Idiopathic Edema: Pathogenesis, Clinical Features, and Treatment

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Previously published findings are reviewed and new data are presented relating to the clinical features, pathophysiology, and treatment of the idiopathic edemas, a group of disorders diagnosed by exclusion of the known causes of edema. The disorders occur almost exclusively in women, show diurnal (postural), not "cyclic" fluctuations in severity, often cause discomfort and occasionally pain, and may be aggravated by prolonged orthostasis, hot environments, menses, and some drugs. Among the pathophysiologic factors known to be important in edema formation, in general: (1) hypoproteinemia is more commonly the result than the cause of idiopathic edema; (2) elevated capillary hydrostatic pressure is seldom the primary cause, except perhaps in rare cases of occult congestive heart failure; (3) changes in tissue pressure may limit the progression of, but do not initiate, the edema; (4) changes in capillary wall permeability and (5) changes in capillary diffusion area, perhaps because of excessive dilatation of precapillary sphincters appear to be of importance; (6) abnormalities of lymphatic flow are not demonstrable; and (7) the upright posture is an important contributor to the excessive transudation in over 80% of the patients studied ("orthostatic edema") but not in the remaining minority of patients ("nonorthostatic edema"). By balance studies with constant diets and by an abbreviated "posture test," it has been shown that (A) the majority of patients with "orthostatic edema" have excessive orthostatic sodium (Na) retention that results from an excessive orthostatic fall in glomerular filtration rate, frequently associated with excessive renal tubular reabsorption of the subnormal filtered Na load because of orthostatic hyperaldosteronism, and (B) about 30%–40% of patients with orthostatic edema have "orthostatic water retention," demonstrable by an inability to excrete more than 55% of a 20 ml/kg water load during 4 hr in the upright posture. In most of these patients but not in most other types of edema, orthostatic excretion of the water load is restored to normal by ethanol (a known inhibitor of vasopressin release). Improvement in orthostatic renal excretion by external compression of the legs and persistence of excessive orthostatic changes in leg volume despite restricted Na intake support microscopic evidence that a capillary "leak" may be the primary cause of most orthostatic edemas. Reduced dopamine excretion has been reported and linked to the causation of some types of idiopathic edema. Obesity is often associated with edema that differs from other idiopathic edemas in that it usually disappears with caloric restriction and weight loss. In occasional patients, undue sensitivity to heat may play a role as important as that of posture. Treatment of idiopathic edema includes avoidance of excessive salt intake, reduction of the duration of standing and sitting, and administration of conventional diuretics, preferably at 7 or 8 p.m., followed by recumbency for

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several hours before sleep. Hyperaldosteronism has responded to subtotal adrenalectomy (which is not recommended) and constitutes a strong indication for the use of spironolactone, which facilitates recumbent excretion of Na retained in the upright posture. Sympathomimetic amines (ephedrine, phenylephrine, and preferably dextroamphetamine) are the only agents that will usually significantly reduce the excessive weight gain from morning to evening (the hallmark of orthostatic edema), perhaps by preventing excessive capillary pooling and transudation. They have been used safely, effectively, and without loss of their efficacy, for up to 20 yr in several patients. Elastic stockings and garments are occasionally useful and regular exercise, especially swimming, may be beneficial.

IDIOPATHIC EDEMA is a disorder or group of disorders that is diagnosed by exclusion of the many known types of excessive fluid retention. These include such common conditions as congestive heart failure, kidney disease of the nephrotic and renal insufficiency types, hepatic cirrhosis with ascites, and venous and lymphatic obstruction. Edema may also occur in protein malnutrition, various allergic and inflammatory states, hypothyroidism, hyperthyroidism, hypoproteinemia, hypercortisolism, anemia, and hypertension. When the physician has considered and excluded all of these and other known causes of edema, his patient may be said to have idiopathic edema. Mach et al.[1] were the first to report, in a patient with edema of unknown cause, that aldosterone excretion was excessive. Although this observation was made on only three urines, two of which had been collected during restriction of Na intake (the aldosterone-stimulating effect of which was not well appreciated in 1955), it was confirmed a few years later by Luetscher and Lieberman,[2] whose findings stimulated investigations in several other clinics. The importance of the upright posture in the mechanism of fluid retention was reported a few years later,[3] and analysis of the postural factor has revealed evidence that, of the several types of idiopathic edema that can be recognized,[4] the largest group of patients may reasonably be said to have "orthostatic edema."

CLINICAL FEATURES

Age and Sex

Idiopathic edema occurs almost exclusively in women. One male has been reported[5] who had bouts of edema, usually lasting about a week and recurring every 25–30 days, associated with fever and suppressible with prednisolone therapy. We have seen another male whose edema could apparently be aggravated by psychologic disturbances.[6] In the past 15 yr, a third male with idiopathic edema has been studied; he was emotionally stable and quite unconcerned about severe (4+) pitting edema of both legs, which he had ignored completely until it was pointed out to him. His edema was first observed 13 yr ago when he was referred for florid thyrotoxicosis; the swelling was unchanged by 12 yr of euthyroidism following radioactive iodine therapy in 1964 or by the past few months of hypothyroidism, and postural changes have had little effect on the severity of his edema. In many respects, the edema in these three males was very different from the commoner types of idiopathic edema in females, as will be evident later in this review. In females, the disorder has never been reported before puberty; it usually continues or may first be observed after menopause.

Periodicity

In most women with idiopathic edema, a strong postural component in the pathogenesis is responsible for the predominantly diurnal periodicity. Edema is worst after the end of the day's activities—or the night's activities, as we have frequently seen in nurses on nightduty—and is aggravated by spending long hours in the upright posture. It is also frequently more severe in hot weather. In some, but not in all women, there is a superimposed premenstrual aggravation of the edema. Many thousands of twice-daily body weight measurements on patients with idiopathic edema made during the past 25 yr have shown that recurring bouts of edema formation and dissipation only very rarely show sufficient regularity to warrant use of the terms "cyclic" or "periodic" edema, which are therefore inaccurate and best avoided.

Distribution of Edema

When edema results from a diffuse disorder, as occurs in most idiopathic types, gravity controls its distribution. It is worst in the feet, the ankles, the legs, the abdomen, and sometimes the breasts toward the end of the day, and it is often noticed in the eyelids, the face, and the fingers upon awakening and for a short while thereafter, descending to the lower parts of the body as the day progresses. These facts are often of diagnostic value in excluding specific, known types of edema. Thus, eyelid edema that continues throughout the day is more likely to result from myxedema, exophthalmos, allergies, or a local cause in the eyes or face, while edema that is restricted to the legs and never noticeable in the face or fingers may result from venous or lymphatic obstruction or other more local causes in the lower limbs. Abdominal swelling may increase so severely during the course of the day that a few women with idiopathic edema find it necessary to change into a larger skirt in the afternoon. Edema of the feet may be so severe that a patient who removes her shoes at 5 or 6 p.m. is unable to fit into them again an hour later unless she has spent the hour recumbent. For the physician, it is most important not to discount histories of this type, or indeed the entire complaint of swelling or "bloating" on the basis of finding no pitting edema below the malleoli at a 10 or 11 a.m. office visit. It is reasonable to doubt the history of edema obtained from an otherwise apparently reliable witness only if there is no pitting edema over the feet or over the pretibial area (where it sometimes tends to be more readily evident), at 6 or 8 p.m. after a normal day's activity.

Symptomatology

Most women seek help because they are concerned about the implications of edema—they can be reassured that, with isolated exceptions,[7,8] the disorder is almost never progressive. Others are bothered by a mild to moderate aching, "tired" feeling in the swollen legs. At times there may even be more severe pain in the swollen area, but this is usually coupled with other evidence of an inflammatory process (redness, tenderness, and increased temperature over the legs) attributable to thrombophlebitis, lymphangitis, cellulitis, or some other local cause. In many patients the legs may become somewhat suffused or show a mottled, cyanotic appearance after standing for 3–5 min, as is seen in hyperbradykininism.[9] Swelling of the hands may aggravate the pain and other

symptoms of the carpal tunnel syndrome enough to require surgical decompression, unless medical therapy is sufficiently effective.

Complaints of headaches and a tendency to feel confused, "stupid," or "groggy" may occur, especially in the mornings when these symptoms might conceivably be attributable to mild cerebral edema. Psychologic abnormalities are present in many, but certainly not all, patients with idiopathic edema. In a few individuals these abnormalities are so striking, so severe, and so unpleasant to deal with that they make a profound impact on the patient's family, and on her physician. The changes range all the way from a complaining disposition or a mild depression to a frank psychosis. Among those who have psychologic abnormalities, there are several who show compulsive-obsessive behavior. Some patients are excessively involved in committee work or are over-diligent in what they conceive to be their social responsibilities. Others appear to feel a compulsive urge to rid themselves of every ounce of fluid that can be extracted from their bodies and will use increasing doses of diuretics or purge themselves even when edema is not detectable to the impartial examiner. The extent to which psychic abnormalities may be intimately involved with the pathogenesis of idiopathic edema has been considered,[10] but the evidence is equivocal. However, there seems to be no doubt that the complaints of many of these patients become progressively amplified as they unsuccessfully seek help and sympathy from the succession of physicians whom they consult. Effective therapy often, though not always, reduces the complaints of the patients in direct proportion to the therapeutic reduction of their edema.

Patients with orthostatic types of edema frequently notice that the volume of urine passed when they are up and about during the day is small, and that sleep most nights is interrupted two or three times by nocturia. In the rarer types of nonorthostatic edema, there may be irregularly recurring periods of oliguria, sometimes associated with excessive thirst, weight gain, and edema formation, followed after several weeks or a few days by bouts of spontaneous diuresis.

Apart from the evidence of pitting edema, there are usually no abnormal physical findings present. Blood pressure is almost always normal and usually shows no orthostatic decrease.[4]

Aggravating Factors

Warm weather increases the severity of edema in many patients, and prolonged standing or sitting, especially when unaccompanied by muscular activity, greatly accentuates the edema in most patients. There may or may not be premenstrual aggravation of the edema. Several drugs tend to increase fluid retention, especially indomethacin, ibuprofen, phenylbutazone, and phenothiazine tranquilizers.

PATHOPHYSIOLOGY OF IDIOPATHIC EDEMA

Figure 1 shows the factors that are known or postulated (question marks) to be primarily involved in the pathogenesis of edema. As is well known, edema may result from derangements of any of the three main Starling's forces. Such derangements include increased capillary hydrostatic pressure resulting from hypervolemia and/or venous hypertension, decreased plasma protein oncotic pressure resulting from one of the several possible causes of hypoproteinemia,

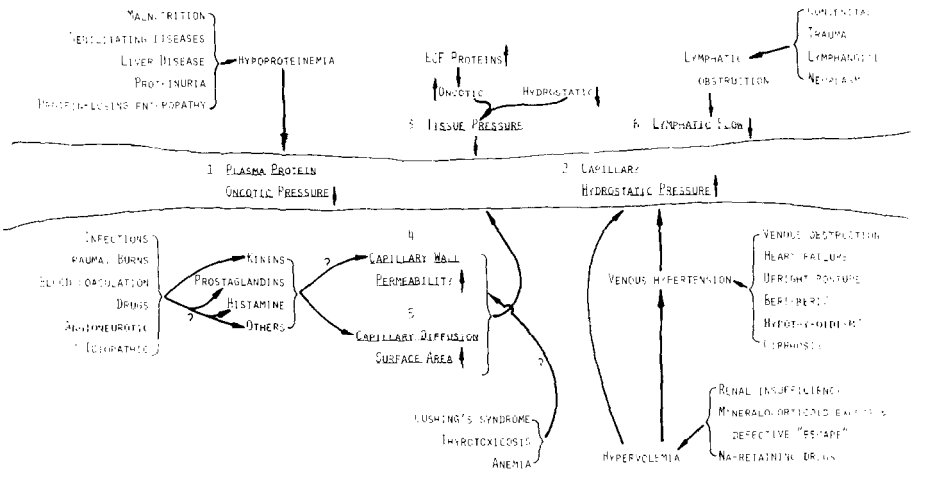

Fig. 1. Primary mechanisms in the pathogenesis of edema. Since all mechanisms result in leakage of fluid from the vascular into the extravascular space, the extent of edema would be limited by the fall in blood pressure with developing hypovolemia were it not for secondary mechanisms (not depicted), which result in renal retention of Na and water: e.g., secondary aldosteronism, possible vasopressin release, and intrinsic renal changes (e.g., fall in GFR).

and increased oncotic pressure of the extracellular fluid. In addition to abnormalities of these Starling's forces, changes in the capillary wall permeability (factor 4, Fig. 1) and increases in the area of the perfused capillary bed (factor 5) may cause or predispose to edema formation. These changes are probably brought about by relaxation of the precapillary sphincter under the influence of one or more locally acting "tissue factors." Bradykinin, and perhaps prostaglandins and other factors, play an important role in mediating the effects of infections, trauma, burns, and other noxious influences on capillary perfusion and transudation. Various types of lymphatic obstruction may give rise to lymphedema.

