JCI The Journal of Clinical Investigation

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J Clin Invest. 1941;20(6):637-653. https://doi.org/10.1172/JCI101257.

Research Article

EFFECTIVE RENAL BLOOD FLOW IN SUBJECTS WITH ESSENTIAL HYPERTENSION [1,2]

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(Received for publication June 16, 1941)

Sixty patients with well-established essential hypertension form the basis of this report. These patients were selected from the Hypertension and Nephritis Clinic of the New York University Clinic. A few subjects with radiologic evidence of uropathology are included, but none who have evidence of glomerular nephritis or other specific renal disease.

A major difficulty in a problem such as is considered here is that the investigator cannot readily observe a particular patient pass from health through various stages of the disease, nor yet pass from any stage of the disease back into health. The perturbations of function in essential hypertension are so insidious in onset and generally so slow in progress that they can be discovered only by a comparison of subjects in many phases of the disease with a number of normal subjects. Although this comparative method contains certain obvious dangers, we believe that the facts presented in this study demonstrate significant differences in renal function in hypertensive and normal subjects.

Pertinent clinical data are summarized in Table I, and the important data on renal function in Tables II and III. The only points needing explanation are that the blood pressures in Tables II and III represent the average of several values observed by the auscultatory method during the measurement of the diodrast clearance. Each datum on the inulin clearance and diodrast clearance is the average of three or more urine collection periods, each datum on diodrast *Tm* the average of five periods. Additional basal observations, comparable with those of Table II, are presented in Table III for purposes of reference in examining the effects of renal hyperemia. The data in Table II and the control data in Table III refer to the basal condition, uncomplicated by any therapy.

We have previously shown the advantage of comparing renal function in various normal subjects in terms of their respective values of diodrast *Tm* (9), and have amplified the reasons for this method of analysis, in respect to the diseased kidney, in the preceding paper (12). This relative method of analysis is followed here, the data on hypertensive subjects being presented against a statistical background afforded by the behavior of the normal kidney. The data for this purpose are drawn from Table IV of a previous paper (9) where men and women are treated as one series, sex differences being negligible.

1. Diodrast clearance and diodrast Tm

Figure 1 shows the diodrast clearance (C_D) in relation to diodrast Tm (Tm_D). Each subject is recorded once only, the average basal values of C_D and Tm_D taken from Tables II and III being used. In normal subjects (9) the ratio, C_D/Tm_D, has a mean value of 13.4 ± 1.4; this mean normal value is represented by the solid line, M, the lines above and below M denoting multiples of the standard deviation. The ellipse is calculated to contain 70 per cent of the normal observations and actually contains 72 per cent.[3]

[1] Aided by a grant from the Commonwealth Fund.

[2] Preliminary communications on this subject have appeared elsewhere (8, 16).

[3] This ellipse and the corresponding ellipse in Figure 2 were not calculated in the paper in which the normal data were presented.

The area on a scatter diagram within which we may theoretically expect 70 per cent of the observations to fall by chance alone is an ellipse formed by the equation

$$\chi^2 = \left(\frac{x^2}{\sigma_x^2} - \frac{2rxy}{\sigma_x\sigma_y} + \frac{y^2}{\sigma_y^2}\right)\frac{1}{1-r^2},$$

where χ^2 is taken from recorded χ^2 tables (10) and is determined by P, the proportion of observations which may be expected to fall outside the ellipse by chance alone, and by n, the degrees of freedom in the system. Here P is 0.30 (*i.e.*, 70 per cent within the ellipse) and $n = 2$; hence, $\chi^2 = 2.408$. In the above equation x is the distance from

If we were to start with a normal kidney in which $C_D/Tm_D = 13.4$ and were to reduce the quantity of tubular excretory tissue and the renal blood flow by proportional amounts, we would pass down the line M until we reached the intersection of the zero ordinates. This is not to imply that the statistical regression line relating C_D to Tm_D in normal subjects extrapolates to zero, for it does not; the concept of proportional regression is merely an artifice convenient to functional interpretation. A variation of mean $C_D/Tm_D \pm 2\sigma$ (13.4 ± 2.8) should contain 95 per cent of the normal observations, and it is in keeping with the artifice of proportional regression to conceive that any distribution of the hypertensive data disproportionate with this statistical expectation is indicative of significant functional changes in C_D, Tm_D or both.

The following facts are to be noted in Figure 1:

With the exception of three subjects (F. O., R. D., and G. T.), Tm_D is below the mean of the normal value (51.6 mgm. of iodine per minute) and ranges from slightly subnormal to very low values. As shown in Table I, the lowest values of Tm_D are found in subjects with advanced retinopathy and significant proteinuria. In the latter instances it is evident on a statistical basis that impairment of tubular function, as judged by the loss of the capacity to excrete diodrast under conditions of saturation, has occurred. Whether or not Tm_D has been reduced in those subjects in whom this value approaches the normal value cannot be answered from statistics alone, but it is inferred that such is the case,

mx along the x axis, y is the distance from my along the y axis, σ_x and σ_y are the standard deviations of the distribution in the x and y direction, respectively, and r is the coefficient of correlation. x is determined for various values of y by resolving the above equation in the quadratic:

$$x = \frac{-ay}{2} \pm \sqrt{\left(\frac{a^2}{4} - b\right)y^2 - c}$$

and writing

$$a = -\frac{2r\sigma_x}{\sigma_y}$$

$$b = \frac{\sigma_x^2}{\sigma_y^2}$$

$$c = -(1 - r^2)\chi^2.$$

An ellipse on a scatter diagram within which 70 per cent of the observations may be expected to fall by chance corresponds roughly to a distance from -1σ to $+1\sigma$ on a linear scale for one variable (68 per cent of the observations).

TABLE I

Clinical data on hypertensive subjects

(The subjects are arranged in order of decreasing diodrast Tm, this value being the average of all observations under basal conditions.)

Subject	Diodrast Tm (*mgm. iodine per minute*)	Range of blood pressure during hospitalization	Retina*	Enlarged heart	Proteinuria	Hematuria	Anemia†	Necropsy
R. D.	56.3	168/120–174/124	1	Y	0	0	N	N
G. T.	53.4	124/ 88–130/104	0	N	0	0	N	N
F. O.	53.2	106/ 80–112/ 99	0	N	0	0	N	N
C. V.	48.9	142/ 86–194/150	1	N	0	0	N	N
G. G.	48.3	150/ 95–165/120	1	N	0	0	N	N
M. J.	46.8	152/ 80–174/110	1	N	0	0	N	N
A. M.	46.2	160/100–180/110	0	N	0	0	N	N
A. Mc.	45.1	170/106	1	N	0	0	N	N
M. G.	44.7	134/ 90–180/120	1	Y	0	0	N	N
C. T.	44.7	158/ 84–210/108	1	N	0	0	N	N
M. C.	44.3	164/112–192/126	1	N	0	0	N	N
S. K.	42.7	160/110–210/134	1	Y	+	0	N	N
A. N.	41.9	138/ 78–158/100	2	N	0	0	N	N
M. A.	40.9	178/120–226/140	1	Y	0	0	N	N
E. G.	40.1	160/102–190/120	1	Y	0	0	N	N
L. Js.	40.1	112/ 80–182/124	1	Y	0	0	N	N
R. Mc.	39.0	165/105–230/128	1	Y	0	0	N	N
M. Jo.	38.6	132/100–170/124	1	N	0	0	N	N
A. G.	38.6	192/ 90–230/130	2	Y	0	0	N	N
M. M.	37.9	148/110–160/110	1	N	+	0	N	N
V. V.	37.5	134/ 88–186/116	1	N	0	0	N	N
C. B.	36.7	116/ 80–196/120	0	N	0	0	N	N
S. W.	36.5	190/110–220/128	1	Y	0	0	N	N
E. H.	36.2	154/ 94–190/130	2	Y	0	0	N	N‡
H. N.	35.4	148/100–164/120	1	N	0	0	N	N
M. T.	35.1	160/104–180/124	1	Y	0	0	N	N
F. S.	34.4	175/ 95–208/114	1	Y	0	0	N	N
R. Y.	34.2	180/125	1	Y	+	0	N	N‡
K. S.	33.5	210/130–260/180	1	Y	0	0	N	N
L. S.	32.8	190/120–240/150	1	N	0	0	N	N
R. L.	32.6	200/125–240/140	1	Y	0	0	N	N
A. Mg.	32.6	160/ 98–196/110	1	Y	0	0	N	N
R. La.	32.6	130/ 80–170/105	1	N	0	0	N	N
U. B.	32.5	190/118–200/140	1	Y	0	0	N	N
F. K.	31.6	144/ 92–170/112	1	N	0	0	N	N
W. N.	30.9	162/110–238/170	1	Y	0	0	N	N‡
J. O.	30.5	152/106–230/146	2	Y	0	0	N	N
L. J.	30.1	102/ 76–178/128	0	Y	0	0	N	N
L. K.	29.5	160/ 90–224/128	1	N	0	0	N	N‡
E. D.	28.9	154/110–210/140	1	Y	0	0	N	N
E. Wa.	28.2	154/108–216/126	2	N	0	0	N	N‡
A. B.	27.1	154/104–180/130	1	Y	0	0	N	N
M. P.	26.6	190/110–230/130	2	Y	0	0	N	N
H. U.	26.5	164/ 90–230/134	2	N	+	0	N	Y
D. C.	25.7	132/ 78–200/120	2	Y	0	0	N	N
T. T.	24.9	174/102–180/112	1	Y	0	0	N	N
G. F.	24.6	180/118–230/118	1	Y	0	0	N	N
G. L.	22.7	148/110–270/170	1	N	0	0	N	N
J. M.	19.8	194/162–220/152	3	Y	++	Y	N	Y
J. M.	16.6	220/130–280/180	3	Y	++++	+	Y	Y
G. H.	14.8	222/ 96–244/132	3	Y	+++	Y	N	N
H. G.	12.3	180/100–250/148	3	Y	+++	Y	Y	N‡
E. J.	8.9	204/130–270/160	3	N	++	Y	Y	N‡
J. Br.	4.6	166/112–202/145	3	Y	+++	Y	N	N‡
J. L.	4.3	170/ 95–210/110	3	Y	+++	0	Y	Y
N. S.	3.0	164/ 96–178/110	3	Y	+	Y	Y	Y
BILATERAL SYMPATHECTOMY								
B. Fo.	37.0	140/ 90–210/120	3	Y	+	Y	N	N
W. Mc.	27.2	230/155	1	Y	0	0	N	N
UNILATERAL NEPHRECTOMY								
J. G.	37.2	150/ 88–154/ 94	1	N	0	0	N	N
W. S.	33.8	164/108–298/160	1	Y	Y	Y	Y	Y

* 0 = negative; 1 = vascular changes; 2 = 1 + retinopathy; 3 = 2 + papilledema.

