12-17-1999

Physiologic tailoring of therapy for resistant hypertension: 20 years' experience with stimulated renin profiling

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AJH 1999;12:1077–1083

Physiologic Tailoring of Therapy for Resistant Hypertension: 20 Years' Experience With Stimulated Renin Profiling

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Renin profiling to assist in management of hypertension was first proposed about 27 years ago. However, it is still not widely used, perhaps because it was initially emphasized for management of primary hypertension, which is usually relatively easy to manage. Our experience in more than 4000 patients with referral hypertension screened since 1977 suggests that this approach, which I call "Physiologic Tailoring" of management, is particularly helpful in resistant hypertension, especially in cases of adrenocortical hypertension. Three cases of resistant hypertension spanning the 20 years of the clinic's existence, are presented to illustrate the contribution of renin profiling to the diagnosis and management of adrenocortical hypertension. It is suggested that adrenocortical hypertension is virtually always due to bilateral hyperplasia and that true curable solitary nodules may not exist if patients are followed long enough; and that adrenocortical hyperplasia is much more common in blacks and patients of African origin. A study to test the cost-utility of a renin-based algorithm for management of resistant hypertension is recommended. Am J Hypertens 1999;12:1077–1083 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: **Physiologic tailoring, adrenocortical hypertension, bilateral hyperplasia, blacks.**

This paper was presented at a Renin Day in honor of Dr. John Laragh, who, as far as I know, is the person who first understood the importance of renin profiling, and first proposed this approach to management of hypertension in about 1970.[1] With his colleagues Sealey, Brunner, Buehler, and others[2–4] Laragh explored the role of renin typing, particularly in the management of essential hypertension. I believe the initial emphasis on so-called "essential" hypertension has largely been the reason that renin profiling has been inappropriately underutilized for the cases in which it is most helpful, ie, in those with resistant hypertension. By this I mean that most cases of primary hypertension are relatively easily controlled, so the usefulness of renin profiling was not apparent to most physicians who tried it early on, and as a result of that disappointing experience the approach was not widely embraced.

In 1975, Dr. Keith Dawson and colleagues[5] proposed the use of stimulated renin profiling as a tool for diagnosis of secondary hypertension. They reasoned that the high sodium intake in most North Americans causes normal random renin levels to be so low that they are difficult to distinguish from abnormally low levels. By pushing up the normal range with a dose of furosemide, the abnormally low levels, due mainly to suppression because of salt and water retention caused by excess mineralocorticoid hormones, are

Received September 24, 1997. Accepted April 12, 1999.

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0895-7061/99/$20.00
PII S0895-7061(99)00154-5

then more readily differentiated from normal levels. High renin levels are simply pushed higher.

ESTABLISHMENT OF A CLINIC USING RENIN-BASED DIAGNOSIS AND TREATMENT

On the suggestion of my chief, the late Dr. Adam Linton, I based the so-called "care map" (although we didn't call it that at the time) for my new hypertension clinic, established in 1977, on the paper by Dawson and colleagues.[5] Since that time we have screened more than 4000 patients referred for hypertension, of whom approximately 2000 were cases of resistant hypertension.

Patients were referred by family physicians, internists, and other specialists in the region. In the early years, the great majority of cases were referred because of resistant hypertension; over time, the clinic has evolved into a multiple–risk-factor management clinic, largely for patients with vascular disease such as carotid stenosis. The care map provided for a history and physical examination focused on hypertension and vascular disease, routine laboratory investigations such as urinalysis, complete blood count (CBC), electrolytes, plasma glucose and fasting lipids, plasma catecholamines, and a stimulated plasma renin level without drugs that suppress renin (such as β-blockers, clonidine, methyldopa). The plasma renin level was drawn either 30 min after intravenous 0.5 mg/kg furosemide or 4 h after 0.5 mg/kg oral furosemide, depending on the patient's circumstances with respect to the distance of the clinic from their home. Usually patients who received intravenous furosemide were lying down when the renin was drawn, but those who took it at home 4 h earlier had been up and about during the intervening 4 h. (Patients who had to drive in from 3 h away would experience significant difficulty with frequent stops for urination if they had taken oral furosemide just before leaving the house. For this reason the usual procedure was to give intravenous furosemide if the patient was not taking any drugs that suppress renin at the time of their first presentation; oral furosemide was used for local patients who had to be tapered off suppressing drugs and could go for blood sampling at their convenience with respect to the day of sampling.) We did not routinely do aldosterone levels until I was persuaded to start doing so by Richard Gordon at the ISH meeting in Melbourne in 1993.