Hypoproteinemia

Every patient with edema of obscure origin should be checked for hypoproteinemia. When it is severe and associated with an obvious cause such as nephrosis, the edema loses its idiopathic label. Mild hypoproteinemia associated with no recognizable cause has been considered to be the cause of idiopathic edema by Gill et al.[11] Their observations showed a lowered concentration and total circulating pool of plasma albumin. These changes were attributed to a significantly accelerated movement of albumin from the intravascular compartment to an enlarged extravascular pool. The finding of hypoproteinemia has not been confirmed,[4,8,12-17] and plasma volume has been found to be normal in other series of patients with idiopathic edema.[4,8] Although it may be doubted that hypoalbuminemia is a general finding in patients with idiopathic edema, there is good evidence that rapid leakage of protein from the circulating plasma compartment and hypovolemia occur in occasional patients with what appears to be a rare, special type of idiopathic edema associated with massive edema[18,19] and with shock-like episodes of hypotension.[7] In most patients with the commoner forms of idiopathic edema, however, plasma protein concentrations

actually rise to an extent at least as great ($\pm 10\%$) as in normal subjects during 4 hr in the upright posture,[4] indicating that loss of protein from plasma into the interstitial space is usually no more rapid than in healthy individuals.

Capillary Hydrostatic Pressure

Elevation of the volume and/or pressure of blood on the venous side of the circulation, either generally or locally, will raise capillary hydrostatic pressure and lead to increased transudation and edema formation. Several of the factors (depicted in Fig. 1) that are known to overdistend the veins are excluded, by definition, when the diagnosis of idiopathic edema is made. These include: congestive heart failure, renal insufficiency, therapy with Na-retaining drugs, local causes of venous obstruction in the limbs that can usually be recognized clinically and that have been excluded by routine phlebography in at least one series of patients,[4] tightly fitting panty girdles,[20,21] and portal hypertension in patients with cirrhosis, leading first to ascites and later to edema of the legs. Whether thiamine deficiency and hypothyroidism cause edema by the mechanism suggested is unknown, but these disorders, too, can readily be excluded from potential causes of idiopathic edema by clinical and laboratory studies. It was of some interest to find that the presence of hypothyroidism was recently documented in 7 of 31 patients with idiopathic edema.[4] However, hypothyroidism probably had no direct role in the pathogenesis of the edema, since edema persisted unchanged when euthyroidism had been restored with appropriate doses of thyroid hormone. Of interest, also, is the fact that thyrotoxicosis sometimes causes edema in the absence of other clinical evidence of congestive heart failure.[22] We have seen several thyrotoxic patients with edema; in most the edema disappeared when euthyroidism was restored, and their disorder should therefore be considered thyrotoxic in origin.

Since aldosterone secretion and excretion rates were normal in the recumbent posture in 29 of 31 patients on a 200-meq daily Na intake,[4] a primary excess of aldosterone is seldom if ever the cause of idiopathic edema. Excessive excretion of deoxycorticosterone (DOC) from adrenals with bilateral nodular hypertrophy has been associated with edema, metabolic alkalosis, syncopal episodes, and cutaneous flushing in a patient described by Biglieri.[23] Since edema persisted after bilateral adrenalectomy, on cortisol therapy alone, the author concluded that it was not caused by the DOC excess, but probably resulted from a vascular disturbance. Excessive production or administration of mineralocorticoids, either aldosterone or DOC, usually does not cause edema in man because of escape from the Na-retaining action of the mineralocorticoid after a few days.[24] Marieb and Mulrow[25] have described a patient with idiopathic edema whose aldosterone secretion rate was low-normal but who failed to escape from the Na-retaining effects of DOC and consequently gained 7.7 kg while developing generalized edema over a 7-day period of uncontrolled posture in the hospital. When the study was repeated in recumbency, DOC escape occurred normally. Edwards and Bayliss[8] reported that eight of nine patients with idiopathic edema escaped normally from the Na-retaining action of fludrocortisone (fluorohydrocortisone), while the ninth patient failed to escape and developed circulatory overload and pulmonary edema. Unfortunately, the posture of these patients does not appear to have been controlled. It is evident from these data, however,

that failure of mineralocorticoid escape in the upright posture might play a role in the fluid retention of some patients with idiopathic edema.

While classical forms of congestive heart failure can be readily excluded by physical examination as potential mechanisms of fluid retention in patients with idiopathic edema, occult forms of heart failure are not easily excluded and may sometimes be the cause of the edema. Thus, Gill et al.[26] described a 26-yr-old female who presented with apparently idiopathic edema associated with no distension of the cervical veins, no enlargement of the heart, no hepatomegaly, no pulmonary rales, a heart rate of 70/min, and some fatigue, but no history of exercise intolerance. Her escape from the Na-retaining action of DOC was delayed until the 12th day of its administration. Cardiac catheterization disclosed elevation of right and left ventricular end-diastolic pressures that increased further, with no change in the stroke work index, after muscular exercise for 8 min and after imposing a pressure load on the left ventricle by the i.v. infusion of angiotensin II. Treatment with digoxin produced diuresis, weight loss, less fatigue, loss of the delayed escape from DOC, and disappearance of the edema. These results were confirmed, using different methods, by Obeid et al.,[27] who studied 11 patients with idiopathic edema. Ten were found to have normal hemodynamic indices, but one showed a fall in stroke volume as the pulmonary capillary wedge pressure induced by exercise rose, like two patients with obvious congestive heart failure who were studied at the same time. There was no loss of weight or reduction of the pitting edema during digitoxin therapy for 3 wk in 10 patients with idiopathic edema. However, the 11th patient whose hemodynamic measurements simulated those of congestive cardiac failure lost 5.9 kg during 3 wk of treatment with digitoxin and has remained free of her previous edema for the subsequent 10 yr on digoxin and no diuretic therapy. She resembled the patient of Gill et al.[26] in that her history and physical findings provided no suggestion of the presence of congestive heart failure. These observations indicate that occult heart failure is probably the unrecognized mechanism of apparently idiopathic edema in a small percentage of patients.

Tissue Pressure

According to Starling's law of capillaries[28] under equilibrium conditions, mean capillary hydrostatic pressure plus tissue oncotic pressure equals plasma protein oncotic pressure plus interstitial fluid pressure. Direct measurements made by using hypodermic needles[29] or glass micropipettes[30] have shown that tissue pressure is normally 0 to +5 mm Hg and increases to +13 to +17 mm Hg when venous obstruction is induced by a cuff inflated for 20-30 min.[31] However, Guyton has shown more recently,[32] in experiments on the interstitial fluid that collected in subcutaneously implanted plastic capsules, that after at least 1 mo tissue pressure was always negative, averaging -6.4 ± 2.0 mm Hg. Tissue pressure fell further during intravenous dextran infusions, but rose pari passu with the development of ascites and peripheral edema during rapid intravenous infusions of physiologic salt (Tyrode's) solution in large volumes. When edema was present, there was a good correlation between interstitial fluid pressures recorded within a plastic capsule and those measured with hypodermic needles. Interstitial fluid pressure also rose in proportion to the estimated amount of peripheral edema induced by rapidly injecting saline into the leg. After the

edema had been present for 30 min or more, interstitial pressure fell to lower positive values, and these changes were interpreted to indicate that after edema had been present for some time the tissues underwent "stress relaxation." These observations are probably relevant to the finding in patients with idiopathic edema that the amount of edema induced by remaining upright for 12 hr each day increased strikingly each day for 3 days but tended to increase more gradually or not at all if the upright posture was maintained for more than 3 days.[3,4] Thus, transudation of fluid from the vascular compartment into the dependent limb presumably increases interstitial pressure to the point where further net transudation is prevented and edema is stabilized. These observations also provide a rationale for the effectiveness, at least acutely, of external pressure applied in the form of elastic stockings, elastic bandages, or a pressure suit.

The protein concentration in normal interstitial fluid has been estimated to average 2.1 g/100 ml, equivalent to an oncotic pressure of approximately 5 mm Hg.[30] The oncotic pressure of the interstitial fluid is probably not increased in most patients with idiopathic edema. However, in some rare instances where there is evidence of rapid leakage of protein-rich fluid from the capillaries into the tissues, the oncotic pressure of the interstitial fluid almost certainly rises sufficiently to aggravate the edema further.[7,18,19]

Capillary Wall Permeability and Capillary Diffusion Surface Area

Permeability to protein appears to increase in response to bradykinin, histamine, and other dilators of the precapillary sphincter, probably largely through the elevated capillary hydrostatic pressure that results[33-35] and possibly, in part, through a direct action on the capillary wall.[35] There is also evidence that bradykinin increases the capillary and vascular surface area available for diffusion by reducing precapillary resistance and opening up larger numbers of capillaries to perfusion.[34,36] These combined effects of kinins and other "tissue hormones" greatly increase transudation and cause edema.[34] Observations on patients with hyperbradykininism[9] have indicated that kinins might be involved in increasing the peripheral vascular pooling of blood in the upright posture and in causing the pitting or brawny edema sometimes seen in this disorder. Although there are no published measurements of plasma kinin concentrations in patients with idiopathic edema, many of the findings observed in the upright posture in these patients are very similar to those that would be expected to result from excessive peripheral action of bradykinin (see below). The severe capillary protein leak described in occasional patients with idiopathic edema, and sometimes associated with episodes of shock,[7,18] would also be consistent with bouts of spontaneous release of large amounts of kinin, though there is no direct evidence to support this possibility.

Lymphatic Flow

There is abundant clinical evidence that edema results from widespread obstruction of flow through the lymphatics due to congenital malformation, surgical scar formation, chronic lymphangitis, or neoplastic invasion of the lymph nodes. Lymphangiography in patients with idiopathic edema has shown no abnormalities.[4,13,37] There is, therefore, no evidence to suggest that obstruction of the normal flow up the lymphatics plays any role in the pathogenesis of idio-

pathic edema except when there is a strong component of brawny edema present.

Role of Posture and Other Observations

The disappearance of previously obvious pitting edema of the legs 1 day after a patient had been admitted to the hospital and before any treatment had been given[6,38] prompted studies that led to the recognition that the upright posture plays an important role in the pathogenesis of edema in these patients.[3,6,38] The role of posture has been widely confirmed[4,8,12,13,16,25,39 46] and will be discussed below.

Changes in Normal Subjects

It should be appreciated that urinary excretion of sodium and water falls in most normal subjects when they assume the upright posture.[47 53] These changes are greater when the subjects are tilted to 60° (head up)[47,53] or stand motionless[50 52]—circumstances that often reduce venous return sufficiently to cause syncope—than when muscular activity is encouraged in the form of slow ambulation.[39] In confirmation of the reports of Pearce and Newman,[53] we have found[39] that 25 ml of 95% ethanol will reduce the normal fall in urine flow rate and in free water clearance during the first $\frac{1}{2}$ hr of slow ambulation to values that closely approximate those seen in patients with diabetes insipidus. Since ethanol increases urine flow rate and free water clearance largely, if not exclusively, by inhibiting antidiuretic hormone (ADH) release,[54] it seems reasonable to conclude that increased ADH release is the mechanism of the antidiuresis that occurs in the first $\frac{1}{2}$–1 hr or more of standing. However, while patients with diabetes insipidus, like normal subjects given ethanol, show negligible orthostatic reductions of urine flow rate in the first $\frac{1}{2}$-hr of standing, they do show significant and large (approximately 50%) reductions during the third or fourth $\frac{1}{2}$ hr of standing; the reductions during this time are actually more severe in the patients with diabetes insipidus than in untreated normal subjects.[39] It is likely, therefore, that an increase in ADH release is not the only mechanism of the reduced urine flow rate and free water clearance during prolonged orthostasis in healthy subjects.

