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THE AETIOLOGY OF ESSENTIAL HYPERTENSION

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Fishberg¹ (1930) stated "the concept of essential hypertension includes those cases of chronic hypertension which neither clinically nor anatomically can be demonstrated to have evolved from antecedent inflammatory disease of the kidneys or urinary obstruction" and in this definition are included all classes of hypertension which are not of nephritic origin. Clinical research has already separated within this large group several subgroups of clearly separate aetiology; for example, hypertensions due to rise of intracranial pressure, to adrenal cortical tumours, etc., and the term has come to be applied to a definite and familiar clinical picture^{2, 3, 4, 5}. The prealbuminuric stage of Mahomed is equivalent to the latent arteriosclerosis of van Basch, to Allbutt's hyperpiesia, to the presclerosis of Huchard, to the hypertensive cardio-vascular disease of Janeway, the benign sclerosis of Volhard and Fahr, and the essentielle hypertonie of Frank^{6, 7, 8, 2}. Of 82 cases of chronic hypertension coming to post-mortem, 88 per cent were found to show the typical pathological arteriolar lesions of essential hypertension⁹ and five only of the 72 cases involved had, during life, shown any signs of renal insufficiency. Gull and Sutton, in 1872, first communicated that the arteriolar sclerosis was not always confined to the kidneys; they advanced the theory that the hypertension was due to the increased peripheral resistance¹⁰. Johnson, in 1868, had suggested that the disease was due to the failure of the kidney to excrete some compound causing peripheral spasm, to which the rise in B.P. and the histological changes were secondary¹¹. Hasenfeld and Hirsch¹² thought the rise in pressure due to sclerosis of the arterioles of the splanchnic area. Evans¹³ found the small vessels of the spleen to be involved as often as those of the kidney whereas the coronaries were almost always normal. Fahr¹³ in 1922 believed that changes in the renal arterioles were the primary cause of essential hypertension. Volhard in 1923¹⁴ held that the onset of renal insufficiency synchronised with the onset of a generalised vasoconstriction. In essential hypertension Weiss and Ellis¹⁵ found the capillary pressures over the sternum normal; Blumgart and Weiss¹⁶ found that in the absence of heart failure circulation times were normal, and Steele and Kirk¹⁷ found normal skin tem-

peratures. However, Pickering¹⁸ and Prinzmetal¹⁹ find that the rate of flow through the forearm is, under similar conditions, the same in patients with essential hypertension, malignant hypertension, and chronic nephritis. Blood viscosity is normal. The increased peripheral resistance if distributed throughout the body would balance the effect of the raised arterial blood pressure on blood flow. When the vasoconstrictor nerve impulses to the cutaneous vessels are inhibited, the rate of blood flow in hypertensives is not greater than in normal subjects, therefore Pickering considers the increase of peripheral resistance to be of chemical and not of nervous origin.

The pathological findings at postmortem in benign essential hypertension⁹ are of terminal arteriolar sclerosis, affecting in nearly every case the vasa afferentia and interlobulares of the kidney, the splenic arterioles in two-thirds of cases, the pancreatic arterioles in half, the hepatic in less than one-third, and the cerebral in one-fifth of cases. A true generalised arteriolar sclerosis does not exist; if then the rise in pressure is due to an evenly distributed increase in the peripheral resistance, then the constricting agent is probably chemical, and the anatomical vascular lesions develop as a result of the raised blood pressure.

In less than 10 per cent of cases of essential hypertension acute progressive renal insufficiency develops with characteristic retinal changes; this is the malignant form or phase. Anatomically the arteriolar sclerosis is not more developed than in benign essential hypertension, but there is in addition necrosis and endarteritis of the renal arterioles^{16, 20}. There is some evidence that these lesions may be produced by the rapid reduction of the glomerular blood flow following the narrowing of the vasa-afferentia^{21, 22}. The postmortem findings strongly suggest that malignant hypertension develops as a phase superimposed on a previous, often unrecognised, benign essential hypertension¹ of long or short duration.

Clinical observers have noted predisposing facts to the development of essential hypertension. Of deaths over the age of 50 years 23 per cent are due to the disease or to its consequences, but 90 per cent of cases are over the age of forty years when symptoms first occur. It has been widely held that the greater stress and strain of modern life is responsible for the increasing incidence of the disease which is rare in African negroes and in Orientals. An hereditary factor is undoubted. Both sexes are affected; in females the age incidence and the proportion of cases is slightly higher

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than in males; the former is attributed to the inhibiting action of ovarian secretions²³. The obese have an arterial pressure 10 mm. Hg higher, the very thin 12 mm. lower, than those of normal development. High protein diets have been suggested as predisposing to the development of hypertension; Strouse and Kelman²⁴ found the arterial pressure in patients with essential hypertension to be unaffected by long periods of high or low protein diet. Eskimos, whose diet is almost completely carnivorous, do not have a high incidence of essential hypertension²⁵. In rabbits, rats, and puppies the feeding of large amounts of protein for considerable periods produced arteriosclerosis and changes in the kidneys which show no microscopic similarity to those of essential hypertension^{26, 27, 28, 29}. Similar changes were produced by the injection of aminoacids³⁰. Other experimenters have found only renal hypertrophy to result from high protein feeding^{31, 32, 33}. A temporary rise of blood pressure was recorded in the early stage of cholesterol feeding in rabbits³⁴ but was not confirmed³⁵. Hypercholesterolaemia of small degree has been claimed to be common in cases of essential hypertension³⁶. In diabetes 19 per cent of cases between 21 and 50 years of age, and 33 per cent over 50 years of age have essential hypertension. Essential hypertension, diabetes, and obesity are often found associated or spread over members of a family, but there is no evidence that diabetes causes hypertension³⁷. No correlation was found between the height of the blood pressure and the sodium chloride content of the blood³⁸, although the KCl content was found slightly raised and the calcium content slightly lowered in essential hypertension³⁹. Although some endocrine disorders are associated with essential hypertension, very few cases of essential hypertension show either clinically or at postmortem any endocrine changes¹.

