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HYPERTENSION AND THE KIDNEY

I. CLINICAL, PATHOLOGICAL, AND FUNCTIONAL DISORDERS, ESPECIALLY IN MAN*

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[WITH SPECIAL PLATE]

I can in some part follow the dictates of the Goulstonian Trust, since it specifically states that lectures shall be given on two or three or more diseases, and the present subject certainly covers more than that number, and the main problem is to discern the connecting thread. To choose this subject so close to the recent commemorations of Richard Bright invites invidious comparison, especially as in 1833 he was the Goulstonian Lecturer, when he discussed "The Functions of the Abdomen and some Diagnostic Marks of its Disease," and in his second lecture "Renal Disease and the Changes in the Urine by which it may be Recognized." It was at this time that he established the relation between renal disease and an enlarged heart. He said: "With regard to the affection of the heart to which I have referred, I have occasionally been able to trace the gradual approach and increase of the hypertrophy coming on many months after the albuminous condition of the urine has been established"; and later: "But in several instances the affection has been hypertrophy and dilatation of the left ventricle" (Osman, 1937).

It was not until the blood-pressure was seriously measured later in the nineteenth century that the hypertrophy was recognized as attributable to high systemic blood-pressure. With such recognition the argument subsequently has revolved round the primary or secondary role of the kidney in any form of hypertension. I hope to analyse some of the data so as to give an appreciation of the role of the kidney. In so doing it is necessary to be ruthlessly selective, and I have tried to pick out only what I consider the most revealing aspects and have deliberately neglected other interesting points of view. This field is striking for the way in which clinical observations have supplemented and, alternately, been supplemented by pathological and experimental ones.

After Bright, the next major advance so far as the relation of the kidney to hypertension was concerned occurred in 1898 in the Karolinska Institute, Stockholm, where Tigerstedt and Bergman discovered the enzyme renin in extracts of the kidney, and described most of its important properties as a pressor substance. Their observations lay fallow until the next advance in 1934, when Goldblatt and his colleagues produced hypertension by clamping the renal artery in animals. Attempts to relate the last two observations and to

explain this type of experimental hypertension, and to correlate it with human hypertension, have occupied the succeeding years. There is no doubt there is one outstanding situation in man which gives clues as to one function of the kidney in hypertension, and that is unilateral renal disease, for this is the main curable form of renal hypertension, and this especially applies to unilateral renal-artery obstruction.

Types of Renal Disease

First I wish to look at the pathological and histological changes which occur in the kidney in association with hypertension to see if there is any pattern which might help us in seeing why it is that certain diseases are associated and others not. There is such a wide variety that it is pointless merely to consider all the conditions without seeking for the common factor. Thus we have to be able to associate acute and chronic glomerulonephritis, pyelonephritis, polyarteritis nodosa, polycystic disease, Kimmelstiel-Wilson kidney, irradiation nephritis, and renal-artery stenosis, and to explain why not all cases of pyelonephritis, or tubercle, or hydronephrosis, or polyarteritis nodosa affecting the kidney, have hypertension, and why the renal failure associated with acute glomerulonephritis seems different in its effects on blood-pressure compared with acute tubular necrosis.

Failure of Excretion

I would next like to consider the proposition that failure of renal excretion may be concerned in human hypertension, and to contrast acute glomerulonephritis with acute tubular necrosis. It is not widely appreciated that in man it is possible to have quite gross renal failure without a rise in blood-pressure in the presence of tubular necrosis alone. The best examples of this occur in abortions induced by introducing soap into the uterus, but it is common after hypotensive episodes produced in a variety of ways—as, for example, by post-partum or concealed accidental haemorrhage. Table I shows the findings in four typical cases to illustrate the point. It can be seen that even where the blood-pressure was high before anuria developed (case T. W.) there is no further rise despite the presence of gross renal failure. In all these cases the blood-urea level rose steadily and the figures of blood-pressure given represent the main range, and, while in two of the patients (McG. and C.) there were occasionally higher readings, they were very occasional. In the series reported by Bull *et al.* (1956) only two out of

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eight patients with anuria following an abortion had hypertension. In cases of concealed accidental haemorrhage in pregnancy it is common for "toxaemia"

TABLE I.—*Blood-pressure in Anuria due to Tubular Necrosis*

Patient	Diagnosis	Duration (Days)	Blood-pressure (mm. Hg)		Final Blood Urea (mg. per 100 ml.)
			Start	End	
D. B. . .	Abortion	14	130/30	124/75	600
McG. . .	"	12	120/70	130/70	450
			(occasional readings up to 150/90)		
C. . .	"Toxaemia" and concealed haemorrhage	27	110/70	120/60	800
			(occasional readings up to 150/90)		
T. W. . .	Aortogram	20	210/90	180/90	400
			(210/90 before aortogram)		

to have been present with some hypertension beforehand, and these patients often remained hypertensive (Bull *et al.*, 1955). Where renal cortical necrosis is found hypertension is very common. However, the point that anuria with failure of renal excretion will occur without hypertension in man seems convincingly made. In patients with similar degrees of renal failure due to acute glomerulonephritis hypertension is almost always present.

