CHAPTER 6 - ABERRATIONS OF BLOOD PRESSURE CONTROL

A. HYPERTENSION

Normal Blood Pressure Control.

Blood pressure is normally controlled very precisely from minute to minute, even from beat to beat, largely due to the aortic and carotid baro-receptors sensing the pressure and giving immediate (neural) feedback to the medullary centres which act on both heart rate (a vagal effect) as well as the arterioles (sympathetic effect). The vascular smooth muscle of the arterioles is very different from other smooth muscle, especially that of the gut. Thus, vascular arterioles are very sensitive to sympathetic nervous stimulation, have a high basal tone, are also sensitive to local metabolic and humoral factors, not very sensitive to stretch, and have no pacemaker activity. This is in contrast to the visceral smooth muscle which has little sensitivity to sympathetic nervous activity, but a great deal of sensitivity to local factors, an intrinsic rhythmic contraction, sensitivity to stretch, and pacemaker activity. Smooth muscle in the vascular pre-capillary sphincters are particularly reactive to local metabolites.

Some of the sympathetic nervous control of blood pressure is exerted via a direct (beta-adrenergic) effect on cardiac output (altering both rate and strength of contraction), but its main (alpha-adrenergic) effect is on peripheral arteriolar resistance. The order of sympathetic nervous influence in the various organs tends to increase as follows: brain, coronary circulation, skeletal muscle, kidney, splanchnic bed, skin. Tone in arteries and larger arterioles is influenced by the sympathetic nervous system, though blood flow is normally auto-regulated at the small arteriolar level by metabolic factors. In any particular bed, arteriolar tone depends on both neurogenic and myogenic activity, local metabolites (auto-regulation), and circulating factors such as angiotensin II & noradrenaline.

The total circulatory peripheral resistance, and with it the level of arterial blood pressure, is determined by the sum of the resistances of the different vascular beds, so we cannot simply equate local arteriolar constriction with hypertension. For example in exercise, blood pressure does not tend to rise very much, because there is a great redistribution of blood due to sympathetic nervous activation shutting down skin, splanchnic and renal blood flow in the interests of maintained perfusion of the brain, and the increased blood flow requirements of the exercising skeletal muscles.

Although baroreceptors control blood pressure closely, they do so only around a given set point, i.e. if for some reason blood pressure is elevated, e.g. by an angiotensin infusion, over a period of even a few days, the baro-receptors initially antagonise the effect of the hypertensive stimulus, but this is soon overcome, and the arterial baroreceptors eventually "reset" to regulate the blood pressure around the new level. As time goes by, hypertension itself may have an effect to stiffen the arterial

wall, and limit its ability to stretch etc., so that the slope of the pressure-response curve of the baroreceptor reflex may be flatter than normal and less sensitive to blood pressure alteration.

CLINICAL OVERVIEW & PATHOGENESIS

In dealing with clinical hypertension , we enter the field of preventive medicine. In its early stages, indeed often for many years, hypertension is symptomless. But we need to detect it early not so much for its own sake, but to avoid its later complications related to large vessel atheroma, including stroke, angina, heart attack, and intermittent claudication.

The are problems with such a 'primary preventative' approach to treatment of any asymptomatic patient. First, you must measure blood pressure in all patients, regardless of symptoms. Second, you should not embark on drug treatment lightly, and when you do, you need to explain exactly why you are doing so, outline the action of the drugs in simple terms, why the need for long-term treatment, and make sure that the patient understands that he/she will not be able to decide the need for continuing treatment by any symptoms they may or may not have. The treatment of even moderate hypertension will only be undertaken if there are associated cardiovascular risk factors such as a raised cholesterol, diabetes. Side-effects of medications also create a problem long term treatment, and unless you carefully tailor drugs to suit the individual, patients may finish up with more symptoms than they ever came with. How can you then expect them to comply with your therapy? First do no harm.

Asymptomatic presentation also means that the history will not usually be of much value in clinical problem-solving or diagnosis. Indeed, in one sense we are not dealing with a clinical diagnostic problem at all. Nonetheless, history and clinical examination can be very useful in solving the four major diagnostic questions in hypertension, particularly bearing in mind that we are, in this situation, trying to prevent large vessel atheromatous complications later in life. These questions are:-

1. What is the degree or severity of the hypertension? (Functional diagnosis)

2. What is the cause of the hypertension? (Aetiological diagnosis)

3. What have been the effects of the hypertension on the patient so far? (Functional)

4. What are the other 'risk factors,' quite apart from hypertension, which may compound the predisposition to atheroma. And just as importantly, are there any factors predisposing to those sudden atheroma plaque complications which so often immediately precede acute clinical coronary syndromes? (Aetiology) That is: Is this patient more prone to acute sudden cardiovascular complications.'

We should consider first the patho-physiology of chronic hypertension.

Pathophysiology of Hypertension

In general haemodynamic terms, elevated blood pressure may be brought about by an increased cardiac output or an elevated peripheral vascular (arteriolar) resistance. The commonest (95%) form of human hypertension has no known cause and is referred to as 'essential hypertension.' These patients usually have a family predisposition to hypertension, with elevation of blood pressure being precipitated by environmental influences such as stress (increased sympathetic activity), with or without excessive salt intake & obesity.

