Orthostatic Hypotension, Anhidrosis, and Impotence

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Anhidrosis and impotence occur frequently with idiopathic orthostatic hypotension. Two new cases of this syndrome, which occurs chiefly in males over 40 years of age, are herewith described. Postural vertigo and/or syncope, weakness, and anhidrosis or hypohidrosis are common symptoms, and a marked fall in systolic and diastolic blood pressure is noted when the patients stand. The pathologic physiology of the syndrome is discussed and various forms of therapy, none of them especially satisfactory, are reviewed.

In 1925 Bradbury and Eggleston reported the occurrence of a hitherto unrecognized clinical phenomenon, orthostatic hypotension, which they observed in three males, all of whom sustained a fall in systolic and diastolic blood pressure when they assumed upright posture. Their patients also exhibited a slow, unchanging pulse rate, dizziness, syncope, and anhidrosis or hypohidrosis. Subsequently, many instances of postural or orthostatic hypotension have been reported. In general, two types may be defined: (1) those due to known cause, among which are sympathectomy, tabes dorsalis, diabetes mellitus, myasthenia gravis, Addison's disease, hypopituitarism, syringomyelia and hematomyelia; and (2) those due to unknown or ill-defined disease of the central nervous system. In the latter group of patients a wide spectrum of signs and symptoms has been observed, but the findings in some of the patients cannot be considered to conform to the clinical syndrome originally described by Bradbury and Eggleston. For purposes of this study arbitrary criteria have been established to emphasize the concomitant occurrence of postural hypotension, anhidrosis and impotence a triad to which attention was first called by East and Brigden. Only those cases, therefore, manifesting significant systolic and diastolic postural hypotension,* with an unchanging or only slightly increased pulse rate, and anhidrosis or hypohidrosis have been included. With the two cases which we have observed and which are herein described, a total of 37 cases has been gathered from the literature.

Case Reports

Case 1. E. W. (B. H. 182971), a 65 year old white married painter, was admitted to the Barnes Hospital for the first time on April 1, 1950, for study of "low blood pressure." His chief complaints were dizziness and lightheadedness of two years' duration. Three years before entry he noted that he ceased sweating on the left side, and one year before entry he stopped perspiring on the right side. Two years before admission he also began to feel "lightheaded" whenever he stood up. Concomitantly dizziness appeared when he was erect, and he had a rather sudden lapse of sexual desire and potency. About one year before entry he consulted a physician who told him that his blood pressure was 140/70 when he was sitting, but 60/40 when he stood up. Aside from slight dyspnea on exertion he had no other immediate complaints.

The past history revealed that the patient had had gonorrhea at age 23, and syphilis at 51. For the latter disease he was treated with 18 injections of an arsenical compound, and subsequently four serologic tests were negative. He had never had a lumbar puncture. Five years prior to entry he had transient nocturnal diarrhea. His weight had been quite constant for several years. His skin had always been rather dry.

The patient had been married three times. Until

* A fall in blood pressure of at least 35 mm. Hg systolic and 20 mm. Hg diastolic was considered to be significant.

† Referred by Dr. James Allee, Columbia, Mo.
the rather sudden onset of loss of libido and the development of impotence two years before, he had continued to have intercourse frequently, usually once or twice a week. He had worked as a painter for many years.

Physical examination at the time of entry revealed the patient to be an obese white man who did not appear ill. His temperature was 37 C. The blood pressure in the arms, with the patient recumbent, was 120/65 mm. Hg; with the patient recumbent but with his legs elevated, the reading was 150/90 mm. Hg. When he stood his blood pressure fell to 84/40 mm. Hg. The pulse remained constant at 80 during all of these determinations. The skin was extremely dry and rather sealy, particularly on the hands and forearms. The axillas were slightly moist. The left pupil was round, the right somewhat elliptical, but both reacted well to light and accommodation. Physical examination was otherwise entirely negative.

