WHY HAS THE TREATMENT OF HYPERTENSION BECOME SUCH A DEPLORABLE FIASCO?

An Interview with Dr. John Laragh

Director of the Cardiovascular Center at the
New York Presbyterian Hospital-Cornell Medical Center
and Weill Medical College and
Editor-in-Chief of the *American Journal of Hypertension*

By Paul J. Rosch, MD, F.A.C.P.
THE AMERICAN INSTITUTE OF STRESS

PART I

People with uncontrolled high blood pressure are:

3 times more likely to develop coronary heart disease

6 times more likely to develop congestive heart failure

7 times more likely to have a stroke

Despite over one hundred antihypertensive drugs that have been approved as being safe and effective, the sad fact is that we have not been very successful in controlling hypertension. A survey reported in the July 9 issue of *The Journal of the American Medical Association* found that **nearly one in three U.S. adults have hypertension**. Of the estimated 58 million affected, "**almost 30% were unaware of their illness, 42% were not being treated, and at the time that their BP was measured, 69% did not have their hypertension controlled**!"

Another survey published in the *British Medical Journal* in June found that **97% of patients taking antihypertensive medications had suffered from significant side effects at some time and 17% continued to do so**! Four out of five patients had serious concerns about side effects they had not been informed of, possible long term dangers and wondered if they still needed drugs or could use other approaches.

An article in the February issue of the *Journal of Human Hypertension* was entitled "Cost of poor blood pressure control in the UK: 62,000 unnecessary deaths per year." According to a September Reuters report, "**half of the people with high blood pressure who are at risk of a stroke are not identified, half who are identified are not treated, and half who are treated aren't treated properly**." Yet, all we keep hearing from the media and the government is about how much progress is being made with new and allegedly "breakthrough advances" that imply the war on hypertension has been won. The somber reality is that things have been getting progressively worse rather than better and that the incidence of hypertension and stroke will probably rise even more as the obesity epidemic and the over 80 population continue to escalate.

I believe that the main reason for this misinformation is the government guidelines for the treatment of high blood pressure disseminated by NHLBI (National Heart, Blood, and Lung Institute) in their recent ALLHAT and JNC-VII reports are dictated more by politics rather than

science. This is vividly illustrated by their contention that all Americans should drastically reduce their dietary sodium intake, that most people over the age of 55 and all diabetics should be taking statin drugs regardless of their cholesterol or LDL levels and especially following the latest hypertension treatment advice. All of these could likely be prescriptions for disaster, particularly because alternatives proven to be safer and more effective have been completely ignored.

John Laragh And The Renin Hypothesis

In my opinion, the most likely person to have a solution to this dismal state of affairs is John Laragh. His credentials are impeccable. After graduating from Cornell Medical College in 1948 he took his residency training in medicine and cardiology at Columbia University College of Physicians and Surgeons and Presbyterian Hospital, where he later founded the first Hypertension Center and became Chief of Nephrology and Vice-Chairman of the Board of Trustees. He returned to New York Hospital-Cornell Medical Center in 1975 where he developed a cardiovascular research program supported by NIH for a quarter of a century. Over 25 researchers he trained now head their own academic units at prestigious medical facilities here and abroad. He is currently Director of the Cardiovascular Center at the New York Presbyterian Hospital-Cornell Medical Center and Weill Medical College.

He founded the American Society of Hypertension in 1986, became its first President, established the *American Journal of Hypertension*, and still serves as Editor-in-Chief. He is a Past President of the International Society of Hypertension and the author of over 900 articles and several texts dealing with hypertension.

Dr. Laragh has been the recipient of numerous awards and was featured on Time magazine's cover in 1975 for discovering the role of the renin-angiotensin-aldosterone system in regulating normal blood pressure and causing fatal malignant hypertension. He has long maintained that essential hypertension in most patients is caused by excess renin and can be permanently controlled and useful life extended with one drug by determining whether the problem is primarily sodium (volume) related or due to increased renin actions. The key to this is being able to accurately measure renin activity, a procedure that he pioneered over three decades ago.

I have known John for over 65 years; we both grew up in the same area of Northwest Yonkers and he has been a member of the Board of Trustees of The American Institute of Stress since its founding in 1978. We and our wives are avid golfers and Marguerite and I have enjoyed their hospitality at Winged Foot and Shinnecock. We also share some professional concerns, such as how the practice of medicine has become more of a trade than profession since we entered practice. I have referred many patients to him and have always found him to be a very caring as well as skilled clinician. Many authorities share my belief that implementation of his approach could markedly reduce the prevalence of poorly controlled hypertension as well as its complications and costs.

What is difficult to understand is why has this been inadvertently overlooked (if not deliberately omitted) in official recommendations for the treatment of hypertension, such as the recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII)? While familiar with how John's treatment program evolved, I wanted to fill in a few blanks and also obtain his opinion about these latest official recommendations.

How The Renin Story Began And Evolved

PJR: *What led to your interest in renin?*

JHL: At Columbia, as an intern and resident in medicine and then in cardiology I was surrounded by frontier clinical science, the direct product of Robert Loeb's passion for new knowledge and its basic link to clinical excellence. Loeb spawned many professors of medicine, but what is generally not known is that his department also produced 6 Nobel Laureates including Dickinson Richards, André Cournand, Barry Blumberg, Dan Nathan and Carleton Gajdusek, an incredible record. For about 10 years I used to meet with Loeb almost daily at 8 AM in his office along with other house staff and young faculty members. With his help and advice I was working on congestive heart failure, and on the roles of sodium and potassium balance on edema formation and especially on aldosterone secretion, soon after its discovery in 1953. After he became interested in my work he couldn't get enough of it, and sometimes would come back to my lab in the afternoons for a second round! I also worked a bit and talked a lot with Marcel Goldenberg, a marvelous scientist whose lab was near mine. Marcel discovered noradrenalin in the adrenal medulla and defined its differences from adrenalin. To block its biosynthesis, he introduced alpha methyl DOPA (Aldomet) to Merck. Marcel fits into my story too, because I was also his physician. He died of renin caused malignant hypertension due to scleroderma. We could have easily saved him today but all this occurred before we had figured out what causes malignant hypertension and had introduced the antirenin R drugs to correct it.
What first led to my interest in renin was a 57-year-old CEO of a large company that Loeb had referred to me in 1957. He had malignant hypertension with grade III retinopathy and generalized muscle weakness from very low serum potassium levels. His aldosterone secretion was over 800 mgm/day while our normal values were less than 50. We were very proud of our aldosterone assay even though it could take up to 6 weeks to complete a test since it required labeling aldosterone with radioactive H3 and then injecting a tracer I.V. into our patients and ourselves. The degree to which the radioactivity was diluted by the amount of aldosterone in the patient's own blood in 24 hours gave us the daily secretory rate. Unlike

everybody else, we found aldosterone to be quite normal in essential hypertension. But, to our amazement, it was massively increased in fatal malignant hypertension. We removed the adrenals in 4 such patients to eliminate all plasma aldosterone but it was without any benefit, since they all died on schedule.
Thus, we showed that malignant hypertension and its diffuse vasculitis were not caused by their high aldosterone since this fatal condition progressed in the absence of the adrenals when there was no aldosterone. There had to be something else circulating in these patients that (1) raised blood pressure, but most importantly, this substance should also (2) produce prompt and progressive injury to blood vessels in the heart, brain and kidneys resulting in the rapidly fatal heart attack, stroke, heart or kidney failure typical of malignant hypertension. **Because adrenalectomy did not help, it was obviously not anything manufactured in the adrenal so the most likely cause appeared to me to be excess renin from the severely damaged kidneys of these patients.**
In 1898, Tigerstedt and Bergman had published a classic article in a Scandinavian journal describing an amazing and powerful blood pressure raising substance they had isolated from saline rabbit kidney extracts. They called this substance renin. But subsequent scientists failed to confirm Tigerstedt and Bergman's findings so there was little interest in renin until 1934 when Harry Goldblatt published the landmark results of his dog experiments. Harry induced what appeared to be the equivalent of essential hypertension in humans by constricting either one or both renal arteries with a silver clamp. In addition, more severe renal ischemia produced in this fashion resulted in a syndrome that closely simulated malignant hypertension that was also assumed to be due to more increased renin release. It was therefore very disappointing that numerous attempts showed absolutely no evidence that plasma renin levels were increased in patients with essential hypertension compared to normal people or even that renin had any significant physiologic action of its own in humans.

