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CHLOROTHIAZIDE AS AN ADJUNCT IN THE TREATMENT OF HYPERTENSIVE CARDIOVASCULAR DISEASE

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It is a remarkable tribute to the group effort in modern medical science that chlorothiazide† in less than one year from the date of reporting its synthesis[1] has been carefully studied and reported upon and made available for wide use in the treatment of edema and hypertension.[2,3]

We report here its use in patients with sustained high blood pressure which has affected the structure or function of the heart as evidenced by cardiomegaly on chest x-ray or left ventricular hypertrophy on EKG. Particular attention was given to the mode of blood pressure measurement[7,8] in order to avoid misleading conclusions which might result if more variable casual blood pressures were used. All of the patients reported here were on moderate salt restriction as a basic part of their antihypertensive therapy, some on 400 mg. sodium diets and some with instructions to avoid highly salted foods and to refrain from the addition of salt at the table or in cooking.

A group of eight patients, who were under treatment with rauwolfia or rauwolfia and hydralazine,†† came in once a week for basal blood pressure determinations for one month prior to starting chlorothiazide as an addition to their program of treatment. Thereafter, basal blood pressure determinations were made once a week after chlorothiazide was instituted. The findings on these patients are summarized in Table 1. The average blood pressure for the group before chlorothiazide was 171 systolic and 105 diastolic. During the period of treatment with chlorothiazide, the average blood pressure for the group was 147 systolic and 89 diastolic, representing a reduction of 24 mm. of mercury systolic and 16 mm. of mercury diastolic for the group. The blood pressure was lowered in every instance. Of the eight patients reported, four continued on the same treatment plus chlorothiazide with blood pressures at lower levels; three were able to discontinue reserpine‡ or reserpine and hydralazine and one decreased the dose of reserpine. All had good blood pressure control on chlorothiazide as an adjunct or alone. The majority of the patients felt well and experienced no undesirable side effects attributable to the drug.

A second group of eight patients in the out-patient clinic were under treatment with ganglionic blocking agents and used home blood pressure recordings as a guide to therapy. These patients and others on ganglionic blocking agents are educated to check their blood pressure in the sitting and standing position just before time for the dose of the ganglionic blocking drug. They are usually instructed to omit the dose of ganglionic blocking drug if the systolic standing blood pressure is below 120 mm. of mercury just before time for the dose. With this home guide to therapy, faithfully followed, few patients encounter harmful effects from an overdosage. The same method of checking blood pressure just prior to the dose of mecamylamine§ was used as a

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method of making suitable reductions in the dosage of this drug when chlorothiazide was added to the program. The findings on these patients, all with hypertensive cardiovascular disease treated with mecamylamine and all using home blood pressure recordings as a guide to the dosage of mecamylamine, are listed in Table II. The blood pressure readings listed in Table II represent averages by the week of all standing blood pressures thus measured for a number of weeks before starting chlorothiazide and after starting chlorothiazide. Usually this represented a one month pre-and post-treatment period, although observations extending to two months or more have been essentially the same. The average blood pressures in the pretreatment period were 174 systolic and 109 diastolic with a reduction of 23 mm. systolic and 10 mm. diastolic as the average for the group. The blood pressures were lower in every case when chlorothiazide was used. Three patients were able to discontinue mecamylamine; two were able to reduce the dose by 50% of the previous amount and one to reduce the dose 30% of the previous amount (Fig. 1, 2). Two other patients continued on the same dose of mecamylamine with lower blood pressures and considerable clinical improvement. The average doses of mecamylamine were 28 mg. per day prior to the institution of chlorothiazide and with chlorothiazide the average dose was 13 mg. per day for the group. These patients generally experienced relief from fatigue, less dyspnea, less nocturia and a better work tolerance, indicating a gain from additional reduction of the blood pressure. At the same time, they benefited by a reduction or