Follow-up investigations were only done if there were abnormalities on the initial screening results. For patients with a high stimulated renin we have been doing a nuclear medicine renogram with technetium diethylenetriaminepentaaceitc acid (DTPA) and a renal ultrasound for the past 10 years or so (initially we were doing intravenous pyelograms and then digital intravenous angiography of the kidneys). For patients with abnormally low stimulated renin levels in whom surgery was contemplated because of either difficulty with blood pressure control or excessive adverse effects from the amount of medication required to achieve control, we were doing adrenal computed tomography (CT) scans and iodocholesterol scanning before and after dexamethasone suppression (1 mg four times a day beginning 1 week before the second scan and continuing for the week of the scan) for the first several years. The scans without dexamethasone were abandoned after the first 100 or so failed to show a single case of unilateral adenoma; what we found was that approximately two-thirds of patients had hot nonsuppressible glands and one-third had bilateral hot glands that were suppressible with dexamethasone.

TABLE 1. CAUSES OF SECONDARY HYPERTENSION AMONG 4000 PATIENTS, (HALF OF WHOM WERE RESISTANT)

Renal hypertension	± 500
Polycystic	± 10
Old pyelo, reflux, stones	± 100
Hypernephroma	8
Renovascular	> 400
Angioplasty	± 200
Surgery	24 (endarterectomy/bypass) 8 (nephrectomy)
"Adrenocortical"	± 200 (How many Liddle's?)
Conn's?	5 (before 1980)
Hyperplasia	± 195 (1/3 suppressible)
Adrenalectomy	16
Pheochromocytoma	49
Adrenomedullary hyperplasia	6 surgical and another 6 medical
Licorice	4
Aortic coarctation	3 (2 familial)
Renin-producing secondaries (breast cancer)	1

± connotes an estimate.

Table 1 gives the distribution of diagnoses from among the approximately 2000 cases of resistant hypertension, updated from a previous summary.[6] The proof of the method is that of the seven cases admitted for further investigation because their problem was not resolved by outpatient investigation, six turned out to be noncompliance; the seventh was due to consumption of a licorice-containing tonic obtained through a health food store.

CASES

Three cases are presented that span the 20-year experience in the clinic and illustrate several points. For the sake of brevity, they are presented in Tables 2 through 4.

TABLE 2. CASE 1: RM

42-year-old man from Swaziland, referred in 1979 because of a blood pressure (BP) of 174/130.

Medications: Off medication 1 week at presentation.

Examination: Overweight African man with pronounced keloid formation around ritual tribal scars; swelling of the left leg with chronic venous stasis changes about the left medial malleolus; hemorrhages and exudates in the optic fundi; BP 154/120.

Investigations: Stimulated plasma renin 0.89 ng/ml/h, serum potassium 3.7 before furosemide, 2.8 mEq/L after furosemide.

Iodocholesterol scan before and after dexamethasone showed bilaterally enlarged and overactive glands, which did not suppress with dexamethasone. Compared with baseline, the suppression scan showed that the right adrenal suppressed by only 30%, and the left by only 4%. The adrenal CT scan did not show any significant abnormality.

Course: Treated with triamterene 50 mg/HCTZ 25 mg twice/day and propranolol 40 mg twice/day. Three months later, blood pressure was still 160/116; serum potassium 4.2 mEq/L. Because he was scheduled to return soon to Swaziland, and was concerned about the possibility that his blood pressure might not be adequately controlled, we elected to push on to bilateral subtotal (approximately 90%) adrenalectomy.

Pathology: Bilateral nodular hyperplasia, which in some locations affected mainly the zona glomerulosa. Postop BP 110/70, so he was discharged off medication; 1 month later BP was 128/104; then two months postop, 2 days before his scheduled return to Swaziland, his pressure was 122/96.

Because he was returning to a hot country I elected not to treat him; indeed I sent with him a referral letter warning that he might require supplementation with mineralocorticoids. It was my concern about his returning to a hot climate after bilateral adrenalectomies that led to the hypothesis to be discussed in the text regarding adrenocortical hyperplasia in patients of African origin.

