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Idiopathic edema: Role of diuretic abuse

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Case presentations

Patient 1. An obese, 45-year-old woman was admitted to Charing Cross Hospital because of persistent edema of unknown cause for three years. At age 31, the patient went to India to work in a leper colony as a missionary nurse. At age 42, she returned to England on leave, where she underwent a hysterectomy because of menorrhagia due to fibroid tumors. On returning to India, she was unaccustomedly overcome by the heat, stated that then she became anuric for 3 days, and was hospitalized when she became semiconscious. She reported that during her recovery, her urine output returned slowly to normal and that she was given nitrofurantoin for a suspected urinary tract infection. She alleged that she had been told to take bendrofluazide to increase her urine flow. The patient noticed that she occasionally had edema that could be prevented if she increased the dosage of her diuretic; at the time of admission to hospital, she was taking 10 mg/day of bendrofluazide.

The patient had been chronically lethargic and complained that she was not able to work as hard as she had previously. Her weight had risen steadily despite several attempts at weight reduction. During the 9 months she lived in England prior to this admission, her weight had increased from 82 kg to 92 kg. During that time, she had ingested approximately 2700 calories and approximately 200 mmol of sodium per day. At age 24 the patient had poliomyelitis, which had resulted in residual weakness in her left leg. The family history included obesity in members of her father's family. The patient reported that, since living in India, she had become allergic to nickel, talcum powder, deodorants, and detergents.

On examination, the patient was cooperative and pleasant; her height was 5′ 2.5″, and she weighed 92 kg (203 pounds). Her blood pressure was 150/92 mm Hg, and her pulse was 80. Mild pitting edema of both ankles was present. She had no proteinuria and no red or white cells in her urine. A chest x-ray and intravenous pyelogram were normal. Laboratory tests revealed: hemoglobin, 13.3 mg/dl; plasma sodium, 137 mEq/liter, potassium, 3.1 mEq/liter; chloride, 101 mEq/liter; total carbon dioxide, 25 mmol/liter; and serum creatinine, 0.9 mg/dl. The plasma uric acid was 8 mg/dl; total protein, 6.6 g/dl; albumin, 4.0 g/dl; bilirubin, 0.5 mg/dl; and alkaline phosphatase 5 KAU/dl. The plasma thyroxine level was 9.2 μg/dl, and the thyroid-stimulating hormone was measured as less than 2 mU/liter. The 24-hour creatinine clearance was 81 ml/min. The patient's plasma volume was 2.66 liters; calculated red cell mass, 1.49 liters; total blood volume, 4.16 liters; extracellular fluid volume, 18.3 liters. These values had been predicted to be 2.90 liters (plasma volume), 1.70 liter (red cell mass), 4.60 liters (total blood volume), and 17.7 liters (extracellular water).

In the Metabolic Ward, the patient was encouraged to be up and about and dressed most of the day. Her hospital diet corresponded to her preadmission intake, and she was given 10 mg of bendrofluazide per day for 13 days (Fig. 1). Before the diuretic was discontinued, plasma renin activity varied between 12.3 and 5.6 ng/ml/hour, and the 24-hour urinary aldosterone excretion was 51 to 26 mmol. Plasma renin measurements are made between 10 A.M. and noon, when the patients are sitting upright and when the dietary sodium intake is 100 to 200 mmol/day. The normal range for plasma renin activity under these conditions is 0.5 to 2.5 ng/ml/hour. Urinary aldosterone excretion is 10 to 25 nmol/24 hours. When no longer given the diuretic, the patient gained 2 kg by the fourth day but then gradually returned to her previous weight. The weight gain was accompanied by much discomfort, including facial bloating, abdominal distention, and increased ankle edema. The plasma renin activity fell to 0.93 ng/ml/hour at her highest weight, but subsequently leveled out at 2.05 ng/ml/hour as the urinary aldosterone excretion decreased gradually to 7 nmol/day. Plasma volume, total body volume, and blood pressure rose transiently and then returned to earlier values.

On discharge, the patient was relieved to learn that she no longer needed diuretics, but she was disappointed that her weight was similar to that on admission. She was advised to follow a 1000 calorie diet. One month later, before she returned to India, she had lost 4 kg, and she stated that she felt more cheerful and that her energy had returned. Residual edema of her considerably fat ankles remained.

Patient 2. A 30-year-old woman was admitted to Charing Cross Hospital because of edema of unknown cause over 15 years. She has a nonidentical twin sister and an older sister, both of whom are slender. At age 11 years, the patient weighed 63 kg (139 pounds); she was acutely conscious of her obesity particu-

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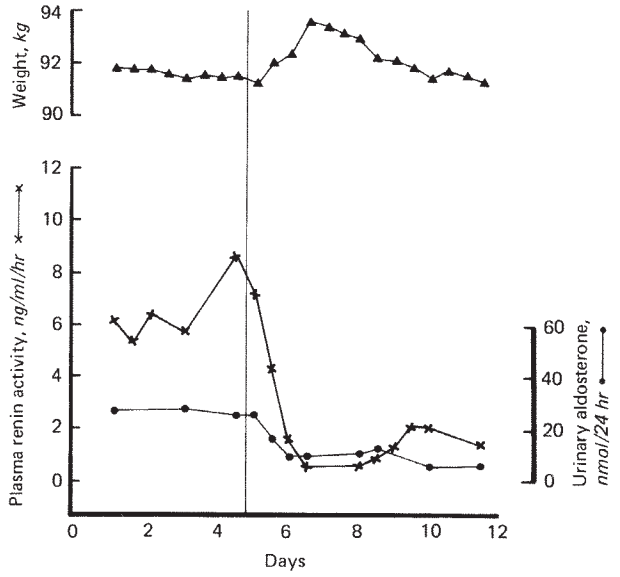

Fig. 1. Body weight in kgs (upper panel) relative to plasma renin activity and urinary aldosterone excretion (lower panel) before (left) and after (right of vertical line) cessation of bendrofluazide in Patient 1. See text for details.

larly as it contrasted with the slimness of her sisters. The school doctor prescribed a reducing diet, but it made her feel ill. She was still overweight when she left school at age 16. Her general practitioner then prescribed a diuretic to alleviate her questionable ankle edema. At age 20, the patient became pregnant, and her diuretic was temporarily discontinued. Edema and hypertension developed during the pregnancy, and she was in hospital for many weeks. The baby had convulsions after the delivery but survived.

