. The explanation of this may be, in part, due to differences in the shape and electric charge of the molecules. Another difference does, however, exist between the plasma proteins and P.V.P. molecules in solution, which may be of importance. No protein molecule can uncoil, and hence change its cross-sectional area, without undergoing irreversible denaturation. Scholtan (1951) has shown that the P.V.P. molecule, like most flexible, long-chain, synthetic polymer molecules, is, in solution, randomly kinked and, unlike the protein molecule, continually undergoes reversible changes in the actual degree of kinking. There is a most probable configuration and cross-sectional area, which, for P.V.P. of a higher molecular weight, may prevent passage through the kidney. Reversible changes in the degree of kinking, however, could yield molecules of smaller cross-sectional area which might then be capable of passing through the kidney. It may be this mechanism which allows P.V.P. molecules of high molecular weight to pass slowly through the kidney.

A comparison of the histograms of Figs. 4 and 5 shows that there is more P.V.P. of a low and less of a high molecular weight recovered in the urine than was infused into the patient. Some form of degradation of P.V.P. molecules must, therefore, occur during their passage through the body, but the mechanism of this change is at present unknown. These observations, which can be due only to a limited degradation of P.V.P., are not in disagreement with those of Steele and his colleagues (1952), who found that after infusions of C^{14} tagged P.V.P. only a very small amount of radioactive carbon dioxide was expired.

Evidence is now available that P.V.P. is very rapidly excreted in the 48 hours after an infusion. Table IV indicates that there is no delay in the beginning of excretion. Table III shows that where there is no loss of P.V.P. between 65 and 90% (corrected weights) is excreted in the first 24 hours after infusion. In the first 12 hours over 50% is excreted. From the above figures it follows that, 24 hours after an infusion, between 10 and

35% of the P.V.P. is left in the body. This must represent the maximum present in the blood stream at 24 hours, since some of the P.V.P. may be, at least temporarily, in other body fluids or tissues.

In conclusion, these excretion studies indicate that the P.V.P. in "plasmosan" as at present constituted is not permanently stored in the body. It would appear that clinically beneficial results can be obtained with a grade of P.V.P. which is excreted as rapidly as the present studies indicate. Whether an improved plasma substitute would result from using a grade of P.V.P. which is excreted more slowly can be decided only by further studies.

Summary

Clinical studies are described of the renal excretion of polyvinylpyrrolidone (P.V.P.) from 15 patients.

Over 90% of the infused P.V.P. can be accounted for in the urine of those patients in whom there was no loss of P.V.P. due to bleeding or to incomplete collection of urine.

If a threshold molecular weight exists above which P.V.P. would not be excreted by the normal kidney, this is in excess of 100,000.

There is a very rapid excretion of P.V.P. in the first 24 hours after an infusion.

There is evidence for degradation of P.V.P. during its passage through the body.

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REFERENCES

- Arden, G. P., Mandow, G. A., and Stoneham, F. J. R. (1951). *Lancet*, **1**, 1099.
 Bargmann, W. (1947). *Virchow's Arch. path. Anat.*, **314**, 162.
 Bayliss, L. E., Kerridge, P. M. T., and Russell, D. S. (1933). *J. Physiol.*, **77**, 386.
 Boyd, A. M., Fletcher, F., and Ratcliffe, A. Hall (1953). *Lancet*, **1**, 59.
 Campbell, H. (1953). *Ibid.*, **1**, 148.
 ——— and Hunter, G. (1953). *Ibid.*, **1**, 197.
 ——— Kane, P. O., and Ottewill, I. G. (1954a). To be published.
 ——— (1954b). *J. Polymer Sci.*, **12**, 611.
 Ebert, R. V., Stead, E. A., Warren, J. V., and Watts, W. E. (1942). *Amer. J. Physiol.*, **136**, 299.
 Fresen, O. (1949a). *Zbl. Chir.*, **74**, 65.
 ——— (1949b). *Ärztl. Forsch.*, **3**, 308.
 Haler, D., Clift, A. F., Jameson, M. H., and Swinton, C. F. (1953). *Med. Press*, **230**, 131.
 Hawk, P. B., Oser, B. L., and Summerson, W. H. (1947). *Practical Physiological Chemistry*, 12th ed., Blakiston Co., Philadelphia.
 Hecht, G., and Weese, H. (1943). *Münch. med. Wschr.*, **90**, 11.
 Korth, J., and Heinlein, H. (1943). *Arch. klin. Chir.*, **205**, 230.
 Russell-Stoneham, F. J. (1953). Plasma Substitutes Symposium, organized by the International Blood Transfusion Society, Switzerland.
 Schoen, H. (1949). *Klin. Wschr.*, **27**, 463.
 Scholtan, W. (1951). *Makromol. Chem.*, **7**, 209.
 Steele, R., Van Slyke, D. D., and Plazin, J. (1952). *Ann. N. Y. Acad. Sci.*, **55**, 479.
 Thrower, W. R., and Campbell, H. (1951). *Lancet*, **1**, 1096.
 Wallace, J., and Sharpey-Schafer, E. P. (1941). *Ibid.*, **2**, 393.