The clinical findings therefore offer considerable evidence of predisposing causes of essential hypertension, but that relating to the actual cause of the disease is largely negative; the work of Pickering¹⁸ and of Prinzmetal and Wilson¹⁹ suggests that the causal agent is probably chemical. The pathological and clinical findings are of importance for comparison with those resulting from hypertensions of experimental production, and on the latter type of work are based the present views of the aetiology of essential hypertension.

Experimental Hypertension

Experimental methods used in the production of essential hypertension.

Just as a study of hypertension in man was delayed until the discovery of the mercury manom-

etric method by Poinseulle, the study of the blood pressure in animals was further delayed by technical difficulties until the development of the carotid loop, in 1911, by Van Leersum⁴⁰. Auscultation results had given unsatisfactory results in animals (⁴¹ and others); an especial dog cuff was designed by Ferris and Hynes⁴². Auscultation methods requiring special reference are those of Brewer and Brotman for small animals⁴³, and the Kolls-Cash sphygmomanometer⁴⁴. After denervation of the carotid sinus, the Van Leersum loop was shown to give reliable readings of the mean arterial pressure in conscious, trained and resting dogs⁴⁵.

From the time of Richard Bright's observations on the association of cardiac hypertrophy and kidney disease, a renal origin for hypertension was suspected. Later clinical work had, however, revealed the existence of essential hypertension unaccompanied by renal insufficiency; the renal arteriolar changes came to be regarded as a secondary result of the raised blood pressure, and attention ceased to be focussed on the kidney as causal agent. The numerous attempts made to produce an experimental hypertension of more than transitory duration met with no real success until the fundamental work of Goldblatt and his collaborators in 1928. It is of interest briefly to summarise some of the methods by which various forms of hypertension were produced, and which were in use mainly before the work of Goldblatt had again focussed the attention of both clinical and experimental workers upon the kidney as an important factor in the aetiology of essential hypertension. By their study it is clearly shown that a mechanical elevation of the blood pressure alone cannot be responsible for the selective arteriolar changes occurring in this disease.

Moderator Nerve and Carotid Sinus Hypertension

Following on from the work of Cyon and Ludwig on the depressor nerve, and that of Hering on the carotid sinus, Koch and Mies⁴⁶ were able to show that a rise in blood pressure results from section of the depressor nerve, and bilateral denervation of the carotid sinus. Only Heymans⁴⁷⁻⁴⁹ and Nowak⁵⁰ have been able to obtain persistent hypertension by such means. Heymans by improved technique found a blood pressure of 250-300 mm. Hg. to be maintained in dogs for 9-26 months. Removal of the sympathetic ganglia and chain from the stellate to the pelvis prevented or cured the hypertension. Nowak, by total excision of the bifurcation of the carotid arteries and removal of part of the depressor nerve in the neck, obtained lasting hypertension in 90 per cent

of dogs. After complete sympathectomy, a small rise of pressure occurred on section of the moderator nerves; section of the splanchnics caused only a small drop in blood pressure, and total sympathectomy was required to abolish this type of hypertension. Some evidence of a vasoconstrictor agent in the blood of dogs with moderator nerve hypertension was obtained⁵¹. It was claimed that denervation of the kidneys prevented or cured this type of hypertension, but this was not confirmed⁵²⁻⁵⁴; bilateral partial adrenalectomy and division of the splanchnics was also without effect⁵⁵.

Postmortem findings revealed no change in the arterioles of the kidney^{57, 58}, neither was any alteration encountered in the function or in the histology of the kidneys of dogs which had had a moderator nerve hypertension of two years standing⁵⁷.

Cerebral Anaemia

It was shown by Cushing in 1903 that a rise of intracranial pressure resulting in cerebral anaemia causes hypertension⁵⁸. By perfusion of a head whose only remaining connection with the body is the spinal cord, acute anaemia of the cerebral circulation was shown to produce a marked rise of blood pressure⁵⁹. Injection of kaolin into the cerebrospinal fluid of dogs resulted in months or years of hypertension⁶⁰. In rats the capillary pressure and the mean arterial pressure are raised from the fifth day after kaolin injection, but the hypertension is only temporary, lasting up to two months⁶¹⁻⁶³. Denervation of one kidney decreases the hypertension, removal of this kidney is followed by a rise of the blood pressure again, but if instead the normal kidney is removed, the blood pressure remains down⁶⁴. Perfusion of blood from a dog with kaolin hypertension to a normal dog, or to a dog with denervated kidneys, results in a considerable rise of blood pressure for several hours. Blood from a normal dog to a kaolin hypertensive dog produces no result; blood from a dog with denervated kidneys produces a fall in the blood pressure of a kaolin hypertensive animal⁶⁵. Kaolin hypertension persists after adrenalectomy⁶⁶, but it was shown in perfusion experiments that the pressor effect of blood from a dog with kaolin hypertension was removed if the donor had been adrenalectomised⁶⁷. At postmortem, internal hydrocephalus is found, and after 27 months of hypertension, no arteriolar changes have developed⁶⁸.