The patient had persisted in her attempts to lose weight over 14 years and had successfully reduced her weight to 55 kg, but fearing obesity, she tried various weight-reducing "gimmicks" and spent considerable money to control her weight despite the fact that she was no longer overweight. She stated, "I have a phobia about my weight in case I put on weight again." Her daily diet comprised one meal of meat and salad, but on the weekends she ate much more and drank a generous supply of alcohol. These dietary excesses were associated with marked weight gains and uncomfortable exacerbations of ankle edema. She smoked 30 cigarettes per day.

Since age 16, the patient's use of diuretics had increased. When admitted to the hospital she was taking 320 mg of furosemide and 24 mEq of potassium daily; she had experienced one episode of symptomatic hypokalemia. The patient complained of constant thirst, had diurnal polyuria, dizziness on standing, and frequent nausea.

Physical examination revealed a slim, brittle woman, 5 feet 3 inches tall, who weighed 52 kg (115 pounds). She was rather guarded about her social history. She appeared well but thin and had slight ankle edema. Her blood pressure was 100/60 mm Hg but one morning it was recorded to be 70/40 mm Hg. No other abnormal physical signs were present. The urine was sterile. A chest x-ray was normal. Laboratory tests included: hemoglobin, 14.0 g/dl; plasma sodium, 134 mEq/liter; potassium, 3.3 mEq/liter; chloride, 94 mEq/liter; total carbon dioxide, 26 mmol/liter; BUN, 6 mg/dl; creatinine, 0.7 mg/dl; plasma total protein, 7.1 g/dl; albumin, 4.9 g/dl; and bilirubin, 0.16 mg/dl. The plasma volume was 2.05 liters, the calculated total blood volume was 3.27 liters, and the extracellular fluid volume was 13.3 liters (predicted, 2.23 liters, 3.54 liters, and 12.6 liters, respectively). The total exchangeable potassium was 2152 mmol, and the exchangeable sodium was 2192 mmol (predicted, 2207 and 2128, respectively).

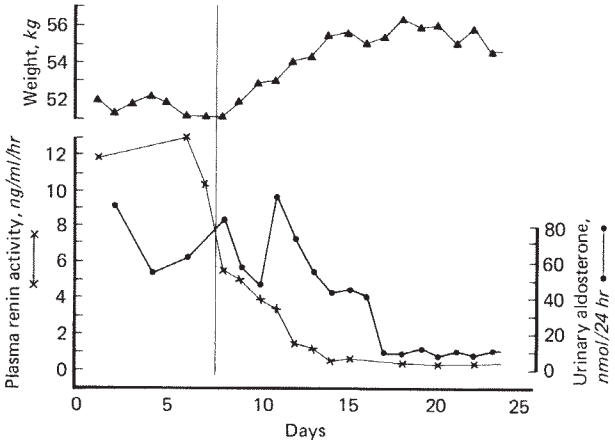

Fig. 2. Body weight in kgs (upper panel) relative to plasma renin activity and urinary aldosterone excretion (lower panel) before (left) and after (right of vertical line) cessation of furosemide in Patient 2. See text for details.

The patient was admitted to the Metabolic Ward and given an 1800 calorie diet, containing 80 mmol of sodium per day, which corresponded to her preadmission intake. She continued taking 320 mg of furosemide daily for 11 days (Fig. 2). During that time, her weight decreased by 1.3 kg to 50.7 kg, the plasma renin activity varied between 9.8 and 14.0 ng/ml/hour, and the 24-hour urinary aldosterone excretion ranged from 63 to 92 nmol. When she stopped taking the diuretic, she rapidly gained 6 kg in 10 days, and her weight rose to 56.9 kg. The weight gain was accompanied by a marked increase in leg edema and discomfort in her abdomen, legs, arms, and face; she also complained that her ring was too tight on her finger. The blood pressure remained at 90/60 mm Hg while she anxiously awaited the anticipated weight loss. At her heaviest weight, the plasma volume was 2.53 liters, the total blood volume was 3.68 liters, and the extracellular water was 16.8 liters. When the diuretic was discontinued, the plasma renin activity fell, at first precipitously and then slowly, to 0.20 ng/ml/hour. The urinary aldosterone excretion remained high for the first 10 days but suddenly fell to 6 to 8 nmol. The packed cell volume and total blood volume rose to 2.69 liters and 3.9 liters, respectively. Thirty days after the diuretic was discontinued, the exchangeable sodium was 2545 mmol, a 353 mmol increase from the time she was taking diuretics. The jugular venous pressure was unchanged.

Although she lost some weight during the 3 weeks following cessation of diuretics, her weight remained at more than 54.8 kg. Because her weight did not return to baseline, sodium intake was reduced to approximately 40 mmol/day. This reduction in dietary sodium resulted in a gradual loss of weight to 52 kg during the next month and a considerable reduction in ankle edema. On repeated follow-up visits as an outpatient, she reported that she was no longer thirsty, and that she had no postural dizziness, no nausea, and less tiredness. But she complained about having to follow a low-sodium diet. She managed to comply with it for approximately 6 months. Her edema disappeared and weight gain was only associated with premenstrual fluid retention. Her referring physician reported, however, that the patient had started taking diuretics again and that she refused to return to the hospital.