To understand the possible pathogenesis of chronic essential hypertension, we must first refer to simpler experimental models, for example the placing of a constrictive clip on one renal artery and removal of the opposite kidney in the rat. Here, as we would expect, reduction in renal blood flow to the clipped kidney leads to a rapid elevation of plasma renin with corresponding elevation of angiotensin and aldosterone. And during the first few weeks there is indeed a very good correlation between the degree of angiotensin elevation and the level of hypertension. However, as the weeks and months go by, this correlation becomes less and less; the blood pressure continues to climb during that time whilst angiotensin levels trend back down to normal. This situation is not brought about by any change in vascular smooth muscle sensitivity to angiotensin, because pharmacological angiotensin blockade may have very little effect to lower blood pressure in this chronic renal hypertensive model. Nor are any other hormones found to have taken over as a separate humoral drive to the hypertension in this situation.

The clue to understanding this change from early to late hypertension lies in the fact that it is seen with almost all forms of experimental hypertension, including other forms of renal hypertension, and steroid-induced conditions like mineralocorticoid hypertension. Now, the only factor common to all of these very different situations is the blood pressure elevation, so it must be this, or something closely correlated with it, that is effecting the change. And this has turned out to be so, because we now know from the work of Folkow that chronic blood pressure elevation is associated with the development of structural arteriolar changes, in particular medial hypertrophy, which tends to encroach upon the vascular lumen, so producing a structural narrowing and increase in peripheral arteriolar resistance which eventually takes over from the functional one. Just how this comes about is debated. Folkow's view is that it represents a 'structural adaptation' on the part of the arteriolar medial smooth muscle to the high blood pressure.

However, there are several difficulties with the 'structural arteriolar adaptation' concept of chronic hypertension.

1. The structural changes often appear histologically more like a response to damage than any physiological change - although the media is indeed hypertrophied, there is also evidence of

hyperplasia, as well as increased connective tissue, and not only within the media but within the other coats of the wall, including the adventitia and the intima.

2. Folkow views the stimulus to "structural adaptation" as an increase in arteriolar circumferential wall tension. But this, according to the law of LaPlace is directly proportional to both the pressure inside the lumen and radius of diameter of the arteriole, and in a situation where the arterioles are constricting, these two forces must have some tendency to cancel out, particularly in the more distal arterioles where the pressure will have already been lowered by upstream resistance.

3. Folkow holds that most structural arteriolar change is indeed present in the more proximal arterioles, but some studies show it right down to the smallest arterioles, and our own investigations (ref 1.) have shown structural change to be *irregularly* distributed along arteriolar lengths - very hard to reconcile with the usual concept of a smooth profile of pressure drop across arterioles. In any event, LaPlace's law is now known not to hold in actively constricting vessels. It is therefore difficult to talk about circumferential stretch in a situation where the smooth muscle is actively constricting, quite the reverse, i.e. compression of the wall structures.

4. In response to arguments like this, Folkow has argued that it may be the work of vascular smooth muscle constriction that makes for hypertrophy. But again, the histological changes are not confined to medial smooth muscle hypertrophy alone. Also, in any physiological "structural adaptation", arteriolar narrowing should be a compensatory change, with the original stimulus (angiotensin II plasma levels in the above example of renal-clip hypertension) being suppressed back towards, but not right to normal as sometimes happens. In practice, angiotensin levels may even be suppressed to*below* normal, more consistent with a pathological change where response would not be expected to be so finely attuned to stimulus.

Because of these considerations, I have made an alternative suggestion, which takes into account that much experimental functional arteriolar constriction tends to occur focally and irregurlay, rather than uniformly, along the lengths of arterioles (as indeed does much structural arteriolar change). The idea is that structural arteriolar change is a pathological result of focal haemodynamic increases in blood flow velocity, and therefore of wall shear stress, at points of focal arteriolar constriction. In this respect, I draw an analogy with the situation already discussed in the previous chapter on the pathogenesis of focal atherosclerosis, namely that focal arteriolar constriction, by increasing local blood flow velocity, and with it wall shear stress, damages the local endothelium and leads to pathological changes in the underlying wall, including smooth muscle hypertrophy, hyperplasia, an increase in connective tissue ground-substance and lipid, and luminal narrowing.

The above discussion about the nature and pathogenesis of structural arteriolar narrowing in chronic hypertension is controversial, but is put forward to stimulate your interest, and to show that much of what is accepted needs to be looked at critically, and in a constructive way, if our understanding of various disease mechanisms is ever to advance. The future in this respect is yours, not mine.

The important point clinically is that, no matter how this structural arteriolar change comes about, it certainly contributes to the increased peripheral resistance of any chronic hypertension. Moreover, because it is a structural change, it is not readily reversible when the initiating stimulus is removed, particularly after many years of hypertension. This almost certainly underlies the difficulty we sometimes have in controlling hypertension, particularly in older patients, even after reversing an apparently remediable cause such as renal artery stenosis. When the hypertension has been present for many years, it may nonetheless persist. On the other side of the coin, in the intermediate stage of hypertension, structural change is not necessarily as fixed, and may be partially reversible at least, albeit slowly. This is important in any drug or other approach to long-term therapy of hypertension, viz. the longer one goes on treating the hypertension, the more the blood pressure eventually tends to subside. As a corollary, if you stop long-term anti-hypertensive treatment for any reason, always follow BP up long term, even if it falls to normal initially - it may slowly creep up off therapy if the underlying cause persists.

