The renal isoform of 11β-hydroxysteroid dehydrogenase (11βHSD2) is responsible for the conversion of cortisol to its inactive metabolite cortisone in the distal nephron, but also in other tissues, such as the salivary glands, colon or the placenta. Conversion of cortisol to cortisone normally prevents its fixation to mineralocorticoid receptors (MR) for which it has a high affinity, whereas cortisone does not. By contrast, in inherited or acquired conditions associated with a decreased activity of 11βHSD2, cortisol accumulates and binds to the MR, which leads to hypertension, hypokalemia and suppressed renin and aldosterone. Such conditions include excessive liquorice or carbenoxolone intake, but also inherited impairment of 11βHSD2 due to mutations in the corresponding gene, HSD11B2 [1–3].

Such mutations are found in a rare autosomic recessive form of monogenic hypertension which has been called apparent mineralocorticoid excess (AME) because the mineralocorticoid effects are mediated by cortisol, whereas aldosterone is suppressed. An elevated ratio of urinary free cortisol to urinary free cortisone (F/E ratio), or urinary cortisol to cortisone metabolites (tetrahydrocortisol + allo-tetrahydrocortisol to tetrahydrocortisone), is considered pathognomonic for this disorder. In addition to the hallmarks of mineralocorticoid excess mentioned, other possible features of AME include nephrocalcinosis, nephrogenic diabetes insipidus and rhabdomyolysis. Interestingly, this condition has also been associated with intrauterine growth retardation and post-natal failure to thrive [1–3].

In view of the critical role of 11βHSD2 for ensuring selectivity of the MR in the distal nephron, it was tempting to hypothesize that more subtle genetic abnormalities might contribute to the pathogenesis of common essential hypertension [3]. This may occur either directly through unrestricted binding of cortisol to MR in the collecting duct and distal tubules [3], or through unrestricted transfer of cortisol through the placenta of pregnant women, leading to inhibition of fetal growth and subsequent hypertension in adulthood [4,5]. The latter mechanism is in agreement with the well-known, although still debated, epidemiological link between low birth weight and adult hypertension, as well as with a few studies in animals. In particular, in rats, placenta 11βHSD2 activity is inversely correlated with placental weight and directly correlated with term foetal weight [4].

Furthermore, in patients with AME, a close correlation has been found between disease phenotype and genotype [6,7]. Indeed, patients harboring mutations resulting in very low or no 11βHSD2 activity present early in life with a severe phenotype, and the ratio of cortisol to cortisone metabolites is clearly increased. By contrast, patients with mutations resulting in a partially functional 11βHSD2 protein present in late adolescence or early adulthood with a so-called mild form of AME (referred to as AME type 2), and this ratio is in the normal range or only slightly increased [8–10]. These findings suggest the existence of a continuum between caricatural forms of AME due to mutations drastically affecting the activity of the enzyme and more subtle genetic alterations resulting in milder phenotypes, which are easily labelled ‘essential hypertension’ [8].

Despite this promising rationale, the first attempts to demonstrate the implication of a decreased 11βHSD2 activity in the pathogenesis of so-called essential hypertension were disappointing. Indeed, although some investigators found increased cortisol plasma half-life and/or higher cortisol to cortisone metabolites ratios in hypertensive compared to normotensive individuals [11–13], these results were not confirmed by others [14], even in low renin essential hypertensives (LREH) [15]. In addition, hypertensive patients who developed hypokalemia under diuretic therapy had similar ratios compared to those individuals who did not develop hypokalemia [16]. Finally, the existence of a correlation between placenta 11βHSD2 activity and placenta weight has not been confirmed definitively in humans [5].

Such discrepancies might be due to the heterogeneity of essential hypertension. Rather than studying unselected essential hypertensives, it would appear to be more appropriate to identify those subgroups that display at least a part of the features of AME, such as salt or liquorice sensitivity [17] or low renin essential hypertension. In this view, the association of lower 11βHSD2 activity and salt sensitivity was well demonstrated in...
mild essential hypertensive [18] and normotensive subjects [19].

In addition, it has been advocated that F/E ratios might not be sensitive enough to reflect the influence of subtle genetic changes such as those expected in essential hypertension [8]. In a first attempt to address this concern, Bocchi et al. [20] measured 11βHSD2 activity in sweat gland ducts collected from skin biopsies in hypertensive and normotensive subjects. The activity of 11βHSD2 was significantly lower in hypertensives. However, as noted by the authors, it remains to be demonstrated that such a decrease is also found in organs directly involved in blood pressure regulation, such as the vasculature or distal nephron [20].

