HYPERTENSION is a complex pathophysiological state primarily expressed as chronic high blood pressure (BP). If unchecked and uncontrolled, it affects major vital organs, including the kidney, heart, arteries, adrenals, and brain. As a result, untreated high BP is one of the most important risk factors for stroke, congestive heart failure, myocardial infarction, end-stage renal disease, and peripheral vascular disease (20, 46, 52). Studies from the last several decades have implicated a hyperactive renin-angiotensin system (RAS) as one of many neurohumoral factors participating in the development and maintenance of human primary hypertension (19, 38, 41, 50). Thus it is not surprising that tremendous efforts have been directed toward the understanding of the RAS and its involvement in the control of BP and other cardiovascular functions. Investigations have led to the characterization of both an endocrine and a paracrine/autocrine RAS (Fig. 1).

The endocrine RAS generates circulating angiotensin II (ANG II) by coordinated activities of the kidney (which produces renin), the liver (which produces angiotensinogen), and the lung (which produces angiotensin I-converting enzyme (ACE)). In contrast, the paracrine/autocrine RAS is responsible for the generation of ANG II within a particular tissue. It has been suggested that the circulating ANG II is responsible for most of the “short-term” effects of ANG II (5, 42). These effects include control of BP, arteriolar vasoconstriction, Na⁺, and H₂O reabsorption; renal hemodynamics; cardiac inotropic effects; control of ischemia, aldosterone secretion by the adrenals, water consumption, and vasopressin secretion; and baroreflex and regulation of sympathetic activity by the central nervous system (Fig. 1). In contrast, the tissue ANG II, produced by the paracrine/autocrine RAS, seems to be important in the “long-term” effects of ANG II. They primarily include regulation of cardiac hypertrophy and vascular remodeling of the arteries (Fig. 1). Thus coordinated activities of both the circulating and tissue RAS are important in angiotensin’s effect on BP, and alterations in the balance between the two have been implicated in the development and establishment of hypertension.

The understanding of the circulating and tissue RAS has been highly relevant in the design of traditional therapy for the management of hypertension. Traditional agents that either inhibit the formation of ANG II (renin and ACE inhibitors) or the actions of ANG II [AT₁-receptor (AT₁R) antagonists] have been highly successful as anti-hypertensive drugs. These agents are reliable and easily affordable, and their short duration of actions makes them an excellent choice for reversible short-term drugs (Table 1). However, there are major limitations and disadvantages with the use of this traditional treatment. Because their effects are short lived, they have to be administered on a regular basis. In addition, traditional therapeutic agents produce significant side effects. These limitations have created a major compliance problem with patients (Table 1). Although effective in the control of high BP, these agents do not always reverse or prevent other morphological and pathophysiological complications associated with hypertension. Finally, these agents are excellent in the control of hypertension but hold little promise in its cure. In summary, traditional therapy based on inhibition of the RAS has been highly successful in the control of hypertension, but it possesses major disadvantages. As a result, there is a need for improvement in an attempt to cure this disease.

From recent advances in the field of gene delivery/gene transfer coupled with our better understanding of RAS pharmacology, many investigators have begun to explore gene therapy as a useful and improved method of treatment for hypertension. On a conceptual level, such an approach could offer major advantages over the traditional therapy. It could eliminate the issue of compliance, because long-term and/or permanent antihypertensive effects could be achieved. Genetic control also could be influential in its cure if appropriate target genes controlling hypertension could be identified. Finally, gene therapy may be the key to minimizing or eliminating side effects inherent with traditional therapy. Thus the key for the successful use of gene therapy for hypertension will be based on the following: 1) identify appropriate target gene(s); 2) develop an ideal vector system that would be able to deliver the targeted gene with high efficiency; and 3) control the expression of transgene when desired. The objective of this editorial is to discuss these issues in an attempt to
provide some perspective for the use of gene therapy for hypertension. In addition, we summarize some data from our research group on the use of the antisense approach in the long-term control of hypertension.