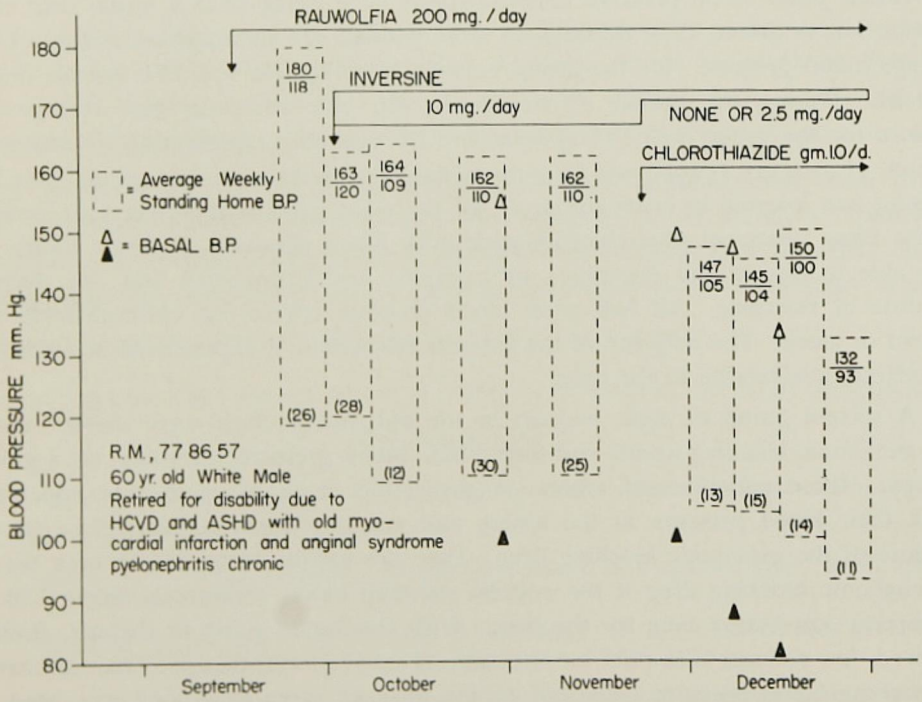

Figure 1

Numbers in parenthesis at the bottom of each dashed rectangle are the number of home blood pressure readings averaged for the week. Home readings were just prior to time for dose of mecamylamine (Inversine), consequently these represent the highest readings. In this case, Basal Blood Pressure determinations in the out-patient clinic were done several hours after the medication was taken at home. Data on this patient is also tabulated in Table II.

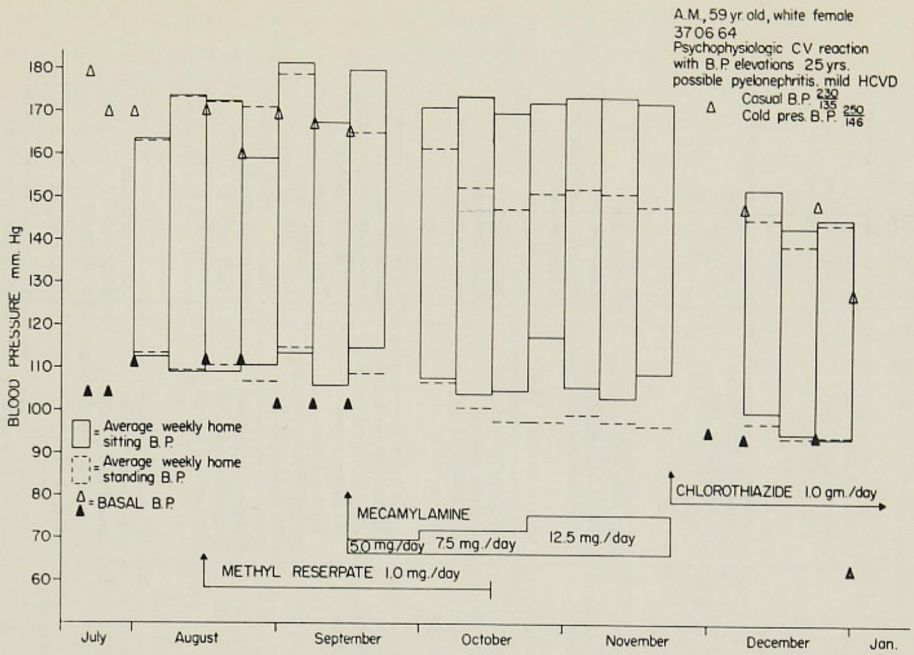

Figure 2

Graphic record of BP from patient with pre-treatment fixed blood pressure of 170/110. Eight months prior to study, treatment with Reserpine had produced depression and fatigue.
Note orthostatic hypotensive effect of mecamylamine with no change in sitting BP. Chlorothiazide alone lowered both sitting and upright BP without much orthostatic difference.

