Experience with arterial changes in the pulmonary vasculature in pulmonary hypertension suggested a search for like changes in the systemic circulation in the case of systemic hypertension. The mechanism by which a rise in the pulmonary arterial pressure follows widespread obstruction within the limited pulmonary circulation, however, was not expected to be aped in the case of a raised systemic blood pressure, because it has been unusual in patients with systemic hypertension to find such severe and universal obstruction affecting the more extensive systemic arterial circulation. Moreover, a common pathology for the two clinical states would appear to be inconsistent with the current impression that it is rare to find the two conditions side by side in the same patient. In the case of pulmonary hypertension the cardiac output is so reduced as to subdue any tendency that might be present to cause the systemic pressure to rise; but should systemic hypertension be established in the first instance, the addition of pulmonary hypertension is not similarly retarded, and indeed there is evidence that this association does take place, creating a state of holohypertension (Evans, 1959 b).

Renal disease has been long identified with certain forms of hypertension, and ever since the brilliant researches of Goldblatt and his co-workers (1934 and 1937) identified renal ischaemia as a cause of hypertension in the experimental animal, it has been natural to suggest that changes in the vasculature of the kidney in man may produce the same persistent rise in blood pressure, which in turn initiates changes in the extrarenal arterial system. For this reason, and especially having regard to the changes described in the pulmonary arteries in pulmonary hypertension (Gilmour and Evans, 1946; Evans, 1951; Evans et al., 1957; Evans and Short, 1957 and 1958; Evans, 1959 a), a study of the arterial system, particularly of the kidney, was continued in patients with systemic hypertension.

The Investigation. The work was carried out in three parts. First, kidneys obtained from necropsies of subjects in whom neither renal disease nor hypertension had been discovered in life were examined histologically, as well as kidneys removed surgically for one reason or another from patients without hypertension. Such a group provided examples of the normal renal arterial architecture. Secondly, in that the rate of dye excretion by the kidney might provide a clue as to the state of the renal circulation, inadequate though it be as a test of the efficiency of the whole renal vasculature, it was estimated in 22 patients in whom there was hypertension without clinical evidence of associated renal disease. In three patients where a significant delay in excretion was confined to one side, the affected kidney was removed surgically and subsequently examined histologically. Thirdly, renal and other arteries were examined in patients who had died from one of the complications of hypertension.

Whenever a diagnosis of systemic hypertension had been made in life, it always depended on finding clinical, electrocardiographic, and radiological evidence of specific cardio-arterial derangement in addition to the raised blood pressure readings (Evans, 1957). This adherence to a definition of hypertension was a particular care, for a less exacting appraisal of a raised blood pressure would inevitably lead to a wrong conclusion on the incidence of arterial lesions in the condition. In the
past, a failure to insist on such a rigid definition of hypertension has sullied the inference drawn from painstaking research into the subject.

The findings of the investigation are given for the three named clinical groups, and relate consecutively to normal renal arteries, arteries of kidneys removed in hypertension, and the systemic arterial system (including the renal arteries) in cases of hypertension examined at necropsy.

**THE NORMAL RENAL ARTERIES**

Examination of the vasculature of the normal kidney was made in two groups of cases, the one in bodies where death had taken place from a non-renal cause and where hypertension was absent, and the other where kidneys had been removed from patients without hypertension. The examination sometimes included preliminary arteriography, and always microscopy, where sections were suitably stained for elastic tissue.

*Renal Arteriography.* The arterio-arteriolar pattern of the kidney was obtained by radiography following injection of a radio-opaque substance after the manner described by Short (1957) for pulmonary arteriography.

In normal kidneys the radiogram showed a constant pattern where the main arterial stem

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**Fig. 1.—Renal arteriogram. (A) Healthy kidney. (B) Systemic hypertension, showing loss of finer branches and tortuosity of terminal branches.**
THE AETIOLOGY OF SYSTEMIC HYPERTENSION

gave rise to branching which in turn divided into lesser twigs, and eventually ended without interruption in diminutive thread-like extensions representing arterioles of a diameter of 0.05 mm. (Fig. 1). Such a characteristic pattern ensured the absence of obstructive arterio-arteriolar disease at a subsequent histological examination.

**Histology.** The renal arteries are muscular arteries with a media bounded by an outer and inner elastic layer, and are continued into arterioles, which measure less than 0.1 mm. in diameter, with walls consisting of a single elastic layer.

![Fig. 2.—Normal renal arteries from three subjects.](image)

<table>
<thead>
<tr>
<th>A</th>
<th>Single internal elastic layer in (A) (280µ diam.)</th>
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<tbody>
<tr>
<td>B</td>
<td>Double internal elastic layer in (B) (430µ diam.)</td>
</tr>
<tr>
<td>C</td>
<td>Multiple internal elastic layers in (C) (430µ diam.)</td>
</tr>
</tbody>
</table>

It is generally recognized that in most muscular arteries, soon after birth, the normal intima consists of two layers, Thoma's musculo-elastic coat and Jores' hyperplastic intimal coat, but according to Turnbull (1915) these separate layers are not present in the renal arteries of young subjects, and only develop there in abnormal states. In older subjects, however, the finding of two, or sometimes even three, internal elastic layers in the muscular arteries of an otherwise normal kidney, and in the absence of hypertension, is so common as to be accepted as a natural finding (Fig. 2). Such limited intimal reaction is never so intense as to trespass on the arterial lumen enough to diminish significantly its usual bore. In older subjects too, the larger arteries occasionally show local plaques of atherosclerosis.