An orthostatic fall in Na excretion was found to occur in 19 of 21 normal subjects during constant loading with 0.14% NaCl solution (150 ml/$\frac{1}{2}$ hr).[40] The mean rate of sodium excretion during 2 hr in the upright posture was 55.6% ± 5.3% (SEM) of the rate in recumbency ($p < 0.001$)—less of an orthostatic change than the fall to 38.4% of the recumbent Na excretion rate observed during the tilt-table experiments of Pearce and Newman.[53] Pearce and Newman[53] found that the orthostatic fall in Na excretion could be greatly diminished from 38.4% to 62.9% of the recumbent Na excretion rate—by wrapping the legs of their subjects with 3-in Ace bandages. Bandaging the legs was far less effective in reducing the orthostatic fall in urine flow rate, however, which was 34.7% of the recumbent rate without and 44.2% of the recumbent rate with the bandaging (a difference that is not statistically significant). Since the orthostatic fall in sodium excretion starts within the first $\frac{1}{2}$ hr of standing,[39] and since the effects of injected aldosterone on sodium transport are not usually evident in the first hour,[55,56] it is unlikely that the known orthostatic increase in aldosterone

secretion rate[4,57] could be responsible for the early phase of orthostatic sodium retention, though it might contribute to Na retention during more prolonged standing. Streeten and Speller[39] showed that orthostatic sodium retention was no less severe in adrenalectomized patients receiving hydrocortisone replacement therapy only than in normal individuals. Therefore, it is evident that, while orthostatic hyperaldosteronism might aggravate orthostatic Na retention during prolonged standing, it is certainly not the only and probably not the main mechanism of orthostatic Na retention in man.

Activity of the sympathetic nervous system and administration of sympathomimetic amines are known to affect renal excretion of Na.[40,58] Since there is increased sympathetic nervous activity in the upright posture, Cuche et al.[59] measured urinary catecholamines and reported that in the upright posture normal subjects excrete more epinephrine and norepinephrine but less dopamine than in recumbency. They found a correlation between the urinary excretion of dopamine and Na, both on 135- and 10-meq Na diets. These observations suggested that the orthostatic fall in dopamine excretion might have been involved in the mechanism of the orthostatic reduction in Na output. This hypothesis is certainly plausible since dopamine administration has been shown to cause natriuresis, associated with an increase in renal plasma flow and glomerular filtration rate in man.[60,61] Alexander et al.[62] found that urinary excretion of dopamine was increased and that of norepinephrine was decreased when normal subjects changed from a 9- to a 209–259-meq daily Na intake. More acutely, a saline infusion increased dopamine excretion significantly. The observed correlation between dopamine and sodium excretion and their inverse correlation with adrenergic activity suggested that renal dopamine might play a physiologic role as a natriuretic hormone[59,62] that could be of special importance in the normal and abnormal changes in Na excretion in the upright posture.

Observations in Idiopathic Edema

A systematic study was made by Streeten et al.[4] of the effects of posture on renal function, body weight, leg volume, aldosterone secretion rate, plasma renin activity, and plasma volume in 31 patients with idiopathic edema and 6 normal females. Metabolic balance was first achieved at least 10 days after stopping previous diuretics and after at least 7 days on a constant weighed intake of 200 meq Na, 3 liters of fluid, 65–90 meq K, and maintenance calories. The patients and the normal subjects then remained on their feet from 8 a.m. to 8 p.m. for 3 days except during their 3 daily meals, when they were allowed to be seated for 30 min. On the following 2 days, the subjects all remained recumbent constantly day and night, after which the 3-day period in the upright posture from 8 a.m. to 8 p.m. was repeated.

Changes in body weight and leg volume. Of the 31 patients with idiopathic edema, 26 showed a greater cumulative weight gain after 3 days of orthostasis than did any of the normal subjects (i.e., > 0.72 kg) and a greater cumulative weight loss during 2 days of recumbency than did any of the normal subjects (i.e., > 0.87 kg). These 26 patients were therefore considered to have "orthostatic edema" while the 5 others had "nonorthostatic edema." Measurements of leg volume by a simple water displacement technique[4] showed, as expected, that there was a significantly greater than normal cumulative increase in leg

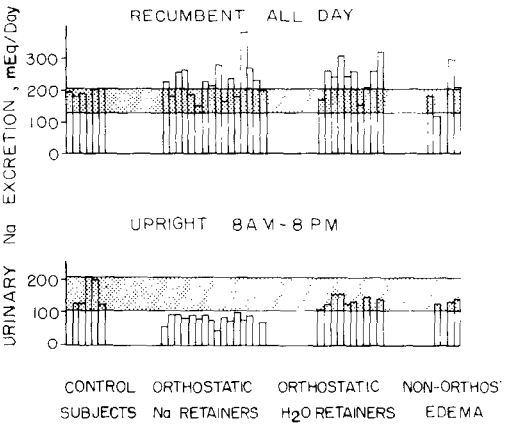

Fig. 2. Na excretion in 6 normal females and 31 patients with idiopathic edema on the second day of all-day recumbency and on the first day of maintaining the upright posture for 12 hr. The subjects had all ingested 200 meq Na and 3 liters fluid daily for at least the preceding 7 days. In recumbency, Na excretion approximated Na intake in the normal subjects and usually exceeded intake in the edema patients, reflecting loss in recumbency of edema fluid previously accumulated in the upright posture (except in the small group of patients with nonorthostatic edema). In the upright posture, Na excretion was 115–205 meq in the normal subjects, it was below this normal range in 15 patients with orthostatic Na retention, and it was within the normal range in the patients described as having orthostatic water retention and nonorthostatic edema.

volume during 3 days of orthostasis and a significantly greater than normal cumulative reduction of leg volume in 2 days of recumbency in the patients with orthostatic edema but not in the patients with nonorthostatic edema. Thus, the posturally induced changes in weight reflected the measured changes in leg volume that resulted from accumulation and loss of obvious edema in the legs.

Changes in Na excretion. Measurements of Na excretion in these experiments showed that the normal subjects excreted less Na on the days (especially the first and second days) spent in the upright posture than on the days spent in recumbency. Na excretion changes allowed the orthostatic edema patients to be divided into two subgroups (Fig. 2): (1) 16 patients whose urinary Na excretion on the first (and almost invariably also on the second) day of orthostasis was lower than that of any of the normal subjects, called "orthostatic sodium retainers," and (2) 10 patients whose urinary Na excretion was within the normal range on the first day (and usually on the second day) in the upright posture, called "orthostatic water retainers." Na excretion was usually normal in both the recumbent and upright periods in the patients with nonorthostatic edema (Fig. 2).

Changes in aldosterone and renin. Aldosterone secretion and excretion rates were generally normal in the patients with nonorthostatic edema and with orthostatic water retention. However, aldosterone secretion and/or excretion rates were consistently elevated in the upright posture (but very seldom in recumbency) in 7 of the 16 orthostatic Na retainers.[4] That this hyperaldosteronism was of pathogenic significance was suggested by the fact that urinary K excretion was significantly greater ($p < 0.02$) in the 7 patients with orthostatic hyperaldosteronism when they were upright than when they were recumbent; this did not occur in any of the other groups of patients. These observations of orthostatic hyperaldosteronism in 7 of the 31 patients with idiopathic edema perhaps explains the discordance between the reports in the literature that claim that aldosterone excretion is always, never, or sometimes elevated in the smaller series of patients that have been reported elsewhere.[2,13,15,17,37,46,63,64] Somewhat surprisingly, plasma renin activity was virtually never above normal, recumbent

or upright, in our patients with idiopathic edema,[4] suggesting that the hyperaldosteronism in some of the orthostatic Na retainers was mediated by a mechanism other than the renin–angiotensin–aldosterone system. The finding of normal plasma renin activity in patients with idiopathic edema has also been reported by other authors.[15-17,63,64] However, Kuchel et al.[13] found that plasma renin activity was significantly elevated and Gill et al.[37] found an insignificantly raised plasma renin activity in patients with idiopathic edema. Since Kuchel et al.[13] made no mention of how long their patients had been off diuretic therapy when the plasma renin measurements were made, it is conceivable that their elevated plasma renin activities might have reflected persistent Na and/or K depletion from antecedent diuretic therapy.

Renal hemodynamic changes. Streeten et al.[4] measured inulin and PAH clearances in the 31 patients with idiopathic edema described above and in 10 normal subjects during $1\frac{1}{2}$ hr of recumbency and 2 hr of slow ambulation around the foot of the bed. They found that under these conditions renal plasma flow and glomerular filtration rate (GFR) fell only slightly in the upright posture in the normal subjects (7.6% ± 4.1% and 5.2 ± 3.5%, respectively) and did not fall significantly more in the patients with nonorthostatic edema or orthostatic water retention. However, the orthostatic Na retainers showed a profound, progressive, and significantly greater fall in PAH clearance (32.7% ± 5.6%) and inulin clearance (34.7% ± 5.2%) during the 2-hr period in the upright posture.

It was concluded from these studies that the orthostatic changes in Na and water excretion in the patients with orthostatic Na retention were probably mediated by a one-third (mean) reduction in filtered Na in the group as a whole, with inappropriately excessive tubular reabsorption of the filtered Na in about one-half of these patients because of orthostatic hyperaldosteronism. None of these abnormalities was consistently present in the orthostatic water retainers or in the patients with nonorthostatic edema.

A shorter "posture test" was performed in most of the 31 patients described above[39,40,65] and in several others, as well as in 21 normal subjects. This test comprised administration of 150 ml of 0.14% NaCl solution by mouth every $\frac{1}{2}$ hr while the subjects remained recumbent for 4 hr and then upright for 2 hr. The test was performed after cessation of any antecedent diuretic therapy and after ingesting a diet that was unrestricted in its Na content for at least 1 wk. The patients voided every $\frac{1}{2}$ hr and if they were unable to void after the 8th or after the 12th $\frac{1}{2}$ hr, the study was continued for an additional $\frac{1}{2}$ hr in the same posture. The urine passed in the last five (or four) $\frac{1}{2}$-hr periods in recumbency was pooled, as was the urine passed in the four $\frac{1}{2}$-hr periods in the upright posture.

Measurements of mean urine flow rate, urinary Na and creatinine excretion, and urinary osmolality in the urine pools collected in the recumbent and upright positions were then compared. It was found (Fig. 3) that sodium excretion fell during the upright period to 33%–100% of recumbent rates of excretion in the normal subjects. Among the patients with idiopathic edema, urinary Na excretion fell in the upright posture below 33% of recumbent excretion in 30 patients, including 14 of the 15 patients shown by the balance studies to have orthostatic Na retention. Thirty-two patients with idiopathic edema maintained their Na excretion at normal levels (above 33% of recumbent rates) in the up-

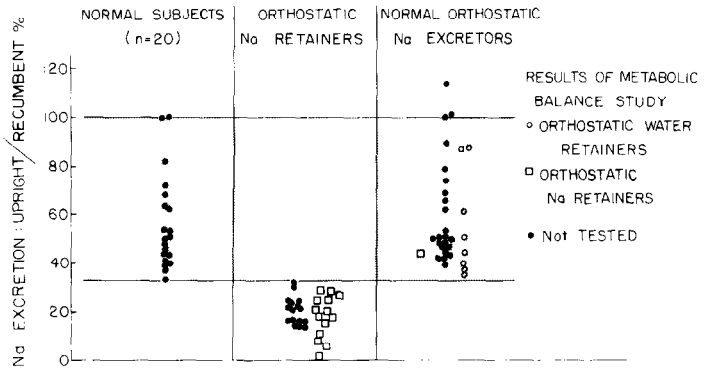

Fig. 3. Na excretion during the upright 2 hr of a "posture test" in normal subjects and patients with orthostatic edema during intake of 150 ml 0.14% NaCl solution every ½ hr. Upright Na excretion is expressed as a percentage of mean Na excretion for the last 2½ hr of recumbency immediately preceding assumption of the upright posture. In patients with orthostatic Na retention, upright Na excretion was less than 33% of recumbent Na excretion, and the 14 of these patients who were studied by the more prolonged "balance" technique were found by that method to be orthostatic Na retainers. Of the patients who did not show orthostatic Na retention by the short posture test, all but 1 of the 9 who were studied by the balance technique were found to be orthostatic water retainers and not orthostatic Na retainers.

right posture, and these patients included 1 of the 15 orthostatic Na retainers and all 8 of the orthostatic water retainers who had been thus classified on the basis of the 8–12-day balance studies.[4] It may be concluded from these observations that the shorter posture test, as described, correlates very well, though not perfectly, with the results of the more prolonged and laborious metabolic balance studies in recognizing the idiopathic edema patients who are orthostatic Na retainers and those who belong to the other subgroups. In these tests it was found (Fig. 4) that urine flow rates tended to fall in the upright posture more profoundly in the orthostatic Na retainers than in the other groups. There was also a greater fall in urinary creatinine excretion in the upright posture in 25 of 47 patients with orthostatic Na retention than in the normal subjects. These findings, not previously reported, are in close accord with the observation[4] that inulin clearance showed a more profound orthostatic fall in the orthostatic Na retainers than in the other groups or the normal subjects.

