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PREHYPERTENSION AND THE EMPEROR'S NEW INVISIBLE SUIT

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Up until a few weeks ago, if you asked anyone, including doctors, what they considered a normal or desirable adult blood pressure to be, 120/80 would have been the most frequent response. Not any more. According to the new JNC-7 guidelines, 120/80 puts you in a new disease category called "prehypertension" and at increased risk for heart attack, stroke, or kidney disease. The recommendations for rectifying this potentially deadly disorder are the usual advice to lose weight, avoid salt and sodium rich foods, exercise regularly, stop smoking and reduce stress. However, we all know how difficult it is to achieve these goals, much less maintain them. And even if you do, the results are not that rewarding, even for patients with blood pressures of 160/100 and higher.

ALSO INCLUDED IN THIS ISSUE

People with prehypertension are even less likely to find that lifestyle modification will normalize their blood pressure, which means that medication will be required. Chalk another one up for the drug companies.

The first advice generally given to all patients with high blood pressure is to significantly restrict sodium intake. However, the vast majority fail to respond to this unless they have certain genetic traits. In some, calcium deficiency can be the culprit and they improve with calcium supplementation. These hypertensives may actually worsen on a low sodium regimen since this would sharply reduce the intake of dairy products that are the major source of dietary calcium. Others benefit from potassium and/or magnesium supplements. Jogging and running may help lower blood pressure for some people but more often has little effect and can even cause a rise.

Hypertension, like fever, is not a diagnosis but rather a description. It is simply an elevated blood pressure reading, on some measuring device, that can have many different causes. That helps to explain why we have some 100 drugs to treat high blood pressure. Unfortunately, there is no algorithm to guarantee which one will work best or be the

safest for any specific patient. Similarly, a fever of 103° in a patient with lupus may require giving cortisone but if that identical 103° temperature reading were due to tuberculosis, cortisone could bring the fever down but might prove lethal. Conversely, appropriate antibiotics would be an effective treatment for tuberculosis but would provide little benefit in lupus.

Risk Factors And Other Fallacies

In order to successfully treat a disease it is necessary to remove or reduce its cause rather than its manifestations or markers. Treating a persistently elevated blood pressure or temperature is very different than treating an elevated blood sugar. While the goal in diabetes is to lower the blood sugar to normal, responses to medication and/or diet are much more predictable and sustained since the cause can almost always be identified.

An elevated temperature can be a purposeful physiologic response to stimulate immune system defenses. Hyperthermia due to artificially induced fever has been used to treat erysipelas, tuberculosis, neurosyphilis and certain malignancies. Giving non-specific drugs just to bring an elevated temperature down to normal could do more harm than good in certain situations. **The same may apply to many older individuals with arteriosclerotic vessels, where a higher blood pressure is needed to maintain adequate blood flow to the kidneys and other vital organs. Whatever happened to the good old days when a normal systolic pressure was 100 plus your age?** Not everyone agrees with this and the upper limit is now usually considered to be 140/90, even for people over 70.

Nevertheless, some senior citizens will consistently complain of weakness and dizziness if their blood pressures are lower than the 120/80 value that is now recommended. This is particularly true for women, who normally tend to have higher blood pressures than men in this age group.

Much of this "one size fits all" approach comes from confusion over what a "risk factor" really represents. Most risk factors for heart disease are merely "risk markers" that simply have some statistical association with an increased incidence of coronary events. There are over 300 risk factors for heart attacks, including a deep earlobe crease, premature vertex baldness, high selenium toenail levels, having a pot belly, not having a nap or one or two glasses of wine a day.

Attempting to treat or remove such markers will accomplish nothing since they do not cause coronary disease. The same can be true for lowering an elevated systolic or diastolic blood pressure unless the treatment is directed at what is causing the problem, which is usually not clear. No randomized clinical trials have ever proven that lowering an elevated systolic blood pressure to 140 reduces the risk for death due to coronary disease. A good example of this was the multicenter Multiple Risk Factor Trial (MRFIT) designed to demonstrate that reducing hypertension, high cholesterol and smoking would lower coronary mortality. After screening some 350,000 middle-aged men, close to 13,000 believed to be at greater jeopardy because of a pre-ponderance of these putative risk factors were selected. They were divided into a treatment group to lower these markers and a control group that received usual care.

After ten years and $115 million, although the treatment group substantially achieved their objectives, they fared no different than controls who received usual care. In point of fact, a subset of **hypertensives treated with diuretics had the highest mortality rates**, probably from ventricular fibrillation due to potassium depletion. The MRFIT objective was to get blood pressures below 140/90. One can only wonder what the mortality rate would have been if under 120/80 had been the goal.