Discussion

Dr. Hugh E. de Wardener *(Professor of Medicine, Charing Cross Hospital Medical School, London, U.K.):* These two patients illustrate most of the factors associated with what is usually referred to as "idiopathic edema" [1, 2], that is, edema not

due to cardiac, renal, or hepatic disease or to another recognized cause. Both women were concerned about their weight. Both had begun taking diuretics some years before admission for reasons that are not clear. Both women found that if they tried to discontinue taking diuretics they rapidly put on weight and felt bloated, particularly around the abdomen. They then developed edema. The second patient, who had been taking more diuretics for a longer time, also experienced many of the complications of excessive diuretic therapy including thirst, polyuria, dizziness on standing, and intermittent nausea; she had had one symptomatic episode of hypokalemia. Both patients stated that they had been closely watching their weight by dieting. The first patient, a nurse, exemplifies the well-known association of idiopathic edema occurring in nursing and paramedical personnel [1, 2]. The second patient admitted that she ate little salt and carbohydrates during the week, but that she tended to have large meals accompanied by a generous supply of alcohol at weekends. In addition, the second patient was noncommittal and ambiguous when discussing her intake of diuretics; after she had been discharged from hospital, she admitted that from time to time she had misled both her own doctor and us about her continued use of diuretics. Neither patient showed any evidence of cardiac, renal, hepatic, allergic, hypoproteinemic, or obstructive venous, or lymphatic disease.

During the first few days after admission, when both patients were given their usual intake of diuretics, they both were hypokalemic. Their blood volumes were in the lower range of normal, and the second patient had a low total exchangeable potassium. These changes were accompanied by markedly high plasma renin activity and a lesser rise in urinary aldosterone excretion. When the diuretics were suddenly stopped, the first patient experienced a gain in weight, a fall in plasma renin activity, and a fall in urinary aldosterone excretion. In the first patient, aldosterone excretion fell to normal; in the second patient, it fell below normal. Yet only the first patient's weight returned to normal. The second patient's weight remained raised in spite of lower-than-normal plasma renin activity and urinary aldosterone excretion. In the second patient, although the plasma renin activity fell rapidly after the diuretics were discontinued, the urinary aldosterone activity first rose, and did not fall to normal until 8 days later. This paradoxical rise in urinary aldosterone excretion in the presence of decreasing plasma renin activity might have been due to the simultaneous correction of preexisting potassium deficiency, which is known to inhibit aldosterone secretion [3–6]. It is probable that after this patient had taken diuretics for 15 years, her adrenal glands were greatly enlarged and that a relatively minor correction of potassium deficiency could produce a large increase in urinary aldosterone secretion. This increase would delay and obscure the fall in aldosterone secretion, which should have accompanied the decrease in plasma renin activity. If this interpretation is correct, the potassium deficiency of diuretic therapy, which usually is present in patients with idiopathic edema, can be viewed as a negative feedback mechanism that diminishes aldosterone secretion and thus the extent of sodium retention and potassium loss from the diuretic-induced secondary aldosteronism.

One hypothesis suggests that "idiopathic edema" results from a reduced blood volume caused by a capillary leak of albumin [7–14]. The bulk of the evidence favoring this hypothesis is that idiopathic edema is associated with a reduced blood volume and raised plasma renin activity and aldosterone levels [7–14]. Associated findings, in keeping with a reduced blood volume, include a tendency toward sodium and water retention, especially when the patient stands [8, 12] or receives a large sodium load, and a variable inability to excrete a water load, again particularly on standing [12]. There is no doubt that patients with idiopathic edema show all the characteristics of chronic volume depletion [15]. But so far the work that has been published to support the view that the low blood volume is due to a leak of albumin from capillaries is confusing, and the claims made are unconvincing. A 1955 paper, often quoted in support of the capillary leak hypothesis, describes a nurse with persistent massive edema, proteinuria, and histologic evidence of cutaneous vasculitis [16]. The likely possibility of systemic lupus was not investigated. Another group of workers claimed that "the rate of loss of isotopically labeled albumin from the intravascular compartment was greater in patients with idiopathic edema than in control subjects" but, for ethical reasons, the control subjects were not given any isotopically labeled albumin [17]. Clearly these workers were in no position to decide whether the rate of loss of isotopically labeled albumin from the capillaries of their patients was abnormal. The only groups who have attempted to measure directly the permeability of capillaries to albumin in patients with idiopathic edema and in normal subjects are Lagrue et al [18] and Behar et al [19]. Isotopically

labeled albumin is injected intravenously and the forearm is then monitored for radioactivity before, during, and after venous occlusion. Radioactivity rises and falls rapidly, and failure of the radioactivity to return to baseline levels is considered an indication of increased permeability to albumin. The results are difficult to interpret. The most pronounced abnormalities were found in patients with cirrhosis who were grossly edematous, and in patients with edema associated with menstruation, but only when the patients were edematous. Prolonged retention of albumin in the forearm only occurred when the patients were edematous, and this abnormality rapidly disappeared as the edema resolved. Thus, it is not clear whether the prolonged retention of albumin in the extravascular compartment of the forearm was a consequence of the edema or its cause. In other words, the possibility that an increased volume of interstitial fluid can delay the removal of radioactive albumin from the interstitial space has not been eliminated.

We have proposed that the edema in most patients with "idiopathic edema" is caused by the use of a diuretic [20]. We have suggested that whatever the initial reason for starting diuretics, the continued use of the diuretic causes a persistent rise in plasma renin activity and secondary aldosteronism. Eventually the juxtaglomerular apparatus of such patients becomes enlarged (personal observations), and it is probable therefore that there is an associated increase in the size of the adrenal glands. A vicious cycle now ensues; irregularity in the dose of diuretics may cause a sharp fall in urinary sodium excretion, a gain in weight, and the rapid onset of the characteristically uncomfortable edema. The edema prompts a quick return to the use of diuretics, which in turn aggravates the secondary aldosteronism. Edema rarely is present while the patient is regularly taking diuretics, but we have come across one such patient, a 22-year-old nurse from another hospital, who was the first patient with this syndrome that we studied [21]. She had been taking 160 mg of furosemide for 18 months. Upon admission her legs were markedly edematous, and they remained moderately swollen until the diuretics were stopped. She then had a 3 kg weight gain over 5 days, following which she began to lose weight. Fig. 3 illustrates how precipitously her weight continued to fall until it leveled out at 4 kg less than her weight when she was taking diuretics. Although some workers deny having seen patients with diuretic-induced edema [22], most agree that the phenomenon does exist [23–26]. Nevertheless, many insist