RAS as a target for gene therapy. Traditional therapy has proven that both ACE inhibitors and AT₁R antagonists are highly effective antihypertensive drugs (1, 4, 17). For example, ACE inhibitors not only exert effects on BP by inhibiting ACE and thereby decreasing levels of vasoconstrictor ANG II but also they regulate the kallikrein system to increase the production of the vasodilatory agent nitric oxide (10, 16, 34). In addition, they influence the fibrinolytic system and oxidative stress pathway to improve endothelial dysfunction (10–12, 16, 34, 49). Numerous clinical trials support this multifunctional aspect of ACE inhibition. Thus it is reasonable to use the RAS as a target for gene therapy. In addition to proven clinical benefits, inhibition of the RAS paradigm can be used to compare the success/failure of traditional treatments with gene therapy.

Inhibition of the RAS at a genetic level has been accomplished by the use of antisense technology. In a normal situation, messenger RNA is synthesized in the nucleus and is transported across the nuclear membrane to the cytoplasm where it undergoes translation involving ribosomes (Fig. 2). Protein produced as a result of translation is appropriately processed and compartmentalized to exert its physiological action. Antisense technology takes advantage of the fact that antisense orientation of RNA for a given protein would hybridize with the active mRNA in the cytoplasm. As a result, normal translation of the mRNA is blocked.
mRNA is degraded, and no translation of the protein occurs (Fig. 2). Thus antisense treatment inhibits translation and decreases the levels of active protein. Both short oligonucleotides and full-length antisense cDNA have been used in an attempt to inhibit components of the RAS. Phillips and his research group (40) were among the first to use antisense oligonucleotides (15- to 18-mer) to angiotensinogen and AT\textsubscript{1}R. They showed that central or peripheral injection of these oligonucleotides resulted in a transient, short-term (7 days) effect in moderately lowering BP in spontaneously hypertensive rats (SHR) (40). Others have used a similar approach (30, 48). These studies were significant in providing conceptual evidence for the antisense approach. However, because of the short transient effect on BP and lack of data on the effects of oligonucleotides on pathophysiological aspects of hypertension, they did not seem to present major advantages over the traditional therapy. Our research group used full-length antisense cDNA for the AT\textsubscript{1}R and utilized a viral delivery method to extend the antihypertensive effects to 3–7 mo with significant prevention of pathophysiological alterations in the renal artery and cardiac tissues (8, 9, 18, 27, 30). These included prevention of hypertrophy, fibrosis, and perivascular necrosis in cardiac tissues. In addition, prevention of endothelial dysfunction, K\textsuperscript{+} and Ca\textsuperscript{2+} channel alterations, and intracellular Ca\textsuperscript{2+} ([Ca\textsuperscript{2+}]\textsubscript{i}) homeostasis has been established in the renal vascular system. Collectively, these studies have indicated that antisense (short or long) to angiotensinogen or AT\textsubscript{1}R could be used to inhibit the RAS at genetic levels with potentially beneficial effects on hypertension.

The key issue is how to best deliver the antisense so that it can be appropriately incorporated into the ANG II target tissues for a long-term transduction process. In the following section, we discuss various delivery systems and describe an ideal vector for transduction of antisense for the RAS components.

Antisense delivery vehicles (vectors). The key to success in gene therapy is primarily dependent on the use of an "ideal vector" that can be applied for the delivery of a given gene into relevant target tissues. The objective is that the transgene be expressed in an appropri-
ate quantity and for a long enough duration to exert its beneficial effects. The time, quantity, and tissue specificity will, of course, vary from a given gene type to the pathophysiological conditions it is designed to correct. Thus the definition of an ideal vector would not be a general one but would depend on a particular physiological/pathophysiological situation. For example, an ideal vector for long-term or permanent control of hypertension should have the following characteristics: (1) it should be able to integrate into a specific location of the chromosome for a long-term expression of a given transgene; (2) the vector genome should be easily manipulated to introduce large segments of DNA; (3) it should be conveniently produced in large quantities containing high concentrations of viral particles \( [>1 \times 10^8 \text{ colony-forming units (cfu/ml)}] \); (4) the vector should be constructed so that tissue-specific expression can be appropriately regulated; and (5) it should have no or very little immune response. In contrast, if one is interested, for example, in using gene transfer for inhibition of restenosis after angioplasty, an ideal vector would not be the one that could produce a long-term effect but rather should be able to cause an immediate and robust transduction of a relevant gene in a transient fashion. It also would be one that is specific for the restenotic site.