elimination of the undesirable effects of ganglionic blocking agents, particularly a reduction in constipation, dryness of the mouth and blurred vision. These benefits were not restricted to patients treated with mecamylamine but also pentolinium* dosage was reduced or eliminated in other patients not reported in Table II.

In addition to the above sixteen patients, eighteen others were studied in the hospital and the out-patient clinic but sufficient follow-up data is not available for tabulation. Nevertheless, clinical observations on these patients seemed worthy of report.

The drug proved to be particularly useful in a number of patients meriting hypotensive treatment who had moderate or severe hypertensive cardiovascular disease and who could not be treated with customary measures. For example, two patients developed paralytic ileus on relatively small doses of ganglionic blocking drug. One patient, E. C. Case No. 29 47 56, on mecamylamine was able to continue with the drug at a reduced dose of mecamylamine by the use of chlorothiazide without subsequent paralytic ileus. Another patient, Mrs. R. Y., Case No. 63 46 02, had developed paralytic ileus on chlorisondamine† and, at x-ray later, was found to have a stenotic loop of bowel at the terminal ileum. A month after chlorisondamine had been stopped, the patient had a resection of this loop of intestine for regional ileitis. There was a breakdown in the anastomosis and an ileostomy was performed. The patient

*Ansolysen by Wyeth
†Ecolid by Ciba

RAUWOLFIA OR RAUWOLFIA & HYDRALAZINE TREATED PATIENTS

Table I

BEFORE CHLOROTHIAZIDE				AFTER CHLOROTHIAZIDE		
Name, Age, Race, Sex, Case No.	Diagnosis	Treatment	BASAL BLOOD PRESSURE ONCE A WEEK Weeks	Weeks	Change in Treatment	Subjective Results Difference in Blood Pressure
C. R. 56, W Male 11 75 56	HCVD	Rauwolfia* 100 mg./d.	4th 168/106 3rd 166/106 2nd 1st Ave. 167/106	1st 140/88 2nd 122/86 3rd 126/70 4th 150/92 Ave. 134/84	Continue Rauwolfia Chlorothiazide 500 mg. q. 12 h.	Transient paresthesias Felt improved —33/—22
M. S. 36, N Female 76 64 29	HCVD Epistaxis Cardiac insufficiency	Rx irregularly with Rauwolfia SR 100 mg. q.i.d.	4th 3rd 134/84 2nd 142/88 1st 180/120 Ave. 152/101	1st 2nd 118/70 3rd 122/70 4th Ave. 120/70	Continued Rauwolfia Chlorothiazide 500 mg. q. 12 h.	Feeling well No dyspnea —33/—29
J. A. 50, W Male 86 96 36	HCVD	Reserpine 0.5 mg. b.i.d.	4th 158/96 3rd 2nd 1st Ave. 158/96	1st. 118/70 2nd 190/120 3rd 132/90 4th 132/80 Ave. 143/90	Reserpine decreased to 0.5 mg. q./d. Chlorothiazide 500 mg. q. 12 h.	Felt better Enuresis once after 1 month on Chlorothiazide —45/—6
R. W. 51, N Male 72 62 30	HCVD	Reserpine 0.5 mg. q./d. Hydralazine 100 mg. q.i.d.	4th 160/100 3rd 170/104 2nd 170/104 1st 134/90 Ave. 160/100	1st 178/100 2nd 142/90 3rd 132/88 4th 106/74 Ave. 139/85	Continue Hydralazine and Reserpine Chlorothiazide 500 mg. q. 12 h.	Improved Less fatique —21/—15
L. S. 52, W Male 77 96 18	HCVD Encephalomalacia (L) internal capsule	Rauwolfia 100** mg. b.i.d. Hydralazine 100 mg. q.i.d.	4th 180/100 3rd 186/112 2nd 1st 160/90 Ave. 175/100	1st 154/76 2nd 138/88 3rd 178/98 4th Ave. 156/87	Stopped Chlorothiazide after 2 wks. Continued Rauwolfia and Hydralazine. Added Mecamylamine 2.5 mg. q. 12 h.	Nausea and no appetite while taking Chlorothiazide Felt worse —19/—13
F. Y. 64, W Male 71 14 21	HCVD Chronic brain syndrome Arteriosclerosis Azotemia (mild)	Reserpine 0.5 mg. q./d.	4th 3rd 2nd 190/110 1st 174/106 Ave. 182/108	1st 172/114 2nd 147/106 3rd 4th Ave. 159/110	Stopped Reserpine Chlorothiazide 500 mg. q. 12 h.	No complaints Felt well —23/+2
Z. S. 65, W Male 03 78 97	HCVD	Reserpine 0.25 mg. q./d. Hydralazine 25 mg. q.i.d. Caused depression	4th 3rd 170/90 2nd 166/88 1st 154/92 Ave. 160/90	1st 154/84 2nd 148/82 3rd 152/90 4th Ave. 151/85	Stopped Reserpine and Hydralazine Chlorothiazide 500 mg. q. 12 h.	No complaints Felt well —9/—5
J. D. 47, N Male 71 44 21	HCVD	Reserpine 0.5 mg. q./d. Hydralazine 25 mg. q.i.d.	4th 3rd 184/124 2nd 200/130 1st 206/108 Ave. 196/120	1st 154/98 2nd 200/110 3rd 158/98 4th 192/112 Ave. 176/104	Continued Reserpine and Hydralazine Chlorothiazide 1 Gram q. AM	Continued to have headaches Felt well —20/—16