† Less than 3 *M.* or less than 70 per cent hemoglobin.

‡ Deceased.

TABLE II

Basal observations on hypertensive subjects

(Columns 4, 5, 6, 7 and 10 are corrected to 1.73 sq. m., column 10 corrected to 98.5° F. (15). Columns 11 and 12 are averages of columns 6 and 4 divided by the averages of column 10. Additional basal data given in Table III are included in above averages.)

Subject	Date	Average blood pressures during C_D determination	Plasma clearances			Effective blood flow	Filtration fraction	Temperature	Tm_D	C_D/Tm_D	C_{IN}/Tm_D
			Inulin	Phenol red	Diodrast						
			cc. per minute	*cc. per minute*	*cc. per minute*	*cc. per minute*	*per cent*	*° F.*			
G. G.	December 6, 1937		116		503	818	23.1	99.6	52.8		
	February 16, 1938		149	305	506	830	29.5	99.0	48.6		
	October 10, 1938*	148/98	106	296	428	652	24.8	99.0	44.3		
	October 21, 1938	148/100	115	276	441	689	26.1	98.8	47.5	9.7	2.51
M. G.	December 17, 1937		124	327	589	1027	21.1				
	December 20, 1937		122	368	576	1027	21.2	99.5	53.2		
	February 9, 1938		123	317	521	921	23.6	98.6	41.3		
	February 26, 1941	152/100	121					99.0	40.7	12.5	2.72
M. J.	May 20, 1940†	150/94	139	369	536	862	25.9	98.5	46.8	11.4	2.97
A. M.	February 25, 1938		135	398	632	1176	21.4				
	March 2, 1938		127	335	584	1003	21.7		46.2	13.2	2.84
A. Mc.	April 22, 1940†	198/118	98.4	261	336	544	29.3	98.0	45.1	7.4	2.18
C. T.	December 4, 1939	206/106	105		510	832	20.6	98.4	44.7	11.4	2.35
M. C.	March 29, 1940†	180/124	149	344	565	835	26.4	98.0	44.3	12.8	3.36
S. K.	October 7, 1940†	196/130	99.6		358	602	27.8	98.6			
	November 8, 1940‡	142/98							42.7	8.4	2.33
A. N.	November 4, 1940†	158/100	120		452	717	26.6	99.7	41.9	10.8	2.86
M. A.	December 27, 1937		142	316	556	1035	25.5				
	December 30, 1937		117	356	598	1075	19.6	99.0	41.9		
	November 6, 1939	204/128	151		490	823	30.8	98.6	41.0		
	November 15, 1939	194/126	122		524	952	23.3	99.2	40.5		
	December 6, 1939	194/128	117		445	686	26.3	99.6		12.7	3.16
M. Jo.	February 21, 1938		118	294	485	824	24.3	98.6	41.1		
	March 21, 1938		132	402	531	848	24.9	99.6	41.3		
	April 4, 1941	194/120	105		461	752	22.8	99.4	35.9		
	May 7, 1941	152/198	83.6		570	877	14.7	99.2	45.1	12.5	2.69
E. G.	December 8, 1937		130	346	475	1002	27.4	98.4	43.4		
	December 22, 1937		113	251	448	999	25.2				
R. Mc.	November 18, 1940†	212/110	94.8		415	728	22.8	98.6	36.9		
	December 9, 1940†	200/120	108		488	856	22.1	98.6	41.1	13.6	2.60
A. G.§	October 4, 1940†	264/126	71.9		354	580	20.3	98.8	38.6	9.2	1.86
L. Js.	December 19, 1940†	136/90	106		568	1062	18.7	98.8	38.3	14.8	2.77
M. M.	April 8, 1940†	200/146	121	297	380	735	31.8	97.2	37.9	10.0	3.19
V. V.	April 22, 1940	140/92	132		732	1118	18.1	97.8	37.5	19.5	3.44
H. N.	May 17, 1940	128/92	101		392	652	25.8	99.9	35.4	11.1	2.85
M. T.	March 3, 1941†	166/108	127		579	982	21.9	98.6	35.1	16.5	3.62
S. W.	November 29, 1940	200/110	70.5		366	666	19.3	98.2	36.5	10.0	1.93
F. S.	November 14, 1940†	204/120	142		504	840	28.2	98.0	34.4	14.6	4.12
R. Y.	March 25, 1938		105	230	323	588	32.5	98.6	34.6		
	April 4, 1938		107	216	324	568	33.0	98.4	33.7	9.5	3.10
K. S.	May 12, 1941†	186/108	136		388		35.1	98.5	33.5	11.6	4.06
C. B.	May 16, 1941	124/75	115		542	822	21.2	98.8	36.7	14.8	3.13
L. S.	April 15, 1940†	250/120	102	245	436	799	23.4		32.8	13.3	3.11
A. Mg.	September 27, 1940†	200/120	112		419	746	26.7		32.6	12.9	3.43
R. L.	November 11, 1940	166/130	112		500	910	22.4	98.8	32.6	15.3	3.43
U. B.	May 19, 1939	198/130	104		416	695	25.0	98.3	32.5	12.8	3.20
J. O.	March 12, 1941	210/138	79.8		347	691	23.0	98.4	29.5	11.8	2.70
F. K.	January 10, 1938		126	304	530	1080	23.8				
	January 24, 1938		117	282	513	930	22.8	98.4	34.0		
	February 2, 1938		126	260	545	1002	23.1				
	March 9, 1938		107	233	487	934	22.0	99.0	29.9		
	May 17, 1938	156/110	92.4	240	473	942	19.5				
	October 26, 1938	154/110	99.4	265	530	1060	18.7				
	November 2, 1938	148/100	96.3	244	497	904	19.4				
	November 11, 1938	148/100	88.2	197	457	774	19.3				
	May 27, 1940†	160/112	131	328	633	1179	20.7		31.4	16.3	3.44

TABLE II—*Continued*

Subject	Date	Average blood pressures during C_D determination	Plasma clearances			Effective blood flow	Filtration fraction	Temperature	Tm_D	C_D/Tm_D	C_{IN}/Tm_D
			Inulin	Phenol red	Diodrast						
			cc. per minute	*cc. per minute*	*cc. per minute*	*cc. per minute*	*per cent*	*° F.*			
W. N.	January 7, 1938		84.8	180	314	575	27.0	100.0	30.9	10.2	2.74
L. J.	October 19, 1938	160/110	97	218	275	500	35.3	101.5	29.1		
	January 3, 1939‖	144/98	111	252	421	668	26.4	99.3	28.2		
	January 18, 1939	144/110	124	321	573	895	21.6	99.2	34.3		
	March 22, 1939	146/110	94		391	610	24.0	99.5	30.3		
	December 2, 1940†		118		419	737	28.2	98.5	29.8	13.7	3.59
L. K.	January 10, 1938		104	191	323	552	32.2				
	January 19, 1938		88.8	150	267	435	33.2	98.6	28.6		
	March 18, 1938		120	171	292	468	41.1	99.4	30.3		
	May 20, 1938	230/130	115	219	333	571	34.5				
	May 25, 1938		86.9	157	295	482	29.5			10.3	3.49
E. D.	June 24, 1940†		102		425	639	24.0	98.5	30.6	14.7	2.96
E. Wa.	April 1, 1940†		81		308	540	26.3	98.5	29.6	10.9	2.82
A. B.	April 15, 1940		68.2		331	535	20.6	98.4	27.1	12.2	2.52
M. P.	December 3, 1937		69.1	191	338	537	20.4	98.6	29.7		
	March 14, 1938		75.4	185	268	435	28.1	99.4	23.5	11.4	2.72
H. U.¶	December 1, 1937		91.4	246	532	960	17.2				
	December 13, 1937		91.8	225	475	763	19.3	99.0	26.6		
	March 23, 1938		110	259	529	896	20.8				
	October 4, 1938†	210/124	105	231	497	822	21.1	99.0	24.2		
	October 27, 1938	196/122	99.0	246	503	889	19.7	99.0	26.5		
	November 17, 1938	192/110	108	221	521	829	20.7			19.8	3.91
T. T.	March 19, 1941	200/110	61.9		280	470	22.1	98.6	24.9	11.2	2.49
D. C.	November 3, 1940	176/100	105		530	888	19.8	98.8	25.7	20.6	4.08
G. F.**	November 25, 1940†	148/100	59.8		303	517	19.7	98.0	24.6	12.3	2.43
J. M.	March 14, 1941	204/110	90.7		375	744	24.2	98.4	22.9	16.4	3.96
G. L.††	December 23, 1940†	170/134	68.4		241	518	28.4	98.3	22.7	10.6	3.01
G. H.	February 11, 1938		40.7	86.6	168	272	24.2	99.0	14.3		
	March 4, 1938		39.2	88.6	154	245	25.5	99.0	15.2	10.9	2.71
E. J.	May 24, 1938		24.5	45.1	79.8	127	30.7	99.0	8.9	9.0	2.87
J. Br.	February 26, 1940	200/156	10.0		38.3	85.2	26.1	98.4	4.6	8.3	2.12
J. L.	December 29, 1937		20.6	32.8	69.6	102	29.6				
	January 5, 1938		16.6	29.5	60.8	88	27.3				
	January 17, 1938		23.8	31.6	77.6	109	30.7	98.6	5.5		
	March 16, 1938		20.7	18.4	42.2	56.2	49.0	98.6	3.0	14.7	4.81
N. S.	February 7, 1938		7.1	10.0	43.0	61.0	16.5	98.8	3.4		
	March 11, 1938		6.9	9.0	31.3	41.7	22.0	98.6	2.6	12.4	2.33
BILATERAL SYMPATHECTOMY											
W. Mc.‡‡	February 28, 1940	188/128	105		339	703	31.0	99.4	27.2	12.5	3.86
B. Fo.§§	May 13, 1940	154/106	88.4		462	683	19.1	98.6	37.0		
	June 3, 1940†	174/120	122	271	396	618	30.8	98.5	37.0		
	June 17, 1940†	170/120	107	274	438	683	24.4	98.5		11.7	2.86
UNILATERAL NEPHRECTOMY											
J. G.‖‖	February 12, 1940	162/108	83.2		354	622	23.5	99.2	37.2		
	February 16, 1940	150/80	89.2		416	885	21.4	99.2		10.3	2.32
W. S.¶¶	October 31, 1938	142/82	122		592	1037	20.6		33.8	17.5	3.61

