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Abstract
Based on a Dissertation read before the Royal Medical Society on Friday, 19th February 1960.
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THE AETIOLOGY OF HYPERTENSION

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The most common cause of death in this country is vascular disease. While it must be admitted that the incidence of vascular disease, and of the other major disease, cancer, increases with age, it is accepted that these diseases proceed often to a fatal conclusion when the victim is still productive. It has been estimated that if deaths due to the results of vascular disease were preventable, life expectancy might increase by some ten years. Were cancer cured, life expectancy would increase by about 2.5 years.

If in the first place we take merely an arbitrary level, say, 150/90 mmHg. above which we can consider pressures to be "high," then we may at once distinguish systolic and diastolic hypertension. Systolic hypertension is due to an increase in the cardiac output or to diminished elasticity of the aorta and large arteries. A rise in diastolic blood pressure if sustained, is usually due to an increase in the total peripheral resistance. The latter is dependent on the degree of constriction of the arterioles. Diastolic hypertension also results in the presence of a raised cardiac output provided that the total peripheral resistance does not fall. Systolic hypertension is not rare and does not appear to have marked deleterious effects. This article will be more concerned therefore with the aetiology of diastolic hypertension, although it must be remembered that the systolic and diastolic blood pressures tend to vary in the same direction. Essential hypertension is due to an increase in the total peripheral resistance without a change in the cardiac output: this causes a rise primarily of diastolic blood pressure, but the systolic pressure also rises.

Currently there is a major controversy regarding essential hypertension: is there a separate clinical entity of patients with high blood pressure? Or do patients presenting with symptoms and signs attributed to hypertension represent merely the upper limit of blood pressures in the general population?

Until about 1955, it was widely accepted that diastolic hypertension—certainly when secondary and probably when "essential"—constituted a clinical disease. But in that year Pickering published the results of statistical surveys of the distribution of blood pressure in a general hospital population. At a given age, the distribution of blood pressures differs from the normal (Gaussian) distribution curve in a positive skewness i.e. more values and wider range of values above the mode than below it. (The mode is that value with the highest frequency). This positive skewness becomes more marked with age, for, although the low pressures tend to persist, the high pressures tend to increase; thus the distribution curve widens. Both systolic and diastolic blood pressures increase with age, so that for an obese woman of 60 years 200/110 might well be accepted as normal. The average systolic pressure increases from 120 mmHg at age

20 years to 170 at age 80 years in man and in woman from 112 mmHg at age 20 years to 190 at age 80 years. The corresponding diastolic pressures are:

In men 70 and 85 mmHg.
In women 70 and 95 mmHg.

The sex difference becomes more marked after the menopause.

Now the distribution curve of all patients at all ages was considered to be unimodal, that is, with only one peak (Fig. 1). Pickering therefore postulated that patients with essential hypertension are merely . . . "that section of the population having arterial pressures above an arbitrarily defined value, and having no other disease to which the high pressure can be attributed . . . the difference is not of kind but of degree."

The other theory is that the difference is of kind: essential hypertension is a disease entity. If this is so, then one would expect a bimodal type

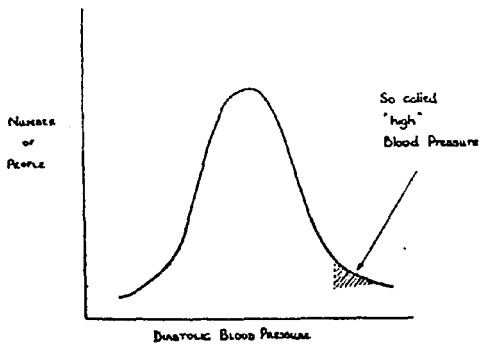

Fig. 1

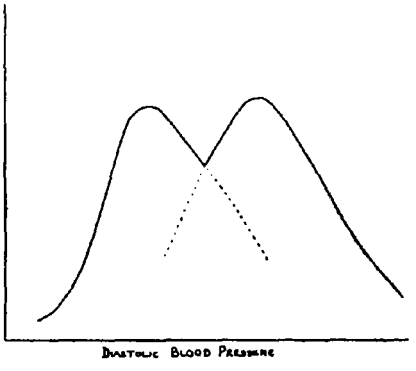

Fig. 2

curve of the blood pressures in the population (Fig. 2). Adherents to this "qualitative" theory maintain that the increased incidence of people with essential hypertension account for the major part of the over-all rise in pressure with age. One must employ special methods of statistical analyses to unmask the bimodality.