Now what is the histological difference between these two kidneys? In the tubular necrosis of abortion the glomeruli are strikingly preserved amidst damaged tubules, whereas in glomerulonephritis the glomeruli, of course, are damaged in addition, usually, to the tubules. Could it be that the distribution of blood to the cortex, and particularly the intimate distribution around the glomeruli, is quite different? Histologically, in tubular necrosis one would think that the glomeruli and the neighbouring tissues would have a reasonable blood-supply. Is this area, then, one of importance in providing renal tissue which has some antihypertensive action, and in glomerulonephritis is this antihypertensive action lost?—or is it that in damage to the glomeruli a pressor substance is formed in response to the blood-flow impairment? As the question of distribution and rates of blood-flow through the kidney in these conditions cannot be satisfactorily answered at present, these questions will also have to remain unanswered. The clues here may well lie beyond the histological, since some structures which may look histologically normal can be behaving in a very abnormal way, and apparent damage histologically may not necessarily be reflected in gross functional change. A former registrar at St. Mary's Hospital, Mahomed (Pickering, 1955), observed that hypertension would often precede the appearance of proteinuria in acute glomerulonephritis, suggesting that some functional effects of the injury in this disease precede the external evidence of them.

Irradiation Nephritis

This point leads naturally to another interesting condition which has been recently recognized—namely, irradiation nephritis. While the effects of x-rays on the kidneys have been known for a long time, their association with hypertension is a relatively recent discovery, and the experimental production of the condition in animals (Hartman *et al.*, 1926, 1927; O'Hare *et al.*, 1926) allowed further investigation. The successive realization that this condition is produced in man during irradiation of the upper abdomen, particularly for metastases for seminoma of the testis, brought it into full prominence (Dean and Abels, 1944;

Luxton, 1953). The cases usually described present the histological picture reproduced in Special Plate Fig. 1, where the characteristic fibrinoid necrosis in the arterioles is well shown. There is usually much interstitial fibrosis and acute necrosis in glomeruli. It is natural to wonder whether ischaemia is playing a role in this kidney, but the observations of Wilson *et al.* (1958) are of very great importance in interpreting what happens in the kidney.

Stimulated by their observation in one fatal case of irradiation nephritis that the renal histology showed much less change than is described above, these authors studied the situation further by experiments in the rat. The most important point that emerged was that the rat can develop high blood-pressure before there are any histological changes in the kidney. This brings changes of function, perhaps of a metabolic type, to the fore, though it would, of course, be of interest to know if there were any actual blood-flow changes in the kidney at this stage.

Tumours of the Kidney

It might be expected that, if there were a structure in the kidney that produced a pressor substance, occasional examples of hyperplasia or malignant disease would provide opportunities for an excess of such a substance to be produced, as occurs in other organs. There is only one tumour which is commonly associated with hypertension, and this is the Wilms type of nephroblastoma. This association was first pointed out by Bradley and Pincoffs (1938) and has been confirmed by Cox and Smellie (1955–6). While it has been thought that interference with the blood supply to the kidney may be responsible, it is surprising that a hypernephroma is not especially associated, and, further, in one of Bradley and Pincoff's cases hypertension disappeared on removal of the tumour, only to return with growth of metastases six months later. An open mind on this question is still necessary.

Pyelonephritis

I now wish to pass over many conditions—such as polyarteritis nodosa, Kimmelstiel–Wilson kidney, and tubercle—which are associated with hypertension, and to say merely that obstruction to the arterial circulation in the kidney appears to be present in all, so that I can give more attention to pyelonephritis, since this has raised the greatest controversy in the field of renal hypertension. In 1944 Goldring and Chasis said that they did not believe there was a greater association of pyelonephritis with hypertension than with normal blood-pressure, and quoted much evidence in support. On the other hand, there is evidence from others, and especially pathologists, to show a high association of these two conditions, and often of unilateral pyelonephritis (Longcope, 1937; Weiss and Parker, 1939). It is likely that these discrepancies are due to selection of patients, and it seems impossible to refute the idea that there is such a connexion in many patients, and that the real problem is why some patients have hypertension while others do not. Kincaid-Smith (1955) has made the valuable suggestion that the real basis of difference is the partial to complete arterial obstruction in those pyelonephritic kidneys associated with hypertension. She believes this leads to the areas of partial infarction described by Fahr (1934). As will be seen later, these areas of partial infarction, which occur in other diseases than pyelonephritis, are often associated with hypertension.

