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FIVE PATIENTS WITH OEDEMA

AN ENTRY FOR THE WIGHTMAN PRIZE IN

CLINICAL MEDICINE, 1962

by

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"A number of dropsical cases offered themselves
to my attention".

William Withering.
"An Account of the Foxglove" (1785).

INTRODUCTION

This is an account of five patients seen in Wards 21, 23 and 24 of the Royal Infirmary, Edinburgh; all the patients suffered from some form of oedema. The severity of the oedema varied greatly in the different patients, as did the factors responsible for its appearance. This account aims merely to recount the clinical histories, with special emphasis on the oedema, and to discuss the causes as revealed in each patient.

In the interests of brevity and clarity, it has been necessary to omit some of the details of the history and clinical findings in each patient where they were not strictly relevant to the problem of oedema, but any details of special interest have also been included. Although this is intended primarily as a clinical account, the discussion of the pathogenesis of oedema in each patient must, as so often in medicine today, delve into mechanisms at a microscopic and even at a molecular level. At this level, the discussion runs the risk of either being too brief and dogmatic, or else too detailed and inconclusive; and at any level the discussion must inevitably be incomplete. Many of the theories of the pathogenesis of oedema are speculative and controversial, and the more complete the reading

of the literature, the more confusing the picture becomes. The author has attempted, in this account, to discuss some of the more important factors in the production of oedema, but has tried to avoid confusing himself and the reader with too much detail.

Oedema, which may be defined as a localised or generalised increase in the volume of the interstitial fluid, can arise in many diseases, and be the result of the interplay of a number of factors. These factors are not well understood - but the first patient suffered from oedema of a type where the simpler explanations would seem to suffice.

"One great cause of dropsical effusion appears to be obstructed circulation - and whatever either generally or locally prevents the return of the blood through the venous system gives rise to effusions of serum more or less extensive."

Richard Bright, 1827

"Reports of Medical Cases."

Patient I

Miss E.M., aged 53. Admitted 13.12.61 to Ward 24.

This cheerful, but anxious, spinster had worked as a book-keeper until about a year prior to admission. She had always been a fit woman until the last 3 years, except that since the age of 22 she had had some swelling of both ankles in the evenings, and she had always been rather overweight at 12 stones.

Her subsequent medical and surgical history is as follows.

1956 Fractured right ankle: healed satisfactorily.

1958 Felt tired and breathless: seen at Bruntsfield Hospital where she was found to be overweight, anaemic and to have ankle oedema. Iron and "saluric" (chlorothiazide) were

prescribed, and she was soon able to return to work - although her ankle oedema persisted.

September 1960 Mild Diabetes mellitus diagnosed at Leith Hospital - treated by diet alone. An X-ray demonstrated gallstones.

31.12.60 Attack of biliary colic: no jaundice.

16. 1.61 Cholecystectomy in Ward 11, RIE. Post operative urinary infection treated with Chloramphenicol. Right leg "swelled to a huge size", with swelling right up to her groin (Episode 1). She was treated with anticoagulant therapy and an elastic bandage applied, the diagnosis being a deep venous thrombosis.

22. 2.61 Discharged to Astley Ainslie. Anticoagulant therapy was discontinued; although the oedema of her ankle persisted. After a further 2 weeks her left leg suddenly swelled, and deep venous thrombosis was again diagnosed (Episode 2) and anticoagulants

prescribed. She recalls having "housemaid's knee" in her left leg at this stage. Anticoagulants were finally discontinued and she left the Astley Ainslie finally on 3.5.61 - nearly four months after her original operation.

She remained in good health, but with persistent swelling of both ankles, until:-

October 1961 She complained of being unable to put her left foot on the ground without pain in the calf, and noticed a vein standing out prominently on the lower part of her left shin (Episode 3). The swelling of both ankles was still present and her doctor prescribed acetazolamide (Diamox) and bed rest. Once more she recovered and was able to get out, although she was still unable to return to work.

10.12.61 On waking in the morning she suffered severe pain in her left calf when she put weight on her foot. However, she went and did

some shopping, and after spending some time in bed was admitted to Ward 24 (Episode 4).

13.12.61 Admitted to ward.

On admission complained of pain in left calf on movement. She gave no history of any chest pain, cough, or haemopysis; there were no other cardiovascular, alimentary, respiratory, or urogenital symptoms. She also complained of a peculiar "tingling" sensation in her fingers, which had lasted for 3 months. Since January 1961 she had been taking 100 mg thalidomide every night.

On examination - An obese, but helpful lady. Her left leg did not appear swollen on inspection. A number of superficial veins were prominent on the anterior aspect of the limb; they were much more obvious than those on the right leg. There was slight pitting oedema of the left leg: there was none on the right. (The patient had been in bed for 4 days.) The left leg

was warmer to the touch than the right. Gentle palpation of the calf caused some pain.

Physical examination of the rest of her body revealed no significant abnormality - there were no signs in the chest, nor was there any sensory change in the limbs or elsewhere.

On the diagnosis of recurrent deep venous thrombosis, she was treated with anticoagulant drugs as a long-term measure: the leg was elevated and after bed rest she made a rapid recovery and was discharged.

Routine investigations showed:

Hb 85%
PCV 41
MCHC 30
ESR 22mm/1st hour
W.B.C. 9,700 cells/cu.mm

Blood Urea nitrogen = 14 mg%

Chest X-ray: Slight increase in transverse diameter of heart. No other abnormality noted.

Discussion

This history is an unusual one; a middle aged and active person developed a deep venous thrombosis in her right leg after an operation, and in the year following this suffered three similar episodes, all in the left leg. The diagnosis was based on various signs on the different occasions - pain in the calf, oedema of the leg, dilated superficial veins, and increased warmth.

Four points seem to call for discussion.

(a) The signs of deep venous thrombosis.

Homans' sign - pain in the calf on doriflexion - is one of the time-honoured signs of deep venous thrombosis, and indeed this patient performed the test on herself, and found it positive on two occasions, when she felt pain in the calf on putting weight on her foot. In spite of the emphasis placed on this sign, it seems certain that other signs - swelling, warmth, and dilated superficial veins - are more constant and appear earlier. All of these signs indicate deep venous obstruction, which occurs as soon as thrombosis has blocked the vessel. Homans' sign if an indication of inflammation of the vessel wall and the surrounding tissues, and may not appear until later.

Indeed, in many cases, the first sign of deep venous thrombosis is pulmonary embolism - which may develop before there are any signs in the leg. A recent study of patients with pulmonary embolism (1) showed that in 7% pulmonary embolism occurred before signs in the leg were present. This patient is fortunate to have been free of serious embolic episodes.

In her first episode the swelling of her leg extended up to the groin, suggesting that thrombosis occurred in the femoral or iliac veins, giving a "white leg". The subsequent episodes were localised clinically to the left calf, suggesting thrombosis in the vessels of the calf muscles.

(b) <u>The aetiology of the patient's deep venous thrombosis</u>.