**THE RENAL ARTERIES IN SYSTEMIC HYPERTENSION**

**Renal Arteriography.** No method is available so far that will accurately portray during life the architecture of the renal arteriolar system. A radio-opaque substance, introduced either by a
translumbar aortic puncture or through a femoral arterial catheter or by selective renal arteriography where the tip of the catheter is guided into the renal artery under radiological visualization, has given information about renal and extrarenal lesions (Murray and Tresidder, 1957; Gregg et al., 1957). Such tests, however, are often difficult to carry out, involve distinct risks, and in the meantime yield scanty information about the state of the small renal arteries.

*Intravenous excretion urography* is similarly inadequate for this purpose. In the belief, however, that limited information might be gleaned about the relative efficiency of the renal circulation on the two sides, the investigation was carried out in 22 consecutive patients with hypertension, each with left ventricular preponderance in the electrocardiogram and with varying evidence of left ventricular hypertrophy on cardioscopy. Following the intravenous injection of uroselectan, radiograms of the kidneys and ureters were taken at intervals of 2, 5, 8, and 20 minutes. No delay in dye excretion was evident in 10 patients. Among the remaining 12, the delay was confined to one side in three and on both sides unequally in nine. The actual rate of excretion in the series is shown in Table I.

**Kidneys Removed from Patients with Hypertension**

The results of the dye excretion tests were conveyed to the three patients where a delay was appreciable on one side (Cases 1, 2, and 3), and when nephrectomy was proposed, it was explained that the procedure was unlikely to prove curative, and that it might not even ameliorate their light symptoms; all three consented to the operation and nephrectomy was accordingly carried out. The fact that each patient insisted that improvement followed the operation was not held to give proof that material benefit had taken place, but certainly no deterioration was noticed during 12 months when they remained under close observation subsequent to nephrectomy. Early in the

<table>
<thead>
<tr>
<th>Case No.</th>
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0=none. + = small amount. ++ = moderate amount. +++ = large amount.

**Table I**

<table>
<thead>
<tr>
<th>Renal Excretion Tests in</th>
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<tr>
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<tr>
<td>Case No.</td>
<td>Amount</td>
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WILLIAM EVANS
THE AETIOLOGY OF SYSTEMIC HYPERTENSION

22 PATIENTS WITH SYSTEMIC HYPERTENSION

<table>
<thead>
<tr>
<th>Case No.</th>
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<th>After 8 minutes</th>
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Second World War all three patients left their homes for rural districts and their eventual progress could not be traced. For that reason too, the opportunity to examine the remaining kidney should they have died, as was expected, from the effects of hypertension which had persisted in each patient following the operation, did not materialize. The immediate post-operative progress of the three patients was described at a meeting of the British Cardiac Society in May 1940, but the account of the meeting was not published.*

A brief summary of each of the three cases will now be given, which will include an account of the changes in the blood pressure following nephrectomy, and in the arteries of the extirpated kidney.

Case 1. A. C., a woman, aged 63, had been subject to headache for many years, as well as shortness or breath on exertion, and chest pain that was not characteristic of cardiac pain. On account of these symptoms she was unable to walk more than 200 yards without resting. The blood pressure was 210/130 when first examined. The peripheral arteries and the retinal arterioles were contracted, the left ventricle was enlarged, and the cardiogram showed left ventricular preponderance. There was neither oedema nor albuminuria, and the blood urea was normal. There was no pulmonary congestion when examined by cardiography. Faulty excretion appeared in the right kidney on two occasions following intravenous uroselectan (see Table 1).

The changes in the blood pressure that followed nephrectomy are shown in Fig. 3. It fell immediately after the operation, but commenced to rise some days later, and it regained its pre-operative level a little over a month after nephrectomy. Her general condition improved, and had not again deteriorated a year later when she was instructed to leave the district because of the partial evacuation of civilians during the war.

The Renal Arteries. The larger arteries were normal having an intima composed of one elastic layer as a rule, or of two layers in places. The lumen of the smaller arteries was partially, and sometimes severely,

* The Secretary of the Cardiac Society entered in the Minute Book that the proceedings of the meeting had not been recorded owing to the invasion of Holland and Belgium by the Germans on the following morning.
reduced by intimal elastoid proliferation that lay adjacent to the media which showed either hypoplasia or aplasia (Fig. 4). There was contraction of these smaller muscular arteries, and the arterioles were narrowed by intimal proliferation.

Case 2. L. H., a woman, aged 60, had complained of tiredness, headache, breathlessness on exertion, mistiness of vision, and sleeplessness for over three years. The blood pressure when first examined was 280/150; for over a year it was recorded at weekly intervals, when innocent medicinal remedies were pre-
scribed, or when periods of rest were tried. At no time was there any appreciable change in the readings. The peripheral arteries and retinal arterioles were contracted. There was no papilloedema. The left ventricle was enlarged, but there was no pulmonary congestion at cardioscopy. The cardiogram showed left ventricular preponderance. There was no albuminuria and the blood urea was normal. Excretion urography was carried out following an intravenous injection of uroselectan. A slight delay occurred in both kidneys, but was more noticeable on the right side; the same result was obtained when the test was repeated (Table I).