We will discuss various clinical counterparts of some of these experimental forms of renal, steroid, etc., hypertension in a moment, but first, I want to look at the haemodynamics and pathophysiology of essential hypertension

HYPERTENSION - HAEMODYNAMICS

Haemodynamics of Essential Hypertension

Until recently, the pathogenesis and haemodynamics of essential hypertension were very obscure, but we are now beginning to understand at least some aspects. In the early phases there appears to be an increased cardiac output with a relatively normal peripheral arteriolar resistance. Moreover, then, the hypertension tends to be relatively labile, even intermittent. At this stage, the peak elevations of blood pressure often occur in relation to sympathetic nervous discharge (probably under the influence of stress). It has certainly been shown (Brod) that patients with a family background of essential hypertension tend to respond to any stressful stimulus by a greater-than-normal elevation of blood pressure, due both to a greater elevation in cardiac output and peripheral arteriolar resistance. And the evidence for an increased sympathetic nervous activity in the early phase of human essential hypertension is increasing (Esler). This increased sympathetic nervous activity probably results not only in arteriolar constriction, but venoconstriction, thereby increasing central venous blood volume and cardiac filling pressure, so as to increase the strength of ventricular contraction (Starling's law). This may be one of the mechanisms underlying the increased cardiac output in this early hypertensive phase. Increased direct (beta-adrenergic drive to the heart is also involved).

In contrast to the early phase, as human essential hypertension progresses, its haemodynamics change quite radically, and eventually patients end up with relatively fixed rather than labile elevations of blood pressure. Moreover, this is no longer related to an increased cardiac output but an elevated peripheral arteriolar resistance. This is not completely understood, but there is little doubt

that structural arteriolar changes occur in chronic essential hypertension just as with any other form, and since the circulation still has mechanisms for compensation, it is likely that the gradually increasing blood pressure from the increasing peripheral arteriolar resistance feeds back upon and suppresses the cardiac output so as to limit the blood pressure rise. The real puzzle is why cardiac output should be suppressed not just back towards normal but right to normal, even below in some cases. This again does not sound like any physiological compensatory response.

To explain this, I have suggested (Refs 2, 3) that early on in essential hypertension, the intermittent and often severe peaks of blood pressure are associated not just with an increased cardiac output but an increased peripheral resistance. I view this latter to be brought about by irregular *focal* constriction along arteriolar lengths, observable in some acute severe experimental hypertension. (Byrom) Further, even if such bouts last for only a short time, they may be associated with endothelial and other arterial wall damage, as observed experimentally with larger arteries. Of course once each bout is over, the arterioles would no doubt quickly heal, but even if such a bout produced a tiny amount of persistent arteriolar narrowing, "base-line" blood pressure would gradually tend to rise over the years. Thus, we can calculate that a rise in basal blood pressure of no more than 0.01 mm Hg/ day from episodic hypertensive damage of this type would produce a 35 mm Hg rise in baseline blood pressure over a ten year period - a relatively short time in the life history of human essential hypertension. Note that in early hypertension, with each bout at any focally constricted arteriolar point, the increase in flow velocity will be compounded by the associated increase in cardiac output, so that even relatively minor points of constriction may become damaged by a change in fluid dynamics.

I stress that this is theory and there are certainly opposing views, but it does provide an explanation for why cardiac output may be suppressed in chronic hypertension not just back towards normal, but even below it, because the chronically increased peripheral arteriolar resistance is considered by my view to be brought about by recurrent pathological arteriolar damage, and as with the model of chronic experimental renal-clip hypertension, we would not expect the final degree of basal blood pressure elevation to be finely attuned to the original initiating stimulus in such a pathological state. Thus, the plateau level of blood pressure achieved by structural arteriolar *damage* could easily be greater than that determined by the original physiological stimulus, and this overly high blood pressure response might well feed back upon and suppress the initiating stimulus to below normal, both haemodynamically (suppression of the cardiac output), and in terms of the basic underlying drive (reduced sympathetic cardiovascular activity), in advanced hypertension.

CLINICAL HYPERTENSION

The specific thrust of this particular chapter is to give you some background knowledge of the pathophysiology of hypertension, and sufficient clinical information to solve problems related to it.

Let us first look at ways of broadly answering our four initial questions.

1. What is the **severity** of the hypertension? If mild, observe for months before passing judgement. And because many patients are stressed by visits to their doctor, get readings from outside the medical setting, e.g. pharmacy outlets.

2. What is the **cause** for the hypertension? Secondary causes can be mechanical (e.g. coarctation of the aorta), renal (unilateral or bilateral renal disease, particularly ischaemia from renal artery stenosis), adrenal (excessive aldosterone or cortisol secretion from the adrenal cortex; catecholamines from the adrenal medulla), or other steroid causes including the oral contraceptive pill; also rare CNS causes, particularly with lesions in the hindbrain affecting the medullary centre of cardiovascular control. Drugs may also cause hypertension (e.g. cyclosporin A) or exacerbate it (eg. NSAIDS, erythropoietin in chronic renal failure).

Diagnosing cause depends on keeping these possibilities clearly in mind during both clinical history-taking and physical examination. In particular, be aware of unilateral renal artery stenosis (potentially reversible), which may be associated with a long, high-pitched bruit to one or other side of the epigastrium. Feel for radio-femoral pulse delay, the hallmark of aortic coarctation. Endocrine causes include acromegaly.

Adrenal causes

Cushing's syndrome (excess cortisol secretion) is usually obvious clinically, and signs of cortisol excess include proximal myopathy, weakness and wasting, easy bruising and poor wound healing, susceptibility to infection, (acne etc.) osteoporosis, truncal obesity, abnormal (pink) striae, a buffalo hump (large pad of fat over the lower cervical and upper thoracic vertebrae) and, in some cases (from adrenal androgen production) masculinisation (increased bodily hair with male distribution, enlargement of clitoris, development of facial hair, temporal recession of head-hair). Biochemical diagnosis helps localize, i.e. if plasma cortisol is high with low ACTH, the primary problem is adrenal, whereas if both ACTH and cortisols are high, the primary problem lies in the pituitary.