One further trouble which falls to the pathologist is, of course, the adequate diagnosis of pyelonephritis, and there is no doubt there is real difficulty with small shrunken kidneys in deciding how much is due to arterial obstruction and how much to old inflammatory change. That the disease need not affect all of one kidney and yet be responsible for the hypertension is shown in various case reports (DeCamp and Birchall, 1958; case W. F., Table II of the present paper). Since mention has been made of the partial infarct of the kidney in pyelonephritis, it is well to illustrate the similarity where an arterial obstruction is known to be present. Special Plate Fig. 2 shows a renal biopsy from a patient aged 19 years who had had an aberrant renal artery tied off during lithotomy and who subsequently developed a fluctuant hypertension. The section shows the typical atrophic tubules and the healthy-looking glomeruli. This illustrates the difficulty in trying to correlate the histological picture with the function of the kidney in relation to hypertension, since earlier the point was made that in tubular necrosis with anuria and without hypertension the glomeruli were usually spared and the tubules appeared damaged. This apparently only means that we are not aware of the precise functions of the kidney and that histology gives only an approximate idea.

Reduction of Blood Supply

Since diminution in blood-supply to the kidney in whole or in part is suggested by many of these pathological conditions, it leads naturally to a consideration of the relation between blood-flow in the kidney and hypertension. Over the past twenty years this has really resolved itself into a conflict between Homer Smith and his colleagues as physiologists on the one hand, and Goldblatt and his colleagues as pathologists on the other. I think it can be seen that this difference of outlook does depend in part on the sort of patients studied and the methods of study. Initially Goldblatt, impressed by the appearance of arterial disease and narrowing in the kidneys of patients with high blood-pressure when he examined them under the microscope, was led to perform with his colleagues in 1934 their "memorable experiment." The success of this experiment of constriction to the renal artery lent support to Goldblatt's view that most hypertension was of renal origin and due to diminution in blood-flow to the kidney. Against this Homer Smith, who was responsible for the introduction of the clearance techniques for the study of renal blood-flow indirectly, took the position that hypertension itself caused changes in the blood-flow to the kidney of a secondary nature, and that there was really no convincing proof that a primary reduction in renal blood-flow led to hypertension. There is no doubt that, using the techniques of inulin and diodone or *para*-aminohippurate (P.A.H.) clearance in most types of human hypertension, there are changes in the values. Smith and his colleagues showed that the early change in most forms of hypertension was a reduction in the maximum capacity of the tubules to excrete diodone. In more severe cases the renal plasma-flow (diodone or P.A.H. clearance) was reduced, and only in the severest of cases was the glomerular filtration rate (inulin clearance) reduced (see Smith, 1951, for references).

One should always keep an open mind about indirect measurements of any function, and when one considers that on this sort of finding Smith and his colleagues suggested that in hypertension the efferent arteriole

from the glomerulus was constricted more than the afferent, and that subsequently Gómez (1951), using the same data, suggested that in reality the afferent was constricted more than the efferent, then acceptance of the conclusions must be reserved. Goldblatt has always been impressed by the organic arteriolar changes in the kidney, but up to the present it may well have been that he was studying well-developed varieties of long-standing disease. We should therefore turn to evidence from renal biopsies; and Saltz *et al.* (1957) have provided such evidence with biopsies taken during the course of sympathectomy in the treatment of hypertension. They say that in early hypertension there is very little arteriolar change to be seen, and that this enters only with the more severe forms of hypertension. In other words, there is a measure of support for Homer Smith's view, though it would have been of great interest to know what the renal blood-flows were in these patients.

A further point used in favour of a non-organic constriction in the renal blood-vessels in early hypertension is that provided by Bradley *et al.* (1945). They showed that pyrexia induced by administering a pyrogen to man caused a renal hyperaemia. This therefore suggested that the renal blood-vessels were capable of dilatation and were not organically narrowed. This is not good evidence, since it is not necessary to suppose that the blood-vessels in the kidney are completely rigid, but merely that there could be narrowing due to organic change in addition to all the other factors which control the state of contraction and thickness of the arteriolar wall. The position may be summarized by saying that hypertension can exist without any obvious disease in the renal arteries, but this does not mean that such disease, when present, may not lead to hypertension.