There was a sudden fall in the blood pressure to normal values following a right-sided nephrectomy, but on the tenth day it commenced to rise, and after another 16 days it had regained its customary high reading (Fig. 6). Her progress during the next year was uneventful, and she was moderately free from her pre-operative symptoms until her evacuation to a rural district because of the war.

![Graph]

**Fig. 6.—Blood pressure readings in Case 2. Arrow indicates removal of right kidney.**

**The Renal Arteries.** There was much intimal elastoid proliferation in the larger renal arteries, whose media for the most part was intact. The smaller arteries were the seat of severe elastoid proliferation which had greatly reduced the bore of the vessels. Such proliferation lay adjacent to areas of hypoplasia, and sometimes aplasia, of the media (Fig. 5). Collateral vessels were sometimes patent, but more often they were partly or wholly filled with elastoid tissue. The muscular arteries were contracted. Intimal proliferation had partly or wholly closed numerous arterioles.

**Case 3.** A. O., a man, aged 56, had remained well except for two attacks of pain in his side, until four months before, when he complained of giddiness. His blood pressure was 205/140. The peripheral arteries and retinal arterioles were contracted. The left ventricle when viewed at cardioscopy was enlarged, but there was no pulmonary congestion. The cardiogram showed left ventricular preponderance. There was neither albuminuria nor papilloedema, and the blood urea was normal. An intravenous pyelogram showed a delay in the excretion of uroselectan on the left side (Table I).

No material change in the blood pressure followed left-sided nephrectomy, except that the diastolic reading was a little lower (Fig. 7). The patient’s progress during a year after the operation was uneventful, and he had remained well up to the time of his compulsory evacuation from the district owing to the war.

**The Renal Arteries.** Much intimal elastoid proliferation was present in the larger arteries, and especially in places adjacent to medial deficiencies. In the smaller arteries, intimal elastoid proliferation had either
**FIG. 7.**—Blood pressure readings in Case 3. Arrow indicates removal of left kidney.

**FIG. 8.**—(A) Severe intimal elastoid and fibroid proliferation almost wholly occluding renal artery (170μ diam.). (B) Organizing thrombotic occlusion of arteriole (60μ diam.). Case 3.

**FIG. 9.**—Magnification of the renal arteriograms shown in Fig. 1. The terminal branches in A (control) are straight, whereas in B (systemic hypertension) they are tortuous, and many are missing.
partly or wholly closed the vessels, and was associated with either hypoplasia or aplasia of the media. The muscular arteries were contracted, and the arterioles were often severely affected by intimal proliferation (Fig. 8).

The Renal Arteries in Reversible Hypertension. In a patient (Case 23) where the blood pressure was sometimes exceptionally high, there was no enlargement of the left ventricle nor frank cardiographic signs of left ventricular preponderance. Moreover, the peripheral arteries and the retinal arterioles were only slightly contracted. Excretion urography demonstrated a serious fault in one kidney only, and it was felt that success might attend nephrectomy in this instance. The clinical history and the progress of this patient are now to be described.

Case 23. A. R., a woman, aged 45 years, had complained of severe headache, tiredness, and shortness of breath, for over 15 years. During the previous nine years her family doctor had found her blood pressure to vary from 280/140 to 300/150, and had confined her to bed on several occasions because of severe headache. In hospital the blood pressure remained consistently high, but other cardiovascular derangement was absent. Intravenous and retrograde pyelography discovered renal ptosis and hydronephrosis on the right side, and when the right kidney was removed, a sharp kink was found at the junction between the renal pelvis and the ureter, and a number of cysts were present in the kidney substance.

The blood pressure fell immediately after the operation, and it never returned subsequently to its previous high level (Fig. 10). Her symptoms also disappeared, and she maintained that she had not felt so well for ten years.

The Renal Arteries. Some of the large arteries were normal, and their intima consisted of either one, or at the most two, elastic layers; others showed plaques of atheroma, especially over occasional medial defects. Intimal elastoid proliferation and arterial contracture had greatly occluded the bore of the lesser muscular arteries, whose media was almost everywhere intact (Fig. 11). The significance of this finding, namely intimal proliferation in the absence of medial hypoplasia, will be discussed in the section dealing with pathogenesis.

Kidneys from Necropsies of Subjects with Systemic Hypertension

In 13 consecutive patients with hypertension whom I had examined during life and found to have contracted peripheral arteries and retinal arterioles, left ventricular preponderance in the cardiogram, and left ventricular enlargement on radiological examination, the kidney was examined

![Fig. 10.—Blood pressure readings in Case 23. Arrow indicates the time of removal of the right kidney.](http://heart.bmj.com/)
histologically following necropsy. Papilloedema had been a terminal finding in three patients, and a constant finding in four. Sometimes renal arteriography was carried out before histological examination.

**Renal Arteriography.** Whenever the kidney was injected with a radio-opaque solution, it gave the same appearance as in pulmonary arteriography in the case of pulmonary hypertension. Thus, a number of renal arterioles and lesser arteries were missing from the arteriogram, giving it a denuded appearance when compared with the normal picture. Moreover, magnification of the arteriogram showed tortuosity of the arcuate vessels and of the finer terminal twigs in the renal cortex. These findings contrasted with the pattern obtained in healthy specimens where the finer vessels assume a straight course (Fig. 1 and 9). Hodson (1957) has described the same changes and he pointed out that narrowing of the true renal cortex naturally diminishes the distance between the zone that contains the arcuate vessels and the surface of the kidney.

