TABLE I. Comparison Between the Inhibitory Effects of Circulin and Streptomycin Against Certain Bacterial Plant Pathogens.

Organism	Strain	Inhibited by μg per ml of C*	S*	Ratio of inhibiting concentrations C/S
Agrobacterium tumefaciens	59	50	100	0.5
Erwinia amylovora	178	3.1	0.2	15.5
E. atroseptica	E-25	6.2	100	0.06
E. carotovora	C-3	3.1	50	0.06
Xanthomonas beticola	72	3.1	50	0.06
X. campestris	W	0.8	50	0.02
X. phaseoli	W	0.4	50	0.01
X. translucens f.sp. *hordei*	P	6.2	0.4	15.5
X. translucens f.sp. *hordei-avenae*	XT-6	12.5	12.5	1.0

* The observations were made after 72 hours incubation. The preparation of circulin sulfate (C) used assayed 5300 units/mg, and contained at least two components, circulins A and B. The streptomycin sulfate (S) used contained 855 units/mg.

also several plant pathogens.* Table I, for illustration, compares the antibiotic activity of circulin and streptomycin, as determined essentially by a method previously described (1). In almost all cases circulin was more effective than was streptomycin. These preliminary data appear sufficiently promising to justify more extensive work in the greenhouse and in the field. Crude broths containing circulin, probably adequate for field trials can be prepared rather easily(1).

Summary. Circulin possesses high *in vitro* activity against several gram-negative plant pathogens.

* The cultures used in this study were kindly furnished us by Dr. Curt Leben, of the University of Wisconsin, and Dr. W. H. Burkholder, of Cornell University.

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Effects of Modified Human Globin in Normal Human Subjects.* (18694)

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(Introduced by William Dock)

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To assess the value of any substance which is to be administered intravenously for the emergency treatment of shock, it is imperative that its effects on the blood flow through the kidneys of normals be determined. It would be unwise to accentuate the renal ischemia which is known to exist in the shock state. By the same token, any substance which is to be administered as a possible therapeutic measure in diseases known to involve renal functional disturbances, must have its effects on the kidney determined.

It is the purpose of this communication to report the absence of deleterious effects of infusions of human globin on certain renal functions in normals, and also the absence of any effect on the agglutinability of the red blood cells of patients receiving this substance. For unlike gelatin, globin does not make blood typing difficult.

Methods and procedure. In the present study, a group of 6 convalescent patients with no evidence of renal disease were observed. All subjects were tested at least 10 hours after their last meal and hydrated with 500-1000 cc of water by mouth at least 1-2 hours before the start of the procedure. The continuous

* The globin was supplied through the courtesy of Dr. Gilbert Bayne of Sharp and Dohme, Glenolden, Pa.

infusion method for determination of renal clearances was performed. Blanks of urine and blood were drawn prior to the test proper. Control periods, before infusing the globin solution, were obtained. 5% glucose solution was used as the infusion fluid during the control periods. The test periods used lyophilized modified human globin dissolved in 3.5% glucose solution which made the globin solution isotonic. Each 400 cc of the globin solution contained 16 grams of pure globin. The control and globin infusions contained PAH in similar concentrations. Infusion rates were regulated at 4 cc-8 cc per minute in different patients. Concentrations of PAH were determined in plasma and urine by the Bratton-Marshall reaction(1). Urinary excretions of sodium were done employing the flame photometer with lithium as the internal standard. Hematocrit determinations were made on heparinized blood in Wintrobe tubes centrifuged at 2500 rpm for 30 minutes. Blood samples were also drawn for sedimentation rates, typing and cross matching before the procedure was started, during the control periods and at the end of the globin infusion.

Results. Table I lists the results of the various procedures in the patients studied. As will be noted in these normal subjects, 2 of the 6 studied received the globin infusion at a rapid rate (8 cc/minute) and 4 at a slow rate (4 cc/minute). In the 2 subjects receiving globin at a rapid rate there was no change in their urine flow or clearances of PAH, and in one of these there was a slight increase in sodium excretion during the globin infusion as compared to the control levels. In the 4 subjects receiving the globin at a slow rate, 3 of the 4 showed a slight fall in urine flow and only one of these any decrease in clearance of PAH. As regards sodium excretion during slow globin infusion 2 showed no change and 2 a slight increase.

It is fair to conclude that in normal persons no very striking or remarkable changes in urine flow, renal plasma flow or sodium excretion may be ascribed to the intravenous administration of globin at these rates.