Laboratory data included a normal hemogram. The urine and stool examinations were negative as was the blood Kahn test. The nonprotein nitrogen was at the upper limit of normal; the fasting blood sugar was normal. An electrocardiogram was normal except for low voltage. The circulation time with Decholin was 17 seconds with the patient recumbent and 30 seconds when he was standing. Two basal metabolic rate determinations were −13 and −16 per cent respectively. Urinary gonadotropin excretion in 24 hours was 8.7 mouse units, a normal value.* The cerebrospinal fluid was normal.

When a heat cradle was applied over the trunk for thirty minutes only slight sweating in the axillae, inguinal areas, and over the sternum resulted. After administration of 10 mg. of pilocarpine subcutaneously much more sweating was noted in all areas of the body. Only a slight subjective sensation of palpititation was produced by the subcutaneous injection of 0.6 mg. of epinephrine. There was no actual rise in blood pressure or pulse rate, and the postural hypotension was unaffected. The pulse rate did not increase when 0.6 mg. of atropine was given subcutaneously. The blood eosinophile response to epinephrine was within normal limits.

The cardiac output, as estimated by the tilt table ballistocardiograph,† did not show a significant decrease when the patient was tilted 45 degrees from the horizontal; his pulse rate remained constant.

A summary of the effects of various drugs upon blood pressure and pulse is given in table 1.

Ephedrine in doses of 25 mg. did not benefit the patient significantly. When ephedrine was given in doses of 50 mg. by mouth, and the patient's legs were kept wrapped tightly with elastic bandages, more improvement resulted than with any of the many other therapeutic measures attempted. Therefore, the patient was discharged on April 7, 1950, and advised to take 50 mg. of ephedrine after each meal and 25 mg. before retiring. In addition, he was instructed to wrap his legs daily with elastic bandages.

**Follow-up Note.** The patient was seen briefly about one month after discharge at which time his condition was essentially unchanged. Two weeks later, after returning to his home, he expired rather suddenly. Unfortunately, he was not seen by a physician and an autopsy was not performed.

**Case 2.**—D. F. (B. H. 84006), a 62 year old white married miner, was admitted to the Barnes Hospital for the fifth time on March 1, 1949, complaining of "fainting spells." The past history was of interest only in that the patient had been constipated for many years.

Twenty-three years before entry, at the age of 39, the patient developed increasing fatigability, weakness, and dizziness on standing. These symptoms persisted until entry, and had become so severe that when he stood up he lost consciousness. Approximately at the same time that the previous complaints began, the patient noted relative impotence which likewise progressed so that he was soon unable to indulge in sexual activity. Sixteen years before entry he became aware that he sweated less than his fellow workers in the coal mine and that the heat seemed to bother him more than the other men. Concomitantly he also had frequent temperature elevations. In the ensuing 16 years there was a progressive decrease in sweating so that by the time of admission the patient had almost completely ceased perspiring.

He first entered the Barnes Hospital in August, 1940, at which time his blood pressure was found to be normal when he lay recumbent, but it was observed to fall precipitously when he stood up, levels of the order of 60/40 mm. Hg being recorded. During his first admission he was studied with the possibility of Addison's disease as the prime consideration, but that diagnosis was not confirmed and he was discharged with a diagnosis of idiopathic hypotension. He subsequently was readmitted four times. Each time he was found to have persistent postural hypotension without evidence of other disease. His temperature was frequently slightly elevated.

In the year prior to his last admission the patient had had progressive increase in weakness and ease of fatigability; he had been unable to drive a car because of blurred vision. During the four weeks prior to entry he fainted on three or four separate

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* This determination was made in the laboratory of Dr. Willard M. Allen, Department of Obstetrics and Gynecology, Washington University School of Medicine.

† The authors are grateful to Dr. Arthur E. Gropper who performed the ballistocardiography.
occasions, and on one of these was unconscious for three hours.

