Renin, Genes, and Beyond
40 Years of Molecular Discoveries in the Hypertension Field

Brian J. Morris

Little did I know when I attended the Council for High Blood Pressure Research meeting in Cleveland, Ohio in 1975 when Lewis K. Dahl received the major award for demonstrating the crucial role of genetics and salt in hypertension (Figure 1) that one day I would receive the award later to be named in Dahl’s honor, nor did I know that this award would include recognition of my own contributions to an understanding of the genetics of hypertension. Lewis Dahl in fact shared the inaugural Ciba Award that year with Jim Davis, who, with Felton Davis at Ciba, had established the laboratory during the first year of a C. J. Martin Research Fellowship from the National Health and Medical Research Council of Australia. It was the only year of my life that I would include recognition of my own contributions to an understanding of the genetics of hypertension. Lewis Dahl in 1975 when Lewis K. Dahl received the major award for demonstrating the crucial role of genetics and salt in hypertension (Figure 1) that one day I would receive the award later to be named in Dahl’s honor, nor did I know that this award would include recognition of my own contributions to an understanding of the genetics of hypertension. Lewis Dahl in fact shared the inaugural Ciba Award that year with Jim Davis, who, with Felton Davis at Ciba, had established the award, and Walter Kempner. I was, at the time, in Jim Davis’ laboratory during the first year of a C. J. Martin Research Fellowship from the National Health and Medical Research Council of Australia. It was the only year of my life that I engaged fully in whole animal pathophysiology and enjoyed this valuable experience. Lewis Dahl was not at the conference, however. He was, unfortunately, dying of cancer at the time and listened by telephone link to his hospital bed as the award was presented to him. It was also in 1975 when the Executive of the Council for High Blood Pressure Research voted to establish the present Journal. The first issue was in 1979 and I was asked to be on the Editorial Board.

Now, I recount in brief my own personal journey in the hypertension field (Figure 2). This started with prorenin, which led me to clone its gene and study the cell and molecular biology of renin and renin gene expression. A study I undertook of a renin gene polymorphism became the first in the molecular genetics of hypertension field. My studies of renin expression and hypertension genetics continue.

In the Beginning
My interest in health sciences was sparked at the age of 15 by a touring American author, Lelord Kordel, promoting his book, Eat Right and Live Longer. I was quickly converted. My high school year book honed in on my promotion of this unpopular topic, concluding that my probable destiny was “Johnny Appleseed.”

Discovery of Prorenin
During undergraduate studies at the University of Adelaide, I became involved in the renin field purely by chance. In November 1970, while looking for a vacation project, I stumbled into a laboratory where Eugenie Lumbers had just finished her doctoral studies with Sandy Skinner. She explained how she had been puzzled by some peculiar renin values obtained using the Skinner method. Renin was stable to pH 3.3, so dialysis of samples at this pH was used in the “plasma renin concentration” assay to destroy angiotensinases before incubation with substrate at pH 7.4. Eugenie found that the pH 3.3 step increased renin activity 10-fold in both amniotic fluid and plasma. She had submitted a paper describing this “inactive renin” to Nature, but it was rejected. So I decided to take up the inactive renin challenge. During a lively discussion after Eugenie spoke at an evening seminar in the Adelaide Hills, I recall blurring out the words, “what about pepsin?” Pepsinogen is activated during acidification, involving an action of pepsin itself. The next day, we immediately set about testing the effect of pepsin and found strong renin activation! In December 1970, Eugenie sent her paper to Enzymologia and was now able to state, “The mechanism of activation of renin during exposure to pH=3.3 to 3.6 is unknown, although investigations in progress indicate that renin may be enzymatically activated.”

When we published the protease data, we “suggested that activation of renin therefore involves conversion of an inactive form of the enzyme to an active form.” We also proposed cathepsin B as a likely candidate for activation within the juxtaglomerular cell, a concept that held sway until recently.

Any further work on inactive renin being a precursor form had to be put on hold. Eugenie left for postdoctoral studies at Oxford and I, attracted by the charismatic Colin Johnston and his enthusiasm for the possibility of an intrarenal renin-angiotensin system, moved to Melbourne to begin a PhD. I soon found that Colin, like others, was decidedly skeptical about this “inactive renin stuff.”