Stress And Pseudohypertension

My personal experience has been that a significant percentage of patients being treated for "essential hypertension" can stop their medication without any adverse effects. When such individuals are admitted to the hospital for surgery or some unrelated condition and these drugs are discontinued deliberately or inadvertently, it is not unusual for blood pressures to fall to normal levels and remain there, only to rise again after discharge. Stress related or "white coat" hypertension is quite common. In one

study published in the *Journal of the American Medical Association*, **more than one in four patients with elevated blood pressures in the doctor's office were found to have normal values on ambulatory monitoring. All were taken off drugs with no adverse effects**.

Decades ago, when healthy young men being examined for insurance policies or entry into the armed services had high readings but no retinopathy, albuminuria or other indication of sustained hypertension, we used to reassure them and have them lie down and relax in a quiet room. After 15 or 20 minutes, repeated measurements were invariably much lower and usually normal. **Busy doctors don't have time for that today. It's much easier and safer for them to prescribe a pill, since everyone knows that hypertension is the "silent killer".** In addition, treating hypertension is easy, doesn't take much time or energy and is apt to be quite remunerative since periodic electrocardiograms and chest X-rays to monitor cardiac size and laboratory tests are readily justified. Only a few questions need to be asked, the patient often does not need to disrobe in an examining room and the entire encounter often takes less than ten minutes.

A not uncommon scenario is when the patient returns after the initial diagnosis of hypertension has been made and a medication has been prescribed, he or she is even more nervous, blood pressure is still high or higher and the dose is increased. This may be repeated on subsequent visits and/or additional drugs are ordered. The result may be dizziness or other side effects that the patient now attributes to a worsening of hypertension, causing even more stress.

It is also not generally appreciated that heart rate and blood pressure shoot up whenever we speak or try to communicate in some other way. The seminal investigations of this phenomenon have been done by Jim Lynch who showed that such elevations are greater if we are talking to someone of perceived higher social stature, more rapidly than usual, and if the content of the conversation deals with some important personal issue. Blood pressure rises in deaf mutes when they use sign language but not when they move their hands meaninglessly but with the same amount of energy. The only time this does not occur is in schizophrenic patients off of medication, possibly because they no longer communicate.

I have been involved in this research with Jim for over twenty-five years. Although these transient spikes in both systolic and diastolic pressure can be alarmingly high, patients are completely unaware of this and have no symptoms. By using an automated blood pressure device that displays systolic, diastolic and mean arterial pressure on a monitor, it is possible to teach patients how to lower their pressures.

We have also found that these rises are not blunted by any antihypertensive drugs and are actually exaggerated by beta blockers. It is not uncommon for anxious patients to talk immediately prior to or even while the doctor is inflating the cuff, which can increase blood pressure up to 50 percent in some people. There is no good evidence that such hyperreactivity is associated with any increased incidence of sustained hypertension. The same is true for **elite weight lifters, who can have pressures of 400/250 or higher** when they perform the supreme Valsalva maneuver.

Another source of pseudo-hypertension is that the same size cuff is used for all adults, which can cause significantly false high readings in fat arms. The width of the cuff should be 40% of the circumference of the arm. This is important because of the large number of obese people and others who are engaged in body building activities. Time of day, room temperature, a full bladder, eating, drinking or smoking within the past hour, standing, sitting or supine can all influence measurements.

Treating Numbers Instead Of A Person

Authoritative advice for treating blood pressure has changed dramatically over the years. Forty years ago, the chapter on hypertension in Harrison's *Textbook of Medicine* stated "Whatever the form of therapy selected, it must not be forgotten that the physician who treats hypertension is treating the patient as a whole, rather than the separate manifestations of a disease.

The first principle of the therapy of hypertension is the knowledge of when to treat and when not to treat. . . . A woman who has tolerated her diastolic pressure of 120 for 10 years without symptoms or deterioration does not need immediate treatment for hypertension. Marked elevation of systolic pressure, with little or no rise in diastolic, does not constitute an indication for depressor therapy. This is particularly true in the elderly or arteriosclerotic patient, even though the diastolic pressure may also be moderately elevated." Today, that would be grounds for malpractice.

The chapter, which was written by John Merrill, a leading authority on hypertension from Harvard, goes on to emphasize that "The physician must constantly weigh the value of making his patient 'blood pressure conscious' by a specific regimen and regular follow-up, against real need for any particular form of therapy. **Above all, in treatment or prognostication, he must avoid engendering in the patient a fear of the disease which may be unwarranted in our present state of knowledge.**" Contrast this with the current cookie cutter approach of treating numbers that are often meaningless instead of people.

