RENAL BIOPSY STUDIES CORRELATED WITH RENAL CLEARANCE OBSERVATIONS IN HYPERTENSIVE PATIENTS TREATED BY RADICAL SYMPATHECTOMY[1]

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The morphologic changes in the kidneys of patients who have died from essential hypertension and its complications are well known. The structural pattern at death is informative, but it offers little clue as to the intervening degenerative processes responsible for the terminal picture. A noteworthy effort has been made in recent years to fill the void. Various investigators (1, 2, 3) have applied the ingenious renal clearance procedures devised by Smith (4) to hypertensive patients and have obtained consistent and definite data. Anatomical studies also have been pursued in living patients, and recently one of us (B. C.) reported a small series of renal biopsies, taken during life from patients with various degrees of essential hypertension (5). The specimens were obtained during operation for sympathectomy, and all showed diffuse vascular disease. Since this preliminary report the number of biopsies has been increased to more than 100.[2] No attempt was made at that time to consider anatomic findings in relation to renal clearance data or to the clinical status. In the first portion of the present communication, such an attempt has been made, and the microscopic appearance of renal tissue from 20 living patients has been correlated with the function of the kidneys. The quantitative clearance procedures include measurement of rate of formation of glomerular filtrate, renal plasma flow, and maximal capacity of the tubules to excrete diodrast.[3] The second portion of the paper deals with renal clearance observations as affected by sympathectomy.

CORRELATION OF RENAL BIOPSIES AND RENAL CLEARANCE DATA

The clinical status of each of the 20 patients conformed to the type usually associated with arterial hypertension. Headache, dyspnea, vertigo, blurring of vision, nausea, vomiting, frequency of urination, nocturia, precordial pain, palpitation, paresthesia, faintness, weakness, and nervousness were frequent complaints. The systolic blood pressure usually was over 200 and the diastolic over 100 mm. Hg. The majority had evidence of hypertensive heart disease as suggested by the electrocardiogram and the measurement of heart size by x-ray. The patients were equally divided in regard to sex. Five of the females gave a history of having had a kidney disturbance or elevation of blood pressure during one or more pregnancies. Two males gave a history of having had

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[2] A report on the microscopic findings in the first 100 cases will be made separately by two of us (B. C.; R. H. S.) J. A. M. A. (In press.)

[3] The clearance studies were performed by two of us (J. H. T. and R. S. M.) according to methods described by Smith and associates (4, 6). The patients were prepared for the test by allowing them to consume one liter of tap water, 12 and 2 hours, respectively, before each test. Most urine specimens were collected by a soft rubber ureteral catheter. Levels of mannitol and inulin in the plasma were maintained at approximately 125 mgm. per 100 cc. The plasma level of diodrast at low levels varied between 1 and 2 mgm. per 100 cc. At high plasma levels for determination of TmD, it ranged from 40 mgm. to 25 mgm. per cc. The duration of the average collection period was 10 minutes. Blood samples for determination of concentration of clearance constituents in the serum were taken at the half-way time in many periods. When this was not deemed necessary, the concentrations were interpolated from data collected during periods immediately before and after. Venous bloods were taken at all times. A stop-watch was used for timing. The observations on glomerular filtration, renal plasma flow, and the effective renal blood flow are the mean for 4 or more 10-minute collection periods. The observations for TmD are the mean of 3 10-minute periods. All the data are corrected for a body surface area of 1.73 sq.M. The determinations were carried out with the patients in the horizontal position in a quiet room where the temperature was 70° F.

cystitis. Three patients had had a cerebral hemorrhage before admission. The duration of symptoms attributed to hypertension varied from 6 months to 14 years.

Particular attention was given to the examination of the ocular fundi. The eyeground findings were graded 1 through 4; the higher the grade, the more extensive the vascular damage observed. Fifteen showed grade 2, 3, or 4.

