patients developed diarrhoea. The value of treating hypertension in people over the age of 80 years is currently being addressed in the SYST-EUR and HYVET studies.

*Dr S. M. Cobbe, University of Glasgow*, spoke on *The impact of treating cardiac arrest in the community*. Half of all cardiac deaths are sudden, unexpected and occur outside hospital. An integrated system of care is required to optimise survival and the components of this are early access to cardiopulmonary resuscitation, defibrillation and advanced care. Heartstart Scotland, a non-randomised controlled study, showed an improvement in survival from 2–3% to 8% with an out-of-hospital defibrillation service. Only 2% of the survivors had neurological sequelae requiring institutionalisation whilst 9% had moderate impairment. Sixteen per cent of initial survivors died from a further cardiac arrest during a four year follow-up. Overall the service reduced community mortality from CHD by 1%. In terms of the lives saved and of useful survival in relation to the number of patients treated it compares favourably with other forms of treatment available for cardiovascular disease.

J. W. BALLANTYNE PRIZE LECTURE

*Dr W. W. Holland, United Medical and Dental Schools of Guy's and St Thomas's Hospitals*, delivered the J. W. Ballantyne Prize lecture and spoke on *Policies on prevention: the hazards of politics*. See page 189.

S. M. SHEPHERD
J. W. T. CHALMERS

*Proc. R. Coll. Physicians Edinb.* 1995; **25**: 227–234

# MOLECULAR BIOLOGY OF HYPERTENSION*

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## INTRODUCTION

Hypertension is a common condition. If defined on the basis of diastolic blood presssure >90 mmHg, >95 mmHg or >100 mmHg the prevalence figures are 25·4%, 14·6% and 8·4% respectively;[1] it is a major risk factor for the development of coronary heart disease and stroke and a reduction in blood pressure is associated with a reduction in risk.

Adoption studies and studies on twins with hypertension indicate that 30–60% of the variability in blood pressure in the population is genetically determined.[2] Identifying the genes that contribute to the pathogenesis of hypertension has been the subject of several recent studies. There was an extensive and now infamous debate in the 1960s between Sir George Pickering and Sir Robert Platt. Pickering argued that because of the unimodal distribution of blood pressure throughout the population, hypertension was probably a polygenic disease, i.e. involving the complex interaction of many different genes. If a single genetic defect was the cause of a significant number of patients with hypertension then a bimodal distribution of blood pressure would have been expected with a more easily recognised Mendelian form of inheritance. Platt on the other hand argued that hypertension could be monogenic, i.e. resulting from a singe gene mutation.

The aim of this review is to highlight how molecular biology has advanced our knowledge regarding the pathogenesis of hypertension. As we shall see the theories of Pickering and Platt are not mutually exclusive, and indeed both have turned out to be correct.

## IDENTIFYING GENES THAT CAUSE HYPERTENSION

Studies have been carried out both in man and in animal models of hypertension. It has been argued that studies of animal models of hypertension (principally hypertensive rat strains) provide more clear genetic evidence than human studies. This may be the case, but studies that suggested linkage of hypertension with a particular gene in a particular hypertensive rat strain (for example the renin gene in the spontaneously hypertensive rat) have not been substantiated in alternative hypertensive rat strains nor in human hypertension.[3] Thus the use of such models to identify genes which may be of relevance to hypertension in man may be misleading.

The methodological principles for the identification of genes in human hypertension can broadly be categorised as follows:

### *A. Population to be studied*

Mutations in genes that cause hypertension can be sought either by association or linkage studies. The former seek to identify a difference in genomic structure between hypertensive populations and controls. However there are several draw-

*Based upon a lecture delivered at the Symposium on *Molecular Perspectives in Medicine: The Way Forward* held in the College on 14 October 1994.

