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I D I O P A T H I C O E D E M A

by

OWEN M. EDWARDS, M.B., B.S., M.R.C.P., M.A.,

DEPARTMENT OF INVESTIGATIVE MEDICINE,
ADDENBROOKE'S HOSPITAL,
UNIVERSITY OF CAMBRIDGE.

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INTRODUCTION

OUTLINE OF THE STUDY

The condition of idiopathic oedema has been poorly recognised in the United Kingdom, whilst well recognised and studied in the U.S.A. and European countries. The occurrence of the condition is almost always confined to women and its diagnosis has usually rested on the exclusion of known causes of oedema, the presence of secondary hyperaldosteronism, and a diurnal weight gain in excess of 1.4 Kg. (Thorn, 1968). The cardinal feature of the condition is the association of excessive diurnal weight gain and peripheral oedema, with the upright position.

In this thesis, the effect of change in position from the supine to the erect was studied, under the experimental conditions of a forced water diuresis, on urinary flow and composition in normal female subjects during the follicular and luteal phases of the menstrual cycle and in pre- and post-menopausal patients with idiopathic oedema. The intra-renal site(s) for the postural fall in urinary flow and composition were identified. No previous study has, to my knowledge, been made on the orthostatic fall in urinary flow and composition in the follicular and luteal phases of both normal subjects and patients with idiopathic oedema. Moreover, no study has compared the orthostatic fall in urinary flow and composition between pre- and post-menopausal patients with idiopathic oedema.

The orthostatic fall in plasma volume, as measured by the change in the packed cell volume and/or the concentration of ^{125}I labelled serum albumin, was studied in both normal subjects and patients with idiopathic oedema. The rate of

loss of ^{125}I labelled albumin from the intra-vascular space in both the supine and erect positions was determined in patients with idiopathic oedema. Correlations between the orthostatic fall in blood volume and the fall in urinary flow and composition were found in normal subjects, patients with idiopathic oedema and in the combined group. The implications of these findings were discussed.

The effect of the administration of a mineralocorticoid, 9α fluorohydrocortisone, to patients with idiopathic oedema was studied.

Conclusions as to the probable pathogenesis of the condition were made and the outline of the future lines of investigation were indicated.

DEFINITION

Idiopathic oedema is a syndrome characterised by intermittent or periodic irregular bursts of generalised oedema; by a diurnal weight gain caused by fluid retention in excess of 3 lb. (1.4 kg.) - this is a cardinal feature of the condition; and sometimes by abdominal distension. The syndrome is confined almost exclusively to adult females who have no cardiac, renal, nutritional, hepatic, hypo-proteinaemic, allergic, obstructive or lymphatic disease.

The oedema may occur at any time in the menstrual cycle,or during phases of secondary amenorrhoea, or after removal of the ovaries, and it may persist after the menopause. Pre-existing disorders may be aggravated during an episode of idiopathic oedema, and prolonged diuretic therapy, or less commonly purgation, may induce additional iatrogenic physical and/or biochemical abnormalities.

SYMPTOMATOLOGY

The syndrome of idiopathic oedema has been described under various names: cyclical idiopathic oedema (Clarkson, Thompson, Horwith & Luckey, 1960; Mach, 1970), periodic swelling (Streeten & Speller, 1966), periodic spontaneous oedema (Mach, 1970). These terms emphasise the dominant characteristic of the syndrome; spontaneous attacks of generalised swelling. The symptoms obtained during an attack are identical to those found in the pre-menstrual tension syndrome, which may indeed co-exist. (Dalton, 1968; Sutherland & Stewart, 1965).

The pre-eminent symptom is described by the patient as "puffiness" and is due to non-pitting oedema of the face, trunk and upper limbs, with pitting oedema of the lower limbs. The patient feels a puffiness of the eyelids on waking in the morning; her fingers and face are stiff and bloated; her rings are tight. There is a sense of fullness and discomfort of the breasts and abdomen, which necessitates the wearing of loose garments; indeed, some patients acquire two sizes of brassieres and girdle - the smaller when oedema-free and the larger when the fluid retention is marked. The symptoms worsen as the day progresses, particularly if the patient remains upright and in a warm environment. By the evening, the fluid retention and puffiness of the upper part of the body has subsided, to be replaced by obvious oedema of the ankles and feet. In Fig. 1 it can be seen how the volume of the leg, after as little as four hours standing, increases far more in patients with idiopathic oedema than it does in normal subjects. During the day, the patient

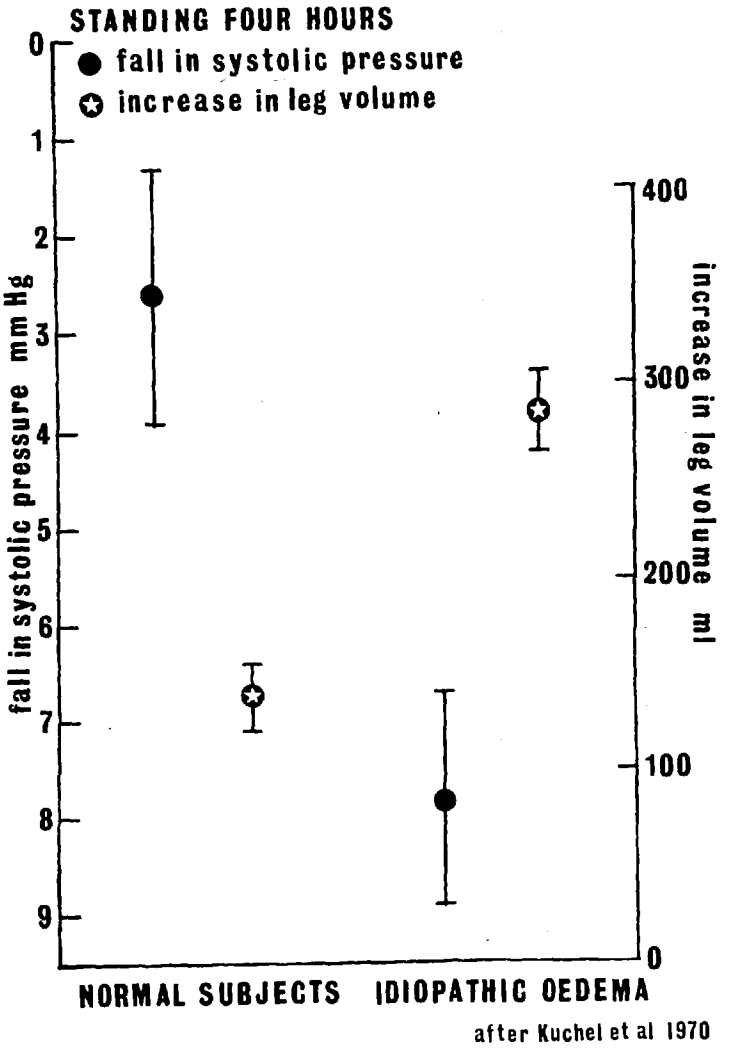


FIG. 1: The comparison between the fall in systolic pressure and the increase in leg volume in normal female subjects and patients with idiopathic oedema.

becomes oliguric, passing small quantities of concentrated urine. Overnight, the patient has a diuresis and may, as did one of my patients, "fill two buckets with pale, dilute urine." Occasionally, during a severe attack, the patient may develop breathlessness on exertion or, as the patient described by Clarkson and his colleagues (1960), die in hypovolaemic schock. The attack may be accompanied by the onset of, or the worsening of, headaches, irritability, depression and an intense feeling of lassitude and tiredness.

The patient may also develop the feelings of faintness in the upright position, symptoms due to postural hypotension. In Fig. 1 the increased fall in the systolic blood pressure on standing is well shown. The postural hypotension may be accentuated by the hypovolaemia caused by concomitant diuretic therapy.

FLUCTUATIONS IN DAILY WEIGHT

The extent of the fluid retention is best determined by weighing the patient accurately in the morning and again at night. The diurnal weight gain is both the key to the confirmation of the diagnosis and the means for the monitoring of therapy. Few normal women gain in excess of 3 lb. (1.4 kg.) during the day, and the definition of idiopathic oedema requires the diurnal retention of fluid during an attack to be in excess of this figure. (Thorn, 1968).

The pattern of the weight gain has two major components. The diurnal weight gain may be in excess of 3 lb., but if the excess fluid is diuresed at night, then the basal morning weight remains unchanged. The diurnal weight gain increases in response to increased environmental temperature, particularly if the patient remains active and upright. If, however, a nocturnal diuresis does not occur, then a pattern of gradually increasing basal morning weights with superimposed diurnal fluctuations is established. In Fig. 2, we see the diurnal weight chart of a pre-menopausal patient with idiopathic oedema, showing that the excessive weight gain is unrelated to the menses. In Fig. 3, we see the diurnal weight chart of a post-menopausal patient, showing both the gradual increase in the basal morning weight, together with the increased diurnal weight gain.

The association of the excessive diurnal weight gain with the upright position, increased physical activity and environmental temperature provides the key to the aetiology of the condition, but also makes it difficult to study under hospital conditions.

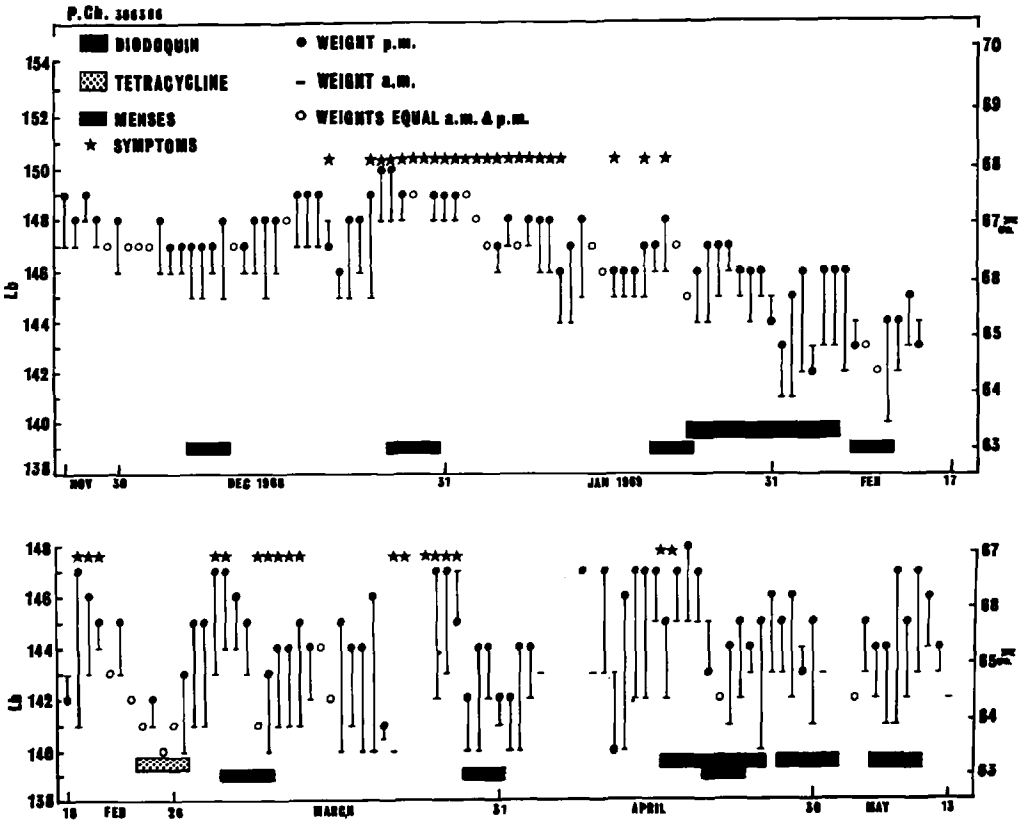


FIG. 2: The diurnal weight chart of a pre-menopausal patient with idiopathic oedema. (Patient No. 7).

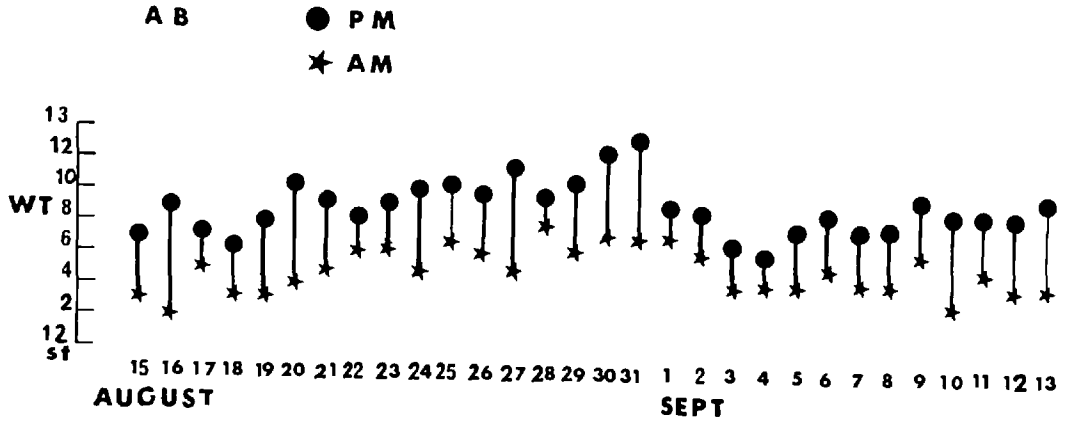


FIG. 3: The diurnal weight chart of a post-menopausal patient with idiopathic oedema showing the gradual rise in the basal morning weight and the excessive diurnal weight gain. (Patient No. 9).

FACTORS INFLUENCING THE DEVELOPMENT OF IDIOPATHIC OEDEMA

Environmental temperature

The geographical distribution of the disease is unknown because, although most of the cases described have been from the United States, this may reflect the fact that the disease has been poorly recognised in the United Kingdom. It is interesting to note the observation of Streeten (1960) that, in a patient with idiopathic oedema, the evening weight was positively correlated with the environmental temperature, Figs. 4 & 5. Further observations on the association between increased diurnal weight gain and increased environmental temperature will be made later. The correlation of the evening weights with house temperature in the same patient were highly significant, Fig. 5. This corresponds with one of my patients, a young missionary, who developed idiopathic oedema whilst nursing in India, but who remained symptom free on return to the United Kingdom. In general, one would expect an increased incidence of the disease in warmer climates and during the summer months, a point of considerable therapeutic importance.

Age incidence

This condition has never been described before the menarche and rarely presents after the menopause, although it may continue after the menopause, whether natural or induced. A few cases have been described as having presented at puberty (Lagrue, Weil, Ménard & Milliez, 1971), but the majority present in the third and fourth decades, Table 1.

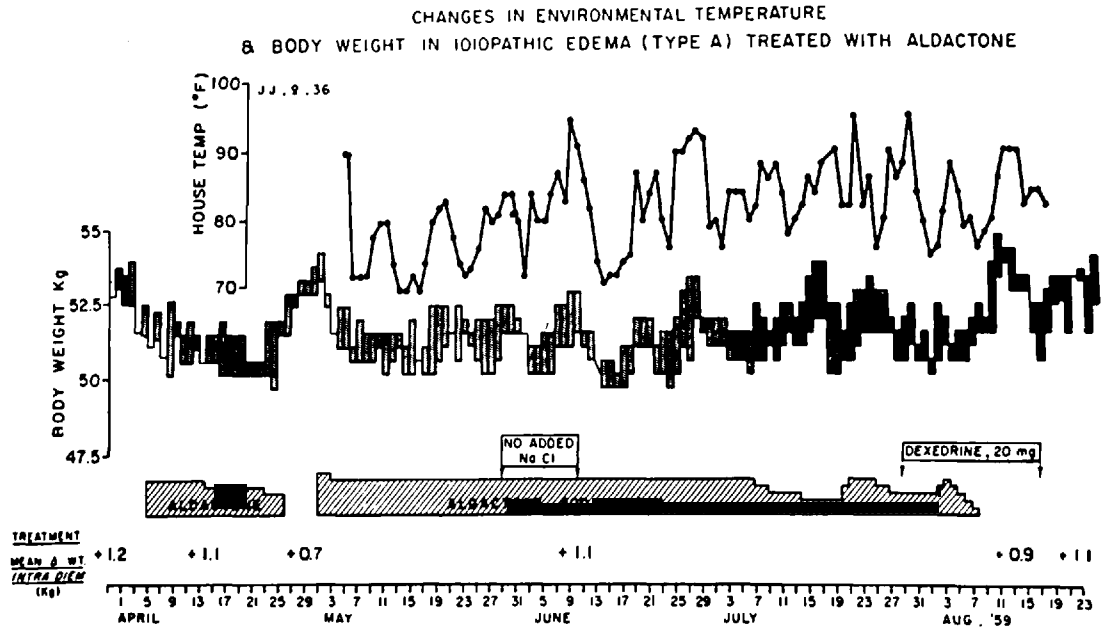


FIG. 4: Changes in environmental temperature (upper line) and body weight in morning (lower borders of rectangles) and in evening (upper borders of rectangles) in same patient before, during and after treatment with aldactone. (Streeten, 1960).

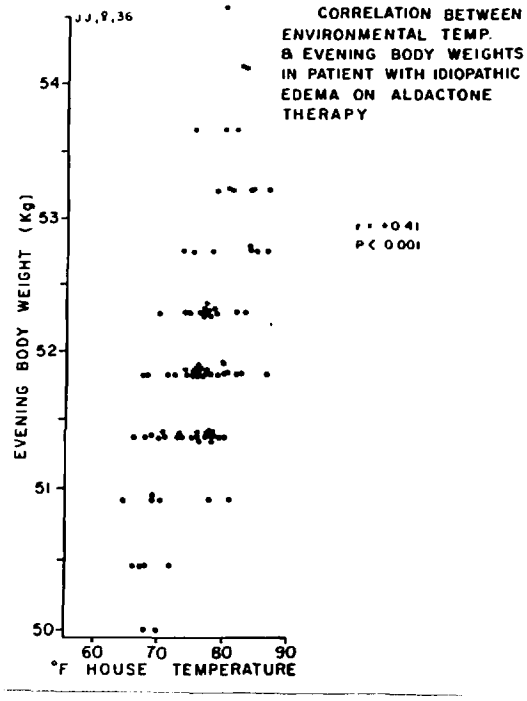


FIG. 5: Correlation of evening body weights with mean daily house temperatures. (Streeten, 1960).

The condition may persist into the sixth decade, Table 1. In several studies, the condition has persisted following bilateral cophorectomy (Clarkson et al, 1960; Sims, Mackay & Shirai, 1965; Lagrue et al, 1971).

In a series in which I collaborated, the majority presented in the third and fourth decade, but a few presented after the menopause, Fig. 6.

TABLE 1: The age of onset and the duration of symptoms before diagnosis of patients with idiopathic oedema in the published series.

Number in the series	Age at onset	Duration of symptoms	Source
1	36	5½ months	Emerson & Armstrong (1955)
1	32	2 years	Clarkson et al (1960)
1	18	20 years	Greenhough et al (1962)
13	14-52	-	Streeten & Speller (1965)
2	51 25	- -	Werning et al (1969)
25	26-48	-	Kuchel et al (1970)
16	4 between 10-20 2 between 20-30 7 between 30-40 3 between 40-50	- - - -	Lagrue et al (1971)
14	23-58	-	Gill et al (1972)
31	3 between 10-20 5 between 20-30 10 between 30-40 6 between 40-50 7 between 50-60	- - - - -	Streeten et al (1973)

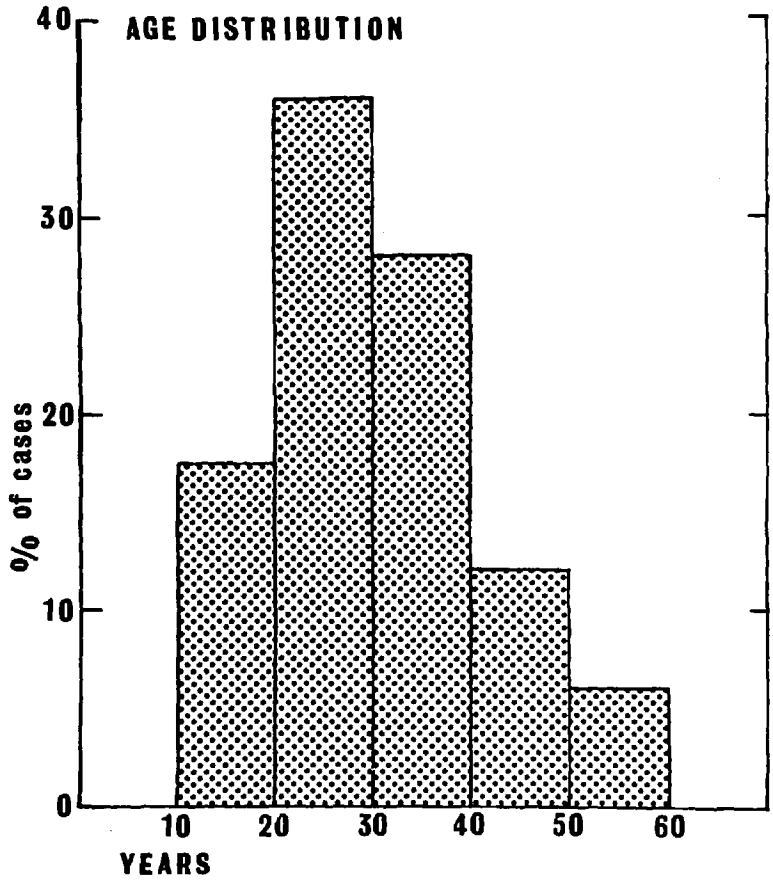


FIG. 6: The age incidence of 54 patients with idiopathic oedema. (Bayliss, Croonian Lecture, 1974. Unpublished Observations).

OTHER FEATURES OF IDIOPATHIC OEDEMA

Although the main complaints of the vast majority of patients are related to the fluid retention, other problems may arise, which become a matter of increasing concern and anxiety.

Postural hypotension

In some cases the upright posture, whilst being associated with increasing fluid retention and leg oedema, is accompanied by a greater than normal fall in blood pressure. This postural hypotension may be accompanied by tiredness, lethargy and, in some cases, syncope, Fig. 1.

Pulmonary venous congestion and anarsarca

In some cases the oedema may be so marked as to cause anarsarca, and the famous case of Clarkson and his colleagues (1968) had several episodes of pulmonary venous congestion and oedema.

Constipation

Constipation is common in patients during a phase of idiopathic oedema and may be due to the hypovolaemia with increased compensatory reabsorption of water by the colon.

Psychological attitudes

The condition of idiopathic oedema has, until recently, been poorly described, and physicians have developed

remarkably little awareness of this common syndrome, a situation which recalls the fact that the pre-menstrual tension syndrome, which affects 40% of women (Sutherland & Stewart, 1965) was not described until 1931 (Frank, 1931). Patients with idiopathic oedema have often described their symptoms to uninterested and disbelieving physicians (Lagrue et al, 1971).

McKendry, Maclaren & Bloom (1966) found a prominent feature of the condition to be an underlying neurotic temperament. The important questions are whether the possession of a neurotic temperament renders the subject more liable to attacks of oedema,or whether recurrent attacks of oedema provoke the neurotic traits, and finally, whether both have a common cause. In order to define personality characteristics, McKendry et al (1966) carried out psychological tests on fourteen patients with idiopathic oedema.

The following statements were thought to be the most descriptive: immature, demanding and egocentric with exaggerated need for affection and sympathy; tendency to a hysteroid nature with secondary gain from the symptoms; unduly occupied about health, home and family and financial security in that order; the pre-occupation with bodily functions being associated with multiple chronic complaints and fixed notions as to their organic basis; tendency to over-control needs and impulses with inability to express emotions in a modulated adaptive way; over-react to threats or make emergency responses in the absence of real danger; reasonably capable of appropriate social behaviour and able to get along with others when they so desire; minimal schizoid or psychopathic features.

Lagrue et al (1971) noted that the incidence of psychiatric disturbance was high and associated with their obsession with their weight was a refusal of therapeutic advice.

The attacks of oedema are often related to stressful situations which ranged in my series from quarrels with a jealous older husband, to worry about a paraplegic younger brother. The incidence of marital disharmony in my series was high, confirming the observations of McKendry et al (1966), who found the incidence of divorce in his series to be 15%, as opposed to the national average in Canada of 0.5%.

Whilst the physician should attempt to gain the confidence of the patient by showing an interest in their history, and above all by regarding their symptoms as genuine (Thorn, 1968), psychotherapy is usually ineffective in preventing further attacks of oedema (Lagrue et al, 1971).

Iatrogenic complications

Treatment of idiopathic oedema may lead to a number of iatrogenic complications.

Hypokalaemia, hypomagnesaemia, hyperuricaemia are common as a result of diuretic therapy. The patient may progress from thiazide diuretics to frusemide or ethacrynic acid. The consequent hypokalaemia, hypomagnesaemia and hypovolaemia accentuate the patient's postural hypotension, weakness, lethargy and irritability (Thorn, 1968; Lagrue et al, 1971).

An iatrogenic complication which has mainly been described in the French literature is chronic interstitial nephritis, caused by analgesic abuse. (Lagrue et al, 1971).

Associated disorders

Certain associated disorders may aggravate the disease. Obesity has been cited as an associated disorder by both Thorn (1968) and Sims et al (1965). In the series of Sims et al (1965), six of his eleven patients were obese (defined as 15% above their ideal body weight).

Thorn (1968) also suggested idiosyncrasies to food or medications may provoke an attack of idiopathic oedema, or aggravate pre-existing oedema.

Gynaecological disorders are said to be particularly common associated disorders. Lagrue et al (1971) found that, of their sixteen cases, four had had a hysterectomy or ovarian irradiation in an attempt to modify the disease process, two patients had menorrhagia, two patients had ovarian cysts and one patient had the polycystic ovary syndrome.

AETIOLOGY

In seeking to find an aetiological and pathophysiological explanation for the oedema in these patients, the following features have to be taken into consideration - features derived from the clinical presentation and simple clinical investigations.

(i) The almost invariable association with the female sex.

(ii) Its absence before the menarche and its occasional persistence beyond the menopause, whether natural or induced.

(iii) The unpredictability of the attacks and the generalised nature of the features of facial puffiness, breast tenderness, abdominal distension and ankle oedema.

(iv) The excessive diurnal weight gain and its exacerbation by standing and amelioration by lying.

(v) The exacerbation of the excessive diurnal weight gain by increased environmental temperature.

(vi) The association of the condition with an underlying neurotic temperament.

EXCESSIVE RELEASE OF ALDOSTERONE IN IDIOPATHIC OEDEMA

Aldosterone, a potent mineralocorticoid, is secreted from the zone glomerulosa of the adrenal cortex in response to a variety of stimuli, and acts on at least two sites, and possibly a third, in the renal tubule. In the distal convoluted tubule, there is a direct exchange of sodium ions for potassium or hydrogen ions (Berliner, 1952); in the ascending loop of Henle, sodium is reabsorbed without such exchange (Morel & Guinnebault, 1961). Further evidence shows a possible action of the proximal convoluted tubule (Nicholson, 1957; Wiederholt, Stolte & Hierholtzer, 1966). Aldosterone is important in the maintenance of extra-cellular fluid sodium concentration and content and, in its absence, the extra-cellular fluid volume decreases rapidly. (Prunty, McSwiney, Mills & Smith, 1954).

The problem of the control of aldosterone secretion is very much complicated by the fact that there is no reason to suppose that changes in aldosterone secretion in response to different stimuli are controlled by the same mechanism. For example, aldosterone secretion may be stimulated or inhibited by alterations in sodium concentration (Blair-West, Coghlan, Denton, Goding, Munro & Wright, 1963; Peterson, 1959), in potassium concentration (Cannon, Ames & Laragh, 1966), in body fluid volume (Bartter, Mills, Biglieri & Delea, 1959), or in blood volume (Bartter et al, 1959). However renin and angiotensin have an important function in the regulation of sodium excretion by the control of aldosterone secretion,

and are stimulated by alterations in plasma volume and extracellular fluid volume (Kelsch, Light, Lucino & Oliver, 1971). Considerable evidence indicates an important role for the sympathetic nervous system in the regulation of renin release (Gordon, Küchel, Liddle & Island, 1967).

Diseases in which the aldosterone secretion rates are elevated, when measured under standard conditions of sodium intake and posture, have been divided into two main groups; primary and secondary hyperaldosteronism. In primary hyperaldosteronism, the over-production of aldosterone by the adrenal is usually independent of factors which normally influence the rate of secretion (Biglieri & Forsham, 1961), although it does not have the autonomy that other adrenal tumours may have (Conn, 1964). In secondary hyperaldosteronism, the elevated aldosterone secretion rate is due to the action of acute or chronic pathogenic factors on the controlling mechanisms. A number of causes of secondary hyperaldosteronism are associated with the presence of oedema, namely congestive cardiac failure (Luetscher & Johnston, 1954; Luetscher, Neher & Wettstein, 1956), nephrotic syndrome (Luetscher et al, 1954) and cirrhosis of the liver with ascites (Dyrenfurth, Stacey, Beck & Venning, 1957). A considerable number of investigators have found increased secretion or excretion of aldosterone in patients with idiopathic oedema (Mach, Fabre, Muller & Neher, 1955; Luetscher & Liebermann, 1957; Mach, 1958, Ross, Crabbe, Renold, Emerson & Thorn, 1958; Hill, Hood, Farmer & Burnum, 1960; Streeten & Conn, 1960; Laragh, 1962; Góth & Pollák, 1963; Luetscher

Camargo, Cohn, Dowdy & Callaghan, 1963; Streeten & Speller, 1966; Veyrat, Robert & Mach, 1968; Werning, Baumann, Gysling, Stiel, Vetter, Wiedmann & Siegenthaler, 1969; Kuchel, Horky, Gregorova, Marek, Kopecka & Kobilkova, 1970; Gill, Waldmann & Bartter, 1972; Streeten, Dalakos, Souma, Fellerman, Clift, Schletter, Stevenson & Speller, 1973). Whilst an increase in aldosterone secretion is one of the few objective signs of this condition, Luetscher et al (1963) was able to demonstrate, in addition, an increased secretion of desoxycorticosterone.

Mach et al (1955) believed the condition to be one of primary hyperaldosteronism, but their evidence is equally consistent with the interpretation that the hyperaldosteronism is secondary to events outside the adrenal cortex. That the elevated secretion of aldosterone is secondary, rather than primary, is shown by the brisk increase in both plasma renin activity and aldosterone secretion in response to changes in posture from the supine to the upright (Kuchel et al, 1970) and that a saline infusion or acute expansion of the intravascular space by an intravenous infusion of dextran will lower plasma renin activity and aldosterone secretion (Veyrat et al, 1968).

The altered regulation of aldosterone is confirmed by the observation that, in idiopathic oedema, an increased aldosterone response is given to a normal renin release (Conn, Rovner & Cohen, 1965). The mechanism of the increased responsiveness of aldosterone to renin is unknown, although

this presumably reflects hyperplasia of the zona glomerulosa allowing a greater aldosterone response to the normal renin release. Altered angiotensin regulation is suggested by the finding of Horky & Kuchel (1967) that there was an increased responsiveness to the pressor effect of angiotensin with concomitant degranulation of the juxtaglomerular cells in patients with idiopathic oedema.

Mach et al (1955), as discussed earlier, believed the condition to be one of primary hyperaldosteronism. This hypothesis led for a short while to a vogue for total or partial adrenalectomy for the condition; surgical exposure of the glands revealing normal, hyperplastic or adenomatous glands (Ross et al, 1958; Streeten & Conn, 1960; Streeten et al, 1973). Streeten et al, (1973) studied two such patients, who had had partial adrenalectomies for idiopathic oedema and severe hyperaldosteronism. Aldosterone secretion was either normal or undetectable in these patients, and they had both experienced considerable amelioration of the severity of their oedema in the eleven and three years since the respective adrenalectomies. The history of both patients was supported by the very mild oedema which both patients manifested during the studies and by the entirely normal cumulative weight changes in the upright posture. However, no mention was made in this report of the diurnal weight gain, which is an important feature of the condition. The apparently central role of hyperaldosteronism in idiopathic oedema has led to the enthusiastic use of aldosterone antagonists, indeed one would expect that the exhibition of such

drugs should prevent or considerably ameliorate the condition. Streeten (1960), in a stu dy on fifty patients with idiopathic oedema, observed a precipitous fall in weight with loss of oedema and a corresponding increase in sodium excretion when these patients were given 500 mg. daily of spironolactone. The fall in weight continued only as long as the spironolactone was administered. Sodium restriction and the administration of chlorothiazide were also effective in many patients, but most became refractory on this regime. Gill, Cox, Delea & Bartter (1971) showed that the administration of 200 mg. of spironolactone for six days to a group of normal subjects and patients with idiopathic oedema consistently induced a greater natriuresis in the abnormal group. This observation has also been noted by Luetscher, Dowdy, Arnstein, Lucas & Murray (1964); Veyrat et al (1968).

However, a marked natriuresis and diuresis has been noted with the exhibition of aldactone in the nephrotic syndrome (Genest, 1960; Slater, 1959), in congestive cardiac failure (Friedberg, 1960) and in hepatic cirrhosis with ascites (Morrison & Chalmers, 1958). Thus, a good therapeutic response to aldactone does not indicate the primacy of causation to aldosterone. Presumably, the diuresis and natriuresis caused with the exhibition of the drug will be in direct proportion to the contributory action of aldosterone. Indeed, in my experience, whilst ameliorating the cumulative basal weight gain, it does not alter the diurnal weight gain, about which the patients bitterly complain. Thorn (1968) recommends the addition of another diuretic with aldactone.

Good therapeutic results have been obtained by the restriction of sodium, administration of diuretics and bed rest (Horky & Kuchel, 1867). Administration of sympathomimetic drugs, such as D amphetamine and ephedrine, in association with spironolactone will diminish the tendency to develop oedema (Streeten & Speller, 1966) and will lower the secretion and excretion of aldosterone (Laragh, Angers, Kelly & Lieberman, 1960; Greenough, Sonnenblick, Janszewicz & Laragh, 1962; Speller & Streeten, 1966).

Hyperaldosteronism is thus a consistent and important feature of this syndrome. Its presence has dominated the diagnostic and therapeutic management of the condition for many years. However, it is a secondary phenomenon and its central role in the orthostatic retention of sodium in this condition must be questioned. I propose to show that this phenomenon is simply one of a series of adaptive and compensatory mechanisms.

FAILURE TO ESCAPE FROM THE SODIUM RETAINING EFFECT OF ALDOSTERONE OR OTHER MINERALOCORTICOIDS

August, Nelson & Thorn (1958) showed that when normal subjects were given a mineralocorticoid, they escaped from its sodium retaining effect in a few days and went into sodium balance. Following the initial period of weight gain and sodium retention, weight gain ceased and sodium excretion returned to approximately control levels (whilst potassium excretion remained elevated throughout the period of mineralocorticoid administration). Initially, in healthy subjects, mineralocorticoids cause sodium retention without much potassium loss, which must imply sodium re-absorption proximal to the distal convoluted tubule. During the escape phase, when potassium is lost, more sodium must arrive at the distal exchange site to allow this increased potassium excretion to occur (August et al, 1958; Senft, 1963; Mantero, Quoidbach, Veyrat & Mach, 1967). Strauss & Earley (1959) suggested that the increase in extra-cellular fluid led to an increase in blood volume, which causes, by augmentation of the glomerular filtration rate, an increase in the filtered load of sodium. However, Davis, Johnston, Howards & Wright (1967) showed that the "escape" phenomenon occurred despite renal artery constriction and thus a lowering of the glomerular filtration rate. Senft (1963) demonstrated in the rat that the tubular re-absorption of sodium is diminished during the "escape phase". Other workers have shown, on a basis of animal experiments

and a systematic comparison of normal subjects with patients with primary hyperaldosteronism, that the "escape phase" is associated with a decrease in proximal tubular re-absorption (Rowner, Conn, Knopf & Hsueh , 1962). Martino & Earley (1968) showed by sequentially administering chlorothiazide and ethacrynic acid and replacing urinary losses that the "escape phase" depended on a decreased proximal tubular re-absorption of salt and water. However, experiments involving the use of diuretics depend on previously presumed sites of action, which may well vary with the conditions of the experiment.

Nelson & August (1959) demonstrated that oedematous patients with heart failure, the nephrotic syndrome, or cirrhosis with ascites and hypoproteinaemia, are unable to escape from the sodium retaining action of mineralocorticoids and progressively retain salt and water. Three chief differences were noted from the normal group. Firstly, sodium retention was more nearly complete; secondly, there was no secondary"escape" from the renal sodium retaining effect of mineralocorticoids; thirdly, increased potassium loss was not demonstrable.

Martino & Earley (1968),using methods described above, demonstrated that, in seven cirrhotics, proximal tubular re-absorption of water and electrolytes remained unchanged, despite the administration of a mineralocorticoid.

In view of the secondary hyperaldosteronism found in patients with idiopathic oedema and the almost invariable association of the latter with the female sex, it is not surprising that some of the earliest concepts of the disease

involved a failure to escape from the sodium retaining effects of aldosterone and oestrogens (Thorn, 1957, 1968). This hypothesis becomes increasingly attractive when one encounters patients who, in addition to abnormal diurnal weight gains, exhibit gradually increasing basal morning weights with dependant oedema. Thus, several studies have been undertaken of the effect of mineralocorticoid administration to patients with idiopathic oedema. Marieb & Mulrow (1964) studied four patients with idiopathic oedema. Three apparently "escaped" normally from the sodium retaining effect of desoxycorticosterone. One of these patients was studied intensively and during two separate periods of normal activity in hospital, administration of desoxycorticosterone (DOCA) for seven days led to progressive generalised oedema and a weight gain of 17lb. Plasma volume increased, haematocrit decreased, and inulin clearances remained within the normal range. However, administration of DOCA while the patient was kept in bed did not stimulate fluid retention. It was postulated that the mechanism of oedema formation in this patient was a failure of the physiological escape mechanism to limit expansion of the extra-cellular fluid volume, this failure being related to the upright posture. Gill et al (1972) gave thirteen patients with idiopathic oedema 0.25 mg. of 9α fluorohydrocortisone every twelve hours for four days, and compared its effect on sodium excretion and daily weight with a control group of nine normal females. They found that the response was similar in the two groups. The

cumulative sodium retention and weight gain for the four days were 529 mEq. and 2.47 kg. respectively for the normal women, and 593 mEq. and 2.61 kg. respectively for the patients with oedema. However, this study was very short and differences might have been revealed in a longer study.

Mills (1962) demonstrated that two female patients with chronic pyelonephritis and peripheral oedema failed to escape from the action of 9α fluorohydrocortisone, and postulated that sodium continued to be re-absorbed at a site proximal to the one exchanging sodium for potassium.

Jones (1973) studied the response of six patients with idiopathic oedema to administration of 9$^{\alpha}$ fluorohydrocortisone. In each patient, intense sodium retention occurred and the steroid had to be stopped after five to nine days. The patients became dyspnoeic and distressed. Pulmonary crepitations and radiological appearances of pulmonary oedema occurred in a few cases. The haematocrit fell excessively and the inference was that excessive fluid had been retained with the intra-vascular space. There was no consistent rise in the glomerular filtration rate.