The First Real Evidence for an Intrarenal Renin-Angiotensin System
The first year of my PhD was spent in Colin’s laboratory in the Department of Medicine, University of Melbourne, Austin Hospital, where Austin Doyle was chairman. At the end of 1972, Colin’s laboratory moved to the Monash University...
Three Years as a Postdoc in the United States
In Jim Davis’ laboratory, I enjoyed learning whole animal cardiovascular physiology and experiencing the outdoor life of middle America. But it did take me away from my prorenin agenda. I had married Julie Robinson, John Funder’s technician, before leaving Australia. It was this 21-year-old who, aspiring to the bright lights of the big city, “encouraged” me, fortuitously as it turned out, to move to the University of California, San Francisco, in mid 1976.

There, in Fran Ganong’s laboratory, I worked on renin secretion in vitro,10 and, via another Australian, Ian Reid, I entered the world of extrarenal renin-angiotensin systems.11,12 I also localized the cells that produce angiotensinogen.13 In this environment, I extended my research on prorenin.14–16 I indulged my enjoyment of field hockey at University of California–Berkeley and played soccer in Golden Gate Park, where I met Joseph Martial, followed by other pioneers of rDNA technology, including John Shine, Peter Seeberg, Axel Ullrich and John Baxter, a colleague of John Funder’s. I convinced Baxter to allow my young wife to work in his laboratory for free. In the meantime, I learned that indulging my passion for laboratory work should not include Christmas, even if testing whether cathepsin D might activate prorenin seemed preferable. Incredibly, despite rushing off a paper to the Journal of Clinical Endocrinology and Metabolism, the Editor died during review, thus delaying its publication inordinately.14 In the Baxter environment, Julie met Bob Ivary, and we divorced. I did not remarry until 1993, to Lilian Mijatovic, who has made me the proud father of 2 delightful daughters.

Direct Demonstration of Intracellular Synthesis of Prorenin
In 1978, my 3-year U.S. visa was soon to expire just as an academic position was advertised at the University of Sydney. I got the job and moved back to Australia. Now I had my own laboratory, albeit with very little money and a laboratory straight from the 19th century. I am still in the Anderson Stuart building, but with a renovated air-conditioned laboratory, which is highly desirable for molecular biology experiments.

At the outset, with my first graduate student, Daniel Catanzaro, we performed in vitro translation and pulse-chase experiments that successfully elucidated the pathway for renin biosynthesis, demonstrating directly for the first time the synthesis of prorenin, and then publishing our findings ahead of competing laboratories.17 I also introduced the new rDNA technology to Sydney. Along the way, I documented many proteases that could activate prorenin18 and provided direct evidence that plasma kallikrein activates prorenin in plasma.19

Renin Gene: Molecular Cloning of Mouse Renin cDNA Reveals Structure of Prorenin
My exposure to rDNA pioneers at University of California, San Francisco, made me decide to clone renin. John Shine had returned to Australia 1 year earlier and had set up Australia’s first rDNA Laboratory at the Australian National University. At a conference in Thredbo in 1980, I convinced John that we should collaborate to clone renin. I chose male
revealed the expected exposure on the surface of prorenin of
in my laboratory building a physical model (Figure 3). This
against a related aspartyl protease, spent a summer “vacation”
lege, University of London, who had been modeling renin
DNA.30 It also revealed a tiny exon, encoding 3 amino acids
sequences confirmed the in vitro biosynthesis data, revealing
mouse submandibular gland because it contains high concentrations of renin.20
Danny prepared RNA extracts of submandibular gland and
made a cDNA library. One clone was picked at random in the
Shine Laboratory to test sequencing protocols and, quite by chance, it exhibited a coding sequence homologous to porcine
tissue kallikrein.21 While the Shine Laboratory immersed itself in cloning and characterizing the mouse kallikrein gene
family, my laboratory used the kallikrein cDNA as a probe and cloned the first human kallikrein gene,22 and then
localized it to chromosome 19q13.3.23 We also cloned the 2 human cardiac myosin heavy chain genes.24
In the meantime, by using renin antibodies to screen expression clones, we isolated 2 mouse renin cDNA,25–28
Rougeon and Corvol did, too, and were the first to obtain the complete sequence.29

