Clinical review

Science, medicine, and the future

Hypertension

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Summary

The abundance of drugs now available for treating hypertension, and evidence that small reductions in blood pressure reverse the associated risk of stroke have shifted clinical concerns away from hypertension. However, we do not understand the cause of hypertension in 95% of patients, fail to achieve a normal blood pressure in 50% of patients, and are unable fully to reverse the cardiac and vascular changes that predate the diagnosis and treatment of hypertension. Consequently, hypertension remains the commonest cause of strokes in Britain and of renal failure in the United States. Essential hypertension is a polygenic disease whose understanding can now be advanced through molecular genetic analyses. Several different syndromes are likely to be recognised; most will be due to interactions between genetic and environmental factors, but there are also likely to be further monogenic syndromes in families with multiple affected members. Recognition of these syndromes will permit accurate genetic prediction of prognosis and optimal treatment and perhaps lead to new and more powerful classes of antihypertensive treatment.

Introduction

Hypertension is the commonest indication in the Western world for chronic, lifelong treatment because of the incontrovertible evidence that such treatment substantially reduces the risk of strokes. About 20% of adults aged over 40 have a blood pressure >140/90

mm Hg, with a risk of stroke at least 100% higher than subjects of the same age with a blood pressure of 125/75 mm Hg.¹ Only half the eligible patients, however, receive treatment, and in only half of these does treatment achieve a blood pressure <140/90 mm Hg.² Consequently, both neurologists (those who treat strokes) and nephrologists still owe a large part of their practice to hypertension. A specific cause can be found in only one in 20 patients with hypertension and, although there is clearly a familial component in hypertension, a genetic basis is definable in less than one in every 100 patients. Interestingly, it is among some of these rare causes of hypertension that single drugs are most effective, often lowering blood pressure by 30-40% compared with the average of 10% for drugs in essential hypertension. Examples are the α blocker phenoxybenzamine in phaeochromocytoma and spironolactone in Conn's syndrome or the genetic syndrome of apparent mineralocorticoid excess (box). All the genetic causes of hypertension identified so far are due to increased sodium retention, prompting speculation that in high risk families salt restriction during growth could forestall development of complications or even hypertension itself.³ Despite the therapeutic successes to date, there is much to achieve—and good prospects of success—if hypertension is to be understood and its devastating sequelae eradicated.

Hypertension can be loosely likened to anaemia before many of the causes had been elucidated. Thus the continuous distribution of haemoglobin concentrations in any random sample of the population would not now deter us from looking for a specific explanation in patients at either extreme of the distribution. This analogy also shows why identification of different hypertensive syndromes can be expected to permit better choice of treatment and prognostication. The diagnosis of B-12 deficiency in a patient with even mild macrocytic anaemia would prompt specific investigations and treatment with B-12 because of the risk of irreversible spinal tract damage, whereas a similar degree of microcytic anaemia in a menstruating woman would be treated with iron, if at all. In hypertension we can only speculate about the importance of the high incidence of strokes in the salt retaining syndromes and greater efficacy of diuretics than β blockers in preventing strokes,^{3,4} but such observations show how improved understanding of

Monogenic causes of hypertension

Syndrome	Genetic defect	Treatment
Glucocorticoid remediable aldosteronism	Chimaera between aldosterone synthase and 11 β hydroxylase, exposing aldosterone synthesis to stimulation by adrenocorticotrophic hormone	Dexamethasone
Liddle's	Activating mutations in epithelial sodium channel	Amiloride
Apparent mineralocorticoid excess	Inactivating mutations in 11 β hydroxysteroid dehydrogenase, exposing mineralocorticoid receptor to cortisol	Spironolactone

Fig 1 Frequency plots of the proportion of siblings receiving antihypertensive treatment. For each index case with at least two siblings the ratio of affected siblings (those receiving antihypertensive treatment) to total number of siblings (not including the index case) was calculated and the frequency of each ratio shown

pathogenesis will eventually permit treatment to be tailored to individual patient's requirements.

Genetic basis of hypertension

The best hope for such understanding comes from the advances in molecular genetics, even if much of hypertension has a non-genetic basis. The popular strategy in most of the common complex disorders like hypertension, diabetes, and asthma is to use the genome wide maps of polymorphic markers to look systematically for the molecules responsible without any prior hypothesis. The British genetics of hypertension study (BRIGHT) is collecting 1500 sibling pairs with hypertension to look for places in the genome where siblings share both alleles of a polymorphic marker more often than expected by chance alone. While we were recruiting 500 affected sibling pairs in East Anglia we found surprisingly that hypertensive patients with siblings split about 2:1 into those with no other hypertensive siblings and those where most of the other siblings were also hypertensive (fig 1).⁵ This discontinuous distribution is evidence that there are different types of essential hypertension and that the families with multiple affected siblings are likely to have a single gene conferring most of the risk of hypertension.