CT, computed tomography; postop, postoperative.

TABLE 3. CASE 2: EM

60-year-old man referred in 1981 with 30-year history of hypertension; becoming resistant, developing congestive heart failure.

Medications: HCTZ 100 mg daily, prazosin 5 mg three times/day, metoprolol 100 mg three times/day, and KCl 8 mEq three times/day.

Examination: Blood pressure (BP) 210/110; mild dependent edema, not Cushingoid, no hemorrhages or exudates in the fundi, and no other remarkable features.

Investigations: His stimulated plasma renin was 0.01 ng/ml/h, and his iodocholesterol scan before and after dexamethasone showed bilateral hot nonsuppressible glands, with the left exhibiting at 3 days approximately twice the activity of that on the right (28% *v* 18% uptake). A CT of the adrenals showed a 1.4-cm nodule in the left adrenal; the right was found to have a very slight bulbous increase in diameter in its superior aspect.

Initial response: with triamterene/HCTZ twice daily, prazosin 5 mg three times/day, metoprolol 100 mg three times/day, and KCl 20 mgEq three times/day. BP in March of 1983 was 138/86. However, by October of 1983 his pressure was back up to 160/100, and we decided to proceed to a left adrenalectomy. Preop plasma aldosterone was 1700 pmol/L (< 860).

Pathology: The gland was enlarged, with a 2-cm nodule, but there was multinodular hyperplasia.

Postop course: He did well for 5 years, with good blood pressure control on much less medication; his aldosterone level fell to 1090 pmol/L by January of 1985. In October of 1986 his pressure was 140/84 on amiloride 5 mg/HCTZ 50 mg twice/day, amiloride 10 mg twice/day, hydralazine 50 mg twice/day, potassium chloride 10 mEq twice/day, and thyroxine 0.2 mg daily. By November of 1987 his aldosterone level had risen to 3197 pmol/L, and he began to require more medication for control; by July of 1991 his pressures were back up to 190/76 despite verapamil 240 mg twice/day, hydrochorothiazide 50 mg/amiloride 5 mg twice/day, amiloride 10 mg twice/day, and hydralazine 25 mg four times/day. In April of 1992 his pressures were up to 184/98 despite amiloride 20 mg twice/day, verapamil 240 mg twice/day, hydralazine 50 mg twice/day, HCTZ 25 mg daily, terazosin 5 mg daily, thyroxine 0.2 mg daily, and chlorpropamide 125 mg daily (because he had developed Type II diabetes). He was also experiencing dyspnea and wheezing on exertion, and dependent edema.

Reoperation: In June of 1992, at age 71, he underwent a subtotal adrenalectomy on the right side, again revealing multinodular hyperplasia

He has done well since. At his most recent follow-up in April, 1996, his blood pressure was 147/82 on nifedipine XL 30 mg daily, indapamide 2.5 mg daily, metformin 500 mg twice/day, simvastatin 20 mg daily, fenofibrate 100 mg three times/day, thyroxine 0.2 mg daily, and warfarin 5 mg daily (because of atrial fibrillation).

Abbreviations as in Table 2.

DISCUSSION

In patients with resistant hypertension, there are three main possibilities to be considered: the patient may be noncompliant; the patient may be consuming substances that aggravate hypertension, such as ethanol, nonsteroidal antiinflammatory drugs, licorice, excess salt, or sympathomimetic drugs; or the patient has secondary hypertension. Naturally, all three may coexist; frequently the patients most resistant to treatment have an underlying cause of hypertension, in addition to poor compliance and excess consumption of sodium or alcohol.

Among those patients with secondary hypertension,

TABLE 4. CASE 3: RH

41-year-old man referred by phone from Nova Scotia in December 1995 with a 15-year history of hypertension, uncontrolled for 5 years, with three hypertensive strokes and a ruptured berry aneurysm over the preceding 4 years. In the summer of 1995 his pressures averaged around 250/150 despite a great deal of medication. He had been investigated in Halifax on several occasions over approximately 8 years; pheochromocytoma had been excluded biochemically and by adrenal CT on two occasions and a renal angiogram was normal. On that basis it seemed likely that he had adrenocortical hypertension, which had not been considered as a likely possibility in part because his serum potassium levels were always normal. I therefore recommended that amiloride 50 mg daily be added to his medications pending admission.