Physical examination at the time of entry revealed his temperature to be 37 C., pulse 76, respirations 18; the blood pressure was 95/60 mm. Hg with the patient recumbent, 75/60 mm. Hg when he sat erect, and 60/0 mm. Hg when he stood. While the erect blood pressure was being determined the patient fainted. His skin was dry and scaly, and he did not perspire. The remainder of the examination was negative.

The laboratory data included a normal hemogram. The urine showed a trace of albumin and many white cells per high power field in the centrifuged sediment. The blood Kahn test was negative. The nonprotein nitrogen was at the upper limit of normal; the fasting blood sugar was normal. The basal metabolic rate was -13 per cent. A chest film was interpreted as showing a tortuous sorta; the heart was normal in size and contour. An electrocardiogram was within normal limits.

The following special study was performed: the arterial blood pressure in the right brachial artery was measured by a Hamilton optical manometer while the blood flow in the right middle finger and toe as well as in the pinna of the right ear lobe was recorded by photoelectric plethysmographs. The patient was then tilted 20 and 45 degrees from the horizontal. The blood pressure fall from 156/80 mm. Hg in the horizontal position to 87/63 mm. Hg at a 45 degree tilt. The pulse rate was 72 per minute with the patient horizontal and increased to only 84 when he was tilted. The subject complained of dizziness and began to black out after 45 seconds in the tilted position. The amplitude of the plethysmographic tracings decreased, suggesting either (1)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Drug</th>
<th>Dose mg</th>
<th>Route of Administration*</th>
<th>Time of Reading Minutes</th>
<th>Position of Subject†</th>
<th>Blood Pressures mm. Hg</th>
<th>Pulse Rate per Minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. W.</td>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>H</td>
<td>120/75</td>
<td>92</td>
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<tr>
<td></td>
<td>Epinephrine</td>
<td>0.6</td>
<td>S.C.</td>
<td>30</td>
<td>H</td>
<td>120/75</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Ephedrine</td>
<td>25</td>
<td>oral</td>
<td>120</td>
<td>H</td>
<td>130/80</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td>0.6</td>
<td>S.C.</td>
<td>15</td>
<td>H</td>
<td>105/75</td>
<td>84</td>
</tr>
<tr>
<td>D. F.</td>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>H</td>
<td>120/72</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td>0.5</td>
<td>S.C.</td>
<td>30</td>
<td>H</td>
<td>140/78</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Ephedrine</td>
<td>45</td>
<td>I.M.</td>
<td>10</td>
<td>H</td>
<td>124/70</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Benzedrine</td>
<td>10</td>
<td>I.M.</td>
<td>30</td>
<td>H</td>
<td>150/90</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Paredrine</td>
<td>20</td>
<td>I.M.</td>
<td>30</td>
<td>U</td>
<td>168/100</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Prostigmine</td>
<td>0.5</td>
<td>S.C.</td>
<td>15</td>
<td>H</td>
<td>152/94</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td>0.1</td>
<td>I.M.</td>
<td>30</td>
<td>U</td>
<td>98/70</td>
<td>94</td>
</tr>
</tbody>
</table>

* S.C. = Subcutaneously
I.M. = Intramuscularly
† H = Horizontal Position
U = Upright Position
D = Head Down Position

The response of the patient's pulse and blood pressure to various drugs is summarized in table 1. It is of interest that 10 mg. of pilocarpine by the subcutaneous route produced generalized sweating.

The patient was discharged from the hospital on March 15, 1949, and was advised to take Prostigmine, 10 mg., three times daily.

Follow-up Note. The patient was seen about 15 months after discharge at which time his condition was essentially unchanged.
Occurrence
The patients with this syndrome have ranged in age between 39 and 72 years, the average being 53. Males have outnumbered females by a ratio of four to one. Occupational factors have not been obvious although it is of interest to point out that there had been significant contact with paint or heavy metals in two of the previously reported cases, and in one of the two added herewith. In all three of these patients the signs and symptoms of the syndrome were advanced.