Clinical tests of renal function included ability to concentrate solids following abstinence from fluid for 12 hours, urinary excretion of phenolsulfonephthalein dye 15 minutes after 1.0 cc. had been given intravenously, determination of concentration of non-protein nitrogen in the serum, and intravenous pyelography. These procedures gave results which were interpreted usually as consistent with unimpaired renal function. None had an elevation of the non-protein nitrogen in the serum, nor was the specific gravity of the urine fixed at a low level. All except 2 were able to concentrate to 1.020. Five were unable to excrete 25 per cent or more of phenolsulfonephthalein dye in the first 15 minutes after the intravenous injection. The examination of the urinary sediment, however, showed casts or blood cells in a preponderant number, while nearly half of the patients showed albuminuria.

An extensive removal of the sympathetic chains by one of us (R. H. S.) was performed at operation (*7*). In most patients, the lower 4 dorsal ganglia and the upper 1 or 2 lumbar ganglia were excised as well as a splanchnic denervation, removing the great splanchnic nerve from the semilunar ganglion to the mid-thoracic level. The extensive retroperitoneal exposure permitted access to the kidney and the opportunity to excise a portion for study. The specimens taken were 6 to 7 mm. wide and 5 mm. deep. Specimens were taken from both kidneys in a few patients. The gross appearance of the kidneys, when fully exposed at operation, was not remarkable. Usually, the size was normal and only rarely was the capsule firmly adherent to the renal cortex. A few minute scars were visible in approximately one-third of the cases, while the remainder of the parenchyma was smooth and appeared normal.

The 20 biopsies were graded 0, I, II, III, IV by one of us (B. C.), according to the severity of the vascular lesions. The criteria for these grades are described in more detail in a study of the large series of 100 renal biopsies of hypertensive patients.[4] A valid objection might be raised that a biopsy is not an adequate sample of the whole kidney. However, great care was taken in each case to select a representative piece for biopsy, and in 25 patients out of the larger series of 100, specimens removed from both kidneys were of the same grade. It is noteworthy that not all specimens graded I and II appeared abnormal at casual inspection. Careful search, however, showed vascular changes in all 20 patients except Nos. 19 and 20, which were graded 0. The vessels were divided into three groups: (*1*) small arteriole, the external diameter of which measured up to 25 microns; (*2*) large arteriole, from 25 to 50 microns; and (*3*) small artery, greater than 50 microns. The last group rarely exceeded 100 microns, since the specimens were from the peripheral portions of the cortex. The vascular lesions could be classified readily under the three terms employed by Moritz and Oldt (8): intimal hyalinization, medial hypertrophy and degeneration, and endothelial hyperplasia. No necrotizing arteriolitis was observed, confirming the theory that this lesion is a terminal one. Most of the specimens showed combinations of these types, but in a few, one type was predominant. No specific type of process was limited to any one of the different sized vessels, although, by and large, the arteries showed endothelial hyperplasia with reduplication of the internal elastic lamella or fibrous intimal thickening, and the arterioles showed either medial hypertrophy or intimal hyalinization or very frequently both processes. Although the biopsy grades were based solely on the severity of the arterial and arteriolar disease, it is interesting to note that a large proportion of the glomeruli appeared normal in most of the cases. Glomerular changes were entirely absent throughout the biopsied material of kidneys classed under grade I. Some slight thickening of the capillary walls and an occasional sclerosed glomerulus were seen in the kidneys of grade II; there was otherwise little change in the glomerular tufts. In the more advanced cases, grades III and IV, often associated with visible scarring, the glomeruli adjacent to or within the scarred area were partially or com-

[4] See footnote 2.

pletely hyalinized. Careful examination was made of the juxta-glomerular group of cells (9) for evidence of hyperplasia, but no abnormality was observed. There were 3 patients classified in grade IV, 8 patients in grade III, 3 patients in grade II, 4 patients in grade I, and 2 patients in grade 0. Renal vascular lesions have been so well illustrated in Moritz and Oldt's paper (8), that it was felt unnecessary to include photomicrographs in this report.