Whenever the renal arteriogram was abnormal in the way described, subsequent histological examination discovered partial or complete obliteration of many of the lesser renal arteries and arterioles by intimal proliferation.

**Histology.** In each of 16 cases of systemic hypertension, 13 examined consecutively at necropsy and 3 where a kidney was removed during life, the histological appearances of the renal arteries were identical. Thus, the smaller muscular arteries were severely affected by intimal, usually elastoid, proliferation, which had always greatly diminished the lumen of the vessels and had sometimes occluded them. Such vessels showed either hypoplasia of the media producing local deficiencies in the wall, or generalized aplasia when no remnant of the media remained (Fig. 4, 5, 8, and 12). The arterioles were also narrowed and frequently occluded by intimal proliferation, which was often elastoid by nature, but was sometimes fibrotic when it was indistinguishable from organizing thrombus (Fig. 8 and 13). These changes are discussed later in relation to the part that they may play in the pathogenesis of systemic hypertension.

**The Extrarenal Arteries in Systemic Hypertension.** The small arteries of the pancreas, liver, gastro-intestinal tract, and spleen were examined histologically in cases of hypertension by Morlock (1939), who measured the thickness of the wall and the diameter of the lumen in each instance. He compared these measurements with those he obtained from normal specimens. In the normal,
the wall to lumen ratio was approximately 1 to 2 in the different organs with the exception of the spleen where the measurements varied. In severe hypertension, the arteries to the pancreas, liver and intestines, showed a wall to lumen ratio of approximately 1 to 1. The smaller coronary arteries were similarly affected, but to a lesser extent. Morlock considered that the alteration in arterial structure was due to hyperplasia with subsequent fibrosis and degeneration of the media and intima, and wondered whether it was a primary change and had caused the hypertension from an increase in the peripheral resistance. Johnson (1868) ascribed these changes to hyperplasia and hypertrophy of the muscular elements of the media, and considered that they were the outcome of increased work secondary to hypertension. Gull and Sutton (1872) in their classical paper described the changes as hyaline and fibroid degeneration of the media.

The extrarenal arteries were also examined histologically, and sometimes by arteriography, in the cases of hypertension examined at necropsy in this series. The most constant and character-
Fig. 13.—Intimal fibroid proliferation of arterioles in three cases of systemic hypertension, causing complete vascular occlusion. (A: renal arteriole from Case 24. 95μ diameter. B: renal arteriole from Case 33. 85μ diameter. C and D: retinal and renal arteriole respectively from Case 26. 50μ and 100μ diameter).

Characteristic finding was arterial contraction as described by Evans and Short (1957 and 1958) in the pulmonary arteries of patients with pulmonary hypertension. This appearance, which was specially noticeable in renal, intestinal, and pancreatic arteries (Fig. 14), gave the false impression of medial hypertrophy, for in spite of their small size, having an external diameter of less than 100μ and in this particular resembling arterioles, they possessed a media bounded by an external and internal elastic layer, and this confirmed that they were muscular arteries that had contracted into the smaller size. Later, Short (1958), studying the arterial bed of the small intestine by post-mortem arteriography in control cases and in patients with systemic hypertension, again concluded that such narrowing was organic and not functional in its inception.

Allusion has already been made to the tortuosity of the lesser renal arteries in systemic hypertension. When this was sought in extra-renal arteries, and when the coronary circulation was selected for this purpose, it did not prove to be a constant finding. Tortuosity of the coronary arteries appeared to be partly related to the degree of myocardial hypertrophy affecting that portion of the heart supplied by the arteries showing this change (Fig. 15).
Fig. 14.—Contracted arteries from the duodenum (A: 40μ diam.) and the liver (B: 75μ diam.) in Case 28 with systemic hypertension. In spite of their small size the presence of media identifies them as muscular arteries.

Fig. 15.—Tortuosity of the coronary arteries in the hypertrophied right ventricle in emphysema (A), and in the hypertrophied left ventricle in aortic regurgitation (C), compared with normal coronary arteries from a subject of comparable age (B).
THE PATHOGENESIS OF SYSTEMIC HYPERTENSION

Although the cause of systemic hypertension has evaded the assiduous researches of so many scientific workers, their exertion has seldom been in vain, for through observation or experiment they have contributed to our knowledge of the usual course of the illness, and so indirectly to its cause. Indeed, since the introduction of the sphygmomanometer, many reasons for a raised blood pressure have been uncovered, e.g. coarctation of the aorta, phaeochromocytoma, and pituitary basophilism. It is the common form of hypertension, usually insidious in its presentation but sometimes appearing more abruptly as its malignant or papilledemic kind, that still eludes an explanation of its etiology that will gain common acceptance.

Before proposing for systemic hypertension a cause based on changes found during histological examination of the renal arteries, it is expedient to mention first the researches, both in the experimental animal and in man, that have helped to a better understanding of the mechanism whereby the blood pressure is both significantly raised and maintained.