Partial Nephrectomy and Renal Insufficiency

The work of Grawitz and Israel⁶⁸ and Rose Bradford⁶⁹ is of historic interest. The reduction of active renal tissue either by excision, infarction,

or by these two methods in combination, has been claimed by some workers to result in moderate increases of blood pressure, e.g. 20-30 mm. Hg.⁷⁰⁻⁷⁷ and 44. These rises when occurring show no regular correlation with the amount of kidney tissue removed, or to the degree of renal insufficiency resulting⁷⁸. Other workers have been unable to produce any rise of blood pressure by these methods^{79, 80, 75}. Contradictory results of this type can only be attributed to differences in operative procedure. In all probability, hypertension when occurring is to be attributed to a reduction in the blood supply of renal tissue surrounding the operative area. In rats, however, polar ligation and excision of renal tissue caused considerable and lasting hypertension; were 80 per cent of kidney tissue removed, polyuria, progressive kidney lesions, and hypertension followed^{81, 82}. A good method for the production of hypertension with renal insufficiency in small animals is that of Drury⁸³, one renal artery of a young rabbit is constricted by tying a silk ligature round the artery and a wire of known bore. From the adult rabbit the normal kidney is removed. Any degree of renal insufficiency can be produced by varying the bore of the wire. Later work showed that a moderate rise of blood pressure was produced with the normal kidney in situ, which was increased by its removal. Postmortem examination showed no changes in the renal epithelium. The rise of blood pressure may therefore be attributed to the renal ischaemia⁸⁴.

Renal Ischaemia

In 1905 it was shown in acute dog experiments⁸⁵ that partial occlusion of the renal arteries caused a slight rise of blood pressure. Little progress was made until the very important work of Goldblatt and his co-workers became known^{86, 87}. Silver clamps were designed by which controlled and varied constriction of a renal artery could be produced. Partial obstruction of a renal artery in dogs caused a rise in blood pressure which lasted for several weeks. Moderate obstruction of both renal arteries gave a sustained rise of blood pressure unaccompanied by renal insufficiency. Severe constriction of both renal arteries gave a great rise in blood pressure, disturbed renal function, and convulsive uraemia. Similar results were obtained for monkeys⁸⁸. Removal of an ischaemic kidney or relief of the partial obstruction, the other kidney being normal, resulted in a return of the blood pressure to normal resting level, in dogs, in about 6 hr.^{87, 89, 90}. Release of bilateral partial obstruction similarly relieves the hypertension. Incomplete occlusion of the arterial blood supply to a single transplanted, hence denervated, kidney causes a rise in blood

pressure relieved by release of the partial occlusion^{89, 91-93}. Constriction of the splenic or femoral arteries causes no hypertension⁸⁶. Constriction of the abdominal aorta just above the origin of the renal arteries caused hypertension, but constriction of the aorta just below the renal arteries caused no hypertension⁸⁶⁻⁹⁶; constriction of the coeliac axis and superior mesenteric arteries is not followed by a rise in blood pressure⁹⁷. The rise in blood pressure is therefore the result of renal ischaemia. This might be brought about either by increased activity of the vasoconstrictor nerves, by increased cardiac output, by increased blood volume, or by increased sensitivity of the smooth muscle of the vascular bed to normal stimuli of contraction, or by the formation of a new chemical compound acting on the vascular bed.

That the hypertension is not due to increase in vasoconstrictor activity is shown by the following data. Hypertension due to renal ischaemia is neither prevented nor cured by denervation of the kidneys⁹⁸⁻¹⁰¹ by cutting the splanchnics, nor by the removal of the anterior nerve roots from D1 to L3^{102, 103}. Neither was the production nor the continuation of the hypertension influenced by the removal in dogs of the entire sympathetic chain in both thorax and abdomen, with denervation of the heart^{101, 104, 105}. Cannon's postulation that the hypertension could result from some agent acting on the prevertebral ganglia causing constriction of the splanchnic vessels and hypertension does not appear to have been tackled¹⁰⁶.

No alteration in blood volume is found in the hypertension of renal ischaemia. An increase in reflex excitability of the carotid sinus mechanism in dogs with this type of hypertension was noted¹⁰⁷. Verney and Vogt¹⁰¹ found the sensitivity of such dogs normal to adrenaline, but to tyramine often increased; they did not believe the hypertension to be due to increased tyramine in the blood. After some discrepancies it was shown conclusively that after bilateral adrenalectomy moderate hypertension does develop if the substitution therapy is adequate^{88, 108, 109}. Hypophysectomy^{110, 108}, thyroidectomy¹¹¹ and gonadectomy¹⁰⁸ do not abolish renal hypertension. The presence of some chemical agent must be held responsible for the production of renal hypertension.

In this country the work of Goldblatt has been confirmed and extended by Verney and Vogt¹⁰¹, who confirmed that renal ischaemia produced the hypertension which was not prevented by denervation of the kidney or by total sympathectomy. They conclude that a chemical agent is responsible for the production of the hypertension by direct action on the vascular bed. They showed that

the degree of hypertension was dependent on the load of work to which the kidney was subjected. Three types of compression unit were designed¹¹² for insertion around the renal artery, such that compression could be applied and released at will in the conscious animal, and the time course of the hypertension studied. The blood pressure was shown to begin to rise some 8 to 18 mins. after partial obstruction of the renal artery had been brought about by compression. The conditions to produce the rise in pressure were found to be critical. The period for the recovery of the blood pressure to the normal resting value was found to be a function of the length of time for which compression had been applied. The presence of a normal contralateral kidney reduced both the rise of blood pressure and the recovery period.

The hypertension of renal ischaemia of moderate degree is not accompanied by renal insufficiency, and the animals remain in good general health. More severe renal ischaemia causes hypertension, renal insufficiency, and convulsive uraemia. A superficial resemblance to the benign and malignant phases of essential hypertension is at once evident, and it becomes of great interest to compare the pathological and clinical findings in experimental hypertension due to renal ischaemia and in essential hypertension in man.