Grade IV renal vascular disease. Advanced vascular disease in both arteries and arterioles was present in the specimens removed from 3 patients. The average glomerular filtration rate and renal plasma flow were 64 cc. and 283 cc. per minute, respectively (Table I). This represents a 50 per cent depression below the normal mean filtration rate, and a 60 per cent depression in renal plasma flow. Patient No. 2 died of a cerebral hemorrhage and uremia before discharge from the hospital.

TABLE I

Correlation of renal clearance observations with renal biopsies *

Patient number	Age	Blood pressure	Retinal changes	PSP excretion in first 15 minutes	Glomerular filtration rate	Plasma flow	Effective whole blood flow †	Diodrast iodine Tm	Filtration fraction
			grade		*cc. of plasma cleared per minute*			*mgm. per minute*	*per cent*
GRADE IV RENAL VASCULAR DISEASE									
1	46	208/138	3	10	56	220	370	19	25
2	36	210/142	3	10	67	250	420		27
3	50	230/110	2	35	69	380	680		18
				Average	64	283	457		23.3
GRADE III RENAL VASCULAR DISEASE									
4	38	190/140	4	25	86	400	660		21
5	34	175/135	1	40	90	480	840		19
6	27	225/145	1	25	70	420	780		17
7	34	205/120	3	30	86	430	770		20
8	34	220/140	3	40	71	320	570		22
9	45	205/112	2	20	105	500	850		21
10	30	215/145	1	45	86	450	760	46	19
11	35	230/120	1	35	121	510	720	41	24
				Average	89.4	438.8	743.8	43.5	20.4
GRADE II RENAL VASCULAR DISEASE									
12	48	204/116	2	25	100	450	750	37	22
13	38	180/100	2	35	90	490	880	42	18
14	40	180/110	1	20	83	470	800	43	18
				Average	91	470	810	40.7	19.3
GRADE I RENAL VASCULAR DISEASE									
15	23	163/114	1	45	127	700		67	19
16	37	148/98	2	38	114				
17	32		1	40	100				
18	56	200/126	1	20	76	410	710	45	19
				Average	104.2	552		56	19
GRADE 0 RENAL VASCULAR DISEASE									
19	39	144/122	1	40	92	520	990		18
20	18	140/100	3	40	96	730	1210	42	13
				Average	94	625	1100		15.5

* The 20 cases are divided into 5 groups according to the grade of renal vascular disease found in the kidney biopsies taken at operation. The renal clearance data are given for the patients in each group.

† Calculated from renal plasma flow by taking hematocrit into account.

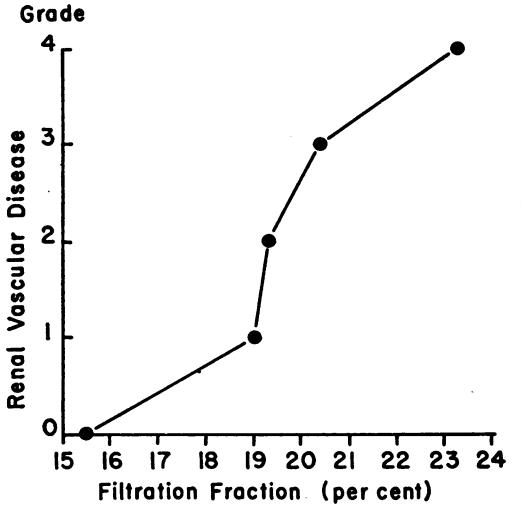

FIG. 1

The average of the filtration fractions for the cases in each biopsy group is plotted against the grade of renal vascular disease. The curve indicates that the filtration fraction increases as does the evidence of renal vascular disease, but was not above the normal of 20 per cent in the lower biopsy groups. The filtration fractions for each case are given in Table I.

This is the only patient reported in this communication who has died.

