

GLOMERULONEPHRITIS. A SURVEY OF THE FUNCTIONAL ORGANIZATION OF THE KIDNEY IN VARIOUS STAGES OF DIFFUSE GLOMERULONEPHRITIS¹

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Several studies of the functional changes which are encountered in chronic renal disease include observations on individuals with diffuse glomerulonephritis (1 to 3). However, the information on glomerulonephritis contained in such studies is meager. This fact, together with the diversity in the manifestations of the disease, precludes a description of its characteristics of renal function from the data available. The present study was designed to satisfy this deficiency in our information and has two specific ends in view. The first is to test the applicability of some of the more modern techniques of evaluating renal function to the situation obtaining in this condition. The second is to obtain a description of the characteristic pattern of functional activity of the kidney in glomerulonephritis. These ends have been achieved and it is now possible to formulate investigations of some of the more specific functional aspects of the disease by subsequent studies of a more limited scope.

Observations have been made on 22 patients with well-documented diffuse glomerulonephritis. The patients studied were selected so that the group contains a fair representation of the different stages of the disease, from a few weeks after its acute inception to shortly before its termination. The general and renal status of each patient were assayed by the usual clinical techniques, as well as by those which yield information on some of the discrete functions of the kidney. Among the latter functions are included the minimal renal plasma flow and blood flow, the glomerular filtration rate, and the maximal rate of tubular excretion of diodrast. These functions were studied in such a way that some of the important relationships between the discrete renal functions can be examined.

CASE MATERIAL

Patients were derived from several sources.² Each was observed for a sufficient period of time to insure a fairly secure diagnosis of diffuse glomerulonephritis before inclusion in the group. Some of the pertinent facts relative to the diagnosis, onset, and course of the disease in each patient are summarized in Table I. Information on the status of the patient just prior to the first experimental observation and the duration of the disease at this time is included (Columns 4 and 5). The type of the onset and the presenting symptoms and signs, as far as these could be determined, are noted, as well as the presence or absence of exacerbations (Column 6). The criterion for the latter diagnosis has been accepted as "an abrupt and marked increase in the degree of hematuria" (4).

Specific note is taken of infections in relation to the onset of the disease (Columns 7 and 8) and of the presence or absence of a nephrotic phase (Column 9) because of the bearing of these factors on the diagnosis. There is common agreement that the acute inception of diffuse glomerulonephritis and the exacerbation are typically preceded by an upper respiratory infection, generally associated with the presence of group A hemolytic streptococci. The latent period between the onset of the infection and that of the nephritis is usually 10 days to 3 weeks, while the latent period between the infection and the ex-

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acerbation is 1 to 4 days (4, 5). Furthermore, a definite nephrotic syndrome is a common intercurrent manifestation of chronic diffuse glomerulonephritis, but except for true lipid nephrosis is rarely found in other renal diseases (6). Generalized edema, serum albumin below 2.5 grams per 100 ml., and serum cholesterol above 400 mgm. per cent have been accepted in the present study as evidence of the presence of the nephrotic syndrome.

Information is also contained on the course of the disease (Column 10). The occurrence of infections during the period of observation (Column 11) is noted because of a possible influence on the progression of the disease (4, 5, 7).

The information available on each case (Table I) leaves little doubt of the validity of the primary diagnosis although the duration of the disease in each case is less certain.

EXPERIMENTAL PROCEDURE

The several renal functions measured were evaluated under standard conditions. The patients were maintained at bed rest and allowed no food or water from the time of the preceding evening meal until the completion of the experimental run. Experiments were begun between 8:00 and 9:00 A.M. and were from 2 to 2½ hours' duration. Studies were not performed if the patient's temperature was above 100° F. (rectal).

The routine procedure was as follows: Simultaneous mannitol and diodrast clearances were determined at constant plasma concentrations of each, during 3 consecutive periods of approximately 15 minutes' duration. The plasma diodrast level was then raised and after allowing 20 to 30 minutes for stabilization of the plasma diodrast concentration, diodrast T_m was determined in 3 additional 15-minute periods. Appropriate amounts of mannitol and diodrast to sustain the desired plasma concentration were administered throughout each experimental run by an infusion given at a rate of 2 ml. per minute. Mid-period bloods were obtained by venipuncture from the antecubital vein. Urine samples were obtained by catheter and followed, in all cases, by a bladder wash with sterile water.

The minimal renal plasma flow has been taken as equal to the diodrast clearance at low plasma levels (see below). Minimal renal blood flow has been calculated from this value and a hematocrit determination obtained at the beginning of the experiment (8, 9). Glomerular filtration rate has been taken as being equal to the mannitol clearance (8 to 11). The calculations involved in each of these measurements, together with that of diodrast T_m , followed the usual methods.

Tubular excretion of diodrast was examined in a limited number of experiments during a progressive increase of the plasma concentration of diodrast. A gradually rising plasma level was obtained as follows: An infusion containing a sufficient concentration of diodrast to sustain the plasma diodrast iodine at approximately 1 mgm. per cent was started at a rate of 2 ml. per minute. A more concentrated solution of diodrast was then added

slowly by gravity to the initial infusion so that there was a progressive increase in the concentration of diodrast in the infusion fluid throughout the experimental observation. Thorough mixing of the infusion fluid was assured by the use of a stirring rod driven by a small electric motor. These arrangements may be adjusted to produce a steady increase in plasma diodrast of whatever rate is desired.

METHODS

1. Diodrast. Diodrast iodine in the plasma and urine was determined by a modification (12) of the Alpert method (13). Protein-free filtrates of plasma and urine were prepared using cadmium (14) and the filtrates treated with bromine in the usual fashion. The flasks containing the bromine-treated filtrates were chilled in an ice bath prior to the addition of KI and titration with thiosulfate. Chilling the solution just prior to the titration produces a sharp and relatively stable end-point for the titration.

Plasma contains a definite and measurable blank with this procedure. The blank is in the order of magnitude of 0.1 to 0.2 mgm. per cent diodrast iodine in the plasma of normal individuals but has been observed as high as 0.5 mgm. per cent in plasma from some individuals with excessive nitrogen retention. Because of the variability of the blank, it was determined routinely by an analysis of plasma, obtained prior to the administration of diodrast. A plasma filtrate was prepared in the usual manner and titrated subsequent to the addition of KIO_3 . The urines of individuals with nitrogen retention may also contain a blank of considerable magnitude. This was estimated in a similar manner and expressed in mgms. of diodrast iodine excreted per unit time.

Recoveries of diodrast added to the plasma, when corrected for such a blank, were found to be quite constant but were only 94 per cent of the theoretical. These findings account for the fact that previous experience with the method (13) showed it to yield 100 per cent recovery at diodrast iodine values below 4 mgm. per cent, with progressively less at higher concentrations. The magnitude of the plasma blank is usually sufficient to balance the small loss of diodrast at the low plasma concentrations.

2. Mannitol and inulin. The method described by Smith, Finkelstein, and Smith (11) was used for the determination of mannitol except that the plasma and urine filtrates were oxidized at room temperature for 90 minutes (12) instead of for a shorter time in a boiling water bath. Protein-free filtrates of plasma were obtained using cadmium (14) except in the experiments where mannitol and inulin clearances were determined simultaneously. In these instances, both analyses were on a filtrate prepared with zinc (15). Inulin was determined by Harrison's (16) modification of the colorimetric method of Alving, Rubin, and Miller (17). Recoveries of known amounts of mannitol and inulin added to plasma and urine were excellent.

