Chapter 2
Epidemiology and the Need for Screening

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Abstract Because of change in the accepted meaning of the term “primary aldosteronism” (PA), and in the methods used to screen for and diagnose it, the “perceived” prevalence of PA (and hence the epidemiology of PA) has undergone and is still undergoing progressive change since the first description of PA. As well, methodology for measuring renin and aldosterone has always been not only variable from centre to centre but often suboptimal. Hence in 2013 there existed an understandable, healthy, scientific and clinical lack of complete agreement on the definition of PA, its prevalence and how it is best identified, by screening and definitive tests, and managed. Nevertheless, the prevailing view among clinicians diagnosing and treating significant numbers of PA patients is that it is a common enough cause of hypertension, associated with unusually high morbidity if not treated early, for (1) early detection to be vigorously pursued by screening, with appropriate education of doctors and the community regarding the need to do so; for (2) identification of unilateral disease to have very high priority because surgery yields best patient outcomes and that (3) a recently proposed, “public health” approach involving the addition of “low-dose” aldosterone “antagonists” to first-line treatment of all hypertensive patients is not an appropriate alternative. It would (1) make diagnosis of unilateral PA difficult or impossible, reducing the quality of outcome for up to one-third of patients; (2) make prevalence permanently unknowable; (3) make deciding the appropriate dosage of aldosterone antagonist impossible when interfering medications are also being taken and (4) carry significant hyperkalemic risk. An increasing understanding of the genetic bases of PA holds promise that one day it may be possible to identify not only most PA patients but also a predisposition to PA early enough to prevent or significantly modify its development. In this chapter perceived prevalence is traced chronologically before attempting any estimates of true prevalence in primary and secondary care.
Introduction

Primary aldosteronism (PA) is currently the commonest specifically treatable and potentially curable form of hypertension. Recognition and appropriate treatment can be life changing and life saving [75, 86]. Only one obvious clinical characteristic distinguishes PA from hypertension without a recognised cause, the so-called essential hypertension. This is unprovoked hypokalaemia. Unfortunately, hypokalaemia is usually a late development in PA, and, in most recently reported series, more than 50% of patients are normokalemic. By the time hypokalaemia develops, and independently of blood pressure level, aldosterone excess may have caused atrial fibrillation, heart failure, stroke or renal impairment. It is therefore mandatory to screen for, and diagnose, PA as early as possible, preferably before hypokalaemia develops. Currently available screening tests for PA, though fraught with problems, are therefore undoubtedly worthwhile. Through more vigorous education of primary care doctors, specialists and the general community, screening should gradually be more widely applied to the large hypertensive population. The precise prevalence and incidence of PA, in general and in defined hypertensive populations, respectively, are unknown, with widely varying estimates depending on the extent of testing and the interpretation of the screening and diagnostic tests [87]. An impediment to obtaining definitive information on prevalence is difficulty establishing a certain diagnosis of PA in all patients included in the survey. After removing an adrenal in unilateral PA and finding an adenoma, ideally, immunohistochemical evidence of appropriate biosynthetic capacity would be established, together with biochemical evidence of disappearance of un-suppressible (autonomous) aldosterone secretion postoperatively [41]. The great hope for future understanding of the prevalence of PA, and for precise diagnostic testing, is an understanding of the genetic bases of PA. This commenced in 1992 [55] with elucidation of the genetic basis of a rare familial form, leading to a specific genetic test, and has recently progressed with identification of several other genetic mutations which cause PA [5, 6, 8, 62, 64], in one case being not uncommon as a somatic mutation in certain aldosterone-producing adenomas (APAs). Evidence so far suggests that there may be geographic and ethnic differences (1) in the frequency of occurrence of APAs in comparison with diffuse or nodular bilateral adrenocortical hyperplasia (BAH); (2) in the currently known inherited forms of PA and in the frequency of a particular genetic mutation and thus, finally, (3) in the overall prevalence of PA. These problems associated with establishing a reliable estimate of the prevalence of PA have led to vigorous controversy, with a minority view that it is sufficiently uncommon not to warrant screening [7, 19, 49–52, 54, 69, 70]. The origins, basis and elements of this controversy have already been
described in great detail [34], including many of the issues requiring discussion here. In fact, little has changed since 2004, apart from growing support for screening and diagnosis of PA, based on the evidence that untreated, potentially curable PA is associated with a significantly higher risk of atrial fibrillation, stroke, heart failure and renal impairment [58, 79, 82] than other forms of hypertension of equal severity in terms of blood pressure (BP) level. A recent proposal that screening be abandoned in favour of including treatment suitable for patients with PA in the first-line treatment of “all” hypertensives will be discussed later.