What sort of molecules might be important in hypertension? Two of the most powerful vasoactive mediators, nitric oxide and endothelin, have been discovered recently and both occur within endothelial cells (fig 2). Nitric oxide is the principal physiological vasodilator while endothelin is the most potent vasoconstrictor. However neither seems important in explaining essential hypertension. Even where there is evidence of reduced nitric oxide production in hypertension it is difficult to distinguish chicken from egg, since hypertension itself seems to reduce nitric oxide production.⁶ Knocking out the gene for endothelial nitric oxide synthase in mice causes hypertension, but studies on the large gene in humans have not yet revealed any genetic defect in hypertensive patients.⁷

We have scanned all but five of the 26 exons of the nitric oxide synthase gene and identified mutations in both the promoter and coding regions.⁸ One of these, a substitution of aspartate for glutamate, was found to be a major risk factor for coronary artery disease but had no effect on blood pressure.

Plasma endothelin concentrations are not raised in essential hypertension, and the knockout experiments in mice also give no support for an important role for the endothelin-1 isoform.^{9 10} We have found silent (non-coding) polymorphisms in each of the genes for endothelin-1, endothelin-2, and the principal endothelin receptor; some of these polymorphisms predict severity of hypertension, and the weak interactions among them may come to be typical of the complexity of polygenic diseases.^{11 12} Weak and variable associations have been reported between silent polymorphisms in several other molecules and hypertension, such as angiotensinogen and adducin.¹³⁻¹⁵ There is, however, real difficulty in determining which of these weak associations are just chance consequences of testing a large number of hypotheses, and it may be best to remain sceptical about incriminating any gene in one of the complex diseases until a clearly functional mutant is shown.¹⁶

Both nitric oxide and endothelin have been obvious candidate molecules in hypertension because of their pharmacological actions. The experience in most genetic diseases, however, has been that they are not due to excess or deficiency of molecules with previously well understood roles, and in the future candidates will come mainly from the genome wide screens. I speculate that few if any of these will be for circulating or locally released mediators. The number of these factors is limited, and their early discovery an accident—or perhaps inevitable consequence—of the order of discovery in physiology and medicine. A larger number of candidate molecules exists among the

Fig 2 Endothelial dilating and contracting factors. Nitric oxide (NO) is a short acting gas produced by endothelial nitric oxide synthase from endogenous arginine. It diffuses into the underlying vascular smooth muscle cells where it stimulates guanylate cyclase to produce cyclic GMP. Endothelin is a long acting and powerful vasoconstrictor that acts on a cell surface receptor causing increased calcium release within the muscle cell. (Adapted from Swales JD, *Textbook of Hypertension*, Blackwell, 1994)

receptors and ion channels in the cell membrane of the cardiac and vascular smooth muscle cells and renal tubular cells, which are the probable origin of hypertension. But the largest number of candidate molecules are contained within the cells and are responsible for the signalling from the membrane receptors and channels to the nucleus and to contractile proteins.

Relation between treatment and cause of hypertension

In patients in whom a specific mutation in one gene is found to confer most of the risk of hypertension, this gene should be the target for a specific and effective treatment. However, the chances of such a drug being developed will probably depend commercially on its accidental development for the commoner, multifactorial syndromes. For these syndromes we are likely to continue to need combinations of drugs to achieve good control of blood pressure unless one of the factors has an essential role in the early development of hypertension and genetic analysis permits earlier prediction of hypertension than is currently possible by measuring blood pressure. However, we will find it harder to identify with certainty the causes of hypertension in the patients where the contribution from any single gene (or other factor) is only partial. By definition in a polygenic condition, many normal subjects will have the same genetic abnormality but not develop the disease because they have only one abnormality. Yet, paradoxically, we can be more optimistic about the practical benefits of genetic studies in common, polygenic hypertension. This is partly because of the greater commercial stimulus from a larger market; but in addition the predictive value of silent genetic polymorphisms for differences in response to particular drugs or in prognosis can be tested empirically without finding functionally important variants in each gene. Multiple genetic polymorphisms can be simultaneously detected, and there will soon be commercial chips containing tens to hundreds of thousands of specific DNA probes.¹⁷ At present, as we found in a recent study in which we rotated newly diagnosed hypertensive patients through each of the main drug classes, the best drug for most patients can be found only by trial and error.⁵ In everyday practice most patients never reach their best drug, and hence the rule of halves described at the start.¹⁸ In my crystal ball the DNA chip for hypertension will be our equivalent of the haematologists' measurement of haematin concentrations in anaemia.