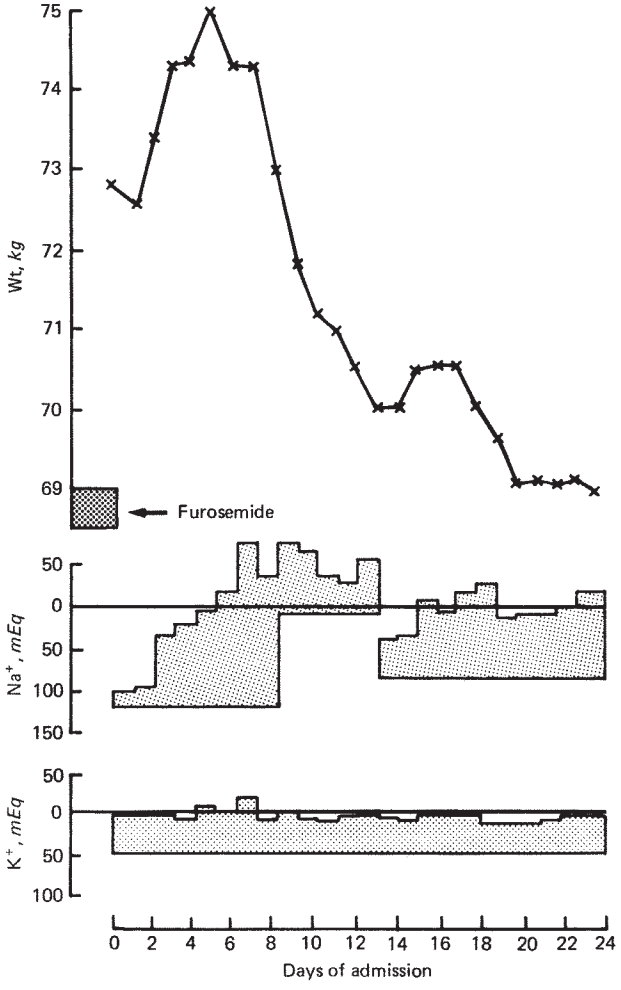

Fig. 3. Body weight in kgs (upper panel) relative to external sodium (middle panel) and potassium (lower panel) balances in a 22-year-old nurse with idiopathic edema. Note initial 3-kg weight gain after cessation of furosemide followed by a 6–7 kg weight loss. See text for details.

that in a few women the edema is primarily due to a capillary leak of albumin. But it is conceded that most, if not all, of these women also take diuretics, so that their chronic volume depletion has two causes and their initial problem is consistently magnified.

We have several reasons for proposing that in the patients examined the cause of idiopathic edema is the continued use of diuretics. As in other studies, all our patients have been women, many of them paramedical workers who have easy access to diuretics. All have had an obsession about their weight and appearance, which are well-known motives for taking diuretics. In addition, the first case report of idiopathic edema was described by Mach et al in 1955 [11], 3 years after the first oral diuretic was described [27]. Mach himself, however, re-

mains convinced that his early patients could not have had access to diuretics [25], because the drugs were still being tested at that time.

Some clinicians have proposed that idiopathic edema was described before 1955 [11], but close inspection of the relevant papers does not substantiate these proposals. For instance, it has been claimed that Jungermann in 1933 first described idiopathic edema [28], but the patient, a 28-year-old man with massive sodium and water retention, had clinical and radiologic evidence of a pituitary fossa tumor and visual field defects. This is a fascinating case, even more so now that increasing evidence suggests that natriuretic hormone probably originates from the hypothalamus [29–32]. But the patient cannot be described as having what is usually named idiopathic edema. There is one way in which Jungermann's patient and other patients suffering from "idiopathic edema" might be connected: On the one hand, the patient with the pituitary tumor might have developed salt and water retention because the tumor involved the floor of the third ventricle and thus impaired natriuretic hormone production. And it is possible, on the other hand, that some patients with "idiopathic edema" might have an impaired ability to secrete natriuretic hormone, and that this inability might be either a primary condition or might probably be due to prolonged ingestion of diuretics.

In many patients, their reason for starting to take diuretics sounds weak and trivial, as in the two patients described today. In other patients, large fluctuations in carbohydrate and salt intake initially might have caused transient increases in weight and symptomatic edema, which prompted the use of diuretics. Many patients confess that in attempting to control their weight they sometimes considerably vary the amount of food they consume, both before and after they start taking diuretics. For example, they might "starve" themselves for several days and then have a few large meals. It is well established that sudden increases in sodium and carbohydrate intake after periods of sodium deprivation combined with fasting can each cause retention of sodium and water. Prolonged low-sodium intake stimulates the renin-angiotensin-aldosterone system [33, 34], and the effects of this stimulation persist for some time after the sodium intake is raised suddenly. The sodium retention that follows a sudden increase in carbohydrate intake is well known and might be related to an associated rise in circulating catecholamines [35–38]. In preliminary experiments in normal women aged 20 to 26, we