3. Plasma proteins. Total plasma protein and albumin

TABLE I

Clinical data concerning onset and course of diffuse glomerulonephritis

1	2	3	4	5	6	7	8	9	10	11
Case number	Sex	Age in years	Status of nephritis at first test	Duration of nephritis before first test	Onset of nephritis	Infection preceding onset of nephritis	Latent period	Nephrotic phase	Course of nephritis	Infections during observation
1	M	13	Healed	18 months	Acute: Smoky urine. Facial edema. Convulsion. BP: 170/125, fell to 110/60	Pharyngitis	3 weeks	No	Apparently healed 14 weeks after onset	None
2	M	25	Healed	4½ months	Acute: Smoky urine. Facial edema. Pain in back. BP: 160/100, fell to 115/70	Pharyngitis	3 weeks	No	Apparently healed some time after 2 months	None
3	M	14	Healing	5 weeks	Acute: Microscopic hematuria. Nocturia. Ankle edema. BP: 180/130, fell to 100/60	Pharyngitis	2 weeks	No	Apparently healed at or shortly after time of first test	None
4	F	13	Acute	3 months	Acute: Microscopic hematuria. Puffy eyes. Ankle edema. BP: 170/95, fell to 125/70	Pharyngitis (Group A hemolytic streptococcus proven)	2 weeks	No	Edema and hypertension disappeared but urine abnormalities persisted	Fever 99 to 100.6° until after 2nd test
5	M	22	Acute	3 weeks	Acute: Microscopic hematuria. Edema. Dyspnea. BP: 160/106, fell to 115/80	Head cold Pharyngitis Otitis media	3 weeks 2 weeks ? days	No	Symptoms disappeared. Urine improving rapidly when last seen	None
6	M	12	Acute	6 weeks	Acute: Microscopic hematuria. Puffy eyes. BP: 170/120, fell to 140/70	Head cold	4 to 6 weeks	No	Apparently healed between second and third tests	None
7	M	44	Chronic	7 months or more	Acute (?Exacerbation): Microscopic hematuria. Facial edema. Ankle edema. BP: 170/100, fell to 140/85	Head cold	1 day	No	No change during observation. Retrograde pyelograms negative	None
8	M	14	Chronic	17 months or more 9 months	Insidious: Routine urine showed albumin. Facial edema. Ankle edema	?		Yes	Mild nephrotic syndrome throughout observation	Upper respiratory infection and catarrhal otitis media, 4 days after 1st test. Head colds at time of last two tests

TABLE I—*Continued*

1	2	3	4	5	6	7	8	9	10	11
Case number	Sex	Age in years	Status of nephritis at first test	Duration of nephritis before first test	Onset of nephritis	Infection preceding onset of nephritis	Latent period	Nephrotic phase	Course of nephritis	Infections during observation
9	F	41	Acute	2½ months	Acute: Gross hematuria. Generalized edema. BP: 170/90, fell to 120/80. (Previous urines and BP normal)	Pharyngitis	2 weeks	No	Steady clinical improvement throughout observation but urine did not clear entirely	Draining abdominal sinus one year, completely healed by third test
10	M	31	Chronic	8 years	Acute: Gross hematuria. Oliguria. Burning on urination	Pharyngitis	?	No	Recurrence of gross hematuria 4 years ago, microscopic hematuria ever since. I. V. and retrograde pyelograms negative	None
11	M	18	Chronic	6 to 7 years	Insidious: Ankle edema	?				
				13 months	Exacerbation: Microscopic hematuria. Facial edema. Leg edema. BP: 160/115, fell to 135/100	Pharyngitis	1 day	Yes	Nephrotic syndrome cleared up approximately 2 months before first test	Pharyngitis (No streptococcus demonstrated), 2 weeks before 1st test.
12	F	15	Chronic	10 months	Acute: Gross hematuria. Facial edema. BP: 140/104, fell to 115/80	Head cold	4 to 5 days	Yes		
					Exacerbation: Gross hematuria	Pharyngitis	1 day		Unobserved episode 7 months before last test suggestive of exacerbation. Asymptomatic at time of last test	Pharyngitis (not observed)
13	M	21	Chronic	1½ years	Insidious: Routine urine showed albumin (urine negative one year before)	?		Yes	Losing edema during observation	Chronic sinusitis and bronchitis throughout observation period
14	F	54	Chronic	6 months or more	Insidious: Anasarca	None noted		Yes	Nephrotic during observation, but edema responded in part to mercupurin	Cellulitis of leg, responded to sulfadiazine, 1 week before 1st test.
15	F	19	Chronic	4 years	Acute: Gross hematuria. Back pain. BP: ?	?		No	Four exacerbations in chronic glomerulonephritis	Chronic purulent sinusitis. 1 month before 5th test. Phlebitis leg, 1 month before 6th test. Pharyngitis twice (not observed)
				2 months	Exacerbation: Gross hematuria. Back pain. Facial edema. Ankle edema. BP: 170/100, fell to 120/60					

TABLE I—Continued

1	2	3	4	5	6	7	8	9	10	11
Case number	Sex	Age in years	Status of nephritis at first test	Duration of nephritis before first test	Onset of nephritis	Infection preceding onset of nephritis	Latent period	Nephrotic phase	Course of nephritis	Infections during observation
16	F	21	Chronic	10 months	Acute: Gross hematuria. Purpura. BP: 140/90	Pharyngitis	2 weeks	No	Marked progression of disease in 8 months between second and third test, no history of infection Died 7 weeks after last test. No autopsy	Grippe, temp.: 102° F. day before first test
17	M	35	Chronic	9 years or more	Insidious: Routine urine showed albumin	? "Grippe"	1 week	No	Hypertension first noted 4 years ago. Gradual progression of disease during observation. Died 7 months after last test Autopsy: Chronic glomerulonephritis	None
18	M	58	Chronic	2 months, probably much longer	Insidious: Anasarca	None noted		Yes	Died in uremia 3½ months after first test. Autopsy: Chronic glomerulonephritis	None
19	F	23	Chronic	6 years	Acute: Puffy face. Ankle edema. ? hematuria. BP: ?	Pharyngitis	?	Yes	Nephrotic phase cleared up approximately 6 months before first test	None
20	M	53	Chronic	6 years or more	Insidious: Intermittent ankle edema	None noted		No	Died in uremia 1 week after last test. No autopsy	None
21	M	47	Chronic	4½ years or more	Insidious: Ankle edema. Facial edema	None noted		Yes	Nephrotic phase cleared up 10 months before first test. Died in uremia 4 months after last test. Autopsy: Chronic glomerulonephritis and renal amyloidosis	None
22	M	24	Chronic	2 years or more	Insidious: Nocturia. Polyuria. Frequency.	None noted		No	Coma and nitrogen retention 6 months before first test. Retrograde pyelograms negative	None

were determined by the micro-Kjeldahl method (18) after precipitation by the Howe technique (19).

4. Quantitative estimations of the 12-hour urinary excretion of albumin and formed elements were performed by the method of Addis (20).

VALIDITY OF FUNCTIONAL MEASUREMENTS

The measurement of glomerular filtration rate. The plasma clearance of mannitol has been accepted, in these studies as a precise expression of the rate of glomerular filtration. This judgment was tentatively based upon those facts which lead one to suppose that the plasma clearance of inulin is such a measure in the normal (10) and diseased kidney (21) and the demonstration that inulin and mannitol clearances are identical in normal man and in women with preeclampsia and eclampsia (11). A similar situation appears to obtain in glomerulonephritis (Table II).

The comparison of the inulin and mannitol clearances was limited to 7 patients (mannitol clearances ranging from 8.0 to 104.0 ml. per minute) and were incidental to the routine observations. The two clearances were not completely identical in several of the patients. However, the differences are small and the filtrate fractions by the mannitol or inulin clearances are much the same. For the present purposes, then, the mannitol clearance may be considered to be an adequate measure of glomerular filtration in glomerulonephritis. It is accepted that for other purposes a more extensive comparison of the two clearances may be desirable.