First Recognition and Clinical Description of PA; Early Recognition of Its Normokalemic Form and of the Importance of Suppressed Plasma Renin Activity in Its Diagnosis; and First Suggestion of High Prevalence in the General Hypertensive Population

In a brilliant example of deductive logic, made possible by wartime experience studying adaptation to tropical climates [9], Jerome Conn in 1954 was the first to recognise and successfully treat a patient with PA due to an APA. Based on that one patient, he described the clinical and biochemical features of the condition [10], which became known as “Conn’s syndrome”, with severe hypokalaemia initially a salient feature. Not surprisingly, with the prevalence of PA presumably as high then as it is today, and hence an untouched population ripe for the picking, Conn was referred many hypokalemic hypertensive patients. By 1964 he could report analysis of 145 cases [16] and come to the reasonable conclusion that it was not uncommon. During the 10-year period following his description of the index case, Conn published a number of seminal observations on PA. These included that suppressed plasma renin activity (PRA) was the hallmark of the condition and not hypokalaemia, having recognised normokalemic PA and correctly deduced that it was an early form [12, 13, 15, 17, 18]. Realising that normokalemic PA could masquerade as essential hypertension [18] and hence go unrecognised, and being aware of a 20% incidence of adrenal adenomas in an autopsy series in which hypertensives were compared with normotensives [80], Conn came up with the idea that as many as 20% of hypertensives might have PA. This provoked alarm and even hostility among his colleagues. He later revised this estimate down to 10% and then to about 7% of “referred” hypertensive patients [11, 14], the latter figure being probably as close to the mark as anyone’s guess today. His Harvey Lecture [14] is well worth reading. Conn’s initial high estimate stimulated investigation by colleagues with an interest in hypertension ([21, 49, 50, 53]), recognising that if Conn was correct in suggesting that potentially curable PA was common, it would be necessary to look for it in all hypertensive patients [21]. A positive answer to this question was capable of dramatically changing accepted medical practice. Grant Liddle’s group at Vanderbilt University studied 90 consecutive hypertensive referrals who had never
had unprovoked hypokalaemia, measuring aldosterone secretion or excretion by the tedious double-isotope dilution/derivative technique in all and PRA by bio-assay in the nephrectomised rat in some [21]. The then current assumption was accepted that aldosterone production had to be above the normal range and that PRA had to be suppressed for PA to be present. Using these criteria, 87 patients had either normal aldosterone or unsuppressed PRA or both, leading by exclusion to a suggested maximal incidence for PA of 3.3 %. Two with raised aldosterone had PRA near the lower limit of normal and were thought to merit further observation. Five of 24 with aldosterone within the normal range had markedly suppressed PRA, and these days would be considered possible PA patients and subjected to a suppression test. Thus the incidence of PA in these 90 referred normokalemic hypertensives remains unclear. It might have been higher than 3.3 % and possibly as high as 11 %. It is fair to say that almost as large a degree of difficulty in deciding on the prevalence of PA based on clinical studies and biochemical changes remains to this day. This and other studies considered “negative” led to a quoted textbook prevalence of PA in the hypertensive population [7, 54] of less than 1 % and advised to look for PA only if hypokalaemia is present. This view persisted for a remarkable 20 years.