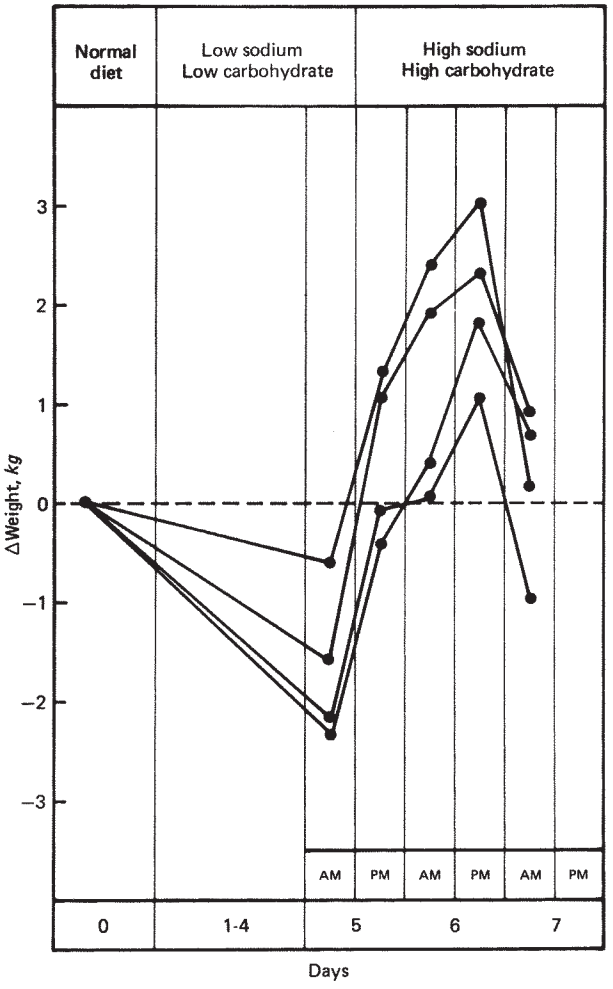

Fig. 4. Changes in weight in 4 normal young women upon changing from their normal diet to a low-sodium, low-carbohydrate diet, and then to a high-sodium, high-carbohydrate diet (from Ref. 20).

have studied the effect of suddenly changing from a low-sodium (10 mmol/day), low-carbohydrate (80 g/day) diet to a high-sodium (350 mmol/day), high-carbohydrate (350 g/day) diet. These sudden simultaneous changes in sodium and carbohydrate intake produced weight increases of up to 4.2 kg in 36 hours and induced edema (Fig. 4). As they gained weight, therefore, these women complained of the same symptoms as those described by patients who have idiopathic edema, in particular a general feeling of bloatedness and a characteristic tightness across the abdomen and ankles. It appears that the particularly characteristic clinical feature of idiopathic edema—the discomfort and the bloated feeling around the abdomen as the edema accumulates—is due to the rapidity with which salt and water are retained, and not to some peculiarity of

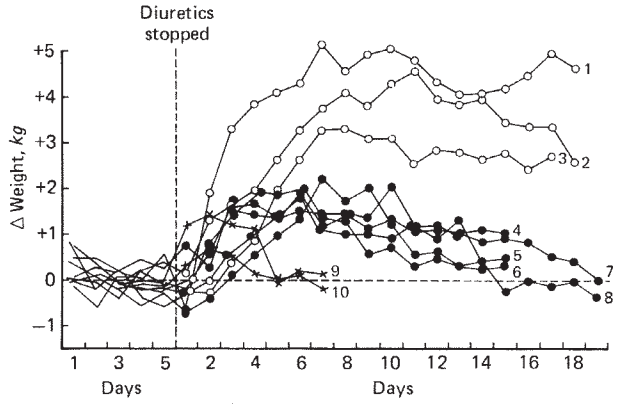

Fig. 5. Changes in weight during a control period and after stopping diuretics in 10 patients with idiopathic edema (from Ref. 20).
○: Patients 1–3 maintained their gain in weight
●: Patients 4–8 had a return of their weight towards normal within 20 days
x: Patients 9 and 10 had a return of their weight to normal within 5 days

the abdominal wall of those who suffer from idiopathic edema.

These observations in normal women suggest that the initial complaints in some patients might be due to fluctuations in sodium and carbohydrate intake caused by these patients' concern for their weight and appearance. Sudden gains in weight, with their attendant discomforts, make these women seek medical advice. The absence of any obvious cause for the edema and the patient's persistence eventually overcome the doctor's reluctance to prescribe diuretics. When the patient begins taking the diuretics, the renin-angiotensin-aldosterone system is persistently stimulated by both the diuretics and the fluctuations in sodium and carbohydrate intake. As a result, both the patient and the doctor believe that edema can only be prevented by the continuous use of diuretics.

Finally, perhaps the most compelling reason for suggesting that idiopathic edema is due to the continuous use of diuretics is the response of most patients when the diuretics are stopped. The weight and edema increase transiently, but within the next 2 to 3 weeks, the weight returns to baseline and the edema clears (Fig. 5). We now have studied in some detail 12 such patients, and 9 responded in this way. These 9 patients, whose weight returned to normal while they were in hospital, subsequently continued to eat their usual amount of sodium and have not needed diuretics to remain free of edema. In the other 3 patients, the weight rose substantially after the diuretics were discontinued, and 3 weeks later the weight was still substantially higher than it had been before the diuretics were stopped. Nevertheless, reduction of the sodium intake in these 3 patients to about 50 mEq/day has caused the edema to disappear in 2 patients. We allowed the sodium intake to increase gradually over the next year, and these 2 patients became able to tolerate a normal sodium intake without developing edema. The third patient, who is the second woman presented here, was not able to control her sodium and calorie intake. She continued taking diuretics, and now has intermittent edema, as before.

Some workers have claimed that in patients whose edema does not subside within a few weeks of discontinuation of diuretics, the edema must be due to some cause other than previous administration of diuretics [25]. This interesting point of view implies that the edema must be due to an excess permeability of the capillaries. The implication, however, is not compatible with the available evidence. First, if the sodium intake is gradually adjusted, some of these patients eventually can become free of edema and can then ingest a normal sodium diet without using diuretics. Second, the fluid retention in patients in whom the edema does not resolve after stopping the diuretics cannot possibly be due to the sequence described earlier—namely, increased capillary permeability, reduced blood volume, increased plasma renin activity and increased aldosterone secretion. Almost daily measurements of plasma renin activity and urinary aldosterone excretion have shown that 3 weeks after the diuretic had been discontinued, these 3 patients still were edematous and had increases in weight of 2 to 3 kg, their blood volumes were raised, and the plasma renin activity and urinary aldosterone excretion in the 2 patients in whom it was measured was *lower* than normal.