**Human Renin Gene, REN, Cloned**
During a visit to San Francisco, I met with Peter Seeburg and
drove in his old wreck of a car, with its ashtray overflowing
with cigarette butts, to Genentech, where Axel Ulrich handed
me a sample of the Maniatis human genomic library to take
back to Australia. With John Shine we screened this using the
mouse renin cDNA as a probe and obtained 2 clones that
together encoded the entire human renin gene.28,30 We published
the sequence in 1984 at the same time as 2 other laboratories, although our sequence was by far the longest
because it included intronic sequences and more flanking
DNA.30 It also revealed a tiny exon, encoding 3 amino acids
not seen in mouse renin, that I termed “exon 5A.” The gene
was then localized to chromosome 1q42.31,32
The structure of the mouse and human renin coding
sequences confirmed the in vitro biosynthesis data, revealing
a 2-kDa signal peptide, a 5-kDa pro segment, and a 38-kDa
renin sequence.30,33 Stephen Foundling from Birkbeck Col-
lege, University of London, who had been modeling renin
against a related aspartyl protease, spent a summer “vacation”
in my laboratory building a physical model (Figure 3). This
revealed the expected exposure on the surface of prorenin of
likely sites of cleavage by proteases, structural features
involved in renin’s catalytic reaction with angiotensinogen,34
and a possible basis for the species-specificity of the latter.35
The sequence around the “activation site” residues explained
why a diversity of proteases can activate prorenin.33 Because
the signal peptide was encoded on exon 1 separately from the
rest of the molecule, I proposed that an alternate transcript
lacking exon 1 could produce an intracellular renin.53
John Baxter, who had helped fund the cloning work via his
company, California Biotechnology, appointed John Shine as
Scientific Chief, and sufficient quantities of human renin
were generated from expression clones to enable structural
studies to help design novel renin inhibitors for clinical use.
Others have used such structural approaches to design
inhibitors of the closely related human immunodeficiency
virus aspartyl protease. I later developed a quite different
interest in human immunodeficiency virus, subsequent to
inventing and patenting in 1987 the first polymerase chain
reaction-based diagnostic test for detection of human papil-
lomavirus types that cause cervical cancer.36–40 Because both
of these sexually transmitted viruses and other infections in
women, as well as in men, are prevented by male circumci-
sion, I was drawn into the male circumcision field over the
years and have become an authority on the extensive medical
benefits of this simple surgical procedure.41–43 authoring the
most extensive academic literature review of male circumci-
sion (http://www.circinfo.net).

**Control of Renin Gene Expression: Studies of Response
in Renin mRNA to Physiological Stimuli**
After the first renin mRNA in situ hybridization histochem-
istry experiments,44 I showed that stimuli to renin secretion
also affect renin mRNA expression.45–48 These included
hormones, a low-sodium diet, and angiotensin-converting
enzyme inhibitors.45,46 In addition, with Judith Whitworth,
changes in renin mRNA in kidneys, adrenal, and hypothala-
mus were documented in 1-kidney, 1-clip hypertension49 and
other rat models.49–52 I showed that the heart was normally
devoid of renin mRNA, but a low-sodium diet plus enalapril
switched-on expression.57

**Regulation of Transcription of the Renin Gene**
After extending the 5’-flanking DNA sequence,53 transient
expression assays involving a range of promoter constructs
showed that the renin promoter was weak.54,55 In a collabo-
ration with Curt Sigmund’s Laboratory at the University of
Iowa, we identified an array of different regions in the human
proximal upstream DNA that had weak positive or negative
effects on promoter activity56 and found a silencer element in
intron 1.56

**How cAMP Stimulates the Renin Promoter**
cAMP was known to trigger renin secretion from renal
juxtaglomerular cells (Figure 4A). So, I arranged a collabo-
ration with Willa Hsueh in Los Angeles and we identified a
functional cAMP response element (CRE) located 218 to 222
bp upstream of REN.57,58 We suggested this would be an
attachment site for CRE binding protein to activate REN transcription. But was this true?