These observations may be taken to indicate that the changes in the glomerular membrane in glomerulonephritis are not such as to preferen-

tially interfere with the filtration of such a large molecule as inulin (10, 21) as compared to the filtration of a small molecule, such as mannitol. Similarly, the reabsorption of such a small molecule as mannitol is not facilitated by the changes in the tubular barrier.

The measurement of minimal renal plasma flow.

The concepts underlying the use of the diodrast clearance for this measurement are well accepted. It may be stated arbitrarily that the diodrast clearance at low plasma concentrations, except in so far as the diodrast in erythrocytes contributes to that currently secreted, is a measure of the minimal renal plasma flow in any situation. However, its general usefulness in functional studies is largely derived from the fact that, in the normal kidney and under certain circumstances in the abnormal kidney, it also constitutes a close approximation of the actual renal plasma flow to the functional elements of the kidney (21). The measurement is still of some value in the absence of such a correlation, but the information in this circumstance is less generally useful.

The advanced stages of glomerulonephritis constitute a condition wherein the mechanism for the tubular transfer of diodrast is severely damaged, or the loss of renal tubular elements is so great, that the diodrast clearance at low plasma concentrations departs widely from the actual renal plasma flow. Calculations of the filtrate fraction in such a situation yield values which are higher than those which actually obtain at the glomeruli and which have little physiological significance. Such data are of little use in the examination of the hemodynamics of glomerular action.

TABLE II
Comparison of mannitol and inulin clearances in patients with diffuse glomerulonephritis

Patient number	Date	Mannitol clearance	Inulin clearance Mannitol clearance	Filtrate fraction	
				Mannitol clearance Diodrast clearance	Inulin clearance Diodrast clearance
		<i>ml. per minute</i>		<i>per cent</i>	<i>per cent</i>
9	October 28, 1942	104.0	1.07	17.2	18.5
9	September 21, 1942	94.0	1.08	17.1	18.5
11	November 1, 1942	88.0	1.04	20.0	21.2
8	August 21, 1942	57.4	1.00	12.0	12.0
13	September 2, 1942	53.0	0.99	11.9	11.9
15	August 31, 1942	38.9	0.97	8.5	8.3
19	October 23, 1932	17.8	1.06	17.6	18.6
18	August 24, 1942	8.0	1.06	11.5	11.9

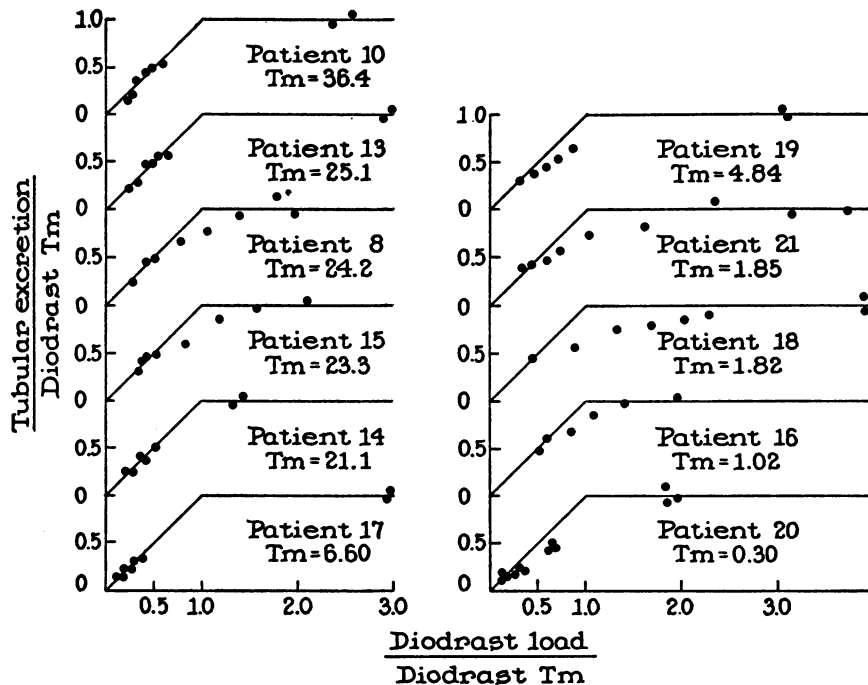


FIG. 1. THE TUBULAR EXCRETION OF DIODRAST IN RELATION TO THE LOAD OF DIODRAST DELIVERED TO THE TUBULES IN A SERIES OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS

The normal relationship is shown by the solid lines. T_m values are uncorrected for surface area. The 6 experiments at the left of the figure indicate a straight line relationship between the load and tubular excretion of diodrast at diodrast load to diodrast T_m ratios below 0.5. The lack of this straight line relationship in the 5 experiments at the right of the figure indicates that true measurements of renal plasma flow could not be obtained in these 5 patients.

It was necessary, for these reasons, to establish the order of magnitude of the tubular impairment which is still compatible with an approximation of the renal plasma flow through a measurement of the diodrast clearance. This was accomplished by studying the tubular excretion of diodrast at different plasma loads in patients with varying amounts of residual renal tissue. The tubular excretion of diodrast in normal subjects is directly proportional to the load of diodrast presented to the tubules until the transport system for diodrast is completely saturated and no further increase in the rate of tubular excretion can occur, *i.e.*, diodrast T_m has been reached. This circumstance results from a situation which is such that, at the lower diodrast levels, the renal tubular excretion of diodrast is limited by the amount delivered to the renal tubules, while at the higher plasma levels

the limitation is within the transfer mechanism itself (22). This relationship is indicated by the solid lines in the graphs of Figure 1 for the normal situation, wherein the transition between the two limitations is quite abrupt (22). The abrupt transition from one limitation to the other does not obtain in certain patients with diffuse glomerulonephritis, as evidenced by a falling off of the observed values from the normal curve as the diodrast load approaches diodrast T_m . This relationship was observed in all patients studied whose T_m values were below 5 mgm. per minute and in Patients 8 and 15 (Figure 1) where properly spaced data were obtained. Such a result may be partly a function of the mechanical distribution of blood to tubule tissue and partly the result of a limitation within the tubule cells whereby higher concentrations of diodrast in the extracellular fluid