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backs with such an approach[4] and to date the most useful information has come from co-segregation linkage analysis or shared allele approach within affected sibling-pairs or multiplex families with hypertension. It is important to note, however, that hypertensive patients have been selected for such studies on the basis either of their blood pressure recorded in the clinic, or their use of antihypertensive therapy. It is established that blood pressures recorded in the clinic may be misleading due to the so-called 'white-coat' effect, and that many patients taking antihypertensive therapy are not hypertensive. Almost certainly then, these population studies are flawed because the hypertensive population is diluted with some 'normal' or non-hypertensive patients.

*B. Principles of linkage analysis*

*Polymorphism* can be defined as a difference in the structure/sequence of a gene between individuals. For any given gene of interest one can identify whether a specific polymorphism co-segregates with a particular phenotype.

*Co-segregation analysis.* If the polymorphic marker of interest has nothing to do with the gene responsible for the phenotype (for example it is located on another chromosome), then this marker will be only randomly associated with the phenotype. Such a marker is said to be in 'linkage equilibrium' with the gene of interest. If however, the marker is closely associated with the gene causing hypertension, it will be found disproportionately more commonly with the phenotype and is said then to be in 'linkage disequilibrium' with the disease. In such a situation 'linkage' has been established. A statistical score can be applied to this phenomenon, referred to as the logarithm of odds score (Lod score). A score of $>3$ is significant, meaning that the likelihood of this linkage compared to that occurring by chance was over 1000:1.

*Shared alleles.* The premise of this approach is that affected hypertensives within a given family will prove to have inherited a locus that contributes to the trait more than can be expected by chance.

*C. Candidate genes*

Because of our knowledge regarding the role of the renin–angiotensin–aldosterone system in the regulation of blood pressure, components of this system, i.e. angiotensinogen, renin, angiotensin-II receptor, angiotensin converting enzyme, have been the subject of study; the most extensive have concentrated on the angiotensinogen (AGT) gene and this will be used to exemplify the approaches used.

The AGT gene is highly polymorphic, containing 15 common mutations in the coding and non-coding region of the gene. One such mutation results in a methionine residue being substituted by threonine at position 235 (M235T) and is found in approximately 50% of the hypertensive population. This mutation was found to be more prevalent in hypertensive subjects than controls in one study,[5] but not in another.[6] An interesting observation regarding this mutation is that patients who are heterozygous for M235T have a 10% increase in plasma AGT levels, homozygotes a 20% increase. Thus this is a mutation which may be more prevalent in hypertensive patients and which may raise blood pressure by increasing plasma AGT.

Further polymorphisms are found in the 3′ untranslated region of the gene, which contains a dinucleotide (GT) repeat region. When this region is amplified



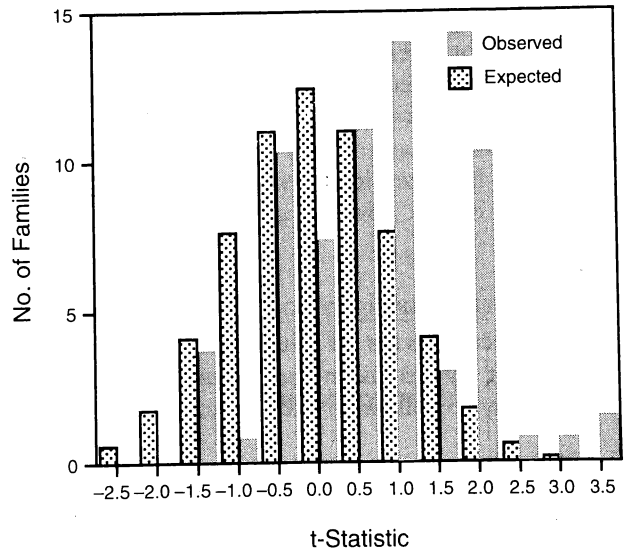


FIGURE 1

Distribution of the observed and expected frequencies of shared alleles from the study of Caulfield *et al.* (reference 6) in 63 multiplex families with hypertension. The *t*-statistic tests whether affected relatives share alleles at a given locus (in this case a 3′-region of the AGT gene) more than can be expected by chance. As indicated a greater degree of sharing was observed in hypertensive families compared to controls. (Reproduced with permission of the authors and the New England Journal of Medicine).

using the polymerase chain reaction, 9–10 different alleles are found. The degree of sharing of alleles at this site can therefore be compared in hypertensive siblings versus controls. Results of two separate studies indicate a greater degree of allele sharing (15–30% excess) at this locus in hypertensive siblings/familes than can be expected by chance (Fig. 1)[5,6] Thus linkage between hypertension and this AGT gene locus has been confirmed. However, 'linkage' may be a misleading term. The gene causing hypertension may not be AGT itself, but may be another in close proximity. Linkage studies therefore can never implicate a single gene.