Orthostatic changes in excretion of water load. In order to investigate the mechanism of the orthostatic defect in patients with orthostatic water retention, the excretion of a simple water load (20 ml/kg ideal body weight, imbibed over about 15 min on an empty stomach) has been studied. Normal subjects and most patients with idiopathic edema of all types excreted more than the administered water load in a 4-hr period in recumbency, and with few exceptions, more than 65% of the load was excreted in this posture. When the water excretion test was administered with the subjects upright for 4 hr, 25 normal subjects excreted 55%–120% of the volume imbibed (Fig. 5). The reproducibility of the results in replicate measurements on the same subjects was acceptable (coefficient of variation was 28%). Of 28 patients whose excretion of the 0.14% NaCl solution had shown them to be orthostatic sodium retainers, 7 excreted less than 55% of the water load in the upright posture, as did 1 of 4 patients with nonorthostatic edema, 1 of 3 patients with lymphedema, and 13 of 17

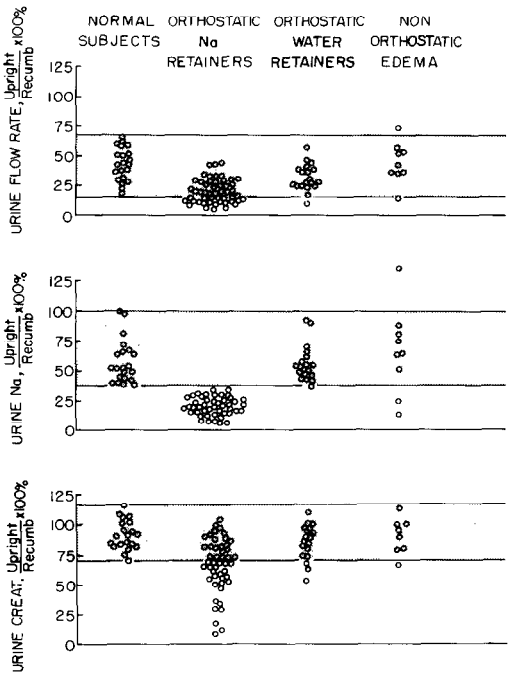

Fig. 4. Upright/recumbent ratios of urinary flow rate, Na excretion, and creatinine excretion in a "posture test" performed on 21 normal subjects, 47 patients with orthostatic Na retention, 19 with orthostatic water retention, and 9 with nonorthostatic edema. Two patients who had been shown by the "balance" technique to have nonorthostatic edema showed orthostatic Na retention in this 2-hr period in the upright posture but could excrete Na normally during a 12-hr period of orthostasis. The greater fall in urinary creatinine excretion in the majority of patients with orthostatic Na retention is evident.

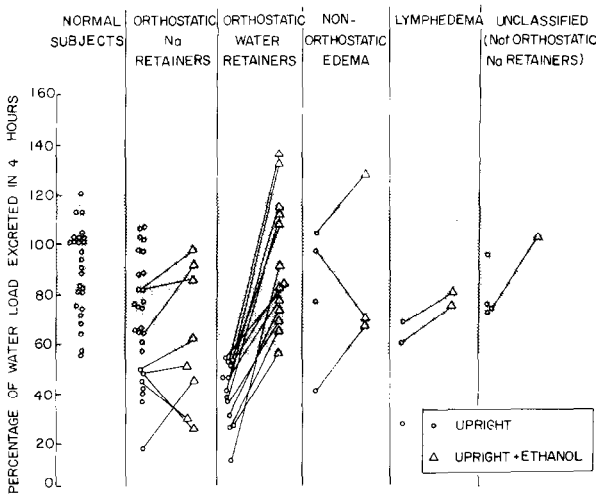

Fig. 5. Percentage excretion of a 20 ml/kg water load during 4 hr in the upright posture and 4 hr-upright after ethanol (25 ml 95% solution) in normal subjects and patients with edema. Excretion of water fell below normal (i.e., below 55% of the load administered) in 13 patients with orthostatic water retention; in all these 13 it was restored to above 55% of the load after ethanol. Upright excretion was also below 55% of the load in 7 of 28 patients with orthostatic Na retention, 1 patient with nonorthostatic edema, and 1 with lymphedema, but in only 2 of these 9 patients could this orthostatic defect in water excretion be corrected by ethanol. Four patients with edema could not be classified since orthostatic excretion both of the water load and of a salt load (in the "posture test") were normal and they were not studied by the "balance" technique.

patients diagnosed by the posture test as not having orthostatic Na retention and, therefore, probably having orthostatic water retention.

In many of these patients a third test was performed in which 25 ml of 95% ethanol, suitably flavored with fruit juice, was given with the 20 ml/kg water load in the upright posture. It is evident from Fig. 5 that in the orthostatic Na retainers ethanol seldom improved the water excretion in the upright posture and only once raised the water excretion from below 55% of intake without the ethanol to above 55% with the ethanol. Similarly, ethanol increased the water excretion in the upright position from below to above 55% of the load given in 1 of the 4 patients with nonorthostatic edema, and in neither of the patients with lymphedema so tested. In striking contrast to these findings, ethanol dramatically increased the water excretion in the upright posture from below to above 55% of the administered load in 13 of the patients who were known not to be orthostatic Na retainers and who may now appropriately be designated orthostatic water retainers. Four patients remain unclassified (Fig. 5) since they were not orthostatic Na retainers by the posture test, they were not orthostatic water retainers by the water load test, and they could not be studied by the balance technique to determine whether they might have had nonorthostatic edema. The 13 patients with orthostatic water retention whose orthostatic defect in water excretion was restored to the normal range by ethanol might be strongly suspected to have an orthostatic excess of ADH, causing their inability to excrete water in the upright posture. These findings, confirming and extending observations reported by us[6,38] in 1959 and 1960, await direct confirmation by radioimmunoassay of plasma ADH levels.

Confirmatory evidence that at least one of the patients diagnosed by such water excretion tests as having orthostatic water retention did, indeed, retain water without a consistent relationship to Na retention is shown in Fig. 6. In this figure the changes in Na and water excretion induced by postural changes are related to weight changes in four patients with idiopathic edema during a metabolic balance study on a constant intake of Na (200 meq) and water (3 liters) daily. There was, as expected, an excellent correlation between water balance and changes in body weight in all patients, indicating that the weight changes reflected changes in water excretion. However, whereas Na excretion also correlated very well with weight changes in the three patients with orthostatic Na retention, there was no consistent correlation between Na balance and weight changes in the patient whose excretion of a water load was restored to normal by ethanol.

Although other evidence has been adduced supporting excessive ADH release as a factor in idiopathic edema,[8,66] some authors have expressed the opinion that ADH excess is not likely to be involved in the pathogenesis of idiopathic edema because (1) edema is characteristically absent in the syndrome of inappropriate ADH secretion (SIADH),[67] and (2) hyponatremia, which is typical of the latter syndrome, is seldom seen in patients with idiopathic edema.[12,17] These arguments may or may not be valid since, if ADH excess is involved in the pathogenesis of orthostatic water retention, it is only an intermittent orthostatic excess, which conceivably could have different effects from the chronic, persistent ADH excess of the SIADH. Furthermore, hyponatremia would be expected to be most severe in the evening and to occur only in patients

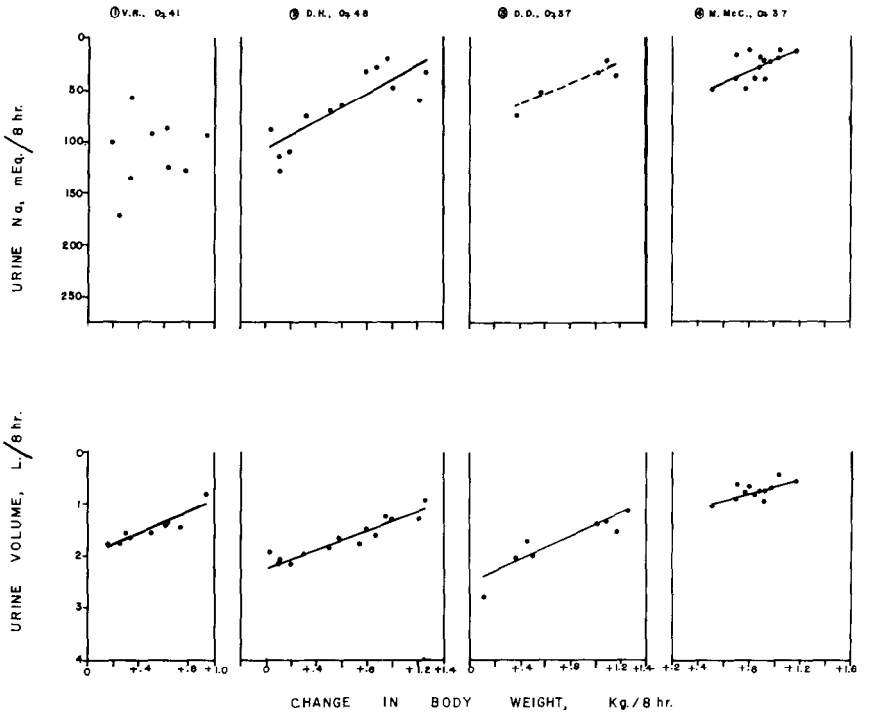

Fig. 6. Correlations between weight changes and changes in urine volume (lower panels) and urinary Na (upper panels) in four patients with idiopathic edema. All patients were studied during days of standing for 12 hr and of recumbency for 24 hr after coming into balance on a constant diet containing 200 meq Na and 3 liters water for at least the preceding week. The correlation between weight change and urine volume was excellent for all four subjects. Correlation between weight changes and urinary Na excretion was excellent for the three patients with orthostatic Na retention (D. H., D. D., M. McC.) but not for the one with orthostatic water retention (V. R.).

with orthostatic water retention, and evening or late afternoon serum Na measurements have not been reported for any of these patients. We have made several measurements of serum Na, body weight and water balance during a day when one of our patients with orthostatic water retention remained upright for 12 hr (Fig. 7). It is evident that this patient, who excreted only 14% of a 20 ml/kg water load in 4 hr in the upright posture and 127% in recumbency, had hyponatremia even in the morning, and that serum Na concentration fell steadily from 123 to 115 meq/liter pari passu, with a weight gain of 1.35 kg resulting from water retention (1.30 liters) while standing from 8 a.m. to 8 p.m. These changes were reversed when she lay down from 8 p.m. that evening until 8 a.m. the next day. During recumbency for the following 24 hr, changes in serum Na (120 → 116 meq/liter), body weight (+ 0.2 kg), and water balance (+ 0.3 kg by 8 p.m.) were far smaller, reflecting minimal water retention. The findings indicate the aggravation of hyponatremia resulting from water retention in the upright posture in an orthostatic water retainer.

The possibility has been explored that the subnormal excretion of a water load in the upright posture might be corrected by the application of external compression to the limbs and trunk. As is shown in Table 1, the mean percent-

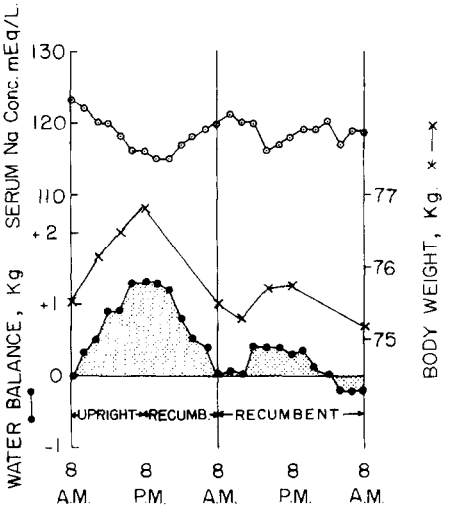

Fig. 7. Effects of posture on serum Na, body weight, and water balance in a patient with orthostatic water retention. When she remained upright from 8 a.m. to 8 p.m., body weight increased by 1.35 kg, resulting mainly from retention of 1.30 kg water (estimated from measurement every 2 hr of intake and output and correction for insensible loss at 100 ml/2 hr), and serum Na fell from 123 to 115 meq/liter. These changes were reversed in recumbency from 8 p.m. to 8 a.m. With continued recumbency the next day all changes were greatly attenuated.

age of the water load excreted in the upright posture was increased from 50.0% ± 7.6% to 81.1% ± 6.8% ($p < 0.001$) in eight patients with orthostatic edema, including four orthostatic water retainers and four orthostatic sodium retainers. These observations suggest that excessive capillary pooling and transudation, corrected by external compression, may be the primary defect initiating the postulated orthostatic ADH excess of the orthostatic water retainers as well as the primary defect leading to Na and water retention in the orthostatic sodium retainers.