The importance of the three factors of Virchow's triad — changes in the blood, change in the vein wall, and stasis - in the aetiology of venous thrombosis, would require a lengthy discussion. Although the blood clotting factors were not specifically investigated, there is no evidence of an abnormality in her routine blood examination, such as polycythaemia rubra vera. Her original thrombosis appears to have been the common postoperative type, in which stasis

and an increased platelet count and clotting time play a part (2) (3). It seems likely that the recurrences in the left leg were related to stasis in the already damaged veins, left without valves after recanalisation.

In recurrent superficial thrombophlebitis there is often an association with visceral carcinoma, particularly of the stomach or pancreas - but throughout this patient's history of thrombosis - which was always deep venous thrombosis - there have been no alimentary symptoms. Nor has there been any evidence of pelvic tumour which might cause pelvic venous obstruction and increase the degree of stasis.

The cause of her recurrent venous thrombosis remains obscure.

(c) Oedema in venous obstruction.

This can be explained satisfactorily on the basis that increased pressure at the venous end of the capillary results in an increased flow of fluid from the tissue spaces. The obstruction of one or more of the main venous channels in the leg forces the blood flow of the limb to return via fewer channels. Thus the pressure in these rises. The increased pressure at the venous end of the capillary counteracts to a greater extent the osmotic pressure of the plasma proteins, and

return of interstitial fluid is diminished.

Collateral venous channels are so plentiful in the limb, and so distensible, that it must require a substantial blockage to produce an increase in venous pressure. In deep venous thrombosis there may well be additional inflammatory element which increases the protein content of the oedema fluid and further reduces the return of interstitial fluid to the vein, by diminishing the osmotic pressure difference.

The patient claimed a history of ankle swelling, especially in the evenings, extending over 30 years. In the absence of any history of deep venous thrombosis, or of varicose veins, there seem to be three possible explanations:

(1) Some venous incompetence, or a defect in the 'muscle pump' resulting in a chronically raised venous pressure. Her obesity and sedentary occupation may have contributed to an inadequate use of the 'muscle pump', producing venous distension and consequent valve incompetence. This seems the most likely explanation.

(2) Some defect of lymphatic drainage.

(3) A constitutional increase in capillary permeability, so that the interstitial fluid was richer in protein than normal.

These last two explanations seem less reasonable.

(d) Paraesthesiae in the hands.

The patient had been taking thalidomide ("Distaval") for 11 months, and had experienced tingling in the fingers for 3 months. In view of the known dangers of thalidomide (4) this may well have been an early manifestation of thalidomide neuropathy - although there were no objective signs of peripheral neuropathy.

Summary

This patient suffered four deep venous thromboses in her limbs, associated with oedema of deep venous obstruction. She also suffered from a longstanding mild ankle oedema, probably associated with a degree of venous incompetence and inactivity. With a view to preventing further attacks and possible serious embolic episodes it seems wise to maintain her anticoagulant therapy indefinitely: the value of anticoagulant in venous thrombosis is more certain than their value in arterial thrombosis (2).

Patient II

Master J.C., aged 16. Admitted to Ward 23 on 25.10.61.

This boy was the fifth in a family of eight, whose father worked on a farm in Fife. At the age of 15 the patient had left school and started work as an apprentice shipfitter at Rosyth dockyard. Until the age of 13 he was fit in every way. His subsequent history was as follows:

March 1959	Appendicectomy.
April 1959	The patient returned to school, but after only two or three days he caught a "cold" - he felt hot and unwell, with a blocked nose, but no sore throat. He went to bed and after two days he noticed that his urine was dark brown, and that he had to pass urine frequently. This was associated with a scalding pain. He was given penicillin tablets and within 10 days he felt well and he had no urinary symptoms. At no time did he notice any swelling of his ankles, face or hands.
21. 8.59	Felt unwell, with a blocked nose.

22. 8.59 The patient complained of a severe sore throat, hindering swallowing, and a tender swollen neck at the angles of his jaw.

23. 8.59 His urine became dark brownish red in colour, and he passed very little. There was no frequency or pain on passing urine. His mother noticed puffiness around his eyes.

24. 8.59 Admitted to R.I.E.

The ward notes for this admission confirmed the presence of oedema around the eyes; there was no oedema elsewhere. The tonsillar glands in the neck were enlarged and tender. His temperature was 99.4° F., and he was sweating profusely. Examination of his throat showed a severe inflammation, with both tonsils red and swollen, and pus exuding from the crypts. Examination of the cardiovascular system showed:- Pulse 80/min., regular in time and force BP 125/75. There was also a soft apical early systolic murmur. No other abnormality was found on physical

examination.

Urine Smoky brown colour; acid reaction

Specific gravity 1.017

Albumin +ve

Sugar -ve

Microscopic

10-15 red blood cells/high power field.

1-2 pus cells/high power field.

1-2 granular casts/high power field.

A few red cell casts.

(all in the unspun specimen).

He was treated with oral penicillin for 3 days, with a low protein diet at first:

In the first four days, a number of investigations were carried out, but these all gave normal results, e.g. Culture of throat swab - no significant pathogens.

Culture of urine specimen - no growth.

Blood urea nitrogen 13 mg%

Creatinine clearance 134ml/min.

Chest X-ray - normal.

Liver function tests - normal.

Plasma protein electophoresis - normal.

Paul Bunnell test negative.

Blood - Hb 89%

White cell count

8,1000 cells/cu mm.

36% neutrophils,

57% lymphocytes,

6% monocytes.

ESR 22 mm./1st hour - raised.

Within ten days of admission, his urine became clear on microscopical examination, and was free of albumin. On the first two days after admission he had passed only 900 and 780 ml. of uring, but by 1.9.59 his urine volume was an average of 1500 ml. daily. He was discharged fit and well after nearly four weeks in hospital.

21.10.61 The patient "felt a cold coming on".

23.10.61 He complained of a sore throat, runny nose, and yellow spit and felt

generally unwell.

24.10.61 Urine became dark red in colour, and he found it painful to pass. He thought he was passing less than usual.

25.10.61 Admitted to Ward 23.

On admission he complained of feeling unwell, with a sore throat and headache. On examination there was no oedema of the face, ankles or hands, and he appeared flushed but not ill. His throat was again inflamed, and the left tonsillar lymph node was swollen and tender. His blood pressure was 122/75. The soft apical systolic murmur noted at the previous admission was present. Otherwise there was no abnormality on physical examination.

Urine Dark red-brown colour.
Specific gravity 1018.
Albumin + (IG/L).
Microscopic examination showed numerous red cells and red cell casts.

In the next few days many investigations were performed.

Blood Hb 70%.

White cell count 5050 cells/ cu mm.

ESR 27.

Thraot swab - pneumococci and haemophilus influenzae, penicillin sensitive.

Blood urea nitrogen 12mg%.

Creatinine clearance 102 ml/min.

192/ml/min.

Proteins - serum Total 7g/100 ml.

Albumin 4.3g/100 ml.

$_1$ glob. 0.3g/100 ml.

$_2$ glob. 0.8g/100 ml.

glob. 0.8g/100 ml.

glob. 0.8g/100 ml.

IVP - normal excretion from large kidneys.

Chest X-ray - enlarged hilar shadows. Otherwise normal.

Blood cultures negative.

Urine culture - moderate growth E. coli, pus cells present.