The evidence that failure to escape from the sodium retaining effect of mineralocorticoids is a significant factor in idiopathic oedema is equivocal. It is hard to visualise this factor as being responsible for the excessive diurnal weight gain, although failure to escape or delayed escape could be responsible for the tendency in some patients for the basal morning weight to rise progressively. This hypothesis was tested in several of our patients and the results are given in Section - page 167-171.

INCREASE IN CAPILLARY PERMEABILITY TO PROTEIN MOLECULES

As discussed in a previous section, the characteristic abnormality of idiopathic oedema is the increased diurnal weight gain when upright. This excessive weight gain is due to excessive water and electrolyte retention in the upright position.

Several studies have demonstrated that the plasma volume is decreased in patients with idiopathic oedema (Thomas, 1933; Emerson & Armstrong, 1955; Ross et al, 1958; Clarkson et al, 1960; Arnoldsson, Belin & Hallberg, 1967; Ertel, 1967; Gill, Waldemann, Delea & Bartter, 1969; Gill et al, 1972).

The cause of this decreased plasma volume has been the subject of much discussion since the condition was first delineated, and earlier workers postulated increased capillary permeability to protein molecules. This attractive hypothesis fulfils most of the postulates given at the beginning of this section.

According to the classical hypothesis of Starling (1896), the exchange of water and small lipid insoluble molecules across the capillary membrane is largely governed by the balance between the hydrostatic and colloid osmotic pressure, the existence of the latter being dependent on the relative impermeability of the capillary membrane to plasma proteins. Starling's concept has been verified by direct experimental measurements (Landis, 1927). However,

in recent years, attention has been drawn to the fact that considerable quantities of plasma proteins, particularly albumin, pass through the capillary wall. Cohen, Freeman & McFarlane (1961), studying albumin turnover in man using ^{131}I labelled albumin, found an overall exchange rate of 117-234% (mean 140%) of the total albumin per day, and an extra-vascular pool greater than the intra-vascular pool. In accordance with the classical Starling-Landis hypothesis, an increase in the net rate of fluid movement out of the microvasculature can result from:-

(a) an increase in the transmural hydrostatic gradient

(b) decrease in the transmural colloid osmotic gradient and

(c) a combination of (a) and (b).

A decrease in the transmural osmotic gradient, and hence an increase in the net fluid movement out of the capillary, can occur either because of a fall in the colloid osmotic pressure of plasma, a rise in the colloid osmotic pressure of tissue fluids, or changes in both, which are in the same direction but disproportionate, so that the rate of return of lymph to the intra-vascular space is temporarily less than the rate of loss from the intra-vascular space. An alteration of capillary permeability to protein will raise the concentration of proteins in tissue fluid. Thus, the capillary permeability to protein governs the ratio of the intra to extra-vascular protein pools. If the colloid osmotic pressure gradient across the capillary wall is decreased, then an increase in hydrostatic pressure on

standing will cause a proportionally greater loss of fluid from the intra-vascular space and a greater decrease in the intra-vascular volume. As has been pointed out by Landis (1946), the permeability of the capillary wall is not easy to measure, as the capillary wall permeability to protein may alter as a function of the transmural hydrostatic gradient. Any change in permeability appears to occur mainly at the level of the venous capillary and venule; these vessels seem to be more distensible than capillaries and more permeable to protein at a given pressure, a property which may be due to ultra-structural peculiarities (Zweifach, 1946b).

In oedematous subjects, an important question is whether there is a generalised increase in capillary permeability, altering the ratio of the intra-vascular to extra-vascular protein pool. Fawcett & Wynn (1960), studying the effect of posture on blood constituents in a heterogeneous group of oedematous patients, found that the ratio of plasma protein concentration to haematocrit altered within fifteen minutes by between 7% and 16%, inferring increased capillary permeability. Another factor which may modify blood flow greatly and affect the rate of filtration from the blood is increased environmental temperature (Drury & Jones, 1927; Landis & Gibbon, 1933).

Very few studies have been made of the variations in capillary permeability to plasma proteins during the menstrual cycle. Jones, Fox, Verow & Asscher (1966), in a study of eight multiparous women with regular menstrual cycles, using the technique described by Landis, Jonas, Angevine & Erb (1932), showed that the protein loss from the forearm capillaries is greater in the second half of the menstrual cycle than in the first week after menstruation, Fig. 7. The differences could not be attributed to an increase in the capillary filtration rate during the second half of the cycle, since filtration rate and protein loss were not significantly correlated. In a previous study, Russo & Pinoli (1956), also using the Landis technique, observed an increase in capillary permeability to plasma proteins on the twenty-first day of the cycle, as compared with the second day of the cycle. The mechanism of the cyclical change in capillary permeability is unknown. It is unlikely to be due to progesterone, As Camurri (1955) showed that progesterone decreases vascular permeability to plasma proteins.

Some of the most persuasive evidence in favour of increased capillary permeability being a cause of idiopathic oedema has come from clinical cases. Clarkson et

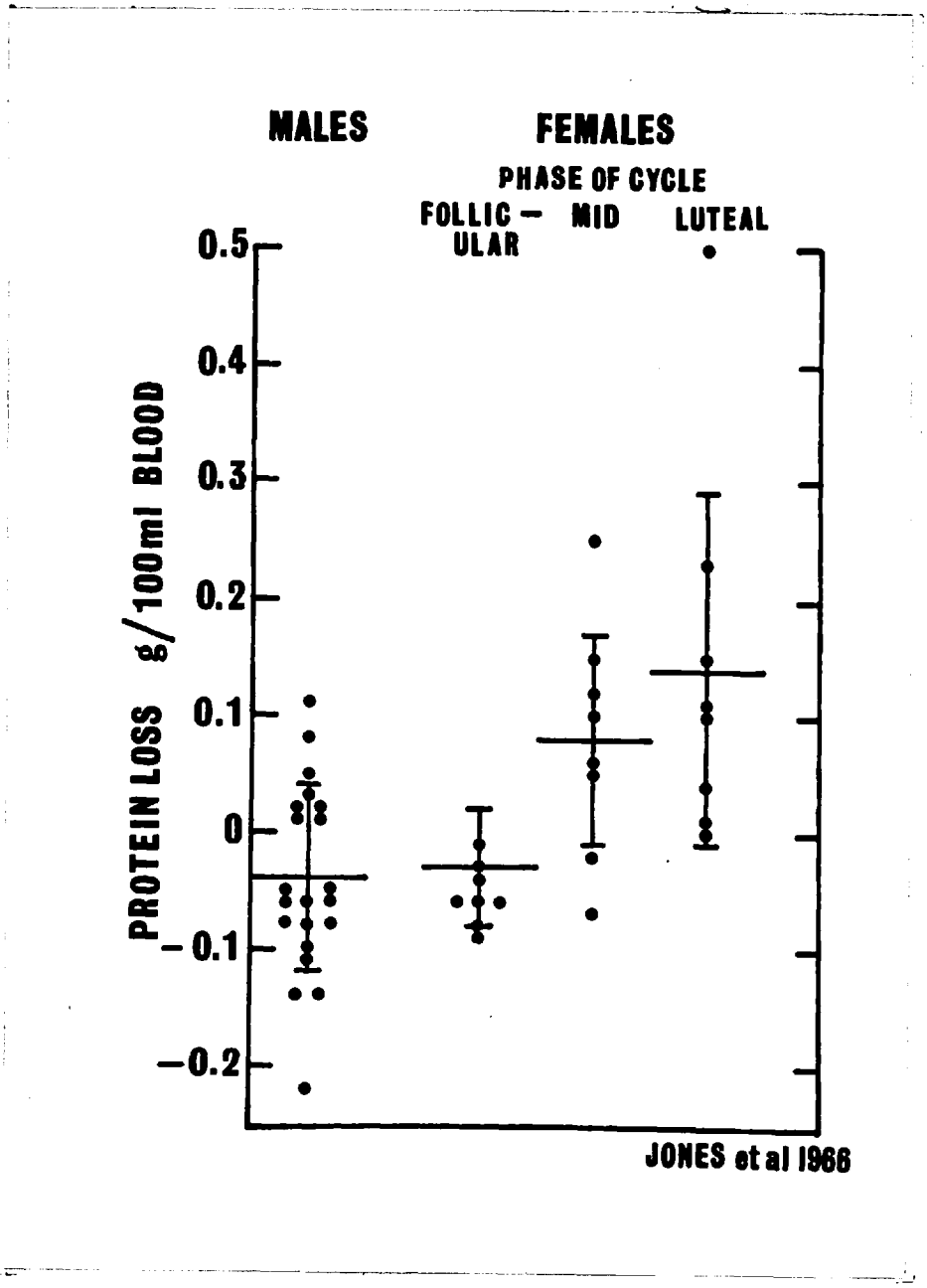


FIG. 7: The protein loss from forearm capillaries using the technique of Landis et al (1932) in normal males and in the follicular and luteal phases of the menstrual cycle in eight multiparous women with normal menses. (Jones et al, 1966).

al (1960) demonstrated in one patient with severe idiopathic oedema with episodes of severe hypovolaemia a profound loss of plasma from the capillary bed by observation of four parameters: haematocrit, plasma volume, T - 1824 dye disappearance curve and radioactive iodinated serum albumin studies. The haematocrit rose from 40%, prior to the onset of hypovolaemic shock, to 57% during an episode. The plasma volume fell to 1,245 ml. during an episode of shock from a calculated normal of 2,846 ml. The rate of disappearance of the T - 1824 and radioactive albumin were 6.2% and 6.3% respectively before an episode of hypovolaemic shock. During an attack, the rate of disappearance of T - 1824 was 32% for the first hour and 17% for the second hour. The rate of disappearance of radioiodinated albumin also increased during an increase of hypovolaemic shock. Plasma obtained from the patient during an episode of hypovolaemic shock induced severe hypotension in rats, whilst plasma obtained when asymptomatic did not do so. No estimations of urinary histamine, catecholamines or plasma, kallikrein and bradykinin were made in the patient. It is of interest that the attacks of oedema and hypovolaemic shock continued after hysterectomy and bilateral oophorectomy. A milder case of cyclical oedema, associated with a contracted blood volume, was reported by Thomas (1933). The patient of Emerson & Armstrong (1955) was studied over a period of eight years, during which she developed several episodes of generalised

oedema, which were treated with infusion of salt free albumin. Analysis of the oedema fluid during an attack gave albumin levels of about 2 gm. per cent, a level greater than that found in nephritic, nephrotic, cardiac and nutritional oedema. The conclusion was drawn that the primary abnormality was increased capillary permeability to protein. Ross et al (1958) described a woman with anasarca, hyperaldostenuria and an adrenal adenoma. The hyperaldostenuria in this patient was ascribed to abnormal capillary leakage of protein. Preston, Russel-Rees & Spathis (1962)and Weinbren (1963) described two male patients with spontaneous periodic oedema, in whom it was shown that the onset of the oedema was associated with a sudden increase in capillary permeability. Both cases were associated with an abnormal circulating gamma globulin.

There are few studies of the rate of loss of radio-active labelled albumin from the intra-vascular space in idiopathic oedema (Gill et al, 1969; Kapitola, Horky & Kuchel, 1968; Lagrue et al, 1971; Gill et al, 1972; Streeten et al, 1973). Of these studies, only Gill et al (1969 & 1972) have undertaken a long term study of ^{125}I albumin in patients with idiopathic oedema.

They showed in fourteen patients with idiopathic oedema that the mean albumin concentration, mean plasma volume and the mean total circulating albumin were all significantly less than the values found in normal female subjects. The total albumin was distributed between an intra-vascular pool and two extra-vascular pools; one slowly exchanging, assumed to be in skin and viscera, the

other rapidly exchanging, presumably in the viscera. In patients with idiopathic oedema, the rate of egress of albumin to the rapidly exchanging pool was increased, as was the rate of return. The distribution ratio, i.e. the ratio of the extra-vascular to the intra-vascular albumin pool, was, however, normal in twelve patients. In two patients, the distribution ratio was abnormally high and equilibrium between the two pools was only reached when the extra-vascular albumin pool was much increased. Edwards, Frankel & Guttman (1967) argued that an increased distribution ratio indicates increased capillary permeability to macromolecules. However, the "normal" distribution ratio in the remaining twelve patients is, in itself, abnormal in the face of a lowered total circulating albumin pool, as it has been shown that normal subjects undergoing plasmapheresis (Anderson & Rossing, 1969), patients suffering from protein malnutrition (Picou & Waterlow, 1962; Cohen & Hansen, 1962; James & Hay, 1968) and nephrotic patients (Jensen, 1969) react to a low albumin concentration by an albumin shift from the extra-vascular to the intra-vascular space, that is, by decreasing the distribution ratio. One may, therefore, argue that the so-called normal distribution ratio was relatively too high and reflects an increase in capillary permeability to protein molecules.

Other studies have been short term. Lagrue et al (1971), using the method of Landis, demonstrated increased capillary permeability to protein in fifteen patients with idiopathic oedema. They also found that the rate of disappearance of ^{131}I labelled albumin from the intra-

vascular space was 8.5±3.5% per hour in their patients with idiopathic oedema when supine (normal 3.5±1.5% per hour), and this rate increased to between 15% and 20% per hour with the patients upright. Kapitola et al (1968) were only able to demonstrate a slight increase in the disappearance rate of radioactive labelled albumin in two of the eight patients studied.

The cause of this increase in capillary permeability is debatable. Mostow, Hamwi & Skillman (1960) demonstrated reactive hypoglycaemia and a high familial incidence of diabetes mellitus in their patients with idiopathic oedema. Since capillary angiopathy may precede clinically apparent diabetes mellitus by many years, Sims et al (1965) studied carbohydrate tolerance and capillary ultrastructure in a group of eleven patients with idiopathic oedema. Seven patients had a family history of diabetes mellitus, four had experienced symptoms of reactive hypoglycaemia and two had given birth to babies above nine pounds in weight. Three patients had abnormal glucose tolerance tests, whilst a further four patients had abnormal cortisone glucose tolerance tests of Fajans & Conn (1961). The capillary basement membrane was found by electron microscopy to be significantly increased. They suggested that thickening of the basement membrane might lead to increased permeability to protein molecules in an analogous way to the glomerular basement thickening of the nephrotic syndrome leading to proteinuria.

However, as they point out, if capillary angiopathy leads to increased capillary permeability, several questions

remain to be answered. It is not clear why the condition should be almost exclusively restricted to women and also why all diabetic women with demonstrable capillary angiopathy do not develop similar oedema.

Plasma or serum of normal individuals contains a number of protein systems, whose physiological activity results in increased vascular permeability. These systems, involving the family of chemical mediators such as histamine and the kinins, could mediate the sequestration of considerable quantities of fluid in the extra-vascular compartment. When plasma in contact with glass is diluted with saline, a factor is generated which enhances vascular permeability. This factor has been designated PF/dil by Miles & Wilhelm (1955) and is inhibited by soybean trypsin inhibitor and activated by Hageman factor. Another vasoactive globulin present in normal plasma, kallikrein, circulates as an inactive precursor, pre-kallikrein, which may be activated by Hageman factor. Kallikrein acts on an α-globulin substrate to release a nonapeptide, bradykinin (Webster & Pierce, 1963). Kallikrein infusion in the dog causes a sharp fall in blood pressure and a rise in haematocrit and total plasma concentration. Radioiodine labelled albumin studies showed a decrease in plasma volume and an increase in the rate of albumin loss from the intra-vascular space, changes which were significantly greater in the nephrectomised animal (MacFarlane, Mills & Wraight, 1972).

The serum of patients with hereditary angioneurotic

oedema does not inhibit C'I esterase. Consequently, free C' esterase can be detected in the plasma of these individuals, particularly during attacks of oedema, and C'esterase, when given intravenously to normal subjects, may promote attacks of angioneurotic oedema (Klemperer, Donaldson & Rosen, 1968). Two patients with this condition also excreted large quantities of histamine between attacks (Granerus, Hallbert, Laurell & Wetterquist, 1967). However, the clinical picture of idiopathic oedema is very distinct from that of angioneurotic oedema, and studies of histamine metabolism and C'esterase in idiopathic oedema have been normal.

In summary, therefore, evidence has been presented showing there is an increase in capillary permeability to protein molecules in idiopathic oedema. Increased capillary permeability, as discussed earlier, leads to a greater extra-vascular protein pool and a smaller intra-vascular protein pool. Thus, the intra-vascular space is decreased, the plasma oncotic pressure decreased, whilst the tissue oncotic pressure is increased. Thus, standing will cause, by virtue of the decreased oncotic pressure gradient, a greater loss of electrolytes and water from an already depleted intra-vascular space. This will, in turn, lead to a greater fall in blood pressure, increased leg oedema, increased percentage fall in plasma volume and, as I will show, a proportionally greater fall in urinary volume and sodium. The renal retention of electrolytes and water will be distributed between the extra- and intra-cellular spaces and, thus, cause the clinical manifestations of this disorder.

ABNORMAL ALBUMIN METABOLISM IN IDIOPATHIC OEDEMA

The serum albumin concentration in idiopathic oedema lies within the normal range. However, various studies have revealed abnormalities of synthesis, catabolism, rate of loss from the intra-vascular compartment, rate of return to the intra-vascular compartment and in the ratio of the intra-vascular to extra-vascular albumin pools.

The albumin concentration in plasma is the resultant of the dynamic interaction of the rate at which albumin is formed, the time the albumin molecules spend in the plasma and, finally, the plasma volume. An abnormal albumin level is merely an indication of a disturbed interaction and does not, in itself, indicate the changed variable or variables. If the reduced albumin concentration is further characterised with its rate of formation, the rate of catabolism or the ratio between its distribution between the intra- and extra-vascular distribution, then its clinical importance increases.

Three-quarters of the colloid osmotic pressure of plasma is due to albumin (Scatchard, Batchelder & Brown, 1944) but the functions of albumin are all unspecific and the protein is not vital. Indeed, in the condition of analbuminaemia, the patients are almost totally unaffected, apart from some dependent oedema (Freeman, 1969). However, its metabolism is subject to control, which is apparent

from experimental and clinical situations in which albumin metabolism is disturbed. By producing a simultaneous fall in albumin concentration, the intra-vascular albumin mass and colloid osmotic pressure by daily plasmapheresis in a normal man, Anderson & Rossing (1969) showed that intra-vascular half-life of albumin was extended, net transport of albumin from the extra-vascular to the intra-vascular pools increased, and the ratio of intra-vascular to extra-vascular albumin fell. The rate of synthesis of albumin increased, whilst the catabolic rate fell. That the controlling variable is the colloid osmotic pressure, rather than the serum albumin concentration or intra-vascular mass of albumin, is suggested by the observation that induction of hypergammaglobulinaemia or infusion of dextran may reduce serum albumin concentration, decrease albumin synthesis and decrease intra-vascular half-life (Rothschild, Oratz, Mongelli & Schreiber, 1965; Rothschild, Oratz, Wimer & Schreiber, 1961). Albumin metabolism is also influenced by female sex hormones. Hönger (1968) found that patients with pre-eclampsia had a higher rate of albumin synthesis than normal pregnant women and, since urinary oestrogen metabolites and pregnandiol excretion is higher in the normal pregnancy, advanced the hypothesis that female sex hormones have an inhibiting effect on albumin synthesis. It has been subsequently found that combined gestagen-oestrogen contraceptives lower albumin concentration in normal women (Pilgeram &

Pickart, 1963) and this lowering seems to be due to a fall in the synthesis of albumin (Honger & Rossing, 1969). Whether there is an effect at physiological levels of oestrogen and progesterone is uncertain, and Gill et al (1972) studied albumin metabolism in six normal subjects and in fourteen patients with idiopathic oedema. They found that serum albumin concentration of 3.27±0.085 g/ 100 ml. (S.E.M.) in patients with idiopathic oedema was significantly lower ($P<0.01$) than their normal subjects. Plasma volume 35.99±1.66 ml./kg. in the patients was also significantly lower ($P<0.01$), so that the total intra-vascular pool was also significantly lower ($P<0.01$). The low value for total circulating albumin could be attributed to an abnormally large fraction of plasma albumin degraded per day in eight patients and to an abnormally low rate of synthesis in three patients. In the remaining patients, the rate of synthesis and catabolism was normal, but the ratio of the former to the latter was below normal in each case. The rate of movement of albumin from the intra-vascular compartment to a large, slowly exchanging extra-vascular pool was significantly greater than normal and in the majority there was a compensatory increase in the rate of return of albumin to the plasma. In two patients, the rate of return of albumin to the plasma was normal, so the ratio of intra- to extra-vascular albumin was significantly higher. In this study, no correlation was made with the time in the menstrual cycle. It is also noted that the mean age of the control group was twenty-three years, whilst that of the abnormal group was forty

years. The effect of age on the variables concerned in albumin metabolism is not known, but plasma albumin is known to decrease with age.

In view of the current concepts of albumin metabolism, certain features in this study are puzzling. If plasma oncotic pressure is low, due to hypoalbuminaemia, and there is no compensatory rise in plasma globulin, the rate of albumin synthesis should have increased (Anderson & Rossing, 1969), whereas it was normal in eleven subjects and low in three subjects.

Streeten and his colleagues (1973) found that the serum proteins were entirely normal, both in total concentration and electrophoresis, in their subjects. They also found that the plasma volumes in their patients were not abnormally low. They postulated that it was possible that the plasma proteins were measured in recumbency in the patients of Gill and his colleagues (1972) and under random conditions of posture in their "normal" subjects, who were not stated clearly to have been hospitalised during their studies. They also pointed out that the subnormal plasma volumes, which Gill et al (1972) reported, might have reflected more severe obesity in their patients.

Thus, abnormal albumin metabolism as a possible cause of idiopathic oedema remains unproven, although it remains a theoretical possibility. However, severely hypoproteinaemic states are excluded by definition.

ABNORMAL RELEASE OF ANTI-DIURETIC HORMONE IN RESPONSE TO STRESS OR CHANGE IN POSTURE

Patients with idiopathic oedema, during a period of oedema formation, pass small quantities of highly concentrated urine. At the same time, they experience facial puffiness, have swelling and breast tenderness, and superficially may resemble the syndrome of inappropriate anti-diuretic hormone (A.D.H.) secretion, first described by Schwartz, Bennett, Curelop and Bartter (1957).

A.D.H. is an octapeptide, which is secreted by neurons which arise in the supraoptic and paraventricular nuclei and terminate in the posterior pituitary (Dingman & Thorn, 1966). Secretion of A.D.H. is controlled by changes in plasma osmolality, intra or extra-vascular fluid volume, and by central nervous system activity. Secretion of A.D.H. in man and animals has been induced by electrical stimulation of the hypothalamus. A variety of centrally acting stimuli, such as noise, pain or the fear of a variety of experimental procedures, may increase A.D.H. secretion. Idiopathic oedema induced by excessive release of A.D.H. alone would be characterised by hypo-osmolality of the plasma and hypertonicity of the urine. Plasma sodium would be low, due to excessive retention of water. These changes are not, however, characteristic of the condition.

Streeten & Conn (1959, 1960), Streeten, Louis & Conn (1960) showed that, in the upright posture, there was an abnormal retention of a water load in patients with idiopathic oedema, as compared with normal subjects. This abnormal water retention could be abolished by the admini-

stration of ethanol. They postulated that this abnormal water retention was due to the excessive release of A.D.H. in the upright position. In a later paper, Streeten & Speller (1966) showed that the excessive fall in urine volume on standing was not entirely corrected with alcohol. The major problem in interpreting these papers is the dearth of urine and plasma osmolality data.

Streeten and his colleagues (1973) delineated a group of patients with idiopathic oedema, who showed excessive retention of water, but not sodium, when upright. Unfortunately, no urine or plasma osmolality data was available and no systematic attempt was made to demonstrate hyponatraemia. It is of considerable interest and relevance to note that the fall in plasma volume on standing was within normal limits in these patients, as opposed to the greater than normal fall in plasma volume in patients who also had excessive retention of sodium. It is also important to note that secondary hyperaldosteronism only occurred in the patients with excessive orthostatic sodium retention. This suggests that the patients who retained water excessively alone were those with the less severe manifestations of the disorder.

Thorn (1957) has, however, encountered a patient with idiopathic oedema in whom oliguria and the symptoms of water intoxication became manifest with great suddenness, after cessation of menstruation.

The available evidence at the moment points to the excessive release of A.D.H. on standing in patients with idiopathic oedema as being a compensatory and contributing

factor in the disease.

OESTROGEN AND PROGESTERONE IMBALANCE

One of the earliest hypotheses advanced to account for the causation of idiopathic oedema and the premenstrual tension syndrome was that of oestrogen and progesterone imbalance (Israel , 1938), and this led to early attempts to control the disorder, using progestational drugs in pharmacological amounts.

The rationale of this hypothesis lies in the metabolic activities of oestrogens and progesterone. Oestrogens have a weak and transient salt retaining action, being chemically related to deoxycorticosterone, which has strong salt retaining properties (Preedy & Aitken, 1956). Progesterone, on the other hand, has a weak natriuretic action in man, possibly by acting as an aldosterone antagonist at the renal tubular level. That progesterone has a natriuretic action was first shown by Landau & Lugibihl (1958), who demonstrated that, in patients suffering from Addison's disease, an increase in urinary sodium could be obtained with progesterone only if aldosterone was given concurrently. Furthermore, Jenkins (1961) showed that the amount of progesterone used was greater than that reached in the luteal phase of the menstrual cycle, and was of the order found in the latter half of pregnancy. However, Landau, Lugibihl, Bergenstal & Dimick (1957b) reported an effect with doses as low as 15 mg. daily.

Neistadt, Schwartz & Schwartz (1966) showed that mestranol has an effect in delaying venous return, which would, in turn, cause excessive sequestration of blood in the legs, decreasing effective blood volume and, thus, in

turn, stimulating the water and salt retaining mechanisms.

The urinary secretion of aldosterone fluctuates significantly during the menstrual cycle, and Nowaczynski, Koiw, Biron, Chretien & Genest (1962) and Reich (1962) found that the excretion in the luteal phase was about double that of the follicular phase. It has been shown (Layne, Meyer, Vaishwanar & Pincus, 1962; Gray, Strausfeld, Watanabe, Sims & Solomon, 1963) that this increase is due to a similar rise in the aldosterone secretion rate, although it has also been shown that oestrogens reduce the aldosterone metabolic clearance rate by about 20% (Streeten & Speller, 1966). Plasma renin (Brown, Davies, Lever & Robertson, 1964; Winer, 1965; Skinner, Lumbers & Symonds, 1969) and plasma angiotensin II levels (Sundsfjord & Aakvaag, 1970) have been shown to rise in the luteal phase of the menstrual cycle, Fig. 8. Kinetic studies by Skinner et al (1969) have shown that the rise in plasma renin activity is due to an increase in the concentration of the enzyme itself, without any change in its substrate angiotensinogen. Oestrogen administration, on the other hand, leads to increased substrate level and thus to increased plasma renin activity in the terms of the renin assay (Helmer & Judson, 1967; Crane & Harris, 1969). These observations suggest that the rise in oestrogen is not the primary stimulus to increased levels of angiotensin II. Since, as discussed earlier, progesterone has a weak salt losing action, it has been postulated that the increase in plasma progesterone in the luteal phase leads to increased sodium excretion and thus to increased plasma renin, angiotensin II and aldosterone. Oestrogen is then, according to the classical

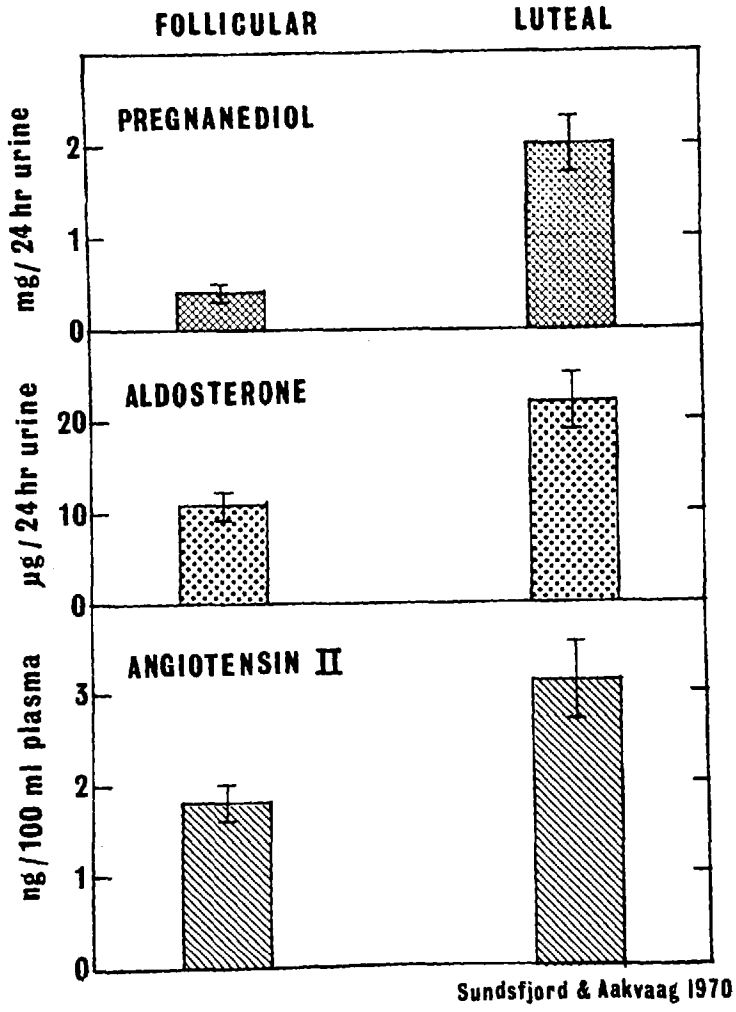


FIG. 8: Urinary pregnanediol and aldosterone excretion and plasma angiotensin II concentration early in the follicular and late in the luteal phase in 9 normal women with regular menstrual cycles. (Mean ± S.E.M.)

theory, to be responsible for fluid retention, while progesterone, through its sodium losing action, is believed to stimulate the renin-angiotensin, aldosterone system and so contributing to further fluid retention. All the factors mentioned above could play at least a permissive role in the development of oedema in the patients. This hypothesis given above would account for the syndrome of idiopathic oedema being almost invariably associated with the female sex and its absence before menarche.

The classical theory given above has been used to account for the pre-menstrual tension syndrome, a condition in which the symptomatology is similar to that found in patients with idiopathic oedema. Indeed, the two conditions may co-exist in the same patients (Thorn, 1957). However, Bruce & Russell (1962), in a review of the literature and in a study of their own using emotionally disturbed women, found no definite correlation between water and salt retention, weight gain and the pre-menstrual tension syndrome, and further stated that the administration of hormones and diuretics, except on an empirical basis, was without logic. They found a significant gain in weight and retention of salt and water at the mid cycle; findings which are in agreement with Thorn, Nelson & Thorn, (1938). There was no increase in symptoms at this time. This mid cycle weight gain coincides with the maximum excretion of oestrogen metabolites, which, as Brown, Klopper & Loraine (1958) showed, occurs from the eighth to the twelfth day of a twenty-eight day cycle. Bruce & Russell

(1962) only studied basal morning weights, and the diurnal weight gains were not estimated. Patients complain bitterly about excessive weight gain during the day, the excessive fluid retained being at night.

Reeves, Garvin & McElin (1970), taking the mean of the morning and evening weight, found a highly significant increase in weight of 0.26±0.06 lb. in the five days premenstrually, but were unable to correlate it to an increase in symptoms. The finding of an increase in weight premenstrually in this series is probably attributable to the experimental design, in that the mean of the morning and evening weights were taken, rather than the basal morning weight alone.

If the classical theory is correct, and fluid retention is brought about by the production of relatively large amounts of oestrogen and progesterone (Leading Article, 1964; Novak, Jones & Jones, 1970; Reeves et al, 1971), then the condition should be associated with ovulatory cycles. Adamopoulos, Loraine, Lunn, Coppen & Daly (1972), estimating oestrogen and pregnanediol excretion in fifteen menstrual cycles from eight patients with pre-menstrual tension, found that eight were anovulatory, but there was no change in the symptomatology. Kuchel et al (1970) found that twelve of his twenty-one patients with idiopathic oedema had menstrual disorders. These patients were studied by basal temperature recordings, vaginal cytology, and eight patients had concurrent measurements of urinary pregnanediol excretions between the nine-

teenth and twenty-third day of the menstrual cycle. Six of the eight patients had undetectable pregnanediol excretion and nine of the twelve patients had, when compared to normal women, an increase in the karyopynotic and eosinophilic index in the luteal phase. These findings point to anovulatory cycles occurring in some patients with idiopathic oedema. The finding of anovulatory cycles in patients with idiopathic oedema and under clinical investigation is not surprising, as stress and psychic disturbance may, in themselves, suppress ovulation. However, the unopposed action of oestrogen could represent a factor in sodium re-absorption, but this is unlikely, as the syndrome of idiopathic oedema may persist beyond the menopause, whether natural or induced.

Could oestrogen have an effect other than that in causing delay in venous return or on sodium metabolism? In the ovarian hyperstimulation syndrome caused by administration of gonadotrophins, a major complication is an increase in the haematocrit leading to thrombosis. In this condition, the production of oestrogens and progesterone is high and apparently leads to an increase in capillary permeability. This will be discussed in a later section.

Thus, there is no major evidence to support the theory that idiopathic oedema or the allied pre-menstrual tension is in some way linked to oestrogen and progesterone imbalance.

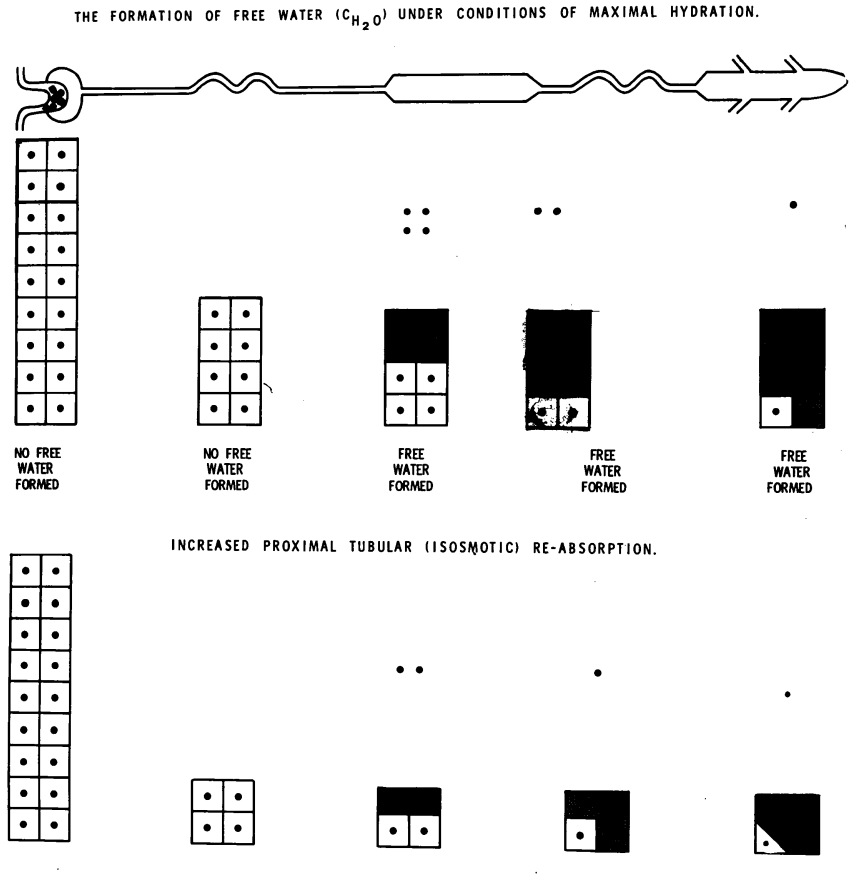


FIG. 9: The diagramatic illustration of the formation of free water (CH_2O) by the nephron and an illustration of the effect on free water clearance of increased proximal tubular reabsorption.

PHYSIOLOGICAL ASPECTS OF THE EFFECTS OF CHANGE IN POSTURE

Change from the supine to the upright position initiates several physiological consequences. Pooling of blood caudal to the heart decreases venous return and cardiac output (McMichael & Sharpey-Schafer, 1944; Stead, Warren, Merril & Brannon, 1945). Hydrostatic forces cause fluid to leave the circulation and the legs increase in volume (Waterfield, 1931a & b; Turner, Newton & Haynes, 1930; Kuchel et al, 1970).

The effect of change in posture on plasma volume

Thompson, Thompson & Dailey (1928) found that, if an individual remained stationary in the erect posture, his plasma volume, as measured by a dye method, gradually diminished over half an hour until it reached a constant level, some 12% less than in the recumbent position. Further, the haematocrit rose in such a way as to indicate that total red cell volume remained unchanged. Concurrent with these changes was a rise in the red cell cound, the specific gravity of the blood and the plasma protein concentration. They postulated that, in the erect posture, there was an absolute diminution in the amount of water and diffusible substances in the circulation and suggested that the loss was the result of filtration through the capillary walls of the legs, due to an increase in the

hydrostatic pressure. Other workers have confirmed the plasma volume contraction on standing (Waterfield, 1931a & b; Ni & Rehberg, 1931; Youmans, Wells, Donley, Miller & Frank, 1934; Asmussen, Christensen & Nielsen, 1940, Brun, Knudsen & Raaschou, 1945; Fawcett & Wynn, 1960; Eisenberg & Wolf, 1965). The study of Fawcett & Wynn (1960) showed that the fall in plasma volume on standing was maximal in normal subjects after about fifteen minutes and did not increase further over the succeeding hour. The average rise in haematocrit was about 7-8%.

Youmans et al (1934) measured the venous pressure in the foot, the colloid osmotic pressure, the haematocrit and the change in leg volume of five normal subjects both in the supine and erect positions. They found that, on standing, the venous pressure in the leg increases markedly to about 100 cm. water, the colloid osmotic pressure by about 42.7% and the leg volume by 272 ml., a 4.1% increase. The increase in the concentration of protein and the osmotic pressure in the leg was approximately twice as great as occurred in the arm. Waterfield (1931b) also measured the change in leg volume on standing, and found that leg swelling was complete by about thirty minutes and that the volume changes in the leg were of an order of magnitude to be expected from the decrease in the blood volume. Turner et al (1930) demonstrated that leg swelling found in normal female subjects was greater than males and that the percentage increase in leg swelling was greatest in the summer.

In conclusion, the relative increase in haematocrit on standing is due to a decrease in the plasma volume, caused by the capillary transudation of water and electrolytes from the circulation. This decrease in plasma volume is greater in females.