Currently, there are a wide variety of systems available to deliver transgenes in vitro and in vivo (15, 45). Table 2 summarizes several gene-delivery vehicles. Naked DNA in the form of oligonucleotides or its facilitation with the use of liposomes or other lipophilic agents has been a method of choice to deliver DNA across the plasma membrane. This method is safe, does not involve viral vectors, and can be successful in many in vitro and some in vivo situations (23, 33, 54). However, it suffers from having high cytotoxicity, poor efficiency, low selectivity, and low transduction. To overcome problems of poor efficiency and toxicity, Dzau and his collaborators (35, 36) have used the hemagglutinating virus of Japan (HVJ) -liposome delivery method. Decoy oligonucleotides to transcription factor E2F have been delivered with the help of HVJ in the carotid artery to block neointimal hyperplasia (35, 36, 47). Although improved, this method still suffers from some of the same problems outlined for the liposome-mediated delivery system. Receptor-mediated delivery of DNA, on the other hand, is a highly selective method. It is based on the principle that DNA combined with a specific ligand can be internalized across the plasma membrane by a specific receptor-mediated mechanism. For example, a given sequence of DNA of interest could be coupled with the asialoglycoprotein for its selective delivery into the liver, based on the fact that a majority of asialoglycoprotein receptors are localized in the liver (31). Despite being highly specific, the ligands bound to DNA are difficult to design, and the method has limitations because not many cells or tissues express exclusive receptors.

Viral vectors, on the other hand, have become increasingly popular vehicles to deliver genes. This is, in part, a result of rapid growth in the developing of “humanized” viral genomes, which are highly efficient and simple to use for scientists who are not virologists. In a humanized viral vector, all the genes and promoters that have the slightest chance of expressing in humans are deleted. As a result, the humanized viral particle is practically incapable of producing and exerting adverse effects in humans. In addition, they have the inherent advantage of recognizing specific receptors on host tissues, thus providing an efficient mechanism for their delivery across the plasma membrane. Both RNA and DNA viral vectors are available, and each of them has its unique advantages. For example, a retroviral vector has a high infection efficiency of transduction and integrates into DNA for long-term expression of transgene. Retroviral vectors are excellent in their ability to infect dividing cells. However, they have a limited ability to infect non-dividing cells. More importantly, excellent packaging cell lines are available, which makes it possible to produce high-titer virus particles. Our studies have established that the retroviral vector could successfully be used to transduce ATR antisense (AS) expression in neurons and astroglial and vascular smooth muscle cells in vitro (28, 29). The antisense is incorporated into the host DNA and expressed subsequently on a long-term basis. As a result, there is a

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significant decrease in the number of AT\(_1\)Rs and AT\(_1\)-mediated cellular responses (9, 18, 27, 28). Intracardial injection of retroviral particles containing AT\(_1\)R-AS in 5-day-old rats results in a long-term expression of AT\(_1\)R-AS in various ANG II target tissues such as the heart, kidney, adrenals, arteries, etc. (18). The expression of AT\(_1\)R-AS begins as early as 3 days after injection and is maintained throughout adulthood. Figure 3 shows a representative experiment for the integration of viral DNA and expression of AT\(_1\)R-AS in tissues from a 210-day-old rat. DNA and total RNA were isolated and subjected to PCR and RT-PCR to determine the integration and subsequent expression of AT\(_1\)R-AS, respectively. There was a significant integration of AT\(_1\)R-AS (Fig. 3A) in such angiotensin target tissues as heart, kidney, and adrenals. This was associated with a robust expression of AT\(_1\)R-AS transcripts. This observation clearly indicates that, despite traditional wisdom, retrovirus has an excellent capability to infect slowly dividing and in some cases nondividing cells. Despite these advantages, there are some concerns regarding its immunological responses in the host and lack of knowledge about its integration location in the genome. However, new generations of retroviral vectors are better, having lower immunogenicity and improved ability to infect nondividing cells (13, 44).