Early morning urine specimens - negative for tubercle L.E. cells not present.

X-rays of nasal sinuses showed thickening of

1. 11.61 The patient started a six day course of intramuscular penicillin, 1 mega unit twice daily, and was kept in bed on the ward diet. The contamination of his urine with red cells diminished over the following ten days.

10.11.61 Renal biopsy: glomeruli showed some endothelial proliferation, with some fibrosis of Bowman's capsule. The tubules sometimes contained eosinophilic material. Report: "could again be mild acute glomerulonephoitis".

21.11.61 Discharged home on Penicillin V. 250 mg orally every day until called to Ear, Nose and Throat Department for tonsillectomy.

Discussion

Two major points merit discussion in this case.

(1) The diagnosis.

This boy suffered from three attacks of haematuria, associated with a febrile illness, in 3 years: two of these episodes were observed in hospital.

(a) The first attack presented with features not present in later attacks - frequency and dysuria, which resolved in ten days with oral penicillin. This symptomatology suggests urinary infection associated with haematuria - but a renal infection in a boy is so rare that an anatomical abnormality, or some instrumental interference with the urethra and bladder - must be postulated. He may have been catheterised for postoperative retention after appendicectomy (but this was one month previously) or the infection might conceivably have been introduced by some instrument by the patient himself. In the absence of further evidence this is difficult to elucidate, and it may well be that a very concentrated urine could cause such symptoms.

(b) The second and third attacks were almost identical, except that oedema only appeared in the second.

Possible diagnoses are:-

i. Acute glomerulonephritis (Type I nephritis).

In favour of this are:-

1. both attacks preceded by a "cold" with fever.

2. typical haematuria, with albuminuria, pus cells, granular and red cell casts.

3. reduced urine output.

4. in the third attack, renal biopsy was compatible with this diagnosis.

Atypical features were:-

1. the interval between the "cold" and the onset of haematuria was never more than 2-3 days. Classical acute nephritis usually presents 1-3 weeks after an upper respiratory infection, although it is common for there to be no such antecedent episode. It is tempting to suggest that the first episode, following an appendicectomy, may in fact have been the sequel to an upper respiratory infection associated with mesenteric adenitis for which the appendicectomy operation was performed.

2. the other atypical feature of these attacks is the total lack of any cardiovascular changes clinically, such as raised blood pressure, or cardiac failure.

Further diagnoses:-

ii. Henoch Schoenlein purpura (Anaphylactoid purpura)

This may also follow a respiratory tract infection, and may present with nephritic symptoms, and a haemorrhagic macular rash in characteristic sites. This boy did have a papular rash in the second episode, but this was in no way typical of Henoch Schoenlein purpura.

It is probably unwise, at any rate, to attempt to classify neatly many such disorders which are in fact a spectrum of clinical presentations with a similar pathological background.

iii. Renal Infection

Tuberculosis:- early morning specimens were negative and the urine microscopic findings were much more typical of nephritis.

Other infections:- midstream specimens were generally sterile on culture.

iv. Disseminated lupus erythematosis

L.E. cells were absent, and the antinuclear factor was not detected, but this does not in fact exclude a "lupoid" nephritis (see Case III). These tests are at any rate non-specific and may be positive or negative in many of the "collagen" disorders. It seems most likely that this boy has had two, and probably three, attacks of acute glomerulonephritis.

(2) The oedema of acute nephritis.

Several factors may be involved.

i. Oliguria, which leads to retention of fluid without a decrease in fluid intake. The effects of this may be minimised if the patient is febrile and loses water and salt as sweat.

ii. Generalised capillary damage, leading to

increased capillary permeability. Since the oedema of nephritis is characteristically in the face, hands and feet, rather than a dependent oedema, then a local cause for the oedema in each site must be sought. The damage which allows, in the kidney, albumin and even red cells to escape from the capillaries may be more extensive and allow the leakage of protein from capillaries elsewhere in the tissues. This would decrease the osmotic gradient between the plasma and the extracellular fluid, and result in oedema. Normal extracellular fluid has a protein content of 0.1 - 0.2G/100 ml, whereas in acute nephritis this is allegedly raised to 0.4 - 0.7G/100 ml, or rarely even higher (5).

iii. Excessive salt and water retention (6). Where cardiac failure and hypertension occurs, this may alter the renal tubular reabsorption of salt and water. A fuller discussion of the mechanism of this change is included in the discussion of Patient IV. Patient II had neither cardiac failure nor hypertension.

iv. Hypoproteinaemia (6).

This is sometimes present in acute nephritis, and, by reducing the osmotic gradient at the ends of the capillaries, it may contribute to the oedema. The cause of the hypoproteinaemia may be:-

(a) haemodilution due to water and salt retention (7).

(b) loss of protein into extracellular fluid (5).

(c) decreased protein synthesis (6).

(d) heavy proteinuria is rare and unlikely to cause significant hypoproteinaemia.

v. It has also been suggested that the following sequence may occur: (8)

acute loss of fluids into extracellular space
transient haemoconcentration
secretion of ADH and aldosterone (see Patient IV)
salt and water retention
oedema.

It is unlikely, however, that the haemoconcentration persists long enough to result in significant salt and water retention.

The mechanism of oedema in acute nephritis is usually slight and transient, and the explanation is not known. The most likely of a number of factors which may be implicated is a leakage of protein from the capillary due to capillary damage.

It must be remembered that there may be a considerable increase in extracellular fluid volume before it is clinically apparent, and the

slight oedema of acute nephritis may well indicate a greatly increased extracellular fluid volume.

"I have never yet examined the body of a patient dying with dropsy attended by coagulable urine, in whom some obvious derangement was not discovered in the kidneys".

Richard Bright.

Patient III

Miss M.E., aged 36. Admitted to Ward 21, 14.9.61.

This patient was a spinster living with her parents in Fife, and until September 1959 working as a schoolteacher. At this time, however, she had a "nervous breakdown" and was admitted to Stratheden hospital where she spent 18 months, with a clinical label of paranoid schizophrenia. She returned home in February 1961 and remained in good health until May, when she began to feel very tired and lethargic and began to put on weight. Over the months she noticed increased swelling of her legs, which gradually increased until by August it extended up her abdomen and she was admitted to Dunfermline Northern Hospital. While in hospital her arms also began to swell, and she became breathless.

Investigations at this time showed:-

Urine Albumin 10-12G/litre

Blood urea nitrogen 55 mg%

Serum cholesterol 1480 mg%

Total serum protein 3.9G/100ml.

She was transferred to the Royal Infirmary on September 14th, and her complaints were limited to her lethargy, her swollen limbs and abdomen, and breathlessness. She had no urinary symptoms, and no previous history of illness apart from scarlet fever at the age of 12 and her "nervous breakdown" 18 months previously.

On examination she was a short, plain woman, with gross oedema of both legs, over the sacrum and abdomen pitting to about ½ inch in depth, and also of her right arm. The left arm was slightly oedematous, and her face was unaffected.

Cardovascular system: Pulse 104/min., regular
Blood pressure 180/130
Apex beat - 5th interspace, just outside mid-clavicular line.
Heart sounds normal - dual rhythm, no murmurs.
Jugular venous pressure not raised.