The autonomic nervous system has a biphasic response to this posturally induced fall in blood volume. It reacts immediately to prevent a fall in blood pressure and has an integral position in more sluggish mechanisms designed to replenish the intra-vascular blood volume. The immediate response in change of posture from the supine to the erect position is an increase in sympathetic nervous activity causing an increase in heart rate and myocardial contractility, veno-constriction and increased peripheral vascular resistance (Brigden, Howarth & Sharpey-Schafer, 1950). This increase in the activity of the sympathetic nervous system is characterised by an increase in plasma catecholamines (Hickler, Wells, Tyler & Hamlin, 1959) and an increase in urinary free catecholamines (Sundin, 1956). The combination of an increase in cardiac output and peripheral vascular resistance serves to maintain the arterial blood pressure.

Other more sluggish mechanisms come into play to re-expand the intra-vascular blood volume and in these the sympathetic nervous system is intimately involved. The increase in sympathetic tone increases the pre-capillary resistance relative to the post-capillary resistance, thus lowering the capillary hydrostatic pressure relative to the colloid osmotic pressure. Thus, the movement of water

and electrolytes into the intra-vascular space is encouraged (Oberg, 1967).

The effect of change in posture from the supine to the upright on urinary flow and composition has been well documented, although it is important to realise that the stress involved may be entirely different and evoke a differing response. For example, in the experiments of Waterfield (1931a & b), the subject stood stationary, partially supported by arm rests, and with his legs as far as possible relaxed, whilst in the studies of Fawcett & Wynn (1960), the subjects walked slowly around the room. If the conditions are not standardised, then the results and conclusions lose validity. In my studies, the conditions of each test were carefully controlled.

The phenomenon of the orthostatic fall in urinary flow and composition was described by Edel in 1901 and Linossier & Lemoine in 1903. It was later studied by other workers (Erlanger & Hooker, 1903; White, Rosen, Fischer & Wood, 1926; Ni & Rehberg, 1931; Waterfield, 1931a & b; Youmans et al, 1934; Asmussen et al, 1939; Brun et al, 1945; Goodyer & Seldin, 1953; Pearce & Newman, 1954; Surtshin & White, 1956; Camp, Tate, Lowrance & Wood, 1958; Streeten & Speller, 1966; Kuchel et al, 1970). Most of these studies have, however, been on men. In the study of Streeten & Speller (1966), tilting tests were not performed at known intervals in the menstrual cycle, whilst in the study of Kuchel et al (1970), the tests were only performed in the follicular phase of

the menstrual cycle in normal female subjects. All the studies have shown that there is a reduction in urine volume, sodium, potassium and chloride on standing, whilst the effect on the creatinine clearance is variable. To my knowledge, however, no observations have been made before on the changes in urinary volume and composition in the follicular and luteal phases of the menstrual cycle when normal well-hydrated subjects are tilted.

The reduction in urine volume observed may be mediated by one or more of three main mechanisms, namely a reduction in glomerular filtration rate, an increase in the distal tubular re-absorption of water, or an increase in the proximal tubular re-absorption of electrolytes and water.

Provided that other changes in renal function do not occur, a fall in glomerular filtration rate will cause a reduction in urine volume, a decrease in sodium and potassium excretion and a reduction in osmolar clearance, together with a fall in free water clearance, by decreasing the amount of osmotically active solute available for re-absorption at distal sites, Fig. 9. Theoretically, a small change in the glomerular filtration rate well within experimental error, particularly in the diuretic phase, could account for the changes observed. For example, a fall of 5% in the average glomerular filtration rate of 100 ml. per minute could mean a change of 70 μM of sodium excreted per minute. Some renal physiologists (White, Rosen, Fischer & Wood, 1926; Wesson, Anslow & Smith, 1948; Selkurt, Hall & Spencer, 1949) place great emphasis on

the reduction in glomerular filtration rate which occurs on standing, as being the cause of the antidiuresis and antinatriuresis. Pearce & Newman (1954) found that the glomerular filtration rate fell by about 10% on being tilted upright and occurred despite the reduction in the antinatriuresis with leg wrapping. They concluded that the fall in the glomerular filtration rate was not an adequate explanation for the effect of postural change on salt excretion. Other workers have observed either no fall in creatinine clearance (Surtshin & White, 1956), or a small reduction, no greater than 10-15% (Epstein, Goodyer, Lawrason & Relman, 1951), when normal subjects are tilted, and have concluded that factors other than a reduction in glomerular filtration rate were responsible for the decrease in salt and water excretion. The nub of the problem is that the percentage fall in urinary volume and sodium excretion on standing is usually much greater than the percentage fall in creatinine clearance. In Figs. 10 & 11, I have attempted to plot the percentage change in the glomerular filtration rate against the percentage fall in urinary sodium excretion or urinary volume on standing from various studies (Brun et al, 1945; Epstein et al, 1951, Pearce et al, 1954; Streeten & Speller, 1966). It can be seen that there is no correlation between the parameters measured.

The increased secretion of anti-diuretic hormone (A.D.H.), known to occur on standing, would cause a decrease in urinary volume, an increase in urinary osmolality, and a decrease in free water clearance, without a change in the osmolar clearance. Streeten & Speller (1966) demonstrated

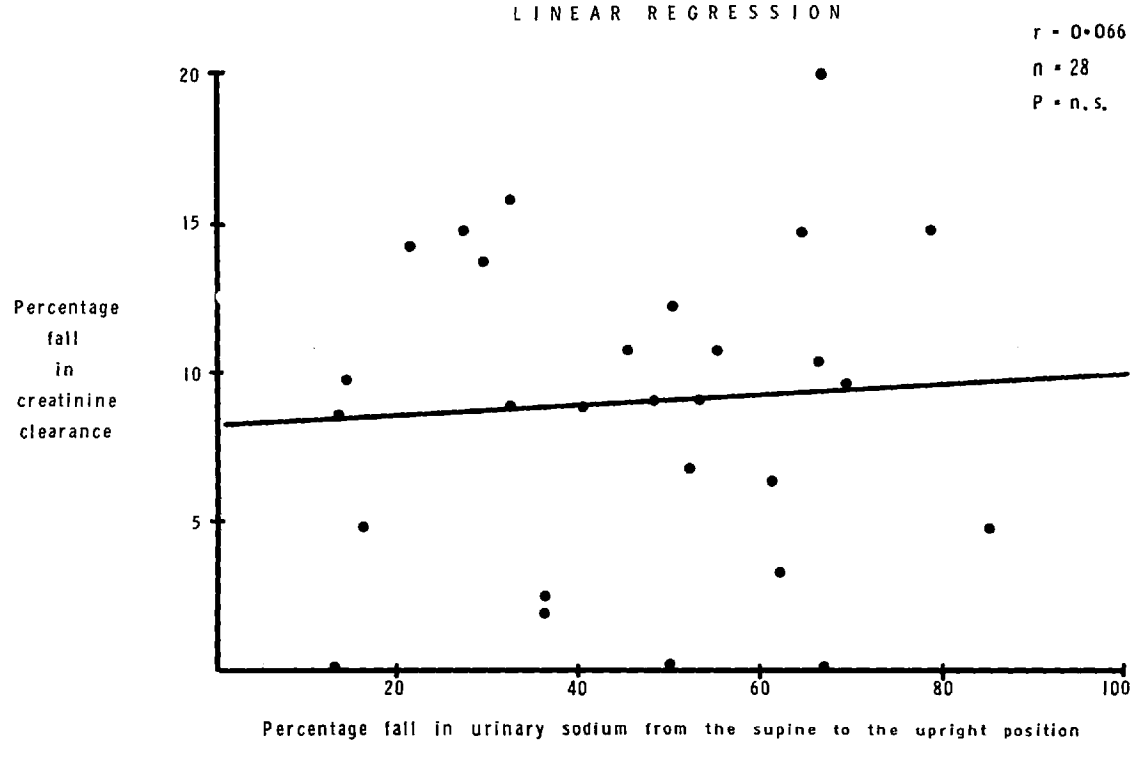


FIG. 10: A scattergram of the percentage fall in creatinine clearance plotted against the percentage fall in urinary sodium. (Brun et al, 1945; Epstein et al, 1951; Pearce et al, 1954).

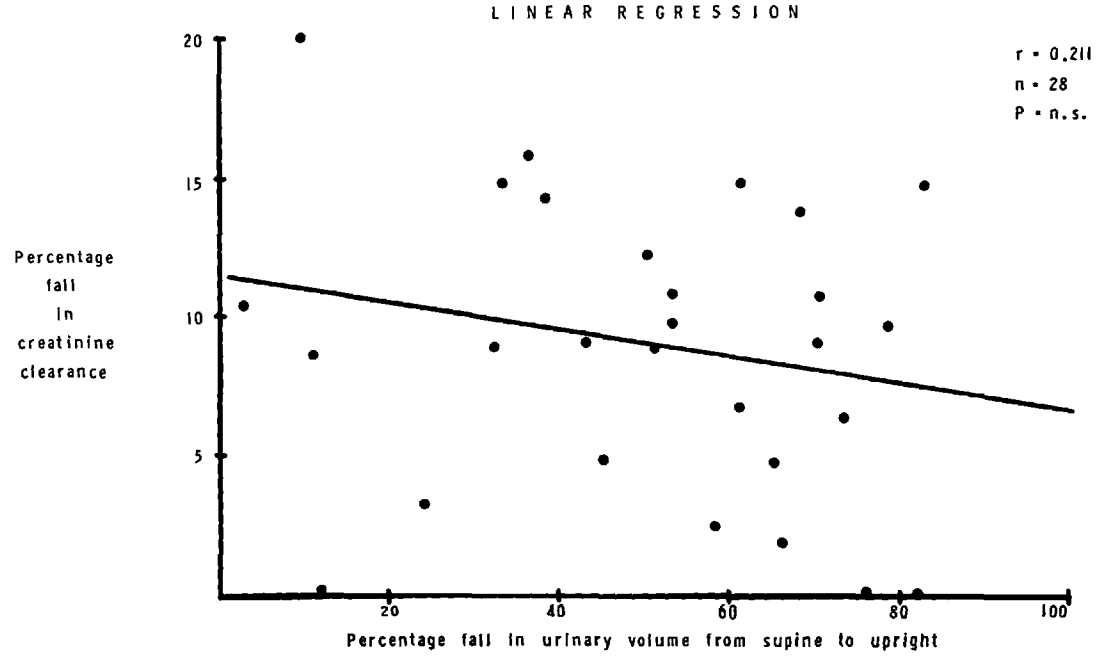


FIG. 11: A scattergram of the percentage fall in creatinine clearance plotted against the percentage fall in urinary volume. (Brun et al, 1945; Epstein et al, 1951; Pearce et al, 1954).

that the administration of ethanol to normal subjects drinking 150 ml. of 0.14% sodium chloride solution half-hourly abolished the orthostatic fall in urine flow and free water clearance known to occur in the first half hour in the upright posture, Fig. 12. Since alcohol is known to inhibit the release of A.D.H., (Kleeman, Rubini, Lamdin & Epstein, 1955), it is postulated that this orthostatic reduction of urine flow in the first half-hour of standing is due to increased release of A.D.H. It was further shown in the same study that this orthostatic fall in urinary flow did not occur in patients with diabetes insipidus. However, since the urine flow subsequently decreased on standing in both groups of patients, other factors must be involved. The same conclusion was reached by Brun et al (1945), who showed that blood drawn from individuals tilted to 60° would consistently reduce urine flow when injected into other individuals undergoing a water diuresis.

Increased proximal tubular re-absorption of water and electrolytes would cause, if other factors remained constant, a decrease in urinary flow, sodium and potassium excretion, a fall in urinary osmolality and osmolar clearance, and, by decreasing the amount of solute available to the distal exchange sites, free water clearance. Various workers (Brun et al, 1945; Epstein et al, 1951; Goodyer & Seldin, 1954; Pearce & Newman, 1954; Camp et al, 1958) have shown significant falls in urinary flow, sodium and potassium on quiet standing, and, since the percentage falls have been greater than the percentage fall in creatinine clearance,

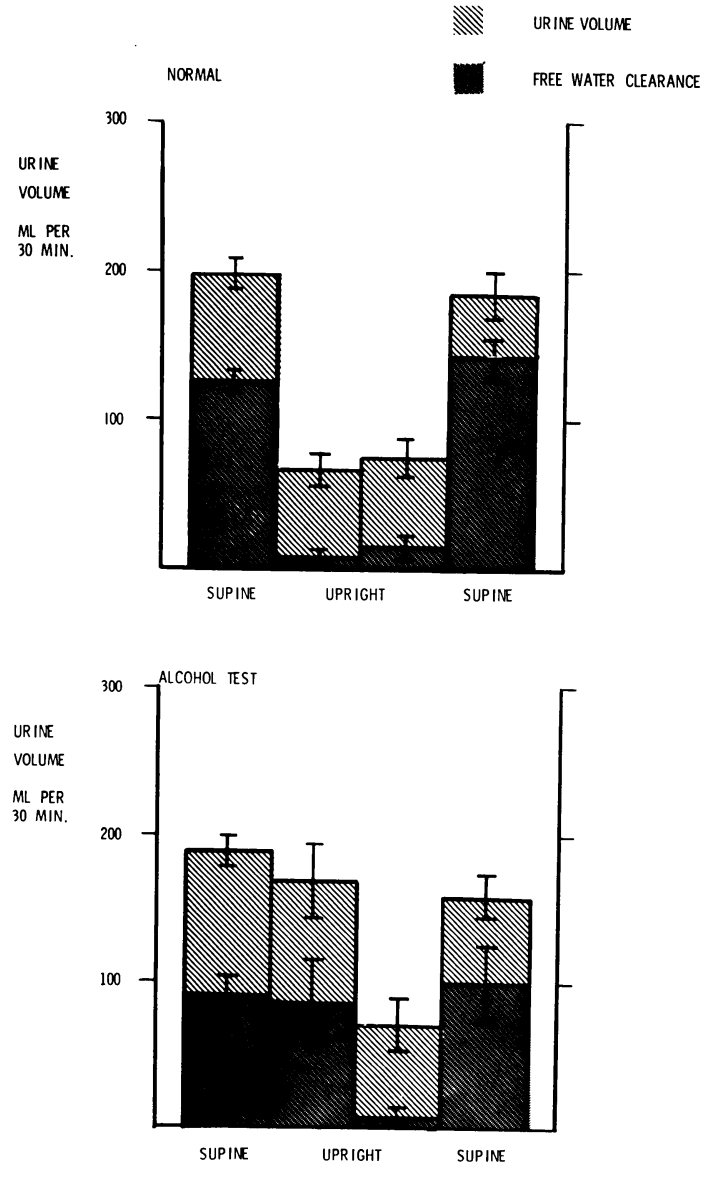


FIG. 12: The fall in urinary volume and free water clearance on standing in 13 normal subjects and the abolition of the initial fall in urinary volume and free water clearance by the prior administration of ethyl alcohol. (Streeten & Speller, 1966).

have concluded that the major cause of this fall was increased re-absorption at the proximal tubule. However, Streeten & Speller (1966), using the stress of quiet walking in normal subjects, found that sodium excretion and osmolar clearance did not fall significantly and that the marked fall in urinary flow and free water clearance was corrected with alcohol. They concluded that these findings in normal subjects could not be attributed to increased proximal tubular re-absorption of cations and water. They point out, however, that their results are at variance with other workers and attribute this difference to the fact that their patients were ambulant, which is less than the stress of being tilted to 60^{o}. No other study has examined the effect of tilt on urinary osmolality, osmolar or free water clearances.

There is very little evidence concerning the role of the distal tubular re-absorption of sodium in the anti-natriuresis of quiet standing. It is known that, on standing, plasma renin activity increases (Cohen, Rovner, Conn & Blough, 1964; Gordon, Wolfe, Island & Liddle, 1966). Balikian, Brodie, Dale, Melby & Tait (1968) showed that, in normal subjects, on standing, the plasma aldosterone concentration increased ten-fold and the blood production rate eight-fold, whilst the metabolic clearance rate decreased by 23%. These results indicated that, in this situation, it is the increase in the secretion rate, rather than the decrease in the metabolic clearance rate, which is the major factor in regulating the plasma aldosterone level. However, the response of this system to standing

is sluggish, taking several hours to act and, therefore, unlikely to be of significant importance during the usual tilting test.

There is at present very little evidence for a direct role for the renal nerves in the anti-diuresis and anti-natriuresis of standing. In a study on one human with a totally denervated kidney, resulting from the transplantation of an identical twin, the response of sodium excretion to changes of extra-vascular and intra-vascular volume was abnormal (Bricker, Guild, Reardan & Merrill, 1956). Also, patients who have renal transplants develop nocturia and increased nocturnal urinary sodium excretion, a phenomenon which may be related to posture (Lines, McMillan & Evans, 1970). The lack of renal arteriolar tone, caused by denervation,might allow the pressure sensitive zone postulated by de Bono & Mills (1965) to be exposed to small pressure changes, thus causing undue salt retention in the upright position.

Our concepts of the afferent control of the renal response to change in position from supine to upright are speculative. It has been pointed out that decrease in sodium excretion may occur in response to quiet standing, haemorrhage (Lombardo, Eisenberg, Oliver, Viar, Eddleman & Harrison, 1951; Goodyer & Jaeger, 1955) leg cuffing to prevent venous flow (Wilkins, Tinsley, Culbertson, Burrows, Judson & Burnett, 1953) and by interrupting the return flow in the inferior vena cava by inflating a balloon within its lumen (Farber, Becker & Eichna, 1953). All

these events may induce sodium retention without significant change in the glomerular filtration rate and the obvious conclusion is that the net renal tubular reabsorption of sodium has been increased. All these procedures have in common a tendency to decrease effective blood volume. Pearce & Newman (1954) abolished the orthostatic decrease in urinary flow and sodium excretion by wrapping the legs with elastic bandages, thus preventing the orthostatic fall in blood volume. On the other hand, Epstein et al (1951) could not abolish the fall in urinary volume and sodium on standing by expanding plasma volume with an albumin infusion. These findings may be reconciled by postulating that it is the effective blood volume sensed by a "volume receptor" situated in the cephalad part of the body rather than the total plasma volume which is important. It is known that, in the early stages of haemorrhage, the blood pressure remains unchanged until about 24% of the blood volume is lost. During this phase, the rate of firing of aortic arch baroreceptors is unchanged. However, the firing of the stretch receptors in the right atrium falls even with small reduction in blood volume (Henry, Gupta, Meehan, Sinclair & Share, 1968). It is well known that sodium retention occurs with haemorrhage, even with no fall in blood pressure (Mills, 1970). Thus, the orthostatic fall in urine flow may be mediated by a combination of stretch receptors sensitive to volume changes, and basoreceptors sensitive to small changes in arterial pressure, caused by volume changes elsewhere in the body.

THE RESPONSE TO CHANGE OF POSTURE IN IDIOPATHIC OEDEMA

The adaptation to change in posture from the supine to the upright position has been well studied in idiopathic oedema. These studies were initially prompted by the clinical observation that the diurnal weight gain was excessive and could be abolished if the patient remains supine. Following this clinical observation and the important lead given by the earlier investigators, many workers studied the renal elimination of standard water loads in patients with idiopathic oedema, in both the supine and upright positions. Later, as the methodology became available, the renin-angiotensin-aldosterone system was examined in relationship to change in position. More recently, attention has been focussed on the haemodynamic changes in this condition on standing. Finally, the possible central position of the sympathetic nervous system in the pathogenesis of idiopathic oedema has been examined. Unfortunately, and this is a constantly recurring theme, the patients studied have been a heterogeneous group and criteria for inclusion vary with the investigators. I propose to review firstly the haemodynamic and blood volume changes on moving from the supine to the upright position in patients with idiopathic oedema; secondly, the various components of the renal response and, thirdly, the changes in the sympathetic and renin-angiotensin-aldosterone system. Finally, I will present a unifying hypothesis for the condition.

As discussed in the preceding section, the fall in the effective blood volume on standing provokes various compensatory adaptive responses. It would be logical to assume that this is a graded mechanism, i.e., the greater the fall in the effective blood volume, the more intense the activity of the compensatory mechanisms. On the one hand, therefore, the excessive orthostatic anti-diuresis and anti-natriuresis of idiopathic oedema could be the appropriate response to an increased fall in effective blood volume; on the other hand, it could be due to the inappropriate over-activity of such compensatory mechanisms. In normal subjects, the plasma volume decreases by up to 7% on quiet standing (Eisenberg & Wolf, 1965). Fawcett & Wynn (1960) showed that, in oedematous patients of varying aetiology, the fall was greater, up to 21%. Whereas the decrease in plasma volume was maximal at fifteen minutes in their normal subjects, the decrease continued and was maximal at one hour in their abnormal group. It is noteworthy that one of their patients suffered from idiopathic oedema and the decrease in plasma volume on standing was 17%. In two patients of Kuchel, Cuche & Barbeau (1969) with idiopathic oedema, the postural fall in plasma volume was 17% and 12% respectively. Gill et al (1971) have shown that mean plasma volume in supine patients with idiopathic oedema was 35.99±1.66 (S.E.M.) ml/kg., which was significantly lower ($P<0.01$) than the mean values 45.5±1.35 ml/kg. in normal subjects. Recent studies have emphasised the greater pos-

tural fall in systolic blood pressure associated with the greater increase in leg volume in patients with idiopathic oedema (Kuchel et al, 1970; Lagrue et al, 1971). In the study of Kuchel et al (1970), a comparison was made of several components of the adaptation reaction to upright posture in a group of twenty-one patients with idiopathic oedema and a group of twenty-one healthy women in the reproductive period. The patients with idiopathic oedema had a greater fall in systolic blood pressure when standing (7.9±1.3 (S.E.M.) against 2.6±1.3 mm.Hg) and a greater increase in calf volume after four hours of walking (284±20 against 137±16 ml.). However, the increase in calf volume be due to either increased capillary filtration or increased venous pooling. Unfortunately, the study did not distinguish between the two mechanisms,Fig.1. A decrease in plasma volume associated with an increase in leg volume suggests that fluid is lost from the vascular system rather than pooled in the leg veins. The critical experiment would have been to compare the change in leg volume within the first half minute of immersion in the water bath with the change after one hour of quiet standing.

In a recent study, Streeten and his colleagues (1973) studied thirty-one patients with idiopathic oedema under standard metabolic conditions. They measured plasma volume using ^{125}I or ^{131}I labelled serum albumin, both in the supine position and one to four hours after getting out

of bed. These tests were repeated whilst on a constant 200 m.mol or 10 m.mol sodium diet. They also measured leg volume by a simple water displacement method. The results obtained were compared with those obtained from ten normal female subjects. They found that, in the normal female subjects, the fall in plasma volume on changing from the supine to the upright was 3.5±2.13% (S.E.M.) at one hour on the 200 m.mol sodium diet, and 4.3±1.48% and 4.51±1.6% at four hours on the high and low sodium diets respectively. In the patients with idiopathic oedema, the fall in plasma volume was only significantly different in the group termed "orthostatic sodium retainers", because of the excessive fall in urinary sodium in the upright position. The fall in this group of plasma volume at one hour was 9.94±1.55%, a difference which is significant statistically ($P<0.05$). The cumulative changes in leg volume were found to be significantly different from the control subjects in the groups termed "orthostatic water retainers" and "orthostatic sodium retainers". The finding that the plasma volume changes on standing were only significantly different in the group termed "orthostatic sodium retainers" is probably due to the criteria for inclusion into the study. The main criteria for inclusion were demonstrable pitting oedema of the legs and sometimes elsewhere, after the usual causes had been excluded. Kuchel and his colleagues (1970) restricted their patient selection to that of Thorn (1968) and to the physiopathologic variety, known since Mach and his co-workers in 1955, namely the patients with un-

explained oedema and secondary hyperaldosteronism. It is, therefore, of considerable interest to note that the group Streeten et al (1973) delineated as "orthostatic sodium retainers" was the group in which a substantial number had secondary hyperaldosteronism. It is probable that, because of their method of patient selection, their subjects represent a heterogeneous group, with the disease varying from the very mild to the very severe.

Some of the most persuasive evidence of the effect of posture in idiopathic oedema has come from case reports. In a thirty-nine year old female patient with idiopathic oedema reported by Greenaugh et al (1962), the presenting symptoms were of postural hypotension and anasarca. In this case, tilting to the upright position lowered the systolic blood pressure, despite an increased plasma volume. It was suggested that these findings could be explained by venous pooling, due to decreased venomotor tone, and the patient responded to sympathomimetic agents with loss of oedema. In a similar case reported by Fischer & Morris (1965), it was postulated that a defect in peripheral venous structure or autonomic innervation had led to excessive blood volume pooling in the lower limbs, which had in turn led to increased retention of salt and water. The measured decrease in blood volume in this case, after ten hours of standing, was 38%. Ross et al (1958) described a woman with anasarca and hyperaldosteronuria, which was attributable to abnormal capillary leakage of protein.

Thus, on standing, there appears to be a greater fall in effective blood volume in patients with idiopathic oedema, a fall which may be either due to increased venous pooling or to increased sequestration of fluid outside the intra-vascular space, or to a combination of the two mechanisms. This greater than normal fall in effective blood volume stimulates other adaptive responses, which will be discussed.

Streeten & Conn (1959) described oedema of unknown origin in six women who demonstrated excessive daily weight gain, reversal of the normal diurnal variation of water excretion, and an inability to excrete a water load normally when erect, whereas a diuresis occurred when supine. Since,then, this abnormal response to a water load has been well documented and the quantitatively greater retention of water and electrolytes in the upright position in idiopathic oedema demonstrated. Many studies have attempted to determine the main intra-renal site for this increased re-absorption.

As discussed before, a fall in glomerular filtration rate, provided other changes in renal function to not occur, will cause a reduction in urine volume, a decrease in sodium and potassium excretion and a reduction in the osmolar and free water clearances, whilst the urine osmolality will remain unchanged. Whilst changes in renal tubular re-absorption are generally acknowledged to be more potent than changes in glomerular filtration rate as a mechanism for the alteration in urinary sodium excretion (de Wardner, 1969; Earley & Daugharty, 1969), it has been

pointed out that a fall in glomerular filtration rate induced by aortic constriction is associated with either no change or with an increase in the fractional tubular re-absorption of sodium, and these changes inevitably result in decrease in sodium excretion, both in rats (Glabman, Aynedjian & Bank, 1965; Rector, Brunner & Seldin, 1966) and in dogs (Lindheimer, Lalone & Levinsky, 1967; Dirks, Cirksena & Berliner, 1965). Streeten & Conn (1960) did not find a consistent decrease in creatinine clearance on standing in patients with idiopathic oedema. Streeten & Speller (1966), in their study, compared thirteen normal female subjects with thirteen patients with idiopathic oedema. The diagnosis of idiopathic oedema was based on the observation of oedema in the late afternoon and a history or obvious evidence of oedema of the face and hands in the morning, the usual causes of oedema being excluded. The time in the menses during which the effect of change in posture from the supine to the upright on urinary flow and electrolyte excretion was not specified in either group. No information was also given as to whether the patients were pre or post-menopausal. They found a reduction of 8.4% in the creatinine clearance on standing in their patients with idiopathic oedema, and thought it unlikely that such a small change could account for the falls of 85% and 80.5% for urinary volume and urinary sodium respectively. Kuchel and his colleagues (1970) studied the effect of change of posture from the supine to the upright on twenty-one patients with idiopathic

oedema, selected initially by the criteria of Thorn (1968),and compared the results obtained with twenty-one normal female subjects investigated in the post-menstrual phase. They doubted the reliability of urinary creatinine estimations in polyuria and could not resolve whether the fall in urinary flow and sodium on standing was due to a fall in the glomerular filtration rate. They later, however, expressed the sodium excretion per gramme of creatinine, in order to compensate for changes in glomerular filtration rate. Streeten et al (1973) found in the group termed "orthostatic sodium retainers" an excessive reduction in the glomerular filtration rate of about 35% on standing, as compared with the control group. However, the glomerular filtration rate in the supine position in "orthostatic sodium retainers" was 24% higher than in the control group, whilst there was no significant difference in the sodium excretion. Furthermore, glomerular filtration rate in the upright position was not significantly different between both groups. There is, thus, very little evidence that the fall in urinary flow and electrolytes on standing in patients with idiopathic oedema is mediated by a fall in the glomerular filtration rate.

In normal subjects, the posturally induced fall in urine flow and sodium excretion on standing is thought to be due to increased re-absorption of water and electrolytes in the proximal tubule. Studies to determine the intra-renal site or sites for the increased re-absorption of water and electrolytes in patients with idiopathic oedema have, in the main, been inconclusive. This is mainly

because they have failed to study the effect of posture on sustained water diuresis and have relied on standard water loads. Few studies have measured the urinary osmolality and free water clearance. Streeten et al (1966), in their study, compared the effect of posture on thirteen normal female subjects and thirteen patients with idiopathic oedema during a diuresis induced by ingesting 150 ml. of 0.14% saline half-hourly. They found a fall in urinary sodium of about 56% in the first period and 81% in the second period in the upright position. The urinary volume also fell, being 76% and 85% respectively. The free water clearance fell also, but the urine osmolality rose, making it difficult to assess the relative contribution between proximal and distal tubular re-absorption of water. However, the fall in urine flow was not entirely corrected with alcohol, suggesting that a factor other than increased anti-diuretic hormone release was responsible for the excessive magnitude of the orthostatic anti-diuresis. That this factor is probably increased proximal tubular re-absorption of water and electrolytes is suggested by the evidence that the fall in free water clearance in the first hour standing after ethanol administration is accompanied by a fall in urine osmolality. Streeten and his colleagues (1966) then administered spironolactone for two days and repeated the tilting tests in an attempt to assess the contribution of increased aldosterone production. They found that the falls in urinary sodium for the first two half hours standing were 60% and 73%

respectively, values which were not significantly different from the tests performed before spironolactone administration. The sodium excretion when supine was significantly elevated following spironolactone administration. There is, therefore, no evidence to support their conclusion that the orthostatic fall in sodium excretion is mediated by increased aldosterone production. No information was given in this paper on urinary potassium excretion.

Kuchel et al (1970) again found increased sodium and water re-absorption in response to change in posture from the supine to the upright in patients with idiopathic oedema. They compared the effect of standard water load on urinary volume and sodium excretion in the upright position in normal subjects and patients with idiopathic oedema, Fig.13 The differences in urinary volume and sodium excretion between the two groups were 45% and 83% respectively. In order to compensate for changes in glomerular filtration rate, they expressed the sodium excretion per gramme of creatinine. Since the sodium excretion per gramme of creatinine was significantly lower in the upright position, they concluded that the observed decrease in sodium excretion may be due to increased proximal tubular re-absorption of sodium. They further concluded that the prevention of excessive postural anti-natriuresis and concomitantly of the excessive postural induced increase in plasma renin activity by bandaging seemed to indicate that the pooling induced hypovolaemia leads, at least in part, to sodium retention by excessive stimulation of the renin-angiotensin-

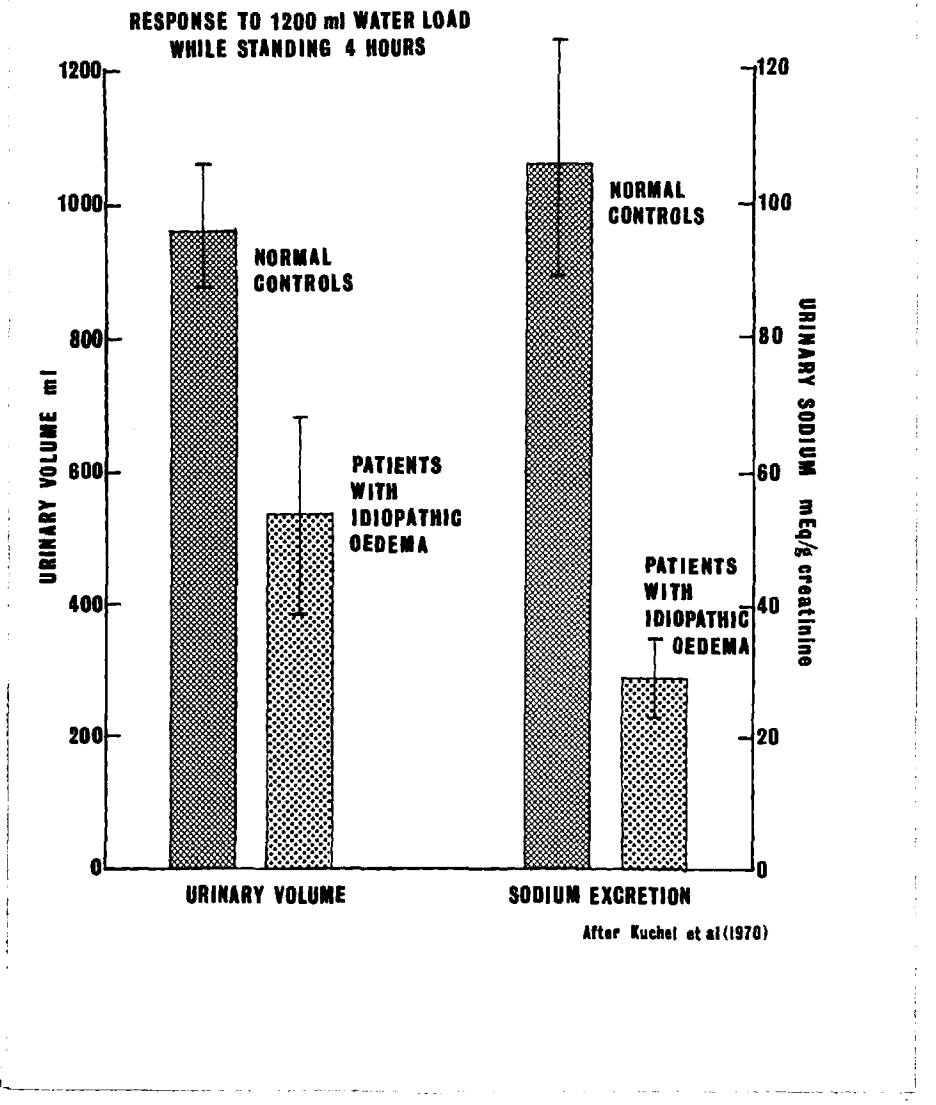


FIG. 13: The response to a 1200 ml. water load while standing for four hours on urinary volume and urinary sodium expressed per gramme of creatinine in 21 normal female subjects and 21 patients with idiopathic oedema in the immediate post-menstrual phase.

aldosterone system. Their final conclusion was that the comparison of the urinary volume, tubular rejection fraction and urinary sodium concentration every hour after the water load increased the possibility of higher activity of antidiuretic hormone in the initial phase, whereas the decrease in urinary volume later was caused by aldosterone-induced sodium retention. This conclusion is hard to sustain, particularly as there is no data on urinary osmolality and urinary potassium excretion. Aldosterone is also not known to have an effect on decreasing urinary flow. Also, the simple reduction in orthostatic anti-diuresis and anti-natriuresis by leg bandaging, presumably by decreasing posturally induced hypovolaemia, may as equally affect other compensatory renal responses. Streeten et al (1963) attributed the fall of sodium excretion on standing in the patients with idiopathic oedema, termed "orthostatic sodium retainers", as being due to a combination of secondary hyperaldosteronism and an excessive fall in the glomerular filtration rate. They postulated that the fall in the glomerular filtration rate was sufficient to overpower the corrective adjustments made by the tubule. However, the finding of excessive fall in glomerular filtration rate on standing in patients with idiopathic oedema has not been generally found.

Orthostatic hyperaldosteronism in patients with idiopathic oedema has been well documented and has been thought to play an important part in the pathogenesis of the condition (Mach et al, 1955; Luetscher & Lieberman, 1957;

Streeten, 1960a; Hill, Hood, Farmer & Burnum, 1960; Streeten et al, 1960; Thorn, 1968; Kuchel et al, 1970; Lagrue et al, 1972; Streeten et al, 1973). These studies have attempted to relate the increased anti-natriuretic and anti-diuretic effect of standing in patients with idiopathic oedema to this increase in aldosterone secretion. However, as shown in the previous paragraph, this is unlikely to be more than a contributory factor. Kuchel et al (1970) demonstrated that the aldosterone excretion between 8 a.m. and noon, with the subjects first recumbent and then upright, on different days, was significantly higher,compared with normal subjects,in both positions in patients with idiopathic oedema. The data on plasma renin activity indicated that, in patients with idiopathic oedema, the recumbent values at 8 a.m. were in the normal range of the control subjects with the same sodium intake. In response to four hours of standing, the increase in plasma renin activity was significantly higher in patients with idiopathic oedema than in control subjects. Leg bandaging during standing prevented any increase in plasma renin activity. The urinary excretion of noradrenaline and adrenaline was not, however, significantly different between the two groups. Since sympathetic discharge is considered an important link between postural-induced hypovolaemia and the stimulation of renin on standing (Gordon, Kuchel & Liddle, 1967), this reported finding of the normal excretion of urinary catecholamines is surprising. However, Gill et al (1972) found significantly

increased daily urinary noradrenaline excretion in patients with idiopathic oedema compared with normal subjects, 78±10 (S.E.M.) µg/day and 44±3.0µg/day respectively. They also found a significantly raised plasma renin activity and aldosterone secretion rates in patients with idiopathic oedema, and concluded that the abnormally high adrenergic activity could explain the abnormally high plasma renin activity. That the increase in plasma renin activity, urinary aldosterone and the decrease in cations and water on standing is related to a fall in effective blood volume has been demonstrated among others by Kuchel et al (1970), who showed that leg bandaging could abolish these changes.