Grade III renal vascular disease. There were 8 patients in this group. The intimal hyalinization of the large and small arterioles in this group was similar to that in grade IV, while the arterial changes and parenchymal scarring was slightly less severe. Approximately 10 per cent of the glomeruli were sclerosed, although in some specimens no hyalinized glomeruli were seen after a careful search. The glomerular filtration rate averaged 89 cc. per minute, and the renal plasma flow, 439 cc. per minute (Table I). Both of these values represent about a 30 per cent depression below the normal.

Grade II renal vascular disease. The 3 cases in this group showed moderate vascular changes of all types, but especially intimal hyalinization. The average glomerular filtration rate, 91 cc. per minute, was only slightly below the average range for normals, while plasma flow, 470 cc. per minute, was depressed significantly (Table I).

Grade I renal vascular disease. There were 4 patients in this group. Slight but definite vascular disease was noted. Glomerular filtration rate in all except patient No. 18 was normal, although plasma flow was depressed slightly (Table I). Patient No. 15 showed high normal values for both functions, the highest observed in any patient reported in this communication. These figures were checked at subsequent examinations and the grade I anatomical changes were confirmed. The average glomerular filtration rate and plasma flow were 104 and 552 cc. per minute, respectively.

Grade 0 normal renal vascular findings. The 2 patients in this group, Nos. 19 and 20 (Table I), had renal clearance data that were at, or slightly below, the lower limit of normal. Nothing was noted preoperatively to suggest an adrenal tumor as being responsible for the hypertension. Paroxysmal episodes were absent in both patients. Nevertheless, patient No. 19 had an adrenal cortical tumor and patient No. 20 had an adrenal medullary tumor. The tumor was on the right side in both patients. That these 2 instances are not unique may be assumed from the observation of 5 additional cases in the larger series of 100 biopsied cases, 4 exhibiting a cortical tumor and the other a medullary tumor.[5] Equally interesting is the fact that the renal vessels were normal in both patients, the only patients who showed no renal anatomical changes in this small series.[6] A good clinical result followed unilateral sympathectomy and excision of the tumor in patient No. 20. Patient No. 19 experienced partial relief from symptoms. He returned 4 months after the first operation for a sympathectomy on the intact side. Renal clearance observations at this time checked remarkably well with those obtained at the first admission.

Filtration fraction. Goldring and associates found that patients with hypertension have a greater percentile depression in renal plasma flow than in glomerular filtration rate, so that the ratio, $\frac{\text{(glomerular filtration rate)}}{\text{(renal plasma flow)}}$, designated filtration fraction by Smith (6), is increased above the normal of 20 per cent. An increase of this fraction has been interpreted as an indication of constriction of efferent renal arterioles. The av-

[5] These 7 cases will form the basis of a more detailed communication by Drs. Smithwick and Castleman.

[6] In the larger series of renal biopsies, there was another patient with cortical adrenal tumor and 4 patients without adrenal tumors who showed no renal vascular disease.

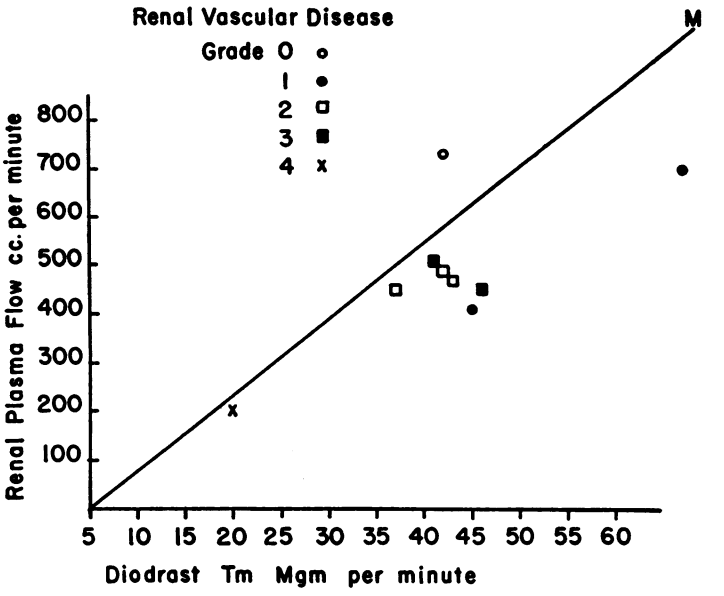

FIG. 2

In this figure, diodrast Tm is plotted against renal plasma flow. These data are available in 9 of the 20 cases. The grade of the renal biopsy is indicated in each instance.