Respiratory system: Clinical examination suggested, and X-ray confirmed, the presence of <u>bilateral pleural effusions</u>.

She was breathless on the slightest exertion.

Abdominal examination showed superficial oedema but no other abnormality: there was a suggestion of ascites as shown by dullness in the flanks which shifted a little.

Central Nervous System appeared normal. There was no obvious mental derangement.

Investigations.

Urine output consistently less than 1 litre in 24 hours.

Proteins (on admission)

	Serum	Urine
Total	4.5G/100ml.	0.84G/100ml.
Albumin	1.0G/100ml.	0.43G/100ml.
Globulins α_1	0.3G/100ml.	0.11G/100ml.
α_2	1.8G/100ml.	0.11G/100ml.
β	1.1G/100ml.	0.10G/100ml.
γ	0.3G/100ml.	0.19G/100ml.

Urine Protein (Esbach) 10-24G/24hrs. throughout stay in hospital.

Blood Hb 96%

PCV 41

MCHC 34.5

ESR 75mm/1st hour

Total white count 9,200 cells/cu.mm.

X-rays

1. Chest - bilateral hydrothorax
   cardiac enlargement
2. Intravenous Pyelogram (Dunfermline)
   Poor function on both sides
3. Retrograde Pyelogram
   Normal on right side
   Not visualised on left

ECG normal

Progress and management (see chart)

In the following 6 weeks every effort was made to induce a diuresis, with a view to allowing a safer and simpler renal biopsy in the absence of gross oedema. Once renal biopsy had been performed, more definitive treatment could be started.

Methods used in an attempt to produce a diuresis included:-

1. "SKF 8542" (see later)
2. Chlorothiazide
3. Aminophylline
4. Mersalyl
5. Chlorthalidone

These drugs were used in various combinations without effect, and it was not until the patient

was given intravenously 200 grams of salt-poor albumin, over 2 weeks, that a satisfactory diuresis resulted which persisted with the administration of chlorthalidone.

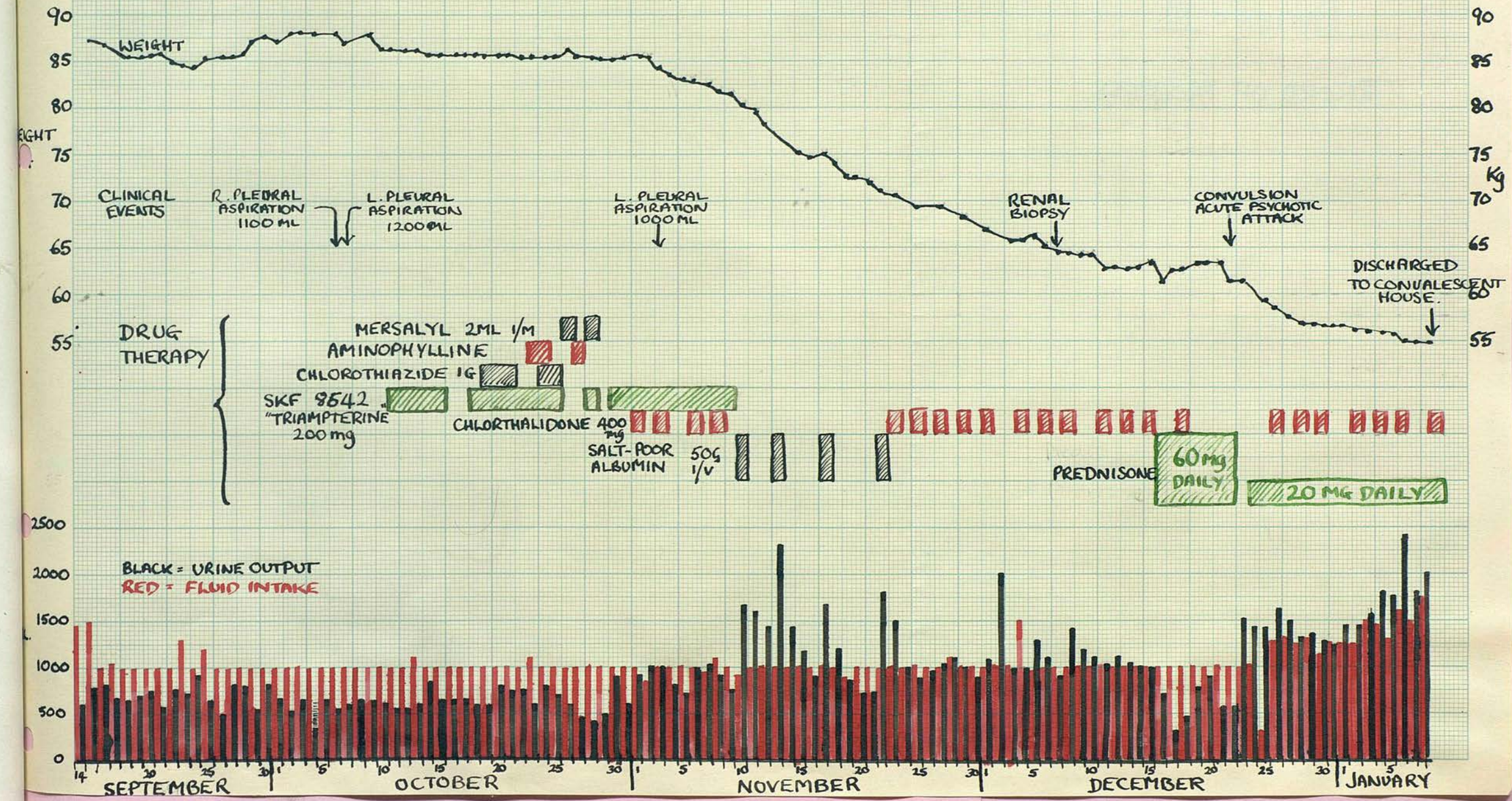
In the meantime efforts to establish the pathological diagnosis had failed: repeated tests showed that no lupus erythematosus cells (L.E. cells) were present, nor was the antinuclear factor detected in the serum.

On 7th December, after 12 weeks in hospital, her oedema was greatly diminished and renal biopsy was performed.

On 15th December, the report on the biopsy stated that "some glomeruli show patchy endothelial proliferation, with granular necrosis of Glomerular capillaries". The conclusion was that the kidney was affected by an acute proliferative glomerulonephritis consistent with disseminated lupus erythematosus, or possibly acute or subacute glomerulonephritis.

Treatment with 60mg. of prednisone daily was begun, and immediately the urine output fell, the blood urea nitrogen, previously never above 60mg%, rose to 93mg%, and the serum potassium levels also rose. After seven days on this dose she had a convulsion followed by acute psychotic symptoms which required heavy sedation. Prednisone was

MISS M.E., AGED 36, NEPHROTIC SYNDROME.



stopped, and started again after one day, at a dose of 20mg. daily. On this dose, in combination with chlorthalidone, she had an excellent diuresis, and she was discharged to Convalescent House oedema free, ambulant, and mentally normal.

Her total weight loss while in hospital amounted to 34Kg = 60 pints - if all this were oedema fluid. Urinary protein loss continued at 12G/24 hrs.