Table II

Table II

BEFORE CHLOROTHIAZIDE					AFTER CHLOROTHIAZIDE	
Name, Age Race, Sex, Case No.	Diagnosis	Treatment	Blood Pressure Ave. by weeks of Standing Home Recorded Blood Pressure — Weeks	Weeks	Change in Treatment	Subjective Results and Difference in Blood Pressure
B. W. 48, W Female 86 31 71	Pyelonephritis L. nephrectomy HASCVD Cardiac Insufficiency and Angina	Reserpine .5 mg. b.i.d. Mecamylamine 2.5 - 5.0 mg. q. 8 h.	4th 191/107 3rd 179/110 2nd 182/104 1st 173/102 Ave. 181/106	4th 172/101 5th 170/99 6th 7th Ave. 171/100	Reduced Mecamylamine to 2.5 mg./d. or more often none. Chlorothiazide 500 mg. q. 12 h. Continue Reserpine	Improved. No dyspnea. More strength. —10/—6
S. D. 47, N Male 43 98 64	HCVD Cardiac Insufficiency Creatinine 1.7	Rauwolfia 400 mg. q.i.d. Hydralazine 400 mg. q.i.d. Mecamylamine 20-30 mg. q. 8 h.	4th 196/122 3rd 189/124 2nd 188/113 1st 194/118 Ave. 192/119	1st 135/92 2nd 157/102 3rd 144/90 4th 143/96 Ave. 145/95	Reduced Mecamylamine to 10 mg. q. 8 h. Chlorothiazide 1.0 Gm. q. 12 h. Continue Rauwolfia and Hydralazine	Able to work for first time in 3 mo. Less constipation, less dry mouth and less blurred vision. —47/—24
C. F. 50, W Male 71 50 98	HCVD Duodenal ulcer	Mecamylamine 12.5 mg. q. 8 h.	6th 157/113 5th 150/113 3rd 160/110 1st 160/114 Ave. 157/113	1st 156/110 2nd 146/106 3rd 140/104 4th 137/103 Ave. 145/106	Reduced Mecamylamine to 10 mg. q. 8 h. Chlorothiazide 1.0 Gm. q. AM	Less dyspnea. Less nocturia. Feels better. —12/—7
A. S. 60, N 44 89 44 Male	HCVD	Methyl Reserpate 0.25 mg. q.i.d. Mecamylamine 2.5 mg. q. 12 h.	4th 167/89 3rd 199/103 2nd 216/108 1st 197/108 Ave. 194/102	1st 156/93 2nd 149/90 3rd 4th Ave. 154/91	Chlorothiazide 500 mg. q. 12 h. Continue Methyl Reserpate and Mecamylamine same	Felt much better. —40/—11
R. M. 60, W Male 77 86 57	Pyelonephritis, HCVD, ASHD Old M. I. & Angina	Rauwolfia 100 mg. q.i.d. Mecamylamine 5.0 — 7.5 mg. q. 12 h.	6th 163/120 4th 164/109 2nd 162/110 1st 160/110 Ave. 162/112	1st 147/105 2nd 145/104 3rd 150/100 4th 132/93 Ave. 143/101	Reduced dose of Mecamylamine to none or 2.5 mg./d. Chlorothiazide 500 mg. q. 12 h. Continued Rauwolfia	Improved. Less fatigue. —19/—11
C. McC. 56, W Male 27 90 33	HCVD Asthma	Rauwiloid 6 mg. per day Mecamylamine 20 mg. q. 12 h.	4th 160/84 3rd 163/90 2nd 167/87 1st 166/94 Ave. 164/89	1st 145/89 2nd 143/89 3rd 142/87 4th 141/86 Ave. 143/88	Reduced Mecamylamine to 10 mg. q. 12 h. Chlorothiazide 500 mg. q. 12 h. Continue Rauwiloid	Improved. Less dyspnea. Better work tolerance. —21/—1