* G. G. Left renal omentopexy on June 14, 1938.
† Unilateral method.
‡ S. K. No change in renal blood flow in sitting position.
§ A. G. Studied ten days after recovery from congestive heart failure.
‖ L. J. Right nephropexy on October 12, 1938, for costovertebral pain and hematuria.
¶ H. U. Left omentopexy, June 14, 1938. Attempt at right omentopexy on July 10, 1939, abandoned because of inability to bring omentum to kidney.
** G. F. Tm_D done in sitting position.
†† G. L. Denervation of right renal pedical, June 4, 1940. On December 23, 1940, right kidney was functionless.
‡‡ W. Mc. Bilateral sympathectomy in June, 1938.
§§ B. Fo. Bilateral sympathectomy, left side on May 18, 1939, and right side on June 9, 1939.
‖‖ J. G. Right nephrectomy on August 30, 1939. Diagnosis, atrophy of kidney with hydronephrosis.
¶¶ W. S. Right nephrectomy in 1936. Diagnosis, renal tuberculosis. Not hypertensive.

TABLE III

Observations on hypertensive subjects during induced hyperemia

(Compared with last preceding observation made under basal conditions, usually one week previously. Asterisk marks the hyperemic study.)

Subject	Date	Mean blood pressure during C_D determinations	Plasma clearance: Inulin C_{IN}	Plasma clearance: Diodrast C_D	Effective blood flow	Filtration fraction	Rectal temperature	Tm_D	D-load/Tm_D	C_D/Tm_D	ΔC_{IN}	ΔC_D	ΔTm_D
			cc. per minute	*cc. per minute*	*cc. per minute*	*per cent*	° *F.*	*mgm. iodine per minute*			*per cent*	*per cent*	*per cent*
R. D.	June 24, 1940	168/120	150	726	1088	20.7	99.0	56.3	2.41	12.9			
	*June 28, 1940	140/92	136	1000	1494	13.6	99.3	54.7	5.14	18.3	−9	+38	−3
F. O.	June 17, 1940	118/74	130	768	1227	16.9	99.2	53.2	1.65	14.4			
	*June 26, 1940	112/64	117	1097	1797	10.7	99.2	53.8	3.90	20.4	−10	+43	+1
C. V.	May 29, 1940	216/116	96.8	406	664	23.8	98.6	48.9	1.63	8.3			
	*June 5, 1940	176/96	86.3	610	931	14.1	98.5	34.9	5.05	17.5	−11	+50	−29
M. G.	January 6, 1939		111	555	925	20.0	98.8	43.5	1.50	12.8			
	*January 11, 1939	136/88	114	1010	1683	11.3	99.6	45.6	3.50	22.2	+3	+80	+5
M. Jo.	May 1, 1939	144/98	114	556	785	20.5	98.8	29.8	1.75	18.6			
	*May 8, 1939	130/88	106	717	1094	14.8	99.6	34.0	6.35	21.1	−7	+37	+14
E. G.	January 12, 1939	210/120	130	492	910	26.4	98.4	36.9	1.80	13.3			
	*January 16, 1939	170/90	116	886	1610	13.4	99.8	39.2	4.50	22.6	−11	+88	+6
V. V.	April 5, 1940	148/106	125	775	1215	16.1	98.6	37.5	4.97	20.6			
	*April 30, 1940	144/86	124	1318	2042	9.4	98.4	43.0	7.56	30.6	±0	+75	+15
J. O.	June 10, 1940	188/132	93.9	408	752	23.0	98.6	32.4	2.47	12.6			
	*June 19, 1940	186/126	88.3	685	1262	13.0	99.3	33.3	3.73	26.5	−6	+68	+3
F. K.	March 13, 1939	168/102	121	604	1105	20.0	98.8	30.9	9.8	19.6			
	*March 20, 1939	164/90	116	914	1375	12.7	99.4	29.6	13.3	23.1	−4	+72	−4
	March 1, 1940	158/114	140	579	1108	24.2	99.0	32.0	2.91	18.1			
	* May 24, 1940	166/120	122	752	1400	16.2	99.3	40.8	3.72	18.4	−13	+42	+18
L. J.	March 27, 1939	134/90	120	471	785	25.5	99.3	29.0	3.87	16.2			
	*April 3, 1939	128/90	116	622	1056	17.3	99.8	31.4	4.71	19.8	−3	+46	+8
E. D.	May 27, 1940	196/142	69.3	386	601	18.0	98.6	27.1	3.21	14.2			
	*June 3, 1940	184/118	63.1	571	857	11.1	98.7	27.8	4.35	20.5	−9	+41	+3
E. Wa.	April 8, 1940	174/108	78.0	344	583	22.7	98.3	26.8	3.72	12.8			
	*April 24, 1940	178/108	80.4	827	1343	9.7	98.6	32.0	7.33	25.8	−3	+157	+19
A. B.	April 1, 1940	170/120	77.2	393	660	19.6	98.1	27.1	3.85	14.5			
	*April 26, 1940	174/118	70.8	659	1096	10.7	98.3	25.9	5.92	25.4	−8	+82	−4
H. U.	March 29, 1939	198/112	111	544	899	20.4	99.3	24.4	9.73	22.3			
	*April 10, 1939	172/102	103	567	831	18.2	98.5	22.6	10.58	25.1	−7	+8	−7
	*April 17, 1939	160/88	117	850	1315	13.8	100.0	24.5	14.08	34.7	+5	+62	±0
	March 8, 1940	172/104	92.6	582	956	15.9	98.8	31.0	3.64	18.8			
	*May 1, 1940	152/90†	48.5	394	606	12.3	99.0	35.0	3.07	11.3	−59	−25	+13
R. L.	March 10, 1939	230/132	145	570	976	25.4	99.0		2.43				
	*March 17, 1939	182/110	118	758	1330	21.1	99.0	41.0	7.91	18.5	−19	+33	
J. M.	May 6, 1940	232/158	51.0	156	252	32.7	98.4	16.6	2.76	9.4			
	*May 15, 1940	248/162	46.3	152	241	30.4	98.7	10.9	5.64	13.9	−9	−3	−34
H. G.	April 19, 1939	240/160	63.2	207	362	30.5	100.0	12.3	5.77	17.0			
	*April 24, 1939	236/136	67.1	241	400	27.8	99.0	14.1	4.43	17.1	+6	+17	+15
	*May 12, 1939	248/142	60.8	212	348	28.8	99.0	16.4	3.60	12.9	−4	+2	+33
E. H.	May 3, 1940	230/138	76.4	296	539	25.8	99.1	36.2	2.57	8.2			
	*May 8, 1940	206/122	86.2	654	1120	13.2	99.5	28.8	7.11	22.7	+13	+121	−21
AFTER UNILATERAL SYMPATHECTOMY ON LEFT SIDE, MAY 20, 1940‡													
	*June 12, 1940	210/128	R 41.8 L 42.2	284 280	415 409	14.7 15.1	98.8				+10 +10	+92 +89	
BILATERAL SYMPATHECTOMY													
W. Mc.	February 28, 1940	188/128§	105	339	703	31.0	99.5			12.5			
	*June 7, 1940	198/130	115	443	832	25.9	99.4	27.2	1.20	16.2	+10	+31	
B. Fo.	May 13, 1940	156/108‖	88.4	462	683	19.1	98.6	37.0	4.29	12.5			
	*May 20, 1940	146/90	83.2	628	925	13.2	99.4	41.8	2.7	15.0	−6	+45	+13

† During pyrogenic reaction symptoms of circulatory failure occurred. Recorded blood pressure probably not representative.

‡ Left sympathectomy on May 20, 1940. Reference values for C_{IN} and C_D taken as one-half of bilateral values obtained on May 3, 1940.

§ Basal Tm_D not available, so equated with value obtained on June 7, 1940. Bilateral sympathectomy in June, 1938.

‖ Bilateral sympathectomy in May and June, 1939.