Indeed, this elevation in the plasma renin activity may be considerably reduced by the exhibition of propranalol, a β adrenergic blocker, Fig.14 . Streeten et al (1973) found surprisingly that plasma renin activity was sometimes elevated in the "orthostatic water retainers" but virtually never elevated in the "orthostatic sodium retainers", whilst the latter group contained the subjects with secondary hyperaldosteronism. They postulated that the hyperaldosteronism in these patients is either not mediated by the renin-angiotensin-aldosterone system, or results from increased aldosterone secretion in response normal amounts of plasma-renin activity. This finding is in contradistinction to that found by other workers. They also showed that about half of the patients with "orthostatic sodium retention" had orthostatic hyperaldosteronism and that this group excreted significantly more

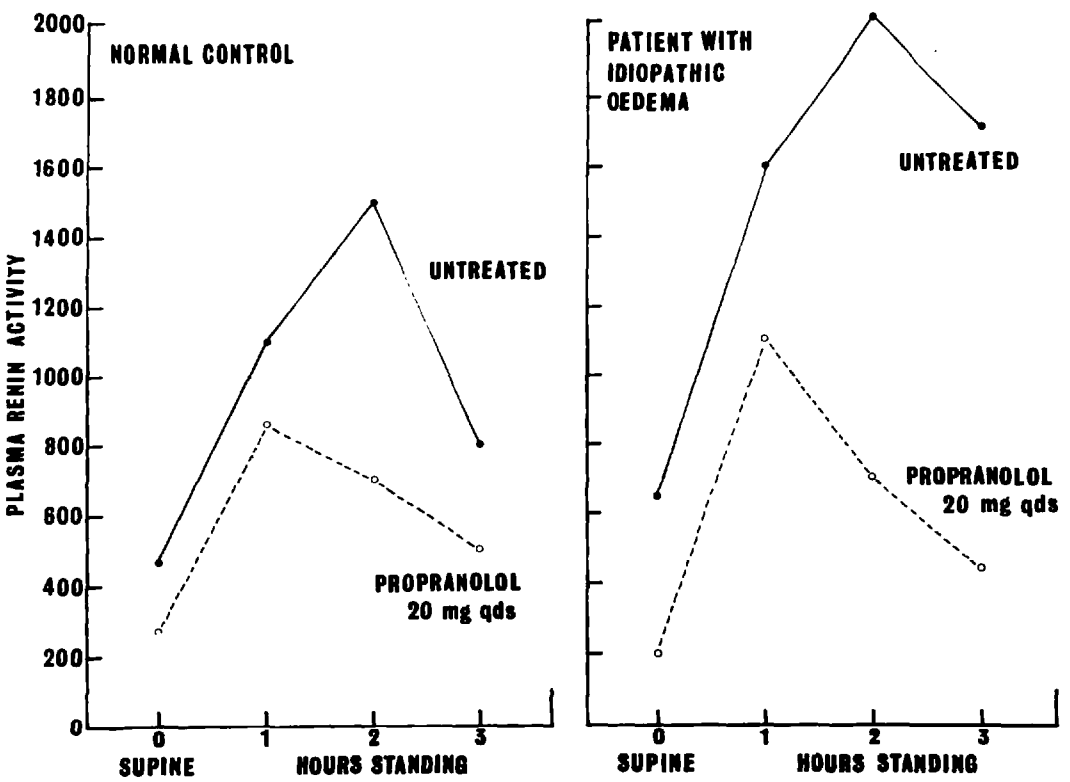


FIG. 14: The effect of propranalol, a β adrenergic receptor blocker, on the posturally induced rise in plasma renin in the normal subject and on the greater rise in a patient with idiopathic oedema. (Bayliss, Croonian Lecture, 1974. Unpublished Observations).

potassium in the upright position. They concluded that hyperaldosteronism was, therefore, an important mechanism in the orthostatic anti-natriuresis.

Increased release of anti-diuretic hormone in the upright position would decrease urinary volume and free water clearance and increase urine osmolality, but leave urinary excretion of electrolytes unchanged. Streeten & Conn (1959) showed that patients with idiopathic oedema could be sub-divided into two groups on the basis of their response to a water load in the upright position following the prior administration of ethanol: in one group the prior administration of ethanol, a potent inhibitor or A.D.H., abolished the orthostatic anti-diuresis, whilst in the other it did not. Streeten & Speller (1966) found that the excessive magnitude of the orthostatic diuresis could not be completely overcome by ethanol. Kuchel et al (1970) could not resolve whether the posturally induced anti-diuresis of the first hour standing was due to decreased glomerular filtration rate or increased tubular re-absorption of free water, due to increased A.D.H. secretion. Streeten et al (1973) found a group of patients with idiopathic oedema,whom they categorised as "orthostatic water retainers" because they retained water but not sodium excessively in the upright position. They postulated that this orthostatic anti-diuresis was mediated by increased A.D.H. secretion, but unfortunately no urinary osmolality data was available. As discussed previously, it is important to note that this sub-group did not have an excessive fall in plasma volume or glomerular filtration

rate on standing, or have secondary hyperaldosteronism. They, therefore, probably represent a group with the less severe manifestation of the disease.

The effect of increased environmental temperature on postural anti-diuresis and anti-natriuresis in a patient with idiopathic oedema, studied by Streeten (1960), is seen in Fig. 14 . The patient was tilted from the supine to the upright position in a cold room and then in a warm room. The gain in weight and the anti-diuresis was greater when the patient was tilted in a warm room. This is presumably the reason why there is such a good correlation between environmental temperature and evening body weight, Figs. 4 & 5 , and for the increased frequency of the condition in warmer climates.

It is apparent that, having delineated this disease on the basis of the clinical criteria,much attention has been focussed on the renal response to change in position from the supine to the upright. I propose to show that the renal response is compensatory for the excessive fall in effective blood volume on standing.

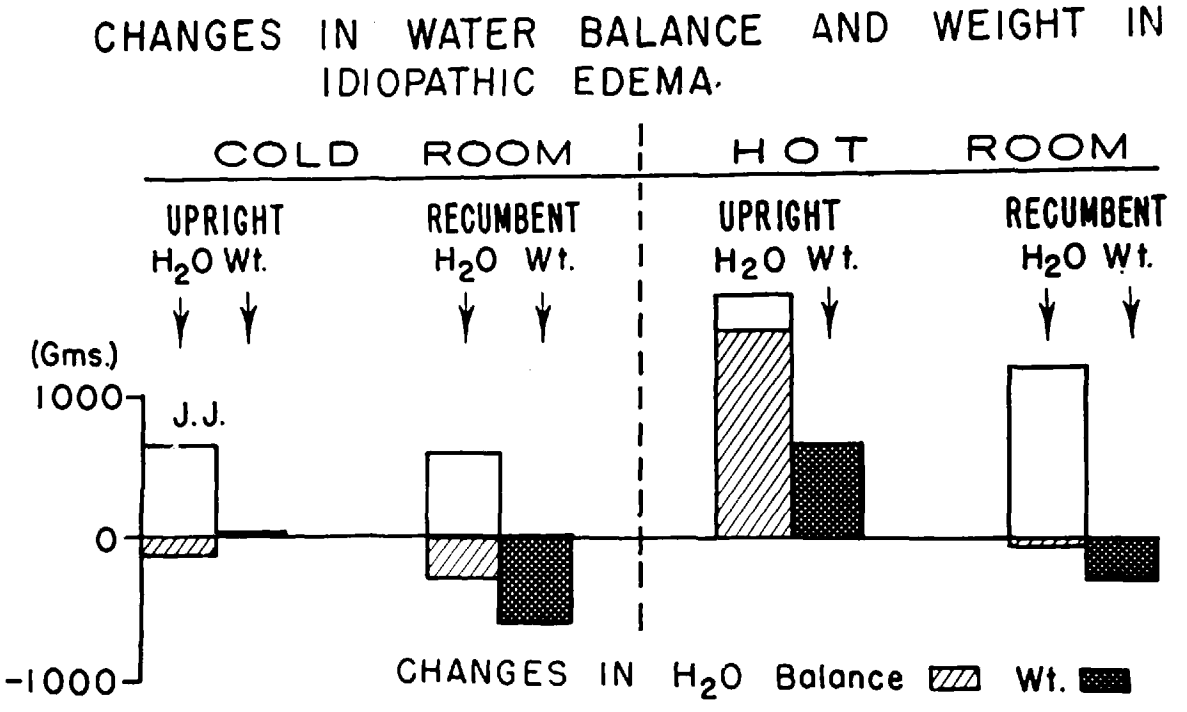


FIG. 15: Changes in water intake, urine output and weight in a woman aged 36 years with idiopathic oedema over 7-hour periods in the upright or supine position. Temperature in the cold room: 0-7°C, in hot room: 33-35°C. Water intake plotted from base line upward, urine output from top of intake column downward. Weight gain plotted upward, weight loss downward from base line. (Streeten, 1960).

SUBJECTS AND METHODS

SUBJECTS

The control subjects for the tilting tests were all healthy female medical students with regular menses, aged between eighteen and twenty-four years. They gave no history of oedema and were not taking oral contraceptives.

The eleven patients with idiopathic oedema were diagnosed in all instances by a typical history of irregular bouts of non-pitting oedema affecting the face, breasts and hands, together with abdominal distension and pitting oedema of the lower limbs. A daily weight chart was kept in which they recorded their morning and evening weights and a daily weight gain in excess of 1.4 Kg. was taken as evidence of excessive daily weight gain. The patients showed no evidence of heart disease, hypertension, intrinsic renal or hepatic disease, thyroid disease, hypoproteinaemia or allergic disease. A careful clinical history and physical examination was performed and the following routine investigations conducted: chest X-ray, electrocardiograph, blood urea and electrolytes, creatinine clearance, urinalysis, liver function tests, i.e. serum bilirubin, alkaline phosphatase and serum glutamic pyruvate transaminase, plasma protein electrophoresis and thyroid function tests, Tables 2 & 3.

TABLE 2: The clinical data on the patients with idiopathic oedema.

Patient No.	Age at Test (years)	Menses	Length of History (years)	Weight (Kg.)	Blood Pressure (mm.Hg.)	Test	Other
1	39	+	6	52.2	130/90	1	
2	34	+	3	57	100/70	1	
3	27	+	3	54	110/70	1	Acute pyelonephritis
4	51	+	7	65	125/80	1,2,3	
5	39	+	2	55	120/80	1,2	
6	23	+	4	52	120/76	1,2	
7	32	+	7	66	110/70	1	
8	51	O	2	107.8	140/90	13	
9	49	O	20	82.5	110/70	1,2,3	
10	53	O	5	76	120/80	1	
11	54	O	12	51.2	130/90	1	Raynaud's disease
12	32	+	2	55	125/80	2	Recurrent abortion
13	49	+	20	66.8	140/90	2	
14	48	+	20	77.1	130/90	3	
15	22	+	3	61.8	110/70	3	
16	23	+	8	70	110/75	3	
17	34	+	1.5	74	125/85	3	Gilbert's disease
18	45	+	3	73	130/90	3	Chronic cholecystitis
19	19	+	3	57	128/60	3	

Abbreviations: O, post-menopausal; +, pre-menopausal, Tests: 1, tilting test, 2, plasma volume and capillary permeability estimation using ^{125}I labelled albumin, 3, the response to the administration of 9α fluorohydrocortisone.

TABLE 3: Clinical and laboratory data on patients with idiopathic oedema.

Patient No.	Blood urea (mg/100ml)	C_{cr} (ml/min)	Urinalysis		E.C.G.	CXR	P_{pr} (gm/100ml)	Liver Function Tests	
			Proteinuria	Glycosuria				S.G.P.T.	Alkaline phosphatase
1	22	99	O	O	N	N	6.9	N	N
2	20	95	O	O	N	N	7.4	N	N
3	-	83	O	O	-	N	N	N	N
4	20	90	O	O	N	N	7.9	N	N
5	24	87	O	O	N	N	7.1	N	N
6	25	74	O	O	N	N	8.6	N	N
7	-	95	O	O	-	N	N	N	N
8	34	108	O	O	N	N	7.1	N	N
9	17	94	O	O	N	N	7.5	N	N
10		111	O	O	N	N	6.8	N	N
11	27	99	O	O	N	N	7.8	N	N
12	23	-	O	O	-	N	7.2	N	N
13	15	-	O	O	N	N	6.7	N	N
14	26	84	O	O	-	N	7.0	N	N
15	17	140	O	O	-	N	6.7	N	N
16	22	99	O	O	-	N	6.2	N	N
17	20	91	O	O	N	N	6.8	N	N
18	20	110	O	O	N	N	7.2	N	N
19	20	98	O	O	-	N	6.7	N	N

TILTING TESTS

Observations were made on each pre-menopausal subject on the eighth to ninth day and again on the twentieth to twenty-first day of the menstrual cycle. On each occasion a light breakfast was allowed, but smoking forbidden. No attempt was made to standardise the diet during the preceding days. At 09.00 hours, the subject emptied her bladder and was weighed. She then lay supine on a tilting table and drank 20 ml. of water per kilogram of body weight. During the period of the study, the bladder was emptied hourly and a volume of water was drunk equal to that of the urine voided. When a constant diuresis had been established, usually by 11.00 hours, urine was collected hourly for analysis for two hours (11.00 to 12.00 and 12.00 to 13.00 hours). At the end of this time, usually by 13.00 hours, the subject was tilted 80° towards the upright position and urine collected for a further hour. The tilted position is referred to hereafter as "upright".

An indwelling catheter was inserted into a forearm vein under local anaesthesia between 09.00 and 10.00 hours. Blood samples were taken without veno-constriction at 13.00 and 14.00 hours, at the end of the supine and upright periods respectively. The observations were made in a quiet, warm room with only essential personnel in attendance.

The same procedure was performed in post-menopausal patients a fortnight apart.

CHEMICAL METHODS

Urinary and serum creatinine was measured by the Jaffe reaction according to the method of Wooton (1964). Sodium and potassium were measured, using an E.E.L. flame photometer. Osmolality was determined without delay on an "Advanced Instruments" osmometer. Packed cell volume (PCV) determinations were made in duplicate in Wintrobe tubes, using a centrifuge of 15 cm. radius at 3,000 r.p.m. for fifty-five minutes.

CALCULATIONS

Free water clearance (C_{H_2O}) was calculated as the excess of solute free water relative to the simultaneous osmolal clearance (C_{osm}) from the formula

$$C_{H_2O} = V - \frac{U_{osm.}V}{S_{osm}}$$

where U_{osm} and S_{osm} are urinary and serum osmolality in mosmol/kg. and V is the urinary volume in ml./min.

The percentage of the filtered load of sodium excreted in the urine (the fractional sodium excretion or E_{Na}) was calculated as $(U_{Na.}V/F_{Na}) \times 100$, where $U_{Na.}V$ = urinary sodium excretion (μmol/min), F_{Na} = filtered sodium = $S_{Na}.f.GFR$, where S_{Na} = serum sodium concentration (m.mol/l.), f = Gibbs-Donnan factor (0.95) and G.F.R. = glomerular filtration rate in ml./min, as estimated by endogenous creatinine clearance. None of these results was connected to standard body surface area. The amount of sodium excreted was expressed in both absolute terms or per 100 ml. of creatinine clearance. The difference between the sodium excreted per 100 ml. of creatinine clearance in periods 12.00-13.00 hours and 13.00-14.00 hours was expressed as a percentage of the period 12.00-13.00 hours.

THE ESTIMATION OF CHANGE IN PLASMA VOLUME ON STANDING AND CAPILLARY PERMEABILITY TO PROTEIN IN PATIENTS WITH IDIOPATHIC OEDEMA

Subjects

It was felt to be unethical to give normal female volunteers even small amounts of radioactive iodine, so the tests were performed only in patients with idiopathic oedema and reliance was placed in the published results for values in normal subjects, Tables 2 & 3.

Method

Iodinated (^{125}I) human albumin injection B.P., as supplied by the Radiochemical Centre, Amersham, in single dose disposable syringes (Code I.M.45P). The activity injected was between 3-5 UCi ^{125}I bound to between 10-20 mg. of human albumin. Not more than 5% of the iodine was free. Pre-treatment of the patients with potassium iodide was not performed.

The intravenous injection of the labelled albumin was given during the second collection hour whilst supine. Three blood samples were taken without cuff pressure from the opposite arm at approximately fifteen minute intervals. The patient was then tilted to the upright position and a further three samples taken. Difficulty in taking blood samples was occasionally experienced, particularly when upright.

Measurement

The activity of the syringe before and after injection was measured. Samples of plasma were counted against a ^{125}I standard in a sodium iodide well-type scintillation counter for 10,000 counts. The measurement was repeated and the mean of the two results was expressed as a percentage of the dose injected per litre of plasma.

Calculation

The logarithms of the plasma concentration results were plotted against time. Best fit lines were calculated for the "lying" and "standing" points, using the least squares method. Extrapolation to zero time yielded the initial concentration of ^{125}I and the plasma volume was obtained by dividing the injected dose by this initial concentration. From the slopes of the lines, the rate of loss of activity was found and expressed as a percentage loss per hour. The difference between the lines at the time of the change in position expressed as a percentage and multiplied by the plasma volume gave the change of volume with posture. These calculations were performed on the University of Cambridge Titan computer.

THE EFFECT OF 2-METHYL-9 ALPHA FLUOROHYDROCORTISONE IN PATIENTS WITH IDIOPATHIC OEDEMA

Patients with idiopathic oedema were given a low salt (10 mEq sodium) daily diet to which 5 gm. of sodium chloride was added in the form of gelatin capsules. The patients were weighed daily and the blood pressure estimated at least twice daily. Urine was collected in daily aliquots. When the weight and sodium excretion were stable, the effect of 2-methyl 9 alpha fluorohydrocortisone (1 mg. every four hours) was studied. Careful observations were maintained for the signs of heart failure or excessive weight gain and the test stopped if these occurred. Otherwise the test continued until the patient was in sodium balance, Tables 2 & 3.

RESULTS

URINARY EXCRETION OF WATER AND ELECTROLYTES IN NORMAL FEMALES DURING THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE: THE EFFECT OF POSTURE.

The results of each individual subject are given in Table 4.

Constancy of hydration

The adequacy of the method used to maintain a steady state of hydration was assessed, whilst the subjects were supine, by comparing the mean urinary excretion in the first and second hour (11.00-12.00 and 12.00-13.00 hours) during both the follicular and luteal phases. At neither time in the menstrual cycle was there any significant statistical difference between the observed or calculated results obtained in the first as compared with the second hour, Table 5 . A trend towards a higher sodium excretion was noted, which did not, however, become statistically significant.

Differences between the follicular and luteal phases in the supine position

When the subjects were in the supine position, the mean values for the volume and urinary composition during the follicular and luteal phases of the cycle were not statistically different, Table 6.

TABLE 4: The urinary composition packed cell volume in the supine position (11.00-12.00 and 12.00-13.00 hours) and during the upright position in eight normal, well hydrated subjects in the follicular and luteal phases of the menstrual cycle

Case no. & phase of cycle	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	U_{Na}/K	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
1_F	S	12.6	74		3.2	9.4	229	116	327	2.0	70		0.40		2.4	
	S	13.7	58	288	2.7	11.0	291	102	331	2.9	88	144			2.4	
	U	12.9	66		2.9	10.0	273	71	300	3.8	91		0.42	+5	2.2	-9
1_L	S	12.5	79		3.4	9.1	227	101	191	2.2	119		0.39		1.4	
	S	12.8	82	288	3.6	9.2	270	138	344	2.0	79	141			2.6	
	U	10.0	82		2.8	7.2	211	110	192	1.9	110		0.41	+5.2	1.4	-44
2_F	S	14.4	69		3.5	10.9	285	69	244	4.1	117		0.40		1.8	
	S	17.1	78	285	4.7	12.4	344	61	222	5.6	155	140			1.7	
	U	14.1	78		3.8	10.3	187	28	220	6.6	85		0.42	+5	1.7	-1
2_L	S	12.7	72		3.2	9.5	172	105	116	1.6	148				0.8	
	S	13.8	52	283	2.5	11.3	237	57	155	4.2	153	146	0.39		1.1	
	U	10.3	58		2.1	8.2	127	33	95	3.8	133		0.42	+7.6	0.7	-39

Case no. & phase of cycle	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_K.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	U_{Na}/K	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
	S	14.8	63		3.3	11.5	271	108	230	2.5	118				1.75	
3_F	S	15.8	67	285	3.7	12.1	315	121	246	2.6	128	138	0.43		1.9	
	U	11.5	56		2.3	9.2	226	72	229	3.1	99		0.45	+4.7	1.7	-7
	S	15.1	46		2.5	12.6	140	165	135	0.8	104		0.41		1.0	
3_L	S	13.2	46	282	2.1	11.1	168	138	200	1.2	84	138			1.5	
	U	11.3	51		2.0	9.3	117	58	111	2.0	105		0.44	+7.3	0.85	-44
	S	16.5	68		4.0	12.5	313	56	244	5.6	129				1.8	
4_F	S	14.5	56	276	2.9	11.6	210	65	167	3.2	126	140	0.40		1.3	
	U	12.5	47		2.1	10.4	143	61	98	2.3	146		0.43	7.5	0.7	-41
	S	14.4	70		3.6	10.8	291	92	239	3.2	122				1.8	
4_L	S	12.5	69	282	3.0	9.5	220	67	198	3.3	111	140	0.40		1.5	
	U	9.8	57		2.0	7.8	124	45	109	2.8	115		0.42	5.0	0.8	-45
	S	13.3	-		-	-	-	-	-	-	-				-	
5_F	S	14.5	88	279	4.6	9.9	293	132	220	2.2	133	152	0.44		1.52	
	U	11.3	73		3.0	8.3	172	73	132	2.3	130		0.47	6.8	0.90	-40
	S	14.2	64		3.4	10.8	144	170	117	0.8	123				0.9	
5_L	S	12.7	77	266	3.7	9.0	152	159	124	0.9	123	139	0.42		0.9	
	U	6.3	66		1.6	4.7	49	55	52	0.9	95		0.46	9.5	0.4	-58

Case no. & phase of cycle	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
	S	16.6	65		4.0	12.6	243	116	234	2.1	104				1.6	
6_F	S	15.8	64	272	3.7	12.1	206	89	204	2.3	101	147	0.38		1.5	
	U	12.0	52		2.3	9.7	168	76	153	2.2	110		0.40	5.3	1.1	-25
	S	14.2	63		3.3	10.9	250	98	251	2.6	99		0.37		1.9	
6_L	S	15.3	61	275	3.4	11.9	273	101	255	2.7	107	142			1.9	
	U	10.0	55		2.0	8.0	127	45	156	2.8	81		0.41	10.8	1.2	-38
	S	10.9	70		2.6	8.3	175	68	178	2.6	98				1.3	
7_F	S	10.7	74	286	2.7	8.0	192	61	191	3.1	100	142	0.41		1.4	
	U	10.2	68		2.4	7.8	163	18	159	9.0	102		0.43	+4.9	1.2	-17
	S	12.7	64		2.9	9.8	155	87	167	1.8	93				1.3	
7_L	S	11.7	60	282	2.5	9.2	148	72	144	2.1	103	141	0.40		1.1	
	U	7.4	68		1.8	5.6	85	23	109	3.7	78		0.43	+7.5	0.8	-24
	S	13.3	49		2.5	10.8	183	77	137	2.4	134				0.98	
8_F	S	12.5	50	262	2.4	10.1	149	47	115	3.1	130	146	0.39		0.8	
	U	8.8	46		1.5	7.3	83	23	70	3.6	118		0.41	+5.1	0.5	-39
	S	14.3	47		2.4	11.9	175	81	120	2.2	145				0.9	
8_L	S	13.7	49	282	2.4	11.3	187	61	124	3.1	152	138	0.37		0.9	
	U	10.2	40		1.5	8.7	91	34	70	2.6	129		0.40	+8.1	0.5	-42

Abbreviations used are: F, follicular phase; L, luteal phase; S, supine position; U, upright position; V, urine flow (ml/min); U_{osm}, urine osmolality; P_{osm}, plasma osmolality; C_{osm}, osmolal clearance; C_{H_2O}, free water clearance; $U_{Na.}V$, urinary sodium excretion; $U_{K.}V$, urinary potassium excretion; $U_{Na.}V \times 100/C_{cr}$, sodium excreted expressed per 100 ml. of creatinine clearance; $U_{Na/K}$, urinary sodium/potassium ratio; C_{cr}, endogenous creatinine clearance; S_{Na}, serum sodium concentration; PCV, packed cell volume; %ΔPCV, the difference in the packed cell volume between the supine and the erect positions expressed as a percentage; $E_{Na\%}$, percentage of filtered sodium excreted in the urine; %Na excretion between S and U, percentage difference in sodium excretion per 100 ml. of C_{cr} between the supine and upright positions.

TABLE 5: Assessment of the constancy of urinary excretion and a comparison of urinary composition during two periods (11.00-12.00 and 12.00-13.00 hours) in the follicular and luteal phases of the menstrual cycle in eight well hydrated normal female subjects in the supine position (Mean ± S.E.M.)

Menstrual Phase	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	$E_{Na\%}$
	11.00-12.00	14.1±0.7	65±3.0	3.3±0.2	10.8±0.6	243±19	87±10	227±22	3.1±0.5	110± 8	1.7 ±0.2
Follicular	12.00-13.00	14.3±0.7	67±4	3.4±0.3	10.9±0.5	250±25	87±12	212±22	3.1±0.4	120± 8	1.6 ±0.2
	Mean	14.2±0.5	66±3	3.3±0.2	10.9±0.4	247±15	87±11	219±15	3.1±0.3	115± 6	1.65±0.1
	11.00-12.00	13.7±0.3	63±4	3.0±0.2	10.7±0.4	194±20	112±12	167±19	1.9±0.3	119± 7	1.3 ±0.2
Luteal	12.00-13.00	13.2±0.4	62±5	2.9±0.2	10.3±0.4	207±18	99±14	192±26	2.4±0.4	114±10	1.4 ±0.2
	Mean	13.5±0.3	63±3	3.0±0.1	10.5±0.3	201±13	106±9	180±16	2.2±0.2	117± 6	1.35±0.1

Abbreviations: As in Table 4.

TABLE 6: A comparison of urinary composition over the periods (11.00-12.00 and 12.00-13.00 hours) in the follicular and luteal phases of the menstrual cycle in eight well hydrated normal female subjects in the supine position (Mean ± S.E.M.)

Menstrual Phase	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	$E_{Na\%}$
Follicular (a)	11.00-12.00	14.1±0.7	65±3	3.3±0.2	10.8±0.6	243±19	87±10	227±22	3.1±0.5	110± 8	1.7±0.2
Luteal (b)	11.00-12.00	13.7±0.3	63±4	3.0±0.2	10.7±0.4	194±20	112±12	167±19	1.9±0.3	119± 7	1.3±0.2
P	(a) versus (b)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Follicular (c)	12.00-13.00	14.3±0.7	67±4	3.4±0.3	10.9±0.5	250±25	87±12	212±22	3.1±0.4	120± 8	1.6±0.2
Luteal (d)	12.00-13.00	13.2±0.4	62±5	2.9±0.2	10.3±0.4	207±18	99±14	192±26	2.4±0.4	114±10	1.4±0.2
P	(c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

Differences between the supine and upright positions in the follicular and luteal phases.

Statistically significant differences were obtained when the subjects were upright in both the follicular and luteal phases.

The urine volume, osmolal clearance, the free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in the upright position, Table 7. The urine osmolality, urine potassium, ratio of urinary sodium to potassium and the creatinine clearance did not alter significantly.

Differences between the follicular and luteal phases in the upright position.

When the subjects were upright, a number of statistically significant differences were found in the composition of urine during the luteal as contrasted with the follicular phase of the menstrual cycle. Statistical comparisons for the group, by using Student's 't'-test for parametric data and the Willcoxon signed ranks matched paired test for the percentage difference in sodium excretion, given in Table 7.

The volume of urine passed, the osmolal clearance, the free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in the

TABLE 7: A comparison of urinary composition over the period (12.00-13.00 hours) when supine and the period (13.00-14.00 hours) when upright. (Mean ± S.E.M.)

Menstrual Phase	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (μmol/min)	$U_{K}.V$ (μmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{Cr} (ml/min)	$E_{Na\%}$
	(a) 12.00-13.00	14.3±0.7	67±4	3.4± 0.3	10.9±0.5	250±25	87±12	212±22	3.1±0.4	120± 8	1.6±0.2
Follicular	(b) 13.00-14.00	11.7±0.6	61±4	2.5± 0.2	9.2±0.4	176±20	53± 9	170±26	4.1±0.9	110± 7	1.3±0.2
	P(a) versus (b)	<0.001	n.s.	<0.01	<0.001	<0.01	<0.01	<0.005	n.s.	n.s.	<0.005
	(c) 12.00-13.00	13.2±0.4	62±5	2.9±0.2	10.3±0.4	207±18	99±14	192±26	2.4±0.4	114±10	1.4±0.2
Luteal	(d) 13.00-14.00	9.4±0.6	59±4	2.0±0.1	7.4±0.6	116±17	50±10	111±16	2.6±0.3	105± 7	0.8±0.1
	P(c) versus (d)	<0.001	n.s.	<0.01	<0.001	<0.001	<0.005	<0.001	n.s.	n.s.	<0.001
	P(b) versus (d)	<0.02	n.s.	<0.05	<0.05	<0.01	n.s.	<0.05	n.s.	n.s.	<0.05

Abbreviations: As in Table 4.

luteal than in the follicular phase of the cycle. The urine osmolality, urinary potassium, ratio of urinary sodium to potassium and the creatinine clearance did not alter significantly.

Differences on changing from the supine to the upright position in the follicular as compared with the luteal phase.

In changing the subjects from the supine to the upright position, certain significant differences were noted between the follicular as compared with the luteal phase of the cycle, Table 8. Thus, the upright positions in the luteal phase induced a greater percentage rise in PCV and a more marked decrease in the percentage of filtered sodium excreted in the urine than it did in the follicular phase.

TABLE 8: A comparison of the changes found when normal subjects are upright in the follicular and luteal phases of the menstrual cycle (Mean ± S.E.M.).

Menstrual Phase	$U_{Na\%}$ (S → U)	PCV		ΔPCV	ΔPCV%
		S	U		
Follicular	-22±6	0.406±0.007	0.428±0.008	0.022±0.002	+5.53±0.4
Luteal	-42±3	0.394±0.006	0.423±0.007	0.029±0.003	+7.94±0.7
P	<0.01	n.s.	n.s.	<0.05	<0.02

Abbreviations as in the previous Tables. $U_{Na\%}$, percentage difference in sodium excretion between the supine and tilted position.

URINARY EXCRETION OF WATER AND ELECTROLYTES IN PATIENTS WITH IDIOPATHIC OEDEMA: THE EFFECT OF POSTURE.

PRE-MENOPAUSAL PATIENTS

The results for each individual patient are given in Table 9.

Constancy of hydration

The adequacy of the method used to maintain a steady state of hydration was assessed, whilst the patients were supine, by comparing the mean urinary excretion in the first and second hours (11.00-12.00 and 12.00-13.00 hours) during the follicular and luteal phases. At neither time in the menstrual cycle was there any statistical difference between the observed and calculated results obtained in the first as compared with the second hour, Table 10.

Differences between the follicular and luteal phases in the supine position.

When the subjects were in the supine position, the mean values for volume and urinary composition during the follicular and luteal phases of the cycle were not statistically different, Table 11.

TABLE 9: The urinary composition packed cell volume in the supine position (11.00-12.00 and 12.00-13.00 hours) and during the upright position in seven well hydrated pre-menopausal subjects with idiopathic oedema.

Case no. & phase of cycle	Posi-tion	V (ml/ min)	U_{osm} (mosmol/ kg.)	P_{osm} (mosmol/ kg.)	C_{osm} (ml/ min)	C_{H_2O} (ml/ min)	$U_{Na}.V$ (µmol/ min)	$U_K.V$ (µmol/ min)	$\frac{U_{Na}.V}{C_{cr}}$ x100	$U_{Na/K}$	C_{cr} (ml/ min)	S_{Na} (m.mol/ l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
	S	5.8	68		1.4	4.4	5	35	5	0.14	101				0.05	
1_F	S	5.4	80	292	1.5	3.9	5	38	4.4	0.13	113	138	0.44		0.03	
	U	0.6	169		0.3	0.3	0.5	10	0.6	0.05	83		0.49	+11.3	0.005	-86
	S	5.3	71		1.3	4.0	6.7	33	6.2	0.2	109				0.05	
1_L	S	4.7	77	280	1.3	3.4	5	22	4.5	0.23	112	133	0.40		0.04	
	U	2.2	114		0.9	1.3	0.7	13	0.8	0.05	86		0.45	+12.5	0.006	-82
	S	12.5	54		2.4	10.1	156	40	162	3.9	96				1.1	
2_F	S	12.5	56	279	2.5	10.0	155	50	155	3.1	100	149	0.38		1.1	
	U	10.0	50		1.8	8.2	82	25	74	3.3	111		0.40	+5.3	0.52	-52
	S	-	-		-	-	-	-	-	-	-				-	
2_L	S	10.8	41	282	1.6	9.2	119	47	128	2.5	93	143	0.38		0.94	
	U	6.7	46		1.1	5.6	53	29	70	1.8	76		0.42	+10.5	0.5	-45

Case no. & phase of cycle	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_K.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}}$ x100	U_{Na}/K	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
3_F	S	15.0	66		3.4	11.6	228	43	275	5.3	83				2.1	
	S	14.7	70	288	3.6	11.1	197	39	219	5.1	90	141	0.40		1.6	
	U	5.3	65		1.2	4.1	77	14	56	5.5	137		0.42	+5	0.6	-74
3_L	S	14.7	67		3.5	11.2	235	51	345	4.6	68				2.4	
	S	14.7	73	283	3.8	10.9	252	50	394	5.0	64	149	0.40		2.8	
	U	5.8	73		1.5	4.3	110	24	164	4.6	67		0.45	+12.5	1.2	-58
4_F	S	9.8	93		3.2	6.6	196	137	157	1.4	125				1.3	
	S	12.0	74	281	3.1	8.9	192	155	178	1.2	108	132	0.39		1.4	
	U	6.8	72	274	1.7	5.1	103	82	156	1.3	66	131	0.42	+7.7	1.3	-12
4_L	S	8.3	126		3.7	4.6	133	167	160	0.8	83				1.2	
	S	7.3	122	282	3.1	4.2	145	73	190	2.0	76	142	0.40		1.4	
	U	1.7	155	280	0.9	0.8	40	12	60	3.3	67	135	0.44	+10	0.5	-68
5_F	S	7.6	67		1.8	5.8	91	47	105	1.9	87				0.8	
	S	11.0	67	282	2.6	8.4	132	77	105	1.7	126	137	0.30		0.81	
	U	1.6	84	280	0.4	1.2	22	13	23	1.7	95	136	0.34	+13.3	0.18	-78
5_L	S	8.5	76		2.3	6.2	136	77	136	1.8	100				1.06	
	S	9.0	92	278	2.9	6.1	180	90	165	2.0	109	135	-		1.28	
	U	6.3	92	277	2.0	4.3	120	65	94	1.8	127	135	-		0.74	-43

Case no. & phase of cycle	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}}$ x100	$U_{Na/K}$	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	$E_{Na\%}$	%Na excretion between S and U
6_F	S	8.3	50		1.4	6.9	80	28	108	2.9	74				0.84	
	S	8.3	53	281	1.5	6.8	103	27	151	3.8	68	135	0.42		1.18	
	U	7.7	53	278	1.4	6.3	100	23	137	4.3	73	135	0.45	+7.1	1.07	-10
6_L	S	9.4	70		2.4	7.0	103	377	132	0.27	78				1.04	
	S	9.6	70	270	2.5	7.1	88	330	113	0.27	78	134	0.42		0.88	
	U	3.8	63	276	0.9	2.9	12	38	17	0.31	70	136	0.47	+11.9	0.13	-85
7_F	S	13.7	68		4.4	9.3	184	67	194	2.7	95				1.4	
	S	14.1	75	270	3.9	10.2	283	99	285	2.9	99		0.44		2.1	
	U	7.5	58		1.6	5.9	94	62	96	1.5	98	142	0.48	+9.1	0.7	-66
7_L	S	19.8	41		2.8	17.0	232	172	314	1.3	74				2.2	
	S	17.7	34	284	2.1	15.6	275	217	280	1.3	98		0.45		2.0	
	U	12.7	40		1.8	10.9	172	110	143	1.6	120	152	0.49	+8.9	1.0	-49

Abbreviations: As in Table 4.

TABLE 10: Assessment of the constancy of urinary excretion and a comparison of urinary composition during two periods (11.00-12.00 and 12.00-13.00 hours) in the follicular and luteal phases of the menstrual cycle in seven well hydrated patients with idiopathic oedema (Mean ± S.E.M.).

Menstrual Phase	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	E_{Na}%
	(a) 11.00-12.00	10.4±1.3	67±5.0	2.6±0.4	7.8±1.0	134±29	57±14	144±32	2.6±0.6	94±6	1.1±0.2
Follicular	(b) 12.00-13.00	11.1±1.2	68±4.0	2.6±0.4	8.5±0.9	152±33	69±17	157±33	2.6±0.6	101±7	1.2±0.2
	P (a) versus (b)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	(c) 11.00-12.00	11.0±2.2	75±11	2.7±0.4	8.3±2.0	141±35	146±52	182±52	1.5±0.7	85±6	1.3±0.4
Luteal	(d) 12.00-13.00	10.5±1.7	73±11	2.5±0.3	8.0±1.6	152±35	118±43	182±47	1.9±0.6	90±7	1.3±0.3
	P (c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

TABLE 11: A comparison of the periods (11.00-12.00 hours and 12.00-13.00 hours) in the follicular and luteal phases of the menstrual cycle in seven well hydrated patients with idiopathic oedema (Mean ± S.E.M.)

Menstrual Phase	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	E_{Na}%
Follicular	(a) 11.00-12.00	10.4±1.3	67± 5	2.6±0.4	7.8±1.0	134±29	57±14	144±32	2.6±0.6	94±6.0	1.1±0.2
Luteal	(b) 11.00-12.00	11.0±2.2	75±11	2.7±0.4	8.3±2.0	141±35	146±52	182±52	1.5±0.7	85±6.0	1.3±0.4
	P (a) versus (b)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Follicular	(c) 12.00-13.00	11.1±1.2	68± 4	2.6±0.4	8.5±0.9	152±33	69±17	157±33	2.6±0.6	101±7	1.2±0.2
Luteal	(d) 12.00-13.00	10.5±1.7	73±11	2.5±0.3	8.0±1.6	152±35	118±43	182±47	1.9±0.6	90±7	1.3±0.3
	P (c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

Differences between the supine and upright positions in the follicular and luteal phases.

Statistically significant different differences were obtained when the patients were upright in both the follicular and luteal phases.

The urine volume, osmolal clearance, the free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in the upright position. The urine osmolality, the ratio of urinary sodium to potassium and the creatinine clearance did not alter significantly, Table 12.

Differences between the follicular and luteal phases in the upright position.

When the patients were upright, no statistically significant differences were found in the composition of urine during the luteal as contrasted with the follicular phase of the menstrual cycle. The mean values for the group, compared statistically using Student's 't'-test for the parametric data and the Willcoxon signed ranks matched pairs test for the percentage difference in sodium excretion, are given in Table 12.

These results are in contradistinction with the findings in normal subjects.

TABLE 12: A comparison of urinary composition over the period (12.00-13.00 hours) when supine and the period (13.00-14.00 hours) when upright.

Menstrual Phase	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	$E_{Na\%}$
Follicular	(a) 12.00-13.00	11.1±1.2	68±40	2.6±0.4	8.5±0.9	152±33	69±17	157±33	2.6±0.6	101± 7	1.2±0.2
	(b) 13.00-14.00	5.6±1.3	79±15	1.2±0.2	4.4±1.1	68±15	33±11	78±21	2.5±0.7	95± 9	0.6±0.2
	P (a) versus (b)	<0.005	n.s.	<0.005	<0.005	<0.01	<0.005	<0.01	n.s.	n.s.	<0.005
Luteal	(c) 12.00-13.00	10.5±1.7	73±11	2.5±0.3	8.0±1.6	152±35	118±43	182±47	1.9±0.6	90± 7	1.3±0.3
	(d) 13.00-14.00	5.6±1.4	83±15	1.3±0.2	4.3±1.3	73±24	42±13	78±23	1.9±0.6	86±10	0.6±0.2
	P (c) versus (d)	<0.005	n.s.	<0.01	<0.001	<0.01	<0.001	<0.01	n.s.	n.s.	<0.005
	P (b) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

Differences on changing from the supine to the upright position in the follicular as compared with the luteal phase.