There is absolutely nothing new about prehypertension, which was previously referred to as "high normal" at levels higher than 120/80. This would still be a preferable description since nobody knows whether these individuals will go on to develop sustained hypertension or are at any significantly increased risk for its complications. **All that these new guidelines essentially accomplish are to convert 45 million healthy Americans into new patients by creating fear.** This is precisely what the experts emphasized we should take pains never to do! How could so many doctors have been so wrong for so many years?

Whatever happened to the Hippocratic dictum *Primum non nocere* (First of all, do no harm)? It used to be the primary concern of all doctors but seems to have now been sidelined or forgotten in the frenetic and impersonal pace of modern medical practice. The recommendations in this new Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) are not very different from the first JNC report. This was published in 1977 following several studies showing that blood pressure could be lowered with thiazide diuretics. Subsequent JNC reports repeatedly recommended the use of diuretics as initial treatment based on additional reports demonstrating their efficacy.

Despite this, the use of diuretics actually declined over the next decade or so, possibly because many went off patent and were no longer profitable. In addition, newer drugs were being vigorously promoted and the 1993 JNC 5 guidelines added angiotensin-converting enzyme (ACE) inhibitors and beta blockers as first-line therapy. Their sponsors argued that these more expensive drugs might be preferable since thiazide therapy could be associated with diabetes and abnormal heart rhythms, especially at higher doses. These medications had other side effects but it was claimed that they were more likely to reduce complications such as heart attacks and stroke.

However, many were not as effective even at higher doses or when combined with other new anithypertensives. Specialists soon found that half of such patients with pressures >160/100 on two or more of these drugs improved rapidly when diuretics were added or their dosage was increased. ACE inhibitors and beta blockers were removed in JNC 6 and the new guidelines are about the same as those proposed over 25 years ago, save for this new and confusing diagnosis of prehypertension.

However, diuretics are not the most effective or safest treatment for all hypertensives and other drugs are clearly superior for certain patients. **What is wrong is that physicians are treating a reading on a blood pressure machine in a cookbook fashion rather than the patient or the cause of the problem.**

What Causes Hypertension?

Blood pressure (BP) is essentially determined by cardiac output (CO) or the force with which blood is pumped out of the left ventricle and the degree of systemic

vascular resistance (SVR) that is encountered. This is much like Ohm's law governing the strength of an electrical current, so that BP = CO x SVR. Hypertension can be caused by increased cardiac output, increased vascular resistance or both. Although the cause of essential or primary hypertension in a patient may not be known it is safe to say that it is mediated by one or both of these two mechanisms.

Prior to these new guidelines, 120/80 was considered to be optimal and 120-129/80-84 was within the normal range. High normal was 130-139/85-89 and Stage 1 or mild hypertension was 140-159/90-99. Stage 2 (160-179/100-109), Stage 3 (179-209/100-110) and Stage 4 (>210/>120) reflected increasing degrees of severity. **What should you do if one number is high and the other is normal or below? Which is more important, the systolic (upper) or diastolic (lower) measurement?** The previous emphasis on diastolic pressure was based on early studies on young people. Diastolic pressure, which is the pressure when your heart relaxes between beats, rises until around age 55 and then starts to decline. Systolic pressure is the pressure when your heart beats and it increases steadily with age.

A systolic pressure above 140 with a diastolic pressure below 90 is referred to as isolated systolic hypertension. It is common in older individuals due to hardening of the arteries and slight elevations were not considered serious. Studies now show that an elevated systolic pressure is an independent risk factor for complications that is far greater than the risk associated with a high diastolic pressure in older patients with hypertension.

Most patients with hypertension have no symptoms and blood pressure elevations are often discovered during a routine physical examination or if measurements are obtained in connection with application for life insurance, employment, or blood donation rather than any complaint due to its presence.

It is important to reemphasize that blood pressures are very variable and that emotional stress and numerous other factors such as smoking, coffee, over the counter drugs containing caffeine or decongestants, a cold room, full bladder, improper cuff size, etc., can all give false high readings. Measurements should be taken with the arm supported at the level of the heart and not until the patient has been sitting for at least five minutes. If an elevation is found, the blood pressure should be taken after five minutes in the supine position and then immediately on standing and two minutes later to rule out postural effects.

At least two readings should be made at each visit separated by as much time as possible. Three sets of readings at least one week apart are advised before prescribing drugs that may have to be taken perpetually. Measurements should be made in both arms and the higher one selected to monitor. Every effort should be made to rule out known causes of hypertension, such as coarctation of the aorta, sleep apnea, obesity, polycythemia, pregnancy, oral contraceptives and other drugs.