Medications on admission January of 1996: atenolol 200 mg three times/day, amlodipine 20 mg twice/day, amiloride 25 mg twice/day, HCTZ 25 mg daily, terazosin 10 mg twice/day, and minoxidil 20 mg twice/day. From the time of his admission, the nurses observed and charted the swallowing of his tablets, with no change in his pressure over 3 days.

Examination: No distress; not Cushingoid; no hemorrhages or exudates in the fundi; no bruits in the carotid or renal arteries, not in congestive heart failure. He had residual findings from his previous strokes, including slight facial weakness on the right, slight dysarthria, a subtle right hemiparesis, and hyperreflexia bilaterally, with an extensor plantar response on the right and an equivocal plantar response on the left.

Course: Tapered off atenolol for renin testing; hydralazine 50 mg three times/day was added, his amiloride was increased to 60 mg/day and spironolactone 100 mg twice/day was added. During the time off atenolol his pressures at first came down to 190/100, and then rose back up to 220/120.

Investigations: Serial potassium levels, urea, and creatinine levels were:

January 1996	5	12	19	20	21
Serum K^+	3.6	3.8	3.4	3.8	4.0
Urea	5.3	5.8			
Creatinine		81	104		

After 5 days off atenolol, his stimulated renin level was only 0.47 ng/L/s despite a month of amiloride 50 mg/day, and a week of spironolactone 200 mg daily. His plasma aldosterone level was 288 pmol/L (< 400); cortisol am 559 μm/L (165–745), and the catecholamines were normal: norepinephrine 996 pmol/L (< 2800), epinephrine 91 pmol/L (< 321).

CT of the adrenals showed thickening of both glands, with a 1-cm nodule on the left.

Subsequent Course: Atenolol was reinstituted, and the other medications were continued at the same doses; his BP initially came down to 170/90, which the patient described as the best he had seen in 5 years. His BP then climbed back up to 200/100 despite his enormous doses of many medications.

Initial surgery: January 30, 1996 left adrenalectomy.

(Continued)

TABLE 4. CONTINUED

Pathology: Multinodular cortical hyperplasia with a 1-cm nodule, and a hemorrhage into the adrenal.

Postoperative course: BP the next day was 113/60 on atenolol 50 mg alone. One month later his BP was 140/80 on atenolol 200 mg, amlodipine 20 mg, and amiloride 20 mg.

Right adrenalectomy was delayed by development of chest pain in March 1996, leading to coronary angiography. On follow-up in May 1996, his blood pressure had risen again to 190/100, on amlodipine 5 mg daily, atenolol 100 mg daily, and amiloride 10 mg daily. He subsequently underwent attempted angioplasty with a myocardial infarction. At follow-up in November of 1996, his pressure was back up to 220/130 despite amiloride 25 mg twice/day, atenolol 100 mg three times/day, amlodipine 20 mg daily, doxazosin 4 mg twice/day, isosorbide dinitrate 30 mg three times/day, fenofibrate 200 mg daily, and ASA 325 mg daily, and a combination of folic acid, pyridoxine, and vitamin B_{12} for hyperhomocyst(e)inemia.

To rule out the diagnosis of ectopic adrenal receptors to gastrointestinal hormones as a cause of his hypertension, plasma cortisol levels were done fasting and at intervals after a standard meal consisting of a can of dietary supplement (Sustacal). Baseline levels were 196 and 199 nmol/L at 5 and 0 min before consuming the dietary supplement, and the levels were 196, 192, 190, and 185 nmol/L at 5, 10, 15, and 30 min, respectively.

Reoperation: April 16, 1997, right total adrenalectomy.

Pathology: Multinodular cortical hyperplasia.

Postop course: Blood pressures were much improved, with much less medication: On July 17, 1997 the pressure was 140/96 on atenolol 100 mg twice/day, prednisone 15 mg daily, fludrocortisone 0.5 mg twice/day. In March 1998, his blood pressure was 140/90.

