HEALTH AND STRESS

The Newsletter of
The American Institute of Stress

October — SPECIAL EXPANDED EDITION — 2003

WHY TREATING HYPERTENSION HAS BECOME A DISMAL FIASCO

KEYWORDS: Malignant hypertension, Robert Tigerstedt, Harry Goldblatt, Jean Sealey, ALLHAT study, JNC-VII, Hans Selye, Diseases of Adaptation, stress and PAI-1

Despite over one hundred prescription products 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 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.

The main reason for this misinformation is that **government guidelines for the treatment of high**

ALSO INCLUDED IN THIS ISSUE

blood pressure disseminated by NHLBI (National Heart, Blood, and Lung Institute) are dictated more by politics rather than science. This is vividly illustrated by the belief that all Americans should drastically reduce 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 the latest hypertension treatment advice. This could be a prescription for disaster, particularly since safer and more effective alternatives 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 its 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 can be permanently controlled 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 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 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 wanted to fill in a few blanks and also obtain his opinion about these latest official recommendations. I think that you will find his comments during a recent interview illuminating but our conversation covered so many topics that it would fill two Newsletters. I have summarized some highlights in this expanded issue and the complete interview will appear as a three part series on the web at www.redflagsweekly.com, www.stress.org and other sites.

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 Bob 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 neighboring scientist, who discovered noradrenalin in the adrenal medulla and defined its differences from adrenalin. To block its biosynthesis, he also 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 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. His aldosterone secretion was over 800 mgm/day while our normal values were less than 50. I should say that 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 H_3 and then injecting a tracer I.V. into our patients and ourselves.

The degree to which the radioactivity was diluted by aldosterone in the patient's blood in 24 hours gave us the daily secretory rate. Unlike most everybody else, we found aldosterone to be quite normal in essential hypertension. But, to our amazement, it was massively increased in fatal hypokalemic malignant hypertension. We removed the adrenals in 4 such patients to eliminate aldosterone without any benefit, since they all died on schedule.

Thus, we showed that malignant hypertension and its diffuse vasculitis was not caused by high aldosterone since this fatal condition progressed in the absence of the adrenals and 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 be excess renin from the severely damaged kidneys of these patients.**

In 1898, Tigerstedt and Bergman published an article in a Scandinavian journal describing an amazing and powerful blood pressure raising substance they had isolated from rabbit kidney extracts. They called this substance renin. But subsequent scientists failed to confirm Tigerstedt and Bergman's findings and there was little interest in renin until 1934 when Harry Goldblatt published the landmark results of his dog experiments. Harry had 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 increased renin release.

It was therefore very disappointing that numerous attempts showed absolutely no evidence that plasma renin levels were increased in essential hypertension or even that renin had important physiologic actions of its own.

The Pivotal Role Of Angiotensin

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

JHL: What we and others proved was that renin acted enzymatically on a circulating plasma protein (angiotensinogen) to release an inactive decapeptide (angiotensin I). This was rapidly hydrolyzed by converting enzymes to the most powerful pressor octapeptide known, angiotensin II. It was this vasoconstrictor angiotensin II, released only by renin, that played the crucial role in causing human hypertension. When you give angiotensin II to humans it produces a rapid rise in blood pressure by promoting vasoconstriction and also via a slower effect by stimulating aldosterone secretion to promote sodium retention by the kidney. However, it was many years before either the normal roles of plasma renin or angiotensin would finally be acknowledged and longer still before the establishment began to accept renin as a major cause of human essential hypertension.

But in 1958, when we discovered very high aldosterone levels in fatal malignant hypertension, the octapeptide angiotensin II had just been synthesized by CIBA. They provided samples to us for human research and we cautiously administered tiny subpressor amounts of it intravenously to six normal volunteers. In over 40 such infusion studies, only angiotensin II (but not 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 blood pressure not only via direct angiotensin II arteriolar vasoconstriction but also by angiotensin induced adrenal aldosterone release. Aldosterone expands blood volume by causing the kidneys to retain sodium and thus water.