Using similar approaches, polymorphisms in other genes have been found more commonly in hypertension. The deletion (D), and insertion (I), polymorphism in the angiotensin converting enzyme gene refers to either the absence or presence of an intronic DNA sequence. The DD genotype has recently been found to be more common in patients with left ventricular hypertrophy[7] and also in those with hypertension. Such patients have an increase in serum ACE levels. Similarly a polymorphism in the glucocorticoid receptor (AA) is more prevalent in hypertensive patients who have hypertensive parents, and this may explain an increase in serum cortisol in this cohort.[8]

The advent of molecular biology has facilitated these studies and resulted in the identification of several genes that appear to be implicated in the development of hypertension. Other genes, such as the renin gene appear to have been excluded. The next few years will see a systematic examination of other candidate genes thought to be of relevance in hypertension, for example the insulin receptor, sodium channel, calcium channels and sodium–potassium ATPase.

Perhaps the most useful information, however, will emerge not from the candidate gene approach, but from genomic screening. This technique uses over 100 markers (mini/microsatellites) directed against polymorphic tandem repeat regions across the entire genome, and is the most comprehensive way of screening for genetic linkage. This approach has recently been used to search for susceptibility genes in type 1 diabetes;[9] hypertension seems likely to follow. The difficult part remains the identification of the relevant gene once the polymorphic locus has been identified.

## MONOGENIC CAUSES OF HYPERTENSION

Investigation of the molecular basis of glucocorticoid-remediable aldosteronism (GRA) has confirmed that hypertension can occur from a single gene mutation. Other examples seem likely to follow in the forthcoming years.

### *Glucocorticoid-remediable aldosteronism*

Until recently this was thought to be a rare cause of primary aldosteronism. The condition is inherited as an autosomal dominant trait and results in mineralocorticoid hypertension with suppression of plasma renin activity but elevated aldosterone levels. In contrast to the normal physiological state in which aldosterone is under the control of angiotensin II, aldosterone secretion in GRA is regulated by ACTH, hence the term glucocorticoid-remediable or dexamethasone-suppressible aldosteronism. The molecular basis for this cause of hypertension has now been elucidated. The zonation of the adrenal cortex into zona glomerulosa, zona fasciculata and reticularis is not only of anatomical, but also of functional significance. Normally aldosterone is secreted only from the zona glomerulosa because it expresses the product of the P450 CYP11$\beta$2 gene, aldosterone synthase. This enzyme can carry out the 11$\beta$-hydroxylation and 18-hydroxylation of corticosterone (B) to form 18-hydroxy B and finally aldosterone and is absent from the zonae fasciculata/reticularis. The zona fasciculata and zona reticularis express the product of the P450 CYP11$\beta$1 gene, 11$\beta$-hydroxylase which is involved in the final pathway of glucocorticoid biosynthesis, converting 11-deoxycortisol to cortisol. The CYP11$\beta$1 and CYP11$\beta$2 genes have been cloned, are closely related (95% homologous) and found in close proximity on chromosome 8. Perhaps not surprisingly, in view of their differing function, their regulation differs; CYP11$\beta$1 contains 5′ sequences which enable it to be regulated by ACTH, whilst CYP11$\beta$2 is regulated by angiotensin-II. It is now known that GRA results from the formation of a chimaeric gene which occurs as a result of unequal cross-over between the CYP11$\beta$1 and 11$\beta$2 genes at meiosis.[10,11] Thus instead of the CYP11$\beta$1 gene aligning with its counterpart on the adjacent chromosome, it aligns with the homologous CYP11$\beta$2 gene. Genetic recombinant results in a chromosome with a normal copy of CYP11$\beta$1 and 2, but in addition a chimaeric gene comprising 5′ sequences of 11$\beta$1 and 3′ sequences of 11$\beta$2. The product of this gene can now synthesise aldosterone (possessing 11$\beta$2 sequences) but because it contains 5′ sequences of CYP11$\beta$1, it is regulated by ACTH (Fig. 2).