On changing the subjects from the supine to the upright position, no significant differences were noted between the follicular and luteal phases, Table 13.

TABLE 13: A comparison of the changes found when subjects with idiopathic oedema are upright in the follicular and luteal phases of the menstrual cycle (Mean ± S.E.M.).

Menstrual Phase	U_{Na}% (S → U)	PCV		ΔPCV	ΔPCV%
		S	U		
Follicular	-54±12	0.396±0.018	0.428±0.02	0.032±0.004	+8.4±1.1
Luteal	-63± 7	0.408±0.01	0.453±0.01	0.045±0.002	+11.0±0.6
P	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Tables 4 & 8.

POST-MENOPAUSAL PATIENTS

The individual results obtained in the four patients studied are given in Table 14 . Two tilting tests were performed a fortnight apart in each patient.

Constancy of hydration.

The efficacy of the method used to maintain an adequate state of hydration was assessed as in the previous sections, and found to be satisfactory, Table 15.

Differences between the two tests in the supine position.

When the subjects were in the supine position,the mean values for urinary volume and composition between the two tests were not statistically different, Table 16.

Differences between the supine and upright positions in the two tests.

Statistically significant differences were attained when the patients were upright in both tests.

The urine volume, osmolal clearance, the free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in the upright position. The urine osmolality, the ratio of urinary sodium to potassium and the creatinine clearance did not alter significantly, Table 17.

TABLE 14: The urinary composition packed cell volume in the supine position (11.00-12.00 and 12.00-13.00 hours) and during the upright position in four well hydrated post-menopausal subjects with idiopathic oedema

Case No.	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	U_{Na}/K	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
1_A	S	14.3	83		4.1	10.2	268	68	244	3.9	110				1.9	
	S	14.3	81	283	4.0	10.3	272	85	209	3.2	130	135	0.43		1.6	
	U	6.8	75	281	1.8	5.0	91	28	128	3.3	71	136	0.47	+9.3	1.0	-39
1_B	S	14.8	70		3.6	11.2	222	53	176	4.2	126				1.34	
	S	14.0	72	282	3.5	10.5	228	50	178	4.6	128	138	0.44		1.36	
	U	5.3	72	280	1.3	4.0	65	20	105	3.3	62	138	0.48	+9.0	0.8	-41
2_A	S	10.0	69		2.5	7.5	23	78	26	0.29	88				0.2	
	S	8.8	68	276	2.2	6.6	30	53	38	0.52	80	133	0.44		0.3	
	U	4.6	82	276	1.4	3.2	7	18	8	0.39	92	132	0.50	+13.6	0.06	-79
2_B	S	9.3	124		4.2	5.1	31	93	35	0.33	88				0.3	
	S	9.3	121	274	4.1	5.2	41	74	47	0.6	87	129	0.46		0.4	
	U	5.3	139	276	2.7	2.6	15	15	23	1.0	66	139	0.50	+8.7	0.2	-51

Case No.	Position	V (ml/min)	U_{osm} (mosmol/kg.)	P_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_K.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	S_{Na} (m.mol/l.)	PCV	%Δ PCV	E_{Na}%	%Na excretion between S and U
3_A	S	-	-		-	-	-	-	-		-				-	
	S	14.6	65	282	3.3	11.3	181	64	164	2.8	111	140	0.37		1.1	
	U	7.1	65		1.6	5.5	51	38	55	1.5	92		0.41	+10.8	0.4	-67
3_B	S	-	-		-	-	-	-	-		-				-	
	S	14.3	53	276	2.8	11.5	226	35	188	6.4	120	142	0.34		1.3	
	U	11.2	48		1.9	9.3	101	18	78	5.5	129		0.37	+8.8	0.5	-59
4_A	S	2.8	227		2.3	0.5	100	37	101	2.7	99				0.8	
	S	3.0	222	281	2.4	0.6	75	31	94	2.8	79	154	0.39		0.7	
	U	1.2	295		1.2	-	33	16	26	2.1	123		0.45	+15.3	0.2	-72
4_B	S	5.4	133		2.5	2.9	150	42	169	3.6	89				1.3	
	S	4.8	139	284	2.3	2.5	135	40	157	3.4	86	154	0.41		1.2	
	U	3.2	148		1.7	1.5	62	26	69	2.4	90		0.47	+14.6	0.5	-56

Abbreviations: As in Table 4 . A, first test; B, second test.

TABLE 15: Assessment of the constancy of urinary excretion and a comparison of urinary composition during two one-hour periods (11.00-12.00 and 12.00-13.00 hours) in two tests performed a fortnight apart in four well hydrated post-menopausal patients with idiopathic oedema.

Test	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	E_{Na}%
	(a) 11.00-12.00	9.0±3.3	126±51	3.0±0.6	6.0±2.9	130±72	61±12	123±64	2.3±1.1	99± 6	1.0±0.5
A	(b) 12.00-13.00	10.2±2.7	109±39	3.0±0.4	7.2±2.4	139±54	58±11	126±38	2.2±0.6	95±11	0.9±0.3
	P (a) versus (b)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	(c) 11.00-12.00	9.8±2.2	109±20	3.4±0.6	6.4±2.5	134±56	63±15	126±46	2.7±1.2	101±12	1.0±0.3
B	(d) 12.00-13.00	10.6±2.2	96±20	3.2±0.4	7.4±2.1	157±44	45± 4	143±32	3.7±1.2	104±12	1.1±0.2
	P (c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

TABLE 16: A comparison of the urinary composition over the periods (11.00-12.00 and 12.00-13.00 hours) in both tests performed in four well hydrated post-menopausal patients with idiopathic oedema (Mean ± S.E.M.).

Test No.	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na.}V$ (µmol/min)	$U_{K.}V$ (µmol/min)	$\frac{U_{Na.}V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	E_{Na}%
A	(a) 11.00-12.00	9.0±3.3	126±51	3.0±0.6	6.0±2.9	130±72	61±12	123±64	2.3±1.1	99± 6	1.0±0.5
B	(b) 11.00-12.00	9.8±2.2	109±20	3.4±0.6	6.4±2.5	134±56	63±15	126±46	2.7±1.2	101±12	1.0±0.3
	P (a) versus (b)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
A	(c) 12.00-13.00	10.2±2.7	109±39	3.0±0.4	7.2±2.4	139±54	58±11	126±38	2.2±0.6	95±11	0.9±0.3
B	(d) 12.00-13.00	10.6±2.2	96±20	3.2±0.4	7.4±2.2	157±44	45± 4	143±32	3.7±1.2	104±12	1.1±0.2
	P (c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

TABLE 17: A comparison of urinary composition over the period (12.00-13.00 hours) when supine and the period (13.00-14.00 hours) when upright in four post-menopausal patients with idiopathic oedema.

Test No.	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_K.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	E_{Na}%
A	(a) 12.00-13.00	10.2±2.7	109±39	3.0±0.4	7.2±2.4	139±54	58±11	126±38	2.2±0.6	95±13	0.9±0.3
	(b) 13.00-14.00	4.9±1.4	129±55	1.5±0,1	3.4±1.2	46±18	25± 5	54±26	1.8±0.6	95±11	0.4±0.2
	P (a) versus (b)	<0.001	n.s.	<0.01	<0.01	<0.001	<0.01	<0.01	n.s.	n.s.	<0.001
B	(c) 12.00-13.00	10.6±2.2	96±20	3.2±0.4	7.4±2.2	157±44	45± 4	143±32	3.7±1.2	104±12	1.1±0.2
	(d) 13.00-14.00	6.3±1.7	102±24	1.9±0.3	4.4±1.7	61±17	20±2.3	69±17	3.0±0.9	87±15	0.5±0.1
	P (c) versus (d)	<0.01	n.s.	<0.01	<0.01	<0.01	<0.01	<0.01	n.s.	n.s.	<0.01
	P (b) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table4.

TABLE 18: A comparison of the changes found when post-menopausal subjects with idiopathic oedema are upright (Mean ± S.E.M.).

Test No.	U_{Na}% (S → U)	PCV		ΔPCV	ΔPCV%
		S	U		
A	-64±9	0.408±0.02	0.458±0.02	0.05 ±0.006	+12.3±1.4
B	-52±4	0.413±0.03	0.455±0.03	0.042±0.006	+10.3±1.4
P	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Tables 4 & 8.

Differences between the first and second tests in the upright position.

When the patients were upright, no statistically significant differences were found in the composition of urine during the first as contrasted with the second test. The mean values for the group, compared statistically using Student's 't'-test for parametric data and the Willcoxon signed ranks matched pairs test for the percentage difference in sodium excretion, are given in Table 17.

Differences on changing from the supine to the upright position in the first as compared with the second phase.

On changing the subjects from the supine to the upright position, no significant differences were noted between the two tests, Table 18.

COMPARISON OF RESULTS BETWEEN PRE-MENOPAUSAL AND POST-MENOPAUSAL PATIENTS WITH IDIOPATHIC OEDEMA

Neither in the supine nor in the upright position has a significant difference in urinary volume or composition been found between the tests performed in the follicular and luteal phases of the menstrual cycle in patients with idiopathic oedema. The results obtained in the two phases of the cycle have, therefore, been combined, Table 19 . Similarly, the results of the two tests, carried out two weeks apart, in the post-menopausal patients have also been combined, because no statistically significant differences were found on the two occasions.

No significant differences were found between the pre and post-menopausal patients in the supine position, apart from a significant difference in urine osmolality in the first hour, nor when they were in the upright position, Table 19 . Thus, the results for both groups of patients with idiopathic oedema have been combined.

TABLE 19: A comparison of the urinary composition between pre-menopausal and post-menopausal subjects with idiopathic oedema (Mean ± S.E.M.).

Subjects	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	$E_{Na\%}$
Pre-menopausal	(a) 11.00-12.00	10.7±1.2	71± 6	2.6±0.2	8.1±1	137±22	98±27	161±29	2.1±0.5	90±4	1.2±0.2
Post-menopausal	(b) 11.00-12.00	9.4±1.9	117±25	3.2±0.2	6.2±1.7	132±27	62± 9	125±35	2.5±0.7	100±6.3	1.0±0.3
	P (a) versus (b)	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Pre-menopausal	(c) 12.00-13.00	10.8±1.0	70± 6	2.6±0.2	8.2±0.9	152±23	94±23	169±28	2.2±0.4	95± 5	1.3±0.2
Post-menopausal	(d) 12.00-13.00	10.4±1.6	102±20	3.1±0.3	7.3±1.5	149±33	54± 7	134±23	3.0±1.0	102± 8	1.0±0.2
	P (c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Pre-menopausal	(e) 13.00-14.00	5.6±0.9	81±11	1.2±0.1	4.4±0.8	70±14	37 ±8	78±15	2.2±0.5	91±6	0.6±0.1
Post-menopausal	(f) 13.00-14.00	5.6±1.0	116±28	1.7±0.1	3.9±1.0	53±12	22 ±3	62±15	2.5±0.6	91±9	0.5±0.1
	P (e) versus (f)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Abbreviations: As in Table 4.

COMPARISON OF THE URINARY EXCRETION OF WATER AND ELECTROLYTES DURING THE LUTEAL PHASE OF THE MENSTRUAL CYCLE IN NORMAL FEMALES AND PATIENTS WITH IDIOPATHIC OEDEMA

Differences between the two groups in the supine position.

The urine volume and free water clearance (C_{H_2O}) were just significantly lower ($P<0.05$) in the first hour in patients with idiopathic oedema. No other significant difference was found, Table. 20.

Differences between the two groups in the upright position.

When the subjects were upright, a number of highly significant differences were found between the two groups. The volume of urine passed, the osmolal clearance, free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in patients with idiopathic oedema, compared with the luteal phase of the menstrual cycle in normal subjects, Table 20.

Differences on changing from the supine to the upright position in the luteal phase of normal female subjects and in patients with idiopathic oedema.

In changing the subjects from the supine to the upright position, certain significant differences were noted in patients with idiopathic oedema, compared with the luteal phase in normal subjects, Table 21. Thus, the upright

TABLE 20: A comparison of the urinary composition over the periods (11.00-12.00, 12.00-13.00 and 13.00-14.00 hours) in normal subjects in the luteal phase of the menstrual cycle and patients with idiopathic oedema (Mean ± S.E.M.).

Subjects	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (µmol/min)	$U_{K}.V$ (µmol/min)	$\frac{U_{Na}.V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	$E_{Na\%}$
Normal Luteal	(a) 11.00-12.00	13.7±0.3	63± 4	3.0±0.2	10.7±0.4	194±20	112±12	167±19	1.9±0.3	119± 7	1.3±0.2
Idiopathic Oedema	(b) 11.00-12.00	10.3±1.0	85±10	2.8±0.2	7.5±0.9	137±19	87±20	150±22	2.2±0.4	93± 4	1.1±0.2
	P (a) versus (b)	<0.05	n.s.	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Normal Luteal	(c) 12.00-13.00	13.2±0.4	62± 5	2.9±0.2	10.3±0.4	207±18	99±14	192±26	2.4±0.4	114±10	1.4±0.2
Idiopathic Oedema	(d) 12.00-13.00	10.7±0.9	82± 9	2.8±0.2	7.9±0.8	150±19	79±15	156±20	2.5±0.4	98± 4	1.2±0.14
	P (c) versus (d)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Normal Luteal	(e) 13.00-14.00	9.4±0.6	59± 4	2.0±0.1	7.4±0.6	116±17	50±10	111±16	2.6±0.3	105± 7	0.8±0.1
Idiopathic Oedema	(f) 13.00-14.00	5.6±0.7	94±12	1.2±0.1	4.4±0.6	64±10	32± 5	72±11	2.3±0.4	93± 6	0.5±0.1
	P (e) versus (f)	<0.005	n.s.	<0.01	<0.005	<0.02	n.s.	n.s.	n.s.	n.s.	<0.05

Abbreviations: As in Table 4.

position in patients with idiopathic oedema produced a greater rise in PCV and a more marked decrease in the percentage of filtered sodium excreted in the urine than in the luteal phase of the normal subjects.

TABLE 21: A comparison of the changes found when upright between the luteal phase of normal subjects and patients with idiopathic oedema (Mean ± S.E.M.).

Subjects	U_{Na}% (S → U)	PCV		ΔPCV	ΔPCV%
		S	U		
Normal (L)	-42 ±3.4	0.393±0.007	0.423±0.007	0.029±0.003	+7.94±0.7
Idiopathic Oedema	-58.5±4	0.406±0.008	0.446±0.009	0.04 ±0.002	+10.3 ±0.6
P	<0.05	n.s.	n.s.	<0.02	<0.025

Abbreviations: As in Table 4.

COMPARISON OF THE URINARY EXCRETION OF WATER AND ELECTROLYTES BETWEEN NORMAL SUBJECTS AND PATIENTS WITH IDIOPATHIC OEDEMA

Differences between the two groups in the supine position.

In the supine position, the urinary volume, free water clearance, urinary sodium excretion, creatinine clearance were highly significantly lower in the patients with idiopathic oedema, compared with normal female subjects. There was no significant difference between the two groups in the urinary osmolality, osmolar clearance, urinary potassium excretion, urinary sodium expressed per 100 ml. of creatinine clearance, the ratio of urinary sodium to potassium and the fractional tubular reabsorption of sodium, Table 22.

Differences between the two groups in the upright position

When the subjects were upright, a number of highly significant differences were found between the two groups. The volume of urine passed, the osmolal and free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance) and the percentage of filtered sodium excreted in the urine were all highly significantly lower in patients with idiopathic oedema, compared with normal subjects, Table 22.

TABLE 22: A comparison of urinary composition over the periods (11.00-12.00, 12.00-13.00 and 13.00-14.00 hours) between the combined tests in normal subjects and patients with idiopathic oedema.

Subjects	Time (hours)	V (ml/min)	U_{osm} (mosmol/kg.)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na.}V$ (µmol/min)	$U_{K.}V$ (µmol/min)	$\frac{U_{Na.}V}{C_{cr}} \times 100$	$U_{Na/K}$	C_{cr} (ml/min)	$E_{Na\%}$
Normal (combined)	(a) 11.00-12.00	13.9±0.4	64± 3	3.2±0.1	10.7±0.3	217±15	101± 8	195±16	2.4±0.3	114±5	1.5±0.1
Idiopathic Oedema	(b) 11.00-12.00	10.3±1.0	85±10	2.8±0.2	7.5±0.9	137±19	87±20	150±22	2.2±0.4	93±4	1.1±0.2
	P (a) versus (b)	<0.05	n.s.	n.s.	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Normal (combined)	(c) 12.00-13.00	13.8±0.4	64± 3	3.2±0.2	10.6±0.3	228±16	92± 9	202±17	2.8±0.3	117±6	1.5±0.1
Idiopathic Oedema	(d) 12.00-13.00	10.7±0.9	82± 9	2.8±0.8	7.9±0.8	150±19	79±15	156±20	2.5±0.4	98±4	1.2±0.1
	P (c) versus (d)	<0.01	n.s.	n.s.	<0.01	<0.005	n.s.	n.s.	n.s.	n.s.	n.s.
Normal (combined)	(e) 13.00-14.00	10.5±0.5	60± 3	2.3±0.2	8.3±0.4	146±15	52± 6	141±17	3.4±0.5	108±5	1.0±0.1
Idiopathic Oedema	(f) 13.00-14.00	5.6±0.7	94±12	1.2±0.1	4.4±0.6	64±10	32± 5	72±11	2.3±0.4	93±6	0.5±0.1
	P (e) versus (f)	<0.001	<0.05	<0.001	<0.001	<0.001	<0.025	<0.005	n.s.	<0.05	<0.005

Abbreviations: As in Table 4.

Differences on changing from the supine to the upright position in normal subjects, as compared with patients with idiopathic oedema.

In changing from the supine to the upright position, certain highly significant differences were noted between normal subjects and patients with idiopathic oedema. Thus, the upright position in patients with idiopathic oedema induced a greater percentage rise in PCV and a more marked decrease in the percentage of filtered sodium excreted in the urine than in normal subjects, Table 23.

TABLE 23: A comparison of the changes found when upright between the combined tests in normal subjects and patients with idiopathic oedema.

Subjects	$U_{Na\%}$ (S → U)	PCV		ΔPCV	ΔPCV%
		S	U		
Normal (combined)	-32 ±4.1	0.40 ±0.005	0.426±0.005	0.026±0.002	+6.6±0.5
Idiopathic oedema	-58.8±4.5	0.406±0.008	0.446±0.009	0.04 ±0.002	+10.3±0.6
P	<0.001	n.s.	n.s.	<0.001	<0.001

Abbreviations: As in Table 4.

STUDIES ON THE PLASMA VOLUME AND CAPILLARY PROTEIN LOSS AS MEASURED WITH ^{125}I ALBUMIN IN PATIENTS WITH IDIOPATHIC OEDEMA: THE EFFECT OF POSTURE

The plasma volume and rate of loss of albumin from the intra-vascular space was measured in six patients with idiopathic oedema, in both the supine and upright positions.

Changes in the plasma volume on standing, as measured with ^{125}I labelled albumin.

A typical test performed on a pre-menopausal patient with idiopathic oedema is shown in Fig. 16. In this patient, the rate of loss of ^{125}I labelled albumin was 11.8% per hour when supine and 8.1% per hour when upright. The plasma volume decreased by 12.6% on standing and, by frequent blood sampling over this period, it was found that the fall was virtually completed in ten minutes.

Plasma volume when supine

The plasma volume per kilogram body weight in six patients with idiopathic oedema was 43±5.6 ml./kg. (mean ±S.E.M.), as compared with 45.3±1.35 ml./kg. found in normal subjects (Gill et al, 1972), a difference which was not statistically significant, Table 24.

Percentage fall in plasma volume on standing.

The mean fall in plasma volume on standing was 14.9±3.2% (mean±S.E.M.), as compared with up to 7% in

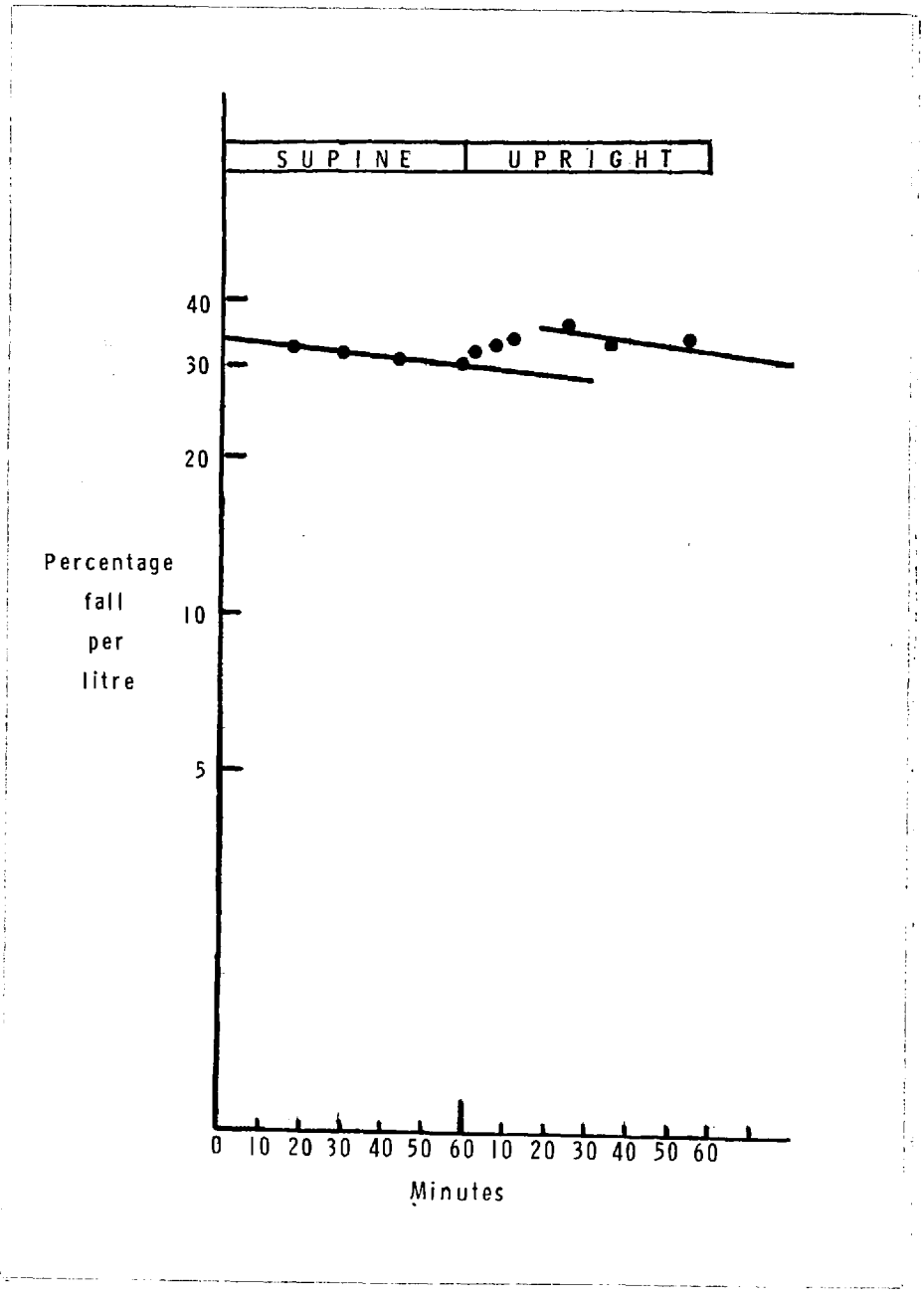


FIG. 16: The estimation of the rate of loss of ^{125}I labelled albumin in both the supine and the erect position in a pre-menopausal patient with idiopathic oedema. (Patient No. 13).

TABLE 24: The plasma volume, rate of loss of ^{125}I albumin in both the supine and upright positions, and the absolute fluid loss from the intravascular space in six patients with idiopathic oedema. The percentage change in the plasma volume as calculated from the changes in ^{125}I albumin concentration and changes in the packed cell volume are given. (Mean ± S.E.M.).

Case No. & phase of menstrual cycle	Plasma Volume (l)	Plasma Volume (ml/kg/body weight)	Rate of loss of ^{125}I albumin in the supine position (%/hr)	Rate of loss of ^{125}I albumin in the upright position (%/hr)	Absolute fluid loss from the intravascular space between S & U(ml)	Percentage change in plasma volume between S & U	Percentage change in PCV between S & U
5_F	2.84	51.6	-7.1	-10.7	-378	-13.3	-11.2
5_L	1.95	35.5	-7.0	-1.7	-301	-15.4	-13.3
6_F	3.73	71.7	-10.3	+6.3	-165	-4.4	-8.5
12_F	2.04	37.1	-18.2	-9.7	-512	-25.1	-19.5
12_L	2.32	42.2	-13.1	-25.1	-820	-35.3	-25.8
13_F	2.03	30.1	-11.8	-8.1	-154	-12.6	-7.7
13_L	2.08	31	-8.8	+3.5	-512	-7.4	-7.1
Mean	2.43±0.3	43±5.6	-10.9±1.5	-6.5±4.0	-406±88	-16.2±4	-13.3±2.6

Case No. & phase of menstrual cycle	Plasma Volume (l)	Plasma Volume (ml/kg/body weight)	Rate of loss of ^{125}I albumin in the supine position (%/hr)	Rate of loss of ^{125}I albumin in the upright position (%/hr)	Absolute fluid loss from the intravascular space between S & U(ml)	Percentage change in plasma volume between S & U	Percentage change in PCV between S & U
POST-MENOPAUSAL PATIENTS							
4*	1.99	306	-65	+2.5	-214	-10.8	-10
9	2.69	32.4	-8.2	-5.9	-265	-9.8	-10
Mean	2.34±0.4	32±0.9	-7.4±0.9	-1.7±4.2	-239±26	-10.3±0.3	-10±0
Mean both groups	2.41±0.22	40.2±4.6	-10.1±1.3	-5.6±3.2	-369±3.2	-14.9±3.2	-12.6±2.1

Abbreviations used: S, supine position; U, upright position; P.C.V., packed cell volume. Case numbers used refer to patients in Tables . *Tests performed when post-menopausal.

normal subjects (Eisenberg & Wolf, 1965), whilst the range varied between 4.4% and 35.3%.

Rate of loss of ^{125}I albumin from the intra-vascular space when supine.

The average rate of loss of ^{125}I albumin from the intra-vascular space was 10.1±1.3% per hour, as compared with up to 3.5±1.5% per hour found in normal subjects by Weil et al (1971), whilst the range varied between 6.5% and 18.2% per hour.

Rate of loss of ^{125}I albumin from the intra-vascular space when upright.

The average rate of loss of ^{125}I albumin from the intra-vascular space was 5.6±3.2% per hour in the upright position, as compared with 15 - 20% per hour found by Weil et al (1971) in their patients when upright, Table 24.

BLOOD VOLUME CHANGES ON CHANGING FROM THE SUPINE TO THE UPRIGHT POSITION IN NORMAL SUBJECTS IN THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE AND IN PATIENTS WITH IDIOPATHIC OEDEMA

The validity of the assumption that changes in the venous haematocrit on standing are related to changes in the whole body, packed cell volume (PCV) was tested by plotting the changes in the blood volume, as calculated from ^{125}I labelled albumin studies, against changes in blood volume, calculated from the forearm venous PCV, Fig. 17. The change in blood volume, as calculated from ^{125}I labelled albumin studies and from the venous PCV, were highly correlated (P 0.001, r=0.976, n=9). Thus, changes in the venous PCV may, under these experimental conditions, correlate with changes in the whole body packed cell volume and, assuming that red cells are not lost from the circulations or abnormally sequestrated, with changes in total blood volume. Thus, the rise in the venous PCV on standing will reflect the loss of fluid from the intravascular space.

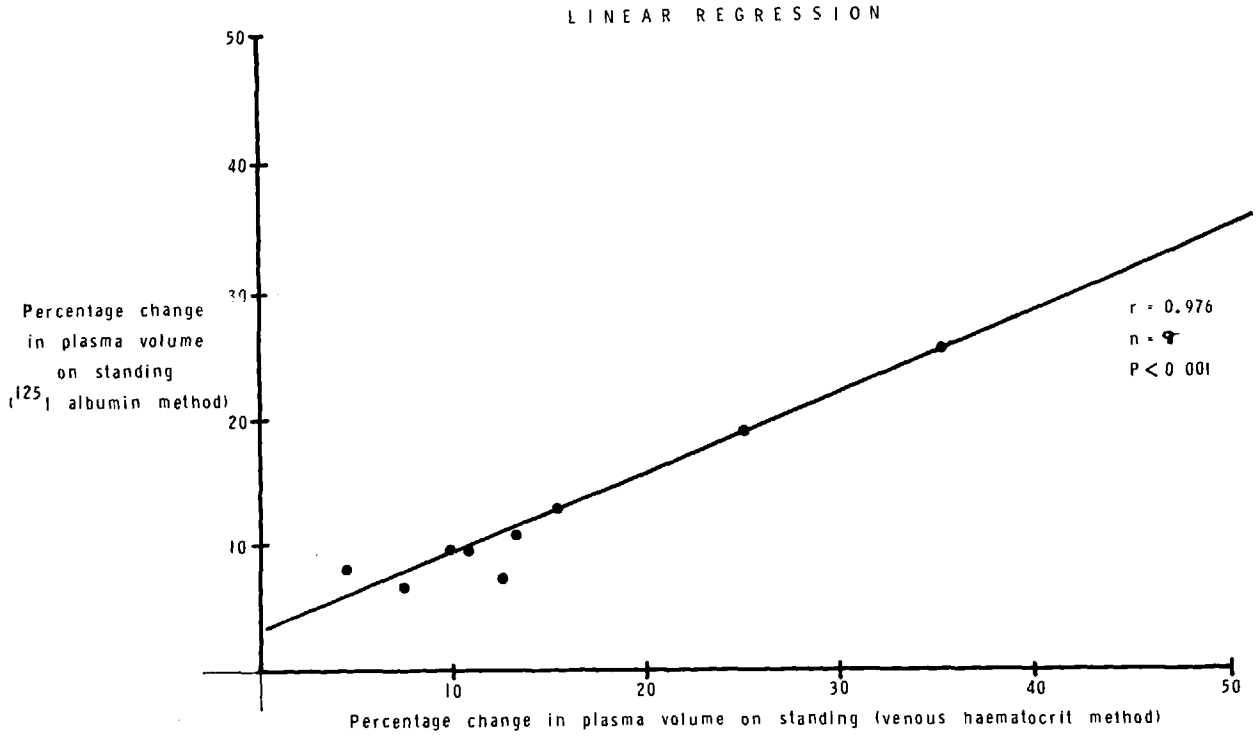


FIG. 17: A scattergram of the percentage change in plasma volume on standing as measured with ^{125}I albumin plotted against the percentage change in plasma volume (venous haematocrit method).

CHANGES IN BLOOD VOLUME ON STANDING

Normal subjects

The PCV in the supine and upright positions during the follicular and luteal phases was not significantly different. The percentage change in PCV from the supine to the upright position was 5.53±0.4 (±S.E.M.) in the follicular phase and 7.94±0.7, a difference which was statistically significant ($P<0.02$), Table 8.

Pre-menopausal patients with idiopathic oedema.

The packed cell volume (PCV) in the supine and upright positions during the follicular and luteal phases was not significantly different. The percentage change in PCV from the supine to the upright position was 8.4%±1.1 (±S.E.M.) in the follicular phase and 11.o%±0.6 in the luteal phase, a difference which was not significant, Table 13.

Post-menopausal patients with idiopathic oedema.

The PCV in the supine and upright positions during both tests was not significantly different. The percentage change in PCV from the supine to the erect position in the first test was 12.3%±1.4 (±S.E.M.) and in the second test 10.3%±1.4, a difference which was not significantly different, Table 18.

Patients with idiopathic oedema.

There was no statistically significant difference in the PCV in the supine and upright positions between pre-menopausal and menopausal patients with idiopathic oedema. The values were, therefore, combined.

Comparison between the packed cell volume (PCV) in the luteal phase of normal subjects and in patients with idiopathic oedema.

The PCV in the supine and upright positions in the luteal phase of normal subjects and patients with idiopathic oedema was not significantly different. The percentage change in PCV from the supine to the erect positions in the luteal phase of normal subjects was 7.94%±0.7 (±S.E.M.) and 10.3%±0.6 in patients with idiopathic oedema, a difference which was statistically significant ($P<0.025$), Table 21.

Comparison between the PCV and changes in the PCV on standing in normal subjects and patients with idiopathic oedema.

The PCV in the supine and upright positions in normal subjects and patients with idiopathic oedema was not significantly different. The percentage change in the PCV from the supine to the erect position in normal subjects was 6.6%±0.5 (±S.E.M.) and in patients with idiopathic oedema 10.3%±0.6, a difference which is highly significant ($P<0.001$), Table 23.

THE RELATIONSHIP BETWEEN CHANGES IN BLOOD VOLUME AND THE URINARY EXCRETION OF WATER AND ELECTROLYTES IN NORMAL FEMALES DURING THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE AND IN PATIENTS WITH IDIOPATHIC OEDEMA : THE EFFECT OF POSTURE.

Correlation between changes in blood volume on changing from the supine to the upright position, as measured by PCV, and changes in urinary flow and composition in normal female subjects in the follicular and luteal phases of the menstrual cycle.

A scattergram of the percentage fall in blood volume from the supine to the upright position was plotted against the percentage fall in urinary flow, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance), the percentage fall in the filtered sodium excreted in the urine, Figs. 18, 19, 20 & 21.

The fall in blood volume on standing was positively correlated with the percentage fall in urinary volume, ($r=0.577$, $n=16$, $P<0.05$), urinary sodium ($r=0.668$, $n=16$, $P<0.01$), urinary sodium expressed in relationship to the creatinine clearance ($r=0.578$, $n=16$, $P<0.05$) and the filtered sodium ($r=0.543$, $n=16$, $P<0.05$).

Correlation between the changes in blood volume on standing with the changes in urinary flow and composition in patients with idiopathic oedema.

A scattergram of the percentage fall in blood volume

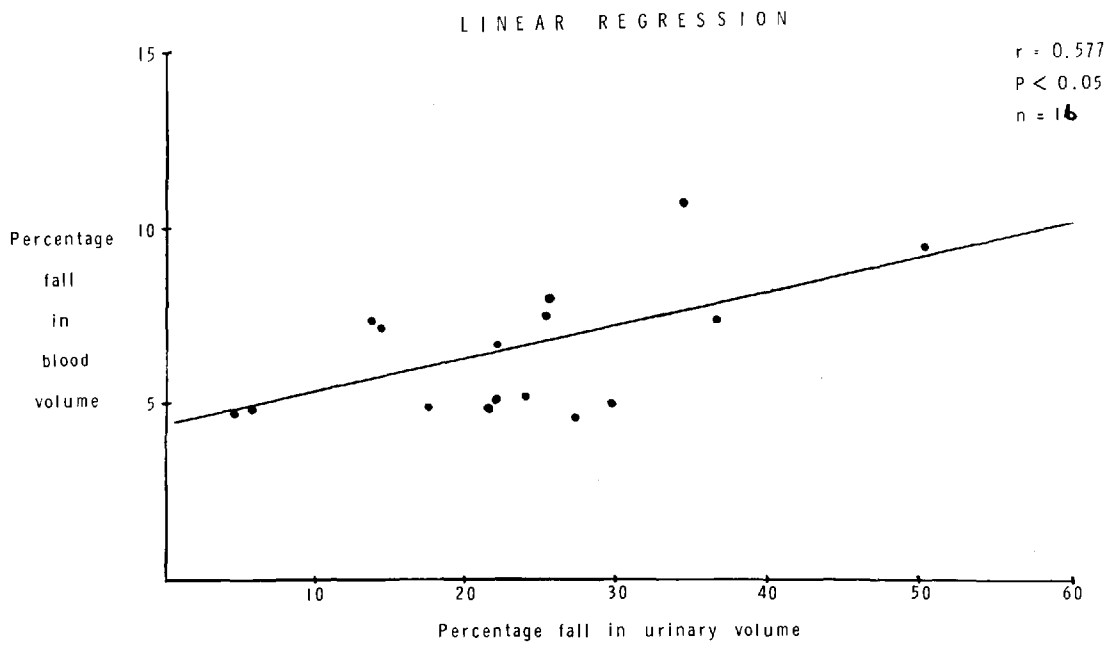


FIG. 18: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary flow in normal female subjects with regular menstrual cycles.

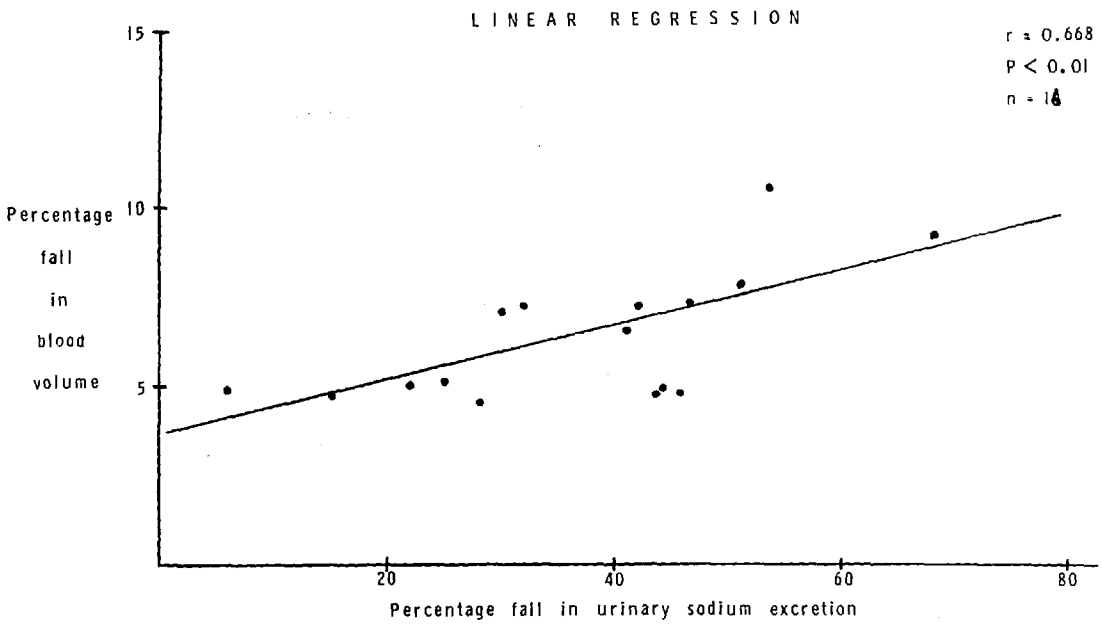


FIG 19: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary sodium in normal female subjects with regular menstrual cycles.