Early Diagnostic Methodology for PA and Observed Microscopic Features of APA

During a lull in further information forthcoming on the prevalence (or incidence in discrete populations) of PA, attention was paid to methods of screening and diagnostic testing [92]. Up to a week of dietary salt restriction in order to demonstrate chronically suppressed PRA was often employed as a screening test, followed by a salt loading test to demonstrate lack of suppressibility (autonomous secretion) of aldosterone as a definitive test. Interest was taken in the gross and microscopic features of APAs, many of them paradoxically composed of predominantly zona fasciculata-type cells which in the normal adrenal are responsible for cortisol, not aldosterone, production. It was noted that in many patients with APAs plasma aldosterone (which circulates in 1,000th the concentration of cortisol and is therefore much more difficult to measure accurately) fell with upright posture following overnight recumbency (instead of rising, as in normals), and this was proposed as a diagnostic test to aid in diagnosis of APA and its separation from bilateral adrenal hyperplasia (BHA), in which aldosterone also rose with upright posture [28]. It was appreciated that there were exceptions to this rule, but they were thought to be rare. The University of Queensland Endocrine Hypertension Research Unit, Greenslopes Hospital, Brisbane, Australia, began in 1987 to describe the contrasting clinical and biochemical characteristics of patients with posture [and angiotensin, by infusion [23, 94]]-unresponsive APAs (AII-U APAs) and of posture- and angiotensin-responsive APAs (AII-R APAs). The AII-R APAs on posture testing could be mistaken for BHA or essential hypertension [37, 38]. They differed from AII-U APAs...
in having normal levels of plasma and urinary 18-oxo-steroids, as did patients with BHA [31, 37, 38]. AII-R APAs also showed morphological differences [35, 90, 91], being composed predominantly of zona glomerulosa or hybrid-type cells, in contrast with the AII-U APAs which were composed predominantly of zona fasciculata-type cells. Interestingly, recent genetic studies have revealed another probable difference between the two tumour types, somatic KCNJ5 mutations being more commonly found in AII-U APAs of fasciculata-type morphology [5, 6].

Importantly, in the Greenslopes Hospital series, relying on adrenal venous sampling rather than plasma aldosterone response to posture and organ imaging in order to recognise unilateral aldosterone production suitable for unilateral adrenalectomy, AII-R APAs proved to be just as common as AII-U APAs [30, 41]. This, together with adoption of universal screening for PA by measurement of aldosterone/renin ratio in all new hypertensives (see later), led to the numbers of patients having unilateral adrenalectomy in the Greenslopes Unit increasing from 3–5 per year to 25–30 per year [41]. Clearly, PA was “not uncommon”, just as Jerome Conn had suggested [12, 14] 30 years earlier.

**The Impact of Application of the Aldosterone/Plasma Renin Activity Ratio to Screening on the Diagnosis and Apparent High Prevalence of PA**

The possibility of measuring renin and aldosterone simultaneously and calculating the ratio of aldosterone divided by renin (ARR) permits recognition of early forms of primary aldosteronism before either hormone has moved out of the wide normal range [32, 33, 34, 41, 84]. Hiramatsu and colleagues [47] initiated a resurgence of interest in PA by showing that it could be detected in an unselected population of hypertensives by measuring the aldosterone-to-PRA ratio. It much later became apparent that measuring the concentration of the enzyme renin (PRC or DRC) in order to generate the ratio, rather than PRA which incorporated the effect of substrate levels, gave different and sometimes misleading results, especially in females [3, 4, 71, 85]. Hiramatsu and colleagues screened 348 hypertensives and diagnosed and removed nine APAs. This was an incidence of 2.6 %, much higher than expected in 1981. Furthermore, six of the nine were normokalemic, confirming Conn’s predictions and personal findings which had been largely ignored. The incidence of PA would almost certainly have been higher, because small adenomas and all bilateral hyperplasia (BHA) causing PA would have been undetected by the methods available and employed [34]. As well, the effects of antihypertensive medications on the ARR had been unexplored at that time. This promising use of the ARR stimulated the Greenslopes Hospital Unit to study the aldosterone/PRA ratio in 18 patients with known hypokalemic PA (12 APA, 4 BHA, and 2 FH-I) after cessation of aldosterone antagonists and angiotensin-converting enzyme inhibitors [46]. A cut-off point of 25 ng/ml/h for PRA appeared to most likely discriminate PA from normals
and other hypertensives. It was concluded that the ratio was very promising, but further study of its consistency and of the effects of sodium and potassium balance and of antihypertensive medications was required. With further experience, significant limitations of the ratio became apparent, as did the need for great care in the collection of samples and the assay methods used [33, 34, 40, 78, 83, 85]. Current guidelines for performing the ARR are set out in detail in other chapters in this book. However, despite significant problems, the carefully applied ARR can produce a very important yield of specifically treatable and sometimes curable hypertension, as is detailed in the following sections.