Changes in plasma volume. Studies of plasma volume during the development of idiopathic edema might reasonably be expected to throw light on the pathogenesis of the disorder and on the role, for instance, of the upright posture. Since plasma volume is influenced considerably by sodium intake[68] and perhaps by posture, time of day, relationship to meals, environmental temperature, and many other factors, it is important that plasma volume be measured under strictly standardized conditions. It is also well known that plasma volumes expressed in terms of body weight fall with increasing obesity. For this reason, the basal plasma volumes of fasting, recumbent subjects who were "in balance" on a known, standardized intake of salt and water were found to vary widely, from values as low as 31.7 ml/kg in an obese (109.5-kg) patient to some as high as 52.0 ml/kg in a lean (62.8-kg) patient with apparently similar types of idiopathic edema associated with orthostatic Na retention.[69] These findings may at least in part explain the discrepancies in the literature between authors who have described basal plasma volumes in idiopathic edema as being sub-

Table 1. Percentage of 20 ml/kg Water Load Excreted in 4 hr Upright

	N	Control	G-Suit	p
Normal subjects	24	88.8 ± 3.7	—	—
Orthostatic water retainers	4	36.0 ± 8.7	71.3 ± 8.9	<0.01
Orthostatic Na retainers	4	64.0 ± 7.8	91.0 ± 8.3	<0.01
Orthostatic edema (both types)	8	50.0 ± 7.6	81.1 ± 6.8	<0.001

Values are means ± SEM.

normal[11,37] and those who have found them to be normal.[4,8,41] These basal plasma volume measurements also appear to exclude the theoretical possibility that hypervolemia and consequent elevation of capillary hydrostatic pressure might be involved in the mechanism of edema formation in the majority of patients with idiopathic edema.

Of greater importance than the absolute value of the basal plasma volume is the change in plasma volume that occurs as edema accumulates in these patients. The unusual patient who manifested shock-like episodes[7] was found to experience a precipitous fall in plasma volume as edema accumulated and blood pressure fell. In the more usual patients, remaining upright for 1 hr without food or fluid intake resulted in greater falls in plasma volume in orthostatic Na retainers (9.94% ± 1.55%) than in normal subjects (3.50% ± 2.13%, $p < 0.05$), but the changes in five orthostatic water retainers (6.44% ± 2.35%) and three nonorthostatic edema patients (4.00% ± 1.80%) were not significantly different from normal.[4] After 4 hr in the upright posture, during which a high-salt breakfast and about 1 liter of fluid were taken in, plasma volume reductions were not significantly different in the normal subjects (4.30% ± 1.48%) from those in the patients with orthostatic Na retention (6.18% ± 1.73%), orthostatic water retention (5.65% ± 2.59%), or nonorthostatic edema (0.86% ± 5.77%). Edwards and Bayliss[8] have reported that the orthostatic decrease in plasma volume in patients with idiopathic edema (14.9 ± 3.2%) occurs rapidly, being virtually complete in 10 min. Thus, although a fall in plasma volume, presumably by transudation into the tissues, occurs rapidly in these patients, an adequate intake of Na and water restores the plasma volume if the patients remain upright. It seems likely that the fall in plasma volume which is seen in the orthostatic Na retainers may be the stimulus to orthostatic hyperaldosteronism which some of these patients manifest, even though plasma renin activity is not involved.[70]

Evidence of a capillary defect. There is microanatomic and functional evidence of a capillary lesion in patients with idiopathic edema. Sims et al.[14] first showed that the basement membrane of capillaries in biopsy specimens from the gastrocnemius muscle was significantly thicker in 11 patients with idiopathic edema (4700 ± 1900 Å (SD)) than in 7 normal control subjects (2600 ± 210 Å, $p < 0.05$). They also found that 7 of their patients with idiopathic edema had family histories of diabetes mellitus, 3 had frankly diabetic glucose tolerance tests, and another 4 had abnormal cortisone–glucose tolerance tests. The findings suggested that the microangiopathy observed might be of the type seen in diabetes mellitus.[71] Coleman et al[19] confirmed the thickening of capillary basement membranes in a patient with idiopathic edema and pointed out that such lesions have been demonstrated in many diseases, including polymyositis, systemic lupus erythematosus, scleroderma, arteriosclerosis, and diabetes mellitus. There are, therefore, reasons for uncertainty about the specificity of the basement membrane thickening, as well as its pathogenic significance as the possible cause of increased capillary permeability to protein in patients with idiopathic edema.

Functional evidence for the primary role of excessive capillary transudation in the upright posture is indirect but quite suggestive:

1. External pressure: Application of external pressure to the legs and/or pelvis by means of a G-suit was first shown by Streeten and Conn[3] to reduce orthostatic weight gain by increasing urinary excretion of Na and water in a patient with an orthostatic form of idiopathic edema. Kuchel et al.[13] showed that bandaging the legs tightly would increase urine output of Na from 29 ± 6.3 to 63.1 ± 9.9 meq/g creatinine and of water from 535 ± 150 to 1149 ± 153 ml in a 4-hr period after a 1200-ml oral water load in six patients with idiopathic edema. We have made confirmatory observations showing that after a water load of 20 ml/kg the use of an inflated G-suit significantly increased water excretion during 4 hr in the upright posture both in four patients with orthostatic water retention and in four patients with orthostatic Na retention ($p < 0.01$). Water excretion in the upright posture was not significantly different in the patients treated with the G-suit from the water excretion of untreated control subjects in the upright posture (Table 1).

Figure 8 shows the effects of bandaging the legs of 6 patients with idiopathic edema (orthostatic Na retainers) on the mean recumbent and upright excretion of water, Na, and creatinine in the posture test. It is evident that external compression by the leg and thigh bandages significantly increased the upright excretion (expressed as a percentage of mean recumbent excretion) of water from 12.6% to 26.8% ($p < 0.001$), of Na from 19.3% to 33.8% ($p < 0.001$), and of creatinine from 78.3% to 90.7% ($p < 0.01$) of the respective recumbent values. The values after leg wrapping were still somewhat inferior to those observed in

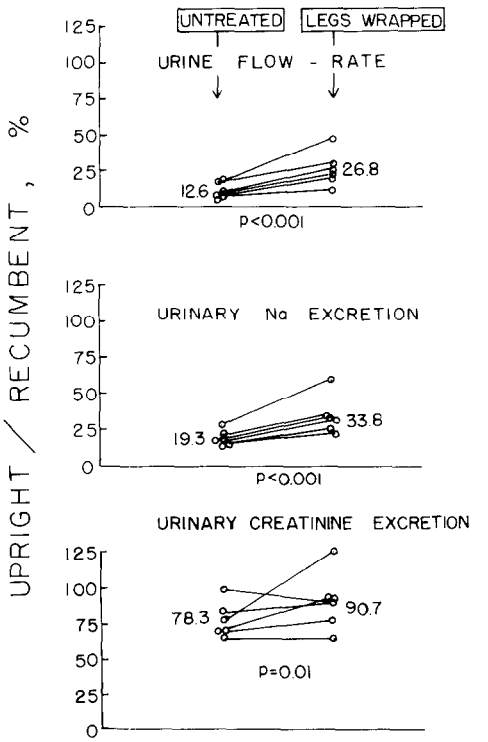

Fig. 8. Effects of wrapping the legs (with Ace bandages) of six patients with orthostatic Na retention. Changes are seen in their upright/recumbent ratios of urine flow rate, urinary Na excretion, and urinary creatinine excretion during salt loading (150 ml 0.14% NaCl solution each ½ hr) in a "posture test." Significant improvement in all parameters resulted from bandaging the legs.

normal subjects, though mean Na excretion was restored to the lower limit of the normal range. This evidence supports the thesis that excessive capillary distension and/or an opening up of a larger capillary bed to perfusion, or some similar abnormality which might have been reversed by external pressure to the lower limbs, might constitute the primary abnormality of idiopathic edema with orthostatic Na retention.

2. Leg volume changes: Measurements during 3 successive days of standing from 8 a.m. to 8 p.m. have shown that in patients with orthostatic Na retention mean leg volume change intra diem (i.e., while the standing continued each day) was +459 ± 24 ml on a 200 meq Na diet and +345 ± 24 ml on a 10 meq Na diet.[4] Similar changes were observed in patients with orthostatic water retention. Since these differences on the high- and low-Na diets were not statistically significant, the results indicate that excessive swelling of the legs persisted, unchanged, in these patients when they were upright in spite of the fact that Na intake was minimal (10 meq/day). Thus, the reason the legs swelled excessively from morning to evening was not because a primarily renal abnormality had resulted in excessive Na retention that then excessively distended the capillaries in the dependent limbs. On the contrary, the legs continued to swell excessively in the upright posture in spite of the fact that renal retention of Na could not possibly have been playing a primary role since there were negligible amounts of Na which could be retained on the 10 meq Na diet. These observations provide indirect evidence that a primary change in the capillary bed, rather than a primary renal retention of salt and water is responsible for the excessive transudation into the dependent limbs in idiopathic edema.

Measurements of catecholamines. Kuchel et al.[13] found no significant differences between urinary excretion of epinephrine or norepinephrine in patients with idiopathic edema compared with normal subjects. In disagreement with these findings, Gill et al.[37] reported that urinary norepinephrine excretion was greater in patients with idiopathic edema (78 ± 10 μg/day) than in normal women (44 ± 3 μg/day). In a more recent publication, Kuchel et al.[72] have confirmed their previous findings of normal urinary excretion of epinephrine and norepinephrine in 16 women with idiopathic edema. Of great interest was their finding that urinary excretion of dopamine was significantly lower in idiopathic edema patients (146 ± 13 ng/min/sq m) than in the normal controls (212 ± 32 ng/min/sq m) in the recumbent posture, though the differences during a 4-hr period in the upright posture were not significant. They also found a significant correlation between dopamine and Na excretion both before and after furosemide administration in the patients with idiopathic edema. The authors suggest that reduced dopamine production may be the underlying mechanism of impaired Na excretion in patients with idiopathic edema, since dopamine has been shown to have natriuretic effects[60,61] and might play the role of an endogenous natriuretic hormone.[59,62]

Role of obesity. As many clinicians are aware, edema of the legs and feet is a common finding in severely obese individuals who appear otherwise healthy. This type of edema will frequently—perhaps always—disappear if and when body weight can be reduced toward normal levels by caloric restriction. The weight records of two women in whom this was accomplished are shown in Fig.

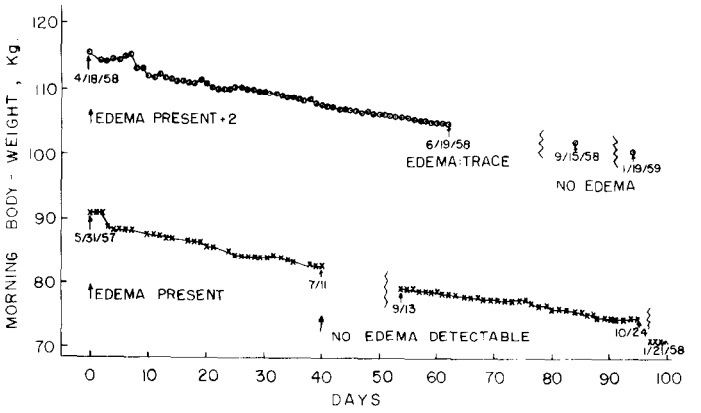

Fig. 9. Disappearance of edema with weight loss in two women with severe obesity.