Clinical Observations

Separation of Clinical Types. Clinical research has done much in the elucidation of distinct entities where the lesion causing hypertension in man has been indisputably identified. Among these may be included coarctation of the aorta, pituitary basophilism, adrenal neoplasm, and certain forms of one-sided renal disease. It has been natural to apply the lessons gathered from a study of these separate clinical states in the search of an explanation of the causative lesion in systemic hypertension, and uppermost among them have been the part that an endocrine disorder or renal ischaemia can play in its etiology.

Hypertonia Distinct from Hypertension. A hindrance to the discovery of the cause of systemic hypertension has been an over-reliance on the blood pressure reading in the diagnosis of hypertension. It has been shown (Evans, 1957) that a blood pressure, even when raised to impressive heights, can be an innocent affair provided it is fugitive and unaccompanied by specific signs indicating cardio-arterial derangement. In the future any search for the cause of hypertension in man should recognize this physiological elevation of the blood pressure and be directed exclusively to instances of true hypertension. The same care is needed in the analysis of pathological findings, whether collected by biopsy or at necropsy; such examination should take place unclouded by the mere knowledge that the blood pressure was raised during life, but relying solely on criteria that permit an unequivocal diagnosis of systemic hypertension.

Lessons from Therapeutic Measures. Special diets, vasodilators, sex hormones, and potassium thiocyanate, have all had their advocates as potent remedies in hypertension, but when these were tried in a series of patients, their hypotensive effects proved to be no greater than a placebo (Evans and Loughnan, 1939). Similarly, anti-renin substances have failed. Adrenalectomy and sympathectomy have had their adherents as beneficial measures, but they have been mostly abandoned. Ganglion-blocking agents are now the vogue but, in my view they too are unable to halt the disease process, or to benefit materially a patient with systemic hypertension where the significantly raised blood pressure keeps company with cardio-arterial derangement.

Probably in no other disease have so many remedies been tried as in hypertension. Hopes of a cure have waxed and waned. So often the physician has introduced a drug with great enthusiasm and later discarded it to turn with equal zeal to exalt the curative properties of some other potion. These excursions into therapeutis have not been in vain, provided they convince that the premise on which the use of an alleged remedy was suggested has been proved false, and have served to turn our minds to the underlying pathological changes that are at the root of systemic hypertension, changes that are both progressive and irreversible.

Hereditary Factor. Valuable information has been collected by several workers who have sought a family history of hypertension in patients suffering from the disease. This task is not an easy one, because as Platt (1947) has pointed out, a study of heredity in hypertension presents a difficulty common to all problems concerned with human genetics, namely that of studying some
THE ETIOLOGY OF SYSTEMIC HYPERTENSION

three generations simultaneously. Thus, in hypertension, the disease does not appear before middle-life, when the affected parent is dead and the offspring are as yet too young to contract it. Moreover, the statement by a patient that a parent had "high blood pressure" is unacceptable evidence of hypertension, unless the illness has been punctuated by a "stroke" or has been confirmed by unequivocal physical signs recorded by the family doctor or in hospital. In spite of these difficulties the assiduity of those investigators who have sought diligently the family history of hypertension in their patients has placed beyond doubt the view that heredity plays a part in its etiology.

Weitz (1923) found that in 63 of 82 patients with hypertension one or both parents had died of heart disease, angina, dropsy, or stroke. It cannot be assumed, however, that all such deaths had in fact been the outcome of hypertension. Ayman (1936) stated that the children of two hypertensive parents had a high blood pressure and a 47 per cent chance of developing hypertension in later life, but that when both parents had a normal blood pressure, the blood pressure in the children was lower and their chance of hypertension was only 3 per cent. Hines (1937) studied the family history of 608 subjects with a normal blood pressure, and 267 with essential hypertension. A positive family history of hypertensive cardiovascular disease was five times as frequent among those who had hypertension or who were hyper-reactors to a standard stimulus test, than among subjects who reacted normally to the test. In a study of 10 pairs of twins and 256 members of 30 families with raised or normal blood pressure, he found that the type of blood pressure reaction to the test followed an inherited pattern of a dominant character. He concluded that his findings provided strong evidence that the hereditary factor plays an important role in the development of essential hypertension. Schroeder and Steele (1941), discussing renal disease in the etiology of hypertension, opined that two separate factors were operating, one a renal lesion and the other a constitutional one, and that although singly each might not give rise to hypertension, acting together they might do so. In that 64 per cent of their 250 cases were descendants of patients with hypertension, they considered that the constitutional factor was primary, and hereditary or congenital, and was dependent on a specific internal derangement of the kidneys.

In 1947 Platt analyzed the records of 116 cases of hypertension with a view to determining whether the ones without a family history were those in whom hypertension was not of the primary or essential kind. The evidence that he collected agreed with the hypothesis that the so-called essential hypertension was a hereditary disease conveyed as a Mendelian dominant with a rate of expression of more than 90 per cent. The great majority of cases of hypertension that did not conform to this rule were not instances of essential hypertension, but were secondary to some renal or other cause. He was not prepared to say whether the inherited factor was specific for hypertension or was a tendency to arterial or arteriolar change affecting in some instances the renal vessels. Perera (1956) also stated that it was tempting to think that a group of people had an inherited susceptibility to vascular derangement as the result of a metabolic abnormality, as in diabetes or gout, so that primary hypertension appeared to be a genetic disorder.

