Normal Hemoglobin Clearances in Chronic Proteinuria.* (18071)

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The mechanism of proteinuria has evaded a satisfactory explanation. Proteinuria may be due to renal or extra-renal factors, such as plasma with abnormal protein, *e.g.*, hemoglobin or Bence Jones protein which pass through normal kidneys into the urine. If protein is due to renal factors (organic damage with or without change in renal hemodynamics), one is confronted with a number of possible explanations: (1) primary or secondary glomerular change which allows the free passage of protein through the glomerular tuft; (2) faulty reabsorption of protein from an ultrafiltrate with a normal protein content; (3) combinations of (1) and (2). There is no evidence that tubular excretion plays any role in the production of proteinuria. That the basic difficulty may be extra-renal should be considered since alterations in protein metabolism or vascular dynamics may be associated with proteinuria without demonstrable changes in the kidney. These extra-renal factors may also contribute, in the damaged kidney, to produce or aggravate proteinuria.

In order to evaluate the role of the glomerular membrane in the production of proteinuria, it was decided to use the hemoglobin molecule (approximately the same molecular weight, size and shape as albumen) as a test substance and to measure its renal clearance simultaneously with inulin, in normal subjects and those with proteinuria. A ratio so obtained has been termed the glomerular permeability by Monke and Yuile(1).

Methods and procedure. Five convalescent patients with no history or evidence of renal damage and without proteinuria were used as a control group. A group of 3 patients with the nephrotic syndrome (5 to 20 g/day of proteinuria) were used as the test group. All patients were tested at least 10 hours after their last meal and hydrated with 500-1000 cc of water by mouth prior to the test. The usual procedure for renal clearances was followed. The urine collection periods varied from 8-30 minutes, depending upon urine flow through an indwelling urethral catheter. Bladder evacuation was assured by the washout, and air injection and expression. Continuous infusion was used throughout with a priming infusion of 75-100 cc of 6% hemoglobin solution‡ and 30 cc of 10% inulin; sustaining infusions contained 3% hemoglobin and a proper amount of inulin using 5% glucose in water as the diluent. The rate of the sustaining infusion was regulated at 4 cc per minute by the use of a Harvard tunnel clamp. Concentrations of inulin in plasma and urine were determined by Dische's method as modified(3), and determination of hemoglobin concentrations in plasma and urine by the method of Turner(4) at a wavelength of 545 λ on a Coleman spectrophotometer.

Results and discussion. Table I lists the data obtained from 5 normals and 3 patients with the nephrotic syndrome. The data represent successive clearance periods in each patient following the appearance of hemoglobinuria.

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‡ Supplied through the courtesy of Dr. Gilbert Bayne of Sharp & Dohme, and is the same as the solution described by Pennell.(2)

1. Monke, J. V., and Yuile, C. L., *J. Exp. Med.*, 1940, v72, 149.

2. Pennell, R. B., and Smith, W. E., *Blood*, 1949, v4, 380.

3. Brandt, J. L., and Baker, K., to be published.

4. Turner, Arthur, *Bull. U. S. Army Med. Dept.*, 1946, v5, 605.

TABLE I.
Renal Handling of Hemoglobin.

Patient*	Age	Diagnosis	C_I	C_H	C_H/C_I
C.W.	67	A.S.H.D.	80.5	2.57	3.19
			61.8	2.10	3.40
			69.2	2.69	3.88
			62.5	2.39	3.85
			61.6	2.83	4.59
F.J.	26	Conv. pneumonia	114.5	1.94	1.69
			105.9	2.38	2.25
			114.7	2.82	2.46
			103.6	3.03	2.94
			115.8	3.53	3.04
			78.1	2.43	3.1
T.J.	34	Bronchiectasis	102.0	2.32	2.27
			111.2	3.02	2.72
			108.3	3.19	2.95
			101.8	2.54	2.52
			73.1	1.86	2.55
M.W.	46	Conv. pneumonia	93.4	1.51	1.61
			91.5	2.37	2.59
			111.5	3.07	2.75
			82.0	2.98	3.63
			99.8	3.39	3.40
M.W.	25	Psychoneurosis	107.8	1.16	1.07
			88.8	1.18	1.33
			119.5	1.75	1.46
			102.6	1.65	1.61
A.W.	24	Nephrotic syn.	21.8	0.67	3.07
			23.4	0.58	2.48
			19.4	0.75	3.87
H.M.	38	Nephrotic syn.	46.3	0.43	0.93
			42.3	0.61	1.44
			33.1	0.60	1.81
			30.1	0.67	2.23
H.L.	65	Nephrotic syn.	12.7	0.22	1.73
			21.5	0.35	1.63
			18.0	0.34	1.89
			17.2	0.39	2.27
			20.2	0.61	3.02

* All males.