Abbreviations as in Table 2.

the possibilities for practical purposes can be reduced to four main categories: adrenomedullary hypertension (pheochromocytoma or adrenomedullary hyperplasia); aortic coarctation; renal/renovascular hypertension; or adrenocortical hypertension. In some ways, aortic coarctation is a special case of renovascular hypertension. I have seen one case of atherosclerotic aortic occlusion both above and below the renal arteries, with acute renal failure on administration of the first dose of angiotensin converting enzyme inhibitor, a physiologic response that is identical to that seen in patients with bilateral severe renal artery stenosis. In two cases of familial aortic coarctation that we have seen, there was concomitant stenosis of the renal arteries.

Renal causes include polycystic kidney disease, obstruction, old pyelonephritis or stones with renal scarring, renovascular hypertension, atheroembolic renal

disease, and what I call tertiary hypertension, which is a special form of what might be considered microvascular renovascular hypertension, ie, malignant hypertension that began as primary hypertension but because of neglect evolved into severe hypertension resulting from hypertensive nephrosclerosis. It is important to note that we have found eight cases of hypernephroma that were diagnosed as a result of renal investigations done because of the high renin levels. One case of extreme high-renin hypertension appeared to be due to renin-producing metastases from breast cancer.

In our experience adrenocortical hypertension appears to be mostly due to adrenocortical hyperplasia. Indeed, as the cases presented may illustrate, I have come to doubt the existence of Conn's syndrome, if it is meant to be defined as a true solitary nodule that cures hypertension permanently once removed.

Because renovascular hypertension (a condition that is increasingly important since the development of angioplasty) is readily diagnosed with imaging techniques including angiography, renin profiling may be thought unnecessary if it is assumed that all patients with resistant hypertension will undergo renal investigation. However, if renal investigations are restricted to those patients with high plasma renin levels (or other indications such as symptoms, hematuria, or proteinuria), renin profiling can be useful in sparing patients unnecessary renal investigations.

In my opinion, the real value of renin profiling lies in two areas: reduction of unnecessary renal investigation and detection of adrenocortical hypertension. Only about a third of patients with resistant hypertension will have a high renin level, and about 10% will have a very low nonstimulable renin, suggesting adrenocortical hypertension. Despite common dogma, it is usual for patients with adrenocortical hypertension to have a normal serum potassium, and unfortunately measuring aldosterone levels without a renin level is useless. It is much more likely (about twice) that a high aldosterone level will be due to secondary hyperaldosteronism, with a high renin, than due to primary hyperaldosteronism. Furthermore, not all patients whose hypertension is due to elevated levels of mineralocorticoid produce aldosterone in excess; some overproduce other mineralocorticoids such as 18-OH DOC; for that reason I believe the term "adrenocortical hypertension" is preferable to the term "primary hyperaldosteronism."

The spectrum of adrenocortical hypertension has changed remarkably in the past 20 years. I was taught in medical school that Conn's syndrome was the cause of the problem, but by the time Biglieri described his first four cases of adrenocortical hyperplasia in 1984,[7] we had already done partial adrenalectomies on 10 cases. By that time we had realized that of 100 patients with a stimulated renin of less than1 ng/ml/h who underwent iodocholesterol scanning, all had bilateral overactivity of the adrenal cortex. There were no unilateral adenomas, and surprisingly, one-third were suppressible by dexamethasone. Ten of these patients had undergone partial adrenalectomies by 1984, and all had multinodular hyperplasia.

I wondered if the nonsuppressible cases of bilateral hyperplasia might be due to aldosterone stimulating factor, described in 1983 by Carey et al,[8] and I thought that the suppressible cases might be due to Laidlaw's syndrome[9] of familial dexamethasone-suppressible adrenocortical hypertension.

We have seen only two cases of Cushing's disease (most in our area are referred to endocrinologists), and two other cases of adrenocortical hypertension with pituitary adenomas that do not produce ACTH, growth hormone, or prolactin, that I am following as possible cases of Chretien's syndrome. Chretien and colleagues[10] described in 1985 a case of adrenocortical hypertension due to a pituitary adenoma producing pro-opio-melanocortin (POMC).

I have not knowingly seen a case of Gordon's syndrome, and have recognized only one case of Liddle's syndrome.[11–13] I only became aware of those syndromes relatively recently, but at least Liddle's syndrome will start to come out of the woodwork now that we are routinely measuring aldosterone along with the renin levels. Liddle's syndrome is a low-renin hypertensive state with low aldosterone levels due to a renal tubular abnormality of sodium transport; the importance of recognizing it is that it responds to amiloride but not spironolactone.