9. Whether the pathogenesis of this "edema of obesity" involves mechanical obstructive effects of adipose tissue deposits, unusual inactivity of the subjects, or other mechanisms is not known. There are no data to show whether edema of obesity is similar to other types of idiopathic edema discussed in this review. While only 29% of the patients in our study of the pathogenesis of idiopathic edema[4] were severely obese ($\geq 15\%$ above Metropolitan Life Insurance Company range of normal) the prevalence of obesity in other studies has not been reported. It seems possible that some of the differences in findings between reported series of patients with idiopathic edema might result from differences in the frequency of severe obesity.

Role of heat. While many patients report that their edema is worst in warm, humid weather, there are occasional patients in whom heat seems to be the predominant factor in the pathogenesis of edema. We have reported studies on the only such patient we have recognized,[73] in whom the excretion of sodium and water was clearly abnormal when she was on her feet in hot environments but was entirely normal during prolonged standing in a "walk-in" refrigerator (at 4°C) or even in a room air-conditioned to below 15°C (59°F). Edwards and Bayliss[8] have reported another patient, apparently of this type, who was troubled with edema while working in India but not in Britain. It is obviously important to be quite sure that the presence of thyrotoxic edema has been ruled out in such patients. Presumably, there is an excessive dilatation of the precapillary sphincter in response to heat but not in response to standing in cool environments in these patients.

Diuretic-induced edema. MacGregor et al.[74] have described two patients who experienced intermittent "attacks of swelling" in spite of treatment with furosemide. When the furosemide was stopped, edema became more severe for a few days, then rapidly diminished and disappeared by the end of 2 3 wk. It is not clear why the hyperaldosteronism that the authors found to be present in at least one of these edematous patients during furosemide treatment was not shut off by fluid retention sufficient to cause edema, unless there was an abnormal tendency to accumulate edema in the first place.

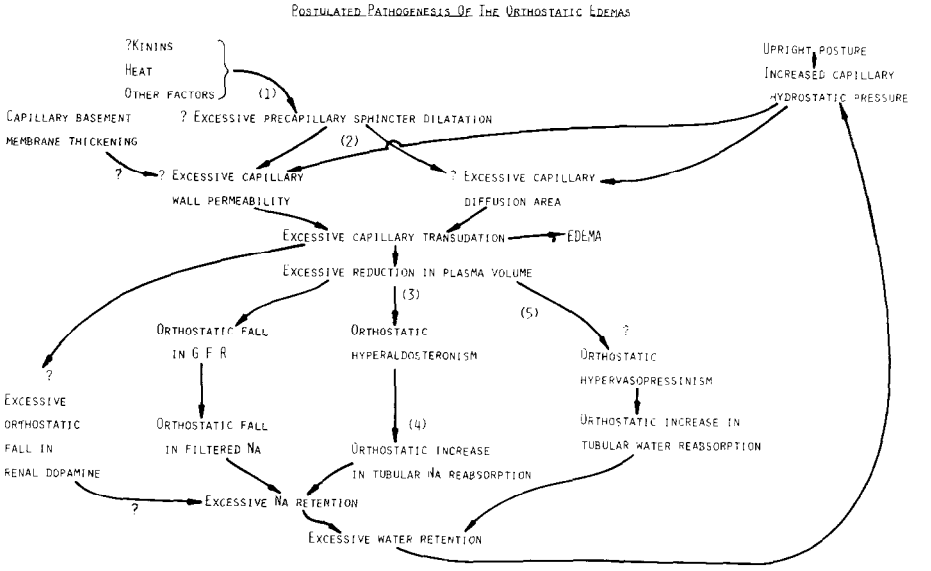

Fig. 10. Pathogenesis of the idiopathic edemas. The postulated or established sites of therapeutic or experimental corrective measures are designated by the ciphers: (1) sympathomimetic amines; (2) external compression of the lower limbs; (3) subtotal adrenalectomy, sympathomimetic amines; (4) spironolactone and conventional diuretics; (5) ethanol.

Summary of Pathogenesis of Idiopathic Edema

Figure 10 summarizes known and postulated steps in the pathogenesis of idiopathic edema of the orthostatic Na- and water-retaining types. The question marks indicate postulated factors that have not been shown to be present and factors that are present but have not been demonstrated to have the effects attributed to them. The central role of the postulated capillary abnormality is evident, as is the secondary role of renal influences (hyperaldosteronism, fall in GFR, probable hypervasopressinism, and excessive orthostatic fall in renal dopamine[72]), which are thought to act by replenishing the reduced plasma volume and in this way maintain capillary hydrostatic pressure so that transudation can continue and edema increase while orthostasis persists. The known or probable sites of several therapeutic and experimental corrective measures are shown.

TREATMENT

General

Since idiopathic edema produces unpleasant and unwanted symptoms but seldom incapacitates patients and has little or no effect on their life expectancy, treatment should be restricted to the minimum needed to correct the symptoms without imposing unwarranted iatrogenic hazards. Patients who can be reassured that the disorder is not dangerous and can be improved with mild salt restriction, reduction of the time spent on their feet, and avoidance of aggravating factors such as severe heat, should probably receive no other therapy at present, except for the occasional use of a mild diuretic when symptoms be-

come more severe, such as premenstrually. In fact, all patients should initially be treated in this way, and they should be encouraged to elevate their feet by lying on a couch or in a comfortable chair with a foot-rest as soon as possible after the evening meal.

Conventional Diuretics

If a conventional diuretic is needed it will produce the most dramatic results when taken at 7 or 8 p.m. with the patient recumbent until the time of going to bed. Patients frequently lose their initial good responses to diuretics taken when they are on their feet during the day, probably because no diuretic will prevent the orthostatic fall in GFR, which appears to be of great importance in the retention of fluid in these patients. Diuretics seldom if ever lose their effectiveness in idiopathic edema when taken in recumbency. Far from causing unpleasant nocturia when taken at 8 p.m., diuretics will usually produce so brisk a diuretic response, if the patient is able to keep her legs elevated, that edema will be greatly reduced by 11 or 11:30 p.m. and nocturia —a common feature of the untreated disorder—may actually be diminished by this treatment. If, and when, the serum K falls below 3.5 meq/liter, it is probably wise to administer supplementary potassium chloride or to supplement or replace the initial diuretic used with spironolactone (Aldactone), preferably in a dose of 25–75 mg daily. Although there are often few or no symptoms clearly attributable to mild degrees of K depletion, prolonged deficiency of K causes vacuolar nephropathy,[75] is conducive to renal tract infections,[76] aggravates or precipitates diabetes mellitus,[77] may predispose to arrhythmias, and may well have other, unknown ill effects.

For those patients who require diuretic or other forms of drug treatment, it is very helpful to try to assess the efficacy of the therapy by having the patient weigh herself after emptying the bladder, on arising each morning, and before retiring at night. Such records serve to indicate whether the therapy administered has had any effect on morning body weight or on the weight gain from morning to evening; a very short written recording of the main symptoms each day is of considerable help in indicating the nature and severity of, and any improvement in, the symptoms.

Treatment of Hyperaldosteronism

Subtotal Adrenalectomy

Ross et al.[78] reported considerable temporary reduction of edema in a patient with idiopathic edema after removal of an aldosterone-producing adrenocortical adenoma. The improvement continued until secondary hyperaldosteronism recurred because of hyperplasia of the remaining adrenal gland. In the late 1950s, before spironolactone became available, subtotal adrenalectomy was used by us in two patients with severe edema associated with marked hyperaldosteronism.[3] Both patients benefited from their reduced capacity to secrete excessive amounts of aldosterone and have required no steroid replacement therapy. Analysis of balance data in one of the patients (Fig. 11) showed that weight gain and urinary excretion of Na and water in the upright posture during the day were quite unaffected by the adrenalectomy.[3] However, the Na retained

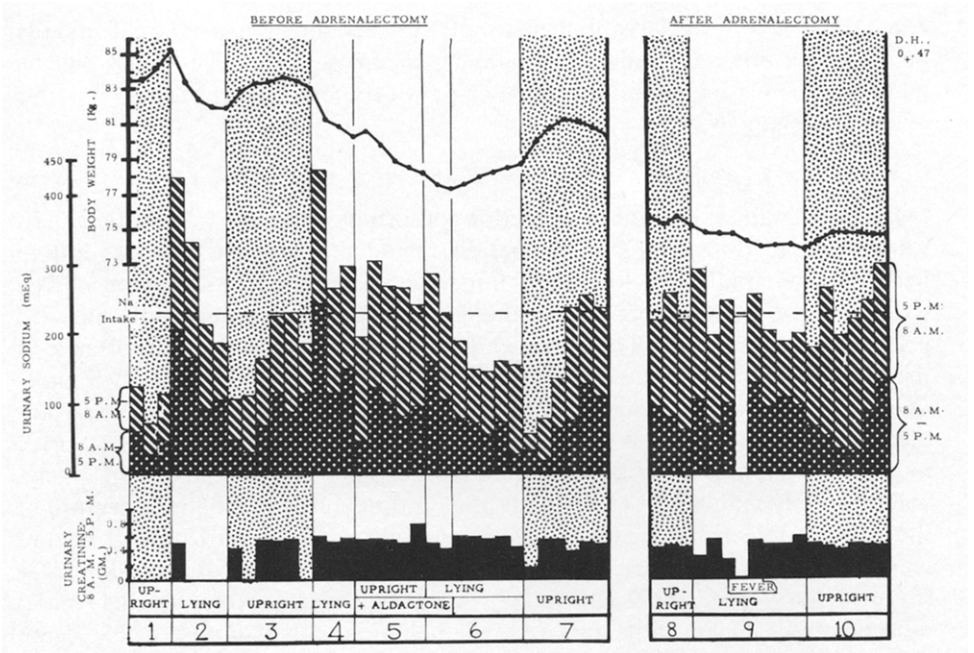

Fig. 11. Pre- and postadrenalectomy changes in body weight and Na excretion in a patient with orthostatic Na retention. Posture was controlled (upright 8 a.m. to 5 p.m. in shaded periods, recumbent all day and night in clear areas) and patient had a constant 230 meq Na intake daily. Note that urinary Na fell far short of Na intake (indicated by dotted line) in the first 3 days of the upright posture preoperatively, when a sharp rise in body weight occurred during periods 1, 3, and 7. In contrast, daily 24-hr urinary Na excretion virtually equalled intake throughout the upright periods preoperatively, when Aldactone was administered (period 5), and postoperatively (periods 8 and 10), because of a striking increase in Na excretion in recumbency (5 p.m. to 8 a.m.) each day (cross-hatched columns), thus preventing any progressive weight gain during the periods in the upright posture.

and the weight gained during the day were rapidly lost during recumbency overnight after the adrenalectomy, mean overnight Na loss increasing from 63.7 meq preoperatively to 161.1 meq postoperatively (Fig. 11). Thus, the cumulative increase in morning weight during 3 days in the upright posture, which averaged 1.8 kg/3 days preoperatively, was reduced to a mean cumulative weight loss of 0.7 kg/3 days in the upright posture after the adrenalectomy. These changes resulted in the rapid disappearance of pitting edema,[3] which has remained improved in the 18 yr since the operation.

Spironolactone (Aldactone)

The effects of treatment with spironolactone[3,79] are very similar to those that follow adrenalectomy. Thus, the excessive weight gain from morning to evening—the hallmark of orthostatic edema—is unimproved by the aldosterone antagonist, but overnight excretion of the Na retained during the day is facilitated, so that the slight, progressive weight gain from one morning to the next is overcome and the morning weight declines while spironolactone therapy continues. Treatment with spironolactone, therefore, while it does not alter the primary defect in idiopathic edema, is a very useful component of the long-term

treatment of patients with severe idiopathic edema of the orthostatic Na-retaining type.

External Compression

Judging from the experimental demonstration of the benefit conferred by external pressure with an inflated G-suit or through Ace bandages tightly wrapped around the legs and thighs, the use of elastic stockings would be expected to be of great therapeutic value in these patients. By preventing the excessive transudation from the capillaries and in this way overcoming edema formation, the need to remove accumulated fluid by the use of diuretics would be expected to be obviated. Thigh-high elastic stockings and customized elastic compression garments of the type supplied by the Jobst Company are worthy of further trial but have given disappointing results. This is probably because if they are sufficiently tight-fitting to be effective they are somewhat difficult to get into and out of and tend to be warm when used in the summer. Few patients continue to use external pressure of these types after the first prescription, in my experience.