Narrowing of the renal artery and kidney disease can cause the release of renin, a powerful hormone that can increase sodium retention and vascular resistance. Up to 10% of such secondary hypertension may be due to endocrine disorders. Primary aldosteronism and Cushing's disease can result in an increase of adrenal cortical hormones that also cause sodium retention. Pheochromocytoma is a tumor of the adrenal medulla that secretes excess amounts of catecholamines like noradrenalin and adrenaline that can increase peripheral resistance as well as cardiac output.

Blood tests can identify these endocrine abnormalities and levels of chemicals like renin and angiotensin that might determine the cause of hypertension or provide a clue as to the best treatment. High renin hypertension is thought to be associated with higher rates of complications and might respond better to angiotensin converting enzyme (ACE) inhibitors than diuretics. However, busy doctors don't have time to go through all the above. It's much easier to prescribe a drug and hope it works. If not, there are plenty of others to try.

The Emperor's Invisible Suit And JNC-7

There was once a very vain Emperor whose main interest was to wear elegant clothing. He had a coat for every hour and often changed his clothes several times a day since his greatest pleasure was to show them off to his people. Everyone knew of his vanity and fetish for fine clothing and two scoundrels decided to take advantage of it.

They introduced themselves at the palace gates as two very fine tailors who had invented an extraordinary method to weave a cloth so light and fine that it was barely visible. In fact, it would be invisible to anyone too stupid or incompetent to appreciate its superior quality. The chief of the guards sent for the court chamberlain who notified the prime minister, who ran to bring this incredible news to the Emperor. The two fake tailors were summoned and told him "Besides being invisible, your Highness, this cloth will be woven in colors and patterns created especially for you." The Emperor couldn't resist this and gave them two bags of gold coins in exchange for their promise to start work at once in a special room in the palace and inquired as to what equipment was needed.

They asked for a loom, silk, gold thread, all of which were immediately procured and they pretended to start working at a furious pace. The Emperor was convinced he had made a great deal: in addition to getting a new extraordinary suit he would also discover which of his subjects were ignorant and incompetent. A few days later, he asked his old, trusted and wise prime minister to check on how the suit was coming along. The two thieves proudly displayed their accomplishments, stating "Here, Excellency, admire the colors, feel the softness!" They reassured him that they were almost finished but needed considerably more gold thread. The old man bent over the loom and tried to see the fabric that was not there.

He could feel the cold sweat on his forehead. "I can't see anything," he thought. "If I see nothing, that means I'm stupid! Or, worse, incompetent!" If the prime minister admitted that he didn't see anything, he would be discharged and disgraced.

"What a marvelous fabric! I'll certainly tell the Emperor and get more gold thread" he told them. The two thieves visited the Emperor to take their final measurements and as they bowed while being ushered in, they pretended to be holding a large roll of fabric. They showed it to the Emperor so he could appreciate the beautiful colors and feel how fine it was.

The Emperor, who felt and saw nothing, felt like fainting, but fortunately, the throne was right behind him and he sat down. The measurements were taken and the tailors began cutting the air with scissors and sewing it with threadless needles. After evaluating the situation, the Emperor realized that no one could know that he did not see the fabric and felt better, since nobody could find out that he was stupid and incompetent. He had to strip down so the new suit could be draped on him and he could view the results in his full-length mirror. He felt embarrassed but was relieved that none of his court seemed to be. "Yes, this is a beautiful suit and it looks very good on me," the Emperor said trying to look comfortable. "You've done a fine job."

All his subjects soon heard about the fabulous suit and clamored to see it so it was necessary to arrange a ceremonial parade in which he stood in his carriage. A group of dignitaries walked at the front of the procession, anxiously scrutinizing the faces of the people who were pushing and shoving to get a better look. Each one marveled at the beautiful colors and fine fabric loud enough for everyone to hear lest they reveal their stupidity and incompetence, until a little child peeked into the carriage and shouted, "The Emperor is naked". His father tried to shut him up but soon everyone cried, "The boy is right. It's true! The Emperor is naked!" The Emperor realized the people were right but couldn't admit it and continued the parade with a page holding his imaginary mantle behind him.

The new invisible and imaginary disease of prehypertension proposed by JNC-7 seems somewhat similar. This is not to imply that its authoritative proponents are dishonest. Although acting in good faith, there is reason to believe they may have been unduly influenced by others with their own private agenda.

Is JNC-7 *Déjà Vu* All Over Again?