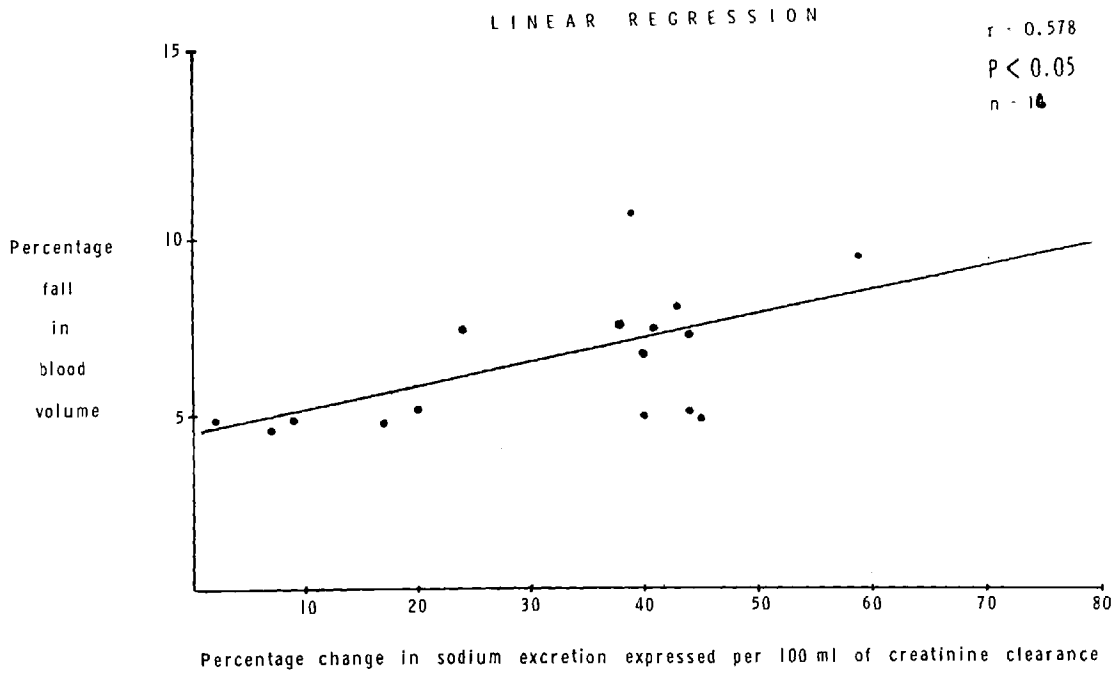


FIG. 20: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in sodium excretion expressed per 100 ml. of creatinine clearance in normal female subjects.

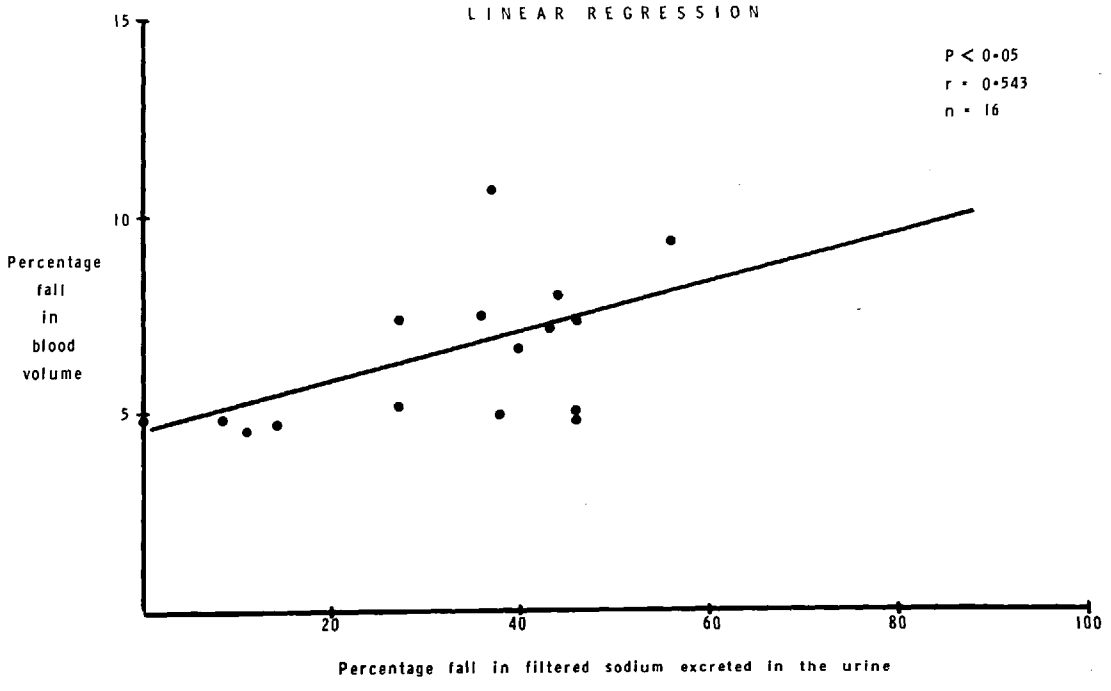


FIG. 21: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in filtered sodium excreted in the urine in normal female subjects.

from the supine to the upright position was plotted against the percentage fall in urinary flow, urinary sodium excretion (expressed either in absolute terms or in relationship to the creatinine clearance), and the percentage fall in the filtered sodium excreted in the urine, Figs.22, 23, 24 & 25.

The fall in blood volume on standing was not significantly correlated with the percentage fall in urinary volume ($r = 0.301$, $n = 21$), but was positively correlated with the percentage fall in urinary sodium ($r = 0.451$, $n = 21$, $P<0.05$), the percentage fall in urinary sodium expressed per 100 ml. of creatinine clearance ($r = 0.485$, $n = 21$, $P<0.05$) and the percentage fall in filtered sodium excreted in the urine ($r = 0.542$, $n = 21$, $P<0.05$).

Correlation between the changes in blood volume on standing with the changes in urinary flow and composition in normal subjects and patients with idiopathic oedema.

A scattergram of percentage fall in blood volume from the supine to the upright position was plotted against the percentage fall in urinary volume, urinary sodium excretion (expressed either in absolute terms or in relationship to the creatinine clearance), the percentage fall in the filtered sodium excreted in the urine, Figs. 26, 27, 28 & 29. The percentage fall in blood volume was strongly correlated with the percentage fall in urinary volume ($r = 0.616$, $n = 37$, $r = 0.001$), urinary sodium ($r = 0.676$, $n = 37$, $P<0.001$), urinary sodium expressed per 100 ml. of creatinine

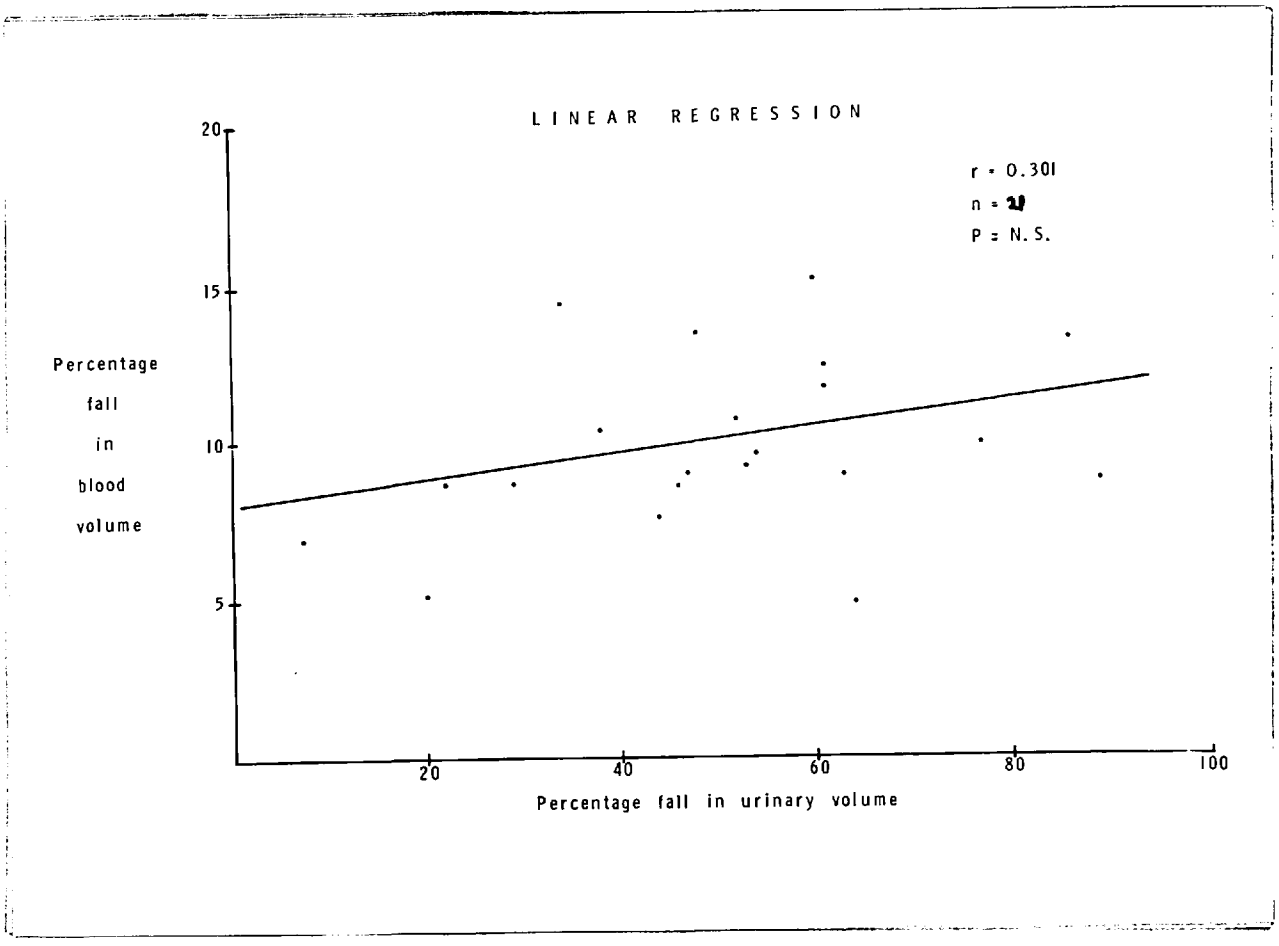


FIG. 22: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary volume in pre- and post-menopausal patients with idiopathic oedema.

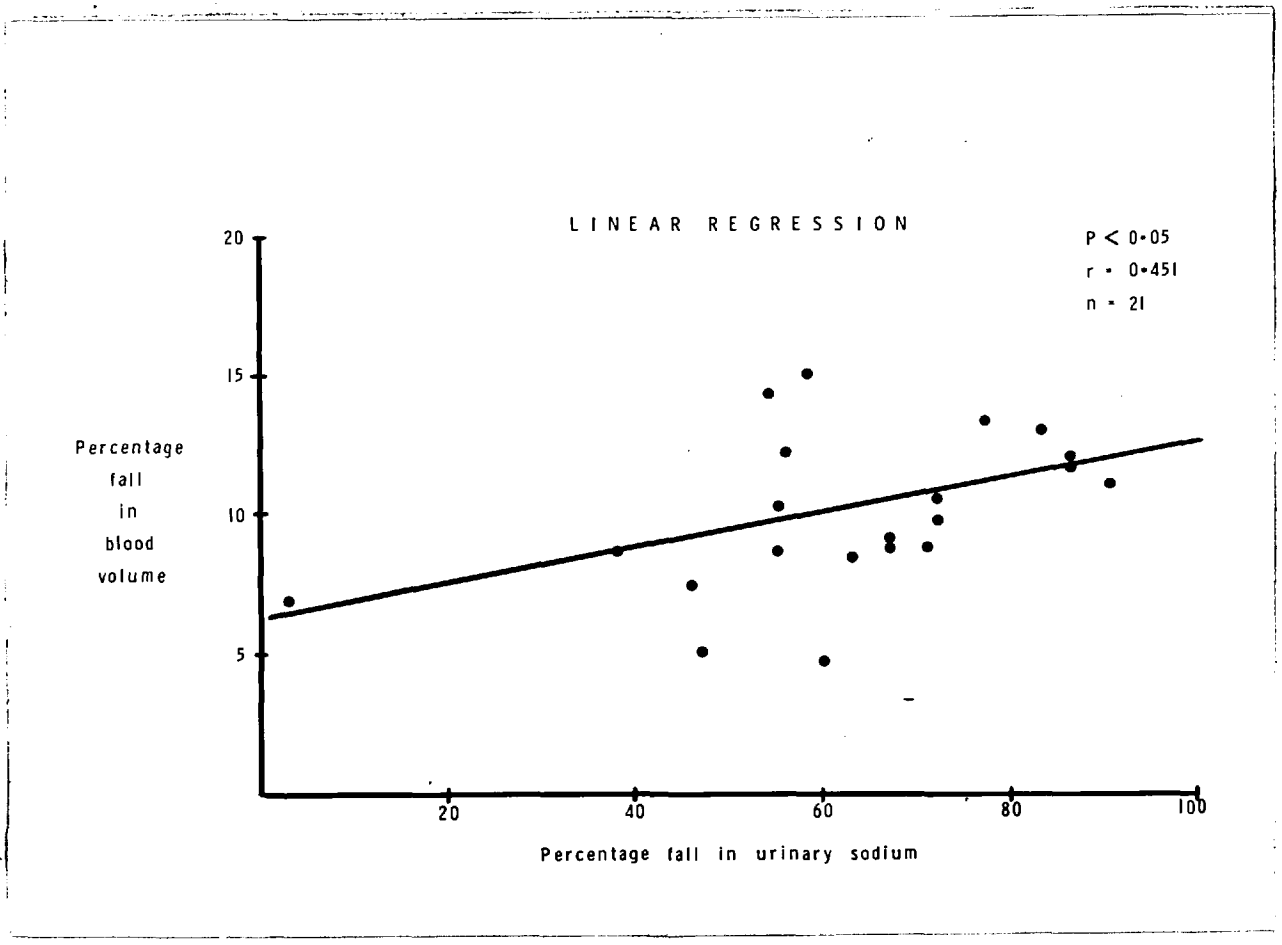


FIG. 23: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary sodium in pre- and post-menopausal patients with idiopathic oedema.

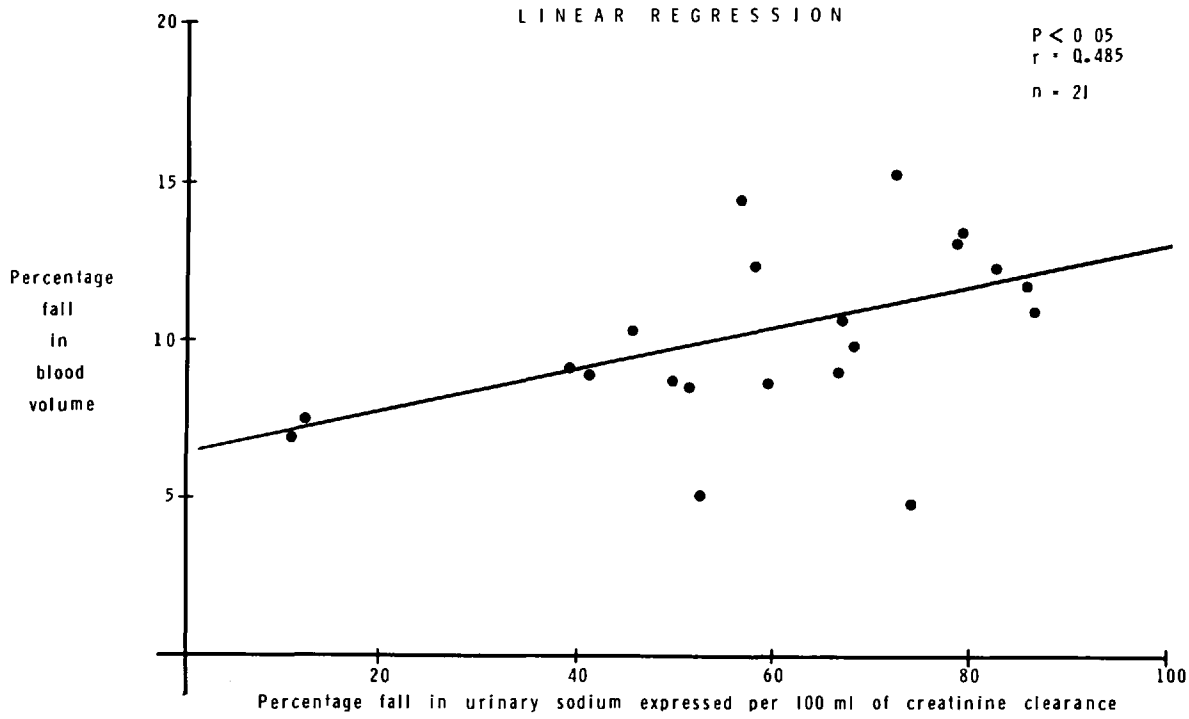


FIG. 24: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary sodium expressed per 100 ml. of creatinine clearance in pre- and post-menopausal patients with idiopathic oedema.

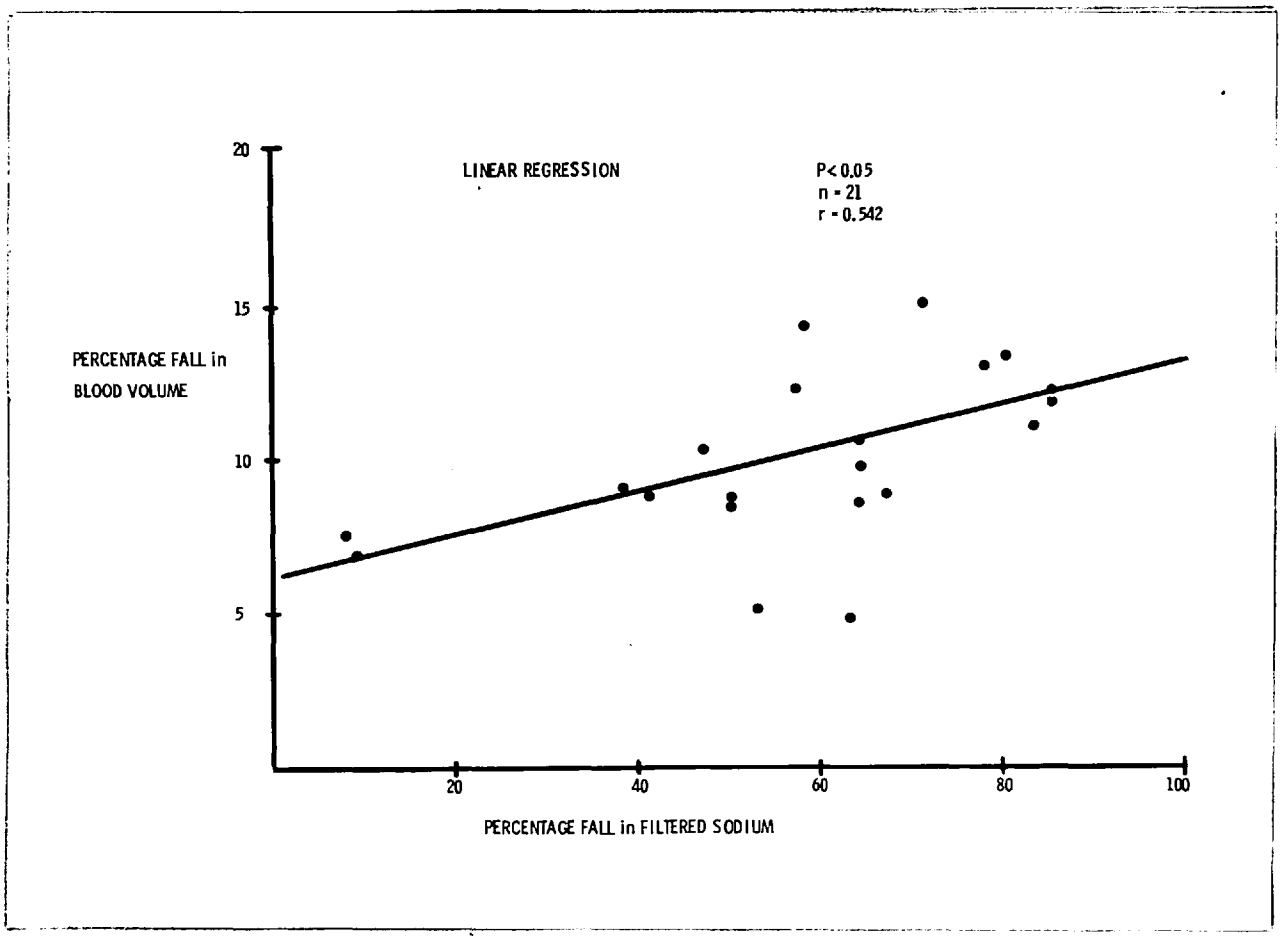


FIG. 25: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in filtered sodium excreted in the urine in pre- and post-menopausal patients with idiopathic oedema.

(r=0.69, n=37, P<0.001) and the percentage fall in filtered sodium excreted in the urine (r=0.693, n=37, P<0.001).

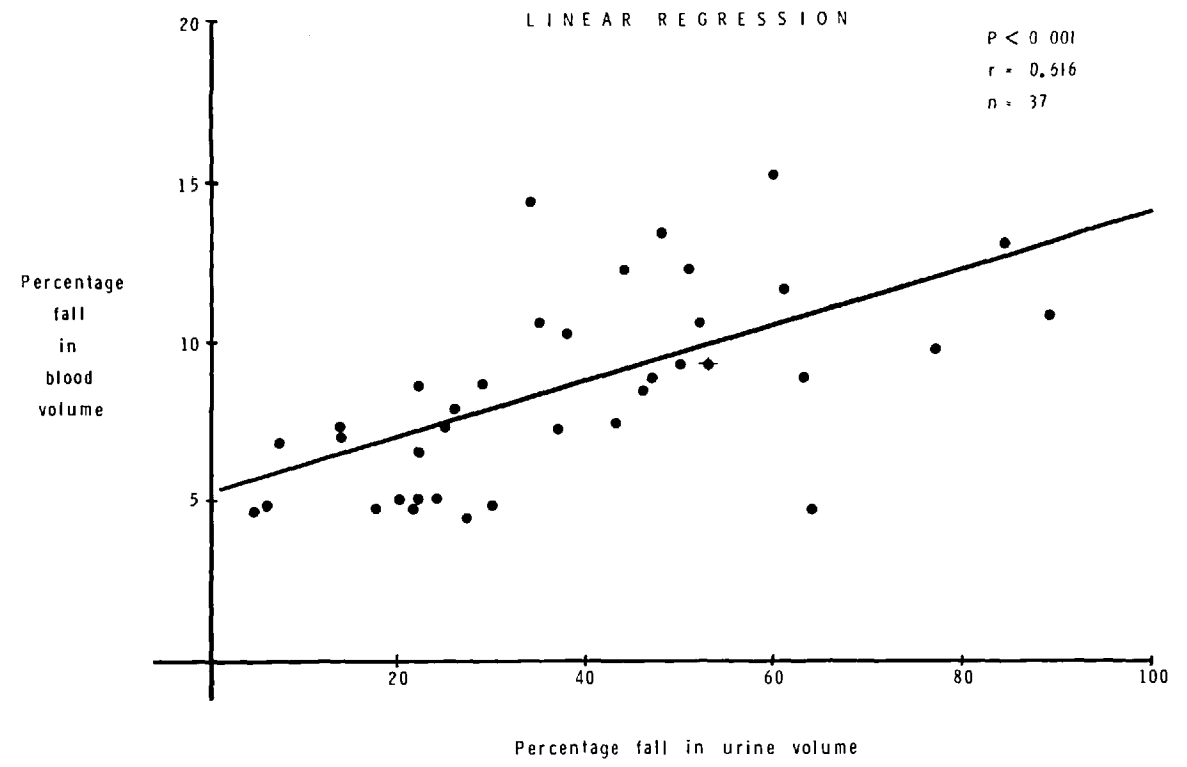


FIG. 26: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary volume in both normal subjects and patients with idiopathic oedema.

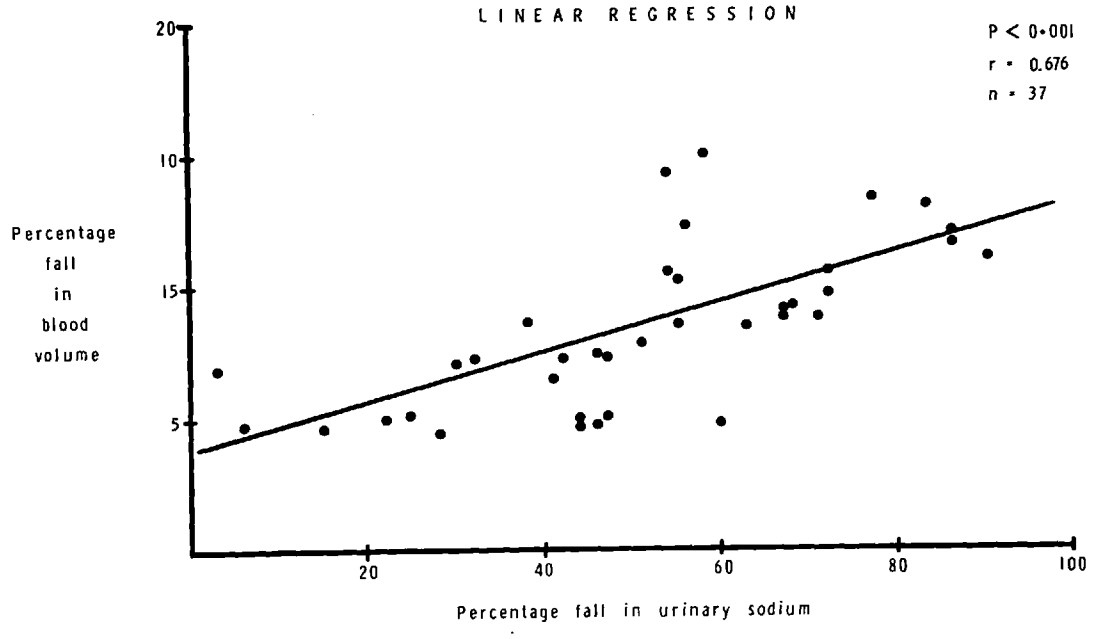


FIG. 27: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary sodium in both normal subjects and patients with idiopathic oedema.

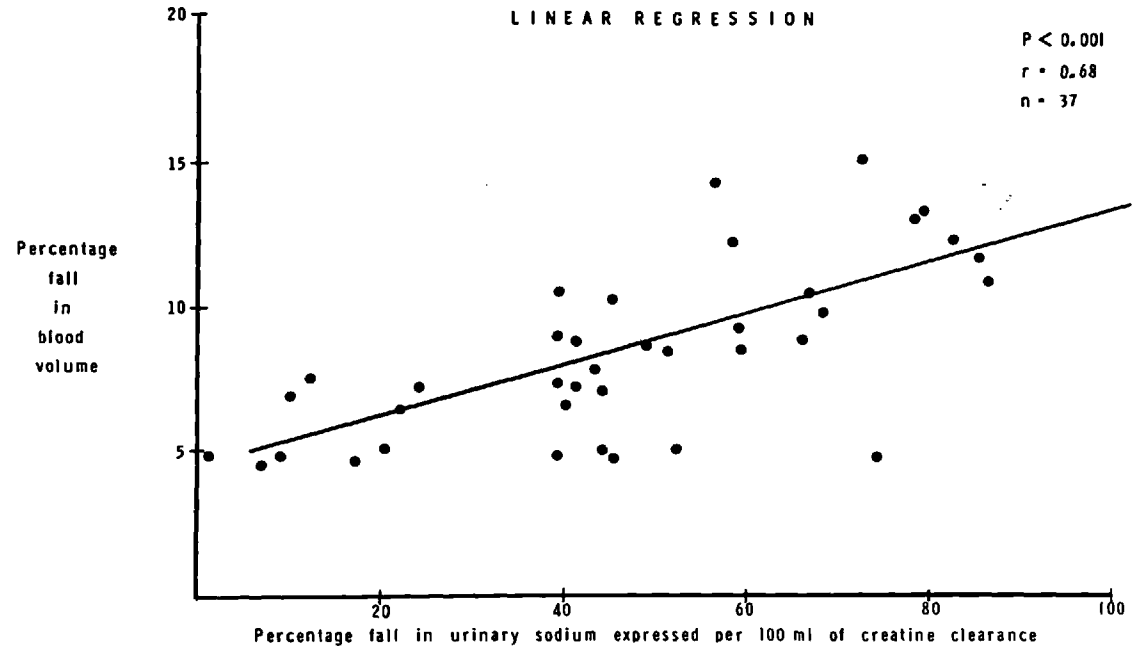


FIG. 28: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in urinary sodium expressed per 100 ml. of creatinine clearance in both normal subjects and patients with idiopathic oedema.

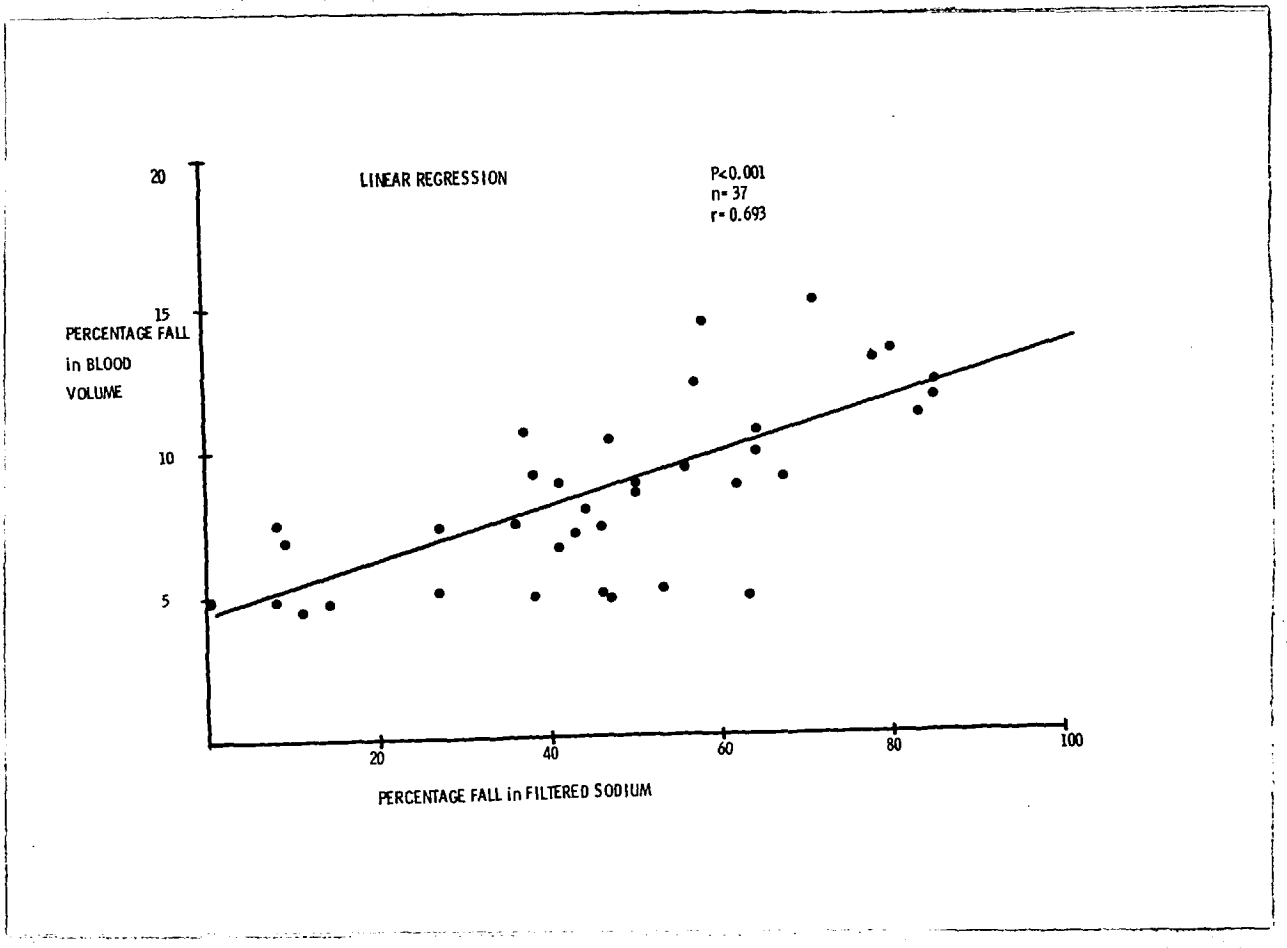


FIG. 29: A scattergram of the percentage fall in blood volume on standing plotted against the percentage fall in filtered sodium excreted in the urine in both normal subjects and patients with idiopathic oedema.

THE RESPONSE OF PATIENTS WITH IDIOPATHIC OEDEMA TO 9 α FLUOROHYDROCORTISONE ADMINISTRATION

The response of nine patients with idiopathic oedema to the administration of 9α fluorohydrocortisone was studied. The detailed results are given in Appendix 1.

A normal "escape" from the sodium retaining effect of 9α fluorohydrocortisone was thought to occur when the patient was in sodium balance without evidence of circulatory overload. A typical "escape" from the sodium retaining effect of 9α fluorohydrocortisone is shown in Fig. 30. It can be seen that, with the administration of 9α fluorohydrocortisone, the urinary sodium excretion falls sharply, fluid is reatined, and the body weight rises. The patient then goes into sodium balance, albeit whilst in negative potassium balance. On stopping the 9α fluorohydrocortisone, there is a marked natriuresis.

One patient failed to "escape" from the sodium retaining effect of 9α fluorohydrocortisone. The sodium balance remained persistently negative and the cumulative sodium balance rose markedly, paralleling the rise in body weight. The potassium balance did not alter substantially. The patient developed peripheral oedema and the jugular venous pressure rose. On stopping 9α fluorohydrocortisone, there was a marked natriuresis and weight loss, Fig. 31.

The combined results of the eight patients who escaped normally from the sodium retaining effect of 9α fluorohydrocortisone are shown in Fig. 32. It can be seen that the administration of 9α fluorohydrocortisone induced an increase

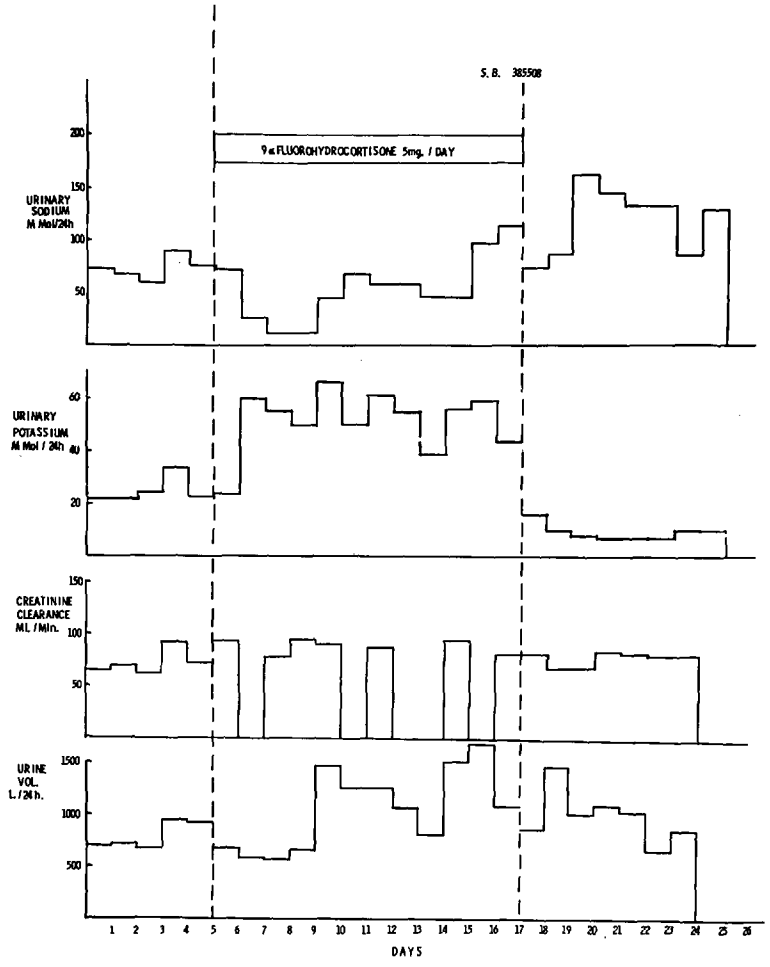


FIG. 30: The normal response of the body weight, urinary sodium and potassium and creatinine clearance in a patient with idiopathic oedema to the administration of 9α fluorohydrocortisone. (Patient No. 4).

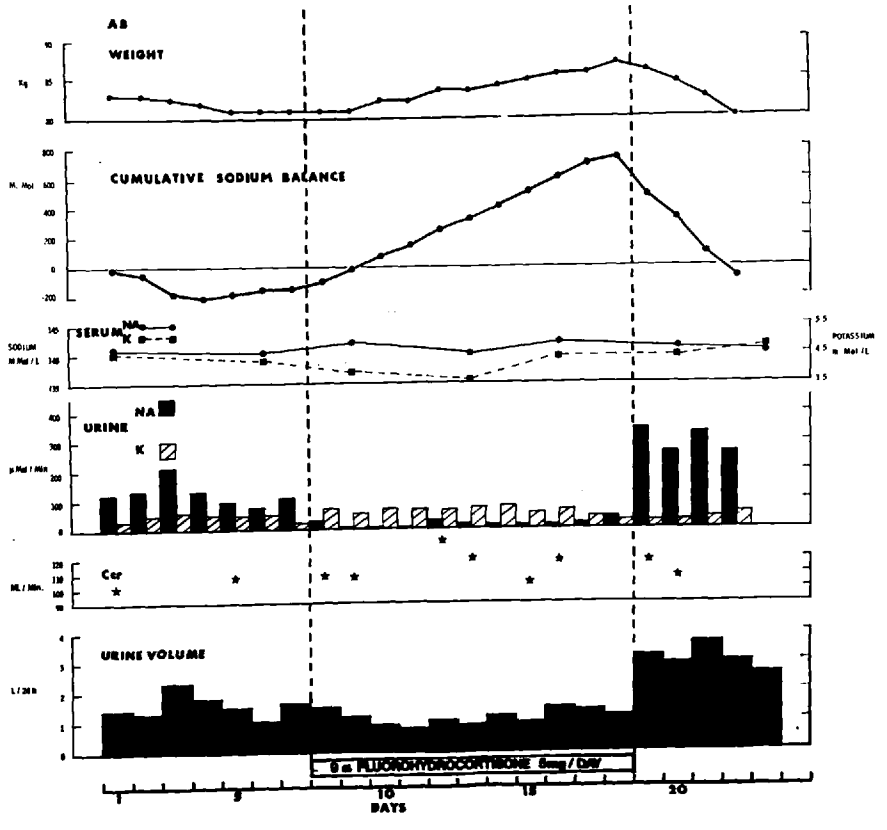


FIG. 31: The response of the body weight, cumulative sodium balance, serum sodium and potassium concentrations, urinary sodium and potassium excretion, creatinine clearance, and urinary volume to the administration of 9α fluorohydrocortisone in a patient who failed to "escape" from its salt retaining action. (Patient No. 9).

in weight, which was paralleled by a decrease in urinary sodium excretion until "escape" occurred at about the sixth to the seventh day. The urinary potassium excretion was also elevated.