PJR: *How did this information help you target treatment to a specific hypertensive patient?*

JHL: The new data led us to propose and later prove that the malignant hypertension syndrome is caused by an unchecked runaway release of renin leading to very high plasma angiotensin levels. This raises blood pressure and also injures coronary, cerebral and renal vessels, rapidly leading to fatal complications.

We were able to correct all of this not only by removing both kidneys, but also by treating each patient with any one of the 3 antirenin (R) types of drugs that we characterized and introduced: first propranolol, a beta blocker, to block the kidney beta receptor activated renin release, then, the snake venom peptide (teprotide), the original intravenous angiotensin converting enzyme (ACE) inhibitor, and finally, intravenous octapeptide saralasin, the first angiotensin II receptor blocker (ARB). Our findings soon persuaded industry to synthesize many orally active analogs of the venom peptide teprotide (e.g. captopril, enalapril, lisinopril) and later on, many orally active ARB's resembling saralasin (losartan, valsartan, cardesartan, olmesartan, irbesartan, telmisartan, eprosartan).

As you know, these explicit antirenin system drugs, together with the beta blockers, another R drug class, have revolutionized the treatment of human hypertension. They have had an even greater impact for preventing or arresting plasma renin-caused fatal consequences, i.e. heart attack, heart failure, stroke and kidney failure similar to the correction of all these by total nephrectomy in patients with malignant hypertension. Collectively, these numerous commercially available antirenin drugs produce similar truly dramatic and lasting correction for patients with renin mediated hypertension lasting for 15 years or more!

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 also showed that milder excesses of renin angiotensin activity were responsible for about 2 out of 3 cases of essential hypertension. In these patients we could also prevent the same but more gradually developed fatal sequelae of heart attacks, stroke, heart failure and kidney failure with one of our three antirenin (R) drug types. However, these (R) drugs did not benefit patients with low renin hypertension who, on the other hand, responded incredibly well to (V) drugs that reduced blood volume.

The Plasma And Direct Renin Assays

PJR: *The key to your treatment method appears to be the ability to measure plasma renin or angiotensin activity accurately. The difficulty that most physicians had was that these were quite complicated and sensitive procedures that were not widely available and were also expensive, since in those days insurance companies did not cover them. 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, but as usual, a little ahead of the curve. Jean Sealey joined our laboratory in 1960 as a biochemist with excellent credentials and she soon showed us how our aldosterone assay could be improved. 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 very inaccurate because they didn't reference the level of renin activity to the current state of sodium balance, poor angiotensinase inhibition, poor pH control and were unaware of the effect of cryoactivated prorenin. Jean showed that a previously unappreciated large amount of prorenin occurs in human plasma and is 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, which is critical for identifying low renin 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 this is absolutely crucial since it is the only way to positively identify and separate the salt-volume "V" patients whose hypertension is caused by salt and have no renin in their plasma.

Quest has been using our Sealey-Laragh method for the past 7-8 years in their New Jersey laboratory since we are close by to help with any problems. They confirmed our results but unfortunately, our 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 predecessors, 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 significant and high enough to **produce a fatal stroke at -12 molar concentrations of renin or 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 < 0.65 ng/m/hr	PRA levels > 0.65 ng/m/hr
Direct Renin < 5 mU/ml	Direct Renin > 5 mU/m
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.**

Treating Volume Vs. Renin Hypertension

PJR: *We don't have enough space left to go into how specific medications are selected based on renin profiling or how to start treatment if renin testing is not readily available. This information is elegantly explained in your recent book*(see below) but perhaps you could give us a brief summary.*

JHL: Yes, essentially, salt-volume (V) hypertension is always associated with low 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 and resembles a *forme fruste* of fatal malignant hypertension. It 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 such patients are denied the precious opportunity for a lifetime of monotherapy with the correct drug type but are condemned to taking 2 - 4 drugs. This increases costs and side effects while providing less net benefit as well as diminished productivity and quality of life.