Søbye (1956), from an investigation of 220 families with essential hypertension and nephrosclerosis and of 2800 healthy subjects, concluded that the two conditions represented a genetic entity, that the inheritance was dominant in kind, and that the morbid risk in the average population was 30 to 40 per cent. Harvald and Hauge (1956), investigating twins and other families by the proband method, found that when this was applied to 36 patients with hypertension, there was some preponderance of concordance among uni-ovular pairs of twins. Although this suggested a hereditary basis for hypertension, they emphasized that the small number of cases they investigated did not permit of a firm conclusion being drawn.

Evidence of Atavism. It has been accepted that polythelia or the presence of accessory nipples, is a manifestation of atavism (Darwin, 1888). The exhibition of atavism in any patient, indicating as it does a departure from the accepted normal for ancestral or more primitive tissue, supports the presence of an inherent tissue weakness or fault. When polythelia was sought in 2000 consecutive cases that presented for examination with suspected symptoms or signs of a cardiovascular
disorder, 1059 were judged to be healthy, and 49 of these showed polythelia, an incidence of 5 per cent. Of the remaining cases that showed some kind of cardiovascular disease, 108 had a blood pressure of 200/100 or over; 66 of these were patients with true hypertension, who showed cardio-arterial changes including left ventricular preponderance in the cardiogram, while the remaining 42 were examples of the innocent condition of hypertonia, in which the blood pressure, although impressively high, was not associated with any cardio-arterial abnormality. Polythelia was present in 23 or 35 per cent of the patients with systemic hypertension and in only 2 or 5 per cent of the subjects with hypertonia (Evans, 1959a). Since this publication the series has been enlarged so that among 110 cases of systemic hypertension there were 42 (39%) with polythelia, compared with 5 (or 7%) among 70 cases of hypertonia. This striking finding is accepted as giving support to the view that a hereditary predisposition is present in systemic hypertension.

Experimental Evidence

The Rôle of the Splanchnic Circulation. Early on, physiologists demonstrated a rise in blood pressure following constriction of the splanchnic vessels, and this gave rise for a time to the belief that an increased vascular tone in this area was the cause of hypertension in man. A lowering of the blood pressure, following dorso-lumbar sympathectomy, appeared to support this view, although the hypotensive effect of such a procedure could be the result of removal of the mechanism that normally adjusts the natural variation in the blood pressure. It has been found that total sympathectomy in the experimental animal can neither prevent nor relieve hypertension. The belief that hypertension might be caused by increased peripheral resistance limited to the splanchnic vessels was also disputed by Prinzmetal and Wilson (1936) who recorded the resting blood flow in the arm in various types of hypertension, and found that it was no greater than in subjects with a normal blood pressure, and that it could be increased to the same extent by heat, reactive hyperaemia, and blocking of the vaso-motor nerves to the arm by novocaine. They concluded that the increased vascular resistance in the different kinds of hypertension was not confined to the splanchnic area, but existed throughout the systemic circulation, so that sympathectomy which aimed at the relief of high blood pressure would not abolish the increased vascular tone that was responsible for it.

The Rôle of Renal Ischaemia. Outstanding among the researches into the cause of hypertension has been the work of Goldblatt et al. (1934) who produced sustained hypertension in the dog by constricting the renal arteries. In 1939 Wilson and Byrom produced hypertension in the rat by constricting one renal artery without disturbing the other kidney. Later (1939) they demonstrated that although removal of the ischaemic kidney sometimes restored the blood pressure to normal, it did not have the same hypotensive effect if the hypertension had been severe: they attributed this failure to vascular damage that the hypertension had wrought in the opposite kidney. Pickering (1945) demonstrated two phases in the establishment of experimental renal hypertension: he found that after removal of a single clipped kidney the blood pressure returned to normal in rabbits with hypertension of one week's duration, but that there was no fall in blood pressure in rabbits with hypertension of eight weeks' duration. Floyer (1957), by way of explaining these results, postulated that one function of a normal kidney is to maintain normal blood pressure, and that this function was lost in the later phase of hypertension: restoration of normal circulation to the kidney restores this function and the kidney brings the blood pressure back to normal. This hypothesis assumes the existence of some mechanism outside the kidney that tends to raise blood pressure but is normally held in check by the kidney, and he named this the "extrarenal pressor mechanism".

The mechanism by which renal ischaemia produces sustained hypertension is still inconclusive, although in the form that immediately follows constriction of the renal artery in the experimental animal, the stages in the process have been propounded. It was Tigerstedt and Bergmann (1898) who first provided the clue when they extracted a substance that they named renin from the
renal cortex in the rabbit. Houssay and Fasciolo (1937) and Page (1938) discovered independently that renin is not itself a pressor substance, but that in combination with a pseudoglobulin in blood plasma, which they named renin activator, hypertension precursor, or hypertensinogen, it produces a dialyzable vascular constrictor agent, angiotonin or hypertensin.