In summary, of the nine patients with idiopathic oedema who were given 9 α fluorohydrocortisone, only one failed to show a normal "escape" from its salt retaining action.

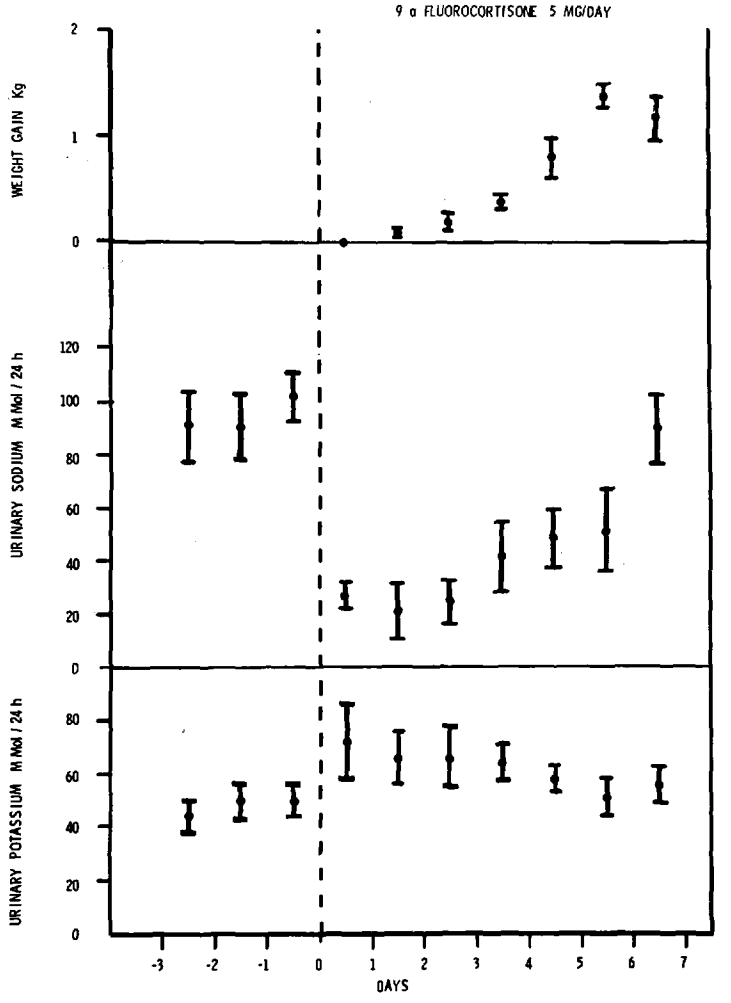


FIG. 32: The combined results of the eight patients with idiopathic oedema who "escaped" normally from the salt retaining action of 9α fluorohydrocortisone showing its effect on body weight, urinary sodium and potassium excretion (mean ± S.E.M.).

DISCUSSION OF RESULTS

URINARY EXCRETION OF WATER AND ELECTROLYTES IN NORMAL FEMALES DURING THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE: THE EFFECT OF POSTURE.

The reduction in urine flow when normal subjects change from the supine to the vertical position has been studied by other workers (Brun et al, 1945 a & b; Epstein et al, 1951; Goodyer & Seldin, 1953; Pearce & Newman, 1954; Surtshin & White, 1956). To my knowledge, however, no observations have been made on the changes in urinary volume and composition in the follicular and luteal phases of the menstrual cycle when normal, well-hydrated females are upright. The reduction in urine volume and urinary sodium excretion observed, which was more marked in the luteal than in the follicular phase, may be mediated by one or more of three renal mechanisms, namely a reduction in glomerular filtration rate, an increase in distal tubular reabsorption of water, or an increase in the proximal tubular reabsorption of electrolytes and water.

As discussed in an earlier section, (page 66), provided that other changes in renal function do not occur, a fall in glomerular filtration rate will cause a reduction in urine volume, a decrease in potassium excretion and a reduction in osmolar clearance, together with a fall in the free water clearance by decreasing the amount of osmotically active solute available for reabsorption at distal sites, Fig. 33. The creatinine clearance on changing from the lying to the upright position fell approximately

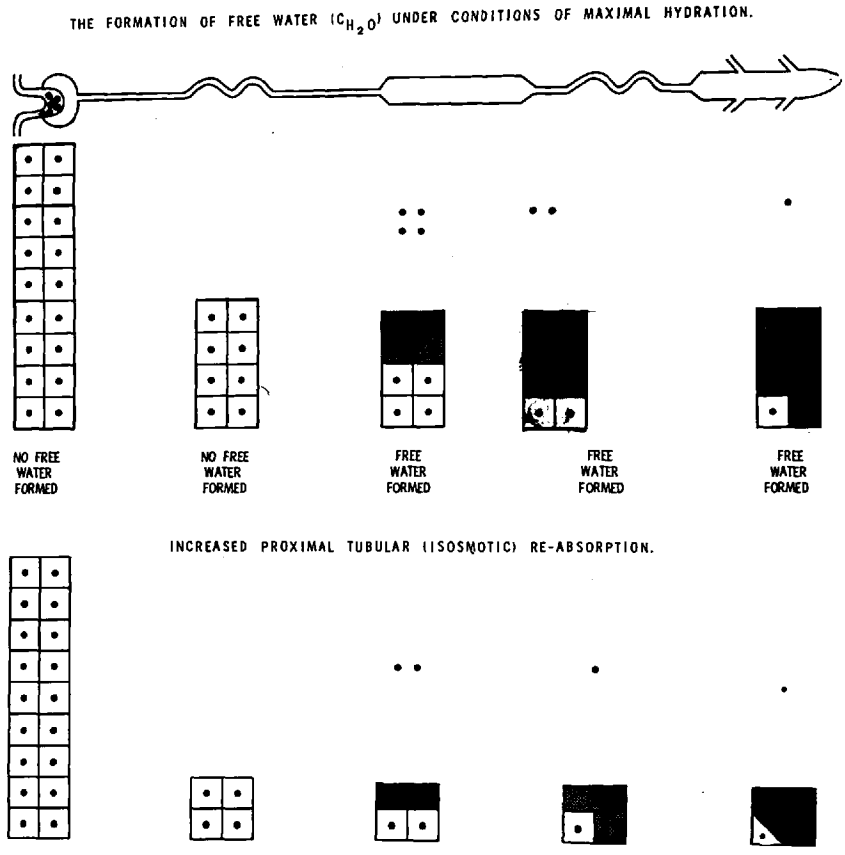


FIG. 33: The diagramatic illustration of the formation of free water (CH_2O) by the nephron and an illustration of the effect on free water clearance of increased proximal tubular re-absorption.

5% in the follicular phase and 7% in the luteal phase, differences which were not statistically significant. It is unlikely that such small changes in the glomerular filtration rate, as judged by creatinine clearance, would be associated with such large observed reductions in urinary volume and sodium excretion, which, in the upright position in the follicular and luteal phases, were decreased by 18% and 30% respectively for urine volume and 22% and 42% respectively for sodium excretion. Other workers have observed either no fall in creatinine clearance (Surtshin & White, 1956) or a small reduction, no greater than 10-15% (Epstein et al, 1951) when normal subjects were upright, and have concluded that factors other than a reduction in glomerular filtration rate are responsible for the decrease in water and sodium excretion.

The increased excretion of anti-diuretic hormone (A.D.H.), known to occur with adoption of the upright position, would cause a decrease in urinary volume, an increase in urinary osmolality, a decrease in free water clearance, whilst osmolar clearance remains unchanged. The experimental design, using forced water diuresis and hypotonic expansion of the extra-cellular fluid, would suppress A.D.H. excretion, thus eliminating this mechanism. The fact that the urinary osmolality remained unchanged or fell in twelve tests and rose only slightly in four, while in fifteen instances the osmolar clearance fell, supports the effectiveness of this procedure.

That the third possible mechanism, increased proximal

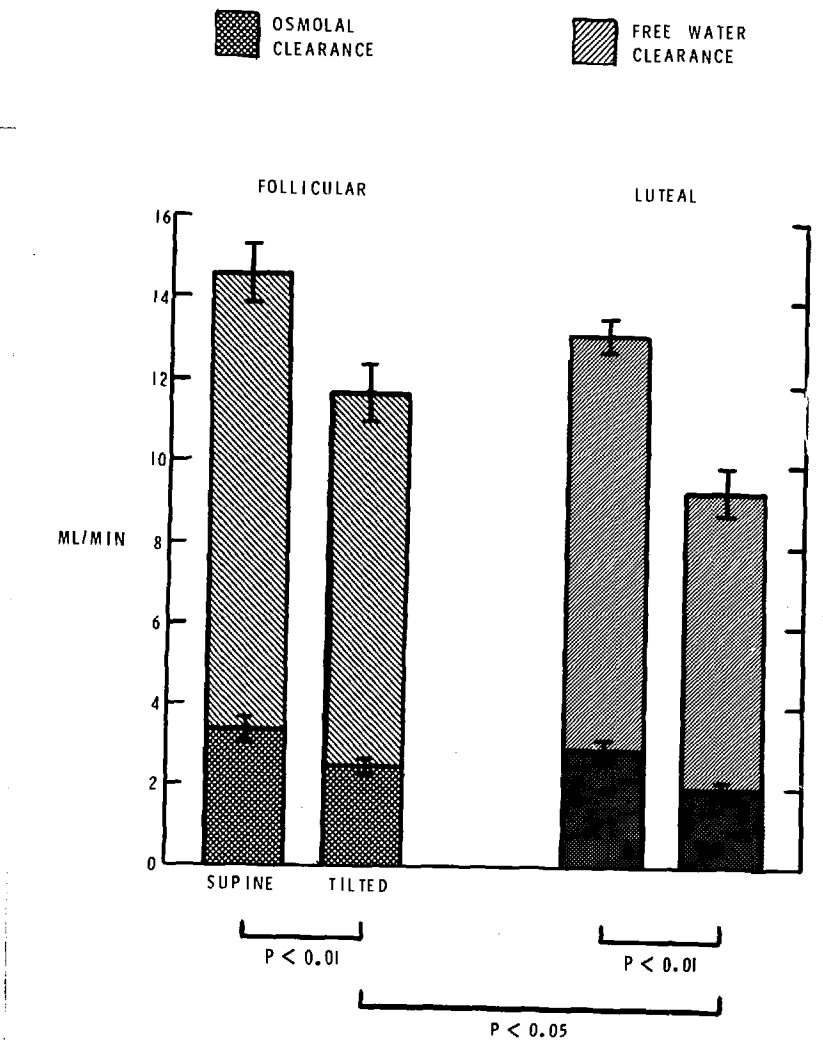


FIG. 34: The urine volume, osmolal and free water clearances in both the supine and upright positions in eight normal female subjects during the follicular and luteal phases of the menstrual cycle. (Mean ± S.E.M.)

tubular reabsorption, was responsible for the observed findings was suggested by the decreased sodium and potassium excretion, and the reduction in both osmolar and free water clearance found in all subjects. These changes were significantly greater in the luteal than in the follicular phase on tilting, and indicate an enhanced degree of proximal tubular reabsorption later in the menstrual cycle, Fig. 34.

The changes in sodium and potassium excretion occurred too quickly to be ascribed solely to the increase in the secretion of renin and aldosterone known to occur on standing (Gordon et al, 1967). Furthermore, in our subjects, the Na/K ratio fell on standing in seven tests and rose in nine, a rise in the Na/K ratio inferring decreased aldosterone activity, whilst a fall infers increased aldosterone activity. (Luetscher, 1956). The potassium excretion invariably fell in the upright posture. The mean fall in potassium excretion was 39% in the follicular phase and 48% in the luteal phase, a difference that was not statistically significant.

In conclusion, the greater posturally induced anti-natriuresis and anti-diuresis found in the luteal phase of the menstrual cycle of normal adult females was ascribed to greater proximal tubular reabsorption of water and electrolytes. The probable mechanism will be discussed later in this section.

URINARY EXCRETION OF WATER AND ELECTROLYTES IN PATIENTS WITH IDIOPATHIC OEDEMA : THE EFFECT OF POSTURE

Pre-menopausal patients

The clinical observations that the symptoms of idiopathic oedema were more pronounced and the diurnal weight gain excessive when upright prompted a number of early workers to study the effect of a water load in the supine and upright positions. They demonstrated an increased retention of water and electrolytes in the upright position (Streeten & Conn, 1959; Streeten & Conn, 1960; Streeten & Speller, 1966; Kuchel et al, 1970; Streeten et al, 1973). None of these studies employed a sustained water load to reduce or eliminate the variable of increased anti-diuretic hormone (A.D.H.) secretion, as has been used in the present study. Moreover, most workers appear to have ignored the possible effects of the menstrual cycle on the adaptive response to change in position, although Kuchel et al (1970) did specify that the tests were all performed in the follicular phase.

The reduction in urine volume and the alterations in urinary composition observed on changing from the supine to the upright position may be mediated by the one or more of the three basic mechanisms discussed in the previous section.

The creatinine clearance on changing from the lying to the upright position fell by approximately 5% in the

in the follicular phase and 5% in the luteal phase, differences which were not statistically significant. Nor was there a significant difference in creatinine clearance in the supine and upright positions during the follicular as compared with the luteal phase. It is unlikely that such small changes in glomerular filtration rate would be associated with such large observed reductions in urinary volume and sodium excretion which, in the upright position in the follicular and luteal phases, were decreased by 50% and 47% for urinary volume and 55% and 52% respectively for sodium excretion. These findings are in contra-distinction to those of Streeten and his colleagues (1973), who, as discussed in an earlier section, found an excessive reduction of 36% in the upright position in the group of patients termed "orthostatic sodium retainers" as compared with their controls. In an earlier study, Streeten & Conn (1960) did not find a consistent fall in creatinine clearance in patients with idiopathic oedema, a conclusion which was supported by a further study (Streeten & Speller, 1966). These findings do not support an abnormal fall in G.F.R. as being the cause of the excessive posturally induced reduction in urinary sodium, potassium and water excretion when patients with idiopathic oedema stand upright.

The changes in sodium and potassium excretion occurred too quickly to be ascribed to increased distal tubular activity secondary to the enhanced secretion of renin and

aldosterone known to occur on standing (Gordon et al, 1967). The Na/K ratio was not statistically different in the supine and upright positions. In eight tests, it rose or remained the same, indicating decreased mineralocorticoid activity (Luetscher, 1956). Furthermore, despite these changes in the Na/K ratio, potassium excretion invariably fell in the upright position. This, little indirect evidence of increased aldosterone secretion was found, nor of an increase in distal tubular activity.

The increased secretion of anti-diuretic hormone (A.D.H.) known to occur on standing and to be exaggerated in idiopathic oedema (Streeten & Conn, 1959 & 1960; Streeten et al, 1960; Streeten & Speller, 1966; Streeten et al, 1973) would cause a decreased urinary volume associated with an increase in urine osmolality. The urine osmolality remained unchanged or fell in eight tests and rose in six tests, whilst in all tests the osmolar clearance fell, supporting the general effectiveness of the experimental design. In one patient (Case No. 1), the urine osmolality rose markedly, indicating that increased A.D.H. secretion was a factor in reducing urine flow in this patient. It is also important to note that the percentage rise in the packed cell volume was 11.3 and the percentage fall in the filtered sodium excreted was 86, among the largest found in my series. This indicates that increased secretion of A.D.H. is a contributory factor in the fall in urinary volume in some patients with idiopathic oedema.

Thus, the posturally induced anti-diuresis and anti-natriuresis found in pre-menopausal patients with idiopathic oedema was found to be qualitatively similar to that found in normal female subjects. The main mechanism of this anti-diuresis and anti-natriuresis was thought to be increased proximal tubular reabsorption of water and electrolytes with other factors, such as increased A.D.H. secretion, playing a subsidiary role. However, there was, despite the qualitative similarity with the response found in normal subjects, a fundamental difference. There was no significant difference between the changes in urinary composition and flow in patients with idiopathic oedema during the follicular and luteal phases of the menstrual cycle. Thus, the posturally induced retention of salt and water is independent of the menstrual cycle, which corroborates the clinical finding that the attacks of oedema are unrelated to the menses.

The conclusion that increased proximal tubular reabsorption of water and electrolytes is the prime mediator of the posturally induced anti-diuresis and anti-natriuresis in patients with idiopathic oedema is in contra-distinction to that of other workers, e.g. Mach et al, 1955; Luetscher & Lieberman, 1957; Streeten et al, 1960 a & b; Hill et al, 1960; Streeten & Speller, 1966; Kuchel et al, 1970, who attributed this role to orthostatic hyperaldosteronism. However, my conclusion is not surprising, as it is generally acknowledged that changes in renal tubular reabsorption

are more potent than changes in glomerular filtration rate, as mechanisms by which sodium excretion may be modified (de Wardner, 1969; Earley & Daugharty, 1969).

Post-menopausal patients

The study of the effect of the change in posture from the supine to the upright position on urinary composition and flow in post-menopausal patients with idiopathic oedema was of great interest, primarily as it provided an opportunity to examine the effect of change in posture without the possible super-added variable of the menstrual cycle. No other comparable study has, to my knowledge, been made.

The posturally induced fall in urinary volume and alteration in urinary composition observed was qualitatively similar to that found in both normal subjects and pre-menopausal patients with idiopathic oedema. There were no significant differences in all the parameters measured between the two tests performed a fortnight apart in these subjects.

The fall in creatinine clearance in all tests was about 10% and, moreover, there was no significant difference in the creatinine clearance between the supine and upright positions. It is unlikely that such small changes could account for the large changes in urinary volume and sodium excretion observed which, in the upright position, fell by 46% and 63% respectively.

The increased secretion of anti-diuretic hormone (A.D.H.) known to occur on adoption of the upright position would cause a decrease in urinary volume, an increase in urinary osmolality and a decrease in free water clearance, whereas

the osmolal clearance would remain the same. In post-menopausal patients, the urine osmolality remained the same or fell in four tests and rose in four tests on standing, supporting the general effectiveness of the procedure. In only one patient (No. 11) was the free water clearance abolished, indicating that increased A.D.H. secretion was an important factor in reducing urine flow. It is of considerable interest that, in this patient, the percentage fall in filtered sodium excreted was 72 and the percentage rise in the packed cell volume (PCV) was 15.3, amongst the largest changes found in my series. Presumably, in this patient, the fall in plasma volume overcame the suppression of A.D.H. secretion by the water load. Thus, it can be assumed that A.D.H. secretion was markedly increased in this patient and moderately increased in another three, thus being a contributory factor in reducing the urine flow.

That the third possible mechanism, increased proximal tubular re-absorption, was responsible for the observed findings was suggested by the decreased sodium and potassium excretion and the reduction in both osmolar and free water clearance found in all subjects.

The change in urinary sodium and potassium excretion occurred too quickly to be ascribed to increased aldosterone secretion. Moreover, the urinary sodium to potassium ratio fell on standing in six tests and remained the same or rose in two tests and there was no statistically significant difference between the supine and upright positions. However, the experimental design would not provide information as

to the aldosterone secretion prevailing throughout the test.

Thus, in post-menopausal patients with idiopathic oedema, increased proximal tubular reabsorption of salt and water was thought to be the prime mediator of posturally induced fall in urinary flow and composition, with increased A.D.H. secretion playing a subsidiary role in occasional patients.

A COMPARISON OF THE RESULTS OBTAINED BETWEEN PRE- AND POST - MENOPAUSAL PATIENTS WITH IDIOPATHIC OEDEMA.

The major findings in pre- and post-menopausal patients were two-fold. Firstly, the changes in urinary flow and composition were not significantly different between the follicular and luteal phases of the menstrual cycle, a finding in marked contrast to that found in normal female subjects. Secondly, there were no significant differences between pre- and post-menopausal patients with this condition.

These findings confirm the contention from clinical observations that, although idiopathic oedema is virtually confined to the female sex, it is not related to the menstrual cycle. Other workers may not share this view and I would concede that the clinical manifestations of the disease may be worse pre-menstrually, but most other studies have, in the main, only performed once in each patient and not at specifically defined times in the menstrual cycle.

COMPARISON BETWEEN NORMAL SUBJECTS AND PATIENTS WITH IDIOPATHIC OEDEMA

When the urinary excretion of water and electrolytes of all the patients with idiopathic oedema is compared with that of the normal subjects, there are no significant differences in the supine position, Table 23.

On tilting, however, the patients with idiopathic oedema show, in comparison with the normal subjects during the luteal phase, a significantly smaller urine volume and reduction in osmolar clearance, free water clearance and sodium excretion. Furthermore, on changing from the supine to the upright position, the patients with idiopathic oedema show a greater increase in packed cell volume.

These findings are in marked contrast to those in normal subjects under identical conditions. In the patients with idiopathic oedema, the urine volume, osmolal clearance, free water clearance, sodium excretion and the percentage of filtered sodium excreted were, in the upright position, significantly less than in the normal subjects during the luteal phase, when such changes are normally more marked than in the follicular phase.

Thus, our studies indicate that the posturally induced anti-diuresis and anti-natriuresis found in patients with idiopathic oedema is quantitatively greater, but qualitatively similar to that found in normal women.

The mechanism responsible for the increased reabsorption in the proximal tubule remains uncertain, as also is

the reason for the greater degree of reabsorption in patients with idiopathic oedema, as compared with normal female subjects in the luteal phase of the menstrual cycle, or in normal females in the luteal as compared with the follicular phase. There is, however, a significantly greater increase in P.C.V. where patients with idiopathic oedema stand upright, as compared with normal women in the luteal phase, and in normal subjects in the luteal as compared with the follicular phase. This change in P.C.V. indicates a decrease in blood volume, and the greater the fall in blood volume, the greater appears to be the renal reabsorption of water and electrolytes. This reduction in blood volume, which is more marked in normal subjects in the luteal than in the follicular phase, may be related to the increased leakage of plasma proteins through the capillary walls found at this time in normal subjects (Jones et al, 1966) and which has also been observed in patients with idiopathic oedema (Ross et al, 1958; Clarkson et al, 1960; Emerson & Armstrong, 1955; Lagrue et al, 1971). The increase in interstitial oncotic pressure induced by extracapillary migration of plasma proteins would, in combination with the increase in capillary hydrostatic pressure on standing, favour increased transudation of water and electrolytes through the capillary walls of the legs. The resultant fall in effective blood volume would stimulate stretch receptors sensitive to volume changes and baroreceptors sensitive to small changes in arterial sodium and water.

BLOOD VOLUME CHANGES ON MOVING FROM THE SUPINE TO THE UPRIGHT IN NORMAL FEMALE SUBJECTS DURING THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE AND IN PATIENTS WITH IDIOPATHIC OEDEMA.

The blood volume, as measured by the venous packed cell volume (PCV) in the arm, invariably rose on standing, reflecting a fall in the total blood volume, assuming the relationship between peripheral PCV and total body PCV. (Fawcett & Wynn, 1960). In normal female subjects, the percentage fall in blood volume during the follicular phase of the menstrual cycle was 5.53±0.4% and in the luteal phase 7.94±0.7%, a difference which was statistically significant. In pre-menopausal patients with idiopathic oedema there was no statistically significant difference in the decrease of blood volume on standing between the follicular and luteal phases, nor between pre- and post-menopausal subjects. The percentage fall in blood volume was thus least in the follicular phase of the menstrual cycle of normal subjects, greater in the luteal phase and greatest in patients with idiopathic oedema, Fig. 36. The differences between the changes in blood volume on standing in the luteal phase of the normal menstrual cycle and patients with idiopathic oedema were statistically significant.

The fall in blood volume on standing has been shown to consist of two components, an immediate pooling of blood in the legs and a slow transudation of fluid from the

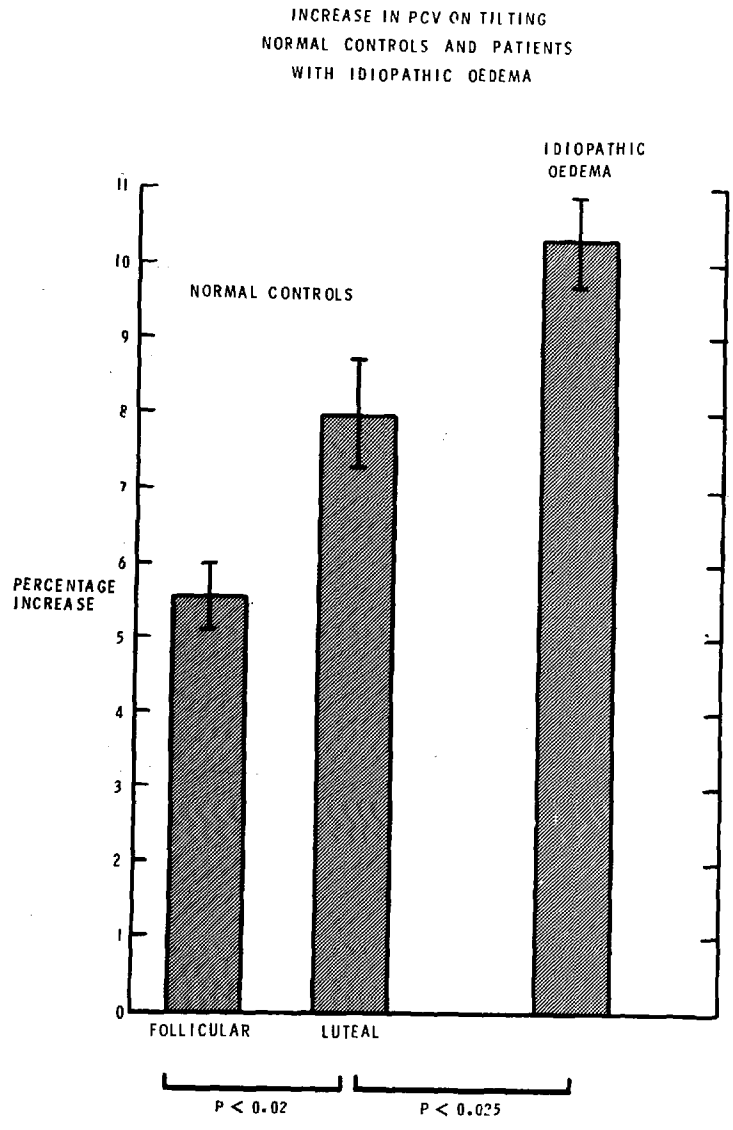


FIG. 35: The percentage increase in the packed cell volume during the follicular and luteal phases of the menstrual cycle in normal females and in patients with idiopathic oedema. (Mean $\pm$ S.E.M.).

intra-vascular space, associated with a rise in the oncotic pressure and the venous PCV in the legs. These responses are essentially over in ten to fifteen minutes, but, in oedematous subjects, may take up to forty-five minutes (Fawcett & Wynn, 1961). My subjects were allowed to move their legs gently, a procedure known to prevent venous pooling in the legs (Waterfield, 1931, a & b), thus the fall in blood volume which occurred was mainly attributable to fluid transudation from the intra-vascular space. This contention was confirmed by the observation that, if the red cell mass remains constant, then the changes in venous PCV will indirectly represent changes in the plasma volume. Thus, if venous pooling of blood in the legs was a major factor, then one would expect a poor correlation between blood volume changes calculated from the venous PCV and the ^{125}I labelled albumin concentration. However, the blood volume changes, as measured by the venous PCV, were strongly correlated with blood volume changes, as measured by ^{125}I labelled albumin. Thus, in my subjects with idiopathic oedema, increased venous pooling in the legs was not a significant factor in the decrease in effective blood volume.

Increased fluid transudation from the intra-vascular space on standing may be due to four main causes, firstly, an inappropriately high capillary hydrostatic pressure on standing due to an inappropriate ratio of the pre- to post-capillary resistance; secondly, a lowering of the plasma oncotic pressure (Gill et al, 1973); thirdly, an increase in the tissue oncotic pressure due to increased capillary

permeability to protein altering the ratio between the intra- and extra-vascular protein pools, and fourthly, an increase in the capillary surface area. If, in addition, there is a decrease in the rate of return of lymph to the intra-vascular space, then this will deplete the intra-vascular protein pool.

In my subjects with idiopathic oedema, the mean plasma volume was lower than in normal subjects, a difference which was not significant. However, in two patients, the plasma volume was greater than normal. The plasma protein concentrations in my patients with idiopathic oedema were entirely normal. This finding is in contradistinction to that of Gill and his colleagues(1972), who found a small but statistically significant difference between normal subjects and patients with idiopathic oedema. The rate of loss of ^{125}I labelled albumin in the supine position was greater than the normal (3.5 ±1.5%/hour) (Weil et al, 1971). However, due to technical difficulties, the rate of loss of ^{125}I albumin in the upright position was 5.6 ±3.2%/hour, which is contrary to the findings of Weil et al (1971), who found an increased protein loss in the upright position. This increased protein loss could have either been due to increased capillary permeability to protein molecules, or to an increase in capillary surface area. Since the plasma volume is decreased whilst the plasma protein concentration is within the normal range, then this increased loss of protein from the intra-vascular space infers the existence of a large

extra-vascular protein pool. Thus, if the tissue oncotic pressure is elevated, then there will be a greater loss of water and electrolytes from the intra-vascular space on standing per unit increase in the capillary hydrostatic pressure. It was thought to be unethical to give our normal female subjects ^{125}I labelled albumin, but an increase in loss of protein molecules from the intra-vascular space has been shown to occur in the luteal as compared with the follicular phase of the menstrual cycle (Jones et al, 1966).

CORRELATION BETWEEN THE CHANGES IN BLOOD VOLUME AND THE URINARY EXCRETION OF WATER AND ELECTROLYTES IN NORMAL FEMALE SUBJECTS DURING THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE AND PATIENTS WITH IDIOPATHIC OEDEMA

The most important observation in this thesis is the statistically significant correlation between the fall in blood volume on standing and changes in urinary flow and composition. This relationship was found to apply in both normal female subjects in the follicular and luteal phases and in patients with idiopathic oedema. However, in patients with idiopathic oedema, the fall in blood volume was not significantly correlated with urinary flow, due probably, as discussed earlier, to increased secretion of anti-diuretic hormone in certain patients. However, when the percentage fall in blood volume was plotted against the percentage fall in urinary volume and sodium in both normal subjects and patients with idiopathic oedema, highly significant correlations were found. This observation has important implications.

The contention of some workers that idiopathic oedema is caused by an inappropriate renal response to change in posture from the supine to the upright is inaccurate (Kuchel et al, 1971). On the contrary, the renal response is entirely appropriate to the excessive falls in blood volume found in idiopathic oedema. Also the fluid retention observed

in the luteal phase of the normal menstrual cycle is an appropriate renal compensatory response to the greater fall in blood volume on standing found at that time. Thus, the greater the fall in effective blood volume on standing, the greater is the compensatory renal mechanism for the retention of water and electrolytes.

Many workers have studied the renal response to change of posture from the supine to the upright in patients with idiopathic oedema and have attempted to divide the disease into various sub-groups on the basis of this response.

Streeten and his colleagues (1973) subdivided his group of patients with idiopathic oedema, chosen as discussed before on wide criteria, into three groups, i.e. non-orthostatic oedema, orthostatic water retainers and orthostatic sodium retainers. It is more probable that, since the renal compensatory response is proportional to the fall in blood volume, that these sub-divisions represent the spectrum of the disease from the less severe non-orthostatic oedema to the severe orthostatic sodium retainers. It is of considerable interest that only in the orthostatic sodium retainers was Streeten and his colleagues (1973) able to demonstrate an excessive fall in plasma volume on standing. Thus, the renal compensatory mechanisms for water and electrolyte conservation, i.e. alteration in the glomerular filtration rate, proximal tubular re-absorption, re-absorption at the ascending limb of Henle, renin-angiotensin-aldosterone system and the increased secretion of anti-diuretic hormone will be gradually and proportionally brought

into play, dependant on the degree of fall of the blood volume. Therefore, when the patient selection is limited, as by Mach et al (1955) or Kuchel et al (1973), to patients with secondary hyperaldosteronism, one is studying a more homogeneous group of patients with the severe manifestations of the disorder. It is, therefore, fallacious to single out one prominent renal mechanism and to attribute to it the pathogenesis of the condition. Moreover, treatment aimed at the effect rather than the cause is not likely to be very efficacious.

The increased fall in blood volume on standing found in idiopathic oedema is simply a quantitative difference, there being a greater fall in blood volume as one progresses from the follicular to the luteal phase of normal subjects to idiopathic oedema, together with an increased reabsorption of sodium, Fig. 36. Thus, the differences between these groups of "normals" and "abnormals" is simply one of degree. Since the control subjects were unselected, apart from their apparent normality, whereas the patients were highly selected on the basis of clinical findings and increased fluctuations in diurnal weight, are we studying the extreme end of a normal distribution? My study is at present too small to answer this question, although certain patients were grossly abnormal. This question must be answered, and one must, therefore, search for a cause or causes within normal physiological mechanisms.

The nature of the controlling mechanism correlating the fall in urinary volume and composition with the fall in

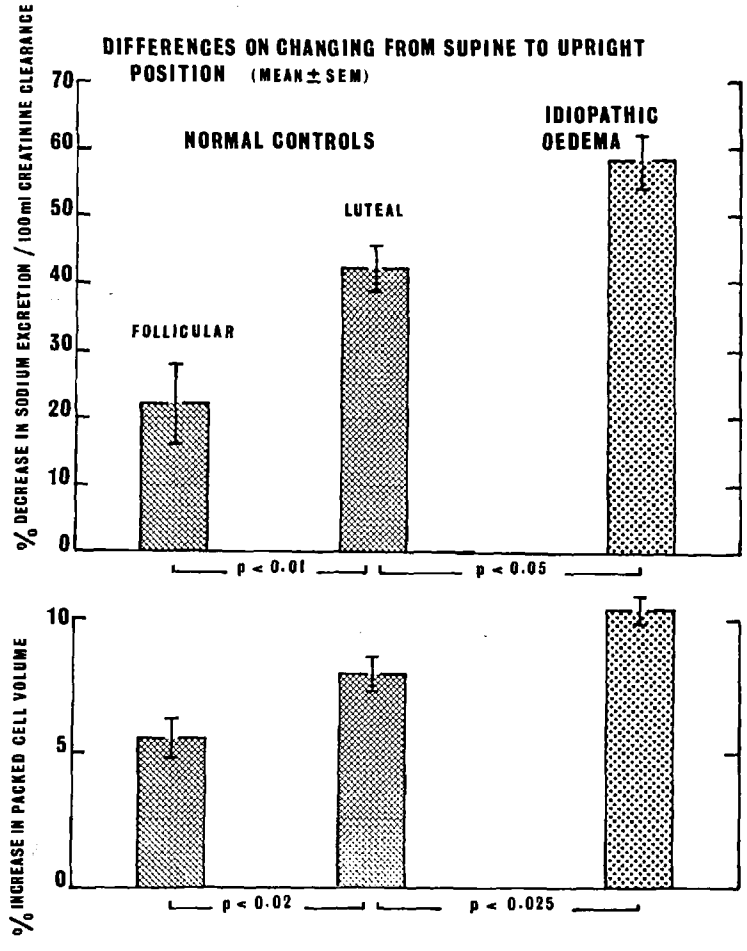


FIG. 36: The percentage decrease in the sodium excretion per 100 ml. of creatinine clearance and the percentage increase in packed cell volume in the follicular and luteal phases of the menstrual cycle in normal female subjects and in patients with idiopathic oedema.

blood volume is speculative. The fall in effective blood volume would stimulate a combination of stretch receptors sensitive to volume changes and baroreceptors sensitive to small changes in arterial pressure and so activate renal mechanisms to conserve sodium and water. A probable central role for the sympathetic nervous system in this mechanism is currently being studied. An increase in sympathetic nervous system activity could, via the renal nerves, alter hydrostatic pressure in the glomerular and peri-tubular capillaries, whereas a rise in plasma protein concentration on standing could, by increasing peri-tubular oncotic pressure, favour sodium reabsorption. Further tilting tests are being performed to elucidate the role of the sympathetic nervous system in this and other oedematous states.

THE "ESCAPE" FROM THE SALT RETAINING ACTION OF 9α FLUOROHYDROCORTISONE IN PATIENTS WITH IDIOPATHIC OEDEMA

Of the nine patients with idiopathic oedema challenged with 9α fluorohydrocortisone, one failed to "escape" from its salt retaining action, whilst the "escape" in the remainder was not unduly delayed, indeed in one patient the "escape" was extremely rapid.

As discussed in an earlier section, failure to "escape" from the sodium retaining effect of a mineralocorticoid is a feature of several oedematous states associated with secondary hyperaldosteronism (Nelson & August, 1959). It was, therefore, initially thought that the primary defect in idiopathic oedema was a failure to escape from the sodium retaining effect of endogenously produced hormones with mineralocorticoid actions. Several workers have examined this hypothesis and have arrived at conflicting conclusions. Gill et al (1972) found no difference in salt retention, whilst on 9α fluorohydrocortisone, between normal females and patients with idiopathic oedema. However, as pointed out in an earlier section, the study was of very short duration (three days). Jones (1973) found a failure to escape from 9α fluorohydrocortisone in a group of six patients with idiopathic oedema who had abnormal diurnal weight gains and clinical evidence of circulatory "congestion" in previous episodes, i.e. oedema with dyspnoea, elevated jugular venous pressure and occasionally pulmonary crepitations.

In my study, of the eight patients, only one failed to

"escape" from the sodium retaining effect of 9α fluoro-hydrocortisone. Her diurnal weight chart is seen in Fig.2. It can be seen that there are two components to the weight chart, the abnormal diurnal weight fluctuations and the gradual increase in the basal morning weight. This gradual increase in weight resembles the gradual increase in weight which occurred when she was given 9α fluorohydrocortisone.

The most interesting observation is that of Mulrieb & Mulrow (1964), who found a patient with idiopathic oedema who failed to "escape" when in the upright position, but did so in the supine position. My interpretation of this phenomenon is that the excessive fall in the plasma volume in the erect position stimulated an appropriate but increased renal retention of salt and water. Thus, increased water and sodium must need to be reabsorbed to expand the intra-vascular space before the volume receptors are stimulated. In the supine position, the plasma volume is only moderately decreased (Gill et al, 1972) and thus expansion of the intra-vascular space occurs earlier, as does the normal "escape".

Thus, one may postulate that the greater the postural fall in blood volume on standing, the greater the delay in the sodium "escape" and indeed the normal "escape" may not occur.

