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Managing Hypertension: Lessons Learned From a Recent Patient

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[1] This is to acknowledge that Dr. Kaplan has disclosed no financial interest or other relationship related directly or indirectly to this program. Dr. Kaplan will not be discussing "off-label" uses in his presentation.

Biographical Information

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Dr. Kaplan has been on the faculty at the University of Texas Southwestern Medical Center at Dallas for more than thirty years. For the last twenty, his teaching, writing, and research have focused primarily upon clinical aspects of hypertension.

CASE REPORT:

Mrs. M.S. is a 62 y/o woman who was found to be hypertensive soon after menopause at age 47 and to be diabetic some 5 years later. Hypertension had been treated with various drugs, currently with: Valsartan, 160 mg *q* d, Verapamil SR 240 mg *bid*, and furosemide 40 mg *q* d. Her recent home blood pressure readings typically were 180/110 mm Hg soon after awakening, 110/70 mid-afternoon, and 150/100 before bedtime.

Despite admonitions to lose weight, she had gained another 10 lbs. over the past year, reaching her current weight of 185 lbs. (Ht = 5'7"). Her dose of glyburide had recently been increased from 2.5 mg *bid* to 5 mg *bid*.

In addition to the antihypertensives and glyburide, she took: Vitamin C, 500 mg *q* d; Vitamin E, 400 u *q* d; an herbal preparation; and ibuprofen 400 mg, usually twice a day for arthritis in her hips and knees. She does not smoke or drink alcohol-containing beverages.

On 3 occasions during the last 6 months, she experienced dizziness, faintness and palpitations. These symptoms came on rather suddenly and slowly receded over 10-20 minutes. In addition, swelling in her feet was usually noted as the day wore on.

Her latest lab data, obtained 2 weeks before referral, included: FBS=148, glycosolated hemoglobin=8.5%, serum sodium=144, potassium=3.0, creatinine=1.6. (The prior lab data, obtained 6 months before, showed serum sodium=138, potassium=4.5, creatinine=1.4.) A 24-hour urine contained 1.2 g protein.

The major issues raised by this patient which will be addressed are:

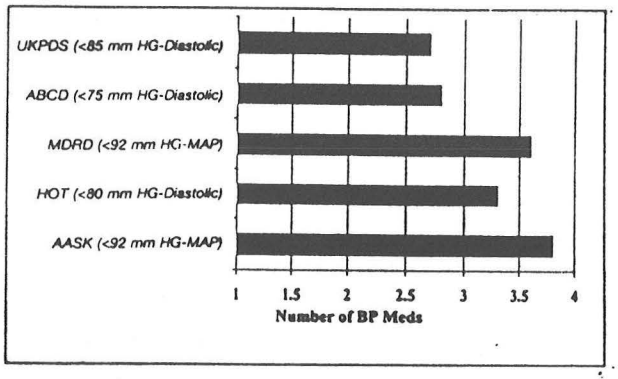
1. Hypertension resistant to multiple antihypertensive drugs with wide variability in home-recorded blood pressures.
2. Recurrent symptoms occurring as spells.
3. Recent appearance of significant hypokalemia.

I. RESISTANT HYPERTENSION

A. Prevalence

Resistance, defined as BP > 140/90 despite prescription of 3 or more medications, was found in 214 of 800 (27%) hypertensive men followed at 5 VA sites in New England from 1990 to 1995[1] . Although such resistance has been reported to be rare (2.9%) among employed hypertensives managed in a work-site clinic[2], it is the most common reason for referral to tertiary hypertension clinics[3] and is associated with 3 to 5 fold greater risks for serious cardiovascular complications[4].

With the recognition of the need for more intensive therapy to lower blood pressures below 130/85 in high-risk patients (such as Mrs. M.S.), a larger number of patients will require 3 or more antihypertensive drugs to achieve the appropriate goal of therapy [5] (Figure 1).



The number of different antihypertensive medications needed to achieve goal blood pressure, noted in parentheses, in five randomized, double blind trials of patients with type 2 diabetes and/or renal disease.

B. Causes [6]

Table 1. Causes of Inadequate Responsiveness to Therapy

PSEUDORESISTANCE
- "White-coat hypertension"
- Pseudohypertension in older patients
- Use of regular cuff on very obese arm

NON-ADHERENCE TO THERAPY

VOLUME OVERLOAD
- Excess salt intake
- Progressive renal damage (nephrosclerosis)
- Fluid retention from reduction of blood pressure
- Inadequate diuretic therapy

ASSOCIATED CONDITIONS
- Smoking
- Increased obesity
- Sleep apnea
- Insulin resistance/hyperinsulinemia
- Ethanol intake of more than 1 oz (30 mL) per day
- Anxiety-induced hyperventilation or panic attacks
- Chronic pain
- Intense vasoconstriction (arteritis)
- Organic brain syndrome (eg memory deficit)