I am also optimistic that genetic testing will help us to be more selective about which patients need earlier treatment or treatment at lower cut off levels of blood pressure because of predictions of prognosis. I referred earlier to the higher risk of stroke in salt dependent hypertension; recently, genetic studies on strains of rat bred for salt sensitivity and risk of stroke have confirmed that genes conferring risk of stroke are separate from those responsible for hypertension and shown that diuretics reduce risk of stroke independently of a fall in blood pressure.^{19 20} The development of left ventricular hypertrophy, the worst prognostic marker in hypertension, and of renal disease, will probably also prove to be genetically predictable and

therefore potentially preventable. Much of the target organ damage in hypertension is irreversible, and hypertension itself is only rarely reversed by prolonged treatment, perhaps because of clinically unsuspected collagen deposition in the affected tissues.^{21 22} We may therefore come to view some types of hypertension itself as an end stage disease, once we are able to predict and prevent their development. The counter argument from the meta-analyses of outcome trials in hypertension is that blood pressure reduction reverses the 40% increased risk of stroke for every 6 mm Hg rise in blood pressure,²³ but in the patients at most risk of stroke the fall in blood pressure required to restore normal blood pressure may be nearer 60 mm Hg, and this is rarely possible with current therapies.

Genetic versus non-genetic factors in hypertension

I have concentrated on genetic mechanisms in hypertension, although I am aware that these are only part of the story. Some investigators, for instance, regard the kidney as the key to hypertension, and it could still turn out that urinary infection in infancy is more important than, say, genetic tubular abnormalities.¹⁵ But genetics is where new technology provides new opportunities that are beginning to break the impasse reached by classical physiology and biochemistry. Furthermore, changes in DNA sequence are black and white changes, readily visualised with the appropriate equipment.

There are two types of structural changes in blood vessels which, even if secondary to the hypertension, may also be important in determining its severity. The first is remodelling of the arteries.²⁴ This means an increase in the ratio of the media to lumen without any increase in the number or size of the muscle cells that comprise most of the media (fig 3). It is clear that this phenomenon occurs in some small arteries (such as those seen on funduscopy) and that it is responsible for the exaggerated vasoconstrictor response to any agent that stimulates smooth muscle contraction. There may still be genetic variation in the degree of remodelling, and both this question and whether reversal of remodelling would reverse the hypertension are still unanswered. The second phenomenon is rarefaction (loss, or non-production) of blood vessels. This is one way in which antenatal influences might affect blood pressure later in life,^{25 26} However, it is difficult to be certain whether rarefaction truly precedes rather than results from hypertension. It is also difficult to disentangle the social and genetic factors that regulate the early life environment and to show that fetal size is more a cause of later blood pressure rather than a consequence of the mother's blood pressure.^{5 27}

Conclusions and predictions

Despite the abundance of antihypertensive drugs available, the choice remains empirical and drug treatment fails to achieve a normal blood pressure in many patients. Genetic analyses promise identification of specific hypertensive syndromes, each with a different prognosis and optimal treatment. Blood pressure tracks from birth, but by the time hypertension is diagnosed clinically it is probably too late to prevent

Fig 3 Remodelling of resistance vessels. When a normal arteriole contracts, circular muscle fibres ride over each other, causing a reduction in lumen size and increase in wall thickness. In chronic contraction due to hypertension there is likely to be deposition of collagen fibres, which impair reversibility of remodelling

structural changes in the heart and blood vessels that are responsible for many of the complications of hypertension and for the irreversibility of hypertension itself. Genetic prediction of risk, either of hypertension or its complications, might enable effective intervention in selected patients before these ensue.

- 1 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J. Blood pressure, stroke, and coronary heart disease: part I, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335: 765-74.
- 2 Mancia G, Sega R, Milesi C, Cesana G, Zanchetti A. Blood-pressure control in the hypertensive population. *Lancet* 1997;349:454-7.
- 3 Lifton RP. Molecular genetics of human blood pressure variation. *Science* 1996;272:676-80.
- 4 Brown MJ, Brown J. Does angiotensin-II protect against strokes? *Lancet* 1986;ii:427-9.
- 5 Brown MJ. The causes of essential hypertension. *Br J Clin Pharmacol* 1996; 42:21-7.