Conn syndrome (increased aldosterone production from an adrenal zona glomerulosa tumour or hyperplasia) is more common in (relatively young) females and produces moderate hypertension with the hallmarks of a low plasma potassium and highish plasma sodium in the presence of a metabolic alkalosis (high plasma bicarbonate). Because of aldosterone's action, the potassium in the urine is high, particularly when looked at in the context of the low plasma potassium, and the sodium:potassium urinary ratio is usually less than 1.0. Plasma aldosterone: renin ratio is high. Sodium retention occurs, but with only mild clinical oedema. Typically, a low plasma K+ is the hallmark of this condition, but there is increasing recognition that this is not always the case (Gordon and Stowasser)

Other mineralocorticoids can produce a similar effect, as exogenously-administered ones like 9 alpha-fludrocortisone, DOCA or other steroids produced endogenously from various adrenal or other tumours. Excessive ingestion of licorice also induces a syndrome of hypokalemia and hypertension (inhibition of the enzyme 11 beta-hydroxysteroid dehydrogena prevents local intracellular renal tubular inactivation of cortisol, so allowing it to stimulate renal mineralocorticoid receptors and produce a syndrome just like Conn's syndrome except that aldosterone levels are suppressed). Potassium loss in Conn's syndrome produces muscular weakness, especially proximally, and also interferes with renal concentrating mechanisms so resulting in polyuria, nocturia, thirst, and polydipsia.

Phaeochromocytoma Think of this in intermittent hypertension particularly if associated with glycosuria (adrenaline effect).

Renal Causes

The kidneys which are characteristically large in polycystic renal disease. Exclude lower urinary tract obstruction. Renal hypertension is most common with renal cortical disease - i.e. those diseases involving the JGA. Listen carefully for a renal artery stenosis bruit. Examine urine, including microscopy. Ask about past history of renal disease, drugs such as excessive NSAID use.

Investigation of Hypertension

If clinical examination has not given any obvious diagnosis, then our usual principles of investigation hold, namely to do simple investigations first. If hypertension is relatively mild, the patient relatively old, or responding very well to little treatment, we need not to do more than the simple noninvasive investigations in excluding secondary causes. But it is important to investigate extensively where there are one or more of the following features:

(a) Relatively young age.

(b) No family history of hypertension.

(c) Severe hypertension.

(d) Hypertension unresponsive to treatment.

Investigate any case where clinical history and/or examination findings provide clues (e.g. a prolonged epigastric bruit suggesting renal artery stenosis).

Investigate is for a *reversible* cause. In this context, unilateral renal disease is important, particularly renal artery stenosis. However, some forms of bilateral renal disease are at least arrestable and are worth discovering. This includes not only bilateral renal artery stenosis, but analgesic nephropathy,

urate nephropathy with gout, vesico-ureteric reflux with secondary nephropathy, and hypercalcaemia producing renal damage. In all of these situations, the deterioration of renal function and continuing rise in blood pressure may well be arrested, and even partially reversed, by appropriate action. An important rule is that if plasma creatinine is elevated more than twice normal, there must be bilateral renal disease.

FUNCTIONAL DIAGNOSIS

This brings us to our third question, namely:

3. What are the effects of the hypertension in this patient?

High blood pressure tends to affect the heart and the vascular system. In the former, it will initially produce left ventricular hypertrophy with a thrusting cardiac apex beat, a fourth heart sound and a loud aortic component of the second sound from the high arterial pressure. When very severe, hypertension may produce pulsus alternans.

In the vascular system it tends to produce changes in both the large and small vessels. The small vessel structural change, as we have seen, becomes a factor in perpetuating and even increasing the hypertension as time goes by. The degree of clinical small vessel change is best observed by direct examination of the retinal vessels by fundoscopy. In doing so, note not only the degree of arteriolar narrowing, but any irregularity in that narrowing along arteriolar lengths. Also look for any arterio-venous nipping; haemorrhages, exudates and papilloedema only occur in severe cases. Urine protein (Alb: creat. ratio) is an important index of renal damage.

The larger vessel change of clinical importance in hypertension is increased predisposition to atherosclerosis, particularly in the coronary artery (angina and heart attacks), internal carotid and vertebro-basilar arteries (strokes and recurrent transient focal cerebral ischaemic attacks), and the femoro-popliteal vessels (intermittent claudication). Aortic and other arterial aneurysms; aortic dissection.

Since the emphasis in this chapter is on pathophysiology it is reasonable for us to ask how hypertension predisposes to atherosclerosis. The usual answer is that it increases arterial wall stress. But although this may underlie the uniform generalised thickening of the various arterial wall coats, (intima, media adventitia) seen as hypertensive *arteriosclerosis*, it is an unsatisfactory explanation of the increased predisposition to *focal* atherosclerosis. In view of that, I have postulated that the increased sympathetic nervous drive to the vascular system extends beyond the arterioles in essential hypertension, to cause irregular focal increases in tone in large *arteries* as well, with all the implications for increased wall stress, endothelial damage, and focal atherosclerosis that has, as discussed in our dissertation on the pathogenesis of coronary atherosclerosis in the previous chapter.

Two points on the functional consequences of hypertension deserve special emphasis.

First, moderate elevations of blood pressure do not cause much renal impairment; this is usually only seen with severe and prolonged elevation of blood presure, certainly persistently greater than 110 mm Hg diastolic. One corollary of this is that if you do see renal disease associated with hypertension of less than 110 mm Hg diastolic, then the cause and effect relationship is probably that the renal disease has produced hypertension rather than the reverse.