She was discharged on:-

Diet - o.5G salt, 40G protein

Unrestricted fluids

Chlorthalidone 400 mg. three times weekly

Prednisone 5mg. 6 hourly.

Discussion

1. The disease and its aetiology

This patient clearly suffered from the nephrotic syndrome, as evidenced by

proteinuria

hypoproteinaemia

oedema

[hypercholesterolaemia]

In search for the cause of the syndrome in this case, none of the commoner ones - such as diabetes, amyloidosis, toxic metals or drugs, or

renal vein thrombosis, could be implicated. There was no previous history of acute glomerulonephritis. The renal biopsy demonstrated a microscopic kidney consistent with a diagnosis of disseminated lupus erythematosus, although no clinical or serological evidence was found to support this. Such findings are not unusual, however, for in a recent series MacDonald (9) found that of 34 patients with protein losing renal disease, in whom there was no clinical or serological evidence of lupus erythematosis, three showed microscopic changes in the kidney typical of the disease. This has been named "lupoid nephritis".

The modern concept of the "collagen diseases" has departed somewhat from the more rigid classifications into clinical types, and the presence or absence of positive serological tests is not specific for any one of the collagen diseases. Frequently only a few of the characteristic textbook features of the disease are present. In a recent case seen by the author at the Western General Hospital, cirrhosis of the liver was present in associated with thrombocytopaenia and positive antinuclear factor tests, but no other stigmata of disseminated lupus erythematosus. In the absence of any obvious aetiological factor for the cirrhosis, it

was considered to be caused by a "lupoid hepatitis".

2. Oedema in the Nephrotic Syndrome

i. Low serum protein levels imply a low plasma osmotic pressure, which allows fluid to accumulate in the extracellular space and cause oedema. The osmotic pressure of the plasma no longer balances the capillary hydrostatic pressures, and does not encourage the return of extracellular fluid to the capillaries in normal amounts.

ii. Reduction in plasma proteins reduces the total blood volume, and this may increase the total aldosterone output and cause excessive salt and water retention. Normal urinary aldosterone output is 15-20μg/24 hrs., but levels as high as 770μg/24 hrs. have been recorded in the nephrotic syndrome (5).

iii. A grossly oedematous kidney constricted in its capsule may suffer from a reduced renal blood flow and glomerular filtration rate. Oedema may be further aggravated.
The primary cause of the oedema is, however, the low plasma protein level. Changes consequent upon this may aggravate the oedema.

3. The use of diuretics in oedema.

In this patient several diuretics were used, initially without effect. By studying their

modes of action and degree of success, it may indicate the importance of various factors in the oedema of this patient.

(A) "SKF 8542".

This was a new preparation under trial, chemically 2-4,7 triamino 6 phenyl tendine, and has allegedly an aldosterone inhibition action, and it may have some further action as it acts as a diuretic in adrenalectomised dogs (11); although the validity of such a preparation may be doubted. A recent report of the use of "SKF 8542" (11) in 13 patients, one of whom had the nephrotic syndrome associated with disseminated lupus erythematosis, reported on a satisfactory response in most of the patients, including what was described as a 'fair' response in the nephrotic patient, and a 'good' response in five patients with congestive cardiac failure.

The lack of response in Miss E.M. suggests:-

(a) That aldosterone excess is not a major cause of the oedema of "lupoid nephritis".

or (b) That "SKF 8542" does not reduce aldosterone levels in the doses used.

(B) Chlorthalidone.

This drug has been introduced fairly recently, and in many ways seems to be similar in action to those of the thiazide group. Although in vitro

its main action is as a carbonic anhydrase inhibitor, in vivo it inhibits the reabsorption of sodium and chloride in roughly equal proportions from the proximal tubule. Potassium loss occurs; the outstanding feature of the drug is its long duration of action, which is over 24 hrs. (12). This failed to produce a satisfactory diuresis in Miss M.E. when used in combination with "SKF 8542", but once the diuresis had begun, chlorthalidone maintained the diuresis.

(C) Mersalyl.

By blocking enzymes with sulphydryl groups in the proximal tubule, mersalyl inhibits reabsorption of sodium and especially of chloride, which is excreted in large amounts. In spite of normal chloride levels, mersalyl failed to affect the oedema in Miss M.E.

(D) Aminophylline.

This may potentiate mersalyl and the thiazide diuretics, and has also a weak diuretic effect on its own. However, in Miss M.E. there was no response when aminophylline was used either with chlorothiazide or with mersalyl.

(E) Chlorothiazide.

The action of the thiazide diuretics is still not clear, but three actions may be concerned:-

i. carbonic anhydrase inhibition, leading to sodium and bicarbonate ion excretion.

ii. inhibition of sodium and chloride reabsorption.

iii. increased potassium loss.

Chlorothiazide failed to produce any diuresis in Miss M.E.

(F) Salt poor Albumin.

This preparation of human albumin, obtained from the Lister Institute, when reconstituted, contained:-

Total protein	5.4G/100 ml.
Albumin	4.7G/100 ml.
α_2 globulin	0.4G/100 ml.
β globulin	0.3G/100 ml.

In all a total of 200G was given, but even the first 50G produced a massive diuresis. The manner in which this occurred is difficult to understand, for such a small amount of albumin made no significant difference to the plasma protein levels. However, it may be suggested that during the infusion, the osmotic pressure rose sufficiently to cause a minimal reduction of the renal oedema; the kidney being constricted in its capsule. Even a slight fall in the volume of kidney tissue could improve the renal blood flow and permit a diuresis.

In view of the salutory effect of salt-poor albumin, it is likely that the renal oedema with reduced renal blood flow was the major factor in the persistence of the oedema in the face of diuretic drugs. Once the vicious circle had been broken chlorthalidone was successful in maintaining a moderate diuresis.

4. Steroids in the treatment of the nephrotic syndrome.

Steroids are generally considered to cause salt and water retention and might therefore be contraindicated where oedema was present. However, as in this patient, steroids often give a massive diuresis in the nephrotic syndrome. Prednisone causes less salt and water retention than other steroids.

Steroids may act:-

i. By reducing glomerular permeability to protein and thus in time correcting the proteinuria. But in Miss M.E. prednisone did not reduce the albuminuria, which continued at a high level.

ii. By reducing aldosterone output, either as a result of increasing the plasma volume (following decreased protein loss) or by adrenal suppression. Neither of these explanations is satisfactory, and the precise mode of action remains obscure.

In this patient, high doses of prednisone (60 mg. daily) produced severe water retention, and potassium and urea levels rose. After seven days she had a psychotic episode, and there are two possible explanations for this:-

i. High dosage steroids may precipitate mental upsets, especially in those with a psychiatric history.

ii. The water retention may have precipitated an epileptic fit, and on waking from this the patient may have had an acute panic reaction on awaking to find herself surrounded by medical personnel in large numbers.

5. Prognosis.

In this patient the prognosis is very poor, as her albuminuria continues, and there is no evidence that steroids affect the progress of the renal lesion. Although as yet her blood urea level is not grossly raised, her creatinine clearance is so poor that renal failure may arise in the near future.