Lentivirus-based vectors are the most recent addition to the rapidly developing field of vectorology. They are human immunodeficiency virus (HIV)-based highly “humanized” vectors that combine the advantages of retroviral and adenoviral vectors. They infect nondividing cells (37, 51), can be produced with high titer, and transduce an introduced gene on a long-term basis with little immunological response (51). This vector has been successfully used to transduce genes into the brain of adult animals with a long-term expression potential (37). However, because of limited research in this field, little is known about its integration location. Also, a good, reliable packaging cell line is not yet available for packaging of viral particles for large-scale production.

Adenovirus-based vectors have been widely used for gene transduction both in vitro and in vivo for gene therapy (2, 21, 28). Adenoviral vector is highly efficient in delivering AT\(_1\)R-AS in vascular smooth muscle cells and neurons in culture. It causes a decrease in the translation of AT\(_1\)R on a long-term basis followed by attenuation of cellular actions of ANG II that are mediated by this receptor subtype (28). The vector has also been used to deliver kalikrein and atrial natriuretic peptide genes in various animal models of hypertension to produce relatively long (4–5 wk) antihypertensive effects (3, 24, 25). The adenoviral vector-mediated delivery of these genes resulted in their transient expression in various cardiovascularly relevant tissues. Expression of genes was associated with beneficial effects on pathophysiological aspects of hypertension in renal and cardiac function (3, 24, 25). Adenoviral vectors have the ability to infect both dividing and nondividing cells with high efficiency. However, the major disadvantages of this vector have been robust immunogenic potential, transient expression, and a lack of understanding about its site of integration in the genome.

Adeno-associated virus (AAV)-based vectors have gained tremendous interest in gene therapy because of their ability to infect nondividing cells safely and efficiently (6, 14, 22). It infects a wide variety of cells, and the virus integrates into chromosome 19. All the properties demonstrate that AAV is an excellent vector for use in delivering genes in cardiovascularly relevant tissues. However, its major disadvantages include small capacity for DNA (~4 kb) and limitation in large-scale production.

It is quite evident from the above discussion that a viral vector that is safe, has high efficiency and permanent expression, and can be produced in a large scale would be an appropriate vector of choice for use in introducing antisense for various components of the RAS. With the use of such a viral delivery system, one could begin to compare the efficiency and benefits of gene therapy with traditional therapy for hypertension. As mentioned above, our research group has used retroviral vector. In the following section, we summa-

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**Fig. 3.** PCR detection of retroviral integration (A) and AT\(_1\) receptor (AT\(_1\)-R)-antisense (AS) expression (B) in 210-day-old spontaneously hypertensive rat (SHR). Control represents DNA and RNA from PA 317 cells infected with LTR-neomycin-SV40 retroviral vector containing AT\(_1\)R-AS (LNSV-AT\(_1\)R-AS). Experimental protocols followed are essentially as described previously (52).
rize those developments and compare the data with traditional therapy.

Prevention of hypertension by retrovirus-mediated delivery of AT1R-AS. Our initial approach was to determine whether the delivery of AT1R-AS would result in its long-term expression in various AT1R target tissues and would prevent the development of hypertension. The rationale for a choice of such an experimental plan was based on the traditional therapy in the SHR, an animal model for primary human hypertension. Studies have previously established that maintenance of SHR pups on an ACE inhibitor for an extended time period would prevent them from developing high BP (43). Thus we essentially followed a protocol that was proven to attenuate high BP by traditional therapy. A single intracardiac injection of viral particles was carried out in the gene therapy protocol instead of maintaining rats on ACE inhibitor every day. Significant and persistent attenuation of high BP exclusively in the SHR was observed with the AT1R-AS treatment (9, 18, 27, 31). The selectivity of the attenuation of BP was similar and comparable to that seen for ACE-I or AT1R antagonists, i.e., a significant decrease in BP in the SHR with little effects in the Wistar-Kyoto rat (WKY) (27). The attenuation was maintained and persisted throughout the experiment (~210 days). Data from a representative experiment are presented in Fig. 4. An impressive attenuation of high BP of ~30 mmHg in the SHR was maintained. Losartan, an AT1R-specific antagonist, failed to further lower BP in the SHR treated with AT1R-AS (18, 27). Despite this exclusive antihypertensive effect of AT1R-AS in the SHR, the ANG II-induced BP responses were observed in both antisense-treated WKY and SHR (18). This indicates that AT1R activity is influenced by the AT1R-AS treatment in both strains of rats; however, the decrease in basal BP was observed only as a result of a hyperactive RAS in the SHR.