Symptoms*
The onset of symptoms in the earliest case occurred in a patient 23 years of age, and the latest onset was noted in a man aged 63. The most pronounced symptoms were postural vertigo, syncope, weakness, blurring of vision and loss of mental acuity prior to syncope. On the other hand syncope usually developed without premonitory nausea, pallor, or other vasoconstrictive aura. Symptoms were characteristic more severe in the morning when the patient first arose, after meals, exercise and in warm weather. In only one of the cases have convulsive seizures been noted; in another patient voluntary shaking movements of the arm preceding the attack of syncope were described.

Anhidrosis or hypohidrosis occurred in all 37 cases. Often anhidrosis was limited to only certain portions of the body and in several cases was unilateral at some time during the course of the patient’s illness. In still other patients only the lower half of the body was involved.†

Direct inquiry concerning impotence was made to only 18 male patients. Since it was present in 17 of them, it is probably much more common than previously appreciated. It was sudden in onset in several patients aged 30 to 50. Nocturia was present in 18 of 20 patients to whom specific inquiry was made in regard to this symptom. Bladder disturbances, such as incontinence, were recorded six times. Six patients were constipated, and four complained of diarrhea.

| Table 2.—Symptoms, Signs and Laboratory Findings in Idiopathic Orthostatic Hypotension |
|-------------------------------------------------|---------------------------------|-----------------|----------|
| Symptoms                                        | Number of Times Sought For | Number of Times Found | Per cent Found |
| Postural vertigo or weakness                    | 37                         | 37               | 100    |
| Postural syncope in addition                    | 37                         | 30               | 78     |
| Anhidrosis or hypohidrosis                      | 37                         | 37               | 100    |
| Impotence or loss of libido                      | 18                         | 17               | 94     |
| Nocturia                                        | 20                         | 18               | 90     |
| Bladder disturbances                            | 8                          | 6                | 75     |
| Diarrhea                                        | 11                         | 5                | 45     |
| Constipation                                    | 11                         | 6                | 55     |
| Signs                                           |                              |                  |        |
| Postural fall of systolic pressure 50 mm. Hg    | 37                         | 30               | 81     |
| Postural fall of diastolic pressure 30 mm. Hg   | 37                         | 31               | 84     |
| Postural fall to systolic pressure 70 mm. Hg or less | 37 | 30 | 81 |
| Postural increase in pulse rate of 10 per minute or less | 36 | 23 | 64 |
| Dry skin                                        | 20                         | 12               | 60     |
| Abnormal neurologic findings                    | 37                         | 14               | 38     |
| Laboratory Findings                            |                              |                  |        |
| Normal ECG                                      | 20                         | 18               | 90     |
| BMR −10% or below                              | 23                         | 14               | 61     |
| Elevated XPN or BUN                            | 21                         | 15               | 71     |
| Sweating induced with pilocarpine               | 14                         | 14               | 100    |
| Unchanging pulse rate after atropine injection  | 11                         | 11               | 100    |

* A summary of the symptoms, signs and laboratory findings in idiopathic orthostatic hypotension is given in table 2; central nervous system abnormalities are shown in table 3.
† An extensive review of anhidrosis has recently been published.