Platt has studied the blood pressures of the siblings, aged 45-60 years, of patients with hypertension and found a bimodal curve. On re-examining Pickering's figures, and taking the readings correct to 5mmHg, he has found significant dips in the systolic and diastolic distribution curves at 150 and 90mmHg. Morrison and Morris have shown a bimodal distribution of the systolic blood pressures of London busmen whose parents died between the age of 45 and 64. (Presumably a higher proportion of these parents had hypertension than people who lived longer.) Similarly a bimodal curve has been shown for the children of hypertensives.

Currently, the pendulum of medical opinion is swinging back towards the "qualitative" theory as being the correct one. If correct this indicates that the hereditary factor in hypertension is probably carried by a single, dominant gene rather than a multiple polygenic mechanism as for height, weight, normal blood pressure and so on.

The extent of the influence of the genetic factor has been studied in some detail; figures of from 4 to 64% have been suggested. The effect of the genetic factor appears to diminish with age. If the genetic effect varies a great deal this might be due to:

(1) A multigenic hereditary mechanism if the quantitive theory is correct.
(2) A dominant gene of varying penetrance and expressivity.

The best work has come from a study of twins and the relatives of hypertensives. A dominant gene might be expected to reveal itself in 50% of the children of parents of whom one is hypertensive, and in all children if both parents are hypertensives. In fact, figures less than these have been found, about 35 and 70%. Apart from varying penetrance and expressivity this could also be explained by

(*a*) presence of other diseases.

(*b*) absence of extrinsic permissive factors such as diet and environment.

There is a very close connection between the blood pressures of uniovular twins, and also, but slightly less so, of binovular twins. A few cases of uniovular twins of whom only one was hypertensive have been reported, and it is interesting that in those cases the twins had quite different personalities. Further, the correlation between the blood pressures of twins is not as high in those who have been brought up in different environments.

So much for heredity. Let us consider the psychological and physical aetiology of hypertension. High blood pressure has been named as a stress disease. The psychiatrists have found, in manic-depressive patients, hypotension in the manic phase and hypertension in the depressed phase. Psychologically-minded cardiologists have related the onset of hypertension to some psychological stress, but such retrospective studies are naturally open to deserved criticism. Others have suggested that high blood pressure is associated with a specific type. It is at least widely agreed that hypertensives show restrained aggression and unexpressed rage and hostility, while patients with essential hypertension respond with a greater and more prolonged rise in pressure to unpleasant situations.

Psychotherapy and prefontal leucotomy have a variable effect on hypertension, but most often results in a temporary fall. Acute and chronic stress in the form of earthquakes and front-line war service have been found to cause a persistent, but not very large, rise in pressure.

Nevertheless it has not yet been adequately established whether personality changes and psychological manifestations result in or from hypertensive disease.

The physical aetiology of hypertension is founded on more salient features. Firstly, the kidney has been implicated clinically and experimentally. As early as 200 B.C. Choun-Jon-J wrote: "When the pulse upon depressing is very firm and upon superficial palpitation very tight, then the disease has its seat in the kidney." Bright described the pathology of the kidney in cases associated with high blood pressure.

A tremendous fillip to the role of the kidney in hypertension was given by Goldblatt; he produced experimental hypertension in dogs by clamping the two renal arteries or by clamping one renal artery after removing the other kidney. The renal arteries were not totally occluded; the aim was to produce renal ischaemia by decreasing the arterial blood flow. It was postulated that the ischaemic kidney released a pressor agent which caused the hypertension. However, if the other kidney was left intact and unclamped, no rise in blood pressure occurred: the intact kidney must have "neutralised" the pressor released by the ischaemic kidney. The vasodepressor action of the normal kidney was emphasised by Gollman's finding that bilateral nephrectomy is followed by hypertension; such hypertension is not due to the rise in extra-cellular fluid volume nor electrolyte disturbance, since it occurs when the animal is dialysed.

Byron and Wilson confirmed these findings after producing renal hypertension by partially occluding only one renal artery in the rat. Such

hypertension occurs after a shorter latent period than after total nephrectomy. Removing the clamp will only restore the blood pressure to normal if it is done within two or three weeks. After that time the blood pressure will remain high apparently because an extrarenal mechanism has taken over and become autonomous.

It is noteworthy that vascular lesions only develop in the unclamped kidney. The clamped kidney is "protected."

These experiments at once present some obvious problems:

1. What is the pressor agent released, and what is the necessary stimulus?
2. How does the normal kidney depress blood pressure?
3. What is the extra-renal mechanism?