The Pivotal Role Of Angiotensin

PJR: *Why is renin so important if it is inactive?*

JHL: What was established by Braun-Menendez was that renin acted enzymatically on a circulating plasma protein (angiotensinogen) to release an inactive decapeptide (angiotensin I), discovered by Leonard Skeggs. He showed that this is rapidly hydrolyzed by "converting enzymes" to form the most powerful pressor substance known, the octapeptide angiotensin II. It is this vasoconstrictor angiotensin II, released in plasma only by renin, which plays the crucial role in causing most human hypertension and its fatal sequelae. When you give angiotensin II to normal humans we showed that it produces a rapid rise in blood pressure by promoting vasoconstriction as well as via a slower and more sustained elevation by also stimulating aldosterone secretion to promote body sodium retention by acting on the kidneys. However, it was many years before these normal roles of plasma renin or angiotensin would finally be acknowledged and much longer still before the establishment began to accept renin as a major cause of human malignant and essential hypertensions. In fact, there are some establishment diehards who will probably go to their graves resisting renin.
Thus, in 1958, when we discovered very high plasma aldosterone levels in fatal malignant hypertension, the octapeptide, angiotensin II, had just been synthesized by CIBA. They provided samples to us for human research. We cautiously administered tiny subpressor amounts of it intravenously to six normal volunteers. In over 40 such infusion studies, only angiotensin II (but never adrenalin, noradrenalin, serotonin or vasopressin) consistently and strikingly stimulated adrenal aldosterone secretion. Thus, we had discovered the missing biologic role for renin. It was to maintain normal ambulatory blood pressures not only via direct angiotensin II arteriolar vasoconstriction but also by angiotensin induced adrenal aldosterone release. Aldosterone then acts to expand blood volume and flow by causing the kidneys to retain sodium and thus water.

PJR: *How did this information help you target drug treatments to specific hypertensive patients?*

JHL: The new data and our studies led us to propose and later prove that the malignant hypertension syndrome is caused by an unchecked runaway release of renin by the damaged kidneys, leading to very high plasma angiotensin levels. This raises blood pressure and also constricts the coronary, cerebral and renal vessels, rapidly leading to fatal complications like heart attacks and stroke. We were able to correct all of this syndrome in malignant hypertension patients not only by removing both kidneys, but also by treating each such patient instead with any one of the 3 antirenin R drug types that we characterized and introduced: first propranolol, a beta blocker, to block the kidney beta receptor renin release, then, the snake venom peptide (teprotide), the original intravenous angiotensin converting enzyme (ACE) inhibitor, and finally, the intravenous octapeptide saralasin, the first angiotensin II receptor blocker (ARB). Our findings with teprotide and saralasin soon persuaded industry to synthesize many orally active analogs of the venom ACE inhibitor (e.g. captopril, enalapril, lisinopril) and later on, many orally active ARB's resembling saralasin (e.g. losartan, valsartan, cardesartan, olmesartan, irbesartan, telmisartan, eprosartan).
As you know, these explicit antirenin system R drugs, together with beta blockers, another antirenin R drug class that we defined, have had a dramatic influence on our understanding and treatment of all human hypertension. And they have had an even greater impact for preventing or arresting the plasma renin-caused fatal consequences, notably heart attack, stroke, heart and kidney failure. These three classes of antirenin R drugs that we introduced and characterized are now represented for clinical use world wide by numerous commercially available chemical analogs, e.g. captopril, lisinopril, enalapril, ramipril. Collectively, they have revolutionized not only hypertension therapy but also its major fatal cardiovascular complications.
Marcel Goldenberg was one of my malignant hypertension patients whose rapidly fatal outcome proved this entire story for us. I cry whenever I think about him because five years later we could have saved him. We then went on to prove that about 2 out of 3 cases of essential hypertension are caused and sustained by their plasma renin levels because blocking renin with one of our antirenin drugs promptly corrects them. In these patients too, we could also prevent the same but more gradually developed fatal sequelae of heart attacks, stroke, heart failure and kidney failure with any one of our three antirenin drug types. However, these R drugs do not benefit patients with low renin hypertension who, on the other hand, respond incredibly well to the natriuretic (V) drugs (thiazides, spirolactone, calcium channel blockers) that reduce body sodium and

thus blood volume.

The Plasma And Direct Renin Assays

PJR:*The key to your treatment method appears to be the ability to measure plasma renin activity accurately. The difficulty that most physicians had was that this measurement was quite complicated because it required incredible sensitivity and thus not widely available, as well as being expensive, since unlike today, it was not covered by health insurance. Paul Brown, who had founded Metpath Laboratories, was a good friend and I recall taking you over to New Jersey around 25 years ago to meet him. Metpath was well on its way to becoming the largest clinical laboratory in the U.S. and since I served as a consultant at the time, I wanted to explore the possibility of providing renin testing as part of a hypertension profile. Nothing apparently came of that but Corning later acquired Metpath, which subsequently became Quest Laboratories. Quest now offers an automated ambulatory direct Renin immunoassay. Is this procedure as accurate as the Sealey-Laragh plasma renin activity assay?*

JHL: I remember our visit with Paul Brown quite well. You were on the right track then, and as usual, a little ahead of the curve. Jean Sealey joined our laboratory in 1960 as a biochemist. She soon showed us how our aldosterone assay could be improved. Then, over the next ten years, Jean worked with us to perfect the world's most sensitive and accurate plasma renin activity assay (PRA). She also worked in Harry Goldblatt's lab for several months to learn his 12 step human renin purification procedure, which gave us a very valuable reagent to use.
All of the previous renin assays were also inaccurate because they didn't recognize and reference the level of renin activity to the current state of sodium balance or achieve angiotensinase inhibition or pH control, and because they were not aware of the distorting effect of cryoactivated prorenin. Jean showed that previously unrecognized large amounts of prorenin occur in human plasma and are converted to active renin *in vitro* when plasma or blood is exposed to cold temperatures. This was why most labs that routinely chilled their plasma samples had very high false results. **As a result, they were unable to measure low renin accurately that is critical for identifying and separating the low renin "salt" hypertension patients.** During this period, although there were constant criticisms and objections to my renin hypothesis, nobody ever questioned the superior accuracy of our testing procedure. Our renin assay remains the only method that can accurately measure the low values, and is absolutely crucial since it is the only way to positively identify and separate out the salt-volume "V" patients whose low renin hypertension is caused instead by salt and requires a different treatment using anti salt drugs instead of the antirenin R drugs that correct the renin type of hypertensives.
Quest has been using our Sealey-Laragh method for the past 7-8 years in their New Jersey laboratory. They confirmed our results, but unfortunately our plasma renin activity (PRA) method proved too skilled-labor intensive for them to put into a mass production mode. Recently, we have helped them to switch to their automated Direct Renin test. While the current Quest-Nichols chemiluminescence Direct Renin assay is much better than all of its preceding competitors, it is still not as sensitive as our PRA procedure for defining and discriminating the low renin salt-volume caused hypertensive patients. However, we are hopeful, since recent comparisons with our assay show that the Quest Direct Renin assay is improving. **Most people don't appreciate that plasma renin activity (PRA) levels can be high enough to produce a fatal stroke at one ten billionth of the molar concentrations of plasma glucose or cholesterol!** This is why very sophisticated detection technology amenable to mass production is required. The pivotal values for these two procedures are shown below.