Sympathomimetic Amines

In an attempt to constrict excessively dilated precapillary sphincters, which we and others have hypothesized to be the cause of orthostatic edemas, since 1956[6,38] we have administered sympathomimetic amines, especially dextroamphetamine, to patients with idiopathic edema. Many patients showed a gratifying reduction in edema and a reduction in weight gain from morning to evening that no conventional diuretic therapy or even spironolactone could accomplish. In 1962, Greenough et al.[80] reported striking natriuretic effects of ephedrine, phenylephrine, and hydroxyamphetamine given separately in large doses to a patient with severe idiopathic edema, as forms of therapy for her associated hypotension. Blood pressure rose slightly, aldosterone secretion rate fell dramatically, and edema disappeared while the sympathomimetic amines were being administered.

Since then the mechanism of the natriuretic action of dextroamphetamine has been analyzed by Speller and Streeten,[40] who found that the natriuresis was associated with reduction of aldosterone excretion in normal subjects and in patients with idiopathic edema. Moreover, no natriuretic effect of dextroamphetamine could be found in patients with primary adrenal insufficiency, confirming that this action was mediated through an effect on adrenal function. A significant negative correlation was found between the excretion of Na and aldosterone during dextroamphetamine therapy. Thus, these observations were in good agreement with those of Greenough et al.[80] that sympathomimetic amines did reduce aldosterone secretion and promoted natriuresis by this mechanism. However, since body weight measurements had shown that the weight gain intra diem was not reduced by adrenalectomy[3] or by antagonizing the action of secreted aldosterone with spironolactone,[79] whereas the weight gain intra diem was reduced by dextroamphetamine, it seemed unreasonable to believe that the action of the amphetamine in idiopathic edema could be exclusively via reduction of aldosterone secretion, though this mechanism might well explain its natriuretic action satisfactorily.

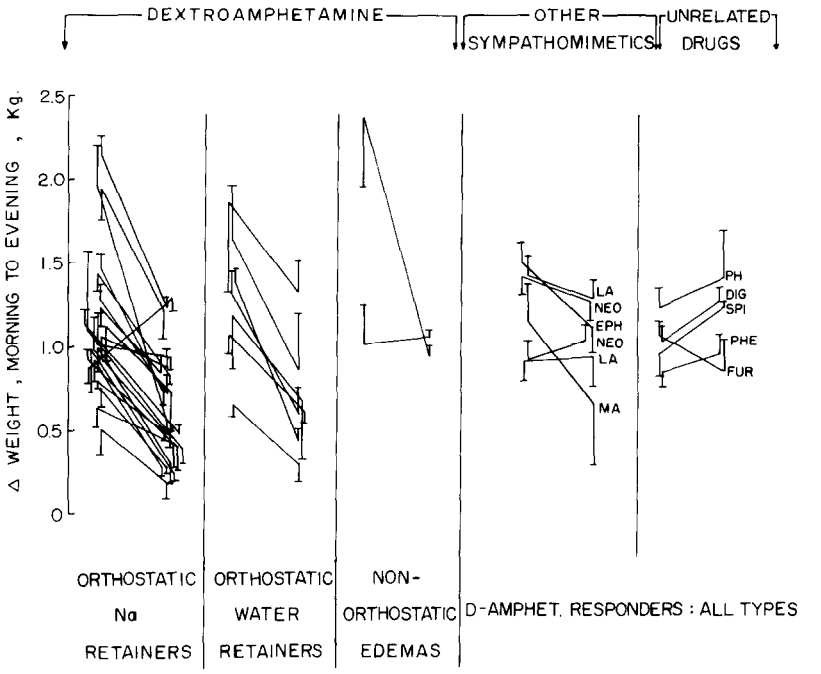

Fig. 12. Effects of therapy with dextroamphetamine and other drugs on weight gain (Δ wt) from morning to evening in 31 patients with idiopathic edema. Mean and SEM of Δ wt for each patient is shown when the drug mentioned was not (on left) and was (on right) being given for periods of 1–18 wk. The changes in Δ wt during dextroamphetamine therapy (10–25 mg/day) were statistically significant ($p < 0.05$ or less) in 15 of 21 patients with orthostatic sodium retention, 6 of 7 patients with orthostatic water retention, and 1 of 2 patients with nonorthostatic edema. Of the sympathomimetic agents and other drugs administered to patients known to be responders to dextroamphetamine, only methamphetamine (MA) lowered Δ wt significantly ($p < 0.05$); the responses to ephedrine (EPH), phenylephrine (NEO), and levo-amphetamine (LA) were not significant. Similarly, phenergan (PH), digitoxin (DIG), spironolactone (SPI), phenformin (PHE), and furosemide (FUR) were ineffective in conventional therapeutic doses.

The effect of various agents on weight gain from morning to evening in different types of idiopathic edema is shown in Fig. 12. In doses of 10–25 mg daily, dextroamphetamine significantly reduced the mean weight gain from morning to evening (p at least < 0.05) in 15 of 21 orthostatic Na retainers, in 6 of 7 orthostatic water retainers, and in 1 of 2 patients with nonorthostatic edema. Among the patients who showed a statistically significant response to dextroamphetamine, one also showed a significant response to methylamphetamine and one to ephedrine (50 mg t.i.d.), while no significant response was seen in other patients given ephedrine (same dose), phenylephrine (50 mg t.i.d.), or the pharmacologically inactive levoamphetamine (60 mg daily). Similarly, no significant effect was observed on the weight change intra diem in response to such agents as digitoxin, furosemide, spironolactone, phenergan, and phenformin (recommended by Shaw et al.[81]). Since all of these drugs were given without any prior knowledge on the part of the investigator or the patient of whether they might or might not be beneficial, the peculiar effectiveness of dextroamphetamine in this respect seems to be specific and is not likely to result from any placebo action.

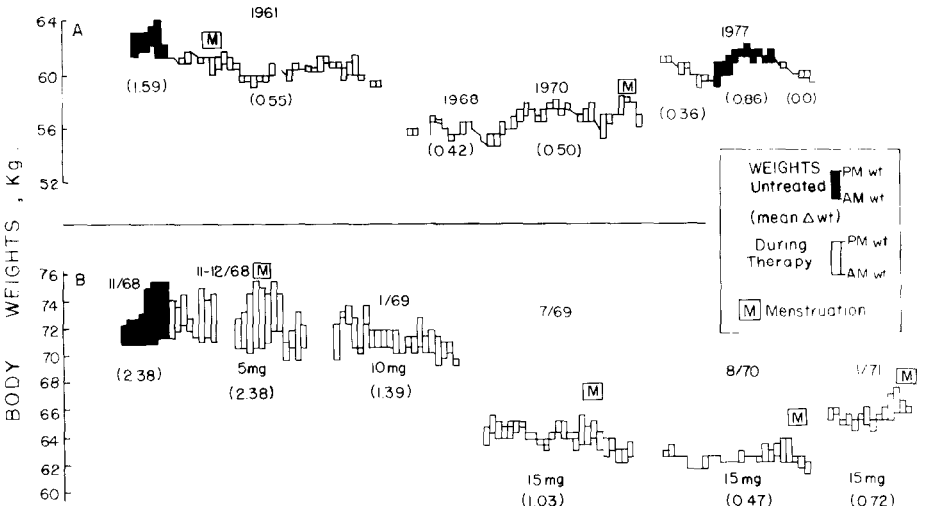

Fig. 13. Effects of dextroamphetamine therapy on morning and evening body weights (bottoms and tops of each rectangle) in two patients with idiopathic edema. Mean weight gain intra diem (shown in parentheses) was reduced by 20 mg dextroamphetamine from 1.59 to 0.50 kg over a 9-yr period in patient A, while doses of 15 mg were required to reduce mean weight gain intra diem from 2.38 to 0.47–0.72 kg over almost 2 yr in patient B. M: menstruation.

A few examples of the effects of dextroamphetamine therapy in patients with idiopathic edema are shown in Fig. 13. Patient A has been treated with dextroamphetamine alone, 20 mg daily, for the past 16 yr. Mean weight gain intra diem before treatment (1.59 kg) was immediately reduced to 0.55 kg and has remained between 0.36 and 0.50 kg, while morning weights have been normal and edema absent ever since. When therapy was stopped for 10 days in 1977, edema recurred and the weight gain from morning to evening increased from 0.36 to 0.86 kg, falling again to 0.0 kg when dextroamphetamine therapy was resumed. Menstruation was irregular before treatment and has been regular ever since, except during three pregnancies, which resulted in the uneventful delivery of healthy offspring. Patient B shows the ineffectiveness of a 5-mg dose of dextroamphetamine daily, and the progressively greater effectiveness of 10-mg and 15-mg daily doses, which decreased mean weight gain intra diem from 2.38 kg to 1.39, then 1.03, and eventually 0.47–0.72 kg. The continued effectiveness of dextroamphetamine therapy on the weight gain from morning to evening for several years is evident in these patients, as it is in many others. Unlike the effects of thiazide diuretics, which usually diminish with time even if given in steadily increasing doses, and unlike the effects of dextroamphetamine on mood, which last only a few weeks at the dose levels used, the action on fluid accumulation in idiopathic edema is usually well maintained for many years.

Dextroamphetamine causes nervousness, insomnia, and excitement in some patients who are better treated with a combination of dextroamphetamine and amobarbital (Dexamyl spansules) or with other drugs. Otherwise, it is extremely well tolerated, has caused no serious side effects of any kind, and has caused no addiction or craving for larger doses—effects that are commonly seen when it is

abused for its mood-elevating effects. The most distressing aspects of its prescription at present are the stern looks of disapproval to which patients are subjected by many pharmacists and self-appointed "experts" on morality!

It is sometimes preferable to use ephedrine (25–50 mg t.i.d.), but this agent tends to cause palpitations more frequently and is generally less effective than dextroamphetamine.

It is tempting to speculate that the action of dextroamphetamine might be mediated by dopamine release since the drug certainly does release this and other cathecholamines from autonomic neurons.[82] Perhaps dopamine itself or such central dopaminergic agonists as bromocriptine[83] would be worthy of therapeutic trial in orthostatic edema in the future, as Kuchel et al.[72] have suggested.

Swimming and Muscular Exercises

Some patients with severe idiopathic edema have learned by experience—supported by body-weight records—that a program of swimming daily is helpful to them. The recumbent posture in which the subject swims, the cooling effect of the water, and perhaps the external pressure of the water when the subject is not horizontal might all have beneficial effects. Moreover, there is evidence from a paper written 47 yr ago[84] that the legs swell less in the upright posture in normal subjects who are in good physical training than in those who are not. Perhaps the commonness of idiopathic edema in the present era is the consequence of the modern sedentary life. Although these last thoughts are purely speculative, a trial of exercise therapy in patients with idiopathic edema would probably be worthwhile and could certainly do no harm!