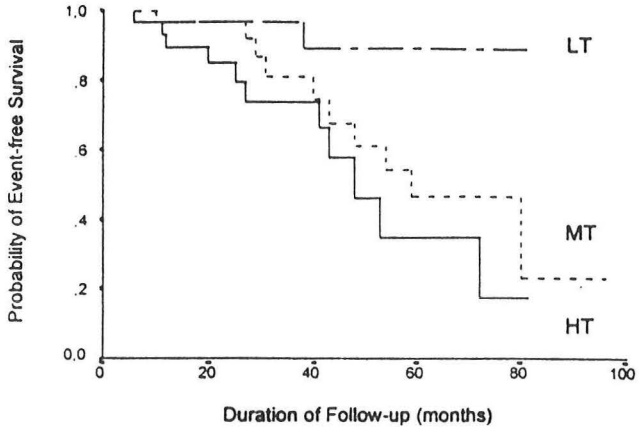
IDENTIFIABLE CAUSES OF HYPERTENSION

DRUG-RELATED CAUSES
- Doses too low
- Wrong type of diuretic
- Inappropriate combinations
- Rapid inactivation (eg, hydralazine)
- Drug actions and interactions
  - Sympathomimetics
  - Nasal decongestants
  - Appetite suppressants
  - Cocaine and other illicit drugs
  - Caffeine
  - Oral contraceptives
  - Adrenal steroids
  - Licorice
  - Cyclosporine, tacrolimus
  - Erythropoietin
  - Antidepressants
  - Nonsteroidal anti-inflammatory drugs

1. Pseudoresistance

In multiple series of small numbers of hypertensives with resistance based on office readings, about half are normotensive with automatically recorded ambulatory BP monitoring (ABPM) [7, 8]. Those with high office but normal ABPM readings have a much better prognosis[9] (Figure 2).

Probability of event-free survival in patients with resistant hypertension grouped by ambulatory BP: LT group (average of ambulatory during the activity DBP <88 mm Hg, n=29), MT group (average of ambulatory during the activity DBP 88 to 97 mm Hg, n=29), and HT group (average of ambulatory during the activity DBP >97 mm Hg, n=29). The comparison of survival curves between the groups shows significant differences between LT and MT groups (log-rank $P<.04$) and LT and HT groups (log-rank $P<.006$). (from Redon et al, reference 9)



Since ABPM is not readily available in the US, self-recorded, home readings can be used to identify the "white-coat" pseudo-resistant patients [10]. Home readings appear to predict cardiovascular morbidity, at least over a 5-year follow-up, better than clinic pressures [11]. Since patients may not record their readings accurately [12] , a relatively inexpensive teletransmission of home BPs will likely become widely used in the near future[13]. At least one vendor has marketed such a technique: Lifelink Monitoring, Inc., P.O. Box 152, Bearsville, NY 12409.

2. Nonadherence to the therapy

If suspected but denied by the patient, nonadherence can be monitored by measurements of drugs in urine or blood specimens, and, in the near future, electronic pill boxes [14]. Since it will always be difficult to maintain lifelong therapy for an asymptomatic disease where there is no obvious immediate benefit provided to the patient, those procedures known to improve compliance should be used. These include:

a. simplification of the regimen with once-a-day, long-acting formulations,

b. home BP monitoring

c. repeated contact with the patient by office personnel.

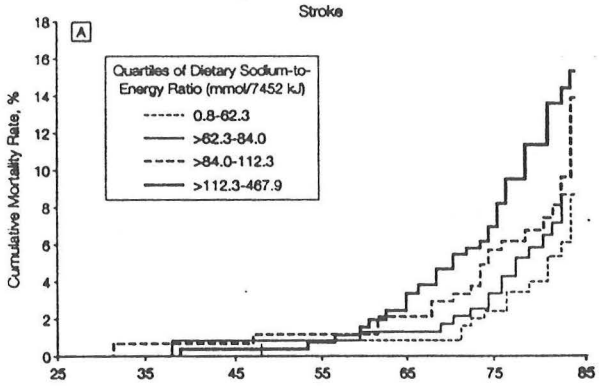
Changing behavior to improve adherence may be possible but the time and effort needed to do so are likely not going to be taken by most practitioners [15].

3. Volume overload

As in this patient, volume overload is the most common reason why patients who are taking their prescribed medications have sustained hypertension. Partly from concerns about the real dangers of previously used high doses of diuretics and partly because they are "old-fashioned," many physicians do not prescribe them. Just as bad, others give once-a-day doses of short-acting loop diuretics, *i.e.*, furosemide. Moreover, most hypertensives consume too much sodium and many have nephrosclerosis from hypertension or diabetes impairing their ability to excrete sodium loads.

a. The value of moderate dietary sodium reduction

Prior concerns about the safety of such degrees of sodium reduction as are attainable have been answered by the re-analysis of the NHANES data [16] (Figure 3). Among the 2,688 overweight subjects, a 100 mmol/d lower sodium intake was associated with a 32% decrease in strokes, a 89% decrease in stroke mortality, and a 44% decrease in coronary heart disease mortality. **No association of dietary sodium intake and** cardiovascular disease risk was found in the **non-overweight** persons.



Cumulative mortality in 931 overweight men and 1757 overweight women over an average follow-up of 19 years according to baseline dietary sodium to energy ratio from A, stroke (log-rank x^2 for linear trend + 8.09, P = .004).