"A dropsy gains ground upon me; my legs and thighs are very much swollen with water, which I should be content if I could keep here, but I am afraid that it will soon be higher. My nights are sleepless and very tedious - and yet I am extremely afraid of dying".

Dr. Samuel Johnson.

Patient IV

Mr. W.T., aged 45. Admitted to Ward 23 on 10.10.61.

This unmarried man worked as a signalman in a manually operated signal box at Saughton, but because of his illness he had only been able to work for five weeks of the 9 months preceding admission. He had been very well until October, 1960, when he became breathless on exertion, and noted that his ankles became swollen, especially in the evenings. He also complained of pain on the inner aspect of his left arm on exertion and of occasional attacks of palpitations lasting a few minutes.

Over the months his breathlessness increased, and his legs became grossly swollen until on admission, he was slightly breathless at rest, and he complained of gross swelling of the legs, scrotum and penis. He did not recall any sudden

attacks of breathlessness at night, and he was able to sleep comfortably with only two pillows. His doctor had treated him with digoxin and chlorothiazide without effect.

He confessed to smoking 30-40 cigarettes daily, and to an unproductive cough of many year's duration. He also admitted that for over 15 years he was accustomed to drinking about 6 pints of beer and 3 whiskies every evening.

There was no relevant previous medical or family history; the patient lived in 'digs' where meals were provided by his landlady.

Examination on admission showed a short, rather overweight, plethoric man; the most striking feature was a gross pitting oedema of both legs, the scrotum, penis, buttocks, and extending up the anterior abdominal wall. This was associated with some cardio-vascular disorder, for further examination showed:-

Pulse - rate 136/min. regular, poor volume.

BP 145/110

Apex beat displaced to 6th intercostal space, mid-axillary line.

Heart sounds - rapid, faint, no murmurs audible.

Jugular venous pressure - 3" above sterno-manubrial joint when reclining at 45°.

Respiratory system - scattered crepitations at both lung bases.

Alimentary system - decayed teeth
distended abdomen, with fluid thrill and shifting dullness - Ascites.
Liver palpable 3 fingers breadth below costal margin, probably, although ascites made palpation difficult.

Central nervous system - no abnormality detected.

Investigations on admission:-

ECG showed atrial flutter with 2:1 block.

Chest X-ray - gross cardiac enlargement.

Management:- see chart for summary.

On the basis of a diagnosis of severe congestive cardiac failure associated with atrial flutter, treatment was immediately instituted with oral digoxin and intramuscular mersalyl.

On the fifth day of admission there had still been no response in that the oedema was still intense, the pulse rate remained high, and urine output remained consistently around one litre

a day.

Bendrofluazide also failed to produce a diuresis.

A further injection of mersalyl produced a moderate diuresis but with the atrial flutter still present, and the severe degree of heart failure reflected in a blood pressure of 130/110, quinidine was given by mouth for 3 days, in an attempt to reverse the atrial flutter. This also failed.

On the tenth day of admission it was decided that in view of the intense congestion of tissues due to cardiac failure, that intestinal absorption of digoxin might be impaired, and accordingly a regime of intravenous and intramuscular digoxin was instituted as tabulated on the chart. A further injection of mersalyl was also given, and in the next four days the patient (i) passed 15 litres of urine

(ii) showed a greatly reduced pulse rate, and an improved pulse pressure.

Unfortunately ECG recordings showed a persistence of flutter, and although quinidine was tried once more the arrhythmia remained. Digoxin was continued - by oral administration - and the diuresis continued.

From the 13th to the 24th day in hospital,

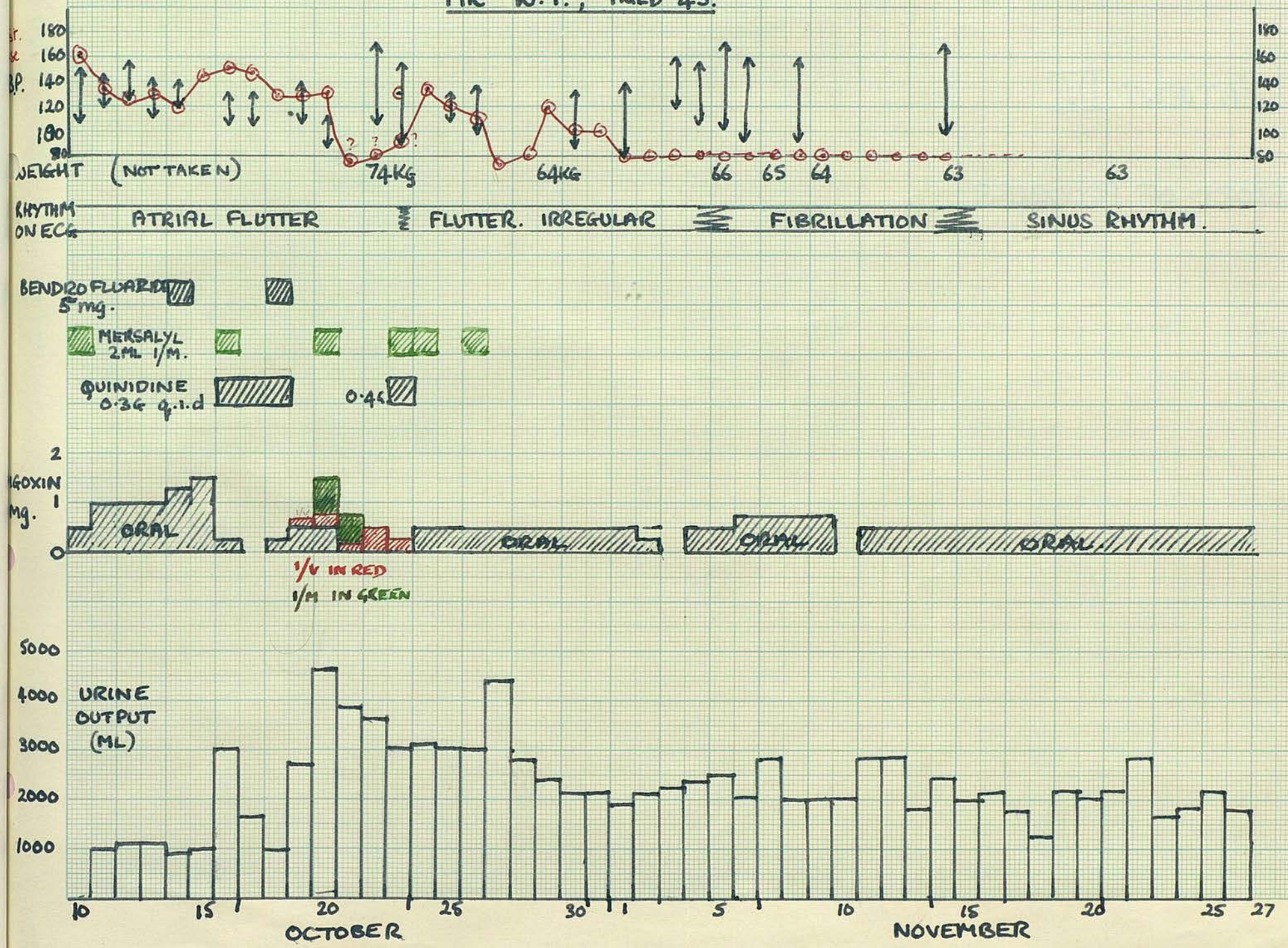
ECG recordings showed that although flutter persisted, the ventricular response had become irregular, and was in fact less frequent - giving an irregular but slower peripheral pulse.