The law requires that all important Federal rules, including guidelines that affect the public must be written and promulgated according to the Government Code. This code 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 leading to the final rules or guidelines that must be published in the *Federal Register*. In addition, if the published guidelines are not consonant with a logical review of the evidence presented, the recommendations may be overturned by legal action.

Since the new JNC-7 guidelines seemed to fall under 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. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) has followed the same format in order to bypass Government rules and regulations.

When NIH officials were questioned about this, they explained that the cholesterol and hypertension guidelines were written by a non-government committee of experts that they had selected and were therefore not subject to the *Federal Register* regulations. This despite the fact that they are presented by government spokespersons at government press conferences and are promoted in the media here and abroad as the latest government guidelines. The new JNC-7 report made its debut at a special session of the American Society of Hypertension annual meeting in New York. This took place on the same day in May as the National Heart, Lung, and Blood Institute Press Conference which was held in Washington and coincided with the appearance of the JNC "Express Report" on the *Journal of The American Medical Association* web site.

My personal suspicion is that powerful pharmaceutical interests were behind much of this, as well as making May National Hypertension Month. Although JNC-7 reverted to the previous advice that inexpensive diuretics were the first choice it also emphasized that **"Most patients with hypertension will require two or more antihypertensive medications to achieve goal pressure."** A Novartis spokesperson lavishly praised the report in a press release, emphasizing that **"Inadequate control of blood pressure has become a public health crisis. We are encouraged that new approaches recommended by JNC-7 will provide impetus for improvement."** That's hardly surprising. Novartis, with its 73,000 employees in 140 countries and U.S. sales of $21 billion/year has all the hypertension treatment bases covered. They manufacture Lopressor, a beta blocker; Lotensin, an ACE inhibitor; Diovan, an angiotensin II blocker; Lotrel, a combination ACE inhibitor and calcium channel blocking agent; as well as products combining these with a thiazide diuretic.

Despite all the hoopla, many physicians were not as enthusiastic. Some were skeptical that the new guidelines offered anything that was either new or helpful. Several prominent authorities on hypertension denounced it as being based on conclusions that were not only unwarranted but also misleading.

Some Thoughts On Pharmaceutical Finagling And Future Hypertension Research

The full study will not be published until the fall and the report in the "JAMA Express" raised some eyebrows. This feature is designed for rapid release of new breakthroughs, for which JNC-7 hardly qualified. The journal's peer review process time for this is 24-48 hours and all 33 JNC authors would have had to respond within 72 hours. This seems doubtful but that wasn't the only complaint. The recommendation for diuretics as first line therapy was largely based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study that many disagreed with. ALLHAT results were also reported early in the JAMA Express and some feel that anything dealing with statins receives this preferential treatment. This holds true for other respected peer reviewed publications such as *Lancet*, which has also expedited statin studies despite the fact that they show nothing new or significant. Conversely, it is very hard to get anything negative about statins published, even when the data is solid. Perhaps this has something to do with the enormous revenues publications derive from statin advertisements.

John Laragh, Director of the Cardiovascular Center at the New York Presbyterian Hospital-Cornell Medical Center, founded the American Society of Hypertension, is Editor-in-Chief of its Journal, and Past-President of the International Society of Hypertension. He is one of the world's leading authorities on hypertension because of his delineation of the renin-angiotensin-aldosterone system, which landed him on the cover of Time magazine. I grew up with John, we have been personal and professional friends for well over 50 years, and he was a founding Trustee of The American Institute of Stress. I was tempted to ask him about his opinion of the new guidelines, but didn't have to. **His objections to JNC-7 and the ALLHAT study** were vividly detailed at a press conference and **were summed up by his colleague, Larry Resnick, as essentially "garbage"**.

Laragh believes that patients with high renin hypertension are more prone to have complications than low renin salt sensitive hypertensives and respond better to drugs other than diuretics. Björn Folkow, another authority and recipient of the Hans Selye award and numerous other honors, has emphasized the role of stress, the sympathetic nervous system and catecholamines. However, I suspect both these good friends subscribe to the decades old "mosaic theory" that **hypertension rarely has a single cause** and can result from disequilibrium in the above and other contributory components. **Researchers are now focusing in on our old friend inflammation** as a cause that may explain its link with coronary heart disease, obesity, diabetes and other disorders. Inflammatory cytokines like Interleukin II released by deep abdominal fat cells that contribute to insulin resistance and metabolic syndrome are increased in hypertension and both angiotensin II and aldosterone have been found to promote inflammation. Increased CRP levels were reported in newly diagnosed untreated hypertensives at the same meeting and another paper showed a correlation between elevated CRP and hypertension complications – so stay tuned!

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