TABLE III—Continued

9	March 9, 1942	Acute	120/80	0.6	56	0	34.7	571	834	86.3	15.1	16.5	2.49	31	6.2	3.2	21	53	1.023	1.002
	March 23, 1942	Acute	120/80	0.17	40	106	34.3	563	840	81.1	14.4	16.4	2.36	33	6.9	3.9	22			
	April 27, 1942	Acute	125/80	0.10	40	33	41.3	596	932	84.0	14.2	14.4	2.06	36	7.0	4.1	22			
	September 21, 1942	Chronic	135/85	2.2	27	66	44.1	550	873	94.0	17.1	12.5	2.14	37	6.5	4.2	31			
	October 28, 1942	Chronic	120/75	0.15	21	0	53.4	603	972	104	17.2	11.3	1.95	35	6.5	4.5	29			
	January 15, 1943	Chronic	128/82	0.17	22	47		579	934	110	19.0	11.3	2.38	38	6.4	4.1	30			
	March 10, 1943	Chronic	130/85	0.20	16	0	44.7	601	910	107	17.8	13.4	2.39	34	6.6	4.3	30	60	1.034	1.002
10	April 24, 1942	Chronic	102/52	0.34	31	264	34.6	496	770	68.4	13.9	14.3	1.98	36	6.8	4.5	31	75	1.015	1.007
	May 1, 1942	Chronic	108/70	0.50	56	250	36.8	521	814	71.8	13.6	14.2	1.95	36	6.8	5.0	40			
	September 11, 1942	Chronic	132/80	0.70	66	2200	37.9	453	755	74.5	16.5	12.0	1.97	40	6.5	4.6	38			
	January 26, 1943	Chronic	190/90	0.59	91	300	35.9	492	757	82.6	16.8	13.7	2.30	35	5.8	3.8	38			1.016
	June 11, 1943	Chronic		0.70	61	600	34.7	690	1255	67.3	9.8	19.9	1.94	45	6.1	4.2	33			
11	February 4, 1942	Exacerbation	145/110	1.6	6	190	31.8	419	709	69.6	16.6	13.2	2.19	41	6.2	4.0	33	65	1.019	1.003
	February 13, 1942	Chronic	135/100	1.5	3	72	27.1	362	612	66.8	18.5	13.4	2.47	41	6.2	4.0	33			
	August 9, 1942	Chronic	160/115	3.9	1	1400	30.5	405	810	84.5	20.9	12.2	2.55	50	6.0	4.0	33			
	November 1, 1942	Chronic	160/105	2.6	3	3000	39.5	439	828	88.0	20.0	11.1	2.23	47	5.7	3.8	30			
	April 12, 1943	Chronic	150/100	0.8	2	1200	41.4	430	826	85.8	20.0	10.4	2.07	48	5.7	4.0	32			
12	July 29, 1942	Chronic	125/80	3.3	900	350	28.2	761	1103	85.0	11.2	27.0	3.01	31	4.1	2.3	27	54	1.029	1.001
	August 10, 1942	Chronic	115/80	5.5	980	72	21.3	646	872	68.3	10.6	30.0	3.21	27	4.4	2.3	27			
	June 22, 1943	Chronic	130/90	0.5	318	3000	2.3	*48	*66	18.1	*37.6	*20.0	7.77	27	4.8	2.8	32			
13	September 2, 1942	Chronic	144/100	5.2	126	136	22.9	447	732	53.0	11.9	19.1	2.27	39	4.7	2.8	44	70	1.020	
	September 18, 1942	Chronic	150/100		43			424	642	45.3	11.4	16.5	1.98	34	4.7	2.8	44			
14	July 8, 1942	Chronic	120/70	2.1	0	120	21.8	452	716	45.7	10.1	20.7	2.10	38	4.4	1.9	35	19	1.015	1.010
	August 17, 1942	Chronic	130/80	1.4	11	2100	20.2	374	526	34.1	9.1	18.5	1.69	29	4.1	1.9	41			
	November 25, 1942	Chronic	110/70	2.2	14	700	34.6	498	766	46.7	9.4	23.4	1.42	35	3.9	2.0	40			
15	May 8, 1942	Exacerbation	120/60	1.3	248	126	19.6	323	467	26.9	8.3	16.5	1.37	31	7.2	4.1	31	50	1.010	
	June 1, 1942	Chronic	130/70	0.8	266	0	26.7	325	458	32.3	10.0	12.2	1.21	29	7.3	4.0	41	45		
	July 1, 1942	Chronic	120/70	0.7	100	0	26.5	339	492	37.0	10.9	12.8	1.40	30	6.1	3.4	46	46		
	August 5, 1942	Chronic	115/70	0.7	49	0	30.2	306	419	40.5	13.2	10.1	1.34	27	6.2	3.9	45			
	September 23, 1942	Chronic	145/70	0.8	74	0	33.5	345	500	46.2	13.4	10.3	1.38	29	6.2	3.8	44			
	November 20, 1942	Chronic	130/70		14	120	27.6	231	345	39.3	17.0	8.4	1.42	33	6.0	3.8	40			
	May 15, 1943	Chronic	135/65		6/HFP	0	29.9	262	403	44.6	17.0	8.8	1.49	35	6.0	3.9	36			
16	January 19, 1942	Chronic	140/90	1.8	2660	580	17.4	268	412	52.1	20.5	14.7	2.85	35	5.0	2.9	34	43	1.024	1.004
	January 26, 1942	Chronic	120/90	2.5	934	520	15.1	290	446	46.5	16.6	19.2	3.08	35	5.5	3.5	35			
	October 5, 1942	Chronic	185/125	1.1	312	160	1.1	*28	*40	8.2	*29.5	*25.5	7.44	30	6.9	4.7	95	0		
17	March 6, 1942	Chronic	210/140	0.4	2	95	13.6	153	273	34.1	22.2	11.2	2.51	44	6.9	4.5	77	15	1.011	1.009
	March 18, 1942	Chronic	220/130	1.0	4	212	13.5	151	270	33.6	22.2	11.2	2.49	44	5.9	4.5	78			
	June 8, 1942	Chronic	240/160	3.8	4	0	7.9	94	145	21.7	23.0	11.9	2.73	35	6.9	4.5	78	25		
	July 10, 1942	Chronic	280/160		4	0	6.0	82	130	20.5	25.1	13.7	3.43	37	5.9	6.9	50			
18	June 17, 1942	Chronic	155/80	2.1	6	105	5.9	223	278	14.3	6.4	37.8	2.42	20	4.0	1.7	54	45	1.012	
	August 24, 1942	Chronic	170/84		8	0	1.8	*69	*91	8.0	*11.5	*39.2	4.52	24	4.4	1.8	67	0		
19	February 2, 1942	Chronic	135/90	0.4	46	100	5.7	*231	*329	22.2	*9.8	*40.2	3.87	30	5.6		61	15	1.010	
	February 6, 1942	Chronic	140/90	0.4	46	100		*105	*146	19.7	*18.8	*19.2	3.60	28	6.1	3.5	64			
	June 13, 1942	Chronic	140/90	3.3	56	220	5.8	*101	*133	17.8	*17.6	*19.9	3.50	24	5.7	3.6	49			
	October 23, 1942	Chronic	145/100	5.5	73	1140	5.1			13.3							61			
20	February 13, 1942	Chronic	230/140	3.6	239	0	1.9	*50	*62	5.7	*11.4	*26.5	2.88	19	6.4	3.3	80	0	1.011	
	February 23, 1942	Chronic	180/110	3.5	3176	0	1.6	*33	*40	6.5	*19.7	*20.6	4.07	19	6.3	3.3	180			
	April 1, 1942	Chronic	210/120		32	0	0.3	*8	*9	3.4	*42.5	*27.4	11.6	14	6.5	3.8	158			
21	April 21, 1942	Chronic	166/104	2.6	6	175	1.9	*42	*61	14.7	*35.4	*22.1	7.84	32	6.5	3.2	39	9	1.013	1.012
	May 18, 1942	Chronic	170/110	4.9	6	890	1.9	*41	*57	13.0	*31.6	*21.3	6.74	28	6.0	3.1	46			
22	October 21, 1942	Chronic	155/90	2.0	0	90	0.8	*15	*19	5.3	*35.3	*18.4	6.48	23	6.3	4.3	135			
	October 30, 1942	Chronic	150/90	2.2	15			*14	*19	4.4				21	6.3	4.3		0		

are essential to saturate the transfer mechanism for diodrast (23), as in fact appears to be the case for phenol red in the normal subject.

It may be assumed for our present purposes that the maximal clearance of diodrast can only constitute a valid approximation of the renal plasma flow when determined at plasma concentrations below the level where the tubular excretion is directly proportional to the load of diodrast presented to the tubules. Also, it appears improbable from the data in Figure 1 that a valid plasma flow can be obtained with present chemical methods in these patients with Tm values much below 6.0 mgm. of diodrast iodine per minute. The lowest plasma levels of diodrast compatible with accurate chemical analysis may be expected to result in a tubular excretion of diodrast which, in these individuals, is not proportional to the plasma load. The apparent renal plasma flow of patients with a Tm value below 6.0 mgm. per minute has been recorded in the summary of results (Table III) but is marked by an asterisk, as are the derived relationships.