The pressor agent may be renin which has been isolated from renal venous blood, following clamping. Renin is an enzyme which can be extracted from the renal cortex; on injection it causes hypertension by splitting off the pressor polypeptide hypertensin from the plasma protein hypertensinogen. Unfortunately renin has not been commonly demonstrated in the blood during acute renal ischaemia in man and never in essential hypertension. Experiments involving partial renal corticectomy are purported to show that the origin of renin is in the outer cortical tissue, perhaps in the juxta-glomerular apparatus.

Another vasoexcitatory material, pherentasin, has been isolated by Schroeder from the blood of experimental renal hypertensive dogs and from cases of essential hypertension and hypertension secondary to renal disease in man. It is not directly a pressor agent but sensitizes the vessels to the normal stimulus of sympathetic transmitter. There are reports of increased sensitivity to intra-arterial injection or nor-adrenaline in cases of essential hypertension.

An interesting theory as to the formation of the amine pherentasin is as follows: the kidney manufactures ammonia from the plasma amino acids; this is achieved in two stages:

1. decarboxylation of amino acid to amine: the reaction is catalised by an anerobic enzyme.
2. deamination of the amine; this reaction is catalysed by an aerobic enzyme.

   Now in the ischaemic kidney one might expect the anaerobic but not the aerobic enzyme to continue to function. This would cause an excess of amines such as pherentasin to be produced.

These clamping experiments show that the onset of experimental renal hypertension is associated with a fall in renal plasma flow. Clinically in the renal lesions associated with secondary hypertension, there is usually a fall in renal plasma flow but not in the glomerular filtration rate so that the filtration fraction increases. The one consistent functional alteration in chronic human hypertension is the presence of renal ischaemia. And we may correlate this with Homer Smith's observation that the so-called neurogenic hypertensive patients, after a psychological stimulus or physical exercise, do show a greater than normal fall in renal plasma flow and a slower return to normal.

Congenital renal lesions, of parenchyma or vessels, are often associated with hypertension, and, if the renal lesion is unilateral, the hypertension may be cured by unilateral nephrectomy. Similarly it is not rare to find hypertension developing in a person with severe pyelonephritis. Pyelonephritis appears to increase an existing hypertension and to magnify the

effects of a congenital lesion, for of patients with congenital lesions presenting with hypertension more than half have co-existing pyelonephritis. Yet to be established is the difference between those patients with chronic pyelonephritis who develop hypertension and those who do not. Many patients with severe bilateral pyelonephritis have a decreased renal blood flow but do not develop high blood pressure.

Goldblatt's experiments on clamping the renal artery have often been criticised as not being remotely connected with the aetiology of clinical hypertension. However in 1939 Blackman found at autopsy that in cases of essential hypertension 84% showed atheromatous narrowing of the renal arteries, whereas only 10% of the controls showed this. Pathologists cut longitudinally into the renal arteries; this obscures atheromatous plaques. A 1mm decrease in the radius of a 5mm radius vessel may appear relatively slight, but one must remember that blood flow is proportional to the fifth power of the radius. Thus a 20% reduction in the radius of the vessel causes a 66% fall in blood flow. Blackman's findings may be correlated with the hypertension following aortic thrombosis above the level of origin of the renal arteries.

The hypertension of coarctation of the aorta has long been attributed to the increased peripheral resistance presented by the narrow, long collaterals. (This resistance is in large vessels and causes predominantly a systolic hypertension above the congenital narrowing.) Yet the femoral diastolic pressure often is increased, although the systolic pressure may be normal or less than normal, with a small pulse pressure. Scott and Bahnson (1957) in a classical series of experiments, produced experimental diastolic hypertension in a unilaterally nephrectomised dog by an artificial coarctation of the aorta. Later they abolished the diastolic hypertension (beyond the obstruction) by transplanting the kidney to the neck.

Similarly the hypertension which sometimes occurs in polyacteritis nodosa may also be explained by obstruction in the renal artery leading to ischaemia.

If a rat's renal artery is clamped and left so for several weeks then hypertension will remain after removal of the clamp. However the hypertension may be abolished by adrenalectomy, and restored by feeding high doses of salt.

Ledingham has demonstrated that totally nephrectomised rats develop hypertension only if their adrenals are intact or if there is an excess of salt in their diet. In a totally nephrectomised and adrenalectomised parabiotic rat (the other parabiotic rat being normal) the blood pressure then remains normal, presumably because of the passage of some humoral factor from the parabiotic twin. Adrenalectomy itself has no effect on a parabiotic rat. Selye has produced hypertension in experimental animals by administering D.O.C.A. (deoxycortisone-acetate) plus salt; the hypertension is not due solely to the increase in e.c.f. volume.