Stenosis of the Renal Artery

The preceding paragraph leads naturally to a consideration of renal-artery stenosis, which has come into prominence recently as a cause of human hypertension. This is the most interesting demonstration of a curable unilateral renal disease in man and is, of course, directly analogous to the experiments of Goldblatt and his colleagues (1934). The reported causes of renal-artery obstruction have varied from a hydatid cyst (Davson, 1941) to muscular hypertrophy (DeCamp and Birchall, 1958), but by far the commonest cause is atheromatous change in the renal artery, usually close to its origin from the aorta. The disease may be bilateral. The type of disease which leads to obstruction in the renal arteries is sometimes more extensive, and thrombosis in the lower abdominal aorta spreading up to involve the renal origin is not uncommon (Leriche syndrome). An example of this is shown in Special Plate Fig. 3. It is worth bringing into prominence again the histological changes which may occur in the kidney beyond the constriction. Special Plate Fig. 4 shows a characteristic partial infarct in a patient with severe hypertension resulting from renal-artery stenosis. The histological changes described are not a consequence of the higher blood-pressure which exists in these patients, and this is shown in Special Plate Figs. 5 and 6 (patient W. F., Table II). Fig. 5 shows the characteristic partial-infarct picture, and this tissue came from the upper pole of the kidney of a patient with a stenosis in the main renal artery supplying this area. Fig. 6 shows the normal histology in the lower pole, which was supplied by an aberrant renal artery without a stenosis. As this

TABLE II.—Results of Function Tests in Patients with Various Forms of Renal Disease

Patient	Diagnosis	Urine Flow (ml./min.)	Na (mEq./l.)	Cl (mEq./l.)	P.A.H. Clearance (ml./min.)	P.A.H. Concentration (mg. per 100 ml.)	P.A.H. Excretion
W. F.	Renal-artery stenosis, left side	R. 4.0 L. 2.0	60 50	52 45	242 95	236 181	— 96%
A. T.	Renal-artery stenosis, right side	R. 0.2 L. 4.5	67 135	32 123	40 234	752 168	— —
H. M.	Not diagnosed; left side	R. 2.1 L. 0.8	156 136	140 111	212 155	325 609	— —
E. J.	Hydronephrosis, left side	R. 3.9 L. 1.1	64 91	48 59	236 56	232 187	— 70%

patient had malignant hypertension, this demonstrates that the changes were not a consequence of this. In the presence of renal-artery stenosis there is not necessarily a marked change of this type, since in another patient who had a severe stenosis with marked reduction in blood-flow there was only slight change. This latter state is, of course, what is usually found experimentally in the kidney with a clamped renal artery; the hypothesis is that the clamp protects from the effects of the hypertension, whereas, as in the rat (Wilson and Byrom, 1941; Byrom and Dodson, 1949), the unclamped kidney develops vascular lesions.

Recognition of the Stenosis

There are certain features which are of special help in recognizing unilateral stenosis or which are associated with it; these are: (1) severe hypertension with no other demonstrable cause at any age; (2) rapid progression of benign to malignant phase; (3) history of other vascular occlusions; (4) loin pain with fever and leucocytosis, especially in the presence of a source of emboli; (5) polyuria and proteinuria; and (6) murmur over abdomen. Some of these points have been considered by Perera and Haelig (1952). It should be stressed that the condition is to be suspected in severe hypertension at any age if there is no other ready explanation, and especially if there is any disparity in size between the two kidneys (Hodson, 1957). The common occurrence of malignant hypertension is especially to be noted, and cases have been reported from the age of 6 months upwards. The change in the course of benign hypertension observed over years is often to be recognized and emerges in the history. For example, a patient aged 45 years had angina pectoris with shortness of breath on exertion. This passed off, and two years later he developed typical cardiac asthma with dimness of vision due to severe retinal changes. He had stenosis of a renal artery (case W.F., Special Plate Fig. 5). This also serves to illustrate a third point, that a history of other vascular occlusions is helpful—in this case angina, but in another case a man who had had intermittent claudication since he was a youth and who abruptly developed cardiac asthma with severe hypertension at the age of fifty. This case was an example of Leriche's syndrome with, in addition, partial occlusion of the renal artery (Special Plate Fig. 3). The state of the femoral arteries therefore becomes a matter of clinical importance. The malignant phase in these patients is often precipitated by a renal-artery thrombosis announced by an attack of loin pain, which may last for some days and which is associated with fever and a leucocytosis. If there is a source of emboli in the

heart, then this should be especially borne in mind, and if this diagnosis is made it should represent an indication for immediate operation.

Now, there is a rarity which I have not personally seen but which figures in four case reports (Deming, 1954; DeCamp and Birchall, 1958; Øster, 1947; Margolin *et al.*, 1957) in association with renal-artery stenosis, and that is polyuria. Large volumes of urine of lower than usual specific gravity are passed. Unfortunately there are few further details of the composition of the urine. In any case, this seems to be an effect exerted on the normal kidney, and clearly it raises the possibility of some humoral effect, since removal of the affected kidney led to a normal urinary output in all these cases, and even to the disappearance of proteinuria. Intensive study of this situation in future cases would help to throw some light on the mechanism of the hypertension.