I am particularly interested in the 3 patients whose weight gain and edema persisted after the cessation of diuretics. The persistence of the edema and gain in weight despite a fall in both plasma renin activity and urinary aldosterone excretion to below normal levels demonstrate that in these 3 patients, sodium continued to be retained via some mechanism other than excess angiotensin and aldosterone. My hunch is that either the edema persisted because plasma concentrations of natriuretic hormone had not increased in the way they should have when the extracellular fluid volumes increased, or that the tubules' ability to respond to a rise in plasma natriuretic hormone concentration was impaired. I would suggest further that either one or both of these mechanisms are consequent upon the

prolonged state of volume depletion caused by the diuretics. This hypothesis is analogous to that invoked in compulsive water drinking, where a prolonged state of excess water ingestion leads to an impaired ability of the hypothalamus to secrete antidiuretic hormone (ADH) and to an impaired ability of the collecting duct to respond normally to the presence of ADH [39]. Favre and Mach have claimed that the concentration of natriuretic hormone in the urine in some patients with idiopathic edema is raised and that the abnormality that causes persistent edema, therefore, is an unresponsiveness of the kidney to the raised levels of natriuretic hormone [25]. Their paper implies that this unresponsiveness is unrelated to the previous administration of diuretics. But we have observed that the persistence of edema after the cessation of diuretics correlates best with the previous intake of diuretics; the 3 patients in our study in whom edema persisted had taken the largest quantities of diuretics. This observation is supported by the fact that these 3 patients had the highest plasma renin activity before the diuretics were discontinued. The suggestion that prolonged administration of diuretics somehow causes edema to persist is further supported by our success in treating 2 of these patients with a prolonged low-salt diet. This gradually allowed them to resume normal salt intake after 12 months.

The concept that the continuous use of diuretics can induce or perpetuate edema has interesting applications to the whole field of diuretic administration. Since finding this phenomenon in patients with so-called idiopathic edema, we have sought it in situations in which the diuretic has been given for the treatment of edema secondary to a known cause. I now have seen diuretic-induced edema in at least 3 patients who had a nephrotic syndrome. The administration of diuretics when the plasma albumin was low and when proteinuria was substantial diminished the edema and made the patient more comfortable. Follow-up examination during subsequent months revealed that although plasma albumin had risen to normal levels, edema returned each time the diuretic dosage was reduced. Unless one is adamant, therefore, such a patient is likely to continue taking diuretics long after the need for them has disappeared. Alternatively, the physician can explain the situation to the patient and reduce the diuretic over a few weeks while in addition temporarily reducing salt intake until the diuretics have been discontinued altogether. I have tried to detect diuretic-induced edema in patients in whom the diuretics had been started because of edema secondary to heart disease. The situation is less precise in such patients, for there is no marker similar to the plasma albumin that can indicate when diuretics are no longer necessary. If the diuretics are stopped too suddenly, there may be a recurrence of pulmonary edema whether or not the diuretics are still needed. But continuing to administer them needlessly can risk the other complications of diuretic therapy. Again, it is best to reduce diuretic dosage in steps while watching the patient's weight and jugular venous pressure.

Questions and answers

DR. JOHN T. HARRINGTON: Dr. de Wardener, as you know there has been a suggestion that idiopathic edema might be due to hypoalbuminemia. Gill and Bartter found that the average serum albumin was 3.3 g/dl in 14 patients with this condition, as compared to 3.8 g/dl in controls [40]. How do you account for their finding of relative hypoalbuminemia when, as far as I know, no one else including yourself has had the same experience?

PROF. DE WARDENER: As I mentioned, the plasma concentration of albumin in our patients was normal but did tend to fall after the diuretics were discontinued. It should be recalled, however, that Gill and Bartter were not studying quite the same thing as we were. They were making measurements in patients whom they thought had stopped taking diuretics. We studied patients while they were receiving diuretics and for about 3 weeks after they ceased taking them.

PROF. D. K. PETERS *(Hammersmith Hospital, London):* It also must be pointed out that about 70% of the albumin pool is extravascular. If the volume of that pool is increased for whatever reason, and the albumin synthesis rate does not increase, then inevitably there will be a reduction in the concentration of serum albumin. I am not sure whether the data of Gill and Bartter showed anything more than an increased extravascular albumin pool, which could be simply the consequence of an increased volume of that pool. In other words, the patients were edematous.

PROF. S. CAMERON *(Guy's Hospital, London):* Dr. de Wardener, you didn't mention the use of purgatives in your patients. I mention this specifically because potassium depletion, as occurred in a few of your patients, can result from laxative abuse and in turn can cause sodium chloride retention [41].

PROF. DE WARDENER: All patients were asked about laxative intake. None of the patients were

taking laxatives at the time of the study as far as we could determine by examining the stools and performing urine tests for phenolphthalein. Nevertheless, I suspect that laxatives can cause edema in a similar way to diuretics.

DR. N. JONES *(St. Thomas's Hospital, London):* Do you think all patients with this syndrome are diuretic abusers? You mention reasons for being suspicious about the allegation that the patient studied by Mach in 1955 did not take diuretics. But Streeten definitely states he was aware of 10 patients with idiopathic edema before diuretics were available in America [42]. Do you have any comments?

PROF. DE WARDENER: It is unfortunate that these 10 patients were never referred to before and that a full account of them was never published. It is possible that these women's weight changes and edema were due to violent fluctuations in sodium and carbohydrate intake. Diuretics are an important additional factor to such fluctuations in food intake, but diuretics might not be necessary causes in all patients.

DR. N. JONES: I think most of us are in a quandary over the certainty with which one can exclude diuretic ingestion by patients. You imply, and I think very reasonably, that those of us who think we have patients who have idiopathic edema with no known diuretic ingestion cannot be absolutely certain that they weren't taking diuretics for some trivial reason. That is a fair point. But is it not also fair to comment that your observations on the prolonged state of remission in patients discharged from hospital who are alleged to have stopped taking diuretics are open to the same objection?

PROF. DE WARDENER: The truth of the patient's statement that she is no longer taking diuretics can be tested by estimating the plasma renin activity. If it is normal, then she is probably not taking diuretics. Plasma renin activity was in the normal range in all our patients on follow-up examination, except in the second patient, in whom it was raised, and she had restarted taking diuretics.

