RENAL BIOPSIES IN HYPERTENSION

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The examination of a piece of kidney cortex taken during sympathectomy for hypertension affords a method of studying the pathological changes during life. The present study has been undertaken to see if the severity of the vascular changes influenced the response to sympathectomy and other surgical methods for the lowering of blood pressure in patients with hypertension. Several other features that emerged in this investigation are also described.

MATERIAL AND METHOD

Portions of renal cortex were obtained from 50 patients with hypertension at the same time as the operations of sympathectomy and/or adrenalectomy were performed. In 5, biopsies were performed on both kidneys, and in the remainder, on one side only. The size of the specimen was of the order of $0.8 \times 0.4 \times 0.3$ cm., and it was taken from the superficial part of the cortex after incising and partially reflecting the capsule. No untoward effects could be attributed to this. The material was fixed in 10 per cent formal-saline and sections cut at $5\text{-}\mu$ thickness in the long axis of the specimen at right angles to the sub-capsular surface. Sections were stained routinely with hæmatoxylin and eosin, hæmatoxylin and van Gieson's stain, and the Hart-Sheridan method for elastic tissue. Where necessary the following stains were used—periodic acid-Schiff, Mallory's phosphotungstic acid hæmatoxylin, 1 per cent toluidine blue, and Gordon and Sweet's method for reticulin.

Grading of Vascular Changes. Castleman and Smithwick (1943) reported their findings in 100 cases of renal biopsy in patients with hypertension and followed this with an account of a further 500 (1948). So that a comparison of the vascular changes observed in the present series could be made with those observed by these two authors, their classification was employed.

Vessels were classified as small arterioles (less than $25\text{ }\mu$ external diameter), larger arterioles ($25\text{--}50\text{ }\mu$), small arteries ($50\text{--}100\text{ }\mu$), and large arteries (over $100\text{ }\mu$). For describing the vascular changes the criteria of Moritz and Oldt (1937) were used, namely intimal hyalinization, medial hypertrophy and degeneration, and endothelial hyperplasia. The severity of the changes was graded O–IV. Grade O showed no vascular changes whatsoever, while Grade IV showed widespread severe changes in the vessels with many hyalinized glomeruli and many atrophic tubules. Grades I, II, and III were intermediate between Grades O and IV.

One modification in the current series was to add an additional group for those cases showing necrotizing lesions in the arterioles, Group N.

Another minor difference was to substitute for the term endothelial hyperplasia, the term intimal thickening, as this may include fibrous and elastic thickening.

MAIN OBSERVATIONS

Group O. One woman. In this the appearance was that of entirely normal kidney tissue with no vascular changes whatsoever. The patient was aged 32 years, with a blood pressure of 220/115 mm. Hg and no evidence of deranged renal function.

Group I. Twelve cases (9 women, 3 men). Early and scattered arteriolar hyalinization and early intimal thickening of some small arteries were the characteristic features of this group. There was no significant basement membrane thickening of the glomerular tufts, although in some cases an occasional tuft was hyalinized. Three of these patients showed small scarred areas, associated with collections of lymphocytes in one.

The ages of the patients in this group varied from 24 to 50 years and the blood pressures from 160/110 to 220/150 mm. Hg.

Group II. Seventeen cases (8 women, 9 men). More extensive arteriolar hyalinization and intimal thickening of arteries were seen. Basement membranes of glomerular tufts tended to show early thickening and scattered glomeruli were hyalinized. Nine cases showed the presence of small scarred areas containing lymphocytes and the tubules were rather atrophic in these scars. The ages of the patients were from 10 to 50 years. The blood pressures extended from 170/120 to 250/170, while the urine contained traces of albumin in several cases.

Group III. Six cases (5 women, 1 man). Arteriolar hyalinization and intimal thickening of larger arterioles and small arteries were generalized and more pronounced than in the previous group. On the whole more glomeruli were hyalinized, although this was by no means a constant feature. Basement membrane thickening of glomerular tufts was prominent. Scarring associated with lymphocytic infiltration was present in 5 of the 6 cases. Atrophic tubules, usually empty, were present in these small scars.