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REFERENCES

1. Mach R, Fabre J, Muller A, et al: Oedème idiopathique par rétention sodique avec hyperaldostéronurie. Bull Mem Soc Med Hôp Paris pp 726–732, 1955

2. Luetscher JA Jr, Lieberman AK: Idiopathic edema with increased aldosterone output. Trans Assoc Am Physicians 70:158–166, 1957

3. Streeten DHP, Conn JW: Secondary aldosteronism in "idiopathic edema." Trans Assoc Am Physicians 73:227–239, 1960

4. Streeten DHP, Dalakos TG, Souma M, et al: Studies of the pathogenesis of idiopathic oedema: The roles of postural changes in plasma volume, plasma renin activity, aldosterone secretion rate and glomerular filtration rate in the retention of sodium and water. Clin Sci Mol Med 45:347–373, 1973

5. Preston GM, Rees JR, Spathis GS: A man with cyclical oedema. Guys Hosp Rep 111:69–79, 1962

6. Streeten DHP, Conn JW: Observations on the pathogenesis of idiopathic edema. First International Congress of Endocrinology, Copenhagen. Acta Endocrinol [Suppl] 51:183, 1960

7. Clarkson B, Thompson D, Horwith M, et al: Cyclical edema and shock due to increased capillary permeability. Am J Med 29:193–216, 1960

8. Edwards OM, Bayliss RIS: Idiopathic oedema of women. A clinical and investigative study. Q J Med 45:125–144, 1976

9. Streeten DHP, Kerr LP, Kerr CB, et al: Hyperbradykininism: A new orthostatic syndrome. Lancet 2:1048–1053, 1972

10. Gordon ES, Graham DT: Metabolic edema. J Lab Clin Med 54:818–819, 1959

11. Gill JR Jr, Waldmann TA, Bartter FC: Idiopathic edema. I. The occurrence of hypoalbuminemia and abnormal albumin metabolism in women with unexplained edema. Am J Med 52:444–451, 1972

12. Thorn GW: Approach to the patient with "idiopathic edema" or "periodic swelling." JAMA 206:333–338, 1968

13. Kuchel O, Horky K, Gregorova I, et al: Inappropriate response to upright posture: A precipitating factor in the pathogenesis of idiopathic edema. Ann Intern Med 73:245–252, 1970

14. Sims EAH, MacKay BR, Shirai T: The relation of capillary angiopathy and diabetes mellitus to idiopathic edema. Ann Intern Med 63:972–987, 1965

15. Oelkers W, Marsen B, Molzahn M, et al: Spontaneous changes in weight, leg volume, renin, aldosterone and sex hormones in patients with cyclical oedema. Klin Wochenschr 53:509–517, 1975

16. Veyrat R, Robert M, Mach RS: Etude de la rénine dans les oedèmes idiopathiques avec hyperaldostéronisme secondaire. Schweiz Med Wochenschr 98:1499–1507, 1968

17. Werning C, Baumann K, Gysling E, et al: Renin und Aldosteron bei idiopathischen Ödemen. Klin Wochenschr 47:1256–1263, 1969

18. Emerson K Jr, Armstrong SH: High protein edema due to diffuse abnormality of capillary permeability. Trans Assoc Am Physicians 67:59–72, 1955

19. Coleman M, Horwith M, Brown JL: Idiopathic edema. Studies demonstrating protein-leaking angiopathy. Am J Med 49:106–113, 1970

20. Ribaudo CA, Formato AA: Panty girdle syndrome. NY State J Med 65:456–457, 1965

21. Craig AB, Dvorak M: Constrictive forces of panty girdle on thigh. NY State J Med 65:1337–1338, 1965

22. DeGroot LJ, Stanbury JB: The Thyroid and Its Diseases (ed 4). New York, Wiley, 1975, p 280

23. Biglieri EG: Hypokalemic alkalosis and edema with increased desoxycorticosterone excretion. J Clin Endocrinol 25:884–894, 1965

24. August JT, Nelson DH, Thorn GW: Response of normal subjects to large amounts of aldosterone. J Clin Invest 37:1549–1555, 1958

25. Marieb NJ, Mulrow PJ: Failure to escape: A mechanism in idiopathic edema. J Clin Invest 43:1279, 1964

26. Gill JR Jr, Mason DT, Bartter FC: "Idiopathic" edema resulting from occult cardiomyopathy. Am J Med 38:475–480, 1965

27. Obeid AI, Streeten DHP, Eich RH, et al: Cardiac function in idiopathic edema. Arch Intern Med 134:253–258, 1974

28. Starling EH: On the absorption of fluids from the connective tissue spaces. J Physiol 19:312–326, 1896

29. McMaster PD: The pressure and interstitial resistance prevailing in the normal and edematous skin of animals and man. J Exp Med 84:473–494, 1946

30. Wiederhielm CA: Dynamics of transcapillary fluid exchange. J Gen Physiol 52:29–61, 1968

31. McMaster PD: The effect of venous obstruction upon interstitial pressure in animal and human skin. J Exp Med 84:495–509, 1946

32. Guyton AC: A concept of negative interstitial pressure based on pressures in implanted perforated capsules. Circ Res 12:399–414, 1963

33. Hauge A, Lunde PKM, Waaler BA: The effect of bradykinin, kallidin and eledoisin upon the pulmonary vascular bed of an isolated blood-perfused rabbit lung preparation. Acta Physiol Scand 66:269–277, 1966

34. Haddy FJ: The mechanism of bradykinin edema, in Sicuteri F, Rocha e Silva M, Back M (eds): Bradykinin and Related Kinins. Cardiovascular, Biochemical and Neural Actions. New York, Plenum, 1970, pp 283–289

35. Kline RL, Scott JB, Haddy FJ, et al: Mechanism of edema formation in canine forelimbs by locally administered bradykinin. Am J Physiol 225:1051–1056, 1973

36. Hyman C, Paldino RL: Influence of intravascular and topically administered bradykinin on microcirculation of several tissues. Bibl Anat 9:38–45, 1966

37. Gill JR Jr, Cox J, Delea CS, et al: Idiopathic edema II. Pathogenesis of edema in patients with hypoalbuminemia. Am J Med 52:452–456, 1972

38. Streeten DHP, Conn JW: Studies on the pathogenesis of idiopathic edema. J Lab Clin Med 54:949–950, 1959 (abstract)

39. Streeten DHP, Speller PJ: The role of aldosterone and vasopressin in the postural changes in renal excretion in normal subjects and patients with idiopathic edema. Metabolism 15:53–64, 1966

40. Speller PJ, Streeten DHP: Mechanism of

the diuretic action of D-amphetamine. Metabolism 13:453–465, 1964

41. Fisher DA, Morris MD: Idiopathic edema and hyperaldosteronuria: postural venous plasma pooling. Pediatrics 35:413 424, 1965

42. Hill SR Jr, Hood WG Jr, Farmer A Jr, et al: Idiopathic edema. Report of a case with orthostatic edema and hyperaldosteronism. N Engl J Med 263:1342–1345, 1960

43. Lagrue G, Ménard J, Weil B: Le syndrome d'oedeme cyclique idiopathique. Presse Med 77:1799, 1969

44. Weil B, Lagrue G, Ménard J: Syndrome d'oedemes cycliques idiopathiques III Études biologiques. Deductions physiopathologiques et thérapeutiques. J Urol Nephrol 77:940 952, 1971

45. Rovner DR: The enigma of idiopathic cyclic edema. Hosp Pract pp 103–110, 1972

46. Böhm P, Franken FH, Irmscher K: Beitrag zum Problem des idiopathischen Ödems. Klin Wochenschr 41:1155–1161, 1963

47. Brun C, Knudsen EOE, Raaschou F: The influence of posture on the kidney function. I. The fall of the diuresis in the erect posture. Acta Med Scand 122:315 331, 1945

48. Kattus AA, Sinclair-Smith B, Genest J, et al: The effect of exercise on the renal mechanism of electrolyte excretion in normal subjects. Bull Johns Hopkins Hosp 84:334–368, 1949

49. Ni T-G, Rehberg PB: On the influence of posture on kidney function. J Physiol 71:331–339, 1931

50. Epstein FH, Goodyer AVN, Lawrason FD, et al: Studies of the antidiuresis of quiet standing: The importance of changes in plasma volume and glomerular filtration rate. J Clin Invest 30:63 72, 1951

51. Surtshin A, White HL: Postural effects on renal tubular activity. J Clin Invest 35:267–271, 1956

52. Thomas S: Some Effects of change of posture on water and electrolyte excretion by the human kidney. J Physiol 139:337 352, 1957

53. Pearce ML, Newman EV: Some postural adjustments of salt and water excretion. J Clin Invest 33:1089–1094, 1954

54. Rubini ME, Kleeman CR, Lamdin E: Studies on alcohol diuresis. II The effect of ethyl alcohol ingestion on water, electrolyte and acid based metabolism. J Clin Invest 34:439–447, 1955

55. Barger AC, Berlin RD, Tulenko JF: Infusion of aldosterone, 9α fluorohydrocortisone and antidiuretic hormone into the renal artery of normal and adrenalectomized unanesthetized dogs: Effect on electrolyte and water excretion. Endocrinology 62:804–815, 1958

56. Crabbé J: Stimulation of active sodium transport by the isolated toad bladder with aldosterone in vitro. J Clin Invest 40:2103 2110, 1961

57. Muller AF, Manning EL, Riondel AM: Diurnal variation of aldosterone related to position and activity in normal subjects and patients with pituitary insufficiency, in Muller AF, O'Connor CM (eds): An International Symposium on Aldosterone. Boston, Little, Brown, 1958, pp 111–142

58. Gill JR Jr: The role of the sympathetic nervous system in the regulation of sodium excretion by the kidney, in Ganong WF, Martini L (eds): Frontiers in Neuroendocrinology. New York, Oxford University Press, 1969, ch 8

59. Cuche JL, Kuchel O, Barbeau A, et al: Relationship between the adrenergic nervous system and renin during adaptation to upright posture: A possible role for 3,4-dihydroxyphenethylamine (dopamine). Clin Sci 43:481–491, 1972

60. McDonald RH Jr, Goldberg LI, McNay JL, et al: Effects of dopamine in man: Augmentation of sodium excretion, glomerular filtration rate and renal plasma flow. J Clin Invest 43:1116 1124, 1964

61. Burns CR, McGiff JC: Mechanism of the natriuretic action of dopamine. Circulation [Suppl 2] 35 36:79, 1967 (abstract)

62. Alexander RW, Gill JR Jr, Yamabe H, et al: Effects of dietary sodium and of acute saline infusion on the interrelationship between dopamine excretion and adrenergic activity in man. J Clin Invest 54:194–200, 1974

63. Rovner DR, Cohen EL, Conn JW, et al: Aldosterone, renin activity and sodium kinetics in idiopathic edema. 47th Endocrine Society Meeting, New York, 1965 (abstract)

64. Ferris TF, Chonko AM, Williams JS, et al: Studies of the mechanism of sodium retention in idiopathic edema. Trans Assoc Am Physicians 86:310–319, 1973

65. Streeten DHP: The role of posture in idiopathic oedema. S Afr Med J 49:462 464, 1975

66. Arzola MP: Idiopathic edema with review of the literature. Bol Asoc Méd Puerto Rico 59:475–479, 1967

67. Bartter FC, Schwartz WB: The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42:790–806, 1967

68. Streeten DHP, Schletter FE, Clift GV, et al: Studies of the renin-angiotensin aldosterone system in patients with hypertension and in normal subjects. Am J Med 46:844-861, 1969

69. Streeten DHP: Unpublished observations

70. Dalakos TG, Streeten DHP: The role of plasma volume in the increase of aldosterone secretion rate during sodium deprivation. Clin Sci Mol Med 48:161-165, 1975

71. Zacks SI, Pegues JJ, Elliott PA: Interstitial muscle capillaries in patients with diabetes mellitus: A light and electron microscope study. Metabolism 11:381-393, 1962

72. Kuchel O, Cuche JL, Buu NT, et al: Catecholamine excretion in "idiopathic" edema: Decreased dopamine excretion, a pathogenic factor? J Clin Endocrinol Metab 44:639-646, 1977

73. Streeten DHP: Primary and secondary aldosteronism, in Moyer JH, Fuchs M (eds): Edema. Philadelphia, Saunders, 1960, pp 121-132

74. MacGregor GA, Tasker PRW, DeWardener HE: Diuretic-induced oedema. Lancet 1:489-492, 1975

75. Oliver J, MacDowell M, Welt LG, et al: The renal lesions of electrolyte imbalance. I. The structural alterations in potassium-depleted rats. J Exp Med 106:563-574, 1957

76. Relman AS, Schwartz WB: The kidney in potassium depletion. Am J Med 24:764-773, 1958

77. Goldner MG, Zarowitz H, Akgun S: Hyperglycemia and glycosuria due to thiazide derivatives administered in diabetes mellitus. N Engl J Med 262:403-405, 1960

78. Ross EJ, Crabbé J, Renold AE, et al: A case of massive edema in association with an aldosterone-secreting adrenocortical adenoma. Am J Med 25:278-292, 1958

79. Streeten DHP: The use of aldosterone antagonists in idiopathic edema, in Bartter FC (ed): The Clinical Use of Aldosterone Antagonists. Springfield, Ill, Thomas, 1960, pp 195-208

80. Greenough WB, Sonnenblick EH, Januszewicz V, et al: Correction of hyperaldosteronism and of massive fluid retention of unknown cause by sympathomimetic agents. Am J Med 33:603-614, 1962

81. Shaw RA, Kryston LS, Fleischmajer R, et al: The rationale for treatment of idiopathic edema. Am J Cardiol 21:115, 1968 (abstract)

82. Lewander T: Urinary excretion and tissue levels of catecholamines during chronic amphetamine intoxication. Psychopharmacologia 13:394-407, 1968

83. Benedek-Jaszmann LJ, Hearn-Sturtevant MD: Premenstrual tension and functional infertility. Aetiology and treatment. Lancet 1:1095-1098, 1976

84. Waterfield RL: The effect of posture on the volume of the leg. J Physiol 72:121-131, 1931