On the 24th day in hospital ECG recordings showed that atrial flutter had been replaced by atrial fibrillation, and ten days later, while still receiving oral digoxin, the patient's heart began spontaneously to beat in sinus rhythm at a rate of 80 beats per minute.

Weight loss: because he was so ill, the patient was not weighed until after the onset of diuresis - on the third day of the diuresis (having lost about 6 litres of excess fluid) he weighed 74 Kg. 20 days later he weighed only 64 Kg. and it may therefore be surmised that his fluid retention was equivalent to some 16 litres = 28 pints.

He was discharged from hospital on oral digoxin - 0.5 mg. daily, in normal sinus rhythm, and without any signs of cardiac failure. X-ray of his chest, however, still showed gross cardiac enlargement.

MR W.T., AGED 45.


180
160
140
120
100
80
WEIGHT (NOT TAKEN) 74Kg 64Kg 66 65 64 63 63
RHYTHM ON ECG
ATRIAL FLUTTER
FLUTTER. IRREGULAR
FIBRILLATION
SINUS RHYTHM.
BENDROFLUAZIDE 5 mg.
MERSALYL 2ML I/M.
QUINIDINE 0·3G q.i.d
0·4G
2
1
0
DIGOXIN mg.
ORAL
ORAL
ORAL
ORAL
I/V IN RED
I/M IN GREEN
5000
4000
3000
2000
1000
URINE OUTPUT (ML)
10 15 20 25 30 1 5 10 15 20 25 27
OCTOBER
NOVEMBER

Discussion

1. The cause of the patient's cardiac failure.

On admission, the principal cardiac findings were

i. atrial flutter

ii. gross cardiac enlargement

iii. diastolic hypertension, with low pulse pressure.

The presence of hypertension for some time prior to admission was suggested by the presence of grade II hypertensive changes in the retinal vessels, and by the fact that even after adequate control of his cardiac failure, his diastolic pressure remained at 100 mm. of mercury. The importance of hypertension in the pathogenesis of his cardiac failure is probably minor, for hypertension would cause a left ventricular failure in the first instance; if Mr. W.T. had had left ventricular failure he would have had far more severe respiratory difficulties, probably with paroxysmal nocturnal dyspnoea, before the onset of congestive cardiac failure with oedema. In fact, he first noticed breathlessness and ankle swelling at much the same time.

The history, and the finding of generalised cardiac enlargement, suggests a general inadequacy

of the heart muscle; and since there is no evidence that the load on the heart was excessive - such as severe hypertension, or valvular disease - it must be concluded that the heart itself became unequal to normal stresses. Clearly the atrial flutter was responsible for much of his disability on admission, but it is unlikely that this had laster over a year - atrial flutter is a dangerous rhythm. There are two possible explanations for his general cardiac failure, with flutter, and in this case both may contribute.

(i) Ischaemia of heart muscle due to atherosclerosis. Atherosclerosis may be gross, even at the age of 45; commonly at this age ischaemia is manifest in sudden acute attacks of myocardial infection for which there was no evidence. In older people ischaemia may be present with the gradual onset of cardiac failure without pain, and arrhythmias may occur and precipitate more severe failure. Although the gradual onset of failure from ischaemic heart disease is rare in younger patients, it is not unknown.

(ii) This patient was an extremely heavy drinker, and cardiac disorders may arise in alcoholics without any other obvious cause. Wood (13) also mentions that atrial flutter is

particularly common in alcoholic cases. How alcohol acts on the myocardium is unknown, as is the role of malnutrition, which so often accompanies alcoholism. There was no evidence, however, of malnutrition in this patient, who had meals cooked for him by his landlady.

In this patient the atrial flutter was only converted into atrial fibrillation after 3½ weeks, and reverted spontaneously, while on digoxin, to sinus rhythm 10 days later. Even at this stage the heart remained grossly enlarged, suggesting some severe myocardial disease, persisting although failure had been effectively treated.

2. <u>The oedema of cardiac failure</u>.

It used to be thought that the oedema of cardiac failure could be expressed on the "backward failure" theory, and that oedema was a direct expression of raised venous pressure. Unlike the oedema of venous obstruction, however, the association between raised venous pressure and degree of anaemia is not a simple one; oedema may be present where the venous pressure is normal, or may be absent even when it is high (13). A number of other factors are involved in the oedema of cardiac failure: one of these excessive sodium and water retention by the kidney seems all-important. As to the mechanism of this sodium

and water retention, the picture is inconclusive and complex. Normally 99% of all the sodium filtered in the glomerulus is later reabsorbed. The majority of this reabsorption takes place actively in the proximal tubule, where the reabsorption may be under the control of aldosterone. Further sodium is reabsorbed in the ascending loop of Henle in accordance with the Countercurrent Hypothesis of Witz, and some is absorbed in exchange for potassium excreted in the distal tubule. Finally a little more sodium is reabsorbed in the collecting ducts (14). In cardiac failure, reduced renal blood flow may lead to a reduced glomerular filtration rate, with slight sodium retention; in health a reduced filtration rate is counteracted by a reduction in sodium reabsorption, but this does not seem to occur in cardiac failure.

It has been suggested that an increased aldosterone level in cardiac failure might increase proximal tubule reabsorption of sodium. In dogs, it seems that a fall in pulse pressure stimulates receptors at the junction of the thyroid and carotid arteries, and via a nervous pathway stimulate the release of a hormone, analagous to corticotrophin, which increases aldosterone secretion (15). The finding that in

normal people prolonged aldosterone administration only gives a very transient sodium retention, and that aldosterone inhibitors are usually ineffective in treating cardiac oedema, suggests that aldosterone is not an important factor in cardiac oedema. The cause of sodium and water retention in cardiac failure remains obscure, although it may be a function of poor renal blood flow.

A very small minority of patients with cardiac failure show a low serum protein level, which may contribute to the oedema. In some of these, there may be actual protein loss from the gut (16), whereas in others there may be malabsorption as a result of congestion of the gut. There is evidence of fat malabsorption, at least, in some patients with congestive cardiac failure (17).

Patient V

Master R.V., aged 15. Admitted to Ward 21 on 1.11.61.

This boy, a scholar of Heriot's School, was of great intelligence, and had very little in common with his unintelligent parents and brothers and sisters. He gave a very detailed history, the main features of which are outlined below.

He was entirely well until 1959, when he began to suffer a variety of digestive symptoms.

July 1959 Struck in abdomen by football. Began to lose his appetite.

August 1959 Began to vomit, about every other day.

October 1959 Pain in left hypochondrium after meals.

December 1959 Barium meal at Leith Hospital showed a small duodenal ulcer.

At this time he complained of

(1) Central epigastric pain, starting 2 hours after meals and lasting for up to 8 hours.