Second, and in the same vein, although it may produce some left ventricular hypertrophy, uncomplicated elevated blood pressure will not usually produce cardiac failure unless the diastolic level is persistently raised to at least 110 mm Hg over a long period of time . So when you see what appears to be heart failure with a BP of less than 110 mm Hg diastolic, think whether it might be primary renal failure with secondary fluid retention and hypertension.

B. HYPOTENSION

In general, blood pressure, particularly in the upright posture, is maintained by an adequate circulating blood volume, cardiac output and peripheral resistance. Reflex drive from baro-receptors of the carotid sinus and aortic arch maintain fine control and limit any tendency to acute blood pressure alteration.

The efferent mechanisms involved in baro-receptor control are vagal (heart rate adjustment), alpha-sympathetic (vascular arteriolar smooth muscle tone) and beta-sympathetic (cardiac output) effects.

Impairment on either the afferent side of the baro-receptors to the brain stem or the efferent side to the heart and blood vessels may produce hypotension. Clearly, such hypotension will be particularly manifest when the patient stands up, because normally in that position blood pressure is controlled not only by arteriolar constriction, but venular constriction which drives blood centrally to improve venous return and prevent peripheral muscular venous pooling. This venoconstriction is thought to be mediated by the alpha 2 subclass of noradrenergic receptors. Impairment of reflex baro-receptor function will usually also lead to an impairment of the usual acceleration in heart rate on standing (vagus) - important in diagnosis. Blood pressure also tends to fall on standing (mostly sympathetic), but normally by no more than 30/15 mm Hg. (See below for standardised tests).

APPROACH TO PATIENTS WITH HYPOTENSION

The patient will usually present with postural dizziness. It is important not only to confirm this by examination (allow at least 30 seconds to elapse before measuring blood pressure after standing) but also to note the pulse rate in the recumbent and upright posture.

Having done a physical examination, paying special attention to circulating blood volume and the circulation in general, we should then be in a position to build up our diagnosis hierarchically as usual. In doing so, the following is a useful order:

1. Is there a normal circulating blood volume?

Check by looking for the usual signs of blood (and interstitial fluid) volume depletion, including reduced tissue turgor; low venous pressure, and slow venous filling (i.e. the rate of external jugular venous filling after compression above the clavicle). Of course, in ECF or blood volume depletion, blood pressure will usually fall on standing, so this per se does not help in differential diagnosis, but where the baro-receptor mechanisms are intact, the pulse rate gives particularly useful information in accelerating markedly with the drop in pressure on adopting the upright posture (contrast with 2 below).

The most common cause of hypovolaemic postural hypotension seen these days arises from the use of powerful diuretics and anti-hypertensives. Be aware of this, particularly the furtive use of diuretics in young females for "weight reduction". If on diuretics, there would usually be associated hyponatraemia, and hypokalaemia with an inappropriately high urinary potassium in the absence of any evidence of renal disease; plasma renin and aldosterone will also rise (from ECF volume depletion). Other causes of hypovolaemia include Addison's disease. There the deficiency of aldosterone determines that little sodium is re-absorbed in exchange for potassium (and/or hydrogen ions) in the distal renal convoluted tubule, so resulting in a low circulating blood volume, a high plasma potassium and a high plasma hydrogen ion concentration (metabolic acidosis). The low circulating blood volume results in (pre-) renal impairment, a correspondingly high plasma creatinine, and an even higher blood urea (urea clearance drops off markedly at low urine flow rates in states of ECF volume depletion).

2. Baroreflex Dysfunction

Postural hypotension in the presence of normal blood volume strongly suggests this, but it is important to determine whether there is any increase in heart rate when the patient stands. Systolic blood pressure normally falls about 10 mm Hg on standing, and diastolic rises 3-5 mm Hg (due to peripheral arteriolar constriction). A blood pressure fall of more than 30/15 mm Hg is abnormal. In patients with a normal heart, pulse rate increases about 10-30 beats per minute on standing, but does not increase at all in classical autonomic neuropathy, especially that maionly affecting the parasympathetic system. The sympathetic aspect of the baroceptor response is best tested by observing BP change to cold pressor/isometric hand-grip/mental arithmetic testing - the first two of

these test both afferent and efferent parts of the sympathetic limb; mental arithmetic tests efferent pathway only.

The intactness or otherwise of the parasympathetic nervous system can also be investigated clinically by looking for the presence or absence of a normal sweating response to elevation of body temperature, checking for normal fall in pulse rate with expiration (sinus arrythmia), and the early pulse rate rise on performing the Valsalva manoeuvre. These and other tests are outlined more precisely at the end of this chapter.

3. Hierarchically Dissecting Efferent vs. Afferent Baro-receptor Sympathetic Dysfunction

Once you have established a defect in the sympathetic nervous system controlling blood pressure you next need to establish the level and type of involvement. To do this, you should look first at the efferent pathway. One of the best methods of doing this is with mental arithmetic (central sympathetic stimulation). Another is the cold-pressor test. Blood pressure should normally rise with these procedures. If it does not, this suggests that the efferent sympathetic pathway is the problem. In that event, an absent blood pressure response to tyramine (an agent which stimulates release of noradrenaline from noradrenergic nerve terminals) will tell you, more precisely, that the (efferent) fault is at the peripheral post-ganglionic sympathetic efferent level.

If the cold pressor and mental arithmetic test of sympathetic efferent baroreflex function are normal then, by exclusion, the fault must lie in the afferent arc of the baroreflex. Confirm this by (gentle) carotid sinus massage which should cause cardiac slowing.