The ages of the patients were from 39 to 53 years and the blood pressures were between 210/130 and 260/145. No evidence of renal failure was found in this group.

Group IV. One man. Arteriolar hyalinization and intimal thickening of larger arterioles and small arteries were widespread and advanced. The intimal thickening in this case was looser than usual and rather basophilic, showing a faintly metachromatic reaction with toluidine blue. About 10 per cent of the glomeruli were hyalinized and basement membrane thickening in the tufts was moderately pronounced. Small scars were frequent and contained lymphocytes and atrophic tubules (Fig. 1).

FIG. 1.—Small scar with lymphocytic infiltration and somewhat atrophic tubules from renal biopsy (hæmatoxylin and eosin, $\times 120$).

FIG. 2.—Fibrinoid necrosis in small artery in renal biopsy from malignant hypertension (hæmatoxylin and eosin, $\times 400$).

This patient was a man of 47 years, with a blood pressure of 200/140. He had moderate albuminuria, a normal blood urea, and no evidence of papilloedema.

Group N. Thirteen cases (7 women, 6 men). As stated before this group has been treated separately because of the presence of necrotizing lesions, characteristic of the malignant phase of hypertension. The necroses were present in arterioles and some of the smaller arteries (Fig. 2). The arteries showed pronounced intimal thickening in nine cases and this was of the fine rather cellular type seen in malignant hypertension (Fig. 3). In some cases metachromasia with toluidine blue was observed in this type of intimal thickening. In the remaining four the intimal changes were not so severe and necroses relatively scanty. The glomeruli often showed basement membrane thickening and in 3 cases showed necroses. Scarred areas with lymphocytic infiltration were found in 9 cases. Tubules were often dilated and contained faintly eosinophilic casts.

The ages of the patients were from 11 to 53 years and the blood pressures 230/150 to 290/180.

RELATIONSHIP BETWEEN VASCULAR GRADINGS AND RESPONSE TO SURGICAL TREATMENT

Of the original 50 patients the subsequent history of 49 is known, the remaining one having gone overseas shortly after operation. The majority underwent thoraco-lumbar sympathectomy of the Smithwick type, but some of the earlier ones had a more conservative lumbar sympathectomy. In some of the latter ones, partial adrenalectomy was also carried out, but because of the small number under review, it was decided not to subdivide them according to the type of operation performed. It was, however, noted that some of the better results were associated with the more limited type of sympathectomy. Some patients have been followed up for 9 years, while others have been under

FIG. 3.—Fine intimal thickening in small artery in renal biopsy from malignant hypertension (haematoxylin and eosin, $\times 400$).

FIG. 4.—Scarred area of chronic pyelonephritis in renal biopsy (haematoxylin and eosin, $\times 120$).

observation for as short a time as one year. Blood pressure readings have as far as possible been taken in the lying position after a 10-minute rest period.

Group O. The only case in this group, a woman of 32 years, maintained a fall in diastolic pressure of 10 mm. after 6 years.

Group I. Women. Of the 9 women in this group, one was an example of chronic glomerulonephritis and death occurred within four months of operation; there had been no reduction of blood pressure. One died after a year from a cerebral hæmorrhage, no reduction in blood pressure having occurred. Of the 7 others, one is alive after 8 years, one after 7 years, three after 6 years, one after 4½ years, and the other after 3½ years. No reduction in blood pressure occurred in two of them. Two showed a fall in diastolic pressure of 20 mm. or more, which has been sustained for over 3 years in each case. One showed a diastolic reduction of 15 mm. after 6 years, and two a reduction of 10 mm. after 3 years.

Men. Two of the three men died after 5 and 6 years respectively. One of these had shown no reduction in blood pressure before he died from a cerebral hæmorrhage, while the other showed a 20-mm. reduction in diastolic pressure after six months, but died from heart failure. The remaining man is alive after 7 years with a diastolic reduction of 20 mm.