With Curt, we stimulated adenyl cyclase using forskolin and showed that cAMP, via activation of protein kinase A, caused phosphorylation of CRE binding protein, which in a heterodimer with already-phosphorylated activating transcription factor-1 (ATF-1), bound to the CRE to activate REN promoter (Figure 4B). We suggested that rapid phosphorylation and dephosphorylation of CRE binding protein might facilitate tight regulation of transcription in response to continuous variation in physiological stimuli. We also noted non-CRE binding protein-related mechanisms were involved as well. In 2000, Louise van der Weyden in my laboratory found a capacity for cAMP-mediated REN promoter stimulation via purinergic pathways involving the P2Y<sub>11</sub> receptor.

**Importance of a Strong, Far-Upstream Enhancer**

I realized that the REN, with its weak promoter and a strong, far-upstream enhancer fitted the on/off (or “variegation”) model of gene expression. With David Adams, a graduate student, this was confirmed in vitro. But we needed in vivo support. So, David and his girlfriend (later wife), Louise, made constructs for targeted deletion of the enhancer. Renin enhancer knockout mice were generated and, with Geoff Head, a colleague and radiotelemetry expert at the Baker Heart Research Institute in Melbourne, were found to have lower blood pressure, marked depletion of renin in juxta-

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**Figure 4.** A, The role of cAMP in stimulation of human renin secretion and renin gene (REN) transcription, as well as posttranscriptional control of renin expression via stimulation of proteins that bind to the 3'-UTR to alter REN mRNA stability. B, REN promoter activation involves cAMP response element (CRE) binding protein-dependent and CRE binding protein-independent pathways in Calu-6 cells. Forskolin, via cAMP, activates protein kinase A, which in turn phosphorylates CRE binding protein, which then forms a heterodimer with already-phosphorylated activating transcription factor-1 (ATF-1). The CRE binding protein ATF-1 heterodimer then binds to the CRE 218 to 222 bp upstream of REN to activate transcription. C, Proposed mechanism for destabilization of renin mRNA. This involves binding of hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein) β-subunit to a destabilizing element in the distal 3'-UTR, leading to recruitment of the cell’s degradation machinery.
glomerular cells, and macula densa hyperplasia. They exhibited a blunted response in renin mRNA after 1 week of low salt plus enalapril and, as a result, were unable to replace renin stores lost through secretion under these stimulated conditions, therefore explaining their reduced blood pressure. The increase in plasma renin was also blunted, as were stress responses, but not prepulse inhibition.

Posttranscriptional Control of Renin Gene Expression

With Curt, posttranscriptional control also seemed very important. cAMP increased renin mRNA stability but this appeared to be indirect, likely involving an action on another gene or genes to account for the 100-fold increase in renin mRNA in response to forskolin (Figure 4A).

In a collaboration with Peter Leedman at the University of Western Australia, David and Louise showed how human renin mRNA stability is controlled (Figure 4A). We identified an adenosine-cytosine (AU)-rich stem-loop sequence in the distal 3'-untranslated region (UTR) that serves as an instability element (Figure 4C). More than 1 dozen cellular proteins bound to the 3'-UTR in vivo. These included HuR and CP1, well-known to stabilize other mRNA, and hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein) β-subunit (HADHB), a mitochondrial protein involved in β-oxidation. Binding was increased by forskolin. Traces of HADHB were also seen in the cytoplasm and nucleoli, whereas HuR was nuclear, albeit absent from nucleoli, and CP1 was widespread, colocalizing with serine-arginine-rich splicing factor proteins in nuclear speckles. HADHB is a thiolase and we found inhibition of thiolase activity increased renin protein, as did siRNA-mediated knockdown of HADHB, which greatly increased the half-life of renin mRNA. But knockdown of HuR halved this. HADHB was enriched within juxtaglomerular cells, whereas the others were distributed throughout the kidney. We suggested that by binding to the AU-rich region, HADHB recruits the degradation machinery of the cell to destroy renin mRNA (Figure 4C).

The various investigations described highlight the diverse mechanisms that achieve overall regulation of renin expression. More details can be found in various invited reviews.