In most of the patients postural hypotension was marked. In 81 per cent of the cases a fall in systolic pressure of more than 50 mm. Hg was observed within a few seconds after the patient assumed the upright position, and the diastolic blood pressure fell 30 mm. Hg or more in 84 per cent of the cases. Sixty-four per cent of the patients showed a rise in pulse rate of less than 10 beats per minute. Carotid sinus
<table>
<thead>
<tr>
<th>Report</th>
<th>Age</th>
<th>Memory Loss</th>
<th>Pupil Abnormalities</th>
<th>Increased Reflexes</th>
<th>Decreased Reflexes</th>
<th>Abnormal Toe Signs</th>
<th>Tremor</th>
<th>Nystagmus</th>
<th>Ataxia</th>
<th>Positive Romberg</th>
<th>Decreased Vibratory Sense</th>
<th>Adiadochokinesia</th>
<th>Relaxed Rectal Sphincter</th>
<th>Other Findings</th>
<th>Neurologic Diagnosis If any</th>
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</thead>
<tbody>
<tr>
<td>Bradbury and Eggleton⁴</td>
<td>M67</td>
<td></td>
<td>Unequal</td>
<td>+</td>
<td>Bilaterally</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left VI nerve palsy.</td>
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<tr>
<td>Moretti⁴</td>
<td>M65</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ptosis of right eyelid.</td>
<td></td>
</tr>
<tr>
<td>Granholm and Horton⁴</td>
<td>M52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Intention tremor R. Arm</td>
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<td>+</td>
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<tr>
<td>Chew and associates⁸</td>
<td>M53</td>
<td></td>
<td>Unequal</td>
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<td></td>
<td></td>
<td>+</td>
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</tr>
<tr>
<td>Langston⁴</td>
<td>M56</td>
<td></td>
<td>+</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td>Emotional swings. Involuntary laughter prior to syncope.</td>
<td></td>
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<tr>
<td>Baker⁴⁷</td>
<td>M61</td>
<td></td>
<td>Left Horner’s</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diffuse sclerosis of CNS</td>
<td></td>
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<tr>
<td>Ewert⁴⁰</td>
<td>M67</td>
<td></td>
<td>+</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Bilateral ptosis. Left lower facial and palatal palsy. Tongue slightly to right. Intermittent atrophy in left hand.</td>
<td></td>
</tr>
<tr>
<td>Jeffers and Montgomery⁴¹</td>
<td>M48</td>
<td></td>
<td>Sluggish</td>
<td>+</td>
<td>Legs</td>
<td>+ L.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bilateral cerebral atrophy demonstrated by pneumoencephalograms.</td>
<td></td>
</tr>
<tr>
<td>Laufer⁴²</td>
<td>M49</td>
<td></td>
<td>Irregular Unresponsive</td>
<td>+</td>
<td>Absent in legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adie’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Hammarstrom and Lindgren⁴⁷</td>
<td>M48</td>
<td></td>
<td>+ No light response on R. Decreased on L.</td>
<td></td>
<td>Ankle Clonus</td>
<td>+ L. and R.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slurred speech; apraxia. Cerebral atrophy demonstrated by pneumoencephalograms.</td>
<td>Diffuse areas of encephalomalacia</td>
</tr>
<tr>
<td>Young⁴³</td>
<td>M43</td>
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<td>+ Fin</td>
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<td></td>
<td></td>
<td>Loss of tone of vocal cord. Masked facies. Flexion position.</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Mawson⁴⁴</td>
<td>F60</td>
<td></td>
<td></td>
<td>+</td>
<td>Ankle</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Possible Raynaud’s syndrome in third finger.</td>
<td></td>
</tr>
<tr>
<td>Nylin and Levander⁴⁵</td>
<td>M69</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cogwheel rigidity in left arm.</td>
<td>Left-sided parkinsonism</td>
</tr>
<tr>
<td>Engel⁴⁶</td>
<td>M54</td>
<td></td>
<td>Unequal</td>
<td>+</td>
<td>Legs</td>
<td></td>
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</table>
pressure was generally ineffective in lowering the blood pressure or slowing the pulse rate. It is of interest that a degree of postural hypertension is also common in these patients; thus, raising the feet above the level of the heart frequently results in a distinct rise in the systolic and diastolic blood pressures.

Central nervous system abnormalities were present in 38 per cent of the patients. The findings were rather diverse, with abnormalities in pupillary reactions and reflex changes noted most often. Adequate criteria for definite neurologic diagnoses were present in only a few cases, but included in the clinical neurologic diagnoses were Adie's syndrome,38 Horner's syndrome,11 diffuse arteriosclerosis or atrophy of the central nervous system,4 12 and parkinsonism.18 41

The skin was dry, coarse and scaly in 60 per cent of the patients in whom skin examination was specifically mentioned. No other consistent abnormalities in the physical findings were recorded.