S. B. 56, N Female 89 27 39	HCVD Grade III fundi	Mecamylamine 5.0 mg. q. 8 h. (Unable to tolerate Rauwolfia)	2nd 197/136 1st 195/131 Ave. 196/134	1st 184/128 2nd 175/120 3rd 160/115 Ave. 168/118	Chlorothiazide 500 mg. q. 12 h. Increased to 1.0 Gm. q. 12 h. 3rd week Continue Mecamylamine same	Heartburn. Not as tired as before. —28/—16
A. M. 59, W Female 37 06 64	HCVD (mild)	Mecamylamine 2.5 — 7.5 mg. q. 8 h. (Unable to tolerate Rauwolfia)	4th 151/98 3rd 152/99 2nd 151/98 1st 148/97 Ave. 151/98	1st 146/98 2nd 139/94 3rd 145/94 Ave. 143/95	Stop Mecamylamine Chlorothiazide 500 mg. q. 12 h.	Better. No constipation due to Mecamylamine. No drowsiness due to Rauwolfia. —8/—3
		TOTALS	Ave. 174/109	Ave. 151/99		—23/—10

had previously had a severe depressive reaction to reserpine so that all antihypertensive drugs were withheld during several weeks in the hospital at the time of her surgery. She developed signs of progressive left ventricular hypertrophy associated with high blood pressure. Reserpine seemed contraindicated in view of the previous depressive reaction with suicidal trends, ganglionic blocking agents seemed contraindicated in view of the complications associated with her intestinal surgery. Methyl reserpate* parenterally was ineffective in lowering her pressure. We resorted to chlorothiazide and with the use of this drug as the sole antihypertensive agent, her blood pressure came close to normal and remained at satisfactory levels.

Another patient, M. M., Case No. 89 55 57, was a man who had had a depressive reaction to reserpine for treatment of hypertensive cardiovascular disease, and was referred by another doctor for evaluation. Between his first visit and waiting for a hospital bed, he developed a severe gastrointestinal hemorrhage presumably from peptic ulcer. The blood pressure was widely variable in view of repeated hemorrhage and transfusion. When the patient had massive hemorrhage, blood pressure would be very low; transfusions would result in extreme rises in pressure and subsequently further hemorrhage would occur. We did not want to use reserpine in view of his previous depressive reaction and preferred not to use ganglionic blocking agents in view of the intestinal hemorrhage. On treatment with chlorothiazide as the sole antihypertensive agent, along with blood transfusions, his blood pressure gradually stabilized at much lower levels and we were eventually able to control him with small doses of mecamylamine plus chlorothiazide for maintenance.