In benign essential hypertension the arteriolar lesions are usually well marked in the kidneys, but a few cases occur with minimal or absent arteriolar lesions¹, and some have been reported with narrowing of the main renal arteries and no renal arteriolar sclerosis¹¹³. In experimental hypertension without renal insufficiency few or no changes are found in the renal arterioles^{100, 86}; this may well be due to the fact that owing to the clamp on the renal artery the pressure cannot rise much in the kidney, and the damage to the renal arterioles is consequently slight. In moderator nerve hypertension¹⁰⁰, thickening of the media has sometimes been seen in the small arteries and the glomerular efferent arterioles; the kidneys are in this type of hypertension subjected to the generalised rise in blood pressure. In rats in which one kidney alone was ischaemic, renal vascular lesions were confined to the nonischaemic kidney¹¹⁴. In longstanding experimental hypertension, in the absence of renal insufficiency⁸⁶ the arterioles and small arteries show thickening of the media, and sometimes hyalinisation of the intima, especially in the retinal arteries. There are fewer changes in the arterioles of the ischaemic kidney than of other organs. In 12 animals examined after varying periods of chronic hypertension¹¹⁵ no changes were found unless the hypertension had been present for some months: in the arterioles the

thickening of the walls and the decrease of the lumen was judged proportional to the degree of and duration of the hypertension. These changes, although generalised, were most marked in the cardiac and mesenteric arterioles. In rabbits with chronic experimental hypertension¹¹⁰ the production of arteriolar lesions appeared to be proportional to the degree rather than to the duration of the hypertension, and affected the vessels of the gastro-intestinal tract, the adrenals, liver, and retina. There is therefore nothing in the postmortem findings to contraindicate the possible common aetiology of essential hypertension, and the experimental hypertension brought about by renal ischaemia. In this review we pass on at once to a survey of the pressor compounds isolated from the kidney or from renal venous blood.

RENAL PRESSOR COMPOUNDS

Tiegerstedt and Bergman in 1898¹¹⁷, found that the intravenous injection of saline extracts of normal rabbit kidneys produced a rise of blood pressure. Such a response was not obtained to saline extracts of other organs. The renal pressor compound was named renin; these workers actually suggested that more renin might be found in the kidneys of hypertensive than of normal patients. As the clinical study of hypertension developed, prior to its successful experimental investigation, clinicians evolved the mechanical theory of essential hypertension; the rise of blood pressure was considered due to an increased peripheral resistance. From this conception it was an easy step to that of a causal toxic agent. Both the schools of Ludwig and Bright had shown increase in the blood urea in many cases of hypertension, and for many years retention as the result of renal insufficiency, of some pressor metabolite was a theory of the aetiology of hypertension which received considerable support. As essential hypertension became clearly established as a clinical syndrome, and the absence of renal insufficiency other than in a very late stage of the disease was widely confirmed, interest in the kidney as a possible causal agent rapidly declined. A search was then instituted for some other pressor agent, and for some time attention was focussed on the adrenals. The frequent coincidence of hypertension with adrenal hyperplasia was noted¹¹⁸. Of eight patients with hypertension, at postmortem examination, four were found to have diffuse hyperplasia of the adrenal cortex, and three to show multiple adenomata of the cortex¹¹⁹. Hyperplasia of the suprarenal medulla was also claimed in hypertension^{120, 121}. But it was shown that the suprarenals of hypertensives contained no more adrenaline than those

of normal persons^{122, 123}. Although a claim was made that epinephrine had been detected in the blood of hypertensives by the dilator effect on the frog's eye¹²⁴, this reaction was shown to be produced by a compound formed during blood coagulation¹²⁵. Plasma from hypertensives was found to have greater constrictor effect on a strip of surviving artery than normal plasma, and this was again attributed to epinephrine¹²⁶, but Halse showed by a very sensitive biological test for epinephrine, which could detect a concentration of 1:700,000,000 that there was no epinephrine in the blood of hypertensives¹²⁷. Moreover, although adrenal cortical adenomata are more frequent in patients with hypertension than in those without, and although adrenal cortical hyperplasia not infrequently accompanies hypertension, the incidence is not as high as was previously supposed, and is by no means a constant finding¹²⁸. The theory of adrenalæmia was perforce abandoned.

The experimental field opened up by Goldblatt again focussed attention on the kidney as a possible source of a pressor compound. Tigerstedt and Bergmann¹¹⁷ showed renin to be heat labile, non-dialysable, and insoluble in alcohol. Their observations were confirmed by Bingel and Strauss¹²⁹, and by Bingel and Claus¹³⁰. The latter workers removed much inactive material by fractionation with ammonium sulphate, the active material being precipitated between 1/3 and 5/12 saturation. After dialysis this fraction was strongly pressor, and they were the first workers to observe the development of tachyphylaxis or refractoriness to repeated doses of renin. A great deal of work was done with kidney extracts, press juices and autolysates. The interpretation of the earlier experiments based on the biological assay on renin in tissue extracts is made difficult by the absence of any technical uniformity, and the great divergence of the results obtained according to the manner in which the tissue was treated, the method of preparation of the extract, and the time for which the extract was stored. The purification of renin, and the elucidation of the way in which it caused a pressor action was carried out by several groups of workers. The various methods for the isolation and purification of renin from pig kidney were critically discussed by Schales in 1924¹³¹ and by Katz and Goldblatt in 1943¹³². The purest preparation so far obtained contained 130 dog units/mg. of enzyme N.¹³³. A dog unit is defined as the amount needed to raise the blood pressure by at least 30 and not more than 35 mm. Hg. in 3 minutes, in at least three unanaesthetised dogs. The response given by dogs of between 10 and 25 Kg. is independent of weight. More accurate biochemical methods for the assay of renin, depending

on the fact emerging from the elucidation of its physiological action will be described later.