Initial Denial Followed by Acceptance of the Concept of a Higher Prevalence for PA

After demonstration of the efficacy of ARR as a screening test [47] and a favourable first “in-house” assessment [46], the Greenslopes Hospital Hypertension Unit employed it in the late 1980s to recognise the presence of PA in a surprisingly high percentage of a small cohort of extremely resistant hypertensives [30, 34, 39]. This convinced them to introduce screening of “all” new hypertensive patients for PA. Their rate of diagnosis of PA (fludrocortisone suppression testing) following at least two positive ARRs increased five- to tenfold [41], and it soon became apparent that PA was certainly “not uncommon” among normokalemic hypertensives [30, 39, 41–43, 45] and might even be the commonest specifically treatable and potentially curable cause of hypertension. The Greenslopes Unit’s findings and reports, not surprisingly, were greeted with considerable caution by those researching in the area of hypertension. However, William F Young Jr from the Mayo Clinic in 1997 noted an order of magnitude increase in his unit’s diagnosis of PA following his application of the ARR as a screening test, and he subsequently enthusiastically advocated its use [60, 95–99]. By 2000, reports supporting the “new higher prevalence” for PA were appearing from Scotland [56], Singapore [57], South Africa [72], Japan [66] and South America [20]. By 2004, Mulatero could draw attention to the “increased incidence of primary aldosteronism, including surgically correctible forms, in centers from five continents” [63]. It is important to point out that it is the incidence of PA confirmed by aldo suppression tests [31, 61] which should be considered in evaluating prevalence, not the incidence of a raised ratio. The observed incidence of raised ARR in a primary care hypertensive population before any suppression testing has been as high as 30 % but falls significantly after suppression testing [29, 76]. It should also be remembered that prevalence of PA is likely to be higher in a specialist hypertension clinic known to be screening for potentially treatable causes than in a general medical clinic and, even more so, in a primary care population. Omura and co-workers [68] reported a surprisingly high incidence of 6 % for PA among Japanese hypertensive patients attending a general medical clinic.
Other Problems with Screening

One of the major problems with screening for PA using the ARR is the fact that most hypertensives have been screened while still taking antihypertensive medications which affect the levels of renin and/or aldosterone and confound interpretation of the ratio, causing false positives and false negatives [2, 3, 33, 34, 85]. False positives are seen in women during the luteal phase of the menstrual cycle when renin is measured as direct renin concentration (DRC), but not when measured as PRA [3, 71]. It is difficult to take patients off interfering medications and even dangerous in some circumstances. Substitution with non-interfering medications is a very worthwhile approach used by the Greenslopes Hospital Unit for many years [85] but time consuming and not always possible. It is therefore highly desirable to screen before treatment is commenced, and this is what the Greenslopes Unit has advocated in presentations and discussions with primary care physicians and specialists. Others also advocate this approach [67], including the Japan Endocrine Society [77]. Therefore, data on prevalence of PA obtained in a primary care setting in “untreated” hypertensives is extremely valuable but rarely available. Such a prospective study was that of Westerdahl et al. [93] in a Swedish primary care setting, finding a prevalence of PA of 5.5 % among 200 patients. This excellent study employed ARR, FST and AVS as investigations and concluded that the diagnosis of PAL should be considered in newly diagnosed hypertensive subjects and that screening is warranted. A much larger, prospective study was performed in 3,000 treated and untreated consecutive hypertensive patients referred between June 1999 and October 2002 to a Hypertension Centre in Pavia, Italy [22]. Interfering medications were painstakingly withdrawn according to a well-reasoned protocol before measuring ARR. A saline infusion test was performed in those with ARR >25 in order to confirm autonomous aldosterone production. Those with aldosterone not suppressing with saline went on to have adrenal CT scans and a dexamethasone suppression test, the latter followed by a chimeric gene test if positive, to diagnose or exclude GSH (FH-I). Of these 3,000 hypertensive patients referred to the clinic by general practitioners, as many as 684 (22.8 %) had ARR >25, but only approximately one-quarter of these (177, 5.9 % of the whole hypertensive population) had, as well, a positive saline loading test, leading to a positive diagnosis of primary aldosteronism. Note the big fall in possible incidence when a suppression test is included after a positive ARR. This was a single-centre study and thus avoided the major problem with multi-centre studies of differences in performance criteria, methodology and “cut-off” points for ARR from centre to centre. One such large, prospective, multi-centre Italian study of 1,125 hypertensive patients who were referred to 14 different hypertension clinics [74] also used ARR to screen (after ceasing or changing antihypertensive medications) and yielded an apparent incidence for PA which was higher at 11.2 % (APA 4.8 %, IHA 6.4 %). Thus we began to see glimpses of a possible prevalence for PA of around 5 % in a primary care hypertensive population and 10 % in a specialist hypertension clinic seeing referred patients.
Epidemiology Changes with New Forms and Definitions of Primary Aldosteronism