Defects in baro-reflex control of the circulation may either be structural (as in the autonomic neuropathies of diabetes, syphilis, Shy-Drager syndrome etc.) or functional as with the administration of anti-hypertensive adrenergic neurone blockers or in the postural hypotensive "neurocirculatory asthenia" which occurs after spending long periods in bed, especially in the elderly.

Treatment of postural hypotension.

If hypovolaemia, correct in the appropriate way, e.g. acute blood volume loss by transfusion, Addison's disease by glucocorticoid and mineralocorticoid replacement.

If idiopathic autonomic/sympathetic neuropathy, (whether afferent or efferent), several general measures may help. The first is expanding the circulating blood volume (even where it is not depleted) by giving mineralocorticoids such as 9 alpha fludrocortisone plus salt. Sometimes pressure support stockings can be very helpful by preventing venous pooling - one of the most important mechanisms underlying postural hypotension. NSAIDs which inhibit prostaglandin production can also help not only by lessening the degree of peripheral vascular dilatation, but also by causing sodium retention through its renal action. Ergotamine and other non-specific vasoconstrictors may also help. More specifically, where the peripheral (post-ganglionic) part of the efferent sympathetic

vasoconstrictor pathways are intact, tyramine (which stimulates the release of noradrenaline from sympathetic nerve endings) can be helpful, particularly if combined with a monoamine oxidase inhibitor (inhibits the normal breakdown of noradrenaline in the nerve ending, so making more noradrenaline available for release by tyramine). However care must be used with such treatment, as severe hypertension may result.

A more difficult situation arises when there is post-ganglionic sympathetic neuropathy, because then no amount of tyramine or monoamine oxidase inhibitor will work (the peripheral sympathetic neurone having degenerated). However, it has been found that clonidine can sometimes be helpful in this situation. This drug is an alpha 2 receptor agonist and it is thought that the nor-adrenergic constrictor receptors in the venules are largely of this alpha 2 sub-type. Of course, there is also a central nor-adrenergic inhibitory pathway normally important in blood pressure maintenance, so that the normal response to usual doses of clonidine is a reduction of blood pressure. You might therefore ask why this drug would not exacerbate hypotension despite its effect on peripheral venules. The answer is that, with post-ganglionic efferent sympathetic neuropathy, neuronal degeneration leads, as in skeletal muscle, to denervation hypersensitivity, so that the alpha 2 receptors in the venules become much more sensitive to circulating clonidine than usual, and than in receptors elsewhere.

When patients not only have problems of post-ganglionic sympathetic control of arteriolar and venous constrictor tone, but also a post-ganglionic sympathetic defect in regulation of heart rate, beta-agonists may also help, along much the same principle as outlined above for clonidine. Thus in post-ganglionic neuropathy involving sympathetic cardiac fibres there is again a denervation hypersensitivity of the cardiac beta receptors, and the appropriate small dose of a beta-agonist (or beta blocker with a high level of ISA such as pindolol) can, on balance, stimulate rather than block these post-synaptic cardio-accelerator beta-adrenergic cardiac receptors.

Giving sympathomimetic drugs can also help. Midodrine is one such alpha1-agonist, and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone.

STANDARDISED TESTS OF AUTONOMIC FUNCTION

Understanding the different types of autonomic neuropathic (parasympathetic versus sympathetic, and sympathetic efferent versus afferent) is essential to rational treatment of the problem. The following are some standardised tests. Unfortunately, none is precise, since there is much variation with age and/or basal blood pressure with many of these test.

A. Tests of vagal/parasympathetic function.

1. Heart rate response to standing. This is a test of *parasympathetic baroreflex efferent function*.The standard test involves running a continuous ECG and calculating the R-R interval (heart period) as an accurate beat to beat reflection of the heart rate. ECG applied with the patient supine for 5 minutes, and continued as the patient stands up. The standard response, called the 30:15 ratio, is calculated by dividing the heart period at the 30th beat by the heart period of the 15th beat after standing. Normal varies from approximately 1.1-1.6, decreasing with age, as with many other tests. Borderline is 1.0-1.1. Abnormal if less than 1.0.

2. Heart rate variation with respiration. Another test of *vagal efferent function*. Patient in a semi-recumbent position breathes deeply at a rate of 6 breaths per minute for 1 minute while ECG heart period (R-R interval) is recorded. The degree of sinus arrhythmia (in beats per minute) is calculated by subtracting the slowest heart rate from the highest. Normal values are 15 beats per minute or more, though decreases with age. Borderline 11-14 beats per minute; abnormal less than 10 beats per minute.

3. Valsalva ratio. Again, largely a test of *vagal efferent function*. Patient semi-recumbent, with rubber clip over nose, blows into mouthpiece (with a small side leak) connected to a mercury manometer, and is asked to maintain a column of mercury at 40 mm Hg for 15 seconds. The Valsalva ratio is calculated by dividing the longest heart period (R-R interval) recorded after the manouevre by the shortest heart period. Take the highest ratio from 3 successive attempts, each separated by 2 minutes. Normal range 1.2-3.0, but tends to decrease with age. Regarded as abnormal if less than 1.1.

B. Tests of Sympathetic function.

1. Blood pressure response to standing. Whereas heart rate response to standing largely tests vagal function, blood pressure response is most influenced by the *efferent sympathetic* branch of the baroreflex arc, though clearly some of the blood pressure response is related to increased heart rate/ stroke volume. Blood pressure tends to fall on standing, but normally by a max. of 30/15 mm Hg.