LABORATORY FINDINGS

No particular deviations from the normal in regard to blood counts or urinalyses were noted. Of particular interest were the results of basal metabolic rate determinations. Approximately 60 per cent of the patients exhibited basal metabolic rates of -10 per cent or lower. All but two32 34 were in the range of 0 to -21 per cent.

An interesting negative finding was the fact that 18 out of 20 patients in whom electrocardiographic tracings were obtained exhibited no abnormalities. In the other two only minor variations from the normal were found. Two patients4 21 exhibited electrocardiographic changes during the episodes of hypotension and these consisted of inversion of T3 and/or T4. Electroencephalograms have been recorded in several patients and have shown no specific changes. In one instance, however, Engel17 observed the electroencephalogram during an episode of postural syncope. He found changes which were typical of cerebral anemia and which have been described in other forms of syncope.

Most of the patients excreted large volumes of urine at night with a small diurnal volume of high specific gravity.25 Decrease in phenolsulfonephthalein excretion,1 creatinine clearance,18 and urea clearance associated with a rise in blood urea nitrogen16 was noted in several patients when they assumed the erect position. In addition some degree of nitrogen retention occurred in 71 per cent of the patients. In one a return of the nonprotein nitrogen level to within normal limits was noted after 10 days of bed rest.23

In patients with anhidrosis, the application of heat in various forms did not induce significant perspiration. Engel17 noted also the absence of a shivering response in his patient. The injection of 5 to 10 mg. of pilocarpine subcutaneously produced marked generalized sweating in 14 patients.

There were normal blood pressure and pulse responses41 45 to the subcutaneous injection of 0.5 to 1.5 mg. of epinephrine in seven of nine patients. One was a hyper-reactor24 who exhibited a marked increase in both the systolic and diastolic pressures. In no case was the degree of postural hypotension lessened. Our first patient was unique in that he had no increase in systolic blood pressure or pulse rate after 0.6 mg. of epinephrine subcutaneously. In none of the 11 subjects given atropine there was an increase in pulse rate.

Although normal subjects exhibit no increase in the arm to tongue circulation time when standing erect,46 an increase was demonstrated in all patients with orthostatic hypotension subjected to the procedure.2 28 82

COURSE

In general there is little spontaneous fluctuation in the course of idiopathic orthostatic hypotension. Stead's first case19 constituted an exception to this statement. The course usually is slowly progressive over a period of many years. One ominous note is sounded by the occurrence of sudden death in two of the three patients reported by Bradbury and Eggleston1 and in our first patient, all of whom presented advanced examples of the syndrome. Other reported deaths were due to unrelated diseases.
TREATMENT

The therapeutic measures are of two types: (A), pharmacologic preparations, chiefly pressor agents; and (B), devices to increase blood volume.

A. Pharmacologic Preparations. In general large doses of vasopressor drugs are given early in the morning, the time when symptoms are usually most marked. These drugs often do not prevent pronounced postural hypotension but do afford considerable symptomatic relief in some cases. Their usefulness is limited by the nervousness, tremor, and insomnia which they produce. Ephedrine gave some relief in 18 of 24 cases, the doses ranging from 12.5 mg. once in the morning to 50 mg. every two hours.\(^3,\, 18\)

In isolated instances Neosynephrine,\(^21\) Benzedrine\(^31\) and Paredrine\(^33\) were effective. A long acting preparation of norepinephrine might well constitute the most effective agent in the treatment of this disease.

B. Measures to Increase Fluid Volume. MacLean\(^35,\, 36\) reported excellent results in patients when the head of the bed was elevated 20 degrees above the horizontal; the beneficial effects were enhanced by the administration of fluid and salt. An increase in circulating blood volume was demonstrated during treatment, and a relapse of symptoms occurred on cessation of therapy. Good results using similar methods were also obtained by Laufer\(^30\) and by Corcoran.\(^47\) The use of desoxycorticosterone acetate and a high salt intake in addition to vasopressor drugs has been reported to afford some symptomatic relief.\(^7,\, 21,\, 29,\, 45\)

Treatment with elastic leg bandage binders and abdominal belts has been generally unsuccessful,\(^31\) although in our first patient, wrapping of the legs in combination with ephedrine was of some value.