The estimation of filtrate fraction. This datum, being the dividend of the glomerular filtration rate and the renal plasma flow, is equal to the fraction of the plasma water which, reaching the glomeruli of the normal kidney, is filtered in the process of achieving pressure equilibrium across the glomerular membrane (8, 9, 24, 25). As such, the filtrate fraction, together with the absolute values of glomerular filtration rate and renal plasma flow, yields information on the hemodynamics of glomerular action. The value of the normal figure is 0.196 ($\sigma = \pm 0.024$). This is the net result of the operation of arterial pressure and mean resistance at the afferent and efferent arterioles, in so far as these define intracapillary pressure and those factors which determine the plasma oncotic pressure and the intracapsular pressure which oppose intracapillary pressure. Also concerned are those factors relating to the characteristics of the glomerular membrane and rate of plasma flow which, together with the pressure relationships, determine the degree to which pressure equilibrium is achieved in the glomeruli. Changes in the filtrate fraction from the normal value are, therefore, of some aid in the interpretation of the functional organization of glomerular action in any situation, providing the same sig-

nificance can be attached to the data as in the normal subject. The latter appears to be probable in glomerulonephritis in those situations where the plasma clearance of diodrast has physiological significance (see above).

Diodrast Tm. Diodrast Tm may be accepted as a functional expression of the amount of tubular tissue (8, 9, 21, 25). Recently, it has been demonstrated that the magnitude of the diodrast Tm may be affected by non-renal factors. It seems likely, however, that the progressive, systematic changes in the diodrast Tm values which have been observed in this study are for the most part a reflection of the loss of renal substance or the alteration of renal tubular function as a result of the diffuse glomerulonephritis. This view is emphasized by the fact that significant changes in diodrast Tm in individual normal (9) or hypertensive subjects (26) are unusual over considerable periods of time.

RESULTS

The data obtained in each of the patients studied is summarized in Table III. The tabulation includes information on the renal plasma flow, renal blood flow, glomerular filtration rate and diodrast Tm (all corrected to a standard surface area of 1.73 sq. m.), the filtrate fraction, and the PF/Tm and GF/Tm ratios. The table also includes normal values for each of the functions studied^{*} (9). The values for plasma flow, filtrate fraction, and the ratio PF/Tm which are marked by an asterisk are from studies where the evidence indicates that the diodrast clearance is no longer a close approximation of the renal plasma flow. The renal plasma flow and plasma flow to diodrast Tm ratio will be lower under these circumstances and the filtrate fraction higher than actually obtains. Other clinical data which bear on the status of the patient at the time of the clearance study are included in Table III. These observations were usually made within a day or two of the clearance study and in all cases were sufficiently close for them to be accepted as characteristic of that time.

The data indicate that a reduction in the amount

^{*} The normal values for the filtrate fraction and the PF/Tm ratio were calculated from the renal plasma flow, glomerular filtration rate, and diodrast Tm figures, given in Table IV of the paper of Goldring, Chasis, Ranges, and Smith (9).

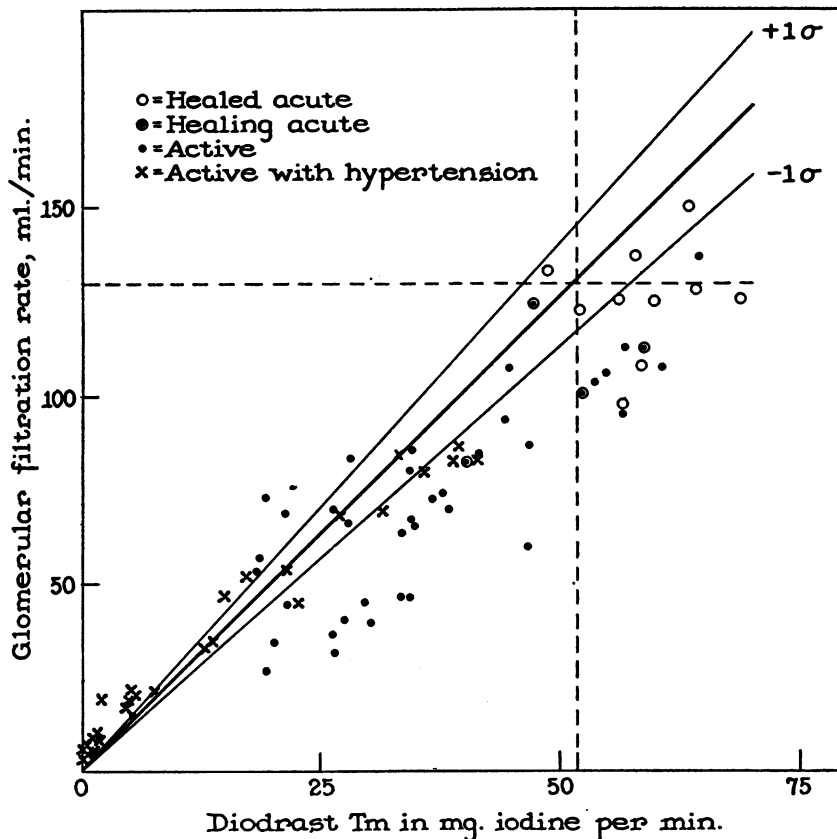


FIG. 2. GLOMERULAR FILTRATION RATE IN RELATION TO DIODRAST Tm IN A SERIES OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS ⁴

The mean normal values for these functions are shown by the dotted lines; the normal relation between the 2 ($GF/Tm = 2.54$, $\sigma = \pm 0.28$), by the diagonal lines. Each datum in this and subsequent figures represents the average of 2 or more consecutive clearance periods.

of functional renal parenchyma, as measured by diodrast Tm, is usually accompanied by a roughly parallel decrease in glomerular filtration rate and in renal plasma flow; the former appears to be a much more sensitive indicator of the disturbance in renal function in this situation. Actually, a reduction in the renal plasma flow was not consistently noted until the diodrast Tm value was below 30 mgm. of iodine per minute. However, as renal damage progressed beyond this value for the diodrast Tm, there was a rapid decrease in the plasma flow to very low values. These relations are illustrated graphically in Figures 2 and 3.⁴

Figure 2 presents the relationship observed between glomerular filtration rate and diodrast Tm. The mean normal values for the variables are indicated by the horizontal and vertical lines; the normal relation between the two, by the solid diagonal line. Data obtained after the healing of an acute diffuse glomerulonephritis are indicated by open circles; those obtained during the healing or probable healing, by dotted circles; and the remainder (active), by solid circles, or by crosses when the diastolic blood pressure was in excess of 90 mm. of Hg. The data indicate that a reduction in glomerular filtration rate is generally accompanied by a decrease in the amount of functional tubular tissue, and also that patients with active diffuse glomerulonephritis characteristically have low GF/Tm ratios until the diodrast iodine

⁴ Figures 2, 3, and 5 were patterned after those of Goldring, Chasis, Ranges, and Smith (26). See also footnote 3.