2. Change in blood pressure with tilting. As above, this tests *both afferent and efferent baroreflex*autonomic control of blood pressure, the efferent aspect depending mostly on *sympathetics*. Standard test is to lie the patient supine on tilt table for 10 minutes and then tilt to 80 deg. for a period of up to 10 minutes provided blood pressure does not fall precipitately. Standard is to take systolic and diastolic BP change at 3 minutes after tilt. Normal range of systolic BP change is from +10 to -20 mm Hg, and diastolic +15 to -10 mm Hg. Results not much affected by age. As with response to standing, BP fall of more than 30/15 mm Hg is abnormal.

3. Cold pressor test. This is again a *test of autonomic function*, but with the *afferent limb being pain sensation from cold via somatic nerves*, rather than baroreceptor autonomic afferents. The heart rate

response tests the vagal component. *Blood pressure rise tests sympathetic function* - normally more than 10 mm Hg following hand emersion in ice water at 4 deg.C for 2 minutes.

4. Isometric hand grip. Increases heart rate and blood pressure via *decreases in parasympathetic and increases in sympathetic nerve activity*. Standard test is to have semi-recumbent patient maintain a pressure of 30% of maximal hand grip (squeeze slightly inflated mercury sphygmo. cuff) for a period of up to 5 minutes. *Diastolic blood pressure response* is largely related to *sympathetic efferents*, and the normal range of response is an increase of at least 15 mm Hg diastolic. Values of less than 10 mm diastolic BP rise are abnormal.

5. Sweating - usually impaired in autonomic disorders affecting the sympathetic efferent pathways, e.g. in Horner's syndrome.

Tests of efferent sympathetic nerve function.

1. Mental arithmetic. Obtain control BP values of blood pressure over 5 minutes. Then ask the patient to do mental arithmetic under stress. Standard is to ask the patient to take a 2 figure number (say 17) serially from a 4 digit number (e.g. 1013). A metronome is set up at 1 beat per 2 seconds, and the patient is then strongly urged to concentrate all his/her efforts on obtaining the correct answers at the right rate, and reproached for any errors! The test continues for 2 minutes. Mean response varies with age but normally about rise of BP 20/5 mm Hg. Abnormal if BP does not rise. This test is helpful, particularly in combination with those above, because it depends on efferent sympathetic function, and therefore, in combination with the others, tests can help distinguish between afferent and efferent sympathetic nerve problems.

MCQs: MECHANISMS IN HYPERTENSION & HYPOTENSION

(A) Mechanisms in Disease - Hypertension.

1. A 26 year old patient presents with severe untreated unilateral renal artery stenosis, said to be producing classical haemodynamic effects. On examination you find a blood pressure of 185/110 mm Hg. and a normal JVP. Which of the following would be typical:

1. Characteristically, questioning would reveal a strong family history of high blood pressure.

2. Postural hypotension is a characteristic haemodynamic sign.

3. Plasma creatinine would typically be elevated more than twice normal.

4. Glomerular filtration rate from the affected kidney would be increased.

5. A long, loud bruit in the hypogastric (supra-pubic) area.

6. A delay in the transmitted impulse from the femoral compared with the radial pulse.

7. Right ventricular hypertrophy.

8. Characteristically, the heart will be dilated.

9. If there are added heart sounds, a fourth heart sound would be more typical than a third.

10. In this situation, impaired function of the stenosed kidney is to be expected.

11. In the early phases of this condition, you would expect to find increased renin in the renal vein draining the affected kidney

.

(**2. Mechanisms in Disease - Hypotension.**

An elderly patient is admitted with a diagnosis of post-ganglionic efferent autonomic neuropathy involving both parasympathetic and sympathetic pathways. The following would be typical:

1. A fall in systolic and a rise in diastolic blood pressure on assumption of the upright posture.

2. A heart rate increase by 10 beats per minute on assuming the upright posture.

3. Reduced tissue turgor.

4. Jugular venous pressure will be low, and the external jugular vein will fill only very slowly on compression above the clavicle.

5. This patient's heart rate and blood pressure response to mental arithmetic and the cold pressor test will be normal.

6. Nonspecific measures to improve the situation may include the administration of extra salt together with a mineralocorticoid.

7. In this situation, a beta blocker with intrinsic sympathomimetic activity (e.g. pindolol) is of recognised benefit.

8. Tyramine will characteristically be useful in preventing postural hypotension in this patient.

9. Clonidine (an alpha 2 nor-adrenergic receptor agonist) may be helpful in reducing venous pooling without aggravating hypotension in such patients.

10. Diabetes is a recognised cause of such a condition.

Answers to MCQs: See end of chapter

Answers at end of Chapter

PROBLEM SOLVING CASE

A 32 year old (1) female patient (2) presents after high blood pressure has been detected on routine examination (3). Direct questioning reveals a six month history (4) of increasing weakness, particularly on climbing stairs (5) and a 2-month history of polyuria, nocturia and thirst (6). There is no family history of hypertension (7) and she has noticed no other specific symptoms (8). No medications.

Examination: a relatively fit woman of normal body habitus (9). Hands and face are normal (10). JVP normal (11), BP 190/115 mm Hg (12). Heart: no enlargement (13), but there is a soft fourth apical heart sound (14), and an increased thrust at the cardiac apex (15). No other changes in the cardiovascular system, in particular no epigastric bruits (16), no radio-femoral delay (17) and no detectable oedema (18). Examination of the nervous system: mild proximal muscle weakness, particularly of the lower limbs (19). No evidence of muscle wasting (20). Normal body fat (21). Temperature 37 deg. C (22).