DISCUSSION

The pathologic physiology of postural hypotension has been studied by a number of investigators. Stead and Ebet\(^19\) have convincingly demonstrated that there is pooling of no more than a normal amount of blood in the lower extremities of these patients. They have concluded that the cause of postural hypotension is an abnormal response to a normal shift in blood volume. Evidence is here reviewed that this abnormal response includes lack of arteriolar and venous constriction and absence of reflex tachycardia. In addition, there is in some cases a greater than normal fall in cardiac output.

Evidence for lack of vasoconstriction is gained from plethysmographic studies which demonstrate (a) absence of normal spontaneous changes in blood flow; (b) absence of variations in blood flow with respiration or temperature,\(^19,\, 37\) and (c) a greater than normal blood flow in the hand for a given fall in blood pressure.\(^19\) That there is lack of arteriolar constriction, when a fall in blood pressure occurs, appears certain. However, it is not likely that arteriolar constriction is entirely absent in all cases. This statement is based upon the plethysmographic studies in our patient, D.F., the results of which are interpreted as indicating that although the vasoconstriction in the upper and lower extremities was not adequate to maintain cerebral blood flow, there was some degree of arteriolar constriction in these peripheral parts.

In our patient E. W., the cardiac output, as estimated by the tilt table balistocardiograph, did not change significantly when the patient was tilted at an angle of 45 degrees, and the pulse rate remained the same. These findings are in agreement with those obtained in previous studies.\(^3,\, 49\) On the other hand, in some cases\(^49\) large degrees of postural hypotension were associated with greater than normal decreases in cardiac output, and under such circumstances, rapid infusion of albumin raised the cardiac output and blood pressure. These observations have been interpreted as suggesting that failure of normal venoconstriction may play a part in the decrease in cardiac output.\(^19\)

Indirect evidence of failure of venous constriction in postural hypotension is obtained from the demonstration of a positive Flack test,\(^36\) in which the subject, while in the erect position, blows into a spirometer with enough force to raise a column of mercury to a height of 40 mm. Normal subjects exhibit little or no change in pulse volume, as measured by the plethysmograph, during this procedure, while patients with postural hypotension become...
pulseless within 10 seconds, and often syncopal, a result indicative of a decrease in venous return.

The physiologic response to hypotension includes reflex tachycardia. A failure of this response may be due to increased vagotonia or decreased sympathetic tone. The absence of an accelerating effect on the heart rate after adequate atropinization eliminates increased vagus tone as the factor responsible for the lack of postural hypotension. Since reflex control of vasoconstriction and sweating is mediated through the sympathetic nervous system, it may be assumed that the sympathetic nervous system is at fault. Stead and Ebert\textsuperscript{19} and Nylin\textsuperscript{18} have reviewed evidence which supports the hypothesis that the central and not the peripheral division of the sympathetic nervous system is involved.

Further evidence for a central lesion as the cause of the syndrome is gained from a consideration of anhidrosis. It has been observed that parenteral pilocarpine produces profuse sweating, but sweating does not occur when the external surface of the body is warmed. There is evidence that pilocarpine acts on the peripheral cholinergic fibers supplying sweat glands,\textsuperscript{50} and perhaps directly on the sweat glands themselves.\textsuperscript{51}

Not enough is known of the pathogenesis of impotence to state whether it is neurogenic in origin, or secondary to the postural shifts of blood volume. Erection is in part a function of the parasympathetic pelvic nerve, but a disturbance of erection was noted in more than half of the patients subjected to a thoracolumbar sympathectomy.\textsuperscript{52} It is possible that the "borrowing-lending" phenomenon (hemometakinesia), as described by De Bakey, Burch, Ray and Ochsner,\textsuperscript{53} is one mechanism causing impotence. Shunting of blood away from the penile vessels into the expansile asympathotonic vascular bed of the lower extremities would interfere with erection.