Such reductions in sodium intake lower BP a bit [17] and improve the efficacy of antihypertensive drugs, in particular the ability of ACE inhibitors to reduce proteinuria[18]. The antihypertensive efficacy of calcium channel blockers does not seem to be enhanced by reduced sodium intake, likely because they have a natriuretic effect which would be more obvious in the presence of a high sodium intake.

b. The need for sustained diuretic action

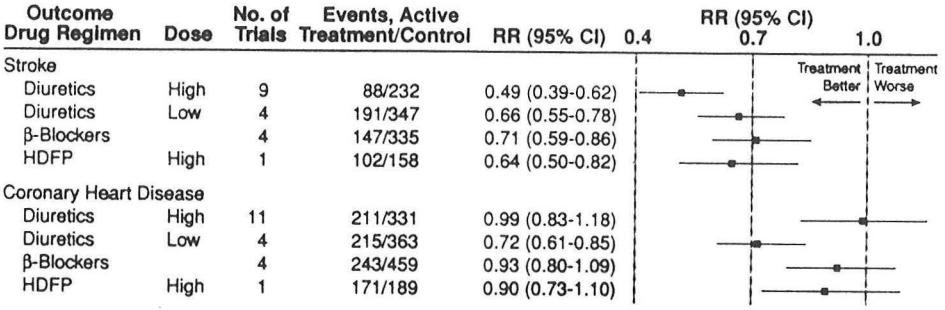
As shown by Wilcox et al [19], a single daily dose of furosemide causes a short-term natriuresis but is followed by retention of all the sodium that is initially excreted during the remaining 18 hours. Therefore, effective intravascular fluid volume is shrunken for only a few hours. The transient but marked effect of her single daily morning doze of furosemide likely induced the relative hypotension in the mid-day noted by Mrs. M.S. Her subsequent sodium retention in the absence of a diuretic likely induced the late PM higher BP which persisted through the night and early morning hours.

For most hypertensives, a single morning dose of hydrochlorothiazide reduces BP for the entire 24 hours [20]. For those with reduced renal function, *i.e.* serum creatinine above 1.5 mg/dl, a single daily dose of metolazone will be effective[21] .

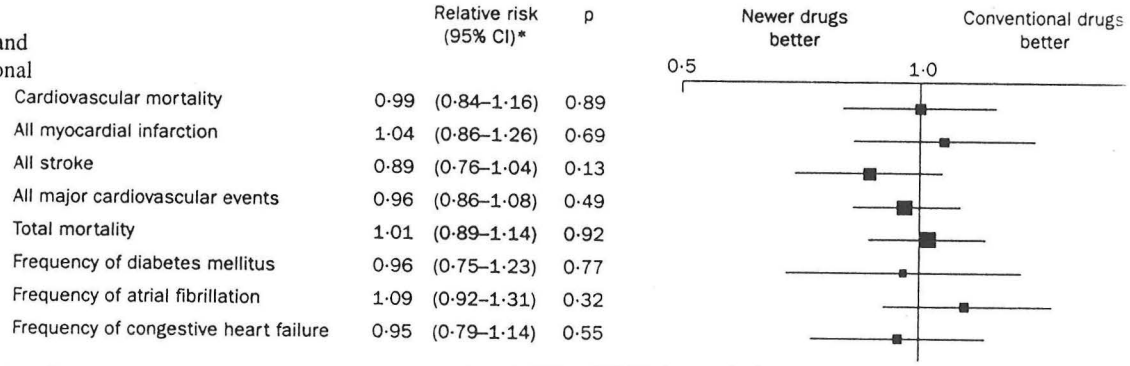
c. The benefits of low-dose diuretic therapy

Multiple trials have documented the ability of therapy based on low doses of thiazide diuretics to reduce morbidity and mortality. In addition to those summarized by Psaty et al in 1997 [22] (Figure 4), more recently published trials have shown equal benefits from diuretic-based therapy as from ACE inhibitor or CCB-based regimens [23, 24] (Figure 5).

4. Meta-analysis of randomized, placebo-controlled clinical trials in hypertension according to first-line treatment strategy. The total number of participants randomized to active and control therapy were 24,294 and 23,926 respectively. RR indicates relative risk; CI, confidence interval; and HDFP, Hypertension Detection and Follow-up Program. (Data from Psaty et al., 1997, reference 22)



5. Relative risk of cardiovascular mortality and morbidity for all newer drugs vs conventional drugs (from Hansson et al, reference 24) *Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.



In diabetic hypertensives such as Mrs. M.S., CCB-based therapy may be better than diuretic-based [25, 26], but the latter was clearly effective in the Systolic Hypertension in the Elderly Program (SHEP) [27].

Not surprisingly, addition of a diuretic was more effective than a beta-blocker in patients not adequately controlled on a combination of an ACE inhibitor and a CCB[28].

4. Drug-related causes

In our patient, at least 2 drug interactions likely contributed to her resistance. Her use of a NSAID could blunt the efficacy of most antihypertensive drugs. This likely applies to the recently introduced COX-2 inhibitors as well [29]. The other interaction will be addressed later.

5. Associated conditions

Mrs. M.S.'s continued and significant weight gain almost certainly contributes to her resistance. Her obesity is central (visceral or abdominal), the configuration long recognized to be associated with greater resistance to therapy, likely related to increased insulin resistance [30].

Although she denies bothersome daytime sleepiness or early morning headaches, her husband described significant snoring through the night so she may have obstructive sleep apnea. Snoring is frequently the tip-off for sleep apnea [31] which is likely much more common than recognized.

Mrs. M.S. did not smoke nor drink alcohol. The former is greatly to her advantage, the latter is to her disadvantage. Diabetics, as nondiabetics, who drink on average 1 portion of alcohol per day have a significantly better survival than those who drink less or none, likely from the cardioprotective effects of ethanol[32] .

6. Identifiable causes of hypertension (Table 2)

The major identifiable causes of hypertension can be identified by simple screening studies that are readily available. If the screening study is abnormal, additional confirmatory data must be obtained, often in tertiary facilities (Table 2).