Investigations reveal an elevated plasma sodium (23) and a reduced plasma potassium (24). Urea and creatinine are both at the lower limit of normal (25) and there is an elevated plasma bicarbonate (26). 24 hr Urine: low sodium, normal potassium excretion (27). No glycosuria (28).

Solving the Problem. Now draw up your usual four columns (widest for "How?" column), and work through to a solution of this problem linking inferences leading to like conclusions. Then make a final overall diagnosis and **answer the MCQs below.**

Graphic Solution: Available in next section as a jpeg. When viewing, centre the picture so that you can see all 4 columns at the same time. The solution is available in two parts, in the next sections - an overall solution, and a more detailed view.

Problem Solving MCQs.

Regarding the Problem-Solving question:

WHICH OF THE FOLLOWING IS/ARE LIKELY TO BE CORRECT?

1. It is unusual for patients at this age and level of blood pressure to be asymptomatic.

2. The polyuria and thirst are probably related to secondary diabetes mellitus.

3. The difficulty in climbing stairs is probably related to weakness in the proximal muscles of the lower limbs.

4. The elevated plasma sodium is probably the most important factor underlying the proximal myopathy.

5. This is the classical picture of furtive diuretic abuse.

6. Characteristically, we would expect the extracellular fluid volume to be increased, even though there is no detectable clinical oedema.

7. Characteristically, this patient would have a ratio of sodium to potassium in the urine of less than 1.0.

8. The high plasma bicarbonate probably reflects a metabolic acidosis.

9. It would be typical to find an elevated plasma renin in this patient.

10. The finding of an elevated plasma aldosterone and suppressed plasma renin would be compatible with the diagnosis of primary hyperaldosteronism.

11. She has an increased risk of developing heart attack and stroke in later years if the hypertension remains untreated.

12. Any risk of arterial atheroma will be increased if the patient continues to smoke her current 20 cigarettes per day.

PROBLEM SOLUTION-1

Hypertension Problem

Where?	What?	How?	Why?
[Cardiac involve-ment (but probably secondary, therefore leave in "HOW?" column.)]	4. 6 / 12 = chronic	3. Hypertension, detected routine exam. 5. Weakness on stairs (= prob. proximal myopathy, = ? metabolic). 6. Polyuria, nocturia, thirst, (i) ? renal impairment (ii) ? metabolic (e.g. diabetes mellitus, diabetes insipidus, electrolyte disturbance, e.g. Ca^{++} excess, K^{+} depletion. (iii) ? 1° increase in water intake.	1. Aet. 32 - rel. young. 2. Female 7. No F. H. of hypertension Therefore ? not essential H/T. i. e. prob. **2° H/T.**
	8,9,20,21. No evid. of weight loss or generalised symptoms / signs. Therefore if tumour probably not malignant.	9,10. Hands & face normal. = not obviously Cushingoid 11. JVP.normal, plus 13. No cardiac dilatation, plus 18. No oedema = no gross circ. vol. overload , e.g. from renal failure or R.heart failure 12. B. P up - mod. severe hypertension . 14. Fourth heart sound, plus 15. Apical cardiac thrust = L.ventric. hypertrophy - prob 2° to H/T. 16. No epig bruit = ? no renal artery stenosis. 17. No radio-femoral delay = no clinical coarctation.	
	20. No muscle wasting. Therefore prob. not a degenerative process. 22. Afebrile; i.e. no evidence of inflammation.	19. Proximal myopathy confirmed espec. lower limbs. ? metabolic. 21. Normal body fat - i.e. not obviously Cushingoid. 23. Elevated plasma Na^{+} = ? sodium retention (or ? H_2O loss). 24. Low plasma $K^{\pm}$, plus 23., = ? excess aldosterone. [Polyuria and prox. myopathy prob. also both 2° to low $K^{\pm}$ - see 5, 6.] 25. Low normal urea, creatinine = (i) normal renal function [This eliminates 6 (i)]. (ii) plasma creat. actually low, therefore ? some increase in plasma vol. causing incr. G.F.R.	
Adrenal glands - zona glom.	27. *Functional over-activity* of adrenals; therefore more likely to be a **hyperplastic or benign neoplastic** than a degenerative process.	26. Incr. pl. bicarb. = ? metab. alkalosis (? 2° to low plasma $K^{\pm}$) 27. Urine electrolytes - low Na^{+} - high K^{+} rel. to plasma K^{+} compatible with **aldosterone excess.** ?1° or 2° 28. No diabetes mellitus. [see 6.(ii)].	**?1°adrenal process or 2° process.** e.g. 2° to renin/ angiotensin stimulation.

PROBLEM: FINAL DIAGNOSIS

Solution to Hypertension Problem

Anatomic Diagnosis
Adrenal Cortex - Zona glomerulosa

Pathological Diagnosis
Chronic (? benign) tumour

Functional Diagnosis
Excessive (? autonomous) aldosterone over-production with
(i). secondary sodium retention (-> hypertension and secondary left ventricular hypertrophy), and
(ii). potassium depletion (->secondary proximal myopathy and polyuria)

Aetiological Diagnosis
Not evident
(i). ?primary, or
(ii). ? secondary hyperaldosteronism, e.g. to increased renin/angio. from , say, a renin-secreting renal J.G.A. tumour.
Measurement of plasma renin would differentiate

MCQS: ANSWERS

Answers to MCQs:

A. Mechanisms in Disease.

1. Hypertension: 9, 10, 11 correct. All others false.

2. Hypotension: 6, 7, 8, 9, 10 correct. All others false.

B. Problem Solving MCQs:

3, 7, 10, 11, 12 correct. All others false.