It is also possible to bypass renin testing by using single file trials of a V and then an R medication to identify which type will correct the hypertension. In addition, you delete drugs that don't work rather than always continuing diuretics as JNC-VII mandates.

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 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 may also deny high renin patients protection from fatal cardiovascular complications that antirenin medications do provide.*

JHL: You are absolutely correct and what is both impressive as well as alarming is the underappreciated harm that can result from traditional diuretic therapy. 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, electro-cardiographic changes and thence to fatal cardiovascular complications. The good news is that all of these complications can be avoided by using spirolactone instead

***** 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: 800-545-2522; www.amazon.com www.barnesandnoble.com)

to correct sodium-volume related hypertension without causing diabetes or depletion of potassium and magnesium.

Our renin hypothesis was 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 heart attack, congestive heart failure and sudden death. This shows that blocking the presence or action of angiotensin II by giving the correct antirenin R drug to this very vulnerable group of patients can prevent fatal plasma renin vasculotoxicity. As emphasized, **R drugs do not help low renin hypertensives, who require and often have dramatic relief from V drug salt depletion. Conversely, V drugs are ineffective and often harmful if given to renin hypertensive patients**.

Guidelines Based on Politics - Not Science

PJR: *Since others have confirmed your hypothesis and NHLBI has funded your research it is puzzling that renin is never 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." 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 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 ALLHAT, 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 abrupt cessation of diuretic therapy in those patients who were placed on comparatively weak dosages of doxazosin 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 elsewhere,* **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

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* 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.

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 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 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 disadvantage. The tragedy is that the ALLHAT recommendations are the basis for the new JNC-VII guidelines.

ALLHAT Versus The Laragh Method

PJR: *One ALLHAT malpractice 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. On entering the study, he had rated his health as "very good" (90 on a 100-point scale). He 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 tissue swelling, 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 drug 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 were not reported or investigated as should have been done. He should also 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." It seems unlikely that this tragedy would have happened with your approach.*

JHL: I don't know the details here but one potential ALLHAT malpractice problem 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 deplorable, especially since this second drug was then titrated up for another 9-12 months. Thus a patient who really required a V drug was essentially taking only 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. As also indicated in our editorial in *The American Journal of Hypertension*, 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. 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.

One can only imagine how frustrating this must have been for treating physicians who recognized such problems but had to abide by the rules of the trial. With respect to law suits, in all fairness, no matter how well any clinical 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. Some of the major basic differences between our approach and ALLHAT and JNC-VII are noted below:

ALLHAT	Laragh Method
Hypertensive patients are treated as if they were all alike in both trial design & analysis.	Hypertensive patients differ in their underlying pathophysiology and in their responses to drugs.
No drug subtractions: Even if a drug is not effective it should not be stopped.	Individual patients have either V or R 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 the vasculotoxic and often fatal complications of hypertension is more important than just treating numbers.

Our research has concentrated on renin but the cornerstone for understanding salt-volume hypertension was the demonstration of desoxy-corticosterone - 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 me ask you a few questions.

The Stress - Hypertension 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 could 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 II in stressful human situations such as surgical procedures or severe burns. Elevation of blood pressure following infusion of angiotensin II 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 b-adrenergic responses 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 steroids secreted by the adrenal cortex into three main categories - glucocorticoids, mineralocorticoids and testoids. Glucocorticoids like cortisone raised blood sugar and had catabolic and anti-inflammatory effects. Mineralocorticoids like desoxycorticosterone (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 mineralo-corticoid, 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 per se caused significant pathology in humans.

The Role Of Inflammation

JHL: *However, recent studies do support Selye's 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 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 lipid lowering. 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 glomerulo-nephritis, so perhaps it can contribute to these as well.