Table 2 = Overall Guide to Secondary HT

	Diagnostic Procedure	
Diagnosis	Initial	Additional
Chronic renal disease	Urinalysis, serum creatinine, renal sonography	Isotopic renogram Renal biopsy
Renovascular disease	Captopril-enhanced isotopic Renogram, duplex sonography	Aortogram
Coarctation	Blood pressure in legs	Aortogram
Primary aldosteronism	Plasma and urinary potassium, plasma renin and aldosterone (ratio)	Plasma or urinary aldosterone after saline load Adrenal CT and scintiscans
Cushing's syndrome	Morning plasma cortisol after 1 mg dexamethasone at bedtime	Urinary cortisol after variable doses of dexamethasone, adrenal CT and scintiscans
Pheochromocytoma	Spot urine for metanephrine	Urinary catechols; plasma catechols (basal and after 0.3 mg clonidine) Adrenal CT and scintiscans

Mrs. M.S. has suggestive evidences of 2 identifiable causes: moderate renal insufficiency and mineralocorticoid hypertension. The elevated serum creatinine likely reflects diabetic nephropathy as further manifested by the proteinuria. The hypokalemia noted on her last blood electrolyte panel could reflect mineralocorticoid hypertension as will be considered later in the presentation.

Beyond progressive renal insufficiency, renovascular hypertension is the most common of the identifiable causes. The slow course of her hypertension and the failure of a marked fall in blood pressure and rise in serum creatinine with an ACE inhibitor or ARB militate against this diagnosis.

In summary, Mrs. M.S.'s resistant hypertension likely reflects a number of factors, including:

1) volume overload from too much dietary sodium, inadequate diuretic, and renal insufficiency.

2) drug interactions with NSAIDs.

3) continued weight gain with central obesity.

4) sleep apnea.

5) possible mineralocorticoid hypertension.

II. THE RECURRENT SPELLS

Mrs. M.S. has had multiple episodes of dizziness, faintness and palpitations. Two diagnoses should be looked for, one common in elderly and diabetic hypertensives, the other common in patients with difficult-to-control hypertension.

A. Postural hypotension

1. Recognition

Postural hypotension, defined as a fall in blood pressure greater than 20 mm Hg systolic or 10 mm Hg diastolic on quiet standing, should be looked for in all elderly hypertensives, diabetics, or patients with dizziness or syncope. If the BP is not taken within 30 seconds of standing, it may be missed[33]. If suspected, repeat BP measurements should be taken for 5 minutes or longer.

Postural hypotension is often associated with postprandial hypotension[34].

2. Prevalence and prognosis

In home-dwelling people over age 70, 30% had postural hypotension[35]. They had a 2-fold greater risk of vascular mortality over the next 4 years than did those without postural hypotension.

Type 2 diabetics, average age 57, had almost twice the prevalence of postural hypotension as age and sex-matched nondiabetics [36].

3. Mechanisms

a. reduced baroreceptor sensitivity [37]

b. hypovolemia [38]

c. excessive venous pooling [39]

d. increased venous return during sleep with night-time natriuresis[40]

e. vasodilating medications

4. Therapy

a. avoidance of hypovolemia. Fortunately, postural falls in BP are not accentuated by chronic thiazide therapy[41].

b. physical maneuvers

1) sleeping with the head tilted up 12° [42]
2) isometric exercise such as standing on crossed legs [43]
3) avoiding large meals
4) drinking 16 ounces of water[44]

c. pharmacological therapies (Table 3) [45]

Table 3. The major actions by which drugs may reduce postural hypotension in neurogenic failure (from Mathias et al., reference 45)

Reducing salt loss/plasma volume expansion
Mineralocorticoids (fludrocortisone)
Reducing nocturnal polyuria
Vasopressin-2 receptor antagonists (desmopressin)
Vasoconstriction—sympathetic
Acting directly on resistance vessels (phenylephrine, noradrenaline, clonidine) and on capacitance vessels (dihydroergotamine)
Acting indirectly (ephedrine, tyramine with monoamine oxidase inhibitors, yohimbine)
Prodrug (midodrine, L-threo-dihydroxyphenylserine)
Vasoconstriction—non-sympathetic
Vasopressin-1 receptor antagonists (terlipressin)
Preventing vasodilation
Prostaglandin synthetase inhibitors (indomethacin)
Dopamine receptor blockade (metocloprimide, domperidone)
Beta2-adrenoceptor blockade (propranolol)
Preventing postprandial hypotension
Adenosine receptor blockade (caffeine)
Peptide release inhibitors (somatostatin analogue: octreotide)
Increasing cardiac output
Beta blockers with intrinsic sympathetic activity (pindolol, xamoterol)
Dopamine agonists (ibopamine)
Increasing red cell mass
Recombinant erythropoietin

1) Caffeine likely of little value [46]
2) Fludrocortisone poorly tolerated [47]
3) Octreotide subcutaneously, particularly for postprandial hypotension
4) Midrodrine, an alpha1-agonist [48]
5) nitrates (transdermal nitroglycerine) applied before bedtime may control supine hypertension without worsening morning hypotension, [49]

Mrs. M.S. had only a 6/3 mg Hg fall in BP upon standing and had never experienced postprandial dizziness. On the other hand, she had become increasingly concerned over the poor control of her hypertension and diabetes. The 3 episodes had occurred while she was thinking about her problems and were associated with tingling of her fingers, a feeling of pressure around her head and in the front of her chest, ringing in the ears, and a sensation of not being able to breathe deeply enough. When she voluntarily hyperventilated in the office, most of her symptoms appeared within 45 seconds. The mechanism for symptoms of hyperventilation was explained and she was shown how to rebreathe into a #6 paper sack.