An Investigation of Zis as a Renin Regulator Goes Off Track in a Good Way

A protein initially termed “Zis” is downregulated in parallel with renin during dedifferentiation of juxtaglomerular cells in prolonged primary culture. To find whether Zis has a role in control of renin expression, David cloned the mouse and human homologs, Zis being renamed Zfp265 and ZNF265 by the respective nomenclature committees. In collaborations involving John Rasko in Sydney, Akila Mayeda in Florida, and Stefan Stamm in Germany, we found that ZNF265 was a spliceosomal protein. It bound to core-splicing proteins U1-70K and U2-AF53 and stimulated alternative splicing. It could also bind cyclin B1 mRNA, suggesting that this ubiquitous factor might be a cell-cycle controller. Thus, its loss during culture could have been contributing to the dedifferentiation of juxtaglomerular cells after 1 week in culture and the concomitant loss of renin. In collaboration with Joel Mackay, a protein structural biochemist at the University of Sydney, the structure of the first zinc finger was solved and ZNF265, now rebadged as ZRANB2, was found to regulate alternative splicing via a direct interaction with pre-mRNA at consensus 5' splice site sequences. My laboratory demonstrated roles for other proteins in alternative splicing.

Molecular Genetics of Essential Hypertension: The First Publication in This Field

After a request by another graduate student on campus to provide human renin cDNA in a study of Charcot-Marie-Tooth syndrome, I quickly realized that approximately one-third of the leukocyte DNA samples from her healthy adult control subjects would be from those with essential hypertension. So, I compared the genotype data for a HindIII polymorphism in the human renin gene in hypertensive and normotensive subjects. The publication arising represented the first molecular genetic study in the field of hypertension. Although there was no association, it began a new objective—to find the genetic basis of essential hypertension. Many association studies followed, some being mentioned in various reviews. I will now highlight several

<table>
<thead>
<tr>
<th>Status</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>HT with 2 HT parents</td>
<td>84</td>
<td>7</td>
<td>0.077</td>
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<tr>
<td>HT with 1 HT parent</td>
<td>77</td>
<td>3</td>
<td>0.038</td>
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<tr>
<td>HT with 1 HT sibling</td>
<td>198</td>
<td>4</td>
<td>0.020</td>
</tr>
<tr>
<td>Normotensive</td>
<td>89</td>
<td>1</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Trend analysis for proportions:
Regression of $P = \text{allele 1}/(\text{allele 1} + \text{allele 2})$ on status:
Slope $= -0.022$, standard error $= 0.0082$, $Z = 2.72$
Overall $\chi^2$ (5 degrees of freedom) $= 8.1$, $P > \chi^2 = 0.043$ (independent of trend)
$\chi^2$ (1 degree of freedom) for trend $= 7.4$, $P > \chi^2 = 0.0066$

HT indicates hypertensive.
molecular genetic concepts that I contributed during this research.

Importance of Choosing Only Subjects With Two Hypertensive Parents
At the outset it seemed important to be judicious in choice of subjects. We enlisted only subjects whose blood pressure status was the same as both of their parents. This led to enrichment of the genetic component of hypertension (Figure 5). Not surprisingly, the hypertensive patients had earlier onset (32 ± 10 SD years) and more severe (175 ± 24/109 ± 18 mm Hg) hypertension than unselected hypertensives. William Wang, a former graduate student who continued to collaborate, showed mathematically the extent of the higher genetic risk of hypertension for subjects having 2 hypertensive parents when compared to subjects having only 1 hypertensive parent or sibling90 (Table).

As a result of this improved biological power, the level of significance in our positive association studies was stronger than that found by others for study groups of comparable size. Examples include our data for the T825 allele of the C285T polymorphism of the G-protein β3 subunit gene (GNB3) with hypertension and blood pressure,90 the A1166C variant of the angiotensin II type 1 receptor gene (AGTR1),91 and the T–344C and A6547G polymorphisms of the aldosterone synthase gene (CYP11B2), especially after analysis of haplotypes,92 among others.93–98 It also might have helped explain why we found no association with hypertension in the case of polymorphisms in certain additional genes for which positive association findings had been reported.99–105 Our glucocorticoid receptor gene (NR3C1) data were, however, weak.98

Major Role for Uncommon Coding Variants in Some Hypertensive Patients
It is now generally accepted that uncommon polymorphisms, present in ≤1% of the population, make a major contribution to complex polygenic conditions in the small proportion of patients having each.106,107 It could explain why even very large genome-wide association studies have been able to find only a small proportion of the expected number of causative genes. A current challenge is to find this “missing heritability.”106

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**Figure 6.** Mechanism by which the uncommon (Ser40) variant of the glucagon receptor Gly40Ser polymorphism most likely causes essential hypertension. w/t indicates wild-type.