(V) Volume Hypertension	(R) Renin Hypertension
PRA levels less than 0.65 ng/m/hr	PRA levels greater than 0.65 ng/m/hr
Direct Renin less than 5 mU/ml	Direct Renin greater than 5 mU/ml
This is predominantly sodium-volume caused hypertension	This is predominantly due to renin-angiotensin caused vasoconstriction

Measuring renin allows you to identify which type of antihypertensive medication is most likely to be effective and possibly safer in any given patient. The advantage here is that once this is established it is possible for patients to have their blood pressure controlled with one drug permanently. **Monotherapy for life is our *nirvana* for hypertension treatment. We seek this for every patient and achieve it in most.**

Treating Volume Versus Renin Hypertension

PJR:*How are specific medications selected based on renin profiling and how can treatment be initiated if renin testing is not readily available? This information is elegantly explained in your recent book*[1]*but could you give us a brief summary?*

JHL: Yes, salt-volume (V) hypertension is always associated with the lower ambulatory plasma renin levels (PRA values less than 0.65). This occurs in about a third of patients with high blood pressure. It is correctly treated with any one of the natriuretic or anti-volume V drugs such as spirolactone, a thiazide diuretic, a calcium channel blocker or an alpha blocker. Renin-angiotensin (R) mediated vasoconstrictor hypertension is twice as common. It resembles a *forme fruste* of fatal malignant hypertension and is thus much more apt to be associated with albeit milder, and more gradually occurring, fatal heart attacks, strokes, heart failure or kidney failure. These (R) hypertension patients should instead be treated primarily with any one of the three types of antirenin R drugs, an angiotensin converting enzyme inhibitor (ACE), angiotensin receptor blocker (ARB) or a beta blocker. The bottom line is that blood pressures for all hypertensives can be controlled with the Laragh Method using one drug for life in over half of both (V) and (R) patients, or in sum, for at least 60 -80% of the total

group. As you noted, this is in sharp contrast to the expensive and unpleasant polypharmacy approach promoted by JNC-VII. The result is that most patients treated using their protocols are denied the precious opportunity for a lifetime of monotherapy with the correct drug type for them but are condemned instead to taking 2-4 drugs. This increases costs and side effects while providing much less net benefit, which means a diminished productive life and an earlier demise.
It is also possible to bypass renin testing by using single file trials of a V and then an R drug to identify which type will correct the hypertension. In addition, I believe you must stop drugs that don't work rather than always continuing drugs you have on board as JNC-VII mandates. In our method, about 20% of the whole may need both a V and an R drug but that's still highly preferable to the JNC-VII protocol that starts with a thiazide diuretic and keeps piling on other drugs until blood pressure is controlled. Since diuretics are not only not indicated but can also raise pressure in the 2 out of 3 patients with high renin R hypertension, most of these will have to keep adding other drugs only to achieve poorer results.

PJR:*I would suspect that placing everyone on diuretics perpetually would lead to potassium depletion, cardiac arrhythmias and a significant increase in diabetes. It could also deny high renin patients protection from fatal cardiovascular complications that you have shown antirenin medications do provide for them.*

JHL: You are absolutely correct and what is both impressive and alarming is the under appreciated harm that can result from traditional diuretic therapy. The thiazide diuretic, hygroton, produced over an 11% incidence of real and permanent diabetes in less than 5 years in the ALLHAT trial, which suggests at least 22% after 10 years and even more later on. In other studies, thiazides have been shown to regularly produce muscle potassium and magnesium depletion that leads to cardiac arrhythmias, muscle weakness, electrocardiographic changes and thence to fatal cardiovascular complications. The good news is that all of these complications can be avoided by using spirolactone instead to correct sodium-volume related hypertension without ever causing diabetes or depletion of potassium and magnesium.
Our renin hypothesis has been widely confirmed in over 120,000 patients who were studied following an acute myocardial infarction in various large clinical trials. Only those receiving an antirenin R drug had a consistent reduction in recurrent myocardial infarction, congestive heart failure and sudden death rates. This shows that blocking the presence or action of angiotensin II by giving an antirenin R drug to this very vulnerable group of patients will consistently prevent plasma renin vasculotoxicity and extend useful life for millions. As emphasized, the **R drugs do not help low renin hypertensives, who require and often have dramatic relief from natriuretic V drug salt depletion. Conversely, V drugs are ineffective and often harmful when given to renin mediated R hypertensive patients because this raises renin levels even higher**.

Are Government Guidelines Based on Politics Rather Than Science?

PJR: *Since others have confirmed your hypothesis and NHLBI has funded your research it is puzzling that renin is not referred to in their official reports. This reminds me of Schopenhauer's observations about discoveries. "All truth passes through three stages: First, it is ridiculed; Second, it is violently opposed; and Third, it is accepted as self-evident." Hopefully, the renin story is reaching the end of this trail. New ideas are most often criticized not because they lack merit, but because they might turn out to be workable, which would threaten the reputations and possibly jobs of many people with conflicting opinions. The disastrous results of this are vividly illustrated by the recent NHLBI sponsored ALLHAT study.*

JHL: None of the numerous studies that confirm the renin hypothesis are ever quoted by ALLHAT or JNC reports, which is reprehensible. **The word renin is rarely or never mentioned, which is like discussing diabetes without ever mentioning the word, insulin!** With respect to this ALLHAT report, there were several flaws in the design and implementation of the study that raise serious doubts about the validity of its conclusions and especially their applicability to clinical practice. Over a third of patients were African Americans who are more apt to respond to diuretics because more of their hypertension tends to be volume (salt) related. The participants were all older than 55 (mean age 67) and 36% were diabetic, so it is also doubtful that any conclusions from such an elderly high-risk group would apply to low-risk hypertensives under the age of 55.
Nine out of ten were already receiving some type of antihypertensive drug therapy and there was no washout or medication-tapering period. On day 1 they were switched to one of four blinded randomized drug limbs: diuretic (hygroton), ARB (doxazosin), ACE inhibitor (lisinopril) or calcium channel blocker (amlopidine), so that "baseline" BP was meaningless as a control point for evaluating efficacy. The withdrawal of certain drugs may have caused subsequent adverse events such as heart failure rather than this being due to the new medication as the study authors concluded. The increased incidence of "heart failure" characterized by poorly defined edema in the doxazosin group that led to its discontinuation is particularly puzzling.
It is more likely that "heart failure" resulted from the abrupt cessation of diuretic therapy in those patients who were then placed on comparatively low dosages of this antirenin drug since heart failure has not been a problem in other studies. The timing and pace at which patients were treated with medications were not consistent with good medical practice and potentially dangerous. As explained in our editorial[2], **many of us would consider failure to achieve effective drug treatment for 6-18 months as overt malpractice**. Drug dose titrations were programmed so that no changes at all were made in non-responders until after six months. Although the second drug was again often the wrong one, it still had to be titrated up for the next 9 to 12 months and it was only after 16 months that a step 3 drug was introduced. Consequently, some patients were put at increased risk for complications due to poor or no control of their pressure for a year and a half or more, during which they would likely also suffer from the side effects of increasing dosages of drugs not appropriate for their type of hypertension. I suspect this could lead to significant ALLHAT study malpractice litigation.
According to the trial protocol, if patients did not achieve the goal pressure on a properly titrated dose of the initial study drug, a second and if necessary a third medication could be added, provided it was not one of the study drugs (diuretic, ACE inhibitor or CCB). Physicians could choose from a beta blocker (atenolol) or centrally acting drugs (clonidine and reserpine). A beta blocker was the main drug that was usually added, which obviously would be most beneficial for non responders on a

diuretic. Conversely, patients who did not respond to an ACE inhibitor were prevented from receiving a diuretic or CCB and were condemned to receiving still another antirenin drug even though the first one failed. Thus, the design of the study was set up to favor a V drug (hygroton) and, either intentionally or inadvertently, to put an R drug (lisinopril) at a gross disadvantage. The tragedy is that the resulting ALLHAT shaped recommendations are the basis for the new JNC-VII guidelines.