It can be seen from the above that, at the present time, a precise description of the epidemiology of primary aldosteronism is impossible, but we can describe “trends”. The true epidemiology of PA will become known, if ever, only when the genetic bases of all forms of PA have been discovered, genetic tests which provide a definite “yes” or “no” for the presence of a known causative mutation are widely available and the prevalence will probably vary depending on location. This will be to some extent explained by genetic diversity in different ethnic populations. For example, the percentage of APAs which harbour a KCNJ5 mutation may be higher in Japan than in Brisbane, Australia, or Cambridge, England. The first widely accepted definition of PA was based on patients with hypertension and hypokalaemia, suppressed PRA and “unsuppressible” aldosterone who harboured an adrenal tumour. There are still some clinicians who favour confining use of the term “Conn’s syndrome” to a solitary, benign, APA. However, there is general acceptance of less classic forms of PA. This follows acceptance of bilateral diffuse or nodular hyperplasia (unilateral or bilateral) and of adrenal carcinoma as being also capable of causing PA. As soon as Conn recognised normokalemic forms, these needed to be and were included in the definition. When Hiramatsu and colleagues in 1981 popularised the ARR as a screening test for PA, adrenal imaging was very difficult and adrenal morphology did not figure prominently in the diagnosis or the definition of PA, except by examination of a removed adrenal which cured the hypertension and, if present, the hypokalaemia—reasonable proof that primary aldosteronism was the cause of the patient’s condition. By the mid-1990s, however, when reliable abdominal organ imaging by computerised tomography (CT) became available, the definition of “possible” PA was expanded to include an adrenal abnormality on CT scanning (typically a hypo-dense nodule) in a hypertensive patient which might be an APA. However, such a nodule could also be an “incidental” finding (during investigation for abdominal pain), and not autonomously producing aldo or any other commonly measured steroid, and sometimes a metastasis. The definition of PA has continued to be challenged by recognition not only of early, less severe, usually normokalemic forms but also by initially rare, but now more commonly diagnosed (including by the Greenslopes Unit), normotensive forms, in which all the other clinical and biochemical (low potassium, low renin, unsuppressible aldo) features of PA may be present. Ito and co-workers [48] looked for and found an incidence of this normotensive form of PA of at least 1.4 % in healthy normotensive subjects. Is it appropriate to call this normotensive PA?

Insights and Questions Arising from Study of Familial Forms

A more recent, completely different challenge to our perceptions of definition and prevalence of PA has arisen. When a normotensive, normokalemic member of a family some of whose members suffer from a form of familial PA such as FH-I is tested and
found to have “the hybrid gene”, would it be best to say that this patient has PA or alternatively to describe this clinical scenario in terms of “a high risk” of eventually developing PA? We have learned much about the evolution (natural history) of PA by the study of families harbouring genetic mutations capable of causing full-blown or classic PA [35, 44, 81] but also early, less florid phenotype. Increasing knowledge of human genetics and advances in methodology and in the interpretation of findings have altered our perceptions of PA in many ways [39], starting in 1992 with the genetic basis of familial glucocorticoid-remediable PA [55], first described clinically 26 years earlier [88]. Some affected members of FH-I families will develop hypertension early, even presenting with stroke [73]. Many will remain normokalemic. Others, especially women, even if hypokalemic, may not develop hypertension until after the menopause, if at all. Developing knowledge of the diversity of genotype as well as phenotype is an ongoing process which is accelerating, with the recent demonstration of causal mutations in the KCNJ5 gene [5, 6, 8, 62, 64].