Aldosterone drives PAI-1 into the plasma and aldosterone concentrations correlate with PAI-1 levels 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 diuretics.

The PAI-1 gene is activated by mental stress and inflammatory cytokines. PAI-1 is one of the most highly induced stress proteins and the magnitude of stress induced PAI-1 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. 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 but am afraid that I 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.

More On NHLBI & JNC-VII Chicanery

PJR: *At the gala National Press Club kickoff media event to applaud the ALLHAT findings, NHLBI Director Claude L'Enfant announced that he was appointing a committee to draw up new hypertension treatment recommendations to be presented in five months at the annual meeting of The American Society of Hypertension. It was no surprise to later 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 flawed and fallacious ALLHAT conclusions of thiazides first and always.*

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. The JNC-VII committee completely failed to acknowledge other large hypertensive trials like INVEST, LIFE and especially ANBP2 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 trial, the diuretic hydrochlorthiazide, was compared with the ACE inhibitor enalapril and at the end of five years, the ACE inhibitor was found to be superior, to the thiazide diuretic.

The ANB2 design allowed physicians to switch drugs whenever the drug used wasn't working. Those receiving the diuretic hydrochlorthiazide stayed on it if it worked and were switched to enalapril if there had been no improvement and vice versa. This stopping and switching, forbidden by the ALLHAT protocol, allowed the ANB2 investigators to correct 65% to 67% of all subjects using one drug and renin mediated hypertensives were prevented from having a heart attack or stroke. 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.

PJR: *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 Yogi Berra said, "It's déjà vu all over again", since this was remarkably reminiscent of how the NHLBI detection and treatment of high cholesterol program had operated. Their first 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 2001 recommendations that tripled the number of Americans advised to take statins were also published prematurely in JAMA. In violation of the Government code there was no public notice of any meetings, meetings were not open to the public, public input was not solicited, detailed records and testimony of committee meetings were not kept nor were they published in the Federal Register as required.*

JHL: The problem was that the very costly ALLHAT study proved nothing and the only thing NHLBI spin doctors could come up with was 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. JNC-VII officials have also repeatedly emphasized this in their interviews and press releases.

What they conveniently failed to mention was that it was not simply a case of either taking a diuretic or some other drug. Nor did they emphasize their quickly later added corrective conclusion that "Most patients with hypertension will require two or more antihypertensive medications to achieve goal pressure". This creates an unprecedented picnic for all drug makers including the generics and it is now "Open Sesame" for the pharmaceutical industry. So, while the public perception was that the government was saving them money by rejecting expensive drugs that offered no advantages, this is very far from the truth. As you have noted, their dietary salt and fat taboos for everyone are also fallacious.

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

PJR: *As Hans Selye was fond of advising 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 drugs (ACE inhibitors, ARB's and beta blockers) have been shown to have salutary effects on 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. In addition to diabetes, diuretics can cause acute interstitial nephritis, their overuse is the most common cause of dehydration in patients with diabetic nephropathy and they are contraindicated in chronic renal failure. Yet, JNC-VII does not consider diabetes or impaired kidney function to be a contraindication to thiazide therapy and never mentions the benefits of ACE inhibitors or ARB's in this regard.

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. 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. At present, blocking or counteracting these harmful responses with antirenin drugs is the best approach based on our research.

PJR: *I suspect that the primary stimulus will be found to originate in the brain, possibly the cerebral cortex. If this proves true, stress could play a crucial role in hypertension, as Hans Selye always alleged. — Stay tuned!*

Health and Stress
The Newsletter of
The American Institute of Stress
124 Park Avenue Yonkers, NY 10703

ANNUAL SUBSCRIPTION RATES:
E-MAIL..... $25.00
PRINT (DOMESTIC)..... $35.00
PRINT (FOREIGN)..... $45.00

ISSN # 1089-148X

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