B. Anxiety-induced Hyperventilation and Panic Attacks

1. Definitions

The criteria for panic attacks [50] (Table 4) are strikingly similar to the manifestations of hyperventilation observed in 96 of 300 difficult-to-control hypertensives referred to me [51] (Table 5). Patients with panic disorder usually hyperventilate[52].

Table 4. Criteria for Panic Attacks and Panic Disorder (from Davis et al. 1999)

A *panic attack* is a discrete period of intense fear or discomfort involving at least four of the following symptoms:

1. Shortness of breath (dyspnea) or smothering sensations
2. Dizziness, unsteady feelings, or faintness
3. Palpitations or accelerated heart rate (tachycardia)
4. Trembling or shaking
5. Sweating
6. Choking
7. Nausea or abdominal distress
8. Depersonalization or derealization
9. Numbness or tingling sensations (paresthesias)
10. Hot flushes or discomfort
11. Chest pain or discomfort
12. Fear of dying
13. Fear of going crazy or doing something uncontrolled

Table 5. Previous Manifestations of Hyperventilation Diagnosed in 96 Patients With Hypertension

Manifestations	Percent
Paresthesias, usually of fingers	96
Lightheadedness or dizziness, nonpostural	90
Palpitations, tachycardia	78
Headache, usually bandlike	74
Fatigue, heaviness of arms and legs	70
Tremor of hands	50
Hot or cold sensations	46
Chest pain, nonexertional	40
Feeling of detachment	23
Nausea	23
Tinnitus	20
Visual blurring or spots	20
Dysphagia	15
Syncope	9
Overt panic attack	5

2. Prevalence

Anxiety disorders are present in up to 15% of the total adult population [53] hypertensives. Higher prevalences, around 35%, of anxiety-panic attacks have been reported from multiple sites among hypertensives [54] [55]. Moreover, among 767 elderly subjects, the prevalence of hypertension progressively increased with increasing levels of anxiety symptoms; men in the highest quartile of anxiety were 3.6 times more likely to be hypertensive than those in the lowest quartile[56].

In a series of 21 patients with severe paroxysmal hypertension, labeled as pseudopheochromocytoma, emotional distress was responsible for the signs and symptoms [57]. From the description of the cases, hyperventilation almost certainly was involved.

3. Associations

Wessely et al [58] make a strong argument for "a substantial overlap between individual functional somatic syndromes; the similarities between them outweigh the differences" (Table 6).

Table 6. Functional somatic syndromes by specialty

Gastroenterology	Irritable bowel syndrome, non-ulcer dyspepsia
Gynaecology	Premenstrual syndrome, chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or non-cardiac chest pain
Respiratory medicine	Hyperventilation syndrome
Infectious diseases	Chronic (postviral) fatigue syndrome
Neurology	Tension headache
Dentistry	Temporomandibular joint dysfunction, atypical facial pain
Ear, nose, and throat	Globus syndrome
Allergy	Multiple chemical sensitivity

(from Wessely et al; reference 58)

It may be going too far to combine all of these syndromes but there is no doubt that patients presenting with dizziness[59], syncope [60], chronic fatigue syndrome [61], or atypical chest pain [62] often have anxiety-panic attacks. The need to recognize and provide appropriate psychological treatment for patients with non-cardiac chest pain has been repeatedly emphasized as a way to prevent functional disability (and repeated admissions and unnecessary diagnostic procedures) [63, 64]

III. MINERALOCORTICOID HYPERTENSION

Mrs. M.S. developed hypokalemia, associated with a slightly elevated serum sodium and bicarbonate. These changes suggested mineralocorticoid excess for numerous reasons: her diuretic dose was small and had not been changed; hypernatremia would not be expected with secondary aldosteronism as would occur with a nephrotic syndrome; nephrotic syndrome was unlikely since proteinuria was moderate, serum albumin was normal, and she had no edema; a tendency for elevated serum potassium would be expected with renal insufficiency and therapy with an ARB.

Multiple forms of mineralocorticoid hypertension have now been identified [65]

(Table 7).

Table 7. Differential diagnosis of mineralocorticoid hypertension

Cause	Mineralocorticoid
Primary aldosteronism Aldosterone-producing adenoma Bilateral idiopathic hyperplasia Glucocorticoid-suppressible hyperaldosteronism Adrenal carcinoma	Aldosterone
Congenital adrenal hyperplasia 11β-hydroxylase deficiency 17α-hydroxylase deficiency	Deoxycorticosterone
Glucocorticoid-receptor resistance Glucocorticoid receptor mutations Metyrapone, mifepristone ingestion	Deoxycorticosterone
Deoxycorticosterone-secreting adrenal tumour	Deoxycorticosterone
Liddle's syndrome	. .
11β-hydroxysteroid dehydrogenase deficiency Apparent mineralocorticoid excess Liquorice and carbenoxolone ingestion Ectopic corticotropin syndrome	Cortisol

(from Stewart, reference 65)

A. Primary Aldosteronism

1. Prevalence

Soon after it was described, Conn and associates identified this syndrome in 20% of the hypertensives seen at the University of Michigan [66]. A number of investigators searched for the syndrome and could find it only rarely so the prevailing opinion was that the high prevalence in Ann Arbor was due to referral of suspected patients and that the true prevalence was well below 1% of the hypertensive population [67, 68].