Finally, I would like to emphasize a lesson which I have learnt personally from my colleagues the vascular surgeons—namely, to auscultate over arteries. In this way it is often possible to pick up loud systolic murmurs from stenosed arteries. In one patient (W. F., Special Plate Fig. 8) the murmur disappeared when the stenosed renal artery thrombosed. Such a murmur may be heard anywhere between the xiphisternum and the navel on either side of the midline, and a similar murmur lower down or over the femoral arteries draws attention to irregularities in the arterial lumen, which are usually due to atheroma and may indicate a similar process at the mouth of a renal artery.

Radiological Demonstration

The demonstration, usually on intravenous pyelography, of the difference in size between the kidneys often calls attention to the possibility of a renal-artery stenosis. That smaller changes may also be noted has been emphasized by Hodson (1957). In our own cases we have found that aortography (see Poutasse and Dustan, 1957) or selective renal-artery catheterization has given the best results. Dr. D. Sutton carried out these investigations. Aortography was performed either by direct puncture through the back or by a catheter inserted upwards through the femoral artery. Selective catheterization of the renal arteries was carried out using the technique of Edholm and Seldinger (1956) and Ödman (1956) (see also Gregg, Allcock, and Berridge, 1957). Special Plate Fig. 3 shows the appearance of thrombosis in the lower abdominal aorta, involving the left renal artery, which was associated with very severe hypertension. Special Plate Fig. 7 shows the normal appearances on selective catheterization with the finer vessels right out to the cortex clearly demonstrated. Special Plate Fig. 8 illustrates a typical example of a stenosis of the renal artery close to its origin (see Special Plate Fig. 5 for histology). This patient had malignant hypertension. This is a typical appearance of an atheromatous block in the artery.

Pyelography

It has been shown that there is a very wide range of pyelographic appearances in normal subjects, and that it is quite possible to have appearances within the normal range even though defective renal function is present (Graber and Shackman, 1956). It has previously been reported that a normal pyelogram may be obtained in the presence of a renal-artery stenosis (Poutasse and Dustan, 1957), and Special Plate Fig. 9 shows a beautiful

example of this. On the right side a very clear pyelogram is shown, and any suspicion would be directed to the left side. However, Special Plate Fig. 10 shows the renal arteriogram with a severe stenosis and dilatation beyond. Further studies of this patient revealed a very marked reduction in blood-flow to the kidney (A. T., Table II). The post-stenotic dilatation shown is often present, but is not yet explained.

Renal Function

The next important aspect of renal-artery stenosis, which probably applies to the obstruction of smaller arteries and arterioles within the kidney itself also, is the effect on function. Earlier, Goldring and his colleagues made some rather sweeping statements about the rarity of unilateral differences in renal function with hypertension (Goldring and Chasis, 1944). This position was surely due to selection of cases, since most subsequent workers have found that studies of bilateral function by clearance techniques with ureteric catheters in place can show differences. Graber and Shackman (1956) produced a careful study in which they showed that nephrectomy might have a successful outcome if the renal plasma flow and glomerular filtration rate were low on one side and normal on the other. However, further studies have been made, especially by Connor *et al.* (1957), who utilized the observations made by White (1950) in the dog. This worker showed that constricting the renal artery led to a reduction in urine flow associated with a fall in sodium concentration. Such observations on urine flow have been made before by Richards and Plant (1922), and on urine flow and sodium excretion by Selkurt (1951). Connor and his colleagues claimed that unless this relation of a low flow and lowered sodium concentration on the affected side were present, nephrectomy would not be successful in relieving the hypertension.

Some of our own results on function are shown in Table II, where the measurements of urine flow refer to equal times of collection from ureteric catheters in both sides, during which time there was no leak into the bladder so that total urine flow is measured. P.A.H. clearance was measured during a similar period. P.A.H. extraction was measured by collecting simultaneously arterial and renal vein samples. It can be seen in the first two cases, both of which had severe stenosis of the renal artery, that the urine flow and sodium concentration on the affected side are both lowered. I would immediately like to contrast this with the findings in the last case (E. J.), in which there is a big difference in the urine flow on the two sides, but the sodium concentration is higher where the urine flow is lower. This patient had a hydronephrosis on the affected side associated with mild hypertension.

To show that the findings do not apply only to blocks in the main renal artery, consideration of patient H. M. will be helpful. On arteriography in this case no blockage of the renal artery was visible, but function studies revealed a lowered sodium concentration on the side of low flow, so that these findings bear out those of Connor and his colleagues; but we have not yet enough experience to comment on the prognostic value after removal of the kidney.*

*The fall in blood-pressure post-operatively in patients W. F. and A. T. (Table II) is shown below.