**Figure 7.** The p36 locus on the short arm of chromosome 1 that my laboratory linked to essential hypertension and hypercholesterolemia has since been confirmed as a locus for hypertension and blood pressure by others and in recent, large, genome-wide association studies.
In a study of a functional coding variant (Gly40Ser) in the glucagon receptor gene (GCGR), I found that whereas the minor allele was present in only 1% of normotensive subjects, in hypertensive subjects its frequency was an astounding 5-times$^{108}$ to 7-times$^{109}$ higher. The use of patients with 2 hypertensive parents was crucial to revealing this association.$^{109}$ Figure 6 shows the likely mechanism by which the Ser40 variant causes hypertension.$^{110}$–$^{112}$

**Survivor Bias**

After reporting an association of the I allele of the angiotensin-converting enzyme I/D polymorphism with hypertension,$^{113}$ others found an association of the D allele with myocardial infarction.$^{114}$ To solve this anomaly, I divided up our genotype data by age group and discovered depletion (from heart attack?) in D allele carriers in the older hypertensive subjects.$^{115}$ I later saw something similar for a promoter variant of the inducible nitric oxide synthase gene (NOS2A).$^{116}$ Researchers therefore should check their data to see whether any association applies to younger and older patients. If it does not, then a different interpretation may apply.

**Other Molecular Genetic Research**

In the early 1990s, I started collecting hypertensive sibships for a genome-wide linkage study, first identifying a locus for hypertension and hypercholesterolemia at chromosome 1p36.$^{117}$ This has now been confirmed by others$^{118}$,$^{119}$ (Figure 7). We discounted 1 candidate$^{120}$ and identified additional loci across the genome.$^{121}$
I tested a number of the hypertension markers in patients with other “metabolic syndrome” disorders and found associations with obesity for variants in the low-density lipoprotein receptor gene (LDLR),\textsuperscript{12,12} the glucocorticoid receptor gene (NR3C1),\textsuperscript{12–16} and the \(\beta_2\)-adrenocceptor gene (ADRB2),\textsuperscript{12,12} but not the C285T variant of GNB3\textsuperscript{12,12} or others. Association with coronary artery disease was seen for the tumor necrosis factor receptor superfamily member 1B gene (TNFRSF1B),\textsuperscript{12,13} NR3C1,\textsuperscript{13} and NOS2A.\textsuperscript{13} And in studies of type 2 diabetic patients, polymorphisms in TNFRSF1B were associated with diabetic neuropathy,\textsuperscript{12} and NOS2A was associated with diabetic retinopathy.\textsuperscript{13}

**Global Gene Expression Differences in Hypertension**

My current research is genome-wide identification of genes differentially expressed in hypertension using Affymetrix arrays in the spontaneously hypertensive rat\textsuperscript{14} (Figure 8), the hypothalamus of Schlager hypertensive mouse, and kidneys of essential hypertensive subjects.\textsuperscript{13} This work, involving graduate student Francine Marques in my Laboratory, Fadi Charchar, his colleagues in Leicester, and bioinformaticians Jean Yang and Anna Campain, has also implicated several microRNA, as well as pathways involved.

**Perspectives**

It has been a privilege to have had the opportunity of performing research in the hypertension field for the past 40 years. As most researchers in any field know, this can be a bumpy ride for all sorts of reasons. My research has led to the elucidation of how renin is synthesized and how its gene is regulated, as well as the role of various genes in hypertension. My earlier interest in the benefits of a healthy diet has expanded to embrace studies of the molecular mechanisms involved.\textsuperscript{13–19} To succeed in research requires persistence, flexibility, deep thought, hard work, recognition of opportunities, an astute choice of collaborators as needed, and, most importantly, the efforts of talented students and postdocs. I find daily quieting of the mind by meditation to be important, too. A particular enjoyment is publication, especially in good journals such as *Hypertension*. It was gratifying to have been recognized for my contributions to molecular knowledge of renin and the genetics of hypertension by having been chosen for the Dahl Award and Lecture in 2010, and I humbly thank the Council for High Blood Pressure Research.

**Disclosures**

None.

**References**


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