PJR:*Quite frankly, it would seem to me that any physician who has not been able to control a patient's hypertension with medication after an eight or twelve month period of treatment because drug switching was not allowed might be liable for malpractice if that patient had some complication and it could be shown that this might have been preventable by following the Laragh Method. Because of its faulty design, the ALLHAT trial left itself wide open for malpractice litigation and one suit has already been filed. The widow of a 60 year old radiologist who died after being in the study for three-and-one-half years sued the principal investigator at a Pennsylvania hospital as well as his colleagues and the hospital in July, claiming that the dangers of the study had been concealed from her husband when they were trying to convince him to enroll. He had developed some edema or soft tissue swelling during the trial, but his treating physician continued to increase the dose of the blinded drug, which turned out to be the calcium channel blocker, a known cause of edema. When there was a slight blood pressure increase, hydralazine, another drug known to cause edema was prescribed in 1999. According to the complaint, ALLHAT patients were never told of the risk of edema, venous insufficiency, and possibly death from blood clots or bleeding. The swelling worsened and in early 2000, the patient developed lupus, another side effect of hydralazine. Nevertheless, he was kept on the given drugs until days before his death in July 2000. He had also developed an abnormal electrocardiogram, muscle pain, and cataracts, all of which were likely caused by study drugs but either went unreported or uninvestigated as should have been done. In retrospect, he should have been pulled from the trial when there was evidence of kidney damage. The cause of death was a blood clot in his lungs, which the complaint alleged was "a consequence of drug induced lupus and end-stage rapidly progressing kidney damage brought on by the continued ingestion of hydralazine." The patient, a physician, had rated his health as very good" (90 on a 100-point scale) just before entering the ALLHAT trial. One claim for superiority of hygroton in ALLHAT was that it reduced the rate of stroke by 15% compared with the ACE inhibitor lisinopril. However, as several critics noted, this could be completely accounted for by the greater stroke rate in black patients given lisinopril who failed to respond and were then put on a beta blocker and then still had significantly higher blood pressures. It is well known that ACE inhibitors or beta blockers are ineffective in low renin hypertension, which is more common in black hypertensives, so that combining 2 antirenin drugs in a low renin patient was inappropriate. I believe you expressed similar concerns in your editorial.*

JHL: Very definitely. It is well established that black patients with hypertension are often more likely to respond to diuretics or the other V drugs than to ACE inhibitors or the other R antirenin drugs. The reverse tends to be true in Caucasians and this was also confirmed in ALLHAT. The malpractice issue here is that the nonresponders to lisinopril had to wait 6 months before another drug was added and the only options available for step 2 were still another antirenin drug, either a beta blocker, clonidine or reserpine. Giving another R drug to a patient who already exhibited failure to respond to this type of medication is a no-brainer, not in keeping with widely recommended practices. This second R drug was then titrated up for another 9-12 months, so that a patient who really required a V drug was essentially taking 2 placebos for 16 months. It was only after 16 months that the step 3 drug hydralazine could be started in a still unresponsive patient who had to continue to take the two other drugs that were not working. Thus, patients who were randomized to lisinopril and did not respond were condemned to at least two more redundant and therefore, ineffectual antirenin drugs while being denied effective antivolume drug treatment for well over a year. One can only imagine how frustrating this must have been to treating physicians who recognized this but had to abide by the rules of the trial. With respect to law suits, in all fairness, no matter how well any trial is designed, patients may have unanticipated adverse reactions. The ultimate responsibility lies not only with the trial designers but also with the programming physicians who need to prepare for such situations and place the patients' interests first instead of those of their government supervisors. As indicated in our editorial in *The American Journal of Hypertension*[2], it would not be an exaggeration to say that I or any one of my colleagues could have accomplished the same drug titrations in four to ten weeks, during which time we would have discarded the medications that obviously did not work. However, such logical and commonly used drug subtractions or substitutions were also strangely barred by the study design, so that by fiat, ALLHAT actually endorsed malpractice.

PJR:*This is of great concern since that the latest governmental guidelines for treating hypertension contained in JNC-VII are based on ALLHAT, which brings up another interesting question. Just exactly what is the purpose of this Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and what authority does it have? The committee grew out of an NIH program to educate the public about the early warning signs and symptoms of hypertension. However, this gradually expanded to include information on the advantages and disadvantages of various medications, and eventually guidelines for their use. The first NHLBI JNC report published in 1976 promoted thiazide diuretics as the preferred drugs for hypertension as did its successors. The 1993 JNC-V guidelines added angiotensin-converting enzyme (ACE) inhibitors and beta blockers as initial therapy choices because of evidence that they were more likely to reduce complications such as heart attacks and stroke. but and only diuretics and beta blockers were approved for first line therapy in the 1996 JNC-VI guidelines. ALLHAT was designed to prove that the government had been correct all along. Although beta blockers were not one of the four types of antihypertensive drugs being compared, they were also dropped as recommended starting medications in JNC-VII, leaving thiazide diuretics to again reign supreme. Thus, according to NHLBI, we apparently have not made any progress in the treatment of hypertension since their first report over 25 years ago.*

JHL: Giving a thiazide diuretic to every hypertensive patient is likely to be the wrong choice more than half the time and continuing it despite the fact that it is not effective makes no sense to me. The JNC-VII committee completely failed to acknowledge other large hypertensive trials whose results were available to them but did not support their thiazide first and always recommendations. The ANB2 (Second Australian National Blood Pressure Study) published in the New England

Journal of Medicine in February found that ACE inhibitors were associated with 11% lower cardiovascular mortality and complication rates compared to treatment with diuretic agents despite similar blood pressure reductions. During the Australian trial, the diuretic hydrochlorothiazide, was compared with the ACE inhibitor enalapril and patients who did not respond to the first drug were switched to the other, rather than being maintained on something that clearly didn't work. Two out of three study participants responded to monotherapy with either drug when, according to the trial design, patients who did not respond to the first drug were switched to the other, rather than being maintained on something that clearly didn't work, again confirming the Laragh Method. At the end of five years, the ACE inhibitor was found to be superior to the thiazide diuretic. I suspect that these findings, which JNC-VII completely ignored, may have more relevance for U.S. clinicians since this population was about 90% Caucasian as opposed to less than two thirds in the ALLHAT study.

PART II

The first part of this interview referred to a recent survey finding that of the approximately 60 million Americans with hypertension, "30% were unaware of their illness, 42% were not being treated, and at the time that their BP was measured, 69% did not have their hypertension controlled!" Another reported that 97% of patients taking antihypertensive medications had suffered from significant side effects at some time 17% continued to do so, and Four out of five had serious concerns about side effects they had not been informed of or possible long term dangers. According to a September Reuters news release, "half of the people with high blood pressure who are at risk of a stroke are not identified, half who are identified are not treated, and half who are treated aren't treated properly." Many authorities believe that the reason for this is the government's failure to recognize that there are two basic types of hypertension that vary in terms of prognosis and that require explicit corrective treatment with two very different classes of drugs.

The key to differentiating this is the ability to accurately measure renin, a procedure pioneered and perfected by John Laragh. We reviewed the origin and evolution of the renin hypothesis and how it led to the Laragh Method of treating hypertension based on determining whether the problem was salt-volume related or due to overactivity of the renin-angiotensin-aldosterone system. This allows two out of three hypertensive patients to control their blood pressure with one drug permanently and protects those with high renin from developing fatal complications like heart attack, stroke, heart and kidney failure and sudden death. This is in sharp contrast to the latest official guidelines recommending that all hypertensive patients should be started first and continued forever on a thiazide diuretic even if this is not effective and that most hypertensives will require taking 2-4 drugs for the rest of their lives. The basis for this is the NHLBI sponsored ALLHAT trial. In this segment, we will explain the numerous defects in the design and implementation of this study and why it can be a prescription for malpractice. The problems associated with long term thiazide therapy proposed by government officials will be reviewed and additional evidence of why this is based on politics rather than science will be presented. In addition, we will explore the links between stress and hypertension and the great potential for the antirenin drugs to prevent fatal vasculotoxic and cardiovascular complications in normotensive patients as well.