Patient W. F.:	mm. Hg	Patient A. T.:	mm. Hg
Initial (29/10/58) ..	260/160	Initial	} (7/1/59) 250/140
Nephrectomy (22/5/59)	220/140	Renal	
Final (13/10/59) ..	140/90	endarterectomy	
		Final (20/10/59) ..	
			160/90

It will be observed that the chloride concentration follows that of sodium precisely. The P.A.H. clearances are low on the abnormal sides in all these examples; but it is worth pointing out that these observations contain the probable answer to the paradox of the excellent pyelogram on the abnormal side. Consider patient A. T. Despite the low flow on the left side, the P.A.H. concentration was much higher than on the normal right side. As diodone is treated similarly to P.A.H. by the tubules it is not surprising that the pyelogram should give such an intense shadow. Information obtained by extraction ratios across the kidney is not great, but a high extraction ratio (see patient W. F.) does not imply a normal kidney, since, if the flow is low enough, presumably the tubules left are capable of extracting the P.A.H. satisfactorily.

Operation

When operation is decided on, the question of which procedure should be used arises. Poutasse and Dustan (1957) recommend that nephrectomy should be

DIAGRAM 1.—Direct measurement of aortic and renal-artery pressure in mm. Hg) at operation in a patient (W. F.) with renal-artery stenosis. The top tracings are before, the bottom tracings after, thromboendarterectomy.

performed if there is much evidence of atrophy and reduced function. However, before that or any other step is decided on, the situation at operation must be assessed. It is especially important to measure the pressure across the stenosis. If it is intended to do any reconstructive surgery it is imperative, since if there is no fall in pressure it is pointless to go farther. Diagram 1 shows the fall in pressure from the aorta to the renal artery distal to a stenosis (patient W. F.), and it can be seen that this is about 50 mm. Hg before endarterectomy, and that it is reduced, but not returned to normal, after operation. Whether an absolute minimum fall in pressure will be required before an operation is considered necessary, only further experience will decide. It should be noted from this figure that there was still hypertension beyond the stenosis before and after the operation. This may mean

DIAGRAM 2.—Treatment of renal-artery stenosis.

that reconstructive surgery is pointless. The importance of this pressure measurement may be illustrated by patient P. P. with malignant hypertension, whose arteriogram is shown in Special Plate Fig. 11. The stenosis in the left renal artery was excised and anastomosis to the aorta performed without pressure measurements. Special Plate Fig. 12 shows the renal histology. Fibrinoid necroses were present in this kidney, which suggests that the fall in pressure across the stenosis was not great and that the operation was unnecessary.

Procedures

The type of operation depends on the local condition, and Diagram 2 illustrates some common approaches to the problem. Nephrectomy is for the very damaged kidney, while the other approaches are there to meet the pathological and anatomical situation.

Post-operative Changes in Renal Function

We have had the opportunity of studying the immediate effects of operation in one case in which ureteric catheters were left in place (see Diagram 3). Before operation there was the usual finding of lower flow and sodium concentration on the stenosed side,

DIAGRAM 3.—Post-operative changes in renal function after relief of stenosis (patient A. T., Table II). Pre-operatively are shown comparisons of sodium concentration during successive 15-minute collections from both kidneys through ureteric catheters. Concentration is always lower on the affected side (R). Post-operatively, after relief of the stenosis, with catheters in place the urine flow rose and the sodium concentration became much higher than on the normal side, even though the urine flows were of the same order.

whereas after removal of the stenosis the urine flow and sodium concentration rose above that on the normal side. Further study is needed if we are to understand this situation.

Results of Treatment

It is worth considering here the results in all unilateral nephrectomies, since it is probably too early to give adequate figures for operations to relieve obstructions in the main renal arteries. The procedure of unilateral nephrectomy for hypertension fell into disrepute because of what might be termed a "wave of scalpels." Homer Smith (1948) raised a dissident voice and asked for selection of cases on good grounds and not on mere

anomalies of pyelographic appearance. The criteria of cure which he demanded are: (1) definite hypertension must be established clearly before operation; (2) post-operatively blood-pressure must be reduced to 140/90 mm. or below; (3) pressure must remain down for at least one year (Smith *et al.*, 1943). Using these criteria he collected most of the cases appearing in the literature and assessed them, starting with the initial demonstration by Butler in 1937 that a cure was possible (Smith, 1956). I have divided the figures into two groups (Table III). It can be seen that even in the last

TABLE III.—Results of Unilateral Nephrectomy: Cases Collected from the Literature (Smith, 1956)

Periods	No. of Cases	"Cures"
1937-56	575	26%
1948-56	333	25%

eight years up to 1956 the cure rate stayed at 25%, and this is probably better than in practice, since many failures will not be reported. This, of course, suggests that more adequate means of selection for nephrectomy will be required, and this applies to renal-artery stenosis as well as any other form of unilateral renal disease. However, in man there are reports of cures lasting as long as 18 years (Goldblatt, 1958a). This author refers to a case of juvenile hypertension treated by unilateral nephrectomy in which the patient grew up to be a normal young woman who had three children and three husbands.