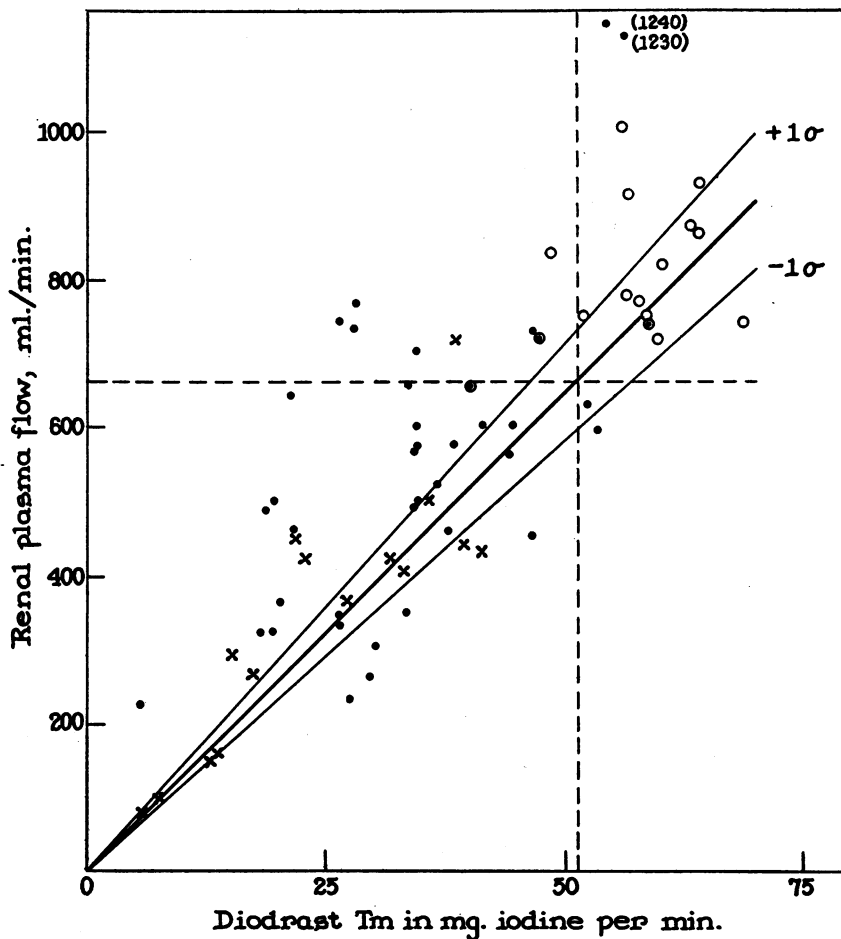


FIG. 3. RENAL PLASMA FLOW IN RELATION TO DIODRAST T_m IN A SERIES OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS^{3, 4}

The mean normal values for these functions are shown by the dotted lines; the normal relation between the 2 ($PF/T_m = 13.0$, $\sigma = \pm 1.4$), by the diagonal lines. The status of the nephritis at the time of each observation is indicated as in Figure 2. Only valid renal plasma determinations are included.

T_m drops below 20 mgm. per minute. The progress of renal damage beyond this value involves a preferential loss of tubular tissue, or of some functional capacity of tubular tissue to do a specific type of work (*i.e.*, transfer diodrast), as compared to the ability of glomeruli to filter water and solute.

The relationship between renal plasma flow and diodrast T_m is summarized in Figure 3. This figure includes only those observations wherein the diodrast clearance is believed to be a close approximation of the renal plasma flow (see above). The general status of the nephritis at

the time of the examination is indicated by different symbols, as in Figure 2. The mean normal values for the two variables are indicated by the horizontal and vertical lines; the normal relation between the two, by the solid diagonal line. The general reduction in renal plasma flow which accompanies the reduction in diodrast T_m is illustrated by the figure. However, it should be noted that high PF/T_m ratios are not uncommon in all stages of diffuse glomerulonephritis and also that when the status of the nephritis is complicated by the presence of hypertension, the observations do not depart from the usual relationship

in any systematic manner. It should be noted further that the scatter of the data is such that a close correlation between the two variables is not a characteristic of the pattern of renal function in glomerulonephritis.

A low filtrate fraction is one of the most consistent findings among these patients with diffuse glomerulonephritis, irrespective of the stage of the disease. This was still apparent in 1 (Patient 2) of the 2 patients studied only after healing, and in 15 of the 20 patients studied during the course of diffuse glomerulonephritis. The studies were made so late in the course of the disease in 2 of the 5 exceptions (Patients 21 and 22) that valid filtrate fraction values were not obtained. The figures recorded for these patients in Table III are higher than the true values.

The valid filtrate fractions obtained in this series of observations are plotted in relation to diodrast Tm in Figure 4. The mean normal filtrate fraction of 19.6 ($\sigma = \pm 2.4$)³ per cent is shown by the solid horizontal lines. The general status of the nephritis at the time of the examination is indicated by different symbols as in Figure

2. The graphical summary emphasizes the frequency with which low filtrate fractions obtain in patients with active diffuse glomerulonephritis. Those with diastolic blood pressures above 90 mm. of mercury contributed almost all the normal and all the high filtrate fractions in the patients with diodrast iodine Tm values below 40 mgm. per minute. It should be noted, however, that hypertension is not inconsistent with a low filtrate fraction, as evidenced by the 3 observations with values of 0.12 or lower (Patients 7 and 13). The filtrate fraction is plotted against the PF/Tm ratio in Figure 5 and it may be seen that many of the observations fall outside and below the normal parameters, and also that the filtrate fractions of the patients with hypertension are distributed somewhat differently than the remainder.

The relation between the functional mass of tubule tissue (Diodrast Tm) and the diastolic blood pressure in the patients is shown in Figure 6. Diastolic hypertension does not appear to be a consistent finding, except during an acute episode, until diodrast iodine Tm falls below 20 mgm. per minute, although it is occasionally found

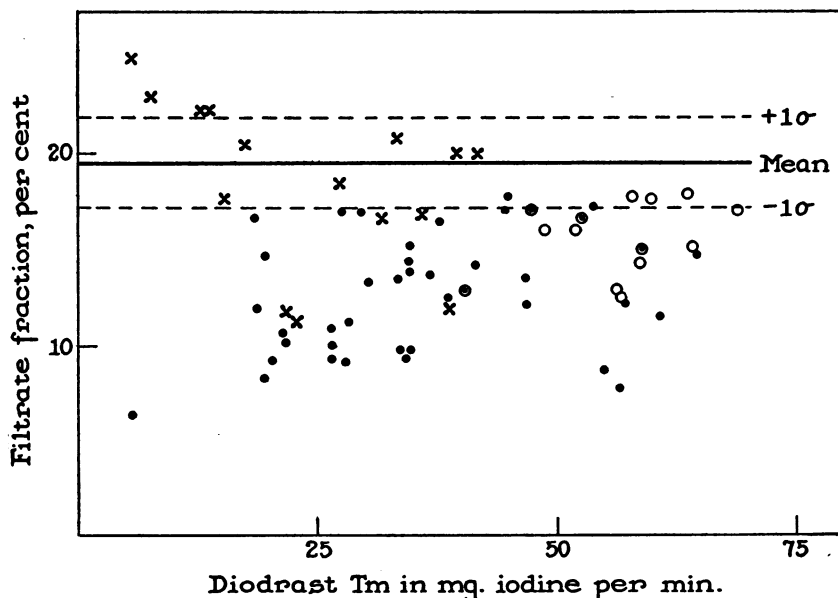


FIG. 4. FILTRATE FRACTION IN RELATION TO DIODRAST Tm IN A SERIES OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS³

The mean normal filtrate fraction ($GF/PF = 19.6$ per cent, $\sigma = \pm 2.4$ per cent) is shown by the horizontal lines. The status of the nephritis at the time of each observation is indicated as in Figure 2. Only filtrate fractions based on valid renal plasma flow determinations are included.

in nephritic subjects whose T_m values are considerably higher.

It has been shown that the renal vascular tree of normal individuals (24) and patients with essential hypertension (26) reacts to pyrogenic material in a manner which produces a marked increase in the renal blood flow. The renal hyperemia is not associated with a significant change in glomerular filtration rate, so that there is an associated fall in the filtrate fraction. Patients 9, 10, 12, and 15 were selected for a limited examination of this phenomenon in glomerulonephritis, and typhoid vaccine (24) was used as the pyrogenic agent. Three of the 4 patients showed a typical reaction, whereas there was a reduction of the filtrate fraction of Patient 12 which was a simple reflection of the fall in glomerular filtration rate. However, the injection of typhoid vaccine in this instance was followed by a severe general reaction and the observation was complicated by the incidental vascular phenomena.