Since the molelcular basis for this condition was defined, many more kindreds have been identified with the condition.[12] Biochemically GRA results in the high urinary excretion of 18-hydroxy and oxo metabolites of cortisol and corticosterone. The chimaeric gene can be easily detected by Southern blot analysis. Of



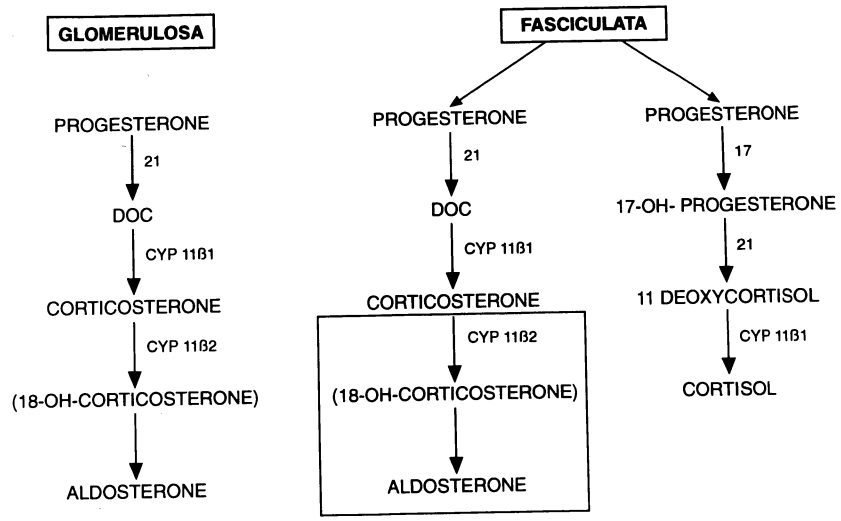


FIGURE 2

Diagram of adrenocortical steroidogenesis depicting the pathogenesis of GRA. GRA results from the formation of a chimaeric gene containing 5′ sequences of CYP11$\beta$1 and 3′ sequences of CYP11$\beta$2. The product of this gene (indicated in the boxed area) can synthesise aldosterone, but is under the control of ACTH.

relevance to this discussion is the observation that some 7% of patients with a family history of hypertension and stroke <50 years of age have been found to have this chimaeric gene (R. Dluhy, personal communication). This observation needs to be confirmed, but if substantiated, GRA will have evolved from being a rare cause of mineralocorticoid hypertension to the commonest genetic mutation to causing hypertension.

### *11$\beta$-Hydroxysteroid dehydrogenase deficiency*

A further single gene mutation causing hypertension seems likely to be uncovered in the so-called 'Syndrome of Apparent Mineralocorticoid Excess' (AME). This topic has been previously discussed in this Journal,[13] but there have been several recent advances in this area. 11$\beta$-hydroxysteroid dehydrogenase (11$\beta$-HSD) converts cortisol to hormonally inactive cortisone in many peripheral human tissues, specifically the kidney. AME is associated with a defect in this conversion of cortisol to cortisone and results in a characteristic urinary steroid metabolite profile with an increase in the urinary ratio of cortisol to cortisone metabolite excretion. In addition plasma cortisol half life is prolonged, though circulating levels are normal due to a concomitant compensatory fall in cortisol production rate. Several studies have now indicated that cortisol and not aldosterone acts as a mineralocorticoid in this condition.[14,15] Dexamethasone, by suppressing endogenous cortisol production rate lowers blood pressure and restores normokalaemia. Subsequent data have indicated that 11$\beta$-HSD plays a crucial role in normal physiology in maintaining specificity for the renal mineralocorticoid receptor. *In vitro*, this receptor binds aldosterone and cortisol with equal affinity; *in vivo* 11$\beta$-HSD inactivates cortisol to cortisone, reducing competition with aldosterone for the MR.[16]