Renin has been found to be a typical heat labile globulin containing no cystine or cysteine¹³⁴, excreted in the urine only after huge doses¹³⁵. It is found in the kidneys of all normal mammalian species. Renin has strong antigenic properties; the development of a high precipitin titre does not reduce the physiological response¹³⁶.

The action of renin was elucidated by the combined efforts of two groups of workers, who used completely different terminology. In this review, the South American terminology is employed, but a table is here appended of the North American names, and of Goldblatt's suggestions for the revision of these.

<i>North America</i>	<i>South America</i>	<i>Goldblatt's suggestions</i>
Renin Hypertensinogen Hypertensin Hypertensinase	Renin Renin Activator Angiotonin Angiotonin Inhibitor	Renin Prehypertensin or Preangiotonin Hypertensin or Angiotonin Hypertensinase or Angiotonase

It was demonstrated that a component, present in blood serum, was essential for the pressor action of renin¹³⁷⁻¹³⁹. This component was shown to be a blood globulin in which the renin acts enzymatically¹⁴⁰⁻¹⁴² to produce a pressor compound, hypertensin.

The enzymatic action of renin was found to be proteolytic; pepsin can replace renin in its action on hypertensinogen to produce a pressor compound. The optimum pH for pepsin is 2 to 6, but for renin 7.5 to 8.5¹⁴³⁻¹⁴⁶. Renin is specific in its action on hypertensinogen, and does not attack other proteins; moreover, there is species specificity: human renin acts on the hypertensinogen of man and on that of any other mammal; renin from other mammals acts on that of all other mammals, etc., the hypertensinogen of man¹⁴⁷. This specificity has been used in the development of the biochemical methods for the assay of renin. The indirect *in vitro* method¹⁴⁸ which measures the hypertensin formed or the hypertensinogen gone after incubation with renin, has been adapted for human renin. Human blood containing renin is incubated with bovine hypertensinogen in the presence of hypertensinase for six hours. Pigs' renin is then used to determine the amount of bovine hypertensinogen remaining, and comparison with controls determines the amount of bovine hypertensinogen attacked by hypertensinase¹⁴⁸.

The site either of renin storage or formation in the kidney has been localised to the proximal convoluted tubules. No renin was found in the

kidneys of adult rabbits in which the proximal convoluted tubules had been destroyed by specific necrosis induced by the administration of tartrates¹⁴⁹. In the pig foetus the mesonephros undergoes progressive degeneration; the tubules degenerate, but the glomerulae remain; during this period there is parallel progressive decrease in the renin content of the mesonephros. Conversely, the metanephros shows progressive tubular development, and steady increase of renin content¹⁵⁰.

The elimination of renin has been studied by South American workers. They used solutions of pig renin of a strength of about 100 units/c.c., a unit of renin being the amount which when incubated for 2 hours at 37 C. with hypertensinase

free hypertensinogen, results in the formation of 0.5 units of pressor hypertensin. When 2 c.c. of such a solution of renin are injected into normal dogs, renin is gone from the systemic circulation in 30 minutes. In nephrectomised, hepatectomised, or eviscerated dogs, renin remains in the circulation for 2 to 3 hours. Only if the injection exceeds 2 c.c. is any renin excreted in the urine. It is concluded that the kidney takes some part in the elimination of renin, but that it is mainly destroyed by the tissues^{151, 152}.

The secretion of renin by normal and ischaemic kidneys has been studied. Just as Pickering's attempt to demonstrate a pressor compound in the blood of patients with essential hypertension by transfusion of such blood into patients with normal blood pressures, in volumes up to 500 c.c. and at a speed up to 100 c.c./min.¹⁵³ failed, so other workers failed to find, in similar experiments, evidence of a pressor compound in the systemic blood of hypertensive dogs and patients¹⁵³⁻¹⁵⁶. These failures are explained by the relatively small volumes of blood transfused from donor to recipient: successful results were obtained in small nephrectomised dogs during continuous balanced cross transfusions from large dogs with renal hypertension¹⁵⁷. Vasoconstrictor action was found in the plasma of blood collected from the renal vein of an ischaemic kidney, when tested on South American toads^{158, 159}, but North American toads failed to respond¹⁶⁰. When injected intravenously into a normal dog, 100 c.c. of blood

from a grafted ischaemic kidney produced a rise of blood pressure¹⁶¹.

After very considerable lowering of the blood pressure from shock or from haemorrhage in normal unanaesthetised dogs, renin was shown to be liberated by the kidney and was demonstrated in the systemic blood¹⁶². Although anoxaemia did not prevent the secretion of renin when the blood pressure was lowered, anoxaemia alone did not cause secretion of renin. The inference may therefore be drawn that the renin is not concerned with the maintenance of normal blood pressure (see also ¹⁶³), but with its regulation. The suggestion that a diminished pulse pressure in the kidney causes the secretion of renin is without experimental proof.

It was claimed that renin was liberated when an isolated dog kidney was perfused with defibrinated blood only after constriction of the renal artery. The renin was demonstrated by the vasoconstricting action of the blood when perfused through an isolated rabbit's ear in the presence of hypertensinogen. No tests were made without the addition of hypertensinogen^{164, 165}. The South American workers found that from a heart-lung-kidney preparation, with the renal artery constricted 80 per cent, the renal venous plasma was pressor when injected in amounts of 10 c.c. into dogs. Although it constricted both dog and toad hind limb vessels, it differed in properties from renin^{166, 167}. Perfusing a dog's kidney with defibrinated blood by one heart lung preparation, and a loop of jejunum by another, the transposition of the kidney to the heart-lung-gut circuit was followed by a fall in perfusion flow through the gut. Similar responses were obtained when fore-limb or large intestine were substituted for jejunum. A single exposure of the gut vessels produced refractoriness to subsequent exposures; no modification of the response was noted in the presence of atropine, nor on the substitution of pump-oxygenator systems for heart-lung preparations, nor after degeneration of autonomic nerves in the gut¹⁶⁸.