More NHLBI And JNC-VII Deception And Chicanery

As I understand it, all Federal rules or guidelines that affect the public are required by law to be written and promulgated according to the Government Code. This mandates formal selection of a committee, pre-announcement of all meetings, open meetings that encourage testimony from all interested parties as well as written records, all of which must be preserved in a special docket. Everything is then reviewed in order to provide a written discussion of all the relevant evidence that led to the final guidelines, which must be published in the Federal Register. In addition, if the published guidelines are not consonant with a logical review of the evidence presented, these recommendations may be overturned by legal action. Since the JNC-VII guidelines seemed to be subject to these rules I accessed the Federal Register but was unable to find anything relevant. When I contacted the Government Printing Office to inquire about this I received a reply confirming they had no JNC records and was referred to a NIH web site. This was remarkably reminiscent of how the National Cholesterol Education Program (NCEP) for the detection and treatment of high cholesterol had operated. The first NCEP report issued in 1988 was timed to coincide with the introduction of Mevacor, Merck's new cholesterol lowering drug. In an unprecedented action. it was released directly to the public weeks before doctors could read the scientific information on which it was based. The last set of revised guidelines in 2001, that tripled the number of Americans advised to take statins, was also publicized prematurely. In both instances, the guidelines were published in the Journal of the American Medical Association but not the Federal Register. There was no public notice of any meetings, the meetings were not open to the public, public input was not solicited, and detailed records and testimony of committee meetings were not kept.

When NHLBI officials were questioned about this they explained that the cholesterol and hypertension recommendations as well as the latest advice for everyone to restrict dietary sodium intake had all been written by outside experts and were therefore exempt from the Government Code and Federal Register regulations. This, despite the fact that they are presented by paid government spokespersons at government press conferences and are promoted in the media as the latest government guidelines. The FDA even authorized a "sodium and hypertension" food label health warning stating that it was based on the Intersalt study. Yet, there had not only been no public input, as required but access to the data on which these faulty conclusions were based was repeatedly denied until legal action was threatened and chicanery in data analysis was discovered.

The ALLHAT Trial - As Yogi Berra Said, It's Déjà Vu All Over Again

The ALLHAT (Anti-hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) was a randomized double-blind controlled five-year study of over 42,000 hypertensives that began in 1994 at 623 centers in North America. Among other things, it was designed to determine whether the choice of first line treatment for hypertension influenced cardiovascular outcomes. This was assessed by comparing the thiazide diuretic hygroton with three other classes of antihypertensive drugs; an ACE inhibitor, calcium channel blocker and an alpha-adrenergic–receptor inhibitor (ARB). The preliminary findings were reported in the December 18, 2002 issue of the *Journal of the American Medical Association*. This was accompanied by a massive media blitz that resembled the premiere of a Hollywood production more than the presentation of a scientific report by a government agency. This began the day before at a carefully orchestrated and coordinated conference held at the National Press Club in Washington during which NHLBI Director Dr. Claude L'Enfant proudly proclaimed "ALLHAT shows that diuretics are the best choice to treat hypertension and reduce the risk of its complications, both medically and economically." Cronies like Jeffrey Cutler also touted thiazide-like diuretics as being "unsurpassed in lowering blood pressure, reducing clinical events, and tolerability" and kept reemphasizing that thiazides "should be considered first for pharmacologic therapy in patients with hypertension." The ALLHAT report would be appearing as a "JAMA express" contribution that is reserved for submissions with major health implications. To expedite publication, the peer-review process time is cut to 24-48 hours and the time for all authors to respond with any changes is 72 hours. It seems doubtful that the findings of both the blood pressure and lipid papers could have been thoroughly reviewed in the time allotted and almost inconceivable that all of the close to 60 authors involved would have been able to respond within 72 hrs, so some corners must have been cut.

Dr. Michael Weber, a past President of the American Society of Hypertension and one of the original principal ALLHAT investigators described the manner in which the results were announced as "flamboyant, irresponsible posturing" from an agency that "supposedly is providing service in the true interests of science and should be scrupulously objective and conservative in interpreting the results of research." He suggested that if a manufacturer held something similar to make such claims about hygroton it would border on being illegal and that "the whole tone of how this has been handled is upsetting." The HAT in ALLHAT stood for heart attack trial and the professed purpose of the study was to compare the ability of different drugs to prevent fatal and non-fatal heart attacks. **Most authorities agree that the main reason to treat hypertension should be to prevent the fatal cardiovascular complications rather than controlling blood pressure per se.** However the message that emanated from ALLHAT seemed to be that treatment should be targeted to controlling blood pressure, no matter how many medications were needed and that chlorthalidone (hygroton) should be tried first and given to all because it was the most effective.

At the gala National Press Club kickoff media event to applaud the ALLHAT findings, Claude L'Enfant also announced that he was appointing a committee to draw up new hypertension treatment recommendations so they could be presented in five months at the annual meeting of The American Society of Hypertension. It was no surprise to subsequently learn that half of this JNC-VII committee were ALLHAT investigators who had also been appointed by L'Enfant and that the latest guidelines were designed to perpetuate the fallacious ALLHAT conclusions. NHLBI spent over $120 million on ALLHAT, Pfizer chipped in another $40 million and this was all money down the drain since the study produced no positive findings. Nonetheless, this did not prevent the authors from making disturbing and alarming outlandish claims and urging unproven, redundant and possibly dangerous drug strategies. The lipid arm too, which involved over 10,000 of the hypertension trial group, failed to show that pravastatin reduced all cause mortality, actually showing that the statin treated group had a slightly higher rate of cardiovascular deaths than controls. In this regard, everyone seems to have overlooked the fact that statins deplete the body of Coenzyme Q10 a vital component in the electron transport chain that converts calories from food to energy. The heart has the highest requirements in the body for Co Q10 and there is good evidence to believe that the current epidemic of congestive failure is related to increased statin use based on biopsy studies as well as the response to Co Q10 supplementation. It might therefore be difficult to determine whether cases of heart failure attributed to antihypertensive drugs may have actually been related to concomitant statin therapy.

As in the past, L'Enfant desperately tried to salvage something to support his party line that diuretics are superior to other antihypertensive drugs (even though they were not) and that thiazides should always be first line therapy. The only thing NHLBI spin-doctors could come up with was that at that time, thiazides were much cheaper than the other antihypertensive drugs. L'Enfant emphasized this in his initial press conference by indicating that between 1982 and 1992 diuretic use fell from 56% to 27% of antihypertensive prescriptions. Had this decrease not occurred, Americans could have saved $3.1 billion and this is what made front page news on The New York Times and other leading publications and I was anxious to get John's comments on this.

PJR:*The editorial you and Jean wrote was highly critical of the ALLHAT design and conclusions and other hypertension experts also objected to this as well as how the findings had been promoted to physicians and the public. However, nobody seems to have challenged the allegations that thiazides would save billions because they are more or just as effective and much cheaper than other antihypertensive drugs. I doubt that either of these allegations are true.*

JHL: Despite the design of ALLHAT that favored thiazide diuretics, they couldn't demonstrate with their data that hygroton was better than any of the other drugs in the study. This was because it was impossible to draw conclusions about first step therapy responses since the protocol made no provision for recording initial baseline blood pressures! The patients' previous medications were never stopped until the switch day to the trial drug. With respect to saving billions, the low cost of hygroton is not germane because at the same time the government is advocating more and more multiple (2-4) drug regimens. But this claim too is doubtful when you think about how many patients on thiazide diuretics have to take potassium supplements. This is an additional expense, not to mention the antacids and/or other medications that are often required because of gastrointestinal side effects they cause. A very sizeable number of ALLHAT patients required potassium supplementation therapy and a very large proportion had dangerously low potassium levels in spite of that supplementation. Hygroton consistently produces losses of potassium and magnesium and many people do not realize that when there is

significant potassium deficiency, cardioprotection is lost even when blood pressure is maintained at satisfactory low levels. We know from other large trials that hygroton causes low potassium ischemic electrocardiographic changes and is also impressively associated with new onset diabetes. In ALLHAT, there was an 11.6% incidence of new diabetes for every 4 years of hygroton so one might anticipate even a more alarming increase in diabetes in patients taking thiazides for ten or twenty years. Spirolactone, which has come off patent, is also quite inexpensive. In addition to being safer, spirolactone is as effective as thiazide or loop diuretics in lowering elevated blood pressure and does not cause potassium and magnesium loss or induce diabetes. The RALES (Randomized Aldactone Evaluation Study), found that in heart failure patients who were already being treated with thiazides, also blocking aldosterone by adding spirolactone produced such dramatic reductions in heart failure symptoms and mortality rates that the trial had to be stopped prematurely. There is also good evidence from numerous studies that thiazide diuretics can increase risk of cardiovascular and renal complications, all of which can dramatically increase the costs of long term thiazide therapy.[3]