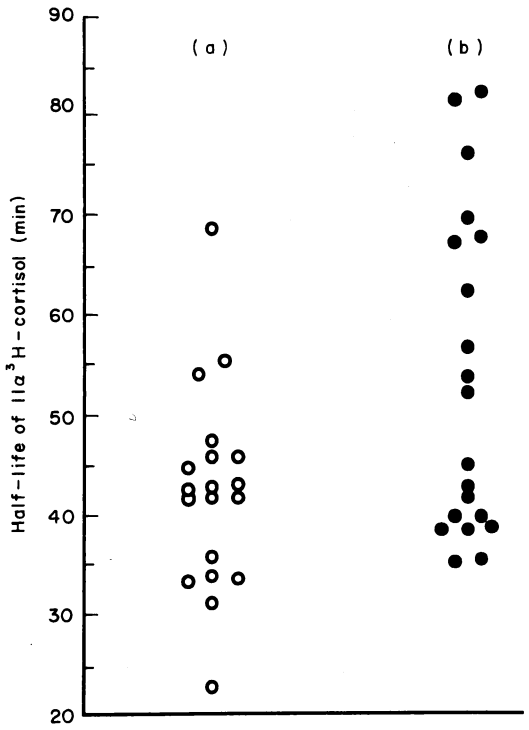


FIGURE 3

Plasma half-life of 11α³H-cortisol in 19 normotensive controls (a) and 20 patients with untreated essential hypertension (b). The plasma half-life of this cortisol isotope directly reflects the activity of 11β-HSD. As indicated the hypertensives appear to fall into two groups, those with a normal half-life for the isotope and 7 patients with an increased half-life suggesting impaired 11β-HSD activity.

There are several pieces of indirect and direct evidence that reduced 11β-HSD activity may be important in hypertension:

1. Inhibition of 11β-HSD is now known to explain the hypertension seen following the ingestion of large quantities of liquorice. Glycyrrhetinic acid, the active component of liquorice inhibits renal 11β-HSD activity.[17].
2. The parents of one of our index cases of AME had been labeled as having 'essential' hypertension. One of them was found to be mildly hypokalemic and had a prolonged plasma cortisol half-life.[15]
3. Dexamethasone in doses which suppress endogenous cortisol production has been shown to lower blood pressure in patients with essential hypertension.[18]
4. Finally two separate studies have indicated reduced 11β-HSD activity in patients with essential hypertension (Fig. 3).[19,20]

Thus there is compelling evidence that 11β-HSD, like aldosterone synthase may be an important mechanism in the development of hypertension. Unlike GRA, however, the molecular basis for AME has yet to be elucidated. There are at least two isoforms of 11β-HSD in human tissues.[21] The type 1 isoform is a low affinity NADP(H)-dependent enzyme which is found mainly in liver and the gonad and behaves primarily as an oxo-reductase (i.e. converts cortisone to



cortisol) *in vivo*. In contrast, the type 2 isoform is a high affinity NAD-dependent dehydrogenase. Only the type 2 isoform is found in human kidney, and it seems possible that a defect in this enzyme may explain AME. The type 1 cDNA and gene have been cloned and the gene, not surprisingly is normal in patients with AME.[22] The human type 2 isoform has very recently been cloned from human kidney[23] and we wait with interest to learn whether the resulting gene is abnormal in patients with AME. Either way, like the CYP11β-hydroxylase genes, this promises to be an important candidate gene to investigate in essential hypertension.