PROF. R. D. COHEN *(The London Hospital, London):* I am very sympathetic with your ideas, Dr. de Wardener. I think most of them are probably right. Nevertheless, as the Devil's advocate, I would like to mention some difficulties. First, some of our patients with this condition are not medical or paramedical personnel and thus do not have easy access to diuretics. Second, why do some patients who take small doses of diuretics for hypertension not get this syndrome? Is it because of the frequency with which they take diuretics? Does diuretic ingestion have to be intermittent for the edema to appear? Finally, in your 3 patients who didn't lose their gain in weight, you have no plasma aldosterone measurements after 18 days. Perhaps plasma aldosterone increases again. Or it might be that after such a long period of secondary hyperaldosteronism, the sensitivity of the tubules to aldosterone or angiotensin is changed. Have you any comments?

PROF. DE WARDENER: Our daily measurements of aldosterone in the patient illustrated in Figure 2 continued up until 24 days. It is true that single measurements at weekly intervals thereafter show that the plasma aldosterone rose into the normal range. I would like to focus, however, on the hypoaldosteronism when the weight gain was the greatest and the patient was unequivocally edematous. I agree that a change might occur in the patient's sensitivity to aldosterone or angiotensin. If this were true, the persistence of the edema would have to be due to an increased sensitivity of the tubule to angiotensin or aldosterone. But it would be unusual that end-organ sensitivity to a hormone would increase as a result of a persistently high plasma concentration of that hormone. It is usually the other way round, as in the case of thyroxin and insulin.

DR. HARRINGTON: Why do you think that these patients are relatively hypotensive and that their blood pressure doesn't rise after the diuretics are stopped?

DR. G. MACGREGOR *(Charing Cross Hospital, London):* These patients are not hypotensive when supine but can have postural hypotension when given large doses of diuretics. When the diuretics are stopped, a widening of pulse pressure is associated with sodium retention but no consistent change in mean blood pressure; these changes probably occur because angiotensin II falls as sodium is retained.

PROF. CAMERON: Could I return to the unanswered question that Professor Cohen raised as to why the many patients who have mild hypertension and who are receiving diuretics do not develop this syndrome? I had always assumed, until I read your papers, that what we were seeing in women with idiopathic edema was an exaggeration of the normal response to posture. So simply by bringing them into hospital and lying them down—and of course, perhaps you would now say, depriving them of diuretics—would promote quite a good diuresis. Can we hear whether you think that salt-retaining

sex hormones are important in this? Why are they young women and not 70-year-olds?

PROF. DE WARDENER: To answer your last question first, I think young women are more concerned about their weight than are older women or men of any age. I think the most important reason that women begin taking diuretics is an exaggerated concern for their appearance and weight. I would agree that in these women, as in normal women, salt and water retention would be greater before each menstrual period, and I find it reasonable that two causes of sodium retention, diuretics and menstrual endocrine changes, might promote a severe exacerbation of edema. Our observations in normal women demonstrate that it is the speed with which the sodium and water are retained that causes so much discomfort. It is unusual for a patient with nephrotic syndrome to complain of a bloated abdomen, even when ascites and widespread subcutaneous edema of the abdominal wall are present. I wonder whether Dr. MacGregor would like to reply to the question about the use of diuretics in patients with hypertension.

DR. MACGREGOR: Older patients, particularly those with high blood pressure, have lower levels of plasma renin activity and angiotensin II initially, and in particular they have a less reactive renin-angiotensin response to diuretics and sodium loss. Also, patients receiving diuretics for high blood pressure tend to take them regularly; these patients have less fluctuation in sodium and carbohydrate intake, and they are less concerned about their body weight in contrast to women who complain of edema. Nevertheless, we have treated several patients with high blood pressure who have developed abdominal bloating and in some cases edema within a few days after their diuretics have been stopped.

DR. JONES: Might the reason why hypertensive patients treated with diuretics in conventional doses do not become edematous be related to the exaggerated natriuresis of the hypertensive state?

DR. DE WARDENER: I believe that the term exaggerated natriuresis is misleading; I think it is a nearer approximation to call the phenomenon an accelerated natriuresis. It must be stressed that it follows the sudden administration of a sodium load. I don't think there is any doubt that the phenomenon is related to a state of continuously corrected volume expansion as occurs after the administration of aldosterone or DOCA.

DR. JONES: Might I also say that Professor de Wardener and his colleagues are convincing me of the importance of diuretics in the perpetuation of edema. But I certainly am not convinced that every patient labeled as having idiopathic edema has abused diuretics, nor am I convinced that we are talking about one syndrome. I would be interested in knowing whether other researchers have found women who have features that I think would justify the label of idiopathic edema but who completely fail to respond normally to the daily administration of 9-α-fluorohydrocortisone. That is, instead of having only a small transient weight gain, these women, when given 9-α-fluorohydrocortisone, have a very large gain in weight. In other words, they do not appear to escape from the effect of the mineralocorticoid. Of the 16 patients with idiopathic edema that I have studied in this way, 7 did not escape. The pattern of their response was particularly interesting: they all developed pulmonary edema with an elevated jugular venous pressure and had a square-wave Valsalva response. We therefore had to stop giving them 9-α-fluorohydrocortisone. But 5 days before they developed pulmonary edema and 5 days later (after 9-α-fluorohydrocortisone had been stopped), the jugular venous pressure and the Valsalva response were normal. These 7 patients seemed to distribute the retained fluid in a fashion different from those who escape completely.

PROF. DE WARDENER: I think that your observations in those 7 patients are consistent with our findings in the 3 patients who had the greatest weight gain and in whom the gain was maintained after the diuretics were stopped. These patients also had an impaired ability to excrete a sodium load and thus developed edema. Our 3 patients were unable to excrete a sodium load that initially was caused by the raised aldosterone and angiotensin levels but which continued after the concentrations of these hormones had diminished to below normal. In your 7 patients, the salt and water retention was due to persistent administration of a salt-retaining steroid. The abnormality is that the patients continued to gain weight whereas they should have been able to cease retaining salt and water and unload most of what they had retained. I maintain that in both groups the mechanism responsible for disposing of a sodium load is impaired and that this impairment is probably due to the previous administration of diuretics.