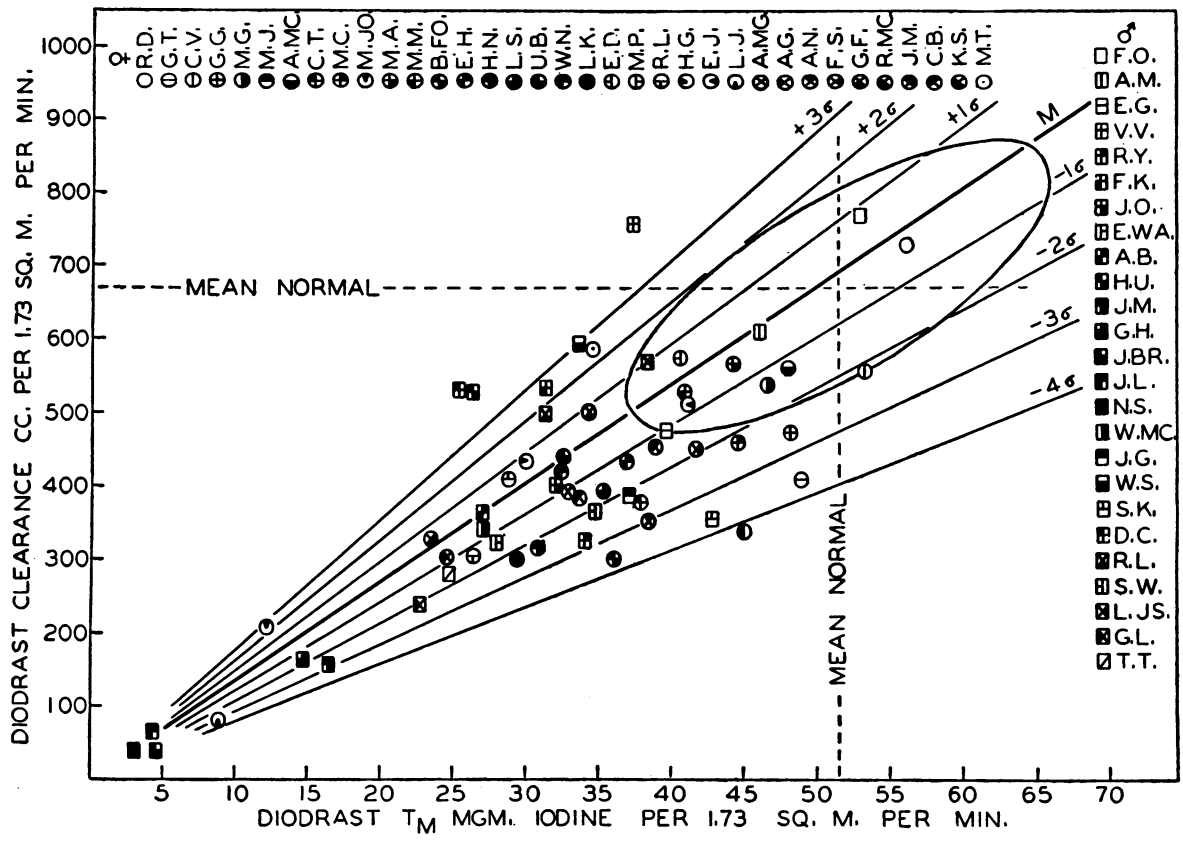

FIG. 1. DIODRAST CLEARANCE (EFFECTIVE RENAL PLASMA FLOW) IN HYPERTENSIVE SUBJECTS, RELATED TO DIODRAST *Tm* (TUBULAR EXCRETORY MASS)

The statistical background is based on data from normal subjects (9), the ellipse being calculated to contain 70 per cent of the normal data, and actually containing 72 per cent.

especially since the present group of patients all had well-established hypertensive disease.

With the exception of three subjects (F. O., R. D. and V. V.), C_D is below the mean normal value (669 cc. per minute) and, like Tm_D, ranges from slightly subnormal to very low values. A reduction in C_D may result from either a decreased total renal blood flow or a decreased extraction ratio (see uncleared blood (12)). Since we cannot at present distinguish between these alternative explanations, we cannot say whether the total renal blood flow, *i.e.*, the sum of uncleared plus cleared blood, is decreased in these subjects or not. A reduction in the volume of blood cleared of diodrast implies, however, a reduction in the volume of blood cleared of such endogenous products as the tubules are normally called upon to excrete, and therefore an impairment of an important renal function. With regard to the reduction in extraction ratio, which probably occurs in these subjects, we have elsewhere (12) emphasized the importance of referring the datum C_D to Tm_D by means of the ratio C_D/Tm_D, which expresses the relative quantity of plasma (C_D) cleared by the residual functional tissue, Tm_D. It is in keeping with the physiological implications of this ratio to speak of increments or decrements beyond the normal or expected limits as a relative hyperemia or ischemia of the residual functional tissue.

As can be seen from data in Figure 1, the ratio C_D/Tm_D is distributed about the mean value in an uneven manner, 45 out of 60 subjects falling on or below *M*. This preponderant distribution below *M* suggests that some factor is operating in hypertensive subjects to produce a relative ischemia in the residual functional tubular tissue. This relative ischemia is, we believe, one of the

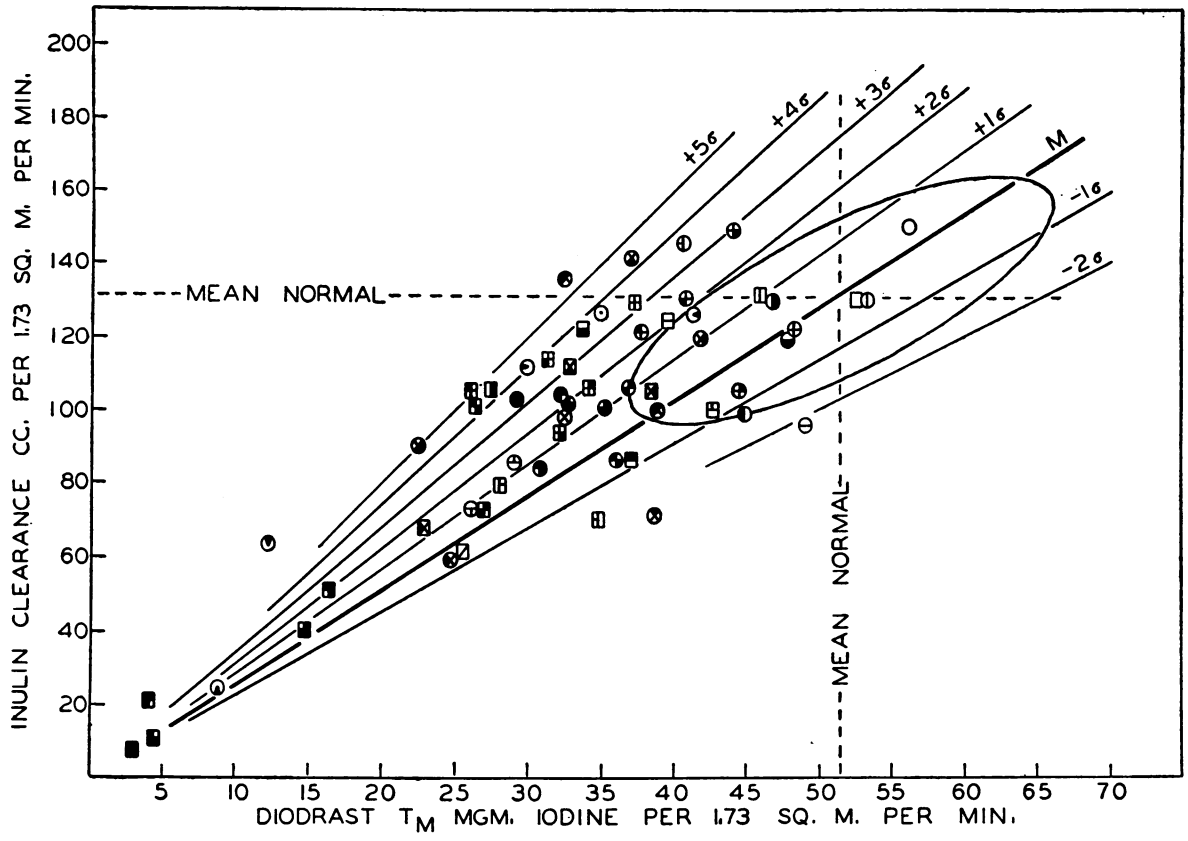

FIG. 2. INULIN CLEARANCE (FILTRATION RATE) IN HYPERTENSIVE SUBJECTS, RELATED TO DIODRAST *Tm*

Statistical background as in Figure 1. The ellipse, again calculated to contain 70 per cent of the normal data, actually contains 75 per cent.

major physiological disturbances characteristic of the hypertensive kidney, and will be discussed later in the paper.[4]

2. *Inulin clearance and diodrast* Tm

Figure 2 presents the inulin clearance (C_{IN}) in relation to Tm_D, the mean normal values of C_{IN} and Tm_D and of the ratio C_{IN}/Tm_D (the heavy line marked *M*) being taken from the normal data referred to above. Again the ellipse is calculated to contain 70 per cent of the normal observations, and actually contains 75 per cent.

In all but five subjects (R. D., M. C., R. L., F. S. and K. S.), C_{IN} is on or below the mean normal value (131 cc. per minute). There is, however, a tendency for C_{IN} to remain within the lower range of normal values (92 to 131 cc.) until Tm_D has been markedly reduced, as shown by the horizontal, leftward displacement of the data.