Diabetes, Kidney Disease And Other Complications of Thiazides

PJR:*I would like to discuss another important point that needs to be reemphasized. Basing conclusions on a study lasting a few years does not allow you to consider long term effects in patients doomed to take a drug for the rest of their life, which could be another few decades. As you suggest, it is possible that over half of patients who take thiazides for 20 years may develop diabetes, which poses a large risk for heart attack of the same magnitude as having primary coronary artery disease. An editorial in the August Journal of The Royal Society of Medicine entitled "Type 2 Diabetes is Cardiovascular Disease" noted,*
"The day of 'wait and see' is past, and the term mild diabetes should be buried forever. Gaining ground is the idea that diabetes mellitus (especially type 2 diabetes) is a 'state of accelerated cardiovascular disease that just happens to be associated with hyperglycemia'. People with type 2 diabetes are between two and six times more likely than those without diabetes to have cardiovascular disease and are more than twice as likely to die from it. ***Among diabetologists there is a widely held belief that cardiovascular risk reduction should take precedence over reduction of blood glucose.****"*
This is consistent with your contention that the primary goal of hypertension therapy should be to prevent its renin mediated vasculotoxic complications rather than simply trying to lower an elevated blood pressure regardless of how many medications are required.
It is also estimated that one third of patients with diabetes will eventually develop chronic kidney failure requiring dialysis or a kidney transplant. In addition to diabetes, diuretics can cause acute interstitial nephritis and their overuse is the most common cause of dehydration in patients with diabetic nephropathy. Since diuretics are contraindicated in chronic renal failure they could really wreak havoc in hypertensive diabetics who would continue to take them under the latest guidelines. JNC-VII makes no mention of the significantly increased incidence of new diabetes in ALLHAT compared to those started on an ACE inhibitor or calcium antagonist. Isn't it totally irresponsible and inexcusable for JNC-VII not to warn about this potential problem?

JHL: Definitely. Thiazide induced diabetes is a permanent consequence of this class of drugs that should be emphasized rather than swept under the carpet as NHLBI has done. The same applies to administering thiazides to patients with impaired renal function, which has also been glossed over. It is important to correct hypertension in patients with diabetic nephropathy, but unlike thiazides, the antirenin drugs (ACE inhibitors, ARB's and beta blockers) have been shown to have salutary effects on proteinuria that cannot be achieved with other antihypertensives like thiazides and calcium channel blockers. Thus, the angiotensin II receptor blockers losartan and irbesartan were recently approved for the treatment of diabetic nephropathy in hypertensives with type 2 diabetes. One of the earliest signs of diabetic nephropathy is albuminuria, which becomes greater as the disorder progresses. Screening for microalbuminuria is essential for all patients with diabetes since aggressive intervention can delay and possibly arrest the progression of symptomatic diabetic nephropathy. This is an example of the intermediate endpoints of subclinical organ damage such as microscopic albuminuria the Europeans wisely included as a tool for the assessment of long-term therapeutic benefits of antihypertensive drugs.
A number of clinical studies have clearly demonstrated that blockade of the renin-angiotensin system by an ACE inhibitor or an ARB not only reduces albuminuria but retards the progressive loss in renal function and improves survival. ACE inhibitors reduce albumin excretion in both normotensive and hypertensive patients with type 1 or type 2 diabetes and losartan, another ARB has now also been shown to reduce albuminuria in type 2 diabetes. Yet, JNC VII does not consider diabetes or impaired kidney function to be a contraindication to thiazide therapy and does not mention the potential benefits of ACE inhibitors or ARB's in this regard. **This is another reason why hypertensive patients must be treated on an individual basis rather than assuming they are a homogeneous group for whom no antihypertensive drug selectivity is relevant, as ALLHAT and JNC-VII routinely have continued to do.**

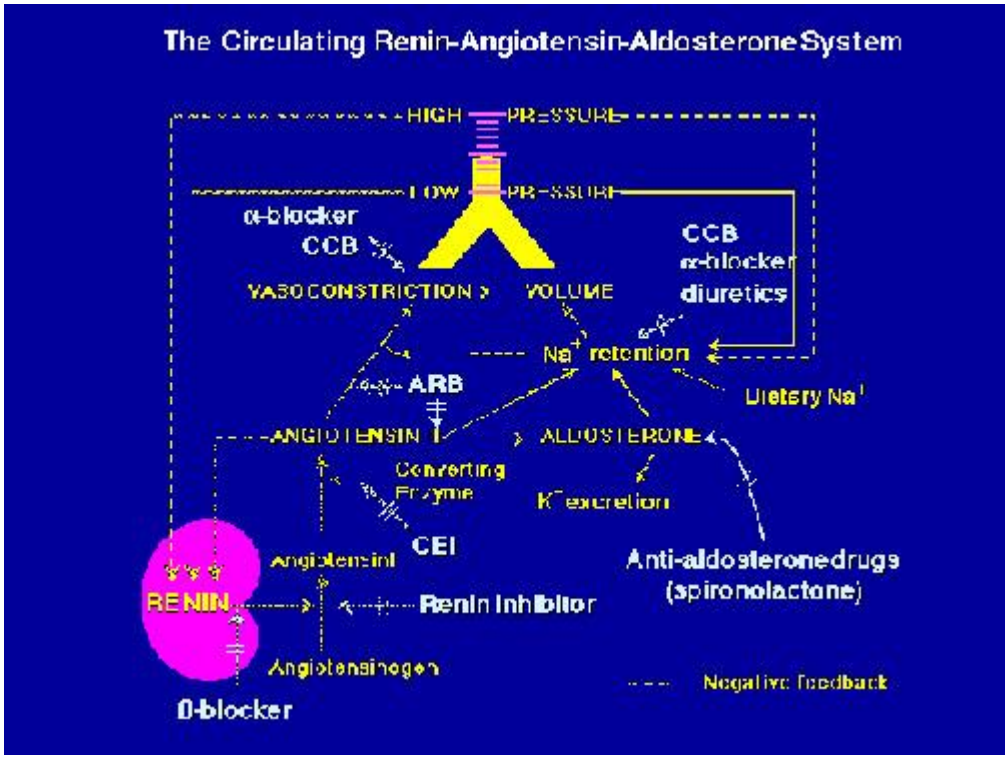
PJR:*An illustration of how well the JNC propaganda has been promoted and the potential for diabetes has been ignored can be found in the August 30 issue of the British Medical Journal, which emphasizes that, "****Current evidence clearly supports using diuretics as first line treatment for hypertension in most patients, including those with diabetes****" and cites JNC-VII as a reference. The JNC-VII media blitz made its debut at a special session of the American Society of Hypertension annual meeting in New York on May 14 along with an NHLBI Press Conference held in Washington with much fanfare and the premature publication of the JNC "Express Report" on the Journal of The American Medical Association web site - all on the same day. As with ALLHAT, officials made a point of reiterating that using diuretics as the first choice would save Americans billions of dollars since the newer drugs were much more expensive without being any more effective or safer. What they conveniently failed to mention was that it was not simply a case of either taking a diuretic or some other drug. So, while the public perception was that the government was saving them money by rejecting expensive drugs that offered no advantages, this was far from the truth. Pharmaceutical companies were far from upset by what most people assumed would augur a sharp decline in sales of their antihypertensive drugs. A Novartis spokesperson lavishly praised the report in a prepared press release the very same day noting that "Inadequate control of blood pressure has become a public health crisis. We are*

encouraged that new approaches recommended by JNC-VII will provide impetus for improvement." That's hardly surprising. Novartis, with its U.S. sales of $21 billion/year has all the hypertension treatment bases covered. They manufacture Diovan, a leading angiotensin receptor blocker Lopressor, a beta blocker, Lotensin, an ACE inhibitor, Lotrel, a combination ACE inhibitor and calcium channel blocking agent as well as products combining most of all the above with a thiazide diuretic to cover all contingencies. Other drug companies also have their own thiazide concoctions. As with ALLHAT, you and many other hypertension experts disputed this as well as other JNC-VII recommendations. For example, 6 months ago if you were to ask anyone, including physicians, what a normal or good blood pressure should be, the most likely response would be 120/80. According to JNC-VII, anyone with a blood pressure of 120/80 will now be labeled as "prehypertensive" and presumably requires treatment, which also provides a picnic for the drug companies. In contrast, the European Society of Hypertension and European Society of Cardiology guidelines published a few months later completely rejected this and continues to consider 120/80 as "optimal" blood pressure. Giuseppe Mancia, the Chair of the ESH/ESC Guidelines Committee, who disapproved of the term "prehypertensive," asked "Would we, for example, call a healthy subject 'prediseased'? It is difficult to tell a patient, 'You are prehypertensive, but don't do anything about it.' Of course the patient is going to think that something is wrong and that he should see the doctor more frequently. He is going to go around asking for medical exams more frequently and he may want to have drugs anyway." Do you agree with this?