Obtaining a Definitive Diagnosis

In addition to the challenge to current definitions of PA represented by the above development of techniques permitting definitive diagnosis of a genetic predisposition to PA, there remain seemingly insurmountable problems to overcome in order to establish its prevalence. The first step towards resolution, not yet taken, is widespread recognition and acceptance that the problems exist, and the second step will be a collective will to solve them. What are these seemingly insurmountable problems? Up to the present time, the best methods for screening and diagnosing PA remain highly controversial. Accurate, robust methods for measuring renin, “renin activity”, angiotensin and aldosterone are still not widely available, 60 years after the clinical description of PAL by Conn, and 50 years after he defined the pathophysiology using a bio-assay in the nephrectomised rat to assess renin activity, and tedious, time-consuming double-isotope derivative dilution techniques to quantify aldosterone. A seminal issue concerns whether measurement of the enzyme renin (present in precursor, inactive and active forms) is helpful or confusing. The end product of the enzyme (renin) reaction with its substrate (angiotensinogen) is angiotensin I (Ang-I) which is rapidly converted to angiotensin-II (Ang-II), and it is this peptide, not renin the enzyme, which is not only the major regulator of aldosterone production but also capable of “feeding back” negatively to suppress renin release. Changes in levels and reactivity of substrate as well as other known and unknown influences on angiotensin generation are ignored if levels of renin in one of its many forms are relied on to assess the activity of the system in terms of its effects on aldosterone levels. More precise and reproducible methods which incorporate mass spectrometry of generated angiotensin I are beginning to appear in the literature, and methods for measuring circulating angiotensin II will almost certainly follow. Methods for measurement of aldo by mass spectrometry are well established [89] but not yet widely available. If the methodological problems can be solved, another significant problem will remain. Importantly and unavoidably, regardless of
the methodology, quoted “cut-off” points for ARR which are utilised when screening, and are accepted as delineating “likely” or “unlikely” PA, are always arbitrary and contentious. They represent a “best guess”, even when statistically derived, for example using receiver–operator curves. Similarly, definitive tests for PA are necessarily arbitrary in discriminating between normality and abnormality. Neither sets of criteria will be transferable from laboratory to laboratory because of differences, sometimes subtle and sometimes not, in methods of collection of blood samples, detailed handling of the samples and precise conditions utilised in the assays. This is why an element of local preference, based on local experience of outcomes, should always override “guidelines” when there is a clash. Hence at the present time, and into the foreseeable future, somewhat arbitrary assumptions have to be made (quite often after treatment has been commenced) regarding the correctness of the diagnosis of PA. Removal of an adenoma with typical histological features has often been regarded as sufficient to unequivocally establish a firm diagnosis of PA, without appropriate immuno-histochemical evidence of aldosterone secretory capacity. Might it have been an “incidentaloma”? Normokalemia and a normal post-operative aldosterone suppression test \[41\] are the best currently available evidence of removal of all abnormal, unsuppressible aldosterone-producing tissue. This provides convincing evidence that PA due to APA was present but is rarely performed. Lack of very strong evidence of a correct diagnosis of PA will always threaten the validity of estimated prevalence or incidence of PA.