(2) Poor appetite: sometimes couldn't eat until teatime.

(3) Diarrhoea up to 6 or 8 times daily - brownish, no blood or

mucus.

(4) Excessive salivation.

(5) Increasing tiredness.

(6) Loss of weight.

These symptoms continued for over 18 months and by September 1961 his complaints were of:-

(1) Anorexia - ate one meal a day at most.

(2) Sore tip of tongue.

(3) Swelling of ankles, and of thighs when standing.

(4) "Burning skin" over right leg, which dragged on walking.

(5) Dry skin.

(6) Muscles weak, and sore after exertion.

(7) Exhaustion.

He was seen by his doctor, who felt a lump in his abdomen and admitted him to the surgical side of the Royal Infirmary. In the course of investigations he was found to have a serum potassium level of 2.6 mEq/L, and he was transferred to Ward 21 for further investigations.

When examined, he was found to be a bright, but rather precocious boy, extremely thin.

Height 5ft. 2 ins.

Weight 36.5 Kg.

(Correct weight for age and height - 51 Kg.).

He showed muscle wasting, and a generalised ichthyosis of the skin with hyperkeratosis of the extensor surfaces of the limbs.

Both ankles showed moderate pitting oedema.

Hair and genitalia were normal for his age.

Alimentary system.

Tongue moist, rather smooth and with inflamed edges.

Abdomen: prominence on Right side, but moved freely. Slightly tender, freely mobile, spherical, firm mass palpable in the right iliac fossa, some 5 cm. in diameter.

Cardiovascular system: normal, apart from slow pulse.

Pulse 48/min., regular, good volume.

Blood pressure 120/75.

Respiratory System, Central Nervous System, normal.

Investigations on admission 1.11.61.

Serum Electrolytes: Sodium 144 mEq/L

Potassium 2.6 mEq/L

CO_2 combining power 30.8 mEq/L

Blood urea nitrogen 6 mg%.

Serum Proteins: Total 6.5 /100ml., Albumin 3.6 /100ml.

ECG: Changes of gross hypokalarmia.

Blood: Hb 87%

ESR 29 mm./1st hr.

White cells 4,700/cu.mm.

Serum B_{12} 308μμg/ml. (normal 100-700μμg/ml.)

Normal (Folic acid excretion tests
(D-xylose absorption test
(B_{12} absorption test

X-rays: Plain film abdomen.

Showed circular calcified mass in Right iliac fossa.

Barium enema.

Showed smooth filling defect in transverse colon corresponding to the calcified area.

Intravenous pyelogram - normal.

Management.

Some difficulty was found in arranging a diet to suit his taste, but his nutritional state was improved with the help of

Vitamin A+D capsules.

Vitamin C 200 mg. daily.

Aneurine tablets.

Folic acid 10 mg. daily.

Cytamen (Cyanocobalamin) 1000μg.

Casilan and complan supplements. His potassium levels were restored to normal levels with oral Potassium chloride, and there was impressive clinical improvement.

Investigations showed that there was no malabsorption, and urine potassium levels were so low that a potassium losing renal condition was unlikely. The clue to the potassium loss was the discovery in his locker of a supply of Sennokot, a vegetable laxative, and on questioning he confessed to the use of purgatives on frequent occasions.

The problem of the abdominal mass remained, and possibilities considered included:

1. a tumour, possibly a potassium secreting tumour.
2. an actinomycotic lesion - he kept budgerigars.
3. a calcified mesenteric cyst or dermoid.
4. a tuberculous lesion.

He was mantoux +ve.

Finally he returned to the surgical side for laparotomy where on macroscopic appearance the mass was considered to be a malignant tumour and a right hemicolectomy with removal of the mass was performed. This was unfortunate, as it proved on

section to be tuberculous in origin, and he was later transferred to the City Hospital for Chemotherapy.

Discussion.

This boy had outstripped his family in intellectual achievement, and had an intelligence which was probably not matched by an equal degree of emotional maturity. It seems probable that this was manifested by the appearance in 1959 of a duodenal ulcer, and over the next two years by an almost total anorexia. To what extent these symptoms could be related to his unusual tuberculous intestinal lesion is uncertain. The anorexia was of such a degree, and no adequate cause of an organic nature was found, that it can be described as an anorexia nervosa - occurring, as it did, in a boy with evidence of emotional abnormality. The eventual discovery of his addiction to purgatives also indicated some neurotic features.

His astonishingly low potassium levels on admission are probably a reflection of his persistent purgation. Schwatz and Relman (18) described two patients - both women - in whom the serum potassium fell to levels of 2.1mEq/L respectively - both confessed to taking massive

doses of laxatives, and their serum potassium levels were restored when laxatives were withheld. In one of these patients the potassium loss in the stools, while taking purgatives, amounted to 50mEq per day.

The oedema - possible factors.

1. His anorexia produced a severe degree of subnutrition and this may have produced a 'famine oedema'. Sometimes this is associated with low protein levels, but in his case the plasma proteins were within normal limits. The oedema of subnutrition may be related to a wasting of tissues without corresponding loss of body water. Deficiency of vitamins, especially of those gathered together in the 'B' group, may also be a factor in the oedema of subnutrition: in the isolated clinical syndromes of Dellagra (nicotinic acid deficiency) and beri-beri (thiamine deficiency) oedema is a common finding. In this patient, the hyperkeratosis, sore tongue, and 'burning skin' of the right leg suggest multiple vitamin deficiencies. All these symptoms regressed with vitamin therapy.
2. Low potassium levels may prejudice renal function, and aggravate oedema (19).

This boy presents a case of oedema with an unusual cause - anorexia nervosa - rare in a boy,

to the extent of producing famine oedema. It is surprising that the presenting complaint was of an apparently quite unrelated tuberculous intestinal lesion, and that only a low serum potassium level drew attention to a state of starvation unusual in Britain.

Conclusion.

The five patients described all had oedema, but in each case the factors involved were different. Among the factors discussed were:

(1) raised venous pressure

(2) increased capillary permeability

(3) excessive salt and water retention as a result of (i) reduced renal blood flow in cardiac and renal disease

(ii) increased aldosterone secretion

(4) low serum protein levels

(5) low serum potassium levels

(6) vitamin deficiencies: famine oedema

Oedema may occur in a variety of other clinical disorders not described in this account - such as hepatic cirrhosis, pre-eclamptic toxaemia of pregnancy, allergic disorders (such as angioneurotic oedema), and in inflammatory lesions, and in lymphatic obstruction. In many of these disorders one or more of the factors above may be implicated, and there may be other factors involved which are as yet unknown.

Oedema is a sign of intense clinical interest, for it may reveal many different disease processes, although the mechanism for the appearance of

oedema is ofter little understood. The whole field, and especially the relationship of oedema to renal function, is a fascinating one, and further research into oedema, a symptom reflecting the abnormal, will help to bring a better understanding of the normal homeostatic mechanisms of the body.

"These great and tangible causes of hydropic swellings betray themselves obviously after death, and are often easily detected during life - yet they include such a great variety of diseases that they still present a very wide field for the observation of the Pathologist".

Richard Bright, 1827
"Reports of Medical Cases".

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