Complete obstruction of the renal circulation for 5 to 6 hours, followed by the release of the clamp, results in the liberation of a pressor agent in the renal venous blood^{169, 172}. It was found that a saline perfusate of a totally ischaemic kidney was pressor when injected intravenously into the same animal. Control perfusates from a hind limb and from a normal kidney without pressor action¹⁷¹. Adrenalectomy, renal denervation, or destruction of the C.N.S. do not modify the production of this pressor agent by the ischaemic kidney¹⁷².

Renin, on intravenous injection, produces a slow rise of arterial blood pressure, maintained

at plateau level for some time, and falling slowly to the resting level. Repeated injections of renin produce progressively less response.; this refractoriness is usually referred to as renin tachyphylaxis¹⁷³⁻¹⁷⁸. Purification of renin does not eliminate the tachyphylaxis. The shorter the time interval between injections of renin, the more rapidly does the tachyphylaxis develop¹⁷⁷. The injection of hypertensinogen into cats and dogs does not prevent the development of renin tachyphylaxis, nor does it arrest tachyphylaxis in the vessels of a rabbit's ear if tachyphylactic dog blood, renin and hypertensinogen are injected¹⁷⁹. Destruction of the central nervous system, or perfusion of large amounts of fresh blood do not alter renin tachyphylaxis. These results led Page to the theory of a renin inhibitor; depressor extracts were obtained from kidney and muscle which on oral administration or on injection were claimed to lower the blood pressure of animals only in the presence of renal hypertension¹⁸⁰⁻¹⁸².

Renin has been shown to be present in the blood in many cases of experimental renal, and essential hypertension, but its responsibility for the hypertension of renal ischaemia cannot be said to have been clearly established by the usual methods of assay¹⁸³⁻¹⁸⁵, and further work is needed to establish whether it is in fact the causative or the only causative agent. The results of slow renin infusion experiments give cause for some doubt as to whether a sustained increase of renin secretion could produce prolonged hypertension; for instance, Hill and Pickering¹⁸⁶ found that by slow infusion of renin into normal unanaesthetised rabbits it was difficult to maintain a rise of arterial pressure of more than 30 mm. Hg. for 4 hours, faster injection caused a larger temporary rise, but this was succeeded by a fall. After the infusion has been continued for some time, tachyphylaxis develops. Normal and hypertensive rabbits respond similarly to renin infusions, and at the end of the infusion the blood pressure returns to the resting level¹⁸⁷. Similar results have been obtained in dogs^{188, 189}. Dogs very soon after nephrectomy react normally to renin injections, but 48 hours after nephrectomy are found to be hypersensitive to renin. Hypophysectomy does not effect renin sensitivity, but adrenalectomy is claimed to reduce it^{189, 190}. The properties of renin would make it appear possible that renin is normally concerned with the regulation rather than the maintenance of normal blood pressure, and the development of tachyphylaxis gives cause for doubt whether excess of renin can be responsible for a persistently elevated blood pressure.

The pressor action of renin, produced through the formation of hypertensin, has been shown to

be due to its action on the blood vessels^{191, 192, 174, 179}. It is not sympathetico-mimetic¹⁹³ and has no action on the isolated heart^{174, 194}. In rabbits a diuresis was produced with a rise in Na and Cl excretion without change in the creatinine clearance¹⁹⁵. On slow infusion into a conscious dog with an explanted kidney there was a fall in the clearance ratio of phenol red to inulin, and in increase in the inulin extraction ratio¹⁹⁶ and a fall in the renal blood flow. These changes would suggest glomerular afferent arteriolar constriction as in essential hypertension¹⁹⁷. A single injection of a pressor dose of renin was found not to alter the stromuhr renal blood flow in an anaesthetised dog¹⁹⁸.

Hypertensinogen

The necessity for the presence of a component of the blood serum was early recognised for the production of the pressor action of renin was early recognised¹³⁷⁻¹³⁹. Hypertensinogen is a blood globulin on which renin acts proteolytically to form the pressor compound hypertensin¹⁴⁰⁻¹⁴⁵. This globulin has been characterised, and electrophoretically identified with the α_2 globulin fraction¹⁹⁹. It is formed in the liver²⁰⁰⁻²⁰¹. No fall in the concentration of the hypertensinogen in the plasma was noted after hepatectomy if the kidneys were also removed²⁰¹, and the hypertensinogen content of the plasma was found normal in patients with hypertension, renal insufficiency, and Addison's disease, but was decreased in hepatic insufficiency²⁰². The exhaustion of the hypertensinogen of the blood was at one time postulated as the cause of renin tachyphylaxis, but this has been disproved¹⁷⁹. Human hypertensinogen is not identical with that of other mammals, being acted upon only by human renin¹⁴⁷. Although pepsin will act proteolytically on hypertensinogen to form a pressor principle physiologically similar to hypertensin, named pepsitensin, hypertensin and pepsitensin are not identical; hypertensin is destroyed by the enzyme hypertensinase; this enzyme, obtained from the red blood cells, did not attack pepsitensin¹⁵⁴.