- 6 Calver A, Collier J, Moncada S, Vallance P. Effect of local intra-arterial N^G -monomethyl-L-arginine in patients with hypertension: the nitric oxide dilator mechanism appears abnormal. *J Hypertens* 1992;10:1025-31.
- 7 Huang PL, Huang Z, Mashimo H, Bloch KD, Moskowitz MA, Bevan JA, et al. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature* 1995;377:239-42.
- 8 Hingorani AD, Liang CF, Fatibene J, Parsons A, Hopper R, Brown MJ, et al. A common variant of the endothelial nitric oxide synthase gene is a major risk factor in East Anglia for coronary atherosclerosis. *Q J Med* (in press).
- 9 Davenport AP, Ashby MJ, Easton P, Ella S, Bedford J, Brown MJ, et al. A sensitive radioimmunoassay measuring endothelin-like immunoreactivity in human plasma. Comparison of level in patients with essential hypertension and normotensive control subjects. *Clin Sci* 1990;78:261-4.
- 10 Kurihara Y, Kurihara H, Suzuki H, Kodama T, Maemura K, Nagai R, et al. Elevated blood pressure and craniofacial abnormalities in mice deficient in endothelin-1. *Nature* 1994;368:703-10.
- 11 Stevens PA, Brown MJ. Genetic variability of the ET-1 and the ETA receptor genes in essential hypertension. *J Cardiovasc Pharmacol* 1995;26 (suppl 3): S9-12.
- 12 Sharma P, Hingorani AD, Jia H, Stevens P, Hopper R, Brown MJ. Quantitative association between a newly identified polymorphism in the endothelin-2 gene and essential hypertension. *Clin Sci* 1996;90:2p.
- 13 Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A. Molecular basis of human hypertension: role of angiotensinogen. *Cell* 1992;71:169-80.
- 14 Hingorani AD, Sharma P, Jia H, Hopper R, Brown MJ. Blood pressure and the M235T polymorphism of the angiotensinogen gene. *Hypertension* 1996; 28:907-11.
- 15 Cusi D, Bianchi G, Tripodi G, Casari G, Salardi S, Barber BR, et al. Renal mechanisms of genetic hypertension: from the molecular level to the intact organism. *Kidney Int* 1994;91:3999-4003.
- 16 Risch N, Merikangas K. The future of genetic studies of complex human diseases. *Science* 1996; 273:1516-8.
- 17 Pennisi E. From genes to genome biology. *Science* 1996;272:1736-8.
- 18 Smith WC, Lee AJ, Crombie IK, Tunstall Pedoe H. Control of blood pressure in Scotland: the rule of halves. *BMJ* 1990;300:981-3.
- 19 Rubattu S, Volpe M, Kreutz R, Ganten U, Ganten D, Lindpaintner K. Chromosomal mapping of quantitative trait loci contributing to stroke in a rat model of complex human disease. *Nature Genet* 1996;13:429-34.
- 20 Levy BI, Poitevin P, Duriez M, Guez DC, Schiavi PD, Safar ME. Sodium, survival, and the mechanical properties of the carotid artery in stroke-prone hypertensive rats. *J Hypertens* 1997;15:251-8.
- 21 Dahlöf B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. *Am J Hypertens* 1992;5:95-110.
- 22 MRC Working Party. Course of blood pressure in mild hypertensives after withdrawal of long term antihypertensive treatment. *BMJ* 1986;293:988-92.
- 23 Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994;50:272-98.
- 24 Mulvany MJ. Resistance vessel structure and the pathogenesis of hypertension. *J Hypertens* 1993;11(suppl 5): S7-12.
- 25 Godfrey KM, Barker DJP, Peace J, Cloke J, Osmond C. Relation of fingerprints and shape of palm to fetal growth and adult blood pressure. *BMJ* 1993;307:405-8.
- 26 Sullivan JM, Prewitt RL, Josephs JA. Attenuation of the microcirculation in young patients with high-output borderline hypertension. *Hypertension* 1983;5: 844-51.
- 27 Churchill D, Perry JJ, Beevers DG. Ambulatory blood pressure in pregnancy and fetal growth. *Lancet* 1997;349:7-10.

One hundred years ago

Cremation at the hairdresser's

The unfortunate occurrence of the death of a lady by burning resulting from the ignition of petroleum hairwash at a fashionable hairdresser's affords abundant material for reflection. The custom of using petroleum preparations for the hair originated some years ago, but the majority of the best West End hairdressers state emphatically that they have never employed them, and that they have persistently declined to do so, even at the request of their customers. How the particular preparation which was being used on this occasion ignited is an open question, but it must be remembered that the more volatile kinds of petroleum give off inflammable vapours, even at ordinary temperatures, and that these vapours when mixed with air form explosive mixtures. That the ignition could have resulted from the heat of the sun on the skylight we can hardly believe, whilst

we reject unhesitatingly the theory that the mere fact of tying up the hair could have generated such an amount of "human electricity" as to produce the result. It is well known that this is not an isolated case, for not long ago a lady who had been using a petroleum hairwash set herself on fire and was burnt to death from striking a match to light a cigarette. It is probable that some restriction will be placed on the sale and use of these explosive preparations. We recently published a report on the composition of face powders and other cosmetics, which showed conclusively that too little care is taken in the concoction of these compounds. It is abundantly clear that before long steps will have been taken to check the vagaries of irresponsible hairdressers. (*BMJ* 1897;ii:296.)