erage filtration fraction in our series of patients showed a slight increase, 21.6 per cent, and there was a definite trend for the percentage to decrease with the less severe renal vascular disease (Figure 1). In biopsy groups 0, I, and II, the filtration fraction was normal in 7 of 8 cases (Table I), while in groups III and IV, the filtration fraction was above normal in 6 of 11 cases.

Diodrast Tm (maximal capacity for excreting diodrast iodine) was determined in approximately half of the patients (Table I). If 45 mgm. per minute is assumed to be the lower level of the normal, only 3 patients had a normal value and the percentile depression followed closely the depression in glomerular filtration rate. In Figure 2, renal plasma flow is plotted against TmD, according to Goldring. All of the data except one are below line *M*, which is drawn so as to represent a reduction in renal plasma flow and tubular excretory mass of proportionate amounts. That is, if some process were operating to reduce plasma flow and tubular excretory mass proportionately, the reduction would follow line *M*. In a heterogeneous group of renal disorders, there should be a scatter of data with points above line *M* as well as below. Inspection of Figure 2 shows that some factor is operating in hypertensive subjects to produce a relative ischemia in the residual functioning tubular tissue.

RENAL CLEARANCE OBSERVATIONS FOLLOWING SYMPATHECTOMY

Renal clearance observations following sympathectomy were obtained in 3 types of patients. (*1*) In 9 patients, the observations were obtained within 2 weeks after the second stage sympathectomy for comparison with the studies before operation. (*2*) In 9 patients, the studies were obtained from 4 to 13 months after the second operation for comparison with studies both before and within 2 weeks after operation. (*3*) In 6 patients, no preoperative or immediately postoperative studies were obtained, but they were made from 18 months to 4 years following operation.

Inspection of Table II shows that the glomerular filtration rate decreased about 20 per cent during the immediate postoperative period, but within a year had returned to about its preoperative level. Although there were no preoperative studies on the 6 patients that were followed from 1½ to 4 years, their postoperative filtration rates did not differ materially from the preoperative values of the other cases. It seems reasonable to conclude,

TABLE II

Effect of sympathectomy on renal clearance *

Patient number	Renal biopsy (Grade)	Glomerular filtration rate				Plasma flow				Effective whole blood flow				Diodrast iodine Tm				Filtration fraction			
		Pre-operative	Postoperative			Pre-operative	Postoperative			Pre-operative	Postoperative			Pre-operative	Postoperative			Pre-operative	Postoperative		
			Within 2 weeks	4 to 13 months	1½ to 4 years		Within 2 weeks	4 to 13 months	1½ to 4 years		Within 2 weeks	4 to 13 months	1½ to 4 years		Within 2 weeks	4 to 13 months	1½ to 4 years		Within 2 weeks	4 to 13 months	1½ to 4 years
2	IV	67	26			250	110			420	170							27	24		
8	III	71	73			320	320			570	520							22	23		
10	III	86	45			450	270			760	430			46	20			19	17		
13	II	90	83			490	540			880	860			42	45			18	15		
4	III	86	58	104		400	340	370		660	580	630						21	17	28	
5	III	90	91	94		480	630	290		840	1020	480						19	14	32	
6	III	70	92	92		420	500	480		780	740	800				39		17	18	19	
7	III	86	71	55		430	440	300		770	660	540						20	16	18	
9	III	105	84	90		500	420	270		850	660	440				38		21	20	33	
1	IV	56		56		220		240		370		385		19		21		25		25	
12	II	100		118		450		400		750		670		37		42		22		27	
15	I	127				700		760						67				19			
21		91		83		350		170		620		300		49		43		26		49	
22	II			57	59			290	250			470	410			28				20	24
23	III		93		64		300		230		530		410		43		30		31		28
24					98												43				
25					74				370				600				41				20
26					96				400				680								24
27					76				320				540				39				24