A number of physiological responses to vasoactive agents on renal arterioles were studied to determine whether attenuation of high BP is associated with the prevention of pathophysiological changes characteristic of the hypertensive state. For example, endothelial dysfunction is characteristic of hypertension, and a significant decrease in the acetylcholine-induced relaxation of preconstricted renal arterioles is found in the SHR (8, 9, 31). AT1R-AS gene therapy prevents this dysfunction (Fig. 5). Similarly, receptor- and voltage-mediated vasoconstriction of the renal arterioles was significantly attenuated by AT1R-AS gene therapy such that the SHR vessel reacted like the arterioles of the WKY rat (8, 9, 31). A fundamental reason why renal vascular resistance may be increased in hypertension is alterations in ion channel function in vascular smooth muscle cells. In fact, increases in Ca2+ current density associated with an increase in [Ca2+]i as well as a decrease in K+ current density in the SHR support this notion (30). Gene therapy prevents alterations in Ca2+ handling in the renal arteriole vascular smooth muscle cells (9, 31). Finally, morphological changes in cardiac and renal tissues are the hallmark of persistent hypertension and are key in the development of end-organ damage and morbidity. Gene therapy prevents left ventricular hypertrophy and cardiac fibrosis (31). In addition, thickening of arterial wall and increased medial-to-lumen ratio in both coronary and renal arterioles of the SHR are significantly reduced by gene therapy.

These observations clearly establish that a single administration of AT1R-AS via a retrovirus-mediated
delivery system attenuates hypertension on a long-term basis. We believe that this treatment is superior to traditional therapy because: 1) only a single injection is needed for a long-term effect; 2) it prevents both high BP and cardiac and renal pathophysiology; 3) in contrast to losartan therapy, no significant changes in plasma ANG II are observed by AT1R-AS treatment (26); and 4) it does not express visible side effects in animals based on weight, morphological, and behavioral parameters. Despite these highly encouraging initial observations, we need to proceed with caution and many more questions need to be addressed to further establish the efficacy of this approach. For example, what is the level of immunological response? Could there be a better route of delivery? Are pathophysiological benefits a result of attenuation of BP or are they two independent effects? What is the cardiovascular role of AT2 receptor? Finally, even if all the above questions are resolved in favor of gene therapy, there remains an issue of its usefulness in the treatment of human hypertension. This is highly relevant because there are no reliable genetic markers based on the RAS that could be used to predict predisposition of hypertension. Lacking this, one has to attempt an alternate strategy, i.e., could antisense gene therapy be used to reverse hypertension once it is established?

Reversal of hypertension by antisense gene therapy: Is it possible? Chao and associates (3, 24, 25) have used a “sense approach” and have shown that the delivery of genes to kallikrein or atrial natriuretic peptide into adult SHR reduces high BP and reverses many pathophysiological conditions associated with hypertension. These observations were among the first evidence to demonstrate that gene therapy strategy is reasonable in reversing the hypertensive state. The reversal was maintained for several weeks. Phillips and co-workers (40) used recombinant adeno-associated virus (rAAV) to deliver AT1R-AS systemically and intracerebroventricu- larly. A significant lowering of BP in adult SHR was observed. The effect was transient and lasted several weeks. However, no data on pathophysiology or morphology are available to indicate whether changes in BP are associated with a reversal of pathophysiology. Our studies with the retroviral delivery system have been encouraging in this regard. Administration of 1 × 10^9 cfu viral particles in adult SHR intracardially resulted in a rapid but persistent reduction in BP, which lasted as long as 36 days. Direct BP measurements showed ~40 mmHg lowering of BP in AT1R-AS-treated SHR (Fig. 6). No such reduction was observed in the WKY. In contrast, the heart rate or body weight did not change with this treatment.