“Need for Screening” Depends on Perceived Epidemiology

The following general points regarding epidemiology apply equally to screening and epidemiology of PA. The intensity of need for screening for a clinical condition will depend on factors such as (a) the seriousness of a negative outcome if the condition is not recognised (that is, “missed”); (b) whether it is sufficiently common to make screening worthwhile and (c) that screening methods are sufficiently robust to unequivocally identify those affected. In the case of PA, the first two of these arbitrarily chosen criteria suggesting a “high need for screening” appear to be well satisfied, while the third is doubtful, as already discussed. Epidemiology is always greatly influenced by the intensity and quality of screening. Epidemiology is the historical record of recognised instances of a condition, such as PA, in a community setting which can range from a very small to a very large community. Epidemiology changes not only with place, but with time, especially if it is due to an infective agent. It will at any given time depend on the reliability and precision of the criteria for recognition (that is, for diagnosis) that the condition is or was indeed present, and this will also vary with both place and time, as diagnostic criteria change and are, or are not, taken up and acted upon to confirm or exclude the diagnosis. Critically, it will depend on (a) identification of an infective or genetic cause or, if not infective or genetic, (b) a tight and universally acceptable definition of what the condition is. This has become a real difficulty for PA, as already discussed.
Most importantly of all, however, it will depend on the prevailing attitudes, global or local, regarding the commonness and importance of the condition, and hence the degree of enthusiasm regarding the need to make the diagnosis. Thus the epidemiology of primary aldosteronism in Brisbane, Queensland, Australia, might be vastly different from that in Dallas, TX, USA. Norman Kaplan has argued persuasively that PA is being over-diagnosed in Brisbane and elsewhere and that screening for it is not only unnecessary but also a waste of “the health dollar”. These fundamental differences in approach and inevitable outcomes (normokalemic PA will rarely be diagnosed in Kaplan’s clinic) illustrate that, most importantly of all, the epidemiology of PA will vary greatly from place to place depending mainly on whether or not it is sought in the local community, illustrating a very important truism—“If you don’t look, you certainly won’t find”.

Such differences of opinion are healthy and form the basis on which science, and certainly biological science, makes its stuttering but seminal advances. It is only problematic if it results in (a) patients who deserve and require specific treatment missing out on such treatment, which is very serious, or (b) health-directed public funds being spent unnecessarily, unproductively and therefore unwisely. This is less serious, but obviously best avoided. In the case of PA, lack of screening is indeed very serious. Dedicated clinicians who follow individual patients closely are strongly moved by unnecessary, permanent morbidity caused by unrecognised and therefore not specifically treated PA, when cerebral, cardiac and renal damage occurs and is irreversible. This is preventable (by screening) and results from failure to recognise PA early in its natural history, and hence make use of the specific and highly effective medical and surgical (in carefully selected cases) treatments available.