A point which must be made immediately is that, as in the early days of nephrectomy for unilateral renal disease shown by pyelographic appearances, operations to relieve renal-artery stenosis will fall into similar disrepute if great care is not taken in the selection of cases and the correlation of function with the outcome of nephrectomy carefully made. To remove kidney tissue which is contributing some excretory function without being sure that it is exercising a harmful influence as well is bad practice.

Points from Results

Some interesting points that arise are that in many patients the high blood-pressure may fall to normal within 24 hours of nephrectomy and stay there. This suggests that, whatever the influence of the kidney in hypertension, in some cases it is very easily removed. This is reminiscent of the hypertensive animal with the clipped renal artery in which a normal blood-pressure is re-established after removal of the kidney in the early weeks of hypertension (Pickering, 1945). As mentioned above, there may be alterations in the function of the opposite kidney—for example, polyuria and even urea excretion—which improve after removal of the affected kidney. This may, of course, be a reflection of the effects of the high blood-pressure itself. It adds further point to the observation that, as in the rat, the presence of a normal kidney is not sufficient to protect from the effects of an abnormal kidney. One striking feature in the study of renal hypertension in both man and animals is that many factors seem to be causally implicated, and it is those who subscribe to a unitarian view who run into difficulties.

To emphasize these varying effects of the kidney I would finally like to describe the results of one of the most striking experiments in human hypertension ever made. This concerns one of the identical twins studied by Murray *et al.* (1958), in whom a transplanted kidney relieved the high blood-pressure while the two

abnormal kidneys were still present. The blood-pressure fell progressively after the transplant, and subsequent removal of the two abnormal kidneys led to no further fall in blood-pressure. It is difficult to visualize that this transplanted kidney was destroying a circulating vasoconstrictor, and it certainly was capable of restoring the excretory situation in the recipient to normal. However, Hume (1958) has reported a case with a similar transplant in which the blood-pressure did not fall until the two abnormal kidneys were removed. This suggests most strongly that we have to expect a wide variety of situations, different from patient to patient, as an explanation for the prevailing level of blood-pressure, and in man no full analysis has been given of any one situation.

[The second Goulstonian Lecture, together with a list of references, will appear in our next issue.]

A "POLYOMA" VIRUS DERIVED FROM A MOUSE LEUKAEMIA

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[WITH SPECIAL PLATE]

Stewart and her colleagues (Stewart, Eddy, Gochenour, *et al.*, 1957; Stewart, Eddy, Haas, and Borgese, 1957; Eddy, Stewart, and Touchette, 1958; Eddy, Stewart, Young, and Mider, 1958; Stewart, Eddy, and Borgese, 1958; Stewart and Eddy, 1959) isolated a filterable agent and found it to produce a wide variety of tumours when inoculated parenterally into very young mice, hamsters, and rats. This "polyoma" virus was present in extracts of induced mouse parotid-gland tumours and in spontaneous leukaemias, and multiplied in cultures of monkey kidney or mouse-embryo cells. The virus was cytopathogenic for the cultures, resisted heating to 56° C., was insensitive to ether, and haemagglutinating for guinea-pig, rat, and human Group O cells at +4° C., but not at room temperature.

Tissue-culture Studies

A virus with very similar properties has now been isolated by us. It was derived from the spleen of a male AK mouse with spontaneous lymphocytic leukaemia, by inoculation of the cells into replicate, seven-day-old cultures of trypsinized embryos from C3H or C57 mice. The cells were grown in roller tubes in a medium comprising lactalbumin hydrolysate, calf serum, and Hanks's salt solution (with added antibiotics). After seven days cytopathic changes were observed in some cultures, and cell-free media from such cultures were used to infect fresh embryo cells. The cytopathic changes appeared within ten days of infection, and were characterized by rounding-up of the cells and a degeneration of their nuclei, which was particularly apparent in Feulgen-stained preparations.

The fluids from these cultures infected fresh mouse embryo cultures at a dilution of 10⁶, and the infectivity

was not reduced by centrifugation followed by filtration through bacteria-tight sintered glass filters. Like the Stewart polyoma agent, this virus agglutinates guinea-pig erythrocytes at +4° C, is heat- and ether-resistant, and its infectivity for cell cultures is neutralized by rabbit antiviral antiserum.