The Rôle of the Adrenal Bodies. Goldblatt (1937) and Blalock and Levy (1937) showed that experimental hypertension that followed renal ischaemia could be annulled by removing both adrenal bodies, and Page (1938) found that hypertension could be reinstated in such animals by treating them with salt and adrenal cortical extract. Similarly, the synthetic adreno-cortical steroid, deoxycorticosterone, will maintain renal hypertension in animals deprived of their adrenal bodies (Grollman et al., 1940). These observations were confirmed by Floyer (1951) and Ledingham (1951). That these experimental findings provide no rational basis for adrenalectomy in the treatment of human hypertension was emphasized by Wilson (1955), because in order to keep alive a patient in whom the adrenal bodies have been removed, substitution therapy with adrenocortico salts is necessary and this restores, in part at least, the normal adrenal function and the pre-operative hypertension.

Pathological Evidence

Renal Biopsy. To obtain a sample of renal tissue by introduction of a special needle into the kidney from the back requires skill and involves certain risks, but it has often been carried out. Ross and Ross (1957) considered that the claims made for it as a diagnostic procedure, were over-rated, and that its usefulness as a guide to prognosis and treatment had not been well substantiated. Certainly, in the investigation of the renal circulation it has limited value because of the small size of the sample obtained. Thoraco-lumbar sympathectomy, once popular in the treatment of hypertension, afforded an opportunity to examine kidney tissue in patients with this disease. Castleman and Smithwick (1948) found minimal or absent pathological changes in 25 out of 100 such cases. The interpretation of this finding, however, requires caution for two reasons, First, the amount of renal cortex resected for examination by this procedure, namely 6 x 5 x 4 mm., is too small to be acceptable as a means of assessing the state of the general renal vasculature. Secondly, the criteria governing the diagnosis of hypertension were not rigidly cast in many of the cases. Indeed, the reported results support the justice of this criticism because a clear association was found between the severity of the renal vascular changes and the extent to which the retina were affected. It would be unwise, therefore, to regard their findings as indicating that hypertension in man may exist in the absence of renal changes.

State of the Renal Arteries. In every case of systemic hypertension in the present series examined at necropsy, the lesser renal arteries showed the same significant change, namely intimal proliferation, which had either occluded the vessels or had materially narrowed their bore to cause renal ischaemia; the nature of this reactive tissue was often elastoid. These changes were not confined to patients who had died of the disease, but were present in the three cases (Cases 1, 2, and 3) where one kidney was removed early in the illness when symptoms were of a light character.

Another invariable histological finding was a deficiency in the walls of the renal arteries so affected by intimal proliferation. This deficiency, or medial hypoplasia, often amounted to aplasia, so that in places, actual absence of the media allowed the inner and outer elastic layers to coalesce, when the vessel appeared more like an arteriole than a muscular artery, except for its greater size.

Significance of the Renal Arterial Changes

Relation of Intimal Proliferation to Hypertension. The thickening that affects small arteries and arterioles in hypertension has been variously designated. Thus, Johnson (1868) referred to it as hyperplasia and hypertrophy of the muscular elements of the media. Gull and Sutton (1872) considered that it was predominantly a hyaline fibroid degeneration. Moritz and Oldt (1937)
regarded it as hypertrophy of the media with hyperplasia of the endothelium, while Morlock (1939) also described it as an increase in the muscular elements of the media with hyperplasia of the endothelium.

Since histological examination of the renal arterio-arteriolar vessels in systemic hypertension has shown invariably that the newer tissue that occludes the vessel forms in connexion with the intima, the term intimal proliferation is preferred here. When hypertension ensues following such occlusive lesions, both renal and extra-renal arteries exhibit contracture, and it is this effect that gives to the media the appearance of being hypertrophied.

That intimal proliferation precedes the hypertension, rather than succeeds it, gains support from a study of obstruction of the pulmonary circulation by certain unusual pathological states. Thus, when the pulmonary arterial pressure was raised to considerable proportions by obstruction from strangulation of the pulmonary veins by a granuloma in one patient, and by a myxoma of the left atrium in two others, no occlusive intimal proliferation had taken place in the small pulmonary arteries in any of the three cases when they were examined at necropsy (Evans, 1959b).

That arteriolar changes in essential hypertension are most prominent in the kidney has been known for some time (Fahr, 1922; Fishberg, 1925; Russell, 1929), but the controversy whether such changes are primary and the cause of systemic hypertension or secondary and a sequel to hypertension has ranged through many years. Fishberg held that anatomical changes in the kidney could not be reconciled with the theory that essential hypertension was due to a disorder of renal function. Volhard (1935) stated that although the malignant type of hypertension was renal in origin, he refused to accept the proposition that the benign phase of essential hypertension was of renal origin. Bell (1951) maintained that primary hypertension and renal arteriosclerosis arose independently although they intensified each other, and that the basic disturbance in primary hypertension was a spastic state of the arterioles and not an organic alteration. Smith (1956) also considered that renal hyaline arteriolosclerosis was increased by essential hypertension, but was not its cause. Johnson as long ago as 1873 proposed the theory that renal disease was the primary condition inducing subsequent diffuse thickening of the walls of the smallest arteries which produced increased peripheral resistance, elevation of the blood pressure, and cardiac hypertrophy. Goldblatt (1951) has given a clear exposition of the subject: he said that although it was generally recognized that vascular disease of the kidneys leads to nephrosclerosis so commonly met with in benign hypertension, yet despite all the work that had been done on the subject it was still not firmly established whether the hypertension or the renal vascular disease came first. The main reason for this difficulty was that in benign essential hypertension, by definition, the hypertension was unassociated with any impairment of the renal excretory function detectable by clinical laboratory methods. This was interpreted by some to mean that the hypertension preceded by some time the development of organic vascular disease in the kidney. Although this was difficult to disprove, Goldblatt believed that the renal vascular disease precedes the establishment of the fixed hypertension associated with it.