Reduction in filtration rate might be caused by (*a*) decrease in blood pressure, (*b*) increase in the resistance presented by the afferent glomerular arterioles or the preglomerular vascular bed, (*c*) thickening of the glomerular membranes to such an extent that equilibrium in respect to filtration pressure is not approached as closely as in the normal kidney, or (*d*) by obliteration of glomeruli. Decreased blood pressure is clearly ruled out, since all these subjects have a mean pressure above normal; although the importance to be attached to the contributions of (*b*) and

[4] Chesley and Chesley (4) have examined C_D in eleven hypertensive women and have also observed a decrease in this datum, associated with an increased filtration fraction, as estimated from the urea clearance, in eight of their patients. Since C_{IN} and Tm_D were not determined, it is not possible to subject their data to the interpretive analysis to which our data are subjected in this paper. On the whole, however, their data are in agreement with our present observations.

(*c*) cannot be evaluated accurately, their total effect in reducing filtration rate, between the extremes of Tm_D, is probably quantitatively less than is the contribution of (*d*).

In spite of the absolute reduction in C_{IN}, its relative value per unit of functional tubular tissue (C_{IN}/Tm_D) exceeds the mean normal value, M, in forty-three out of sixty subjects, and in twenty-one of these it falls above $M + 2\sigma$. Three factors might operate to maintain a relatively high filtration rate in functional glomeruli: (*a*) increased mean systemic pressure, (*b*) dilatation of the afferent glomerular arterioles, and (*c*) the formation of impotent nephrons (12). (In the view that filtration equilibrium is approximately reached in the normal glomerulus (14), it is improbable that increased permeability of the glomerular membranes could significantly increase the filtration rate.) Again, we cannot immediately distinguish between these alternative possibilities, but for our present purposes this fact is not important since the net result upon the blood flow to the residual functional tissue will be the same; namely, elevated mean systemic pressure or afferent dilatation will, by increasing glomerular pressure, increase the postglomerular blood flow, thus producing an active hyperemia; while impotent nephrons will produce a vicarious hyperemia in such functional tissue as may be perfused by the vestigial vascular channels related to the now defunct tissue.

In the expectation that any abnormal value of C_{IN}/Tm_D may be expected to be accompanied by an abnormally high value of C_D/Tm_D, we may attempt a further analysis of the blood flow picture presented in Figure 1, as follows: we will delete from Figure 2 all those subjects, twenty-one in number, in whom C_{IN}/Tm_D exceeds $M + 2\sigma$, since, in the statistical series of normal subjects on which M is based, $\pm 2\sigma$ should con-

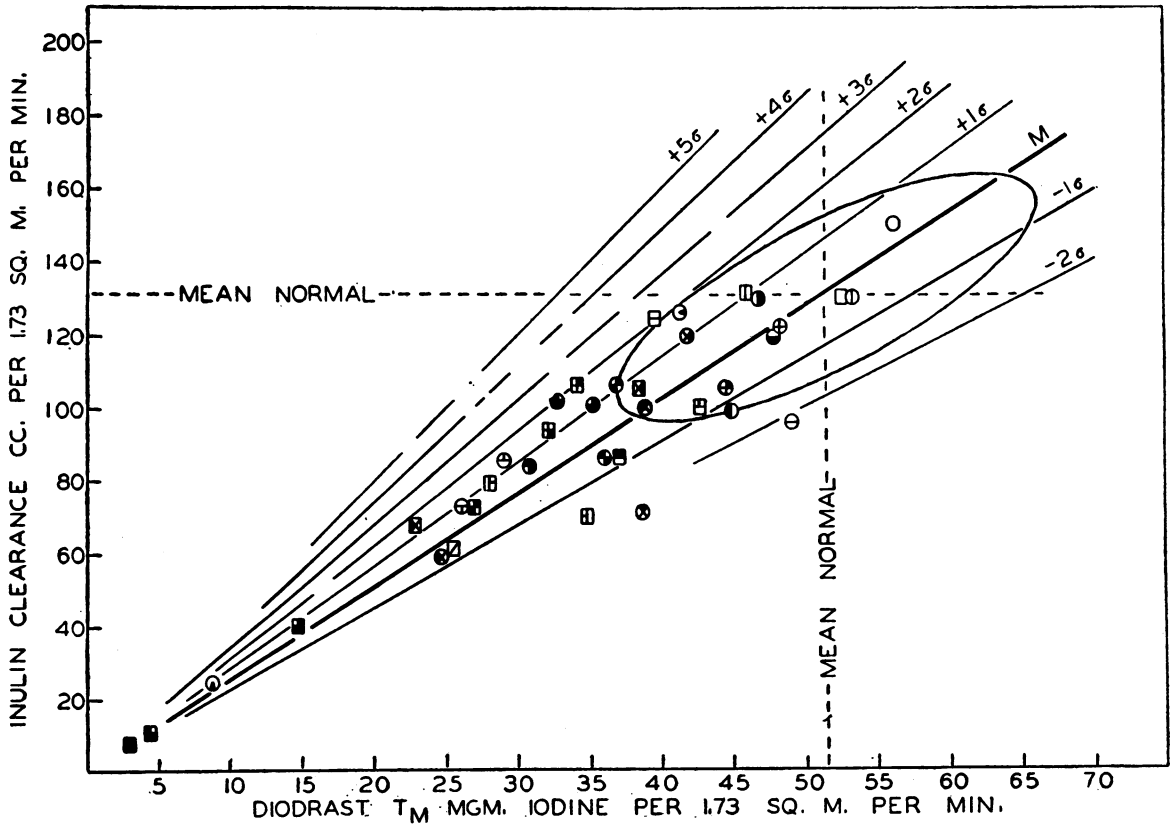

FIG. 3. FIGURE 2 AFTER DELETION OF SUBJECTS IN WHOM C_{IN}/Tm_D EXCEEDS THE MEAN NORMAL VALUE PLUS TWICE THE STANDARD DEVIATION

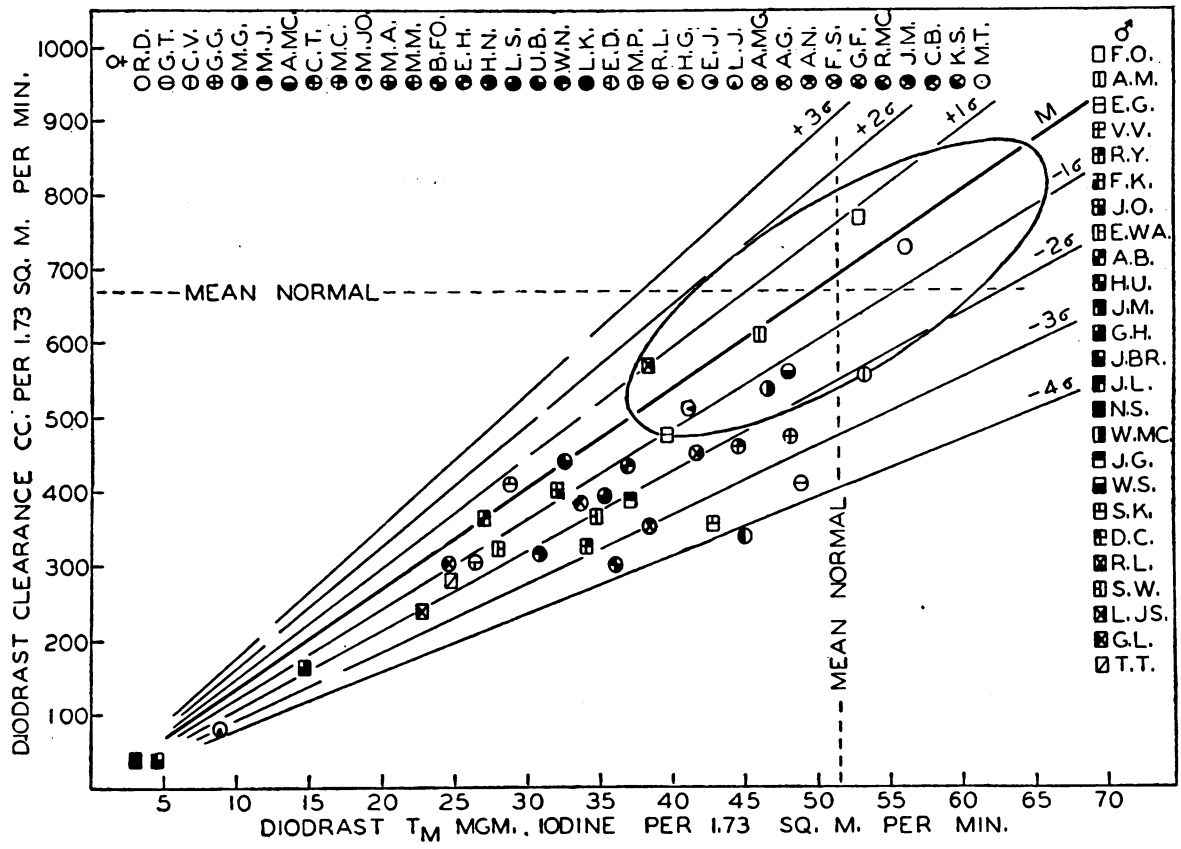

FIG. 4. FIGURE 1 WITH SAME SUBJECTS DELETED AS IN FIGURE 3

tain 95 per cent of the observations.[5] For brevity we may designate the deleted subjects as Group A, the remaining subjects as Group B.

The new picture, after this deletion is effected, is given in Figure 3, which shows that the subjects in Group B are approximately equally distributed above and below *M*.