In carrying out the above clearance procedures it soon became apparent that the time of appearance of hemoglobinuria was extremely variable in both the normals and proteinuric group. It was decided to plot all ratios (CH/CI) against time, establishing the time of appearance of the first pink or red urine (hemoglobinuria) in each patient as zero time (Fig. 1).

It has long been assumed that the presence of large amounts of protein in the urine of patients with the nephrotic syndrome is associated with alterations in the capillary permeability and an increase in the size of these capillary pores which will allow the passage of molecules the size of albumen. If one assumes that there is a point reached following the appearance of hemoglobinuria when the tubules are either saturated or reabsorbing hemoglobin at a maximal rate; then what appears in the urine is proportional to the amount of hemoglobin appearing in the glomerular filtrate. In the normal, the maximum ratio CH/CI appears to be within the range of 2%-5%, at blood levels up to 550 mg % maintained for over one hour (Fig. 1).

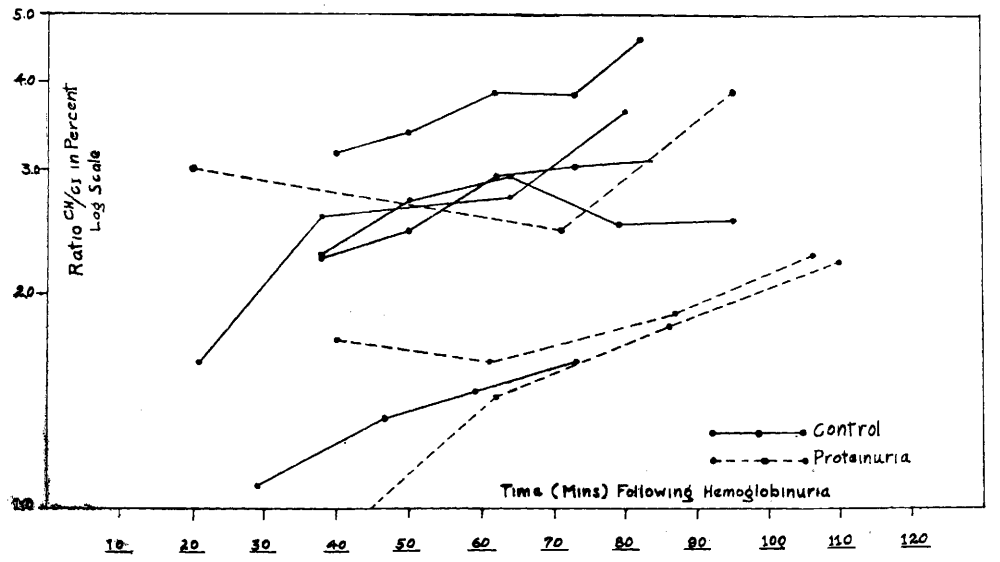

FIG. 1.

It does not rise with further increases in the plasma level of hemoglobin, but may increase with long sustained infusions. Assuming that proteinurics have larger and more numerous "pores" the size of albumen molecules the curves of the nephrotic (proteinuric) patients would necessarily fall in a range considerably above the range as plotted for normals, since hemoglobin is no larger than albumen and escapes normally at plasma levels one-fortieth the albumen concentration. As the curves in Fig. 1 indicate, one is forced to the conclusion that with any particular range of filtering bed in the controls and proteinurics their respective kidneys handle hemoglobin molecules in a similar fashion, if anything the hemoglobin clearances tend to be low in chronic proteinuria.

The data as presented seem to agree very well with the inferences drawn from the observations of Corcoran(5) and his co-workers who carried out similar observations with levan (M.W. 8000). Similarly, Rytand and Rantz(6) have shown that the anti-streptolysin clearances (globulin) of nephrotics follow a logarithmic increase as compared with an arithmetic increase in the quantity of protein excreted in the urine. These observations would tend to lend support to the premise, as suggested by the work described herein, that simple physical porosity of the glomeruli is not increased over normal in nephrotic patients excreting large amounts of albumen in their urine.§ Permeability to large molecules, with large electrical charges, appears to increase far more than that to smaller molecules such as levan.

Conclusions. 1. The ratio of simultaneously determined renal clearances of hemoglobin and inulin, in successive clearance periods in a group of 5 control and 3 patients with the nephrotic syndrome, indicate that the overall glomerular porosity, for hemoglobin, of the patients with proteinuria is no greater than that of normals.

2. It is probable that glomerular permeability, in terms of "pores," is not the factor determining the degree of proteinuria in the nephrotic syndrome.

5. Corcoran, A. C., Beattie, J., and Page, I. H., *J. Clin. Invest.*, in press.

6. Rytand, D. A., and Rantz, L. A., personal communication.

§ Observations similar to those reported here for the nephrotic patients have been made in one case of multiple myeloma and two patients with vascular disease, all associated with marked proteinuria.

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