Reversal of high BP was associated with normalization of endothelial dysfunction as judged by endothelium-dependent relaxation of renal arteriole by acetylcholine (8). The contractile responses of the resistance arterioles to ANG II and KCl are significantly higher in the SHR compared with the WKY; however, these responses were reversed in AT1R-AS-treated SHR (8). These observations indicate for the first time that reversal of high BP by AT1R-AS gene therapy is associated with reversal in pathophysiological changes in the vasculature. This is relevant in that these observations provide conceptual evidence and support for antisense gene therapy in adult animals. However, they also raise an important issue. How is the retroviral vector able to transduce alterations in pathophysiological aspects of hypertension in adult animals? This is an important question in view of a strongly held belief that retroviruses have poor efficiency in infecting nondividing cells. It is quite possible that a significant hypertrophy, hyperplasia, and tissue remodeling in ANG II target tissues of the SHR allows sufficient integration and transduction of the AT1R-AS. It also is possible that the success of retroviruses infecting poorly dividing cells is much better than previously realized. We believe that a combination of the above two mechanisms may be responsible for our observed success in gene delivery in adult animals.

Are RNA viruses and retrovirus-based vectors a reasonable choice for antisense gene therapy for hypertension? We believe this to be the case at least in animal experiments because of the following points. 1) High titer of retrovirus particles can be produced on a large scale, contrary to the current situation with AAV. 2) The next generation of retroviral vectors are currently available that have better integration efficiency and transduction capacity in nondividing cells. In addition, significant improvement in host immunological response has been accomplished with the new generation of these vectors. 3) HIV-based RNA viral vectors such as lentiviral vectors are becoming available. They combine the desirable properties and advantages of retroviral vectors with those of adeno- and AAV-based vectors. Thus use in antisense gene therapy for hypertension and other cardiovascular diseases holds a great promise and future.

Where do we go from here? One can safely conclude from the above review of literature that conceptually, antisense gene therapy would be an important aspect in the control of hypertension. However, many more issues need to be addressed and answers sought by animal experimentalations before one can consider its
application for human treatment. First, one needs to determine the effectiveness of this therapy in other animal models of hypertension. Both genetic models (such as renin transgenic rat and angiotensinogen-renin double-transgenic mice) and nongenetic models (2-kidney, 1-clipped Goldblatt model, DOCA-salt model, high-fructose model) of hypertension should be tested. In fact, Peng et al. (39) recently showed that antisense oligonucleotides to angiotensinogen mRNA or to AT1R were able to attenuate high BP in the cold-induced model of hypertension. Second, antisense to other components of RAS such as ACE, renin, and angiotensinogen should be tested for efficiency and efficacy in the prevention and reversal of hypertension. Antisense to ACE will be of particular importance because ACE inhibitors have a proven track record in the treatment of hypertension and in the protection against myocardial infarction, kidney failure, and prevention of restenosis/remodeling that occurs after balloon angioplasty. Third, a combination of antisenses, for example ACE inhibition/remodeling that occurs after balloon angioplasty. Additionally, another question that needs to be addressed is whether the decrease in BP is the initiator of reversal and prevention of the pathophysiological and morphological changes associated with hypertension or if both effects are independently controlled. Finally, it would be important to determine whether overexpression of genes relevant to vasodilatory effects (i.e., kallikrein, atrial natriuretic peptide, endothelial nitric oxide synthase, etc.) would be equally beneficial for the control of hypertension. Chao and associates (3, 24, 25) have led this aspect and have shown a short-term reduction in high BP and other beneficial effects on pathophysiological parameters. However, a systematic comparison between this “sense” approach to that of the “antisense” approach remains to be explored.

In conclusion, all the existing data indicate that gene therapy, based on the inhibition of RAS at a genetic level, is an effective therapeutic approach for the future. The approach is conceptually sound and experimentally feasible and provides numerous benefits over traditional drug therapy. It holds promise for the control of hypertension on a permanent basis. It is an exciting time for research in hypertension and other cardiovascular diseases as a result of a tremendous explosion in the advancement of molecular biology and genetics. We, as physiologists, are at a crossroad and must take advantage of rapidly evolving genetic and molecular technologies to answer physiological questions and use them to improve and correct pathophysiological states. We must establish productive communication and collaboration with fellow virologists, molecular biologists, and geneticists to integrate their exciting discoveries into our physiological research. The success of our research group in the use of antisense gene therapy has, in part, been a result of such a collaboration. As new and highly efficient vectors become safe and available, it will become easier to use them as delivery vehicles for the treatment and control of hypertension and other cardiovascular diseases.

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