With the use of a much easier screening test, the plasma aldosterone to renin ratio, Richard Gordon and associates at Greenslopes Hospital in Brisbane, Australia, began reporting a much higher prevalence of primary aldosteronism [69]. Over the last few years, they have diagnosed almost 100 patients per year, the majority normokalemic.

Gordon is not alone. Prevalences from 3.6% [70] to 14.4% [71] in presumably non-selected hypertensives have been reported. The diagnosis of primary aldosteronism in these reports, however, has not been documented by demonstration of adrenal lesions or, more importantly, reversal of the syndrome by therapy.

2. Diagnosis

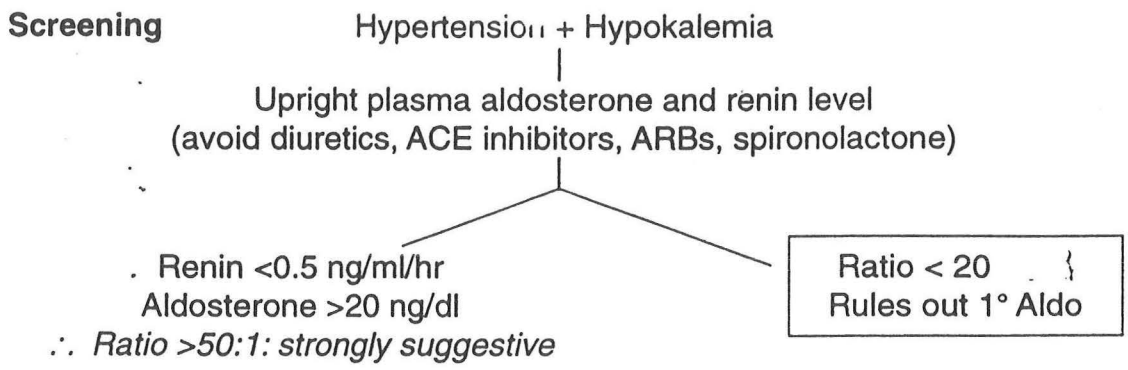
An elevated plasma aldosterone to plasma renin activity ratio (PA:PRA) has been widely utilized as a screening test. A recent study found it to identify 89% of patients with surgically proven aldosteronomas and 70% of patients with bilateral adrenal hyperplasia [72].

Although earlier series defined ratios as low as 20:1 or 30:1 as abnormal, these data confirm the need to exclude "low-renin hypertension" by having an absolutely elevated PA level and a ratio of 50:1 or higher. Low renin levels are common in elderly and black hypertensives, even more so with coexisting diabetes. Obviously, a very low renin, below 0.1 ng/ml/hr, in the presence of a normal PA, would give a very high ratio.

If the PA:PRA is abnormal, further evidence of autonomous hyperaldosteronism should be obtained, preferably before CT or MRI scans are done, particularly since non-functioning incidental adrenal incidentalomas are found in at least 1% of adrenal CT scans [73].

Autonomous hyperaldosteronism is probably best confirmed by failure to suppress plasma aldosterone to below 5 ng/dl by a 4-hour saline infusion or urinary aldosterone to below 14 ug/d by 3 days of a high sodium diet. Once confirmed, a variety of studies are available to diagnose the form of hyperaldosteronism (Figure 6).

Figure 6: Evaluation for Primary Aldosteronism



* Consider glucocorticoid remediable hyperaldosteronism in young with family history of aldosteronism; confirm by genetic testing.

A plasma aldosterone-to-PRA ratio was determined on Mrs. M.S. after the ARB was discontinued for 4 days. The values were: plasma aldosterone=2 ng/dl plasma renin activity=0.2 ng/ml/hr. Although aldosterone synthesis can be suppressed even from an aldosteronoma by hypokalemia, the very low level suggested another cause for her apparent mineralocorticoid hypertension (Table 7).

She was questioned about the nature of the herbal remedy she had been taking for the last 2 months. It was Licorice Extract which had been recommended by a friend as a phytoestrogen and a detoxifying tonic for diabetes. Within 6 weeks after that was stopped, her potassium had risen to 3.9, her sodium fallen to 140. Her blood pressure was better controlled but that may have also been related to the changes in her antihypertensive regimen.

B. Licorice Ingestion

Licorice root, from the plant Glycyrrhiza glabra, has been used as a medicinal and rejuvenator since 1000 B.C. [74]. In colonial America, it was used as treatment for diabetes but its primary medicinal use during the Middle Ages was for treatment of peptic ulcers. The hemisuccinate derivative of the active ingredient, glycyrrhetinic acid, was marketed in the 1960s as carbenoxolone for treatment of peptic ulcers, proving to be the most effective remedy until the introduction of cimetidine.

Nowadays, most licorice is used in the U.S. as a flavoring agent for tobacco products. (In 1962, 40 million pounds were imported.)