F. Y., Case No. 71 14 21, was scheduled for a nephrolithotomy for renal calculus. He had had transient cerebral vascular insufficiency, sustained blood pressure elevation and left ventricular hypertrophy by EKG. It seemed desirable to lower his pressure before surgery and in the postoperative period. We were hesitant about giving him rauwolfia since general anesthesia would soon be indicated and we have encountered a number of serious hypotensive reactions during general anesthesia in patients who have been under treatment with rauwolfia derivatives. Treatment with chlorothiazide reduced his blood pressure in the pre-and post-operative periods and appeared to be satisfactory as the sole antihypertensive agent.

One patient, H. B., Case No. 89 33 18, who developed a psychosis about a month following a subarachnoid hemorrhage seemed to be benefited by chlorothiazide. Reserpine was discontinued because he had a severe agitated depression. The use of ganglionic blocking agents was impractical due to his psychotic behavior. Blood pressures were reduced somewhat by chlorothiazide and this was helpful in differentiating his psychotic symptoms from symptoms which could conceivably have been due to hypertensive encephalopathy. One hospitalized patient, Z. R., Case No. 80 95 11, with mild azotemia, showed slight blood pressure reduction when chorothiazide was used for one week as the only treatment. Later, with the addition of intramuscular reserpine, little benefit was gained and considerable drowsiness and stuffiness of the nose resulted. She was treated with chlorothiazide alone and the follow-up period was too brief for a long term evaluation of the benefit but the basal blood pressure was

*Su.3118 Ciba

150/94 after one month on this treatment. Pre-treatment basal blood pressures were all above 170/104.

With respect to side effects and possible toxic effects of chlorothiazide, one patient is described who stopped the drug due to nausea; L. S., Case No. 77 96 18, listed in Table I. Three other patients discontinued the medication due to undesirable side effects. In one patient, this was described as a nausea and heartburn. Another patient after taking the drug for four days frequently had a feeling of pinching in the chest and of blood rushing to the head. She stopped taking the medicine and felt better. Another patient had noticed diuretic effect from chlorothiazide but also dizziness, faintness, and weakness with an exacerbation of neuromuscular chest pains. She discontinued the drug, resumed it one week later and again had the same undesirable symptoms. These last three cases described all had features of neurotic reactions and it is possible that some of the undesirable effects described were in the nature of placebo reaction to the new medication. This seems especially likely in view of the minimum of side effects reported by most other investigators with chlorothiazide.

Three patients with renal insufficiency associated with hypertensive cardiovascular disease were studied in the hospital, maintained on a 400 mg. sodium diet and were given chlorothiazide as part of treatment for their hypertensive disease. One of these patients, T. L., Case No. 89 80 98 had Grade IV fundi and a serum creatinine of 3 mg. percent. The serum phosphorous was 5.4 mg. percent. His highest serum sodium was 137 Meg./L. At a time of maximum chlorothiazide effect at 2 Gm./d. the serum sodium was 127, potassium 2.9, chloride 83 and CO_2 was 27.4. Chlorothiazide in this patient caused a remarkable potentiation in the postural hypotensive effect of inversine and the greatest orthostatic hypotension occurred at a time when the serum sodium, chloride and potassium were lowest. Patient A. C., Case No. 86 73 70 had encephalopathy and renal failure with serum creatinine 7.4 and phosphorous 9.2 mg. percent. She also showed a reduction in serum sodium, potassium, chloride and a rise in CO_2 when chlorothiazide 1 Gm./d. was added to a 400 mg. sodium diet. A. M., Case No. 86 85 15, with recurrent pulmonary edema and renal failure had serum creatinine 7.5, serum phosphorous 9.0 mg. percent. His highest serum sodium was 137. He was on a 400 mg. sodium diet, chlorothiazide and mecamylamine. Diuresis occurred with relief of pulmonary edema. The serum sodium fell to 120, potassium 3.0, chloride 88 and CO_2 increased to 27.6.