* The renal clearance data are arranged under 5 headings: glomerular filtration rate, plasma flow, effective whole blood flow, diodrast Tm, and filtration fraction. The relation to the time of operation is indicated in each instance. The number of the patient and the biopsy grades are given. (Refer to Table I.)

therefore, that glomerular filtration rate is unaltered by sympathectomy. In only 1 patient, No. 4, was a below normal rate before operation restored to normal by operation.

The renal plasma flow studies did not show any significant change in the immediate postoperative period, but did decrease about 17 per cent within a year and remained approximately the same for the next few years.

The filtration fraction improved somewhat during the 2-week period after operation, but gradually rose during the first year and showed no tendency to return to normal later. This finding suggests that efferent constriction had not been lessened by sympathectomy.

The diodrast Tm observations are too few and scattered to warrant any conclusions.

DISCUSSION

From these data, admittedly few for the malady under discussion, it is evident that in patients with essential hypertension a reasonably constant correlation exists between microscopic evidence of renal vascular disease and renal function as measured by quantitative procedures. A study of Figures 3 and 4 suggests that the reduction in glomerular filtration, and especially in renal blood flow, increases as the vascular disease progresses. Furthermore, it is of interest to note that, in the absence of renal vascular disease (grade 0), or in the presence of minimal arteriolar changes (grade I), the reduction in renal blood flow is slight, if any. It is only in the grade IV biopsy group that renal blood flow is reduced to a serious level. Ex-

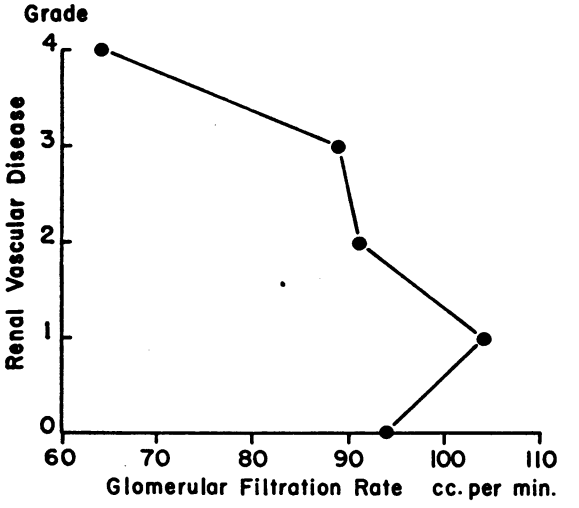

FIG. 3

In this figure, the glomerular filtration rate is plotted against the grade of renal vascular disease. It indicates that the filtration rate decreases as the vascular disease increases. It varies from the normal range to serious reduction, the latter being found only in the grade IV biopsy group.

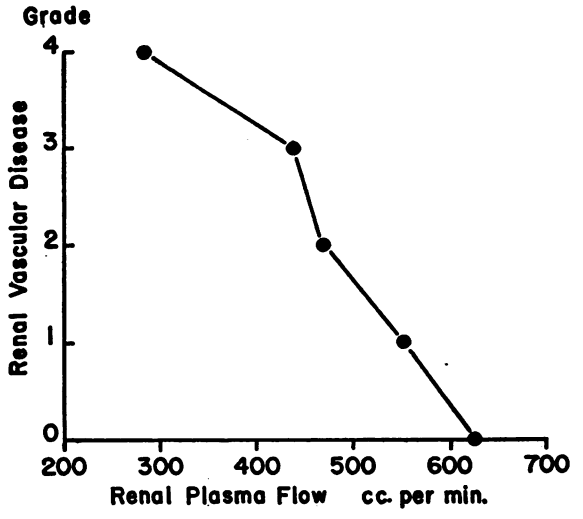

FIG. 4

In this figure, the renal plasma flow is plotted against renal vascular disease as judged by the kidney biopsies. The renal blood flow decreases as the renal vascular disease increases. The range is from the normal level to a marked reduction, the latter being found in the grade IV biopsy group only.