Hypertensin

Hypertensin is the pressor compound formed by the action of renin on hypertensinogen. It is thermostable, dialysable, and fluorescent. It is precipitated by saturation with ammonium sulphate, and by phosphotungstic acid, but not by trichloroacetic acid. It is soluble in various organic solvents, but not in ether. It is more resistant to acids than to alkalis^{139, 203}. It was found that hypertensin was inactivated by tyrosinase and aminopeptidase^{142, 204} and hypertensin was therefore thought to be a polypeptide carrying phenolic

OH groups which were necessary for its pressor action. In accordance with this theory inactivation of the tyrosine by five minutes boiling destroyed its ability to attack hypertensin; but, 40 minutes heating at 60 C. was found to have destroyed the normal enzymatic action of tyrosine, yet it still inactivated hypertensin²⁰⁵; it is doubtful therefore what conclusions should be drawn from the foregoing observations. Hypertensin was isolated from the venous blood of ischaemic kidneys¹³⁹. It has been shown that the same substance can be produced *in vitro* by the enzymatic action of renin on hypertensinogen¹⁴⁷. Ischaemic kidneys secrete renin, not hypertensin²⁰⁶. The injection of hypertensin into six normal persons was found to cause a decrease in heart output²⁰⁷, and hypertensin injected into the maternal blood of a rat caused no change in the foetal blood pressure²⁰⁸.

Hypertensinase

An enzyme that destroyed the activity of hypertensin was detected in the blood, and was named hypertensinase. The optimum pH for its activity was found to be 7, 5 to 8, 5²⁰⁹.

This completes the review of the components of the pressor action of renin.

THE PRESSOR BASES OF URINE

Several pressor bases have been detected in or isolated from the urine. Whether these bases have, or have not, any relationship to the aetiology of essential hypertension is as yet unproven.

Abelous and Bardier in 1908 reported the presence in urine of a very active pressor base, not precipitated either by basic lead acetate, or by mercuric chloride, but giving an oxalate insoluble in ether. The base was reported to have an activity comparable with that of adrenaline²¹⁰⁻²¹⁴. It was found present only in human urine, and not in that of other mammals. The urine of infants contained only a small amount²¹². The base was not isolated in pure form.

Fretwurst and Hertz in 1932 crystallised nicotine from urine as the dipicrate²¹⁵, from a case of acute nicotine poisoning. In 1933 Dingermanse and Freud²¹⁶ identified a compound which they had isolated from urine of cataleptic patients in the form of both picrate and picrolonate, with nicotine; as their patients were smoking, these workers attached no importance to their results. In 1944, a base closely related to l-nicotine was isolated as the oxalate, picrate and platinichloride from the urine of non-smoking human patients, and a similar base was detected in the urine of dogs²¹⁷.

In the same year piperidine was isolated from the urine of cows, being obtained as the picrate,

and having a nicotine-like action^{218, 219}. A volatile base has been detected in the urine of dogs in which one kidney has been rendered ischaemic by surgical means. A similar base is found to be liberated on the alkaline hydrolysis of normal dog and human urine, but the base does not appear free in normal urine. Crystals have been obtained from this base^{220, 221}.

Discussion

The great similarity of the clinical^{222, 223} and postmortem findings^{113, 114, etc.}, in cases of essential hypertension in man and the experimental hypertension due to renal ischaemia in animals is universally accepted, and the mechanism by which the blood pressure is raised in each case has been shown to be a chemical agent; this would therefore indicate the importance of renal ischaemia in the aetiology of essential hypertension, but it does suggest that the actual causative agent in the disease in man is that which produces the renal ischaemia. Although an increasing number of cases of essential hypertension in man are being reported in which evidence of unilateral or even bilateral constriction of the renal arteries was found, in the vast majority of cases coming to post-mortem such evidence is lacking, and the changes in the kidneys are those of bilateral, symmetrical arteriolar-sclerosis. It appears that the first stage of renal arteriolar constriction is attended by an increased glomerular pressure and constriction of the efferent arterioles²²⁴⁻²²⁶; no explanation of the mechanism by which this change is brought about can yet be given; it could be chemical or nervous. No correlation has been established between the weight of the coeliac ganglion and the occurrence of hypertension in man²²⁷⁻²³⁰. No alteration in the renal blood flow, determined by the glomerular filtration rate, was found in patients with essential hypertension who had been subjected to bilateral subdiaphragmatic splanchnectomy with the removal of the lower dorsal sympathetic ganglia²³¹, and a report has been made of 54 patients with essential hypertension who submitted to surgery of the sympathetic nervous system²³²; in all these cases the clinical picture of essential hypertension was already developed, the operations being performed for therapeutic reasons; renal arteriolar changes may therefore have been well-developed, and the period during which a nervous mechanism might have had aetiological bearing on the course of the disease may well have passed. The same difficulty is encountered in the aetiological interpretation of all such results, and could only be met by a large and unjustifiable series of patients submitted to "prophylactic" surgery of the sympathetic nervous system, with the determina-

tion of the incidence of essential hypertension developing subsequently. It should in this connection be noted that evidence of regeneration in the sympathetic nervous system is appearing. Similarly, no evidence has yet been produced of a chemical agent responsible for the renal arteriolar lesions; the uniform and symmetrical involvement of the efferent arterioles, the histological findings, and the extensive work on the aetiology of glomerular nephritis could be used to support this view.