Further localization of the site of the lesion responsible for the syndrome is not possible on the basis of present knowledge. However, it has been shown in experiments on animals that lesions in the hypothalamus more often produce disturbances of one function of the sympatetic system without complete destruction of the others\textsuperscript{55, 56} than do lesions elsewhere in the brain. This evidence may justify the suggestion that the site of the pathologic changes which give rise to this syndrome lies within the hypothalamus.

Postmortem examination has been done in only three cases; in one of these the brain was not examined, and in the other two,\textsuperscript{27} the findings were inconclusive in regard to the primary lesion.

A striking phenomenon observed in patients with orthostatic hypotension is their adaptation to long periods of low blood pressure. They tolerate marked hypotensive blood pressures for as long as ten to fifteen minutes, while most normal persons become immediately uncomfortable at systolic pressures of 90 mm. Hg, and develop syncope at systolic pressures of 70 to 80 mm. Hg.\textsuperscript{37}

It is of interest that in virtually all of the patients with idiopathic orthostatic hypotension convulsions have not developed. A likely explanation for this fact is that the cerebral circulation is almost immediately restored as the horizontal position is reached. Evidence for this hypothesis is gained from the observations of Stead and Ebert.\textsuperscript{19} After their subject had been in the upright position on a tilt table for a given interval, he exhibited generalized clonic movements of the extremities which immediately stopped when he was returned to the horizontal position. Patterson and Cannon\textsuperscript{26} measured cerebral blood flow in a subject with postural hypotension and found a progressive fall in cerebral blood flow until syncope occurred. The plateau values observed in normal subjects was never reached.

Another interesting, unexplained observation is that most of these patients are elderly men who withstand many daily episodes of marked hypotension over a period of years without development of myocardial infarction, and with little electrocardiographic evidence of coronary artery disease. One can only speculate about why such patients, whose ages place them in the population group with the greatest incidence of coronary artery disease, show little evidence of it. There is experimental evidence to suggest that, although in hypotension ab-
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solute coronary blood flow is decreased, it is increased relative to the total cardiac output and cardiac work.55, 60 Coronary flow is relatively increased until a certain low critical level is reached, at which time it is sharply curtailed.61 It appears then that there is relatively adequate blood supply to the myocardium in this type of hypotension even when syncope occurs.

The lack of electrocardiographic changes in idiopathic orthostatic hypotension is in contrast to the situation which obtains in so-called sympathotonic hypotension,18 in which electrocardiographic changes are not uncommon.49, 62, 63

**Summary**

1. The concomitant occurrence of anhidrosis and impotence with idiopathic orthostatic hypotension, a triad first described by East and Brigden, is reviewed and emphasized. Two new cases conforming to this clinical syndrome are described.

2. This syndrome is most common in males over 40 years of age in whom postural vertigo, syncope, weakness, anhidrosis and impotence are the most frequent complaints. The major physical signs consist of postural hypotension, slow, relatively constant pulse rate, and dry skin. Most of the patients have a low normal basal metabolic rate and frequently have slight nitrogen retention, but none of the laboratory findings is diagnostic. Although the application of heat results in little or no sweating, parenteral pilocarpine induces generalized diaphoresis.

3. The treatment of patients with this syndrome is unsatisfactory. Neither vasopressor drugs nor measures to increase fluid volume have been generally beneficial although both have been helpful in certain patients.

4. Evidence in the literature as well as that obtained in the two cases added herewith suggests that the pathologic physiology of this syndrome includes lack of arteriolar and venous constriction and absence of reflex tachycardia when patients assume the upright posture. Central nervous system lesions, as yet incompletely defined, but possibly in the hypothalamus, are thought to be responsible for anhidrosis and impotence.

5. It is of interest that patients with this affliction remain remarkably free of the signs and symptoms of coronary artery disease, despite the unfavorable combination of age and prolonged exposure to marked hypotension. A possible explanation for this observation is presented.

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