Group II. Women. Two out of 8 have died. One of them who died at 18 months from a ruptured berry aneurysm of the circle of Willis had maintained a diastolic fall of 45 mm. up till the time of her death. The other died from heart failure after 3 years, having shown a fall of 20 mm. six months after operation, which was the last recording available. The survivors have been followed for periods up to 9 years. One showed a diastolic fall of 40 mm. after 4 years, two of 20–25 mm. after 4 and 6 years, one of 10 mm. after 6 years, one of 10 mm. after one month, and the remaining case showed no reduction at all, although she is alive after 9 years.

Men. Three out of 9 have died after 3, 4, and 5 years, the cause of death being either cerebral hæmorrhage or heart failure. The remainder have been followed for up to 6 years. Two showed a fall in diastolic pressure of 50–65 mm. at the end of 1 year, while another maintained a similar reduction for 4 years. One showed a fall of 45 mm. after eighteen months, two of 20–25 mm. at 3 and 5 years, while two have had no reduction at all. It has not been possible to trace one of the men in the series.

Group III. Women. Two died in the post-operative period, one from coronary thrombosis and the other from a chest infection. Of the three surviving operation, two are alive after 2 years and one after 7 years. In the latter there has been a 20-mm. fall in diastolic pressure after 7 years, while in the other two there has been no appreciable fall.

Men. The only man in this group is alive after 5 years with a diastolic reduction of 20 mm.

Group IV. This man died from cardiac failure 4 years after operation. He had shown a diastolic fall of 35 mm. which was maintained for over a year, the last occasion on which he attended.

Group N. Of the 13 cases (7 women and 6 men) in this group, 10 showed retinal changes of exudates, hæmorrhages, and papillœdema. Three, although not having papillœdema, had necroses in renal vessels.

Four are still alive. The only man surviving is alive after 7 years with a sustained diastolic fall of 35 mm., but has recently had a coronary thrombosis and is no longer able to work. Of the three women, one has maintained a fall of 30 mm. for 3 years and another a fall of 60 mm. for 6 years, papillœdema having disappeared from both. The other woman who had no papillœdema showed no great reduction and is now after 7 years under treatment with hexamethonium bromide.

Of the 9 fatal cases (4 women and 5 men), two died after operation and seven died within six months from renal failure. None of these showed any reduction in blood pressure. One of the latter had chronic nephritis.

DISCUSSION

The first point to ascertain before drawing any conclusions about vascular changes is whether the changes seen in a small fragment of cortex are representative of the vascular changes of the kidney as a whole. In the renal biopsy it is customary to see 30 to 50 glomeruli and 15 to 30 arterioles and small arteries, and it is unusual to see vessels of more than $150\ \mu$ external diameter. Sections of kidneys of patients with hypertension of varying grades of severity were taken post mortem, and small areas comparable in size with a biopsy were marked out and examined. These were then compared with vessels of comparable size in the rest of the kidney section. It was found that in general the vascular changes were uniform and that the biopsy gave a fairly accurate picture of the state of the arterioles and small arteries.

One most obvious exception to this general rule is the kidney of chronic atrophic pyelonephritis. The patchy nature of the scarring in this condition is associated with a similar patchy pattern of vascular change. In the scarred areas of this condition there is often gross intimal thickening of the arteries which is not prominent in the non-scarred areas, where such vascular changes as occur are probably the result of the hypertension. Thus it is quite obvious that two biopsies from different sites in a pyelonephritic kidney could show completely different vascular changes. Another exception to the rule that the biopsy is adequate is the early case of malignant hypertension, where vascular necrosis may be scanty and may, therefore, not be seen in the small amount of material available.