Figure 4 is Figure 1 with the Group A subjects deleted. In reference to this figure, we may say that, when we exclude from consideration those subjects who show a high filtration rate per unit of functional tubular tissue (presumably because of elevated glomerular pressure and/or the formation of impotent tubules), and in whom we may expect active or vicarious hyperemia to occur in consequence of this fact, the renal blood flow per unit of functional tubular tissue in the remaining subjects is with three exceptions below the mean normal value, and in many subjects it falls to very low values. These facts lead us to conclude that, so far as the effective blood flow is concerned, some factor is operative in these subjects which tends to produce a relative ischemia of the residual functional tissue. This ischemic factor may, of course, be operative in the subjects in Group A, but offset by such factors as were enumerated in defining that group. Since all these subjects have an elevated mean blood pressure, the cause of this ischemia must be an increase in the resistance to perfusion offered locally in the kidney.

3. *Locus of increased renal resistance*

The question whether the increased renal resistance deduced above involves obstruction on the afferent or efferent side of the glomerular bed can be examined by reference to the filtration

[5] This is, of course, an arbitrary selection, but the selection of "limits" in any physiological variable is, under statistical principles, an arbitrary operation and at best expresses a probability.

fraction (C_{IN}/C_D), as plotted in Figures 5 and 6. In normal subjects the filtration rate tends to remain constant when the renal blood flow is increased during pyrogenic hyperemia or decreased by adrenalin, a circumstance which indicates that the locus of changing resistance is at the efferent glomerular arteriole (3, 14).[6] Where the filtration rate is constant, the filtration fraction, *FF*, must vary inversely as C_D, *i.e.*, *FF* when plotted against C_D/Tm_D will describe a rectangular hyperbola, as shown in Figures 5 and 6. In these figures the solid curve and its two dotted parallels represent respectively the course of *FF*, if $FF \times C_D/Tm_D = 2.56 \pm 2\sigma$, the mean normal value of C_{IN}/Tm_D. The hexagon represents an arbitrary area which contains 95 per cent of the normal data under basal conditions; under adrenalin, *FF* rises above the limits of the hexagon, while during pyrogenic hyperemia it falls below the hexagon, though in both instances it remains between the dotted parameters of mean $C_{IN}/Tm_D \pm 2\sigma$ (see Figure 2 of our previous paper (14)).

The data on hypertensive subjects, as shown in Figures 5 and 6, are divided into two categories: those to the left of the vertical dotted line represent basal observations, and those to the right represent observations made during hyperemia. (The data on experimentally induced hyperemia will be discussed in the next section. The effects of adrenalin on hypertensive subjects have not been examined.)

The unselected hypertensive series as a whole (basal data, Figure 5) shows a wide scattering of *FF* relative to C_D, though in almost all instances *FF* is greater than the mean normal value of 19 per cent, and may reach values as high as those reached under the maximal action of adrenalin in normal subjects. Since the relative ischemia in these hypertensive subjects is correlated with a rise in *FF*, we conclude that the ischemia is the result of increased resistance beyond the glomeruli. With no serious consequences if the assumption is not wholly correct, we may suppose that the major increase in resistance in the hypertensive kidney is in the efferent arterioles, rather than located in part in the postglomerular capillary bed. (We recognize that this assumption may have to be abandoned when further information is available on the dynamics of the postglomerular circulation.)

In many instances *FF* is higher than could be explained, in terms of the behavior of the normal kidney, on the basis of efferent constriction alone. Such a result is to be expected if, as suggested in Section 2, there exist in some hypertensive subjects impotent nephrons which are supplying glomerular filtrate but not clearing the postglomerular blood of diodrast, or if the filtration rate in some nephrons is increased by elevated glomerular pressure. Consequently, we have deleted from Figure 5 those subjects in Group A, as defined above, who on the basis of a high C_{IN}/Tm_D ratio were deleted in Figures 3 and 4. The selected group which remains (Group B) in Figure 6 (referring to the basal data only) now shows values of *FF* which, though elevated above the mean normal value, nonetheless fall within the normal parameters with respect to C_D/Tm_D. In short, Group B presents an uncomplicated picture of renal ischemia induced by moderate to severe efferent arteriolar constriction.

4. *The induction of renal hyperemia in hypertensive subjects*

We have previously reported that certain nonspecific pyrogens in adequate doses, accompanied

[6] Lamport (J. Clin. Invest., 1941, **20**, 535, 545) has recently offered cogent and constructive criticisms of our quantitative interpretation of afferent and efferent regulation in the glomerular circulation. Lamport's equation defining the filtration rate when variations in resistance are located in the afferent arterioles yields results not greatly differing from our own, and in any case is of less importance in the present problem than is the equation dealing with variations in efferent resistance. Here our equation leads to a constant filtration rate over a wide range of renal blood flow (neglecting subsidiary factors such as viscosity, etc.), while Lamport's equation leads to a reduction in filtration rate as the blood flow is either increased above or reduced below the basal value by pure efferent constriction; *i.e.*, reduction in blood flow with constant filtration rate would, according to Lamport, require some measure of simultaneous afferent dilatation, which, of course, might follow passively in consequence of an increase in glomerular pressure. Without considering here the premises and equations involved, we may record our uncertainty concerning the validity of this particular interpretation, and note that, even accepting Lamport's equation, which requires some afferent dilatation, ***efferent constriction*** is still indicated as the cause of the relative renal ischemia in group B of our hypertensive subjects.

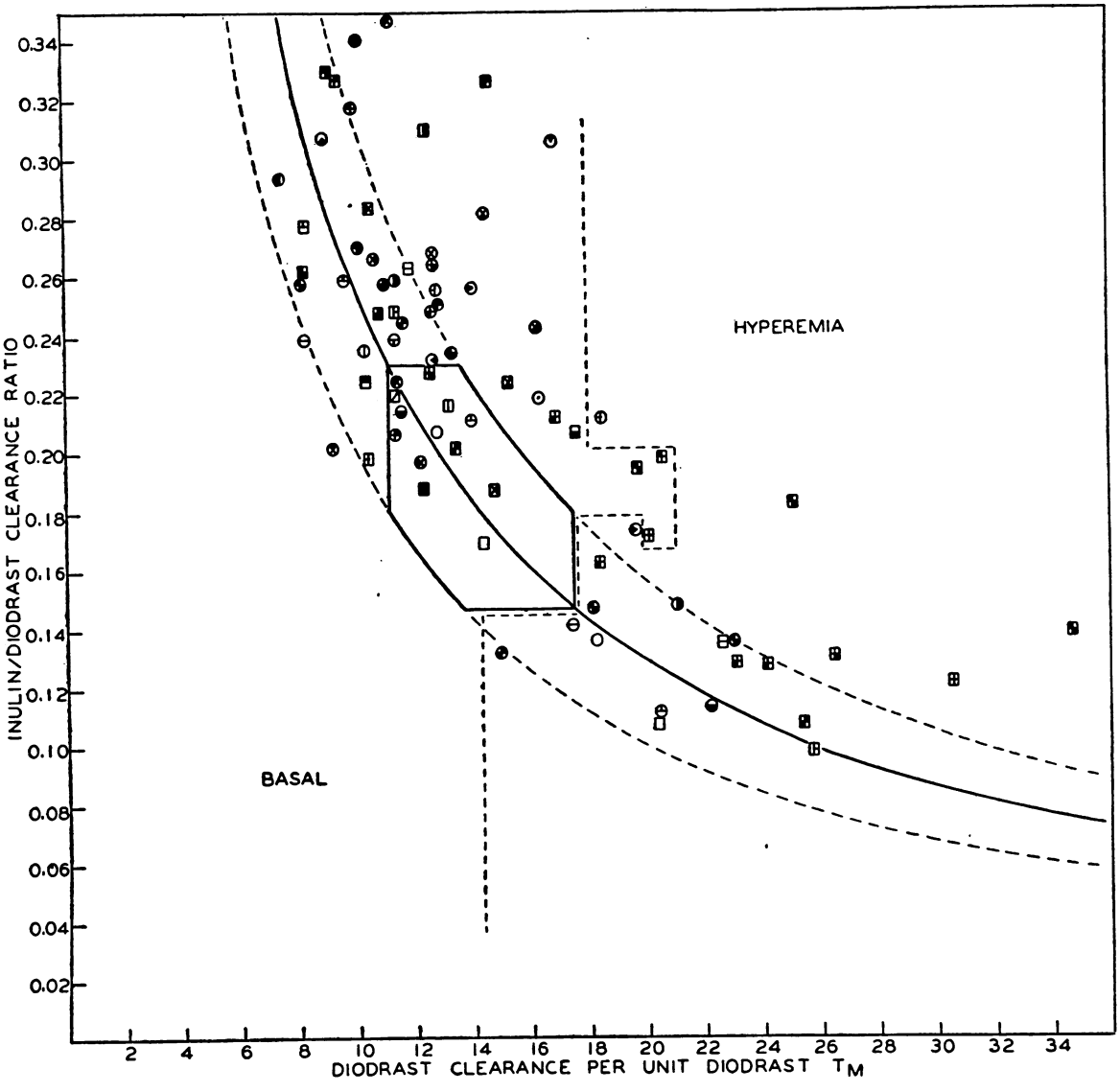

FIG. 5. INULIN/DIODRAST CLEARANCE RATIO (FILTRATION FRACTION) IN HYPERTENSIVE SUBJECTS, RELATED TO THE EFFECTIVE RENAL PLASMA FLOW PER UNIT OF TUBULAR EXCRETORY MASS

The statistical background is again taken from data on normal subjects (14), the hexagon containing 95 per cent of the normal basal data. Basal observations on hypertensive subjects are shown to the left of the vertical dotted line, observations during induced renal hyperemia to the right.

by amidopyrine to reduce or eliminate the general autonomic disturbances of the pyrogenic reaction, produce in normal subjects a moderate to very marked renal hyperemia by efferent dilatation (3, 13, 14). Since this is the only method known to us to induce renal hyperemia, we have utilized it in the examination of the vascular responses of the kidney in hypertensive subjects. The pyrogen used here was a sample of highly pyrogenic inulin which had been used extensively for this same purpose in normal subjects.[7]