JHL: Absolutely. I couldn't say it any better. Nobody knows if this JNC-VII category of prehypertension really exists since there is no proof that it is predictive of anything. As a result, the only thing this new capricious classification accomplishes is to create 45 million more patients by instilling fear. The latest European guidelines also reject thiazides as the first and always drug to treat hypertension. As Professor Mancia noted, "We should not forget that guidelines deal with the disease and physicians deal with individual patients, and these can be quite different situations." Thus, the European guidelines delineate the major indications for which a benefit has been demonstrated in clinical trials and then allows the treating physician to make a choice from a large number of diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers that appear to be most appropriate based on the presence of different risk factors. The guidelines also recognize that the results of therapeutic trials lasting four to six years may have limited value since the life expectancy for middle-aged hypertensive patients is more likely to be 20 to 30 years when other side effects may surface or efficacy may wane. As a result, they have included intermediate endpoints, to detect sub-clinical organ damage such as albuminuria, as tools for the assessment of long-term therapeutic benefits and differences between benefits of various drug classes. **This is quite consistent with our contention that the primary goal in treating all hypertension is not to correct the blood pressure levels per se, but rather to avoid the future occurrence of MI, stroke, renal failure, or heart failure that shorten productive life.** The only drugs proven to protect against these complications are the three anti-renin system drug classes, i.e. ACE inhibitors, angiotensin receptor blockers (ARBs), and the beta-blockers. All of these agents lower or block renin activity to lower blood pressure while providing measurable and prompt protection from such vasculotoxic effects as heart attack, stroke, heart failure and kidney failure. In the LIFE study, losartan, an angiotensin receptor blocker, when combined with a diuretic, was 25% more effective in preventing stroke compared to a beta-blocker combined with a diuretic, which was the winning combination in ALLHAT. JNC-VII also conveniently but reprehensibly ignored this study even though losartan was recently approved for the prevention of stroke. Some of the main differences between their conception of treating hypertension and ours include:

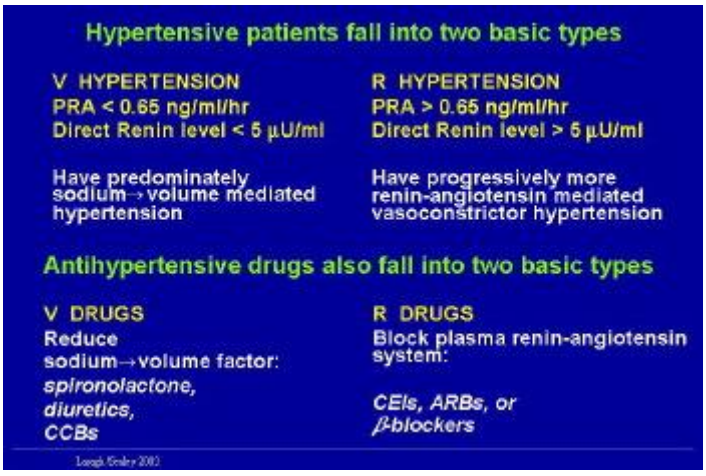
ALLHAT and JNC-VII	The Laragh Method
Hypertensive patients are treated as if they were all alike in both trialdesign and analysis.	Hypertensive patients differ in their underlying pathophysiology and in their responses to drugs.
No drug subtractions or substitutions: Even if a drug is not effective it should not be stopped.	Individual patients have either V or R form forms of hypertension that respond differently to V or R drugs.
Basic philosophy is that any drug is better than no drug in a hypertensive patient. The goal should be to lower blood pressure regardless of what it takes.	Targeted monotherapy that prevents or reduces fatal complications of hypertension is more important than just treating numbers.

Our approach is based on decades of scientific research designed to delineate the various positive and negative influences on the renin-angiotensin-aldostersone system as illustrated in the following diagram taken from the cover of my book[1]:



Click here to enlarge

Our conclusions based on this may be summarized as follows:



Click here to enlarge

Click here to enlarge

Our research has concentrated on the roles of renin, angiotensin and aldosterone but the cornerstone for understanding salt-volume hypertension was the demonstration of desoxycorticosterone - salt induced hypertension in rats by your close friend and mentor, Hans Selye. Since telling you about Selye's research would be like bringing coals to Newcastle, let's switch positions so I can ask you a few questions.

The Stress - Hypertension Connection And Conundrum

JHL: *What do you think Selye's take on all this might be were he alive today with respect to hypertension and its complications as an example of one of his "Diseases of Adaptation" due to stress?*

PJR: I was hoping we might get around to this. Let me start by saying that Selye was very familiar with your hypothesis and devoted a half page to reproducing one of your diagrams showing the synergism of the angiotensin II vasoconstrictor and sodium-volume components in sustaining blood pressure in his massive tome, *Stress in Health and Disease*, published in 1976. He also cited several studies showing increases in renin and angiotensin ll in stressful human situations such as surgical procedures or severe burns. Elevation of blood pressure following infusion of angiotensin ll in monkeys was much greater in animals that were under stress and in rats exposed to repeated electroshocks "the marked rises in plasma concentrations of renin and corticosterone coincided." These elevations were not inhibited by hypophysectomy but were blocked by dexamethasone and propanolol and increased by phentolamine. Selye concluded that stress-induced renin release was mediated via beta-adrenergic receptors and that corticoids could modify this response. Much of his discussion was devoted to evidence that the pressor effects of catecholamines and corticoids released during stress acted synergistically and that the hypertensive actions of mineralocorticoids were augmented by a high sodium diet. The therapeutic efficacy of propanolol and aldactone seemed to support his stress theory but he was puzzled by "occasional instances of hypertension where plasma renin was below normal" He believed that this "hyporenimic hypertension" might be due to increased production of some mineralocorticoid that decreases renin secretion. As you suggest, Selye was much more interested in demonstrating that heart attacks, nephrosclerosis and other vasculotoxic complications of hypertension were Diseases of Adaptation since they could be readily induced during his General Adaptation Syndrome response to stress.
Selye was undoubtedly the leading endocrinologist of his era and was responsible for classifying the several dozen steroid hormones secreted by the adrenal cortex into three main categories - glucorticoids, mineralocorticoids and testoids. Glucorticoids like cortisone raised blood sugar and had catabolic and anti-inflammatory effects. Mineralocorticoids like desoxycorticocosterone (DOC) caused sodium retention and had "prophlogistic" activities that promoted inflammation while testoids acted like weak androgens and had anabolic activities. Selye went to great lengths to demonstrate a teleological basis for this, as Cannon had done for his "fight or flight" responses. ACTH clearly stimulated the production of glucocorticoids and STH augmented mineralocorticoid activities either by increasing production or exaggerating these effects. This suggested that there were checks and balances between ACTH and STH in the pituitary and between glucocorticoids and mineralocorticoids in the adrenal. ACTH and glucocorticoids had strong anti-inflammatory effects whereas STH and mineralocorticoids stimulated inflammatory and proliferative connective tissue responses in his animal studies.