There were no apparent adverse effects in these three patients from the depletion of sodium, potassium and chloride which occurred. The average change in serum electrolytes in Meq./L for the three patients with renal insufficiency was for sodium -7.2, for potassium -0.7, for chloride -14.1, for CO_2+6.4. These electrolyte changes are more marked than those described in most patients on chlorothiazide treatment.[2] This may be due to a combination of renal insufficiency, salt restricted diet and chlorothiazide. Although the depletion of sodium and chloride and potassium was associated with clinical improvement and good hypotensive effects in these patients on concurrent antihypertensive drug treatment, the hazard of salt depletion and low salt syndrome did exist. The changes elicited were reversible readily with cessation of the drug and/or added salt to the diet.

The changes in serum electrolytes of these patients with renal insufficiency were of greater magnitude than those described by Laragh[4] and Ford.[5] Slowly, progressive renal insufficiency as evidenced by a rising creatinine and NPN occurred in two of these three cases but was difficult to relate to undue hypotensive effect or possible nephro-toxic effect of chlorothiazide. In the majority of patients on a higher salt intake with chlorothiazide as reported by Freis[2] no such depletion of sodium, potassium and chloride occurred. A patient reported in Table II, S. D., Case No. 43 98 64, (also charted in Fig. 3) followed a dose of 1 Gm. of chlorothiazide every twelve hours for a period of two months, with no depletion of electrolytes. This patient arbitrarily stopped salt restriction and gained weight not due to edema. It seems likely that this improvement was due to a less monotonous diet and a feeling of well-being associated with a reduction in the dose of his ganglioplegic drug. It is interesting that on a liberal salt intake, this patient continued to have lower average blood pressures than before chlorothiazide. He was able to reduce his dose of mecamylamine by 50 per cent. Three weeks after the start of chlorothiazide at 2 Gm./d. serum sodium was 137, potassium 6.1, chloride 101, CO_2 was 21.7. Six weeks after the start of chlorothiazide his serum sodium was 137, potassium 3.7, chloride 108 and CO_2 was 22.6. It would appear that the danger of salt depletion is not great as long as the oral intake of salt is not severely restricted and as long as there is no unusual loss through repeated vomiting or diarrhea or inability to eat. In the patient

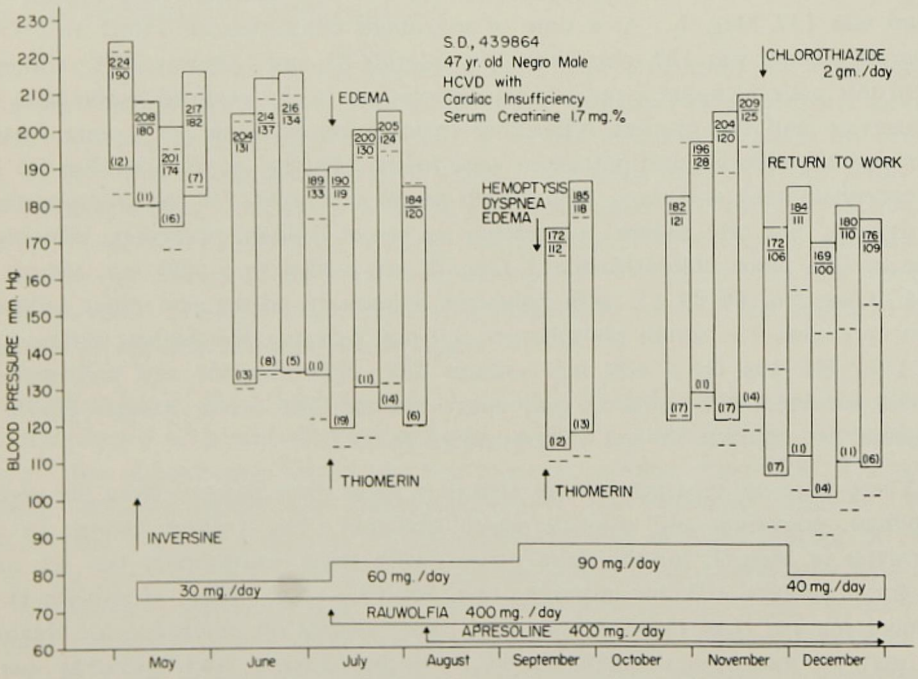

Figure 3

BP record of patient unable to work for 3 months because of recurrent pulmonary edema until chlorothiazide was instituted. Coincident with starting chlorothiazide note: (1) lower average weekly sitting BP (solid rectangles), (2) enhancement of orthostatic hypotensive effect of mecamylamine (dash lines for average weekly standing BP) and, (3) reduction in dose of mecamylamine by more than 50%.