DR. JONES: I suspect that there is some abnormality other than a simple impairment in the patients' ability to excrete a sodium load. These women developed pulmonary edema even though they gained less weight than did the normal controls; the controls escaped from 9-α-fluorohydrocortisone af-

ter gaining approximately 2.5 to 3 kg. That raises the question of whether they have a cardiac abnormality, but I have monitored 4 of these women for more than 8 years and they have shown no evidence of cardiac disease.

PROF. COHEN: Dr. Jones, your findings also raise the question of whether some patients with idiopathic edema have peripheral vasoconstriction, so that an increase in blood volume increases their central blood volume more than it does in a normal person. An acidotic patient does precisely this. The blood volume moves from the periphery to the center, and an infusion of relatively small amounts of saline can precipitate pulmonary edema.

DR. HARRINGTON: The best studies demonstrating that acidemia fosters the development of pulmonary edema during the administration of sodium chloride were performed in patients with cholera [43, 44]. Patients with equivalent acidemia from other causes do not appear to exhibit this tendency. I must say that I have never understood why patients with cholera behave differently. But I do not believe that the pulmonary congestion results from acidemia per se. Are patients with idiopathic edema more likely to develop severe edema of pregnancy, as happened in one of the patients presented today? Or are women who have had prominent physiologic edema of pregnancy more likely to arrive at your clinic later with so-called idiopathic edema?

PROF. DE WARDENER: We have not looked into this question, and I do not remember anyone else investigating it.

DR. B. FOWLER *(Charing Cross Hospital, London):* I don't know how many patients with idiopathic edema are examined in most outpatient clinics, but I personally see about one per week. Such patients generally are obese, and to eliminate the possibility of hypothyroidism I routinely obtain antithyroid antibodies and thyroid function tests including TSH levels. In patients with borderline values, the diagnosis of hypothyroidism might require the performance of a thyroid-releasing hormone stimulation test. About once a month I treat a patient who has an apparently classic case of idiopathic edema and who completely responds to thyroxin. I see these patients every 6 months and they remain well.

DR. HARRINGTON: Professor de Wardener, you alluded to the possible role of natriuretic hormone in patients with idiopathic edema. Has anyone attempted to measure this hormone in patients with idiopathic edema?

PROF. DE WARDENER: The only reference I know is a recent paper by Favre and Mach in which they claim that there was an increased amount of natriuretic hormone in the urine of some patients who had idiopathic edema [25].

DR. J. WHITWORTH *(The Royal Melbourne Hospital, Melbourne, Australia):* If the sodium-retaining effect of angiotensin II is important in these patients, what happens when either converting enzyme inhibitor or angiotensin antagonists are given?

DR. MACGREGOR: Propranolol has been advocated in idiopathic edema on the rationale that it inhibits renin release, but I am unaware of any published work showing a definite effect. We have not investigated the effect of Captopril® in these patients, but we would expect to see fairly profound decreases in blood pressure if this agent were used in conjunction with a diuretic. We have given Captopril® by itself to normal volunteers ingesting a normal diet and have observed a loss of approximately 150 mEq of sodium in each. Thus, the drug might be effective in patients with diuretic-induced edema as claimed in a single case report of idiopathic edema [45].

DR. P. WISE *(Charing Cross Hospital, London):* Professor de Wardener, your theory that idiopathic edema is purely or largely a diuretic-induced disorder seems primarily to rest on the observation that patients with this condition finally return to their previous weight after diuretics are suspended. You suggest that then their ability to handle sodium is normal. Is it not necessary to prove that carbohydrate and sodium intakes were in fact the same at that point as they were before the diuretics were stopped? Without such evidence, how do you know that recovery in these patients was not due to their now ingesting a low-carbohydrate, low-sodium diet? Rather than simply stopping the diuretics, you actually would have done something else: you would have educated the patients in new dietary habits.

PROF. DE WARDENER: That might be true after these patients leave the Metabolic Ward, but it certainly does not explain why their weight returns to normal during their stay in the ward. In the Metabolic Ward, the patients follow the same diet, as nearly as we can determine, as that which they ate before coming into hospital, and they have the same diet every day.

DR. WISE: No, I mean before they even reached you. I am inclined to believe that this disorder is a combination of a variety of underlying factors. It could be myxedema, as suggested by Dr. Fowler

earlier. It could be diabetes and diabetic vascular disease, or it could be a number of other things including large fluctuations in carbohydrate and sodium ingestion. I fully believe that you do the right thing therapeutically by stopping their diuretic abuse. But I also believe that, either consciously or unconsciously, you might be advising them about their dietary habits and that a change in diet is what corrects the problem in the patients whose weight returns to normal. Perhaps the reason that 3 of your patients maintain a higher weight is that they did not change their dietary habits.

PROF. DE WARDENER: I want to emphasize that on the Metabolic Ward this explanation cannot be true. Let me review the course of the 3 patients who had the maximum weight gains and whose weight remained raised in the hospital. Over the course of the following year, 2 of them eventually became free of edema while having a normal sodium intake. This was achieved by reducing the sodium intake and then gradually increasing it back to normal. At the end of a year, the patients were given a normal sodium intake without the use of diuretics and they did not develop edema. I agree that during that year we did not control their carbohydrate intake.

PROF. PETERS: Do you know of any studies in patients who have been cured of this disorder? For example, what is their capacity to excrete a sodium load? How do they respond to diuretics?

PROF. DE WARDENER: That is a very good point. Those studies have not been done. We easily could study the 2 patients whose weight did not return to normal within the 3 weeks after the diuretics were stopped, but who were cured one year later.

DR. JOHN DONOHOE *(Consultant Nephrologist, Mater Misericordiae Hospital, Dublin, Ireland):* What is the long-term prognosis for patients with idiopathic edema? Do they do well? Do they do poorly?

PROF. DE WARDENER: You are asking for information about the natural history of this condition. There is none. I get the impression that most patients drift on a tide of discontent from one doctor to the next. One does not encounter patients over the age of 60 who have idiopathic edema.

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