The second point to elucidate is whether from a point of view of diagnosing the renal disease, the material available is adequate. This can be tested in the same way as before, by examining portions of the subcapsular surface of kidney blocks prepared from autopsy material. Kidneys of essential hypertension, both benign and malignant, and kidneys from hypertension due to renal causes such as chronic glomerulonephritis (Ellis Types I and II) and pyelonephritis were examined. It was concluded that the changes in chronic glomerulonephritis were sufficiently diffuse to enable a diagnosis to be made. One case of Type I nephritis and one of Type II nephritis were encountered in this series. The problem of chronic pyelonephritis has been mentioned and the diagnosis of this condition must remain hazardous. If one of the typical scarred areas (Fig. 4) such as was encountered in some of the biopsies is seen, then the diagnosis can be made, especially when the clinical picture and history are taken into account. If, however, a non-scarred portion is chosen, then it is not possible to differentiate this from essential hypertension. Two biopsies taken at operation for the removal of a phæochromocytoma (not included in this series) showed changes indistinguishable from essential hypertension.

Small scarred areas either with or without lymphocytes are frequently seen in renal biopsies and their interpretation is always difficult. When associated with hyalinized or missing glomeruli and atrophic tubules containing deeply eosinophilic casts, it is most likely that patchy chronic pyelonephritis is the cause. In some cases, however, the scars do not show all these features and it is these cases that are difficult. It has usually been accepted that scarring of the cortex represents the result of ischaemia (Gaskell, 1912), but there is a growing tendency to regard some at least of these as due to the effects of infection. Thus McManus (1950) considers that the scars seen in the kidneys of older people are due to focal pyelonephritis. If this is so, infection of the kidney parenchyma must be extremely common, for cortical scarring is very prevalent, especially in the later age groups. Thus if we are to accept this infective theory we must consider what part, if any, these scattered areas of pyelonephritis play in the production of hypertension. The absence of hypertension in a great number of people showing these scars as judged by autopsy material, and the well known fact that not all patients with chronic pyelonephritis have hypertension, means that caution must be exercised with renal biopsies in claiming that the hypertension is of renal origin.

An attempt was made to correlate the presence of small scars (with and without lymphocytes), with the vascular grading. It was found that scarring was relatively more common in the upper grades, while the greatest proportion of biopsies with no scarring was found in the lower grades.

Thus it appears that there is some correlation between the frequency of scars and the degree of involvement of the vessels, and that the degree of vascular occlusion plays some part in the production of these scarred areas.

What conclusions can be drawn from the available facts? Table I shows the distribution of the biopsies according to their vascular grading. It will be seen that 30 cases occur in the first three

TABLE I
NUMBER OF CASES ACCORDING TO VASCULAR GRADING

Vascular grading ..	O	I	II	III	IV	N
Number of cases ..	1	12	17	6	1	13

groups, where the vascular changes are only mild to moderate. Fig. 5 shows the relation between the various vascular grades and the level of the diastolic blood pressure: high levels of blood pressure can be associated with low vascular gradings; thus 5 cases with Grade I vascular changes have a diastolic blood pressure over 130 mm. and 7 cases with Grade II vascular changes have a diastolic blood pressure over 150 mm. The diastolic blood pressures in Group N are all over 150 mm., which is in keeping with the observation of Wilson and Pickering (1938) who found that

FIG. 5.—Distribution of vascular gradings according to level of diastolic blood pressure.

in experimental hypertension in the rabbit, arteriolar necroses are present only in animals with the highest blood pressures, and attributed the lesions to a rise of intra-arterial pressure above a certain point. The absence of acute arteriolar lesions in patients having diastolic pressures below 150 mm. and the increasing frequency of these lesions as the arterial pressure mounts above this level is in conformity with the hypothesis that the benign and malignant phases of hypertension are chiefly dependent on the extent to which the arterial pressure is raised (Pickering, 1942). The distribution of cases with and without vascular necrosis with regard to the level of blood pressure in the present

series is shown in Fig. 6. Fig. 7 shows the relation between vascular grading and the age of the patient: the only significant point here is the proportionate frequency of the Grade III and IV cases in the later age groups. Bell (1950) has pointed out that intimal thickening of arteries and to a lesser extent hyalinization of arterioles occur as an aging process, and this may partly explain why Grade III and IV changes are associated with blood pressures comparable with Groups I and II.