Even if the existence of an involvement of decreased 11βHSD2 activity in essential hypertensives is taken for granted, the existence of functional variants of HSD11B2 likely to make a significant contribution to essential hypertension remains a matter of debate. Indeed polymorphisms in the coding sequence of this gene appear to be rare [19], with a frequency estimated at less than 1 in 250,000 in Caucasians [3]. Furthermore, the association of these variants with either blood pressure, salt sensitivity or cortisol to cortisone metabolites ratios was found by some groups [18,19] but not confirmed by others [21].

However, it is possible that the variability of 11βHSD2 is not due to exonic mutations leading to decreased activity of 11βHSD2, but to intronic or promoter mutations associated with a decreased expression of the enzyme [3]. In a study by Agarwal et al. [18], salt sensitivity and increased F/E ratio were associated with shorter length of an intron 1 CA-repeat, possibly through a decreased expression of the enzyme. Alternatively, 11βHSD2 inhibition might be due to the presence of endogenous inhibitors named glycyrrhetinic acid-like factors (GALF) [15, 22, 23], which might themselves be genetically regulated.

In this issue of the journal, Carvajal et al. [24] evaluated 11βHSD2 activity, as assessed by F/E ratio, in normotensive subjects as well as low renin (LREH) and normal renin (NREH) essential hypertensives. The mean F/E ratio was significantly increased in LREH compared to normotensives, and a moderate although significant inverse correlation between F/E ratio on the one hand, and serum aldosterone on the other, was found in the LREH subgroup but not in normotensives, in agreement with a decreased 11βHSD2 activity in the LREH subset.

Interestingly, the NREH subjects behaved in all respects as normotensives (i.e. the F/E ratio was similar and no correlation between this ratio and renin–angiotensin–aldosterone system was found), which makes a contribution of decreased 11βHSD2 in hypertensive patients with high or normal renin activity very unlikely. These results emphasize the importance of identifying subsets of essential hypertension with characteristics suggestive of particular mechanisms before testing the corresponding candidate genes. In the long term, this strategy might prove more rewarding than ‘fishing’ for positive associations in large but poorly characterized databases. More surprisingly, even in the LREH subset, the correlation between F/E ratio and systolic or diastolic blood pressure was not statistically significant. This negative finding emphasizes that several candidate genes initially associated with blood pressure were eventually shown to be more directly involved in intermediary phenotypes (salt sensitivity, low renin), target organ damage, cardiovascular or renal complications, high blood pressure being only an epiphenomenon, a hallmark of cardiovascular damage or another remote consequence.

In the same study [24], screening of the entire coding sequence of HSD11B2 in a limited number of patients failed to disclose exonic variants, in agreement with previous work. In an attempt to explain the decrease in cortisol to cortisone conversion in LREH patients, the authors genotyped them for the intron 1 CA-repeat that had already been studied by Agarwal et al. [18]. Although the distribution of this repeat was similar in normotensives and NREH, it was significantly different in LREH and correlated with F/E, serum aldosterone and plasma renin activity within this subgroup. Patients harboring a longer CA-repeat disclosed a higher F/E ratio. This result apparently contradicts those obtained by Agarwal et al. [18] in their series. However, as correctly noted by the authors, it is in agreement with data obtained in vitro by the same group [25]. The exact nature of the link between CA-repeat length and 11βHSD2 expression or activity remains to be explored.

As with every work, the study by Carvajal et al. [24] has limitations. These include a possible bias induced by the ethnic admixture, a lack of control for sodium intake and the absence of exhaustive screening for other variants than the intron1 CA repeat. It would also be worthwhile to extend the analysis to at least a few families of LREH patients to confirm the genotype–phenotype correlation within pedigrees. In addition, urine F/E ratio remains an approximate estimate of what takes place in the distal nephron. As shown by Bocchi et al. [20], determination of 11βHSD2 activity in tissues such as salivary glands, or even better in the vasculature or kidney, may help to uncover subtle differences in subsets of essential hypertensives. Finally, characterization of subjects for sensitivity to
liquorice or its active components, glycyrrhizic and glycyrrhetinic acids, might be a powerful tool to identify those subjects who are likely to harbour subtle inherited defects in HSD11B2 [17]. Although most individuals who consume 400 mg glycyrrhizic acid daily experience adverse effects, some subjects develop signs and symptoms of mineralocorticoid excess with a daily intake of only 100 mg [26–28]. However, the possible genetic differences underlying this large inter-individual variability have not been thoroughly investigated.

Many clinicians and physiologists blame geneticists for generating a huge number of association studies with contradictory results. After a period of initial enthusiasm, these partly justified claims have slowly undermined the credibility of the genetics of hypertension. The appropriate answer would be to invite sceptics to help us describe more precise phenotypes within the mixed population of essential hypertensives and to develop more appropriate diagnostic methods to detect the immediate consequence of subtle genetic changes. Indeed, neither high level statistic, nor exhaustive genotyping can replace a well thought out changes. Indeed, neither high level statistic, nor ex-

**References**