**Current Recommendations for Screening, Including “The Endocrine Society” Guidelines**

Clinical management guidelines issued from time to time by the Endocrine Society (United States) have proved useful to endocrinologists worldwide. Given widely divergent opinions on the prevalence and management of primary aldosteronism over the 50 years since its first description, the Endocrine Society convened a panel of clinicians experienced in the management of primary aldosteronism under the chairmanship of John Funder, of Monash University, Melbourne, Australia. Funder is a medical graduate but not a clinician, with a long and distinguished research record in mineralocorticoid receptors and aldosterone action based predominantly on animal studies. As well, he closely follows clinical studies concerning PA and was very interested in the initial clinical trials in hypertension and heart failure of the aldosterone antagonist, eplerenone, which has negligible interaction with the androgen receptor when compared with spironolactone. The panel addressed the issues of screening (who and how to screen), how to establish a firm diagnosis and subtype differentiation and how to treat PA. A good attempt was made to identify patient groups especially deserving of screening, including those with an expected
higher incidence of PA, such as patients with resistant hypertension, with spontaneous hypokalaemia or with a family history of PA [59]. The guidelines were published in J Clin Endocrinol Metab in 2008 [27] and met with a mixed reception, particularly in Europe, especially with regard to the universality of screening and whether adrenal venous sampling is necessary. Resolving these controversial issues depends particularly on to what extent each patient is assessed as a unique individual and to what extent the patient, following very full discussion, is involved in decision-making. Rather than advocating “one size fits all” and seeking a consensus, an alternative point of view which I strongly favour is to ask the clinician to consider local facilities and local expertise as prime determinants of best possible practice in that patient [36]. Recently, John Funder, who considers PA to be common but treats no PA patients, and Norman Kaplan, a clinician who considers PA to be uncommon and admits to seeing few patients with PA, agreed that the best and cheapest way to deal effectively with PA would be to include low-dose aldosterone antagonists such as spironolactone, eplerenone and amiloride as part of first-line treatment of hypertension [24–26, 52]. Clinicians experienced in managing patients with PA as well as other patients with hypertension could find the recent Funder/Kaplan proposal unattractive for several reasons. The incidence of hypertension increases with age, and the majority of hypertensive patients are old enough to be experiencing a decline in renal glomerular function. Administration of either potassium supplements or drugs which reduce potassium excretion has been known for at least 40 years to carry significant risk of hyperkalaemia in those with declining renal function. For example, the approval of amiloride for clinical use was followed by reports of serious hyperkalemic episodes. Despite well thought out, enthusiastic education of doctors regarding the use of eplerenone and spironolactone in heart failure patients, with apparent safety in tightly controlled clinical trial conditions, most hypertensives are treated by busy general practitioners (GPs or primary care doctors) who are unfamiliar with the delayed onset and offset of the antihypertensive and volume-depleting effects of aldosterone blockade. It is highly unlikely that the slow, cautious approach employed by endocrinologists, nephrologists and cardiologists prescribing these medications would be followed by all GPs, who may be following hypertension treatment guidelines which recommend incremental increase of medication until a target (often impossible to reach in older patients) is reached. Ideally, the dosage of spironolactone, eplerenone or amiloride should be adjusted based on serial measurements of plasma levels of renin, aldosterone, creatinine and potassium. For renin levels to be interpretable, medications which affect them would need to be avoided, or at least taken into account, which requires experience and skill and takes time. This is difficult enough in specialist practice and unlikely to be possible in primary care, where many doctors may also not be sufficiently familiar with the renin–angiotensin–aldosterone system in clinical practice. Because of renin becoming unsuppressed, once aldosterone antagonism is introduced into a hypertensive patient’s treatment, it will be impossible, without ceasing it, to diagnose unilateral aldosterone production due to an APA by adrenal venous sampling, depriving such patients of the possibility of cure and condemning them to life-long drug therapy, probably in increasing doses. As well, some clinicians and institutions will still be
recommending screening of all hypertensive patients for PA, preferably before medications are commenced. These will most likely include the Greenslopes Hospital Hypertension Unit and the Japan Endocrine Society [77] into the foreseeable future.

Conclusions

We have been forced to directly address the question of the definition of PA, not at the beginning of a chapter entitled “Epidemiology and need for screening”, as the reader might reasonably expect, but at the end, because it is constantly evolving and inevitably the subject of controversy. PA is certainly not now as Conn described it, hypertension with severe hypokalaemia. It has moved through normokalemic PA to normotensive PA and, perhaps, even to enough unsuppressible aldosterone in the context of falling nephron numbers and a persisting high salt intake to cause hypertension with suppressed renin, as in the Framingham Offspring study of subjects over 50 years of age [65]. Will PA finally be defined by a variety of genetic mutations either in the adrenal only or in the entire genome? Only time will tell. While knowledge of the genetics of PA began 21 years ago with the discovery of mutations causing the rare glucocorticoid-remediable familial form of PA [55], it is only very recently that meaningful breakthroughs have followed, identifying somatic adrenal and genomic mutations causing PA of varying severity (FH-III), the former not uncommon and the latter rare. If the genetic bases of the more common FH-II can be elucidated, then we might be in a position to identify with certainty many subjects with PA, or at least an inherited tendency to develop PA, following a single blood test. That would give us new, clearer definitions for at least some subtypes of PA on a genetic rather than a clinical, biochemical or morphological basis.

In the meantime, agreement on epidemiology depends critically on widely accepted “working” definitions, not yet available. We have therefore considered only the various estimates of prevalence, how these have changed over time and how dependent they are on criteria used to identify hypertension and to identify PA. They have varied widely, from 2 to 30 % for prevalence of PA in primary care and from 5 to 30% in secondary care. A reasonable guess might be at least 2.5 % in primary care and at least 7 % in secondary care. There seems no doubt that PA prevalence in resistant hypertension is very significant, at least 10 % and probably much higher.

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