It was anticipated that a study of the discrete renal functions and their interrelationships during

the initiation and early stages of acute glomerulonephritis would permit an early differentiation of those patients who subsequently recovered completely, as compared to those who passed into a chronic phase. Such a differentiation has not been achieved in the data collected to date but it may be noted that information on the renal status of the patients during the first week or two following the inception of the disease is not available.

It is of some interest that, in the interval following the acute attack, there was no significant reduction of the absolute values of renal plasma flow, glomerular filtration rate, or diodrast T_m , in Patients 3 and 4, although the filtrate fractions and GF/T_m ratios did reveal abnormal relations. The nephritis of Patient 3 healed, the filtrate fraction rising to normal, but the nephritis of Patient 4 did not heal, although the filtrate fraction showed some progressive improvement. The remaining subjects with acute glomerulonephritis (Patients 5, 6, and 9) showed definite depressions of glomerular filtration rate or diodrast T_m , as well as of the filtrate fraction and GF/T_m ratio.

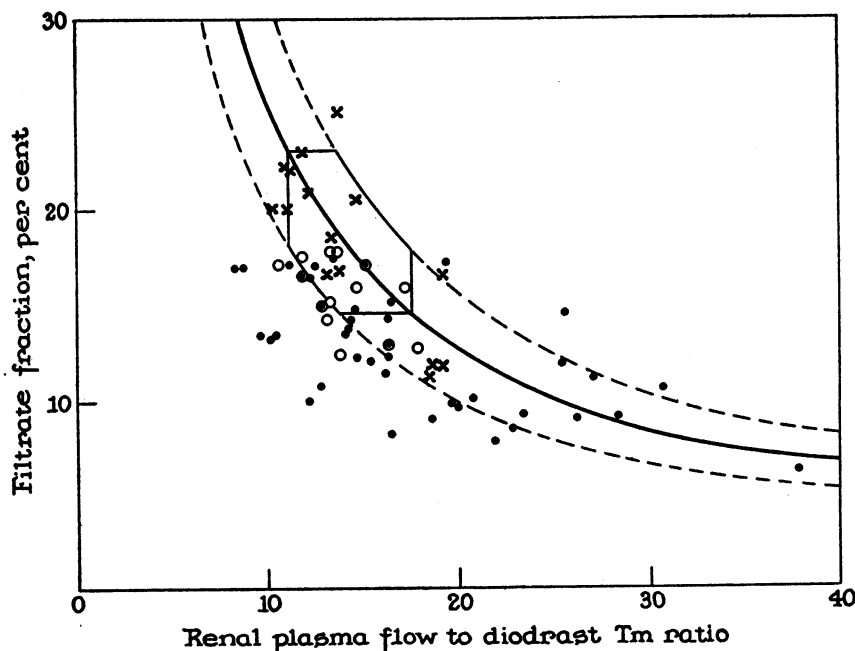


FIG. 5. FILTRATE FRACTION IN RELATION TO THE PLASMA FLOW TO DIODRAST T_m RATIO IN A SERIES OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS^{3, 4}

The hexagon contains 95 per cent of normal basal data (26). The status of the nephritis at the time of each observation is indicated as in Figure 2. Only data based on valid renal plasma flow determinations are included.

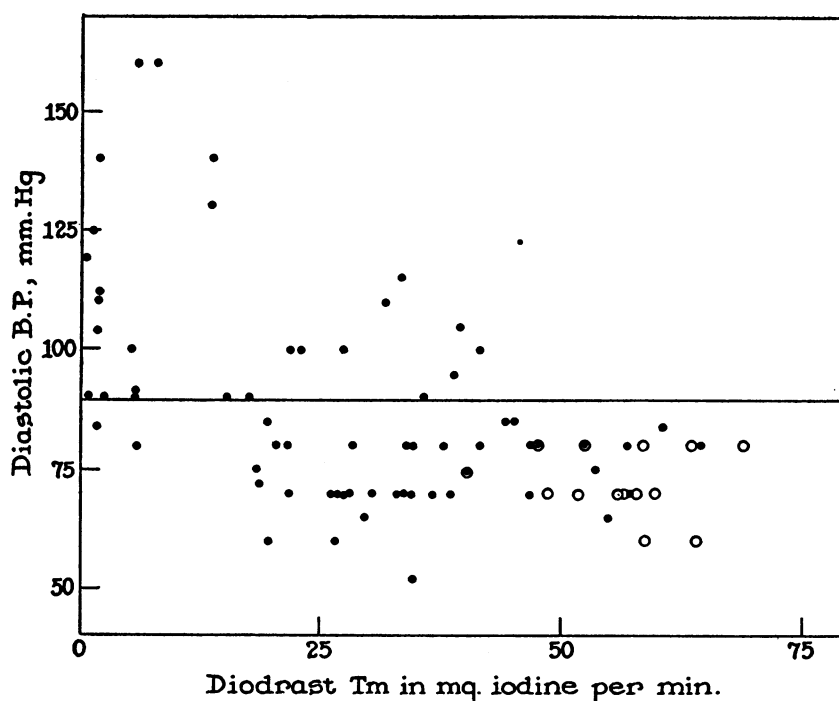


FIG. 6. DIASTOLIC BLOOD PRESSURE IN RELATION TO DIODRAST Tm IN A SERIES OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS

The status of the nephritis at the time of each observation is indicated as in Figure 2. The upper limit of normal diastolic blood pressure (89 mm. Hg) is indicated by the horizontal line.

The nephritis healed in Patient 6, while the process was definitely improving in Patients 5 and 9 when last studied. The discrete functions and the filtrate fraction and GF/Tm ratio in all 3 returned to normal or almost normal values and evidence of continuing kidney damage was derived largely from studies on the renal excretion of albumin and formed elements. Patient 2 still showed a low filtrate fraction 10½ months after the onset of an acute glomerulonephritis that healed according to the ordinary clinical criteria. There is, then, no apparent correlation in these patients between the degree of functional impairment at the time the patient was first seen and the eventual outcome of the acute glomerulonephritis.

Patients 11 and 15 were observed shortly following exacerbations in their chronic glomerulonephritis. The diodrast Tm gradually rose in Patient 11 to a low normal value during the 22 months following the acute episode. The glomerular filtration rate meanwhile rose slightly but did not attain a normal value. The exacerbation of

Patient 15 produced a more severe depression of various functions studied and a greater distortion of their interrelationships. Some gradual improvement was noted in the rate of glomerular filtration and in the diodrast Tm, but these functions eventually stabilized at quite low values. The filtrate fraction rose from 8 per cent to a low normal value, but the GF/Tm ratio remained depressed. An exacerbation also occurred in Patient 12 during the period of observation. The effect of this episode on the progress of the disease could not be determined however, since 7 months elapsed between the time of the exacerbation and the final renal function study.

It is probable that more numerous studies in patients before, during, and after exacerbations will aid in determining the importance of such episodes in conditioning the overall rate of progression of the disease (4). The usefulness of measurements of these functional measurements in yielding information on the rate of the progression as well as on the amount of residual renal

tissue is brought out by the observations on Patients 8, 12, 16, 17, and 20. All of these patients were in the chronic phase of the disease. Patients 8, 12, 16, and 17 were observed serially over considerable periods of time and showed a steady decline in glomerular filtration rate and diodrast T_m . Patient 20, first seen in the terminal phase of the disease ($T_m = 1.91$), manifested a further decline in both glomerular filtration rate and diodrast T_m in the subsequent weeks, prior to death. The PSP test throughout the period of observation in this patient was zero. The declines in glomerular filtration rate in these patients would presumably have been reflected in similarly decreasing urea clearances had these been systematically observed.

In direct contrast to the patients who manifested a progressive impairment of renal function while under observation, Patient 10, studied 8 years after the initial diagnosis of chronic glomerulonephritis, showed no significant change in diodrast T_m and a slight and temporary but definite increase in glomerular filtration rate over a 9-month interval. The improvement of diodrast T_m in Patient 14 was more striking. Such improvements of the renal function of patients with long-standing chronic glomerulonephritis are difficult to understand and may represent improvement subsequent to undetected exacerbations.