[7] The physiological mechanism of this hyperemia is unknown. That it does not involve inhibition of renal vasoconstrictor fibers is suggested indirectly by the fact that in normal subjects the renal vasoconstrictor fibers are basally inactive (17) and in hypertensive subjects renal denervation does not consistently produce renal hyperemia (1, 2, 7). That it does not involve activation of sympathetic vasodilator pathways is suggested by our observa-

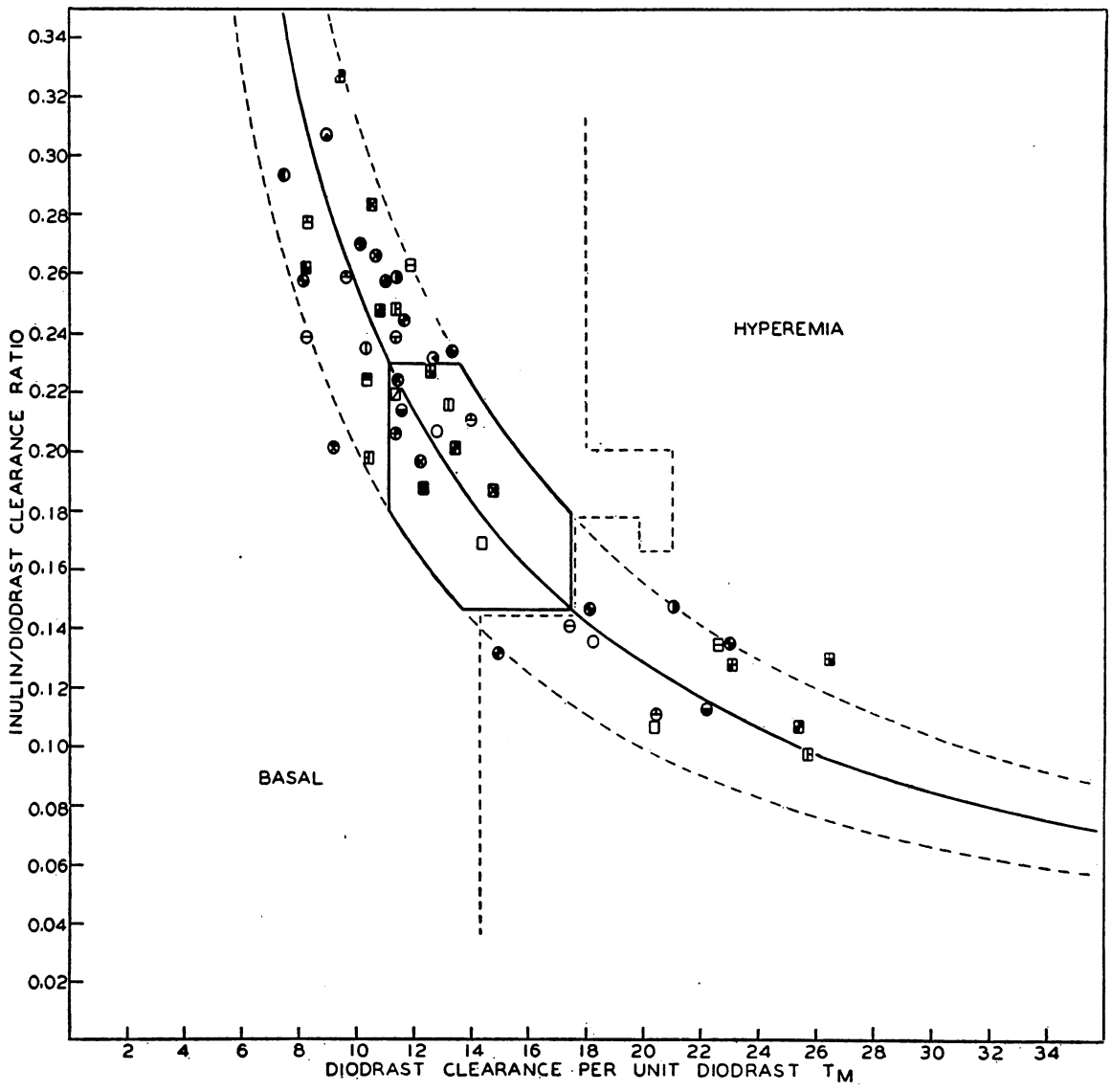

FIG. 6. FIGURE 5 WITH THE SAME SUBJECTS DELETED AS IN FIGURES 3 AND 4

Our method has been to administer 0.6 gram of amidopyrine every four hours, beginning at 1 p.m. on the afternoon before the test. At 8 a.m. on the morning of the test 100 to 200 mgm. of the pyrogenic inulin, dissolved in saline and sterilized by a single boiling of ten minutes, were given intravenously. Clearance collections were begun about 9:30 a.m., three ten- to fifteen-minute periods being taken for C_D and five periods for Tm_D. The results of these observations are given in Table III. In compiling this table we have chosen as a standard of reference for the basal state the last preceding observation made under basal conditions.

tions that a fair degree of pyrogenic hyperemia was observed in three sympathectomized patients, E. H., W. Mc. and B. Fo., as recorded in Table III. But since vasodilator fibers may conceivably reach the kidneys by other than the thoracico-lumbar sympathetics, this does not conclusively demonstrate the humoral nature of the renal reaction.

Until more is learned about the mechanism of the hyperemic reaction itself, it is useless to speculate why pyrogen should produce hyperemia in hypertensive subjects where ischemia is presumably referable to a humoral pressor agent.

In comparing the hyperemic with the basal data, it will be observed that with few exceptions the change in filtration rate is negative, but so slight as to be scarcely significant. (The marked fall in filtration rate in H. U. on May 1, 1940, was associated with a severe reaction involving a period of acute peripheral circulatory failure.)

Only two subjects out of twenty (J. M. and H. G.) failed to show an increase in C_D exceeding 25 per cent of the basal value; since these subjects had marked retinopathy and marked proteinuria (Table I), as well as the lowest values of Tm_D of all the subjects examined with pyrogen, and both died of the renal disease within a month of the observation, we infer that their failure to respond is related to the circumstance that they were in the advanced stage of the disease. It is difficult to evaluate the degree of hyperemia in the other subjects quantitatively. Normal subjects vary considerably in sensitivity to pyrogen and this is doubtless true of hypertensive subjects. In the latter, C_D/Tm_D during hyperemia ranges from 17.5 to 34.7 and averages 22.8, figures which are comparable with those shown in Figure 2 of our previous paper (14) on a smaller series of normals in which hyperemia was induced; consequently, we feel that the magnitude of hyperemia obtained in the hypertensive subjects is equal to that obtained in normals.

With regard to changes in FF during hyperemia, we refer again to Figures 5 and 6, where the hyperemic data are shown to the right of the vertical dotted line. Where FF is abnormally high under basal conditions (*i.e.*, lying outside the normal parameters, as in subjects H. U., V. V. and L. J.), it retains this anomalous relation during hyperemia, a result consonant with the interpretation that in these subjects C_{IN} is high, relative to Tm_D, because of the existence of impotent tubules and/or elevated glomerular pressure. Deletion of those subjects (Group A) who were removed for this reason from Figures 3 and 4 leaves a group (B) in which FF falls within the normal parameters basally, and remains there during hyperemia (Figure 6).

Were the hyperemia attributable to dilatation of the afferent glomerular arterioles, we would expect both C_{IN} and FF to increase markedly; our failure to observe this effect in a single instance reinforces our previous conclusion that the ischemia of the hypertensive kidney is a consequence primarily of increased tone of the efferent glomerular arterioles.

5. *Humoral origin of increased efferent tone*

That the increased efferent tonus in essential hypertension is not caused by a structural, obstructive lesion is, we think, demonstrated by our observations that the renal blood flow can be increased and the filtration fraction lowered by agents which produce these effects in the normal kidney.

That the efferent hypertonus is not of neurogenic origin is indicated by the fact that various operations intended to denervate the kidneys fail in general to increase the renal blood flow, or if the mean blood pressure is not substantially reduced, to lower the filtration fraction (1, 2, 7). The single subject (E. H.) examined by us before and after unilateral sympathectomy [8] showed no difference in C_D or FF between the operated and unoperated side during the development of pyrogenic hyperemia. Nor are these values significantly different from other hypertensive subjects in the two subjects (W. Mc. and B. Fo.) who were examined postoperatively. Admitting the difficulty of establishing complete denervation of the human kidney, and recognizing that the above evidence does not logically exclude a local or myogenic origin for the increased efferent tone, we tentatively accept the humoral theory.

Page and Helmer (11) have prepared a crystalline pressor substance (angiotonin) by the reaction between renin and plasma, and Corcoran, Kohlstaedt and Page (5, 6) have shown that this substance produces renal ischemia by efferent arteriolar constriction in dog and man. Through the courtesy of Doctors Page and Helmer, who have supplied us with some of this substance, we have been able to confirm their observation in normal man. These investigators have suggested that angiotonin is responsible for the increased efferent tonus in essential hypertension. The present study throws no light on this question, but from our experience with pressor amines such as adrenalin (3), neosynephrin, cobefrin, tyramine, paredrinol, etc.

[8] This subject was sympathectomized by Dr. Norman Freeman.

(unpublished data), it seems probable to us that a variety of substances will constrict the efferent arterioles and, until further evidence is available, we hesitate to accept the view that angiotonin or any other one substance is the specific humoral agent involved in hypertensive disease in man.