As with Mrs. M.S., it is available in Health Food stores where, in the Materia Medica Directory, it is described as:

> "a wide-ranging, anti-inflammatory, anti-fungal, anti-spasmodic, anti-bacterial herb, extremely valuable for blood cleansing, nerve, endocrine, and hormone support. A major source of phyto-hormone activity; very important for balancing women's hormones during menopause. Also effective for men against prostate hypertrophy. Important functions include effectiveness as a blood sugar regulant, a healant for gastro-intestinal conditions such as ulcers, and an adrenal nutrient that acts as a natural cortisone."
>
> Stated at the end of an additional description of its uses is: "Contra-indication: avoid if there is high blood pressure."

1. Apparent mineralocorticoid excess

In an elegant series of intake-output balance studies published in 1950, Molhuysen and co-workers [75] elucidated the reason why licorice extract caused some patients to develop edema, headache, and dyspnea: it had "deoxycortone-like action," causing sodium retention and potassium wastage with subsequent hypertension and hypokalemia. This occurred in their nine subjects with normal adrenals but not in a patient with Addison's disease. At that time, this clue could not be used to recognize the mechanism involved.

In 1985, Edwards and co-workers [76] elucidated the mechanism for a rare syndrome of hypertension, severe hypokalemia, and suppressed renin and aldosterone levels, referred to as "apparent mineralocorticoid excess (AME)." Ulick et al [77] had earlier reported an increased urinary excretion of cortisol and lesser excretion of cortisone in such patients and found that cortisol acted as a potent mineralocorticoid in this disorder. For some time, the 11 β-hydroxysteroid dehydrogenase (11 β-HSD) enzyme had been known to catalyze the reversible conversion of cortisol, which has similar affinity to renal mineralocorticoid receptors as aldosterone, to cortisone which does not attach to the mineralocorticoid receptor. The inactivation of the high concentrations of cortisol allows the much lower concentrations of aldosterone to exert the physiological mineralocorticoid actions [78] (Figure 7).

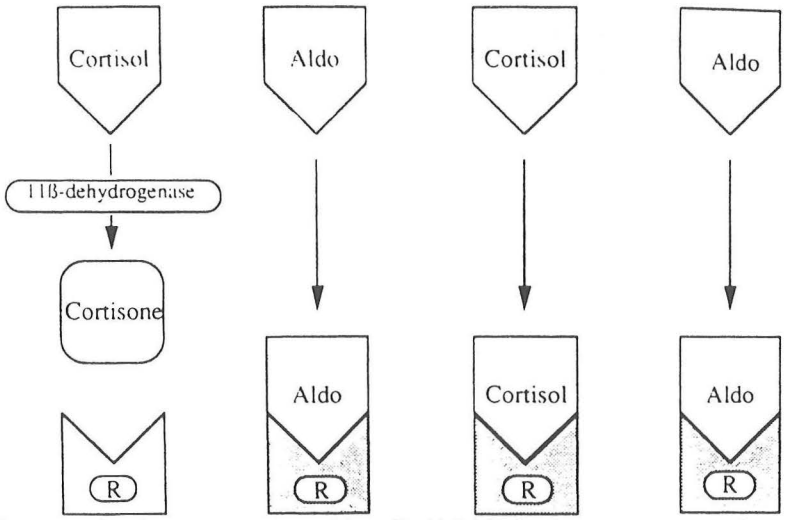


Figure 1 Enzyme-mediated receptor protection. Normally, 11β-dehydrogenase converts cortisol to inactive cortisone, protecting mineralocorticoid receptors (*R*) from cortisol and allowing selective access for aldosterone. When 11β-dehydrogenase is defective, e.g., in congenital deficiency or after licorice administration, cortisol gains inappropriate access to mineralocorticoid receptors, resulting in antinatriureis and kaliuresis. (Reprinted with permission from Walker BR, Edwards CRW. Licorice-induced hypertension and syndromes of apparent mineralocorticoid excess. *Endocrinol Metab Clin North Am* 1994;23:359–377.)

Edwards and co-workers [76] reversed the manifestations of apparent mineralocorticoid excess by suppressing endogenous cortisol production with dexamethasone and postulated that the syndrome was caused by a deficiency of 11 β-HSD.

Two years later, Stewart and co-workers (including Edwards) [79] reported that the multiple "deoxycortone-like" effects of licorice were, in fact, due to its inhibition of the same 11 β-HSD enzyme. Since then, the full effects have been reproduced by ingestion of as little as 50 g of licorice for 4 weeks [80] and cases have been attributed to drinking licorice liquor as pastis [81] and chewing licorice flavored gum [82]. Chewing tobacco, which Blanchley and Knochel [83] had shown to cause hypokalemia from its licorice flavoring, has been reported to be a common cause of the problem [84].

In today's herbal remedy craze, patients such as Mrs. M.S. may become more common. Anyone with unexplained hypokalemia and hypertension should, at the least, be asked if they use such remedies. It is possible to identify glycyrrhetinic acid in the urine [85].

Meanwhile, the use of licorice root by ancient Chinese as an aphrodisiac can hardly be encouraged. When 7 g of licorice tablets were given to 7 Italian men for 7 days, their serum testosterone levels fell from 749 ng/dl to 414, while 17-OH-progesterone levels rose, showing an inhibition of the 17 β-HSD and 17,20-lyase enzymes which catalyze the conversion of 17-OH-progesterone to androstenedione and then to testosterone [86].