I am currently testing this hypothesis in idiopathic oedema.

CORRELATION OF THE SYMPTOMATOLOGY OF IDIOPATHIC OEDEMA AND THE PATHOPHYSIOLOGY

The symptoms of idiopathic oedema, facial bloating, abdominal distension, breast swelling and tenderness, puffy hands, ankle oedema, together with increased irritability and depression, are worsened by standing. These symptoms of widespread fluid retention are associated with a greater than normal daily weight gain when upright, particularly in a warm environment, and ameliorated by remaining supine. These symptoms of fluid retention initially focused attention on renal mechanisms, particularly when it was found that change in posture from the supine to the upright greatly decreased urine flow, as compared with normal subjects.

However, as I have shown, the blood volume is reduced in patients with idiopathic oedema. Moreover, the fall in blood volume on standing is greater than in the luteal phase of normal subjects. Also, in my subjects, the rate of loss of ^{125}I labelled albumin from the intra-vascular space was increased in both the supine and upright positions, inferring that the ratio of the intra-vascular to the extra-vascular protein pool had decreased and, thus, that tissue oncotic pressure had increased. I found that the excessive fall in plasma volume on standing was attributable to a loss of fluid from the intra-vascular to the extra-vascular space, presumably proportionate to this increase in tissue oncotic pressure. The cardinal observation is that the percentage fall in blood volume on standing is directly

related to the percentage fall in urinary volume and urinary sodium excretion. This relationship holds for both "normal" and "abnormal" subjects.

Thus, in patients with idiopathic oedema, there is a greater loss of fluid on standing from the intra-vascular space per unit change in capillary hydrostatic pressure, because of this increase in tissue oncotic pressure. The greater fall in blood volume will then cause an appropriately greater renal retention of salt and water. Since fluid and food intake continues throughout the waking hours, fluid accumulates and is proportionally redistributed between the intra- and extra-vascular spaces. This leads to the widespread nature of the symptoms of facial bloating, breast swelling and tenderness, etc. Fluid will accumulate in areas where the tissue tension is low, e.g. hands, periorbital oedema and breasts causing puffiness and tenderness. The symptoms of abdominal distension may be related to the fenestration of the intestinal capillary endothelium (Folkow & Ungar, 1971). This fenestration would allow a greater tissue oncotic pressure and thus a greater proportional loss of fluid from the intra-vascular space, particularly in the upright position. This fluid transudation would be aided by the low tissue tension. This oedema of the intestinal wall may cause abdominal distension in an analogous way to the occasional presentation of patients in severe congestive cardiac failure with abdominal pain, the unwary surgeon finding oedematous distended small intestine at laparotomy.

It is also of considerable interest that the symptoms

and signs of the pre-menstrual tension syndrome are identical to those of idiopathic oedema, apart from the restriction to the pre-menstruum. I have shown greater changes in blood volume and urinary flow and composition in response to change in posture from the supine to the upright in the luteal phase of normal subjects, compared with the follicular. I propose that essentially the same mechanism and explanation accounts for these symptoms found in this condition as in idiopathic oedema.

The important observation that there was no difference between the tests performed in the follicular and luteal phases of pre-menopausal patients confirms the clinical observation that the condition is continuously present, unlike the pre-menstrual tension syndrome. The finding of no significant difference between the tests performed in the pre-menopausal and post-menopausal patients confirms the clinical observation that the condition may persist beyond the menopause, whether spontaneous or induced, and it also infers that, whilst the condition is related to "femaleness", it is unrelated to the menstrual cycle.

TREATMENT

Treatment which is aimed at the effects of a disease rather than its cause is likely to be unsatisfactory and as at the moment the basic cause of the condition is unknown, one is left with general and symptomatic measures.

General measures

The patient, when she is first seen in the clinic, may be hostile and defensive, mainly due to past contact with disbelieving physicians. She may also at this time be on a variety of diuretics, to which she may be inordinately attached. Initially, the patient is asked to keep a diurnal weight chart, so that one can assess the severity of the condition and also the effect of therapy. A tilting test, as described earlier, is also performed and gives valuable information as to the diagnosis and severity of the condition. The serum uric acid, blood urea and electrolytes are estimated.

An explanation of the known pathogenesis of the condition is given to the patient, and in particular that the condition is more severe when up and about, and hence is aggravated if she keeps late hours.

If the patient is obese, she is given a reducing diet. Other associated conditions, such as constipation, are also treated.

Many of the patients on presentation are depressed, and this is treated with supportative therapy and, in some cases, tricyclic antidepressants.

Diuretic therapy

As the exhibition of diuretic therapy may accentuate the hypovolaemia of these patients and thus the postural hypotension, their use is restricted to a minimum. As can be seen from the diurnal weight chart, Fig. 2, there may be two components, firstly the excessive diurnal weight, and secondly the increase in the basal morning weight.

The excessive daily weight gain is reduced by the administration of chlorthalidone, a diuretic which acts over a prolonged period when the patient is upright and active. The potassium loss is prevented by the concurrent administration of triampterene.

If the patient has a gradual increase in basal morning weight and the nocturnal diuresis does not occur, then aldosterone is given. Some of these patients may show an inability to escape from the sodium retaining effect of mineralocorticoids.

The treatment is carefully monitored with frequent electrolyte estimations and the therapeutic aim is to keep the diurnal weight gain within the normal range.

SUMMARY AND CONCLUSIONS

A survey of the extensive literature on this ill-defined subject has been made. On the basis of this study, the effect of change in posture from the supine to the upright was studied on both the blood volume and the urinary flow and composition in normal female subjects during the follicular and luteal phases and patients with idiopathic oedema under the conditions of a sustained water diuresis.

Normal female subjects

1. Water and electrolyte excretion has been measured in both the follicular and luteal phases of the menstrual cycle in eight normal females undergoing a sustained water diuresis.
2. When the subjects were supine, no differences were found in urinary excretion during the follicular and lutel phases.
3. When the subjects were tilted to the vertical position, the urine volume, excretion of sodium and potassium and the osmolar and free water clearances fell, suggesting an alteration in proximal tubular function. These changes were statistically greater in the luteal than in the follicular phase of the cycle.
4. It is postulated that the enhanced retention of electrolytes and water in response to tilting in the luteal phase is a compensatory mechanism for the reduced effective blood volume at that time.

Idiopathic oedema

1. Water and electrolyte excretion has been measured in both the follicular and luteal phases of the menstrual cycle in seven patients with idiopathic oedema, and also in four post-menopausal patients with this condition.

2. When supine, no differences were found in urinary excretion during the follicular and luteal phases in the pre-menopausal patients, or between the pre-menopausal and post-menopausal patients.

3. When the patients were tilted to the upright position, the urine volume, excretion of sodium and potassium and the osmolal and free water clearances fell, suggesting an alteration in proximal renal tubular function. Increased secretion of anti-diuretic hormone was found to play only a minor contributory role.

4. These urinary changes were not statistically different in the follicular and luteal phases in pre-menopausal patients, or in two tests performed a fortnight apart in the post-menopausal patients. There were no significant differences between pre and post-menopausal patients.

5. In the supine position, no statistically significant differences were found in urinary flow and composition between patients with idiopathic oedema and normal subjects in the luteal phase of the menstrual cycle. When tilted to the upright position, the fall in urine flow and electrolyte excretion was quantitatively greater in patients with idiopathic oedema, but qualitatively similar.

6. It is postulated that the enhanced retention of electro-

lytes and water in response to tilting in patients with idiopathic oedema is a compensatory mechanism for the decreased effective blood volume at that time.

Blood volume changes on standing in normal subjects and idiopathic oedema

1. The fall in blood volume on standing, as measured by the P.C.V., was least in the follicular phase of the normal menstrual cycle, greater in the luteal phase and greatest in idiopathic oedema.

2. The plasma volume of patients, as measured with ^{125}I albumin, was decreased, as compared with normal female subjects. Moreover, the rate of loss of ^{125}I albumin from the intra-vascular space was increased, compared with normal subjects, inferring increased capillary permeability to protein and an enlarged extra-vascular protein pool.

3. The change in blood volume on standing, as measured by the change in the P.C.V., was highly significantly correlated with the fall in plasma volume as measured by ^{125}I labelled albumin.

Correlation of blood volume changes on standing with changes in urinary flow and composition in normal subjects and patients with idiopathic oedema.

1. The fall in blood volume on standing was significantly correlated with the fall in urinary volume, urinary sodium (expressed either in absolute terms or in relationship to creatinine clearance) and to the percentage of filtered

sodium excreted in the urine, in the follicular and luteal phases of the menstrual cycle in normal female subjects.

2. The fall in blood volume on standing was significantly correlated with the fall in urinary sodium expressed in relationship to creatinine clearance and to the percentage of filtered sodium excreted in the urine in pre and post-menopausal patients with idiopathic oedema.

3. The fall in blood volume on standing was highly significantly correlated with the fall in urinary volume, urinary sodium (expressed either in absolute terms or in relationship to creatinine clearance) and to the percentage of filtered sodium excreted in the urine in the follicular and luteal phases of the normal menstrual cycle and patients with idiopathic oedema.

4. The conclusion drawn was that the enhanced retention of water and electrolytes on standing in the luteal phase of normal subjects and patients with idiopathic oedema was a compensatory renal mechanism in response to the increased fall in blood volume. Therefore, as opposed to the conclusion of other workers, the renal response in idiopathic oedema is an appropriate response to the excessive fall in blood volume in patients with idiopathic oedema, Fig. 37.

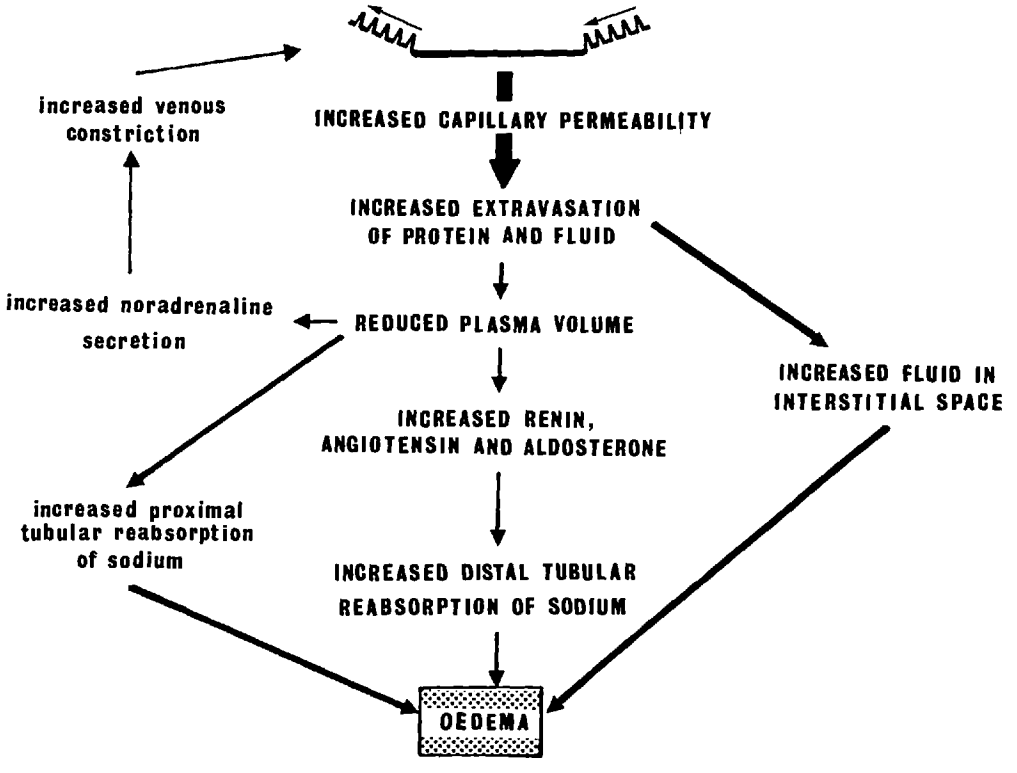


FIG. 37: The diagramatic representation of the possible train of events leading to peripheral oedema in idiopathic oedema.

The response of patients with idiopathic oedema to the administration of 9α fluorohydrocortisone.

1. Nine patients with idiopathic oedema were challenged with 9α fluorohydrocortisone and eight "escaped" normally from its salt-retaining effect.

2. It was pointed out that the patient who failed to "escape" had a severe manifestation of the disorder and the fall in plasma volume on standing was much increased.

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A P P E N D I X

CLINICAL AND LABORATORY DATA OF THE 9α FLUOROHYDROCORTISONE TESTS PERFORMED IN PATIENTS WITH IDIOPATHIC OEDEMA.

PATIENT 4

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l/	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100ml)
1	-	720	68	22	71	142	3.8	20	26
2	68.9	670	60	25	63	-	-	-	-
3	-	950	91	34	92	145	3.5	22	23
4	68.9	890	77	24	73	-	-	-	-
5	68.5	670	27	24	91	-	-	-	-
6	69.3	560	12	60	-	147	4.0	21	21
7	69.5	540	12	55	78	-	-	-	-
8	69.5	660	42	49	94	143	3.0	20	20
9	69.9	1410	68	66	90	-	-	-	-
10	70	1240	58	53					
11	70.5	1250	58	61	87	-	-	-	-
12	70.6	1070	46	57	-				
13	70.6	800	46	39	-	147	2.7	30	18
14	70.2	1500	99	56	94	-	-	-	-
15	69.9	1730	116	59	-	145	2.2	31	18

PATIENT 8

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100ml)
1		800	84	43	108	141	3.9	28	34
2	105	470	53	39	106				
3	-	900	86	40	-				
4	-	790	98	43	127				
5	105	1180	9	92	127				
6		460	6	46	-				
7	105.1	410	8	41	105				
8	-	350	7	37	110	143	3.4	27	26
9	105	500	19	45					
10	105.1	400	12	38		142	3.4	28	30
11	105.7	420	16	44	117				
12	105.5	500	29	55	122	144	2.9	27	26
13	106.3	1170	76	70	-	-	-	-	-
14	106.4	1050	58	43	113	-	-	-	-
15	106	1600	180	35	123	144	2.9	32	16

PATIENT 9

DAY	WEIGHT (KG.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100 ml.)
1	81.4	2380	224	67	-				
2	81.4	1810	132	52	-				
3	81.2	1520	87	47	108				
4	81	1090	73	51	71	141	4.3	27	17
5	81.0	1680	104	39	-				
6	80.8	1500	30	62					
7	80.9	1340	4.0	56					
8	82.4	910	6	55	108	144	3.9	29	13
9	82.4	880	6.2	59	108				
10	82.4	1120	29	65					
11	82.4	920	10	59	122				
12	83	1300	13	61	110	140	3.5	25	19
13	83.1	970	14	71					
14	83.9	1460	12	51	94	144	3.9	28	19
15	84.2	1350	10	58	108				

PATIENT 14

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	H_{CO_3} (m.mol/l)	UREA (mg/100ml)
1	76.2	1220	96	31	-	-	-	-	-
2	75.6	1520	85	20	-				
3	75.8	1040	95	19	98	142	4.6	27	21
4	75.3	1220	133	43	77	140	5.8	27	21
									FLUDROCORTISONE
5	75.2	890	39	52	-	-	-	-	-
6	74.8	865	23	45	59				
7	74.8	1110	49	38	91	-	-	-	-
8	74.8	1112	63	39	104				
9	74.8	1650	89	51	94	142	4.6	27	21

PATIENT 15

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100ml)
1	-	760	82	37	140				
2	-	-							
3	61.8	1060	36	70	-	141	5.3	29	20
4	61.8	1400	122	58					
5	61.8	480	3	44		1.33	3.5	30	13
6	62.7	1800	1.0	79		142	3.7	28	14
7	62.7	-	-	-		-	-	-	-
8	63.6	380	9	70		14.7	3.6	30	12
9	64.1	640	9	45		-	-	-	-
10	64.1	1480	80	57		-	-	-	-
11	64.1	1480	139	47		145	3.0	31	-

PATIENT 16:

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100ml)
1	70	3020	160	65	53				
2	69.5	1800	183	71	99				
3	69.1	1840	115	81	153				
4	-	1940	116	76	135				
5	69.1	1880	24	162	175				
6	69.1	1140	14	75	155				
9	70	2020	25	134	-	143	3.5	26	18
10	70	960	15	89	160				
11	70.5	1730	32	86	180	143	3.0	26	22
12	71.8	1750	30	85	-	-	-	-	-
13	72.3	1400	28	59	-	-	-	-	-
14	72.3	2000	22	77	-	-	-	-	-
15	72.3	2500	90	135		141	2.9	27	20

PATIENT 17

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100ml)
1	74	1600	98	51	123	136	4.1		
2	74.5	2140	98	49	-	-	-		
3	74.4	2380	71	57	-	141	3.8		
4	74.7	1530	86	43	91	-	-		
5	74.6	1540	37	89	96	138	4.0		
6	74.2	1360	13	38					
7	74.9	1780	22	50	97				
8	74.9	2730	112	79	116	143	3.2		
9	74.6	3040	94	52	-	-	-		

PATIENT 18

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l	HCO_3 (m.mol/l)	UREA (mg/100ml)
1	71.5	1630	54	62	-				
2	71.5	1230	84	53	90				
3	71.7	900	67	40	93	148	5.1	24	27
4	71.3	2160	71	48	-				
5	71.0	970	34	49	-	144	3.9	27	22
6	71.0	2420	99	123	106				
7	70.8	1480	67	78	94	141	4.1	34	22
8	70.5	1880	56	79	-				
9	71.3	1300	44	49	60				
10	70.5	2320	102	43	118	148	2.9	32	15
11	70.2	-	-	-	-	144	2.3	34	15
12	70.6	-	-	-	-	141	2.4	34	16
13	70.6	1960	55	59	112	-	-	-	-

PATIENT 19

DAY	WEIGHT (Kg.)	URINE			CREATININE CLEARANCE (ml/min)	PLASMA			
		VOLUME (ml/24h)	SODIUM (m.mol/24h)	POTASSIUM (m.mol/24h)		Na (m.mol/l)	K (m.mol/l)	HCO_3 (m.mol/l)	UREA (mg/100ml)
1	56.9	1870	109	47	84				
2	56.9	1340	92	55					
3	56.9	2240	170	54		144	4.0	27	23
4	57.0	2000	133	51					
5	57.0	1870	45	61		143	3.2	27	29
6	57.0	2000	7	58					
7	57.4	1500	15	65		142	3.2	26	26
8	58.1	1880	26	65	100				
9	59.1	1980	33	63	98	140	2.7	26	20
10	60.1	1480	22	59		140	2.3	28	20
11	60.2	1810	80	73	159				

Author's note

The work this thesis is based on was carried out in the Metabolic Unit at Westminster Hospital, S.W.1 and in the Department of Investigative Medicine, Addenbrooke's Hospital, Cambridge.

The subject of the thesis was suggested by Dr. R. I. S. Bayliss, but the remainder of the thesis was entirely the author's own conception and design. I gratefully acknowledge the supervision and encouragement given to me by Dr. R. I. S. Bayliss and Professor Ivor H. Mills.

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Some of the data presented in this thesis has been published.

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URINARY EXCRETION OF WATER AND ELECTROLYTES IN NORMAL FEMALES DURING THE FOLLICULAR AND LUTEAL PHASES OF THE MENSTRUAL CYCLE: THE EFFECT OF POSTURE

OWEN M. EDWARDS AND R. I. S. BAYLISS

Westminster Hospital and Medical School, London

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SUMMARY

1. Water and electrolyte excretion has been measured in both the follicular and luteal phases of the menstrual cycle in eight normal females undergoing a sustained water diuresis.

2. When the subjects were supine, no differences were found in urinary excretion during the follicular and luteal phases.

3. When the subjects were tilted to the upright position, the urine volume, excretion of sodium and potassium and the osmolar and free water clearances fell, suggesting an alteration in proximal tubular function. These changes were statistically greater in the luteal than in the follicular phase of the cycle.

4. It is postulated that the enhanced retention of electrolytes and water in response to tilting in the luteal phase is a compensatory mechanism for the decreased effective blood volume at that time.

Key words: diuresis, menstrual cycle, renal function, idiopathic oedema, premenstrual tension, posture.

Many of the symptoms and signs of the premenstrual tension syndrome have been attributed to salt and water retention in the late luteal phase of the menstrual cycle. Jones, Fox & Verow (1966) relate this retention to the hypovolaemia induced by the increased leakage of plasma proteins through the capillary walls at that time.

In the present work the excretion of water and electrolytes during both the follicular and luteal phases of the menstrual cycle in normal well-hydrated women undergoing a sustained diuresis was studied. To emphasize any differences between the two phases of the menstrual cycle, electrolyte and water excretion have been studied before and after tilting the subjects into the upright position. The object was to establish whether or not there was enhanced retention of salt and water on tilting to the upright position in the luteal as compared with the follicular phase of the menstrual cycle, and if so, whether or not these changes were related

Correspondence: Dr R. I. S. Bayliss, Westminster Hospital, Dean Ryle Street, London, S.W.1.

to any alteration in the effective blood volume. By studying the pattern of the renal response we have sought to define the site or sites in the nephron that are responsible for the observed alterations.

Changes from the supine to the upright position initiates several physiological consequences. Pooling of blood caudal to the heart decreases the venous return and the cardiac output. Hydrostatic forces cause fluid to leave the circulation and the legs increase in volume. The plasma volume decreases by as much as 12% (Waterfield, 1931; Youmans, Wells, Donely, Miller & Frank, 1934; Fawcett & Wynn, 1960). There is an immediate increase in sympathetic nervous activity causing veno-constriction, increase in heart rate, an increase in myocardial contractility and increased peripheral vascular resistance which all serve to maintain the arterial blood pressure. Other more sluggish mechanisms expand the intravascular fluid volume and sustain the blood pressure by decreasing the urinary excretion of water, sodium chloride and potassium (Pearce & Newman, 1954; Streeten & Speller, 1966). The response to hypovolaemia is graded in that the greater the fall in intravascular volume, the greater is the decrease in water and electrolyte excretion.

SUBJECTS AND METHODS

Subjects

The subjects were eight healthy female medical students, aged 20–24 years, with regular menses who gave informed consent. None had a history of oedema, renal or cardiac disease, or was taking an oral contraceptive.

Experimental design

Observations were made in each subject on the 8th–9th day and again on the 20th–21st day of the menstrual cycle. On each occasion a light breakfast was allowed but smoking forbidden. No attempt was made to standardize the diet during the preceding days. At 09.00 hours the subject emptied her bladder and was weighed. She then lay supine on a tilting table and drank 20 ml of water/kg of body weight. During the period of study the bladder was emptied hourly and a volume of water was drunk equal to that of the urine voided. When a constant diuresis had been established, usually by 11.00 hours, urine was collected hourly for analysis for 2 h (11.00–12.00 and 12.00–13.00 hours). At the end of this time, usually 13.00 hours, the subject was tilted 80° towards the upright position and urine collected for another hour. The tilted position is referred to hereafter as 'upright'.

An indwelling catheter was inserted into a forearm vein under local anaesthesia between 09.00 and 10.00 hours. Blood samples were taken without veno-constriction at 13.00 and 14.00 hours, at the end of the supine and upright periods respectively. The observations were made in a quiet warm room with only essential personnel in attendance.

Chemical methods

Sodium and potassium were measured by flame photometry. Osmolality was determined without delay with an 'Advanced Instruments' osmometer. Creatinine was measured by the method of Wootton (1964). Packed cell volume (PCV) determinations were made in duplicate in Wintrobe tubes by using a centrifuge of 15 cm radius at 3000 rev./min for 55 min.

Calculations

Free water clearance (C_{H_2O}) was calculated as the excess of solute-free water relative to the simultaneous osmolal clearance ($C_{osm.}$) from the formula

$$C_{H_2O} = V - \frac{U_{osm.} \cdot V}{S_{osm.}}$$

where $U_{osm.}$ and $S_{osm.}$ are urinary and serum osmolality in mosmol/kg, and V is the urinary volume in ml/min.

The percentage of the filtered load of sodium excreted in the urine (the fractional sodium excretion or E_{Na}) was calculated as $(U_{Na} \cdot V/F_{Na}) \times 100$ where $U_{Na} \cdot V$ = urinary sodium excretion (μmol/min), F_{Na} = filtered sodium = $S_{Na} \cdot f \cdot GFR$ where S_{Na} = serum sodium concentration (mmol/l), f = Gibbs–Donnan factor (0·95) and GFR = glomerular filtration rate in ml/min as estimated by endogenous creatinine clearance. None of the results was corrected to standard body-surface area. The amount of sodium excreted was expressed in both absolute terms or per 100 ml of creatinine clearance. The difference between the sodium excreted per 100 ml of creatinine clearance in periods 12.00–13.00 hours and 13.00–14.00 hours was expressed as a percentage of the period 12.00–13.00 hours.

RESULTS

The results for each individual subject are given in Table 1. The more detailed results are available in *Clinical Science and Molecular Medicine* Table 73/18 on application to the Librarian, Royal Society of Medicine, 1 Wimpole Street, London, W.1.

Constancy of hydration

The adequacy of the method used to maintain a steady state of hydration was assessed whilst the subjects were supine by comparing the mean urinary excretion in the first and second hour (11.00–12.00 and 12.00–13.00 hours) during both the follicular and luteal phases. At neither time in the menstrual cycle was there any significant statistical difference between the observed or calculated results obtained in the first as compared with the second hour (Table 2).

Differences between follicular and luteal phases in the supine position

When the subjects were in the supine position, the mean values for the volume and composition of the urine during the follicular and luteal phases of the menstrual cycle were not statistically different (Table 2).

Differences between the supine and upright positions in the follicular and luteal phases

Statistically significant differences were obtained when the subjects were upright in both the follicular and luteal phases.

The urine volume, osmolal clearance, the free-water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to the creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in the upright position (Table 3).

TABLE 1. The urinary composition packed cell volume during the second hour (12.00–13.00 hours) in the supine position and during the upright position in eight normal well-hydrated subjects in the follicular and luteal phases of the menstrual cycle

Case no. and phase of cycle	Position	V (ml/min)	C_{osm} (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (μmol/min)	$U_K.V$ (μmol/min)	$\frac{U_{Na}.V}{C_{Cr}} \times 100$	C_{Cr} (ml/min)	PCV	$E_{Na}\%$	% Δ Na excretion between S and U
1_F	S	13·7	2·7	11·0	291	102	331	88	0·40	2·4	
	U	12·9	2·9	10·0	273	71	300	91	0·42	2·2	−9
1_L	S	12·8	3·6	9·2	270	138	344	79	0·39	2·6	
	U	10·0	2·8	7·2	211	110	192	110	0·41	1·4	−44
2_F	S	17·1	4·7	12·4	344	61	222	155	0·40	1·7	
	U	14·1	3·8	10·3	187	28	220	85	0·42	1·7	−0·9
2_L	S	13·8	2·5	11·3	237	57	155	153	0·39	1·1	
	U	10·3	2·1	8·2	127	33	95	133	0·42	0·7	−39
3_F	S	15·8	3·7	12·1	315	121	246	128	0·43	1·9	
	U	11·5	2·3	9·2	226	72	228	99	0·45	1·7	−7
3_L	S	13·2	2·1	11·1	168	138	200	84	0·41	1·5	
	U	11·3	2·0	9·3	117	58	111	105	0·44	0·85	−44

TABLE 1 (*continued*)

Case no. and phase of cycle	Position	V (ml/min)	$C_{osm.}$ (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (μmol/min)	$U_K.V$ (μmol/min)	$\frac{U_{Na}.V}{C_{Cr}} \times 100$	C_{Cr} (ml/min)	PCV	E_{Na}%	% Δ Na excretion between S and U
4_F	S	14·5	2·9	11·6	210	65	167	126	0·40	1·3	
	U	12·5	2·1	10·4	143	61	98	146	0·43	0·7	−41
4_L	S	12·5	3·0	9·5	220	67	198	111	0·40	1·5	
	U	9·8	2·0	7·8	124	45	108	115	0·42	0·8	−45
5_F	S	14·5	4·6	9·9	293	132	220	133	0·44	1·52	
	U	11·3	3·0	8·3	172	73	132	130	0·47	0·90	−40
5_L	S	12·7	3·7	9·0	152	159	124	123	0·42	0·9	
	U	6·3	1·6	4·7	49	55	52	95	0·46	0·4	−58
6_F	S	15·8	3·7	12·1	206	89	204	101	0·38	1·5	
	U	12·0	2·3	9·7	168	76	153	110	0·40	1·1	−25
6_L	S	15·3	3·4	11·9	273	101	255	107	0·37	1·9	
	U	10·0	2·0	8·0	127	45	157	81	0·41	1·2	−38
7_F	S	10·7	2·7	8·0	192	61	192	100	0·41	1·4	
	U	10·2	2·4	7·8	163	18	160	102	0·43	1·2	−17
7_L	S	11·7	2·5	9·2	148	72	144	103	0·40	1·1	
	U	7·4	1·8	5·6	85	23	109	78	0·43	0·8	−24
8_F	S	12·5	2·4	10·1	149	47	115	130	0·39	0·8	
	U	8·8	1·5	7·3	83	23	70	118	0·41	0·5	−39
8_L	S	13·7	2·4	11·3	187	61	123	152	0·37	0·9	
	U	10·2	1·5	8·7	91	34	71	129	0·40	0·5	−42

Abbreviations used are: F, follicular phase; L, luteal phase; S, supine position; U, upright position; V, urine flow (ml/min); $C_{osm.}$, osmolal clearance; C_{H_2O}, free water clearance; $U_{Na}.V$, urinary sodium excretion; $U_K.V$, urinary potassium excretion; $U_{Na}.V \times 100/C_{Cr}$, sodium excreted expressed per 100 ml of creatinine clearance; C_{Cr}, endogenous creatinine clearance; PCV, packed cell volume; E_{Na}%, percentage of filtered sodium excreted in the urine; % Δ Na excretion between S and U, percentage difference in sodium excretion per 100 ml of C_{Cr} between the supine and upright positions.

TABLE 2. Assessment of the constancy of urinary excretion and a comparison of urinary composition during two 1 h periods (11.00–12.00 and 12.00–13.00 hours) in the follicular and luteal phases of the menstrual cycle in eight well-hydrated normal female subjects in the supine position (mean ±SD)

Menstrual phase	Time (hours)	V (ml/min)	U_{osm}. (mosmol/kg)	C_{osm}. (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (μmol/min)	$U_K.V$ (μmol/min)	$\frac{U_{Na}.V}{C_{Cr}} \times 100$	$U_{Na/K}$	C_{Cr} (ml/min)	E_{Na}%
Follicular	11.00–12.00	14·1±1·9	65±8·0	3·3±0·5	10·9±1·6	243±51	87±25	227±59	3·1±1·3	110±22	1·7 ±0·4
	12.00–13.00	14·3±2·0	67±13·0	3·4±0·9	10·9±1·5	250±69	87±31	212±63	3·1±1·1	120±22	1·6 ±0·5
	Mean	14·2±1·9	66±10·4	3·3±0·7	10·9±1·5	247±60	87±28	219±60	3·1±1·1	115±22	1·65±0·5
Luteal	11.00–12.00	13·7±1·0	63±13	3·0±0·4	10·7±1·1	194±55	112±31	167±55	1·9±0·8	119±20	1·3 ±0·4
	12.00–13.00	13·2±1·1	62±13	2·9±0·6	10·3±1·2	207±50	99±41	192±76	2·4±1·1	114±28	1·4 ±0·6
	Mean	13·5±1·0	63±12	3·0±0·5	10·5±1·2	201±52	106±37	180±65	2·2±1·0	117±24	1·35±0·5

Abbreviations as in Table 1. $U_{Na/K}$, urinary sodium/potassium ratio.

TABLE 3. A comparison of urinary composition over the period (12.00–13.00 hours) when supine and the period (13.00–14.00 hours) when upright

Menstrual phase	Time (hours)	V (ml/min)	U_{osm}. (mosmol/kg)	C_{osm}. (ml/min)	C_{H_2O} (ml/min)	$U_{Na}.V$ (μmol/min)	$U_K.V$ (μmol/min)	$\frac{U_{Na}.V}{C_{Cr}} \times 100$	$U_{Na/K}$	C_{Cr} (ml/min)	$E_{Na}\%$
Follicular	(a) 12.00–13.00	14·3±2·0	67±13·0	3·4±0·9	10·9±1·6	250±69	87±31	212±63	3·1±1·1	120±22	1·6±0·5
	(b) 13.00–14.00	11·7±1·6	61±12·0	2·5±0·7	9·2±1·2	176±56	53±25	170±75	4·1±2·0	110±21	1·3±0·6
	P (a) versus (b)	<0·01	n.s.	<0·01	<0·01	<0·01	<0·01	<0·01	n.s.	n.s.	<0·02
Luteal	(c) 12.00–13.00	13·2±1·1	62±13·0	2·9±0·6	10·3±1·2	207±50	99±41	192±76	2·4±1·1	114±28	1·4±0·6
	(d) 13.00–14.00	9·4±1·6	59±13·0	2·0±0·4	7·4±1·6	116±47	50±27	111±44	2·6±1·0	105±21	0·8±0·3
	P (c) versus (d)	<0·01	n.s.	<0·01	<0·01	<0·01	<0·01	<0·01	n.s.	n.s.	<0·01
	P (b) versus (d)	<0·02	n.s.	<0·05	<0·05	<0·01	n.s.	<0·05	n.s.	n.s.	<0·05

Abbreviations as in Tables 1 and 2. n.s., not significant.

Differences between follicular and luteal phases in the upright position

When the subjects were upright, a number of significant differences were found in the composition of the urine during the luteal as contrasted with the follicular phase of the menstrual cycle. Statistical comparisons for the group, by using Student's '*t*'-test for parametric data and the Willcoxon signed ranks matched-paired test for the percentage difference in sodium excretion, are given in Tables 3 and 4.

TABLE 4. A comparison of the changes found when normal subjects are upright in the follicular and luteal phases of the menstrual cycle (means ±SD)

Menstrual phase	U_{Na}% (S→U)	PCV		ΔPCV	ΔPCV%
		S	U		
Follicular	−22±16	0·406±0·020	0·428±0·022	0·022±0·005	+5·53±1·04
Luteal	−42±10	0·394±0·018	0·423±0·018	0·029±0·008	+7·94±2·24
P	<0·01	n.s.	n.s.	<0·05	<0·02

Abbreviations as in previous Tables. U_{Na}%, percentage difference in sodium excretion between supine and tilted positions.

The volume of urine passed, the osmolal clearance, the free water clearance, the amount of sodium excreted (expressed either in absolute terms or in relationship to creatinine clearance) and the percentage of filtered sodium excreted in the urine were all significantly less in the luteal than in the follicular phase of the cycle.

Differences on changing from the supine to the upright position in the follicular as compared with the luteal phase

In changing the subjects from the supine to the upright position, certain significant differences were noted between the follicular as compared with the luteal phases of the cycle (Table 4). Thus the upright position in the luteal phase induced a greater percentage rise in PCV and a more marked decrease in the percentage of filtered sodium excreted in the urine than it did in the follicular phase.

DISCUSSION

The decrease in urine flow when normal subjects change from the supine to the upright position has been studied by other workers (Brun, Knudsen & Raaschou, 1945a, b; Epstein, Goodyer, Lawrason & Relman, 1951; Goodyer & Seldin, 1953; Pearce & Newman, 1954; Surtshin & White, 1956). To our knowledge, however, no observations have been made before on the changes in urinary volume and composition in the follicular and luteal phases of the menstrual cycle when normal well-hydrated subjects are upright. The decrease in urine volume observed, which is more marked in the luteal than in the follicular phase, may be mediated by one or more of three renal mechanisms, namely a decrease in glomerular filtration rate, an increase in distal tubular reabsorption of water or an increase in the proximal tubular reabsorption of electrolytes and water.

Provided other changes in renal function do not occur, a fall in glomerular filtration rate will cause a decrease in urine volume, a decrease in sodium and potassium excretion and a decrease in osmolar clearance together with a fall in the free water clearance by decreasing the amount of osmotically active solute available for reabsorption at distal sites. The creatinine clearance on changing from the lying to the upright position fell approximately 5% in the follicular phase and 7% in the luteal phase, differences which are not statistically significant. Nor was there a significant difference in creatinine clearance in the supine and upright positions during the follicular as compared with the luteal phase. It is unlikely that such small changes in glomerular-filtration rate, as judged by creatinine clearance, would be associated with such large observed decreases in urinary volume and sodium excretion which in the upright position in the follicular and luteal phases were decreased by 18% and 30% respectively for urinary volume and 22% and 42% respectively for sodium excretion. Other workers have observed either no fall in creatinine clearance (Surtshin & White, 1956) or a small decrease no greater than 10–15% (Epstein *et al.*, 1951) when normal subjects were upright, and have concluded that factors other than a decrease in glomerular filtration rate are responsible for the decrease in water and sodium excretion.

The increased secretion of antidiuretic hormone (ADH), known to occur with adoption of the upright position, would cause a decrease in urinary volume, an increase in urinary osmolality, a decrease in free water clearance whereas the osmolar clearance remains unchanged. The experimental design using forced water diuresis and hypo-osmotic expansion of the extracellular fluid would suppress ADH secretion, thus eliminating this mechanism. The fact that urinary osmolality remained unchanged or fell in twelve tests and rose only slightly in four, whereas in fifteen instances the osmolar clearance fell supports the effectiveness of this procedure.

That the third possible mechanism, increased proximal tubular reabsorption, is responsible for the observed findings is suggested by the decreased sodium and potassium excretion and the decrease in both osmolar and free water clearance found in all subjects. These changes were significantly greater in the luteal than in the follicular phase when upright and indicate an enhanced degree of proximal tubular reabsorption later in the menstrual cycle.

The changes in sodium and potassium excretion occurred too quickly to be ascribed solely to the increase in the secretion of renin and aldosterone known to occur on standing (Gordon, Kuchel, Liddle & Island, 1967). Further, in our subjects the Na/K ratio fell when upright in seven tests and rose in nine, although the potassium excretion invariably fell in the upright posture. The mean fall in potassium excretion was 39% in the follicular phase and 48% in the luteal phase, a difference that was not statistically significant.

The mechanism responsible for the increased reabsorption in the proximal renal tubule remains uncertain as also does the reason for the greater degree of reabsorption in the luteal phase of the menstrual cycle. There is, however, a significantly greater increase in PCV in the upright position in the luteal as compared with the follicular phase, indicating a decrease in blood volume. This may be due to the increased leakage of plasma proteins through the capillary walls found by Jones *et al.* (1966) in the luteal phase. This increase in tissue oncotic pressure would in combination with the increase in capillary hydrostatic pressure on standing favour the increased transudation of water and electrolytes through the capillary walls of the legs. The fall in effective blood volume would stimulate a combination of stretch receptors sensitive to volume changes and baroreceptors sensitive to small changes in arterial pressure and so activate renal mechanisms to conserve sodium and water.

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