TABLE I. Effects of Globin Infusions.*

Name, age, diagnosis	Urine flow, cc/min.	R.P.F. C_{PAH}, cc/min.	Na. exer., mM/min.
F. (F) 24	*7.1*	*473*	*.101*
Parasitic	*6.1*	*577*	*.119*
Infestation	4.3	615	.141
I.R.,† 4 cc/min.	2.6	575	.140
Total, 3 g globin	3.1	618	.184
	4.7	411	.205
	3.4	568	.163
G. (M) 33	*9.4*	*784*	*.105*
Pl. Effusion	*10.4*	*940*	*.114*
I.R., 4 cc/min.	*9.0*	*1045*	*.131*
Total, 6 g globin	7.9	1089	.113
	1.3	812	.135
	1.3	810	.127
	1.8	877	.147
	2.6	945	.136
S. (F) 51	*5.5*	*655*	*.072*
Resolving	*3.6*	*573*	*.070*
Pneumonia	*3.6*	*557*	*.079*
I.R., 4 cc/min.	3.6	605	.101
Total, 7 g globin	4.4	436	.099
	3.8	417	.087
	1.3	339	.070
	0.53	358	.072
	0.38	371	.084
	0.40	377	.079
W. (M) 27	*1.3*	*461*	*.086*
Resolving	*1.3*	*402*	*.088*
Pneumonia	3.0	472	.182
I.R., 4 cc/min.	2.8	360	.177
Total, 7.5 g globin	1.6	560	.183
	1.6	504	.168
	1.7	412	.143
	1.1	500	.203
B. (M) 43	*12.2*	*723*	*.190*
Peptic ulcer	*11.8*	*665*	*.167*
I.R., 8 cc/min.	*15.7*	*723*	*.208*
Total, 28 g globin	15.6	730	.219
	12.8	607	.181
	14.1	763	.219
	11.8	659	.172
	11.4	631	.197
	7.8	584	.212
C. (M) 49	*2.9*	*983*	*.202*
Pl. Effusion	*6.6*	*833*	*.174*
I.R., 8 cc/min.	*12.0*	*985*	*.211*
Total, 30 g	13.0	930	.210
globin	8.3	802	.214
	4.5	660	.192
	1.7	730	.253
	2.3	821	.328
	2.9	802	.315

* Figures italicized are control periods; others during globin infusion.
† Infusion rate.

Discussion. It is known that conditions associated with hemoglobinemia and hemoglobinuria have as a concomitant renal effect, a marked reduction in the effective renal

1. Goldring, W. and Chasis, H., *Hypertension and hypertensive disease.* New York, 1944, The Commonwealth Fund.

plasma flow. In normals, when one infuses a solution of hemoglobin renal ischemia is a striking and immediate effect. It has been postulated that perhaps the resulting renal ischemia is brought about through the formation of ferritin by making hemoglobin iron available to the kidney in the presence of hemoglobinemia(2). It is of considerable interest that the iron-free protein, globin which makes up approximately 96% of the hemoglobin of the body has none of the effects noted with hemoglobin, which strikingly decreases urine flow, renal plasma flow and sodium excretion.

As a therapeutic material globin has occasionally some of the renal effects in normal subjects that one encounters with the use of serum albumin(3,4). It is of interest that a very marked proteinuria is apparent shortly after the start of a globin infusion, and it is estimated(5) that as much as 30% of the infused globin may be lost through the kidneys in 24 hours, so that it would require relatively large amounts of globin to produce any significant increase in the protein metabolic pool(6).

It is estimated that when measured at the same concentration 1 g of modified human globin is equivalent osmotically to 2.65 g of normal human albumin. In our series of patients, a diuresis was not evident, and it is possible that the level of the effective circulating blood volume is not critically increased to produce any significant increase in urine flow. There is suggestive evidence(7) that in cirrhosis of the liver, or in cases with a lowered plasma oncotic pressure and a diminished effective circulating blood volume associated with fluid retention, globin may be of distinct value in therapy.

Of importance is the fact that globin does not possess the undesirable effect of substances like gelatin which alter the agglutinability of the red blood cells, thus making difficult typing and cross-matching when a transfusion might be required subsequently. No changes in ease of typing were noted in blood drawn from these cases. No variations in the sedimentation rates were noted to occur after a globin infusion as compared with the controls, which agrees with absence of rouleux formation. The hematocrits remained unchanged with the doses of globin used in these experiments on normals.

Conclusions. 1. The effects of both slow and relatively rapid infusion of modified human globin in 6 human subjects without renal disease were studied. No untoward effects of the infusion were noted. 2. No significant increase in urine flow over control flows was noted. There was no change in the clearances of PAH during the globin infusion as compared with the control levels. There was a slight increase in the rate of excretion of sodium during the globin infusion as compared with control levels in 2 of the 6 patients. 3. No alteration in sedimentation rate and agglutinability of red blood cells was noted as a result of the infusion of globin.

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5. Bayne, G., personal communication.

6. Strumia, M. M., Blake, A. D., Jr., Reider, H. C., and Chornock, F. W., *Am. J. Med. Sc.*, 1946, v51, 211.

7. Brandt, J. L., and Caccese, A., unpublished data.

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