Clinically the high blood pressure seen in Cushing's disease is well known. Schroeder has described a group of female patients with hypertension: common factors include obesity, middle age, and the history of some endocrine abnormality. This group constitutes 20% of female hypertensives. These women have a very low salt content in their sweat and their blood pressure is very sensitive to lowering of their salt intake or to diuretics. It would be interesting to observe the effect of anti-mineralocorticoids such as spirolactone on these patients.

Recently renal ischaemia has been correlated with aldosterone secretion by the adrenal cortex. In renal ischaemia in both man and experimental

animals the juxta-glomerular cells, the specialised cells in the wall of the afferent glomerular arteriole, are more numerous and contain more granules. Dietary restriction of salt in animals causes hyperplasia of the juxta-glomerular cells and of the zona glomerulosa of the adrenal cortex. The zona glomerulosa probably is the site of manufacture and release of aldosterone. The stimulus for the release of aldosterone is unknown: it is not A.C.T.H. After adrenalectomy there is also juxta-glomerular cell hyperplasia. It has been postulated that the juxta-glomerular cells may play some part in the control of aldosterone secretion by the adrenal cortex.

It has been suggested that when the cause for secondary hypertension, such as unilateral renal disease, is removed, but hypertension persists, that hypertension is being maintained by an adrenal mechanism which has become autonomous. In fact, in patients with a short history of renal disease, adrenalectomy will often result in normotension after the unilateral nephrectomy has failed. But some cases remain with high blood pressure after unilateral nephrectomy and total adrenalectomy. Adrenalectomy has not yet met with success in the treatment of essential hypertension.

However, in ALL patients with essential hypertension, salt restriction will lead to a fall in pressure if both sodium and chloride are restricted. The importance of salt may lie not in the Na and Cl ions but in the small proportion of unionised sodium chloride and its effects on the cell membrane. There is suggestive evidence of altered sodium, potassium and chloride ratios between the intra- and extra-cellular fluids of the cells of the blood vessels of hypertensive animals.

Finally, countries in which high blood pressure is common also have high salt consumptions. For example, hypertension is rare in the Orient except in Japan where there is a high salt intake.

A neurogenic basis for essential hypertension acting via renal and/or adrenal effector pathways, has been postulated since stress must act via the central nervous system in causing renal ischaemia and increased production of adrenal cortical hormones. Although experimental neurogenic hypertension can be produced by section of the buffer nerves supplying the baroreceptors, the carotid sinuses and the aortic pressor receptors, this state is not at all kin to essential hypertension in which the pressor reflexes appear normal. Conceivably the baroreceptors, by adaptation, might be "set" to a higher level of blood pressure in essential hypertension.

Recently the influence of sex hormones on the sensitivity of the vascular system has begun to be investigated. Women in the reproductive phase of life have a lower mean blood pressure than men; and overall, women with high blood pressure have a better prognosis than men. Dr Mary Pickford and Miss Sybil Lloyd, experimenting on cats and dogs, have found marked differences in the response of the female cat and dog at different times. In late pregnancy and after oestrogen administration oxytocin has a pressor action, as opposed to its normal vasodilator and depressor effects. Yet the pressor response to nor-adrenaline and the depressor response to acetyl chlorine are unchanged. This changed response to oxytocin can also be produced by ganglion blocking drugs and by post-ganglionic sympathetic blockade with Bretylium tolysate (Darenthin). Part of the response to oestrogens appears to be central because of the effect of decerebration or pithing. The peripheral mechanism may involve altered sodium or potassium ratios between the i.c.f. and the e.c.f. of the smooth muscle in the wall of the vessels.

A final observation of interest is that the pressor action of renin but not of hypertensin is absent during late pregnancy.

Summary

1. Hypertension may be transmitted by a dominant gene of varying penetrance and expressivity.
2. The role of the kidney is
   (*a*) the release of pressor agents such as renin and pherentasin in response to ischaemia.
   (*b*) a normal role of keeping down the blood pressure by an unidentified mechanism.
   (*c*) perhaps control of aldosterone production by the adrenal cortex.
3. The adrenals may sometimes provide a secondary mechanism for maintaining long established hypertension.
4. There is at least one other extra-renal mechanism capable of maintaining hypertension. This may include altered responses of pressor receptors and/or vasomotor centres.
5. Other factors include personality type, environment and sex hormones.

But whatever the primary cause in a given case —hereditary, neurogenic, renal or endocrine—it is probable that other factors are necessary for the hypertension to become manifest. We have thus primary and permissive factors. It has even been stated that hypertension would not occur in an individual, both of whose parents were hypertensive, if, from birth he did not add salt to his food.

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