The most exciting advances in this area have been the discovery by Lifton and colleagues of a form of dexamethasone-suppressible hypertension with high aldosterone levels due to a chimeric 11β-hydroxylase gene.[14] We appear to have three cases in the brief period since we started looking for them, out of about 10 cases in which I have tried dexamethasone suppression. Also intriguing is the discovery by Chretien and colleagues that some patients with excess adrenocortical hormone production have aberrant receptors to gastrointestinal hormones, with marked postprandial elevation of adrenocortical hormones.[15] Because our Case 3 presented here had unremarkable aldosterone levels (although the renin/aldosterone ratio was high), it is possible that his severe hypertension may have been driven by mineralocorticoids in addition to aldosterone; he did not appear to have aberrant adrenal receptors to gastrointestinal hormones.[15]

A striking feature of our experience is the disproportionate representation of patients from Africa, or descendants of African slaves brought to America, among patients with adrenocortical hypertension severe enough to require adrenalectomy. Of the first 10

patients who had adrenalectomy for bilateral hyperplasia, four were of African origin, a proportion approximately 10- to 20-fold greater than the proportion of people of African origin in our community. I believe that this is related to previous observations that black patients have low-renin hypertension, and to the hypothesis enunciated by Clarence Grim and colleagues in 1993,[16] that adrenocortical excess had a survival advantage in the conditions of extreme heat and privation not only during the Atlantic crossing between decks on the slave ships, but during the first few years on the plantations of the Southern United States. Our Case 1, an African from Swaziland, raised in my mind in 1979 the possibility that there might also be a survival advantage to high levels of mineralocorticoid hormones in a hot country far from the sea, where Arab traders carried salt as currency. Our experience suggests that stimulated renin profiling would be particularly useful in patients of African origin, if it is true that adrenocortical hyperplasia is more common in this group of patients. Similarly, it is possible that Liddle's syndrome may be more common among Africans and their descendants.

It is a great mystery to me why stimulated renin profiling is not widely used to assist in the management of resistant hypertension. Measurement of stimulated plasma renin activity is quite inexpensive; approximately $20 should cover sampling costs and assay. This is much less costly than a number of tests routinely done in patients with severe hypertension. The indiscriminate use of renal angiography and other costly renal investigations in patients with resistant hypertension may detect most renal and renovascular cases, but it ignores the usefulness of stimulated renin testing for detection of adrenocortical hypertension, most of which is missed without renin testing. The consequence of missing the diagnosis is that patients are more likely to be poorly controlled and to have adverse outcomes.

I call this approach "physiological tailoring" of hypertension management, as opposed to "shot-in-the-dark" therapy.

In 1989, we found that our outcomes were much better than in a similar large referral clinic elsewhere, and attributed the difference in part to a two-fold higher rate of diagnosis of secondary hypertension, because of the routine use of stimulated renin testing in resistant cases.[17] Based on literature figures for outcomes, a survey of local internists regarding the average frequency of various diagnostic tests in patients with difficult hypertension, and literature figures for utilities of health states and costs of outcomes such as renal failure leading to dialysis, stroke, and death, I have estimated that a renin-based algorithm for management of resistant hypertension costs from one-third to two-thirds the cost/QALY of usual care.[18]

It is the patients with resistant hypertension who have the majority of the adverse outcomes. Given the prevalence of hypertension and the high costs of adverse outcomes such as congestive heart failure, renal failure requiring dialysis, and stroke, a controlled trial of renin-based management of resistant hypertension compared with usual care is overdue. Such a study should be done as a cost-utility study, with the prospective intent of capturing not only direct but also indirect costs.

ACKNOWLEDGMENTS

Management of difficult hypertension requires a team approach. Important players on our team have included Ms. Teresita Daite, who performed the renin levels for many years; Dr. Al Dreidger, who performed the iodocholesterol scans; and Dr. Ron Holliday, who has done all our adrenal surgery over the years. None of this would have happened without the leadership of the late Dr. Adam Linton, who was Chief of Medicine at the time the Hypertension Clinic was established in 1977 at the then Victoria Hospital.

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