FIG. 6.—Graph to show distribution of cases with and without vascular necrosis according to level of blood pressure.

FIG. 7.—Distribution of vascular gradings according to age.

From these findings it is possible to confirm the observations of Castleman and Smithwick (1948), that a high proportion of patients with hypertension (46% in their series) show little or no vascular change (Grades 0, I, and II). Out of the current series of 50 cases no less than 30 showed vascular changes of Grades 0, I, and II. Thus there seems to be little in these observations to support the theory that hypertension is due to changes in the small blood-vessels. Bell (1951) has also pointed out the absence of arteriolar changes in no less than 25 per cent of cases of essential hypertension without renal insufficiency.

Secondly, it has been established that it is usually possible, except for pyelonephritis, to determine whether or not there is a renal cause for the hypertension. The diagnosis has been confirmed in 7 cases that have subsequently come to autopsy, 5 cases of essential hypertension, one of Type 1 nephritis, and one of chronic atrophic pyelonephritis.

The effect of surgical treatment on the blood pressure is shown in Fig. 8 and 9. Fig. 8 shows the effect three years or more after operation, while Fig. 9 shows those followed from six months to three years. It will be seen from these that it is possible to obtain a substantial fall in blood pressure in all groups, and although Groups III and IV are very small the severity of the vascular

changes does not preclude a satisfactory response to operation. Similarly the way in which some of the Group I and II cases failed to respond to surgical treatment indicates that a low grading does not guarantee a satisfactory response to sympathectomy.

FIG. 8.—Effect of sympathectomy on blood pressure according to grading. Cases followed more than three years.

FIG. 9.—Effect of sympathectomy on blood pressure according to grading. Cases followed six months to three years.

Of the cases in Group N a satisfactory reduction in blood pressure was obtained in 3 out of 13, with consequent increased survival time. This is substantially in accord with the thesis of Pickering *et al.* (1952), that if the blood pressure can be reduced below the critical level at which vascular necrosis takes place, then the malignant course can be arrested.

TABLE II
SURVIVAL TIMES ACCORDING TO GRADING

Group	I		II		III		IV		N	
Years followed	No. of cases	No. of deaths	No. of cases	No. of deaths	No. of cases	No. of deaths	No. of cases	No. of deaths	No. of cases	No. of deaths
1	11	0	16	0	6	2	1	0	13	9
2	11	1	14	1	6	2	1	0	13	9
3	11	1	13	1	4	2	1	0	13	9
4	10	1	11	3	4	2	1	0	12	9
5	9	1	11	4	4	2	1	1	12	9
6	9	2	10	5	3	2			12	9
7	6	3	7	5	3	2			11	9
8	4	3	7	5	2	2			9	9
9	3	3	7	5						
10			5	5						

The effect on survival times is shown in Table II. The one case of chronic nephritis in Group I has been omitted as it was thought that the glomerular changes overshadowed all else and were responsible for the early death of the patient. Unfortunately it is not possible to compare this with the figures of other authors as these are all based on clinical gradings. The only comparable figures are those of Smithwick and Castleman (1951) who showed that the prognosis becomes worse as the grading increases. This appears to be the case in the present series, although the number of cases in Groups III and IV is too small to be of real significance.

SUMMARY

Renal biopsies have been studied from 50 patients undergoing sympathectomy for hypertension. The biopsies have been graded according to the severity of the vascular lesions.

The vascular changes seen in a biopsy specimen are thought to be representative of the changes in the kidney as a whole, and with the exception of chronic atrophic pyelonephritis it is possible to differentiate between renal causes of hypertension and essential hypertension.

The fact that no less than 30 of the biopsies showed only slight vascular changes is evidence in favour of the hypertension preceding vascular changes in essential hypertension.

Arteriolar necroses are confined to those cases with the highest levels of blood pressure.

It is possible to obtain as great a reduction of blood pressure in some cases showing advanced vascular changes as in the less severely affected group.

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