with malignant hypertension T. L., Case No. 89 80 98 salt depletion from chlorothiazide occurred in relation to a reduction in blood pressure with marked orthostatic hypotension. This fact suggests that salt depletion is the principle mode of hypotensive action of this novel diuretic in hypertensive patients. Against this theory is the observation that serum electrolytes are relatively unchanged in most of the patients on chlorothiazide when no salt restriction is advocated. Prolonged use of chlorothiazide at 2 Gm./d. on a relatively liberal salt intake in S. D., Case No. 43 98 64, was not associated with salt depletion. At the same time, there was a maintained blood pressure reduction and also a reduction in the dose of mecamylamine. This suggests some mode of action other than salt depletion for the hypotensive effects.

The major benefit of this new diuretic agent for patients with hypertensive disease is the advantage of being able to reduce or omit less desirable hypotensive agents. By virtue of this change, the weakness, stuffy nose and lethargy some patients experience with rauwolfia may be reduced and the blurred vision, dryness of the mouth, constipation and sexual impotence associated with ganglioplegic drugs may be reduced. Many patients experience a sense of well-being or relief from fatigue. This is little wonder in view of the fact that there is a reduction in rauwolfia and ganglionic blocking drugs as part of the response to the new drug. Studies done elsewhere by Freis[2] and Wilkins[3] have also shown that some of their hypertensive patients treated with chlorothiazide alone had adequate control of hypertension. Also, Freis[2] has studied normotensive patients and found that there is no significant reduction in blood pressure in such cases and that there is a specificity for this drug which is unique. Laragh, et al[4] has shown that in doses up to 8 Gm./d. no side effects were noted and that in thirty patients on usual doses of 1 Gm./d. no toxic effects were noted except erythema in one case. The uric acid was higher in patients studied by Laragh et al[4] and characteristic hypochloremic alkalosis was produced. Ford[5] postulated that the mechanism of diuretic action was due to an inhibition of renal tubular reabsorption of sodium. Schreiner[6] showed in thirteen patients with chronic renal failure that the drug was chloruretic and the poorest clinical responses to the drug were in those patients with chronic renal failure. Perhaps the greatest danger is salt depletion and progressive renal insufficiency.

When chlorothiazide was used in the treatment of 34 patients with hypertensive cardiovascular disease, the drug was found to be an effective antihypertensive agent, usually permitting a reduction and occasionally elimination of the dose of other antihypertensive drugs. In the majority of patients for the period of time studied, it seemed to be of most value as an adjunct to therapy rather than sufficient as the sole form of treatment. According to a clinical estimate results could be graded as follows: excellent 15, good 11, fair 4, poor 4. In a group of eight patients treated with rauwolfia or rauwolfia and hydralazine, the change in the average blood pressure after treatment with chlorothiazide was -24 mm. of mercury systolic and -16 mm. of mercury diastolic for the group. In a group of eight patients treated with mecamylamine the average change in blood pressure was -23 mm. of mercury systolic and -10 mm. of mercury diastolic. In eighteen other patients brief sketches of the most pertinent clinical features are described along with some comment about their response to the drug. Three patients with renal insufficiency were on salt restricted diets and with

chlorothiazide treatment developed salt depletion which was reversible and not deleterious but is noted as a possible hazard of therapy. Side effects were usually absent. In those patients who did develop undesirable reactions, these side effects are briefly discussed. The usual dose was 500 mg. every twelve hours, in the morning and at night. The range of dosage was 500 mg. once daily to 2 Gm. daily. In most cases, dosage was continuous daily. Speculations regarding the mode of action are presented. The time period was short for these observations embracing not more than three months at the most; however, the work of Freis[2] and Wilkins[3] covers larger numbers of patients over longer periods of time, and they report similar results.

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