## SUMMARY

Hypertension is common and important as a risk factor for coronary heart disease and stroke. The advent of molecular biology has resulted in the identification and analysis of several candidate genes which may be involved in the pathogenesis of the condition. Of equal importance, the contribution of other genes such as the renin gene appears to have been excluded. It seems likely that in many cases, hypertension will be polygenic in origin, i.e. result from the interaction of many differing genes. However a precedent has been set; hypertension can occur as the result of a single gene mutation. It is not inconceivable that hypertension may be the common phenotype for a series of single gene defects in a variety of genes such as aldosterone synthase and 11β-HSD2. As clinicians we have the unique opportunity to witness normal physiology and to investigate pathophysiology. Even in a disease as common, and some would say, as mundane as hypertension, our ability to detect and evaluate rare or unusual causes of hypertension may prove to be of fundamental importance in our understanding of the mechanism of essential hypertension.

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ADDENDUM

Following this symposium and the writing of this article, a second monogenic cause of hypertension has been elucidated with the description of the molecular basis of Liddle's syndrome. Liddle's syndrome is a further 'rare' cause of endocrine hypertension characterised by sodium retention, but with low renin and low aldosterone levels.[1] Hypokalaemia may occur but is by no means an invariable finding. The phenotype results because of a mutation in the carboxy-terminal domain of the $\beta$-subunit of the human epithelial sodium channel, which, for reasons which are still obscure, results in constitutive activation of the apical sodium channel, sodium reabsorption and subsequent hypertension.[2]

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# LESSONS FROM A SYMPOSIUM ON FIBRINOGEN AND CARDIOVASCULAR DISEASE HELD IN THE COLLEGE ON 1–2 NOVEMBER 1994

*Amanda Lee, Wolfson Unit for Prevention of Peripheral Vascular Diseases, University of Edinburgh*

At the First International Symposium on Fibrinogen and Cardiovascular Disease held in Vienna, 1992, the importance of plasma fibrinogen as a cardiovascular risk factor was established. The multi-disciplinary and international audience at this Second International Symposium consisted of many pioneers in this area of research, together with others who had gained an interest and were keen to learn of recent developments. During the two days, there were sessions on: progress on the measurement of plasma fibrinogen; aspects of the pathogenic role of high fibrinogen levels; the epidemiology of fibrinogen in relation to risk factors and genotype; fibrinogen and ischaemic heart disease, peripheral arterial disease and cerebrovascular disease; and the therapeutic lowering of raised plasma fibrinogen levels.

*Biochemistry and measurement*

The term fibrinogen covers a large family of closely related molecules, which are heterogeneous in each of their three chains: A$\alpha$, B$\beta$ and $\gamma$. Methods for the determination of fibrinogen can be divided into two groups; those that measure clottable fibrinogen (for example, the widely used Clauss method) and those that quantify the fibrinogen molecule in other ways (for example, by heat precipitation or immunologically). Due to the biological variability of fibrinogen (both within and between individuals) and the different assays used by different studies, there was much confusion in recent years as to what the population reference range of fibrinogen should be. In 1991, work was initiated on the formulation of a standard by a scientific sub-committee of the International Society on Thrombosis and Haemostasis. The international collaborative study involving 22 laboratories has allowed the establishment of the 1st International Standard for plasma fibrinogen (89/644). This standard was reported to be a valuable and reliable calibrator for the measurement of plasma fibrinogen over a wide concentration level in clotting assays.

*Fibrinogen and pathogenesis of arterial disease*

There are a number of mechanisms whereby high fibrinogen levels are likely to predispose to atherosclerosis and thrombosis, although most are not fully understood. After vascular injury, the coagulation system acts to secure haemostasis by the production of thrombin and thus the conversion of soluble fibrinogen to insoluble fibrin forming a stable clot. In addition, fibrinogen is an important cofactor in platelet aggregation and also a major determinant of blood and plasma viscosity. Fibrinogen is present in the normal arterial intima and in atherosclerotic lesions. In early proliferative (gelatinous) lesions, fibrin is also present and provides the scaffolding along which smooth muscle cells migrate and proliferate, binds thrombin and lipoproteins; and is a source of fibrin