

# Why the Treatment of Hypertension has Become Such a Deplorable Fiasco, Part I

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**An interview with Dr. John Laragh by Paul J. Rosch, M.D.**

Despite over 100 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 percent were unaware of their illness, 42 percent were not being treated, and at the time that their BP was measured, 69 percent did not have their hypertension controlled!"

Another survey published in the British Medical Journal in June found that 97 percent of patients taking antihypertensive medications had suffered from significant side effects at some time and 17 percent 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 titled "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.

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. 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. I have referred many patients to him and have always found him to be a very caring as well as skilled clinician.

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 and perfected over the past three decades. 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 this has 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 decided to fill in a few blanks and also obtain his opinion about these latest official recommendations in a recent interview. Because of space constraints I have condensed and paraphrased some of his responses as well as my questions, but the entire interview is available at [www.stress.org](http://www.stress.org) and [redflagsweekly.com](http://redflagsweekly.com).

## How the Renin Story Began and Evolved

**PJR:** How did you become interested in renin?

**JHL:** What first led to my interest in renin was a patient that Robert Loeb, chairman of the Department of Medicine at Columbia University College of Physicians and Surgeons had referred to me in 1957. He was a 57-year-old CEO of a large company with malignant hypertension, 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 but, unlike everybody else, we found aldosterone to be quite normal in essential hypertension. However, to our amazement, it was massively increased in fatal malignant hypertension. We subsequently removed the adrenals in four 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 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 should renin be so important if it is inactive?

**JHL:** What had been established by Braun-Menendez was that renin acted enzymatically on a circulating plasma protein (angiotensinogen) to release an inactive substance (angiotensin I) that is rapidly hydrolyzed by "converting enzymes" to form the most powerful pressor substance known, 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. We showed that when you give angiotensin II to normal humans 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 and expand blood volume 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.

**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., rampril) 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.

We then went on to prove that about two out of three 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, spiro lactone, 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 was not widely available, as well as being expensive, since unlike today, it was not covered by health insurance. Paul Brown, who 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 United States, 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 inaccurate because of a variety of procedural errors we were able to identify and correct 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 seven to eight years in their New Jersey laboratory. Recently, we have helped them to switch to their automated Direct Renin test which now shows a good correlation with our more time consuming assay. 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**

- PRA levels less than 0.65 ng/m/hr
- Direct Renin less than 5 mU/ml
- This is predominantly sodium-volume renin-caused hypertension

### **(R) Renin Hypertension**

- PRA levels greater than 0.65 ng/m/hr
- Direct Renin greater than 5 mU/m
- This is predominantly due to 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\*(see below) 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 spiro lactone, 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 percent to 80 percent 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 two to four 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 percent 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 two out of three 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 underappreciated harm that can result from traditional diuretic therapy. The thiazide diuretic, hydrochlorothiazide, produced over an 11 percent incidence of real and permanent diabetes in less than five years in the ALLHAT trial, which suggests at least 22 percent 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 spiro lactone 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 one-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 percent 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 10 were already receiving some type of antihypertensive drug therapy and there was no washout or medication-tapering period. On day one they were

switched to one of four blinded randomized drug limbs: diuretic (hydrochlorothiazide), ARB (doxazosin), ACE inhibitor (lisinopril) or calcium channel blocker (amlodipine), 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,\*\* many of us would consider failure to achieve effective drug treatment for six to 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 nine to 12 months and it was only after 16 months that a step-three 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 (hydrochlorothiazide) 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 percent 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 two 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 nine to 12 months, so that a patient who really required a V drug was essentially taking two placebos for 16 months.

It was only after 16 months that the step-three 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 antivolome 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 lawsuits, 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*<sup>\*\*</sup>, 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 10 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 strokes but ACE inhibitors were dropped 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 excluded as recommended starting medications in JNC-VII, leaving thiazide diuretics to again reign alone as 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 percent 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 percent Caucasian as opposed to less than two-thirds in the ALLHAT study.

### **More NHLBI and JNC-VII Deception and Chicanery**

**PJR:** 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, which 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.