ceptions, however, were noted. Thus, patient No. 18 had grade I vascular disease but a marked diminution in glomerular filtration, while patients Nos. 9 and 11 had grade III vascular disease and normal filtration rates. In the main, most discrepancies, when present, suggested a greater degree of vascular disease than was actually present. This is to be contrasted with ordinary function tests which, in general, fail to indicate vascular disease until it is present in its most advanced form.

The patients in our biopsy group may be compared with a series of 60 patients with essential hypertension, reported by Goldring and associates (1), in whom only renal clearance studies were performed. These patients were not operated upon and no renal biopsies were available. Except for the 8 severe cases in Goldring's group, all but 1 of whom died before his report was published, the patients in our series are believed to have suffered from a more advanced grade of hypertension. This statement is based principally upon the greater observed depression in renal clearance. In Goldring's series, approximately 50 per cent of the patients had a glomerular filtration rate above 92 cc. per minute, while less than one-third of our patients showed as satisfactory a rate. This is emphasized because of the good clinical results that followed sympathectomy in our series. Most of the patients experienced marked clinical improvement and a recent follow-up has shown no death other than that of patient No. 2, who died in the hospital.

An increase in filtration fraction in certain hypertensive patients has been emphasized in the literature as it indicates constriction of the efferent glomerular arterioles. The cause of this constriction is unknown, but it has been interpreted by some to result from the action of a circulating humoral pressor substance. It is of interest to note that in the early stages of renal arteriolar disease, biopsy groups 0 and I, the filtration fraction was normal in 4 of 4 cases. In grade II, it was normal in 2 of 3 patients. In grades III and IV, it was above the normal level in 6 of 11 cases. This suggests that efferent constriction is not present in the earlier stages of renal arteriolar disease.

In order to reduce to a minimum other causes of modified renal blood flow, particularly that due to vasoconstriction, the blood flow determinations both before and after operation were made with the patient in the horizontal position in a comfortable quiet environment. Studies made under other conditions, designed to bring out the effect of vasoconstriction, have been made in other patients and will be reported separately.

There was no significant difference in filtration rate or renal plasma flow following bilateral sympathectomy, after circulatory adjustments had been made.

It is most important, however, to emphasize the fact that glomerular filtration rate tends to be maintained soon after operation, as well as years later, and it may be assumed that renal damage may not progress rapidly thereafter. If this be the only effect of sympathectomy in essential hypertension, it is well worth the surgical risk and effort involved. Patients with a moderate degree of impairment of glomerular filtration (70 to 100 cc. per minute) are not seriously handicapped and it is conceivable that if their kidneys are able to escape further damage, life may not be materially shortened by the vascular changes that have developed up to the time of operation.

SUMMARY

(*1*) Renal clearance studies performed on 20 patients with essential hypertension showed a significant correlation with the microscopic appearance of their respective renal tissues which were removed for biopsy at the time of sympathectomy, *i.e.*, the more severe the renal vascular disease, the more reduced were the glomerular filtration rate and the renal blood flow. In the cases with grade 0 and I renal vascular disease, the renal clearance observations were either normal or only very slightly reduced. Only in grade IV renal vascular disease was renal blood flow seriously reduced.

(*2*) The filtration fraction was normal in 7 out of 8 cases in biopsy groups 0, I, and II. It was increased in 6 of 11 cases in biopsy groups III and IV. These findings indicate that constriction of the efferent glomerular arterioles was not present in the early stages of renal vascular disease.

(*3*) Bilateral radical lumbo-dorsal splanchnicectomy had relatively little effect on renal clearance, when measured in the horizontal position. Although glomerular filtration was reduced in the immediate postoperative period about 20 per cent, within a year it returned to and continued to maintain its preoperative level. Renal plasma flow was essentially unchanged.

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