Summary

Mrs. M.S. presented with multiple problems, including:

1. Hypertension resistant to 3 antihypertensive drugs.

2. Bothersome symptoms occurring in repeated spells.

3. Significant hypokalemia.

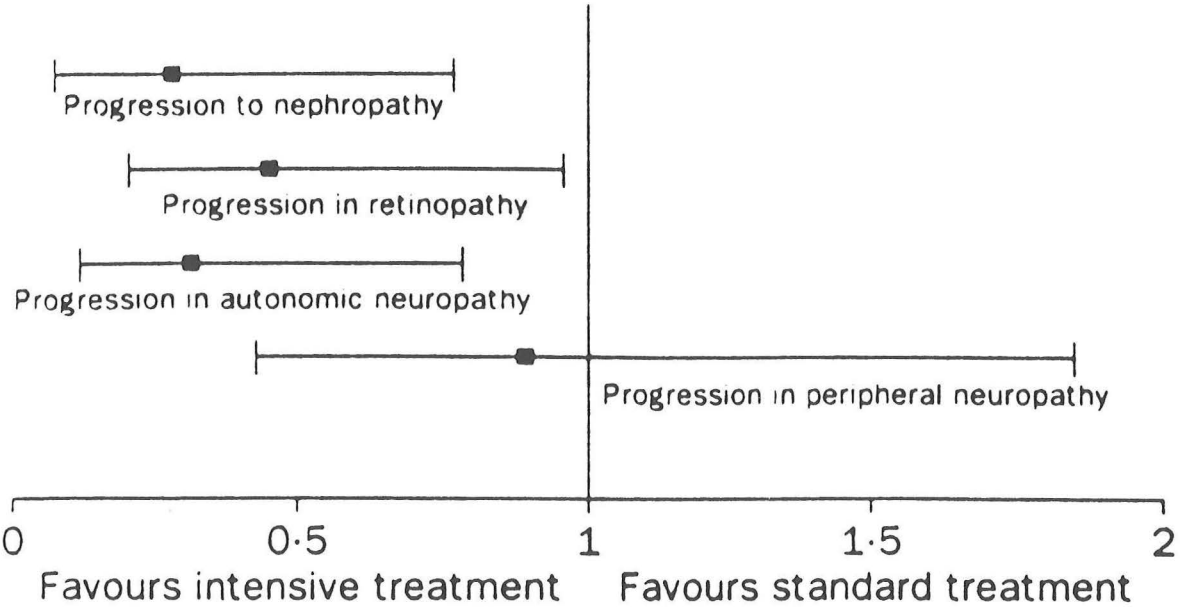
In elucidating these problems, important general principles for the management of hypertension have been emphasized. These include:

1. Common reasons for poor response to antihypertensive therapy: volume overload from too much salt and not enough diuretic; less than 24-hour effectiveness of medications given once a day; interference from weight gain, sleep apnea, and NSAIDs; the presence of other identifiable causes of hypertension.

2. The major role of anxiety-induced hyperventilation in causing symptoms in many hypertensives.

3. The need to uncover the mechanism for mineralocorticoid excess, real or apparent.

Lastly, the critical importance of adequate control of the hypertension in patients such as Mrs. M.S. should be stressed. As noted in JNC-6, all diabetic hypertensives are in the highest category of cardiovascular risk. They must be given intensive therapy to control not only their blood pressure but also their lipids, blood glucose, and all other risk factors. From trials, such as HOT and UKPDS, the need for reduction of blood pressure to below 130/80 in all diabetics has become obvious. The value of multifaceted, intensive therapy has been nicely documented in a randomized trial of 160 type 2 diabetics with proteinuria, patients similar to Mrs. M.S., by Gaede et al [87]. Those given more intensive therapy to lower their blood pressure, glycosolated hemoglobin and lipids to a greater degree along with ACE inhibitors, aspirin and multiple lifestyle modifications, had far less progression of complications than did those left on conventional therapy (Figure 8).



The differences between intensive and standard treatment of type 2 diabetics with microalbuminaturia over a 3.8 year followup (from Gaede et al, reference 87).

As noted by Bakris [5] (Figure 1), 2, 3 or 4 antihypertensive agents will likely be needed to adequately control the hypertension in patients such as Mrs.M.S. as further documented by the impressive protection provided by the ACE inhibitor ramipril in the diabetics enrolled in the HOPE trial [88]. An ACE inhibitor should be the first drug, with substitution of an ARB if a cough develops. A low dose of a thiazide diuretic should be the second drug and a calcium channel blocker likely the third. Concerns that CCBs might aggravate proteinuria and not protect against coronary disease in diabetics have been resolved by the findings of impressive protection in diabetics with CCB-based therapy in the HOT [89] and SYST-EUR trials [26]. In view of the significant protection provided to the diabetic hypertensives in the UKPDS trial by beta-blocker-based therapy [90], a beta-blocker would be a logical fourth drug if needed.

The therapeutic regimen now prescribed for Mrs. M.S. is:

Lifestyle

Continued attempt to lose weight by caloric restriction and increased physical activity.

One-half to one portion of alcohol-containing beverage on most days.

Avoid all processed food with 300 mg or more sodium per portion; add no salt in cooking or at the table.

If symptoms of anxiety-induced hyperventilation recur, rebreathe into a #6 paper sack.

Antihypertensive

Quinapril 40 mg q AM
Verapamil SR 240 mg bid
Hydrochlorothiazide 25 mg q AM

Antidiabetic

Glyburide 5 mg bid
Metformin 850 mg bid

Others

Atorvastatin 10 mg q AM
ASA 81 mg q AM
Acetominophen 600 mg prn arthralgia

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