The findings of the present investigation fully justify the opinion of Goldblatt that the initial changes in systemic hypertension reside in the kidney. Views to the contrary have sometimes presumed that because no clinical evidence of renal abnormality had been apparent in patients who died from hypertension, the associated renal arterial changes must have been secondary to the hypertension, and a late manifestation in the course of the disease. The findings in Cases 1, 2, and 3 oppose this assumption because the characteristic arterial changes were found in the extirpated kidney in each of the three patients with systemic hypertension in whom clinical and laboratory investigation had failed to find any evidence of renal disease. Moreover, the further criticism that in cases of alleged systemic hypertension, renal tissue removed either at biopsy or necropsy has not always shown arterial changes, may be met on two grounds, either that the specimen retrieved at biopsy has been inadequate, or that the raised blood pressure was a manifestation of innocent hypertension, and not of systemic hypertension with its characteristic cardio-arterial changes, while death, if it had taken place, had resulted from some other cause.
The mechanism by which pyelonephritis gives rise to hypertension has been described by Kincaid-Smith (1955) whose careful investigation allowed her to postulate that vascular occlusion producing multiple ischemic areas is largely responsible for the contracted pyelonephritic kidney. The same mechanism explained the development of hypertension in some cases of chronic pyelonephritis, for hypertension was then associated with areas of ischemic renal parenchyma which escaped complete destruction or conversion to thyroid-like areas by acute inflammation.

Relation of Medial Hypoplasia to Intimal Proliferation. In all the cases reported here, medial deficiencies, in the form of hypoplasia or even aplasia, were present in those renal arteries obstructed by intimal proliferation with one exception (Case 23). In this instance although intimal proliferation was present in the renal arteries of the extirpated kidney, their media was intact (Fig. 10). It is presumed in this case that kinking at the pelvic-ureteric junction with resulting distension of the renal pelvis and calyces had interfered with the renal circulation and had caused the occlusive intimal proliferation. This in turn had produced renal ischemia with consequent rise of the systemic blood pressure. Such hypertension was immediately annulled when the offending kidney was removed. It is deduced from this that the presence through several years of this high blood pressure had not produced intimal proliferation in the opposite kidney because of intact arterial media as in the abnormal kidney which was removed. This permits the substantive statement that nephrectomy will never remove a state of hypertension in man unless renal ischemia in the offending kidney is associated with a healthy renal circulation in the other.

That arterial medial deficiencies are not the sequel of hypertension is supported by findings in patients where systemic hypertension results from the occlusion of renal arteries by the peculiar tissue of scleroderma. In this event although the resulting renal ischemia gives rise to hypertension, the blocked renal vessels show no evidence of medial hypoplasia (Evans, 1959b).

Landis (1943) pointed out that with an equal amount of organic renal disease, as in polycystic disease of the kidney or pyelonephritis, hypertension appears in some subjects and not in others. He postulated that this variation may be due to unrecognized differences in the details of the structural damage or to a hereditary defect, and emphasized the variable response of the vascular system to types and grades of renal disease. His first suggestion that the kind of structural damage determines hypertension in pyelonephritis has been confirmed by the findings reported by Kincaid-Smith (1955), and his second suggestion about the presence of a hereditary defect can be related to the finding of associated medial defects in the cases reported here—changes that are regarded as the cause of the occlusive intimal proliferation in the renal arteries and as leading to renal ischemia and in turn to hypertension.

Conclusions

Examination of the renal arteries in systemic hypertension has shown either partial or complete closure of their bore by intimal proliferation, usually of an elastoid kind: in the arterioles the occlusive tissue was of a fibroid character as if developing passively from organized thrombus.

As in pulmonary hypertension, so also in systemic hypertension, the intimal proliferation had preceded or had coincided with the state of hypertension, and it was equally conspicuous in three cases with hypertension in whom one kidney was deliberately removed early in the illness and in the late cases examined at necropsy. A change developing in the course of hypertension, and involving both renal and extra-renal arteries, was vascular contracture and this gave the appearance of medial hypertrophy.

A further significant histological finding was hypoplasia of the media of the lesser renal arteries, and this deficiency in places amounted to aplasia where the single elastic coat gave the impression that the obstructed vessel was an exceptionally large arteriole.

Systemic hypertension owes its inception to the presence of these congenital medial deficiencies, which in turn evoke the formation of intimal proliferation in adjacent arterial segments, proceeding to vascular occlusion and resulting in renal ischemia and ultimately hypertension.
These findings appear to establish the renal origin of systemic hypertension, and also support the suggestion that it is an inherited, rather than an acquired, disease.

Nephrectomy in Cases 1, 2, and 23 was carried out by Mr. Donald Barlow, and the last case was under his care. I am indebted to Dr. J. R. Gilmour for the pathological data in Cases 1, 2, and 3, and to Dr. Reginald Hudson in three cases. Professor Dorothy Russell placed at my disposal the pathological findings in six cases. The arteriogram in Fig. 1 was carried out by Dr. H. Lloyd-Thomas.

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