It being accepted that some unknown initial stimulus must be postulated to account for the onset of renal ischaemia in essential hypertension, the second stage of hypertension and the full clinical picture can be produced experimentally in dogs and monkeys by the artificial narrowing of the renal arteries. The generalised vasoconstriction and rise of blood pressure in both cases has been shown to be due to a chemical agent, and the studies made of the peripheral circulation and kidney function in man is exactly paralleled by that experimentally produced in animals. An exciting search for the chemical agent concerned has revealed the presence of a new important blood pressure controlling mechanism, the renin system. Renin, an enzyme of the kidney cortex acts on a blood globulin, hypertensinogen, with the formation of a pressor compound hypertensin. It has been shown that renin is liberated by ischaemic kidneys, and occurs in the blood of patients with essential hypertension and in animals with experimental hypertension. As yet no direct correlation has been made between the amount of renin in the blood stream, and the degree of hypertension. It might therefore be assumed that the liberation of renin by the ischaemic kidneys was responsible for the production of the raised blood pressure, and, indeed the type of action shown by renin and hypertensin on the blood vessels is such as would produce the clinical picture of essential hypertension but for the phenomenon of renin tachyphylaxis. Although hypertensin was isolated from the venous blood of ischaemic kidneys, it has been shown that the ischaemic kidney liberates not hypertensin, but renin. Repeated injections of renin are attended by progressively smaller pressor response, and it has not been found possible to maintain a persistently elevated blood pressure by the continuous infusion of renin for more than four hours because of this phenomenon. Such a property does leave room for doubt as to whether renin could be responsible for a persistent hypertension, and suggests the possibility that its true physiological function may prove to be that of an emergency mechanism for the control of the blood pressure; on the other hand, renin has not yet been isolated

as a pure protein; the most active preparations* still contain inert kidney material, and although the removal of progressively more inert material has not been attended by decrease in renin tachyphylaxis, this could yet prove to be unassociated with crystalline renin. In favour of the physiological role of an emergency mechanism for the regulation of the blood pressure for renin is the fact that sudden lowering of the blood pressure from haemorrhage or trauma is associated with the liberation of renin from the kidneys. Despite these difficulties it is almost universally accepted that this blood pressure regulating system is responsible for the production of the hypertensive phase of both essential and experimental renal hypertension.

Arising out of studies on the species specificity and antigenic nature of renin came the hope of the effectivity of renin as an anti-hypertensive agent; this hope, although unfulfilled, for no correlation could be shown between the blood pressure lowering produced by partially purified renin and the antirenin titre of the serum, led to the discovery of a separate, as yet unisolated, compound in the kidney material capable of lowering the blood pressure in essential and experimental hypertension when administered in amounts ineffective on the blood pressure of normal subjects. It is possible that this compound when isolated may prove therapeutically effective.

Before terminating this discussion the use of thiocyanate in the treatment of essential hypertension should be reviewed. Claud Bernard in 1857 first described the cardiac depressant action of the cyanates. Pauli²³³ in 1903 published a series of cases of arteriosclerosis which had been treated with cyanates, with good results. Not until 1925 when cyanate preparations were again introduced for the treatment of essential hypertension were the toxic manifestations and conditions for effective therapy carefully studied. A full report of the pharmacological actions of the sylphocyanates has recently been published²³⁴, containing a review of the literature up to this date. It is generally conceded that for effective therapy and the avoidance of toxic symptoms control determinations of the blood thiocyanates are necessary. The methods used are based on those of Schreiber²³⁵ or the micro-method of Griffith and Lindauer²³⁶. A level of 12.5 mg./100 c.c. is regarded as therapeutic, but at this blood concentration toxic manifestations may occur in patients who have no great sensitivity to the drug. Venous thrombosis attributed to the use of thiocyanates has occurred with blood levels of 4.2 g. and 6.5 mg./100 c.c.²³⁷. Goldblatt was unable to produce a lowering in the blood pressure of dogs with experimental renal hypertension

without the use of toxic doses²³⁸. Barker and Davis²³⁹ confirmed by Kunz²⁴⁰, have claimed that sympathectomy increases sensitivity to thiocyanates. Despite the dangers attendant on the use of thiocyanates even when a careful control is kept on the blood concentration, patients are effectively treated by means of the drug, and its use will therefore continue until some less dangerous and equally effective method of therapy can be introduced. Acute variable and painful enlargement of the thyroid with or without signs of myxoedema and maculopapular rash has recently been described in patients treated with thiocyanate²⁴¹.

In conclusion, although much valuable work has been done on the aetiology of essential hypertension, and the syndrome produced by renal ischaemia has been identified with that of developed essential hypertension, the initial cause for the onset of the renal arteriolar changes resulting in renal ischaemia is unknown; as yet no effective therapeutic advance has been made as a result of these researches.

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FRACTURES OF THE SPINE AND PELVIS

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FIRST-AID TREATMENT OF ALL FRACTURES OF THE SPINE

The best treatment when a fracture of the spine is suspected is to leave the patient where he may be lying. He should not be moved unless absolutely necessary. Morphia should be administered to relieve pain and shock. The abdomen should be examined if possible before the administration of morphia, as the latter tends to mask any abdominal signs. The patient should be kept warm. When the ambulance arrives the safest way to

lift the patient is by the use of a strong pole and canvas slings around the head, neck, trunk, pelvis, and lower limbs. He should be carried in the position in which he is lying. No attempt either to flex or extend the spine should be made until X-ray examination has been made.

FRACTURES OF THE CERVICAL SPINE

FRACTURES OF THE ATLAS

Clinically, fracture of the atlas is shown by spasm of the cervical muscles. The head is held forwards in a characteristic manner as if it is tending to fall off. The same curious clinical

DIAGRAM 1.—Fractures of the atlas.

picture sometimes appears with active tuberculosis of the cervical spine. The position of the fracture is shown in Diagram 1.

If fracture of the atlas is associated with paralysis of the limbs due to pressure on the cord skull traction should be applied for several weeks. This is described later. Otherwise, the head and neck are immobilised for three months in plaster.

DISLOCATION OF THE ATLAS

This is due to tearing of the transverse ligament of the odontoid process. There is great risk of the odontoid process pressing backwards on the spinal cord with resulting paralysis, and even death. Thus treatment consists in reducing the dislocation

DIAGRAM 2.—Dislocation of atlas due to tearing of transverse ligaments of odontoid process.