Administration of cortisone to patients with rheumatoid arthritis dramatically reduced painful inflammation and when DOC was used to treat patients with adrenal insufficiency there were reports of focal areas of necrosis in the heart and skeletal muscle, evidence of periarteritis nodosa, nephrosclerosis, and even the development of incapacitating arthritis as had been seen in experimental animals. The tendency to develop hypertension even with very small doses of DOC was also a frequent problem encountered during the treatment of adrenal insufficiency. This supported Selye's theories but DOC is not manufactured in any appreciable amount in humans. When aldosterone, the naturally occurring human mineralocorticoid, became available, attempts to demonstrate its ability to counter the anti-inflammatory effects of cortisone or produce the DOC changes observed in experimental animals were disappointing. It therefore seemed unlikely that aldosterone caused significant pathology in humans.

JHL:*However, when aldosterone is present with increased renin-angiotensin levels it's a different story. Recent studies do support Selye concepts since researchers have now confirmed that aldosterone can contribute to cardiovascular and renal pathology as well as to fibrosis and collagen formation by promoting sodium influx and potassium efflux and hypertrophy in vascular smooth muscle cells, generation of oxygen free radicals, stimulation of growth factors, the plasminogen activator system and via potentiating the pressor effects of angiotensin II.*

PJR: Like angiotensin II, aldosterone stimulates inflammation, which many believe plays a more important role in the pathogenesis of coronary atherosclerosis than hyperlipidemia.

JHL:*In that regard, I sent you a recent article by a respected cardiologist who suggested that "statin therapy should be routinely considered, even in those hypertensive patients whose cholesterol levels are apparently normal." You have written a great deal about statins and I wanted your opinion.*

PJR: Statins have also been recommended for all diabetics, regardless of lipid levels, and are allegedly effective for reducing everything from Alzheimer's disease and atrial fibrillation to emotional stress. Statins may be effective medications but it is increasingly clear that their cardioprotective and other benefits are really due to their anti-inflammatory activities rather than lowering lipids. Therefore, the statin therapy goal of lowering LDL to an arbitrary level that is usually difficult to achieve is not only inappropriate but also dangerous. This can only lead to higher doses and longer duration of therapy, both of which are associated with increased side effects, which are much more common and diverse than generally recognized. C-reactive protein (CRP), a marker of inflammation has been shown to be superior to LDL levels for predicting coronary events and could be a more effective and certainly safer way to monitor statin therapy. In addition, I would remind you that the lipid reduction arm of the ALLHAT study showed absolutely no reduction in mortality from statins.

JHL: *There is also increased interest in the possible role of inflammation in the pathogenesis of essential hypertension. I recognize there are conflicting opinions but do any of these research studies tend to support Selye's contentions about the contribution of stress?*

PJR: Yes and perhaps some comments about aldosterone and the plasminogen activator system (PAS) will illustrate the complex contributions of stress to hypertension and its complications. The plasminogen activator system is best known for its ability to dissolve clots but it also plays other important roles in blood vessel wall and tissue activities that are pertinent. It is inhibited by PAI-1, which has been shown to contribute directly to hypertension and perivascular fibrosis in a variety of different animal models. In humans, PAI-1 is increased in acute MI, disseminated intravascular coagulation and glomerulonephritis so perhaps it can contribute to these as well.
Aldosterone drives PAI-1 into the plasma and aldosterone concentrations correlate with PAI-1levels in hypertensive patients. Although hydrochlorothiazide shrinks intravascular volume the associated activation of the renin-angiotensin-aldosterone system increases plasma PAI-1 by 50% to 80% after a month depending on dosage. This could contribute to some of the adverse effects noted with long term thiazide therapy. Spirolactone obliterates aldosterone and PAI-1 relationships in hypertensives under basal conditions as well as on diuretics, which supports your observation about its superiority over thiazides. The PAI-1 gene is "up regulated" or activated by mental stress. PAI-I is one of the most highly induced stress proteins and the magnitude of stress induced PAI-I increases with abdominal obesity. This suggests that visceral fat is its primary source, as it is for other inflammatory cytokines that contribute to the metabolic syndrome that includes hypertension and diabetes. A very recent study showing that visceral adiposity increases hypertension risk independent of insulin levels suggests that PAI-I activation plays a

key role. Both animal and human studies confirm that stress promotes the development of visceral fat via increased cortisol secretion. Abdominal fat, hypertension and diabetes disappear in Cushing's disease when the condition is corrected and high cortisol levels return to normal. I could go on in greater detail about this but am afraid that we have strayed quite a bit from our original objective, which was to highlight the fallacies of the ALLHAT study and the dangers of implementing its recommendations for treating hypertension as JNC-VII now advocates. I think we have accomplished that mission and perhaps we should close on what you see for the future of renin and its role in hypertension and cardiovascular disease.

Does Renin Cause Cardiovascular & Kidney Disease In Non-hypertensive Patients ?

PJR:*As Hans Selye was fond of reminding me, theories are not important, only facts are. Some theories are meritorious for their heuristic value, in that they encourage others to discover new facts that lead to improved theories. In that regard, the existing facts confirm your hypothesis about the role of renin in essential hypertension. Studies now show that antirenin drugs are effective in treating or preventing cardiovascular and kidney disease not only in hypertensive patients but others with normal blood pressure. Doesn't this imply a much larger role for renin in these disorders than is currently recognized?*

JHL: You are absolutely correct. The antirenin R drugs (ACE inhibitors, ARB's and beta blockers) have been shown to have salutary effects on the proteinuria due to kidney disease that are not achieved with other antihypertensives like thiazides and calcium channel blockers. Thus, the angiotensin II receptor blockers losartan and irbesartan were recently approved for the treatment of diabetic nephropathy in hypertensives with type 2 diabetes. As you pointed out, ACE inhibitors reduce albumin excretion in both normotensive and hypertensive patients with type 1 or type 2 diabetes and angiotensin II receptor blockers have also been shown to reduce albuminuria in type 2 diabetes. A recently published double-blind, randomized crossover trial reported that adding the ARB candesartan to treatment with maximal recommended doses of ACE inhibitors provided superior renoprotection in diabetic nephropathy that was completely independent of blood pressure changes. Candesartan has also been shown to reduce cardiovascular mortality and hospital admissions for congestive heart failure in a broad spectrum of patients already receiving "best treatment" with other drugs. The EUROPA study just reported that the ACE inhibitor perindopril reduced the risk of myocardial infarction and death in patients with stable coronary artery disease, including those with a history of a past myocardial infarction and angina so significantly that **it should be considered for chronic therapy in all patients with coronary disease**. Perindopril has also been suggested to prevent stroke recurrence in normotensive patients. It seems quite possible that we have only scratched the surface with respect to the role of renin in the pathophysiology of vasculotoxic events in normotensive patients at increased risk from diabetes, cardiovascular or renal disease. Gaining insight into what induces overactivity of the renin-angiotensin-aldosterone cascade in all these events could be the key to learning how to prevent or treat essential hypertension. Meanwhile, recognition of the renin factor in patients with (R) hypertension and early use of antirenin R drugs could extend useful life for millions by preventing or delaying fatal heart attack, stroke, or heart and kidney failure.

PJR: *A recent study showed enhanced adrenocortical responses to stress as measured by salivary cortisol levels in hypertension prone men and women compared to controls. Increased aldosterone secretion during stress has also been reported. In addition, emotional stress increases levels of homocysteine, which has been shown to be a significant risk factor for heart attacks and accelerated atherosclerosis and possibly hypertension. My guess is that the primary stimulus for renin angiotensin aldosterone activation will be found to originate in the brain and possibly the cerebral cortex. If this proves true, stress could play a crucial role in hypertension, as Hans Selye always alleged - so stay tuned for more!*

---

1. Laragh, JH (2002): Laragh's Lessons in Renin System Pathophysiology for Treating Hypertension and its Fatal Cardiovascular Consequences. Elsevier Science Inc., New York, NY (To order, 1-800-545-2522; **www.us.elsevierhealth.com**, **www.amazon.com**, or **www.barnesandnoble.com**)

2. Laragh JH, Sealey JE. Relevance of the plasma renin hormonal control system that regulates blood pressure and sodium balance for treating hypertension and for evaluating ALLHAT. 2003; American Journal of Hypertension, 16:407-415.
3. Laragh JH, Sealey JE. K+ depletion and the progression of hypertensive disease or heart failure. The pathogenic role of diuretic induced aldosterone secretion. 2001; Hypertension, 47 [part 2]:806-810.