DISCUSSION

A survey of 22 patients in various phases of diffuse glomerulonephritis indicates, as is to be expected, that the advance of the disease is associated with progressive depression of the renal plasma flow, the glomerular filtration rate, and the mass of functional tubular tissue as reflected by the diodrast T_m . The interrelations of the discrete functions also depart from the normal and yield additional information on the functional organization of the kidney in this disease.

Glomerular changes are perhaps the outstanding anatomical lesion of diffuse glomerulonephritis, early in the course of the disease. These changes commonly consist of a thickening of the capsule and basement membrane and an increased cellularity of the tuft. The arterioles of the glomeruli and the renal tubules are not extensively involved at this stage. The frequent finding of a reduced filtration rate, low filtrate fraction, and

low GF/ T_m ratio would appear to be a functional expression of such a morphological change. Progress in the disease is then accompanied by a progressive ablation of renal tubular as well as glomerular tissue, and all functions fall in a roughly parallel manner with the maintenance of an abnormally low filtrate fraction. The later stages of the disease appear to be accompanied by a greater acceleration in the loss of tubular rather than glomerular tissue or function. This circumstance is reflected in the high GF/ T_m ratios and the relatively low values for the diodrast clearance. The latter stage of the disease is not amenable to simple analysis because of the difficulty in estimating renal plasma flow, as well as the frequent entrance of a complication in the form of a persistent hypertension. The latter may be expected to produce a disturbance in both systemic and glomerular hemodynamics.

The abnormally low filtrate fraction is a reflection of the glomerular changes which effect a greater barrier to the maintenance of glomerular filtration than to the passage of blood through the glomerular apparatus. Viewed in this light, it is not surprising that some of the patients manifest an actual renal hyperemia (Patient 4) whereas in others this is simply reflected in a low filtrate fraction and reciprocal changes in the GF/ T_m and PF/ T_m ratios. The low filtrate fraction may be attributed to changes in the character of the filtering bed which prevent the attainment of pressure equilibrium in each glomerulus, or it may be the result of those factors which determine the equilibrium pressure within the glomeruli. The increased renal plasma flow produced by typhoid vaccine in nephritic patients indicates that the glomerular arterioles are capable of normal reaction in this situation. It is difficult to define the relative importance of each of the various factors which are concerned in determining the change in the filtrate fraction. However, it would be in keeping with the usual pathological findings in diffuse glomerulonephritis to assign a major role to those factors which together determine the rate at which pressure equilibrium across the glomerular membrane is achieved, rather than to those factors which together determine the order of magnitude of the pressures across the membrane. It should be noted in Columns 15 and 17 of Table III that many of the nephritic patients

had low hematocrit and plasma albumin values. An analysis (not presented here) of the relation of these factors to renal plasma flow, glomerular filtration rate, and filtrate fraction suggests that changes among these are dependent upon the disease itself rather than upon any direct relationships between the two groups of factors.

The early impairment of glomerular filtration rate, the low filtrate fraction, and the low GF/Tm ratios of diffuse glomerulonephritis are opposed to the usual findings in essential hypertension (26, 27, 28). Examination of Table III and Figure 3 indicates that patients with diffuse glomerulonephritis, with or without hypertension, do not commonly have low PF/Tm ratios. The graphical plot of the data in Figure 5, however, suggests that the presence of a hypertension in patients with diffuse glomerulonephritis may change the dynamics of glomerular action in such a way that there is an increase in filtrate fraction, above values generally found among non-hypertensive nephritics. It may be noted in addition that hypertension is not necessarily related to a reduction of the amounts of functional tissue, as measured by diodrast Tm, except in that it become more common with progressive lowering of the latter function (Figure 6). However, diastolic hypertension is not found with any considerable regularity until the Tm has been reduced below 20 mgm. of diodrast iodine per minute.

The data upon which the above discussion is based are presented graphically in Figures 2 to 6 which contain all acceptable experiments, done in patients whose diagnoses of diffuse glomerulonephritis were reasonably certain. The status of renal disease in the various patients varied from healed acute glomerulonephritis to terminal uremia. In some patients, the disease was not stationary during the periods of recovery or improvement after acute episodes, while in others, progressive deterioration of renal function was observed. It seems likely, therefore, that the data presented give a fair cross-sectional view of the effects of diffuse glomerulonephritis on the functional organization of the kidneys.

The data reported in this paper contain certain more general implications which may be related to some of the clinical manifestations of diffuse glomerulonephritis. The discrete renal functions

in normal subjects may be viewed as if they were occurring in a single nephron (25, 29). This opinion rests upon the demonstration that all nephrons in the dog (29) and probably in man (30) are continuously active, and that the reabsorptive capacities of the individual tubules are closely correlated with the ability of their attached glomeruli to filter (29). It may be expected, in consequence of this, that symptoms of renal injury may become manifest because of an absolute deficiency in the number of residual nephrons or because of a general distortion of the normal relationships of the component parts of some or all the nephrons. The data indicate that in glomerulonephritis all of these factors probably operate throughout the course of the disease and that its early stages are characterized by a loss of the normal balanced relationship between glomerulus and tubule in at least a major portion of the nephrons. An anatomical basis for this judgment exists in the presence of all possible combinations of glomerular and tubular injury, throughout the course of the disease (31).

It may be anticipated from these considerations that the distortion of the normal quantitative relationship between glomerular and tubular function has important consequences to those mechanisms which are important in determining the rate of excretion of water and electrolyte. This judgment presupposes that these factors are similar in man to those demonstrated for the dog, and that while diodrast Tm is probably not directly proportional to the ability of the tubules to reabsorb sodium and other electrolytes, it is likely that impairment of one tubular function will be accompanied by impairment of others. In nephritis, then, glomerular damage out of proportion to the impairment of tubular function should predispose to the retention of electrolyte and, incidentally, water, as is so common. The opposite combination, however, may contribute to the demineralization which is also seen frequently, but later in the course of the disease. It may be calculated, furthermore, that a small percentage of nephrons, continuously diuretic because of an impairment in electrolyte absorption (32), can result in a urine of low specific gravity. This could explain the relatively long persistence of impaired concentrating power, frequently noted after healed

acute diffuse glomerulonephritis. The final definition of these problems, however, awaits more extensive studies.

SUMMARY AND CONCLUSIONS

1. The glomerular filtration rate (GF), renal plasma flow (PF), and maximal rate of tubular excretion of diodrast (Tm) have been studied in a series of 22 patients in various phases of diffuse glomerulonephritis. There is a depression of all 3 functions as the disease advances, associated with marked distortions in their normal relationships. The glomerular filtration rate is the most sensitive indicator of renal change early in the course of the disease. This is reflected by a low filtrate fraction and a low GF/Tm ratio.

2. Acute glomerulonephritis and exacerbations in chronic glomerulonephritis may be associated with depression of glomerular filtration rate, diodrast Tm, filtrate fraction, and GF/Tm ratio. Any or all of these values may return toward normal as improvement or healing of the acute process occurs. There may be a transient hyperemia as well, indicated by a high PF/Tm ratio. No correlation has been apparent between changes in specific renal functions or their relationships in acute glomerulonephritis and the eventual outcome of the disease.

3. As chronic glomerulonephritis progresses, the tubular function undergoes relatively greater impairment than the glomerular filtration rate, indicated by high GF/Tm ratios and a relatively excessive lowering of the diodrast clearance.

4. The development of hypertension has not been specifically related to the residual kidney mass, although it is not infrequent when there has been more than a 40 per cent reduction in Tm.

5. Certain implications of the results have been discussed.

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