6. Changes in diodrast Tm *during hyperemia*

Diodrast Tm, conceived to be an index of the total active tubular (excretory) tissue (15), has special significance in the hyperemic studies inasmuch as tubules rendered inactive by ischemia under basal conditions might become active, in consequence of opening of vascular channels, during hyperemia. In this connection it must be noted that the contribution of a particular tubule to Tm_D will be maximal only so long as the plasma flow to the tubule is adequate, at the existing diodrast plasma concentration, P_D, to effect saturation. Consequently, the use of Tm_D to detect inactive (ischemic) tubular tissue is contingent upon P_D in the sense that the higher P_D is, the lower must be the blood flow to the ischemic tubular tissue before the latter will cease to contribute to Tm_D. In terms of the overall function of the two kidneys, we may calculate the load of diodrast carried to the tubules as the product of the plasma flow times P_D, minus the quantity of diodrast excreted through the glomeruli; if we take the plasma flow equal to C_D, as observed immediately before Tm_D measurement, then

$$\text{tubular load} = P_D(C_D - FWC_{IN}),$$

where FW is the fraction of free or ultrafiltrable diodrast at the plasma level, P_D, actually present during Tm_D determination. It is convenient to refer the load to Tm_D, as in column 10 of Table III.

In the observations made here, the load/Tm_D ratio has with very few exceptions been greater during hyperemia than during basal conditions (in part because of the increase in C_D); this circumstance would operate, quite apart from any increase in blood flow, to saturate any tubules which might have been unsaturated in consequence of even severe ischemia during the basal state.

In three subjects (C. V., E. H. and J. M.) Tm_D decreased during hyperemia by more than 10 per cent; in C. V. there was a distinct fall in mean blood pressure during Tm_D measurement, which may have reduced perfusion to some parts of the kidney. J. M. was examined during the accelerated phase of the disease and died within one month after the last observation; at necropsy the kidney showed multiple abscesses and necrotizing arteriolar lesions. The observations on E. H. appear to be technically satisfactory. In seven subjects Tm_D increased by more than 10 per cent, the largest increase being +33 per cent (H. G.); while in ten subjects there was no significant change (less than 10 per cent) in Tm_D during hyperemia, despite changes in C_D ranging up to 88 per cent.

In interpreting the fact that Tm_D fails to increase in so many subjects during hyperemia, it may be noted that, although the pyrogenic reaction appears to involve a humoral vasodilatory agent, so far as the efferent arterioles of the kidney are concerned, this is probably not the only vasomotor disturbance. Considered alone, it is difficult to predict whether efferent arteriolar dilatation would necessarily restore perfusion in portions of the renal parenchyma to which the blood flow had been reduced by functional constriction or obstructive lesions in the preglomerular arterial bed; and when combined with a decrease in mean blood pressure and possibly with changes in the status of the preglomerular arterioles, it is not on the whole surprising that a variety of results may be obtained, even in the same individual, in consequence of the experimental induction of hyperemia.

What appears to us to be the important fact is that in some subjects a significant increase in Tm_D has been observed during hyperemia, demonstrating that substantial portions of renal parenchyma capable of excreting diodrast were not available to perfusion under basal conditions.

It is not to be concluded, however, that the local ischemia is necessarily a direct consequence of the increased tone of the efferent glomerular arterioles. We have, in general, been unable to produce any decrease in Tm_D with adrenalin in normal subjects, and it seems improbable to us at the present time that efferent constriction in the normal kidney could completely obstruct the glomerular, and hence the postglomerular, circu-

lation. In view of the well-recognized fact that the arteriolar lesions in the hypertensive kidney are most evident in the preglomerular and afferent arterioles, and that these lesions are in many instances of such a nature as to narrow or obstruct the lumen, we cannot avoid the inference that it is in these lesions that we must at least in part seek the basis of occluded renal parenchyma.

7. *Changes in diodrast* Tm

With regard to the constancy of Tm_D, in studies to be reported elsewhere we have been unable in normal subjects to produce significant changes in this value by the induction of hyperemia or by the administration of adrenalin or caffeine. In ten of the hypertensive subjects listed in Table II we have obtained fair agreement in Tm_D on repeated examination (G. H., E. D., L. K., R. Y., M. Mc., G. G., M. A., F. K., L. J. and H. U.), in some of these over a period of two to three years. In two subjects, however (M. G. and M. Jo.), there have been notable but unexplained changes.

Between December 20, 1937, and February 9, 1938, when the patient M. G. had been continuously in the hospital, her Tm_D fell from 53.2 to 41.3. This latter value was obtained again after a three-year period. It is, of course, possible that this represents a rapid progression of renal disease, but this interpretation is rendered less certain by our observations on M. Jo.

In M. Jo. Tm_D decreased from 41.3 to 29.8 between March 21, 1938, and May 1, 1939, only to rise again to 35.9 by April 4, 1941. Even more striking is the increase from 35.9 to 45.1 on hospitalization from April 4 to May 7, 1941. We have earlier in the paper given reasons for believing that there is a progressive reduction in Tm_D during the course of hypertensive disease and our experience with M. Jo. suggests that in some instances there may occur marked transient fluctuations in this value without apparent clinical changes. Such fluctuations might be caused by extreme focal ischemia of tubular tissue which excluded it from perfusion during Tm_D measurement, or by intrinsic loss of capacity on the part of the tubules to excrete diodrast with subsequent regeneration or compensatory hypertrophy in other nephrons.

With regard to changes in Tm_D, it is pertinent that White, Heinbecker and Rolf (18) have demonstrated that in the dog Tm_D is substantially reduced by anterior hypophysectomy, while Winternitz and his collaborators (19) have shown that *in vitro* autolysates of renal tissue contain cytotoxic agents which attack arteriolar and other tissue throughout the body, and such agents, if present in hypertensive disease, might also be injurious to tubular function. Our data indicate that the progressive loss of tubular function, as measured by Tm_D, is characteristic of the course of hypertensive disease, but whether or not the same factors produce both temporary and progressive changes in tubular function is unknown.

SUMMARY AND CONCLUSIONS

The filtration rate (C_{IN}), diodrast clearance (C_D) and the maximal rate of tubular excretion of diodrast (Tm_D) have been examined in sixty subjects with essential hypertension. Comparison of the data with those previously reported for the normal kidney reveals the following facts:

An extreme reduction in Tm_D occurs in advanced states of the disease, and for the entire series of sixty subjects Tm_D is below or in the lower normal range; these facts lead us to infer that the disease is characterized by a progressive impairment of tubular function which proceeds at varying pace in different subjects.

In some individuals impairment of tubular function appears to outrun impairment of glomerular function (formation of impotent tubules), so that the filtration rate remains within the limits of normal variation when Tm_D has been substantially reduced. In the nature of the renal circulation, elevation of the mean systemic blood pressure or the formation of impotent tubules may increase the quantity of diodrast-containing blood perfusing the residual functional tissue. We believe that in either case the anomalous condition will be revealed by the presence of a high filtration rate per unit of functional tubular tissue.

Deleting such anomalous instances, the effective blood flow per unit of functional tubular tissue, or the ratio C_D/Tm_D, in the remaining subjects, ranges downward from the mean normal

to highly subnormal values, indicating relative renal ischemia. Since this ischemia is associated with an elevation of the filtration fraction, it is attributed to increased tone of the efferent glomerular arterioles. On the available evidence, this increased efferent tone may in turn be attributed to the presence of one or more pressor substances in the blood. The increased efferent tone is functionally reversible, in that renal hyperemia, associated with a fall in filtration fraction (efferent dilatation), follows the administration of suitable doses of pyrogen, as in normal subjects. The absolute values of C_D/Tm_D in hypertensive subjects during hyperemia are of the same order of magnitude as in normals during the hyperemic reaction.

In most hypertensive subjects, Tm_D has been reasonably constant over a considerable period, and has not increased during pyrogenic hyperemia. In some subjects, however, Tm_D was increased during hyperemia, indicating that in these and perhaps in other subjects substantial quantities of tubular tissue may be ischemic under basal conditions. Spontaneous changes in Tm_D have been observed which may reflect changes in the quantity of tubular tissue available to perfusion or trophic changes in the excretory tissue itself.

In brief, the functional picture presented by the hypertensive kidney is consonant with the theory that there is present in the blood in hypertensive disease one or more pressor substances which produce a reversible renal ischemia by constriction of the efferent glomerular arterioles. In addition, there is profound impairment and ultimate destruction of tubular function. Which of these precedes the other is as yet undetermined.

There is no evidence in the present investigation to warrant the conclusion that renal ischemia is the primary cause of essential hypertension. The renal ischemia demonstrated here, which has its origin in increased tone of the efferent glomerular arterioles, appears to be one of the sequelae of the hypertensive process. We may place on record our belief that primary renal ischemia in man can, under proper quantitative circumstances, initiate a hypertensive process, but whether or not the secondary ischemia, associated with efferent hypertonus, which is present in hypertensive subjects generally, contributes to the progress of the disease cannot be answered from this study. Alternatively, the possibility cannot yet be excluded that the appearance of pressor and cytotoxic substances in the blood follows a metabolic disorder in the kidney or in other organs, and is wholly independent of renal ischemia.

The analysts in this work have been Helen A. Keigher, Katharine S. Tilson, Frances E. Marx, Betty J. Crawford and Martha J. Barrett. We are indebted to them, and to Nurse Ann S. Rivoire and Nurse Helen R. McGuire for their unfailing cooperation.

The clearance technique and analytical methods used in this study were identical with those described in a previous paper (9). The inulin for the most part was ampouled material obtained from the U. S. Standard Products Company, Madison, Wisconsin; the diodrast, which was supplied in part by courtesy, was obtained from Winthrop Chemical Company, New York; and the saline was prepared by the Sterisol Ampoule Company (Schering and Glatz, Inc.), New York.

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