Infection of Mice and Hamsters

Cell-free media from infected cultures in which cell degeneration was pronounced were inoculated parenterally into newborn C3H mice and into golden hamsters up to five days of age. Within 28 days the hamsters died or were killed, and were found to have blood-stained peritoneal effusions and haemorrhagic lesions in the liver, uterus, and lungs, and multifocal sarcomas of the kidney and heart and sometimes of the liver. Emboli were present in the lungs and thrombi in the liver, and the vascular endothelium showed a general hyperplasia. Some of the animals died within 14 days in an apparent acute stage of the disease. These all showed typical haemorrhagic lesions and less frequently had tumours, though they had all been inoculated by the intraperitoneal route with cell-free medium from infected cultures.

There was a characteristic dwarfism in mice, which Stewart and her colleagues have also noted. Other animals had kidney sarcomas, and one female mouse killed 80 days after inoculation had multiple mammary carcinomas. These mammary tumours are being serially transplanted, and polyoma virus has been demonstrated by passage in tissue culture. Very young rats can also be infected with this virus, but, in general, lesions can be produced more consistently in hamsters than in mice or rats.

Control cultures of mouse embryo cells have never shown cytopathic changes, and neither the medium nor the cells produce tumours or the other lesions characteristic of polyoma virus after inoculation into mice and hamsters.

Cell-free extracts of the hamster tumours are not infective for newborn or adult hamsters. However, some polyoma virus must be present in these tumours, for the cell-free extracts produce cytopathic effects in mouse-embryo cell cultures and the cell-free medium from such cultures again produces haemorrhagic lesions and tumours in hamsters. The function of the culture in augmenting either the quantity or the virulence of the virus is being studied.

These hamster kidney sarcomas have been successfully transplanted subcutaneously into both male and female hamsters, and to date are in their tenth passage. The tumours develop at the site of inoculation, but grow progressively only in a proportion of the animals inoculated. In the first passage tumours grew in 11 out of 16 hamsters implanted, and in the second passage, from a rapidly growing tumour, in 7 out of 10. However, as the hamsters are bred in a closed colony and not by brother-sister mating, it is not surprising that some of the tumours tend to regress. The tumour-bearing animals do not develop metastases, and no haemorrhagic lesions have been observed. The virus is still present in the tumour, however, and may be demonstrated by the reculture of cell-free extracts in the way already described.

Cell cultures of these hamster kidney tumours have also been established, and these cells liberate virus into the culture medium. The cells, too, retain their

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FIG. 1.—Irradiation nephritis. Fibrinoid necrosis in walls of renal arteries. ($\times 300$.)

FIG. 2.—Partial infarct due to tying aberrant renal artery. Note atrophic tubules with normal glomeruli. ($\times 112$.)

FIG. 3.—Aortogram of patient with thrombosis of lower abdominal aorta which extended up to involve origin of left renal artery, seen to be small compared with right. Nephrogram of left kidney shows it to be much smaller than right. A., aorta; R.A., renal artery; R.K., right kidney; L.K., left kidney.

FIG. 4.—Partial infarct due to renal-artery occlusion by aortic thrombosis, in man with Leriche syndrome and severe hypertension. Note atrophic tubules with normal glomeruli. ($\times 100$.)

FIG. 5

FIG. 5.—Partial infarct from upper pole of kidney with renal-artery stenosis due to atheromatous plaque. (Patient W. F., Fig. 8.) ($\times 94$.)

FIG. 6

FIG. 6.—Normal renal histology from lower pole of same kidney as Fig. 5, which was supplied by an aberrant artery. In renal biopsy material the tubules have a characteristic fluffy appearance which is quite normal. ($\times 94$.)

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FIG. 7.—Normal right renal arteriogram obtained by selective catheterization. Fine vessels can be seen right out to cortex.

FIG. 10.—Selective renal arteriogram showing stenosis at origin due to atheromatous plaque with dilatation beyond. Tip of catheter abuts on plaque at mouth of artery.

FIG. 8.—Selective renal arteriogram showing stenosis at origin of renal artery with dilatation beyond. Tip of catheter abuts on atheromatous plaque at mouth of artery.

FIG. 11.—Aortogram of patient with renal-artery stenosis beyond origin of left renal artery. Right kidney and its artery were small. A., aorta; R.A., renal artery; S., stenosis.

FIG. 9.—Intravenous pyelogram showing well-marked pelvicalicine pattern on right and obscure picture on left. The right kidney was, however, the abnormal one. (See Fig. 10.)

FIG. 12.—Renal histology of kidney shown in Fig. 11. Fibrinoid necroses are seen in three vessels on left-hand side of glomerulus at top of figure. A., arterioles showing fibrinoid necrosis; G., glomerulus. ($\times 100$.)