In presenting notes on the following six cases, which have been of special interest, I wish to thank Dr A. Rae Gilchrist both for his permission to write up the notes, and for his advice regarding the tests in the last two cases.

All the patients were seen in Dr Gilchrist’s ward in the Royal Infirmary, Edinburgh during my membership of the class of Clinical Medicine.

5.6.44.
Cases 1 and 2

Jaundice
Two Cases of Jaundice.

Introduction:

Each of the two following cases will serve to illustrate one of the abnormalities of bile-pigment circulation about to be described.

The history, examination, investigation, and progress of each case will be described; later, in the commentary, the pathogenesis of the different types of jaundice will be considered, with special reference to their clinical manifestations in the two patients under review.

Note on the normal circulation of the bile-pigments:

In this discussion, the terms "haemobilinogen" and "cholebilinogen" will be used to indicate respectively bilimbin, which has not, and that which has, passed through the liver cells; i.e., haemobilinogen is immature bile-pigment not associated with bile salts, whereas cholebilinogen is mature, and is associated with bile salts.

Fig. 1 illustrates the sequence of events in the normal individual. The red blood cells are broken down by the reticulo-endothelial system (especially that in the spleen) and haemobilinogen is formed. This is carried to the liver in the portal venous system, passes through the liver cells, becomes matured—associated with bile salts, enters the bile canaliculi, is conveyed into the main bile duct system, and hence to the intestine as cholebilinogen. During its passage along the intestine it is changed into stercobilinogen and stercobilin, which gives the faeces their normal dark colour.
Not all passes out with the faces, however; some is re-absorbed into the portal blood-stream as the colourless compound urobilinogen which is passed again through the liver cells, travels out by the bile canaliculi and bile-ducts and re-enters the intestine. This completes the "circulation of the bile".

Some of the urobilinogen normally passes the liver and is excreted by the kidney. It is changed to urobilin, a coloured compound, which gives the urine its normal brown colour.

 Normally there is no excess of either haem- or cholebilin in the blood, but under certain circumstances this may occur, producing the condition known as jaundice, manifested clinically by a yellow coloration of skin and sclera, and expressed quantitatively by the icteric index of the serum.

Qualitatively, the Van den Bergh reaction indicates whether the jaundice is due to excess haemobilin or excess cholebilin, or both.

Abnormalities in bile - pigment circulation:

In the Bulletin of Johns Hopkins Hospital, December 1930, Rich classifies jaundice into two main types according to its pathogenesis:

1. Retention jaundice [corresponding to some forms of "haemolytic" and "toxic" jaundice], resulting from an over-production of haemobilin, and often associated with conditions [e.g. anaemia, fever, immaturity] which tend to render the secretory power of the liver sub-normal. Enough haemobilin is thus retained in the blood to stain the tissues yellow.

Fig. 2 illustrates the sequence of events in this condition (see page 4)
This form of jaundice is characterized clinically by:

a) an indirect Van den Bergh reaction by the plasma bilirubin.
b) an increased amount of fecal urobilin.
c) excess urobilinogen in the urine.

These results are readily understood from Fig. 2. on p. 4.

Recurrent jaundice [comprising to some forms of "obstructive" jaundice], caused by reflux of cholebiurubin from the bile canaliculi into the bloodstream. This is due to blockage of the bile-duct system at some point, and its mechanism and consequences are illustrated in Fig. 3. on page 4.

Clinical results of this type of jaundice are:

a) a direct Van den Bergh reaction.
b) subnormal amounts of fecal urobilin, with a consequent pale stool.
c) cholebiurubin in the urine.

Having thus clarified the problem of jaundice and provided ourselves with methods of attack, we shall now consider the two cases under review.

**Case 1**

Mrs. M. L.,

Age: 74. Housewife.

Admitted to the ward on 30.1.42.

Complaints:

\[
\begin{align*}
& \text{Discomfort in the epigastrium after food} \\
& \text{Loss of weight} \\
& \text{Pain in epigastrium after food} \\
& \text{Jaundice}
\end{align*}
\]

6 years

2 years

3 months

2 years

History of present illness:

About 8 years ago the patient began to feel "dull" after a spell of 3 months extra work.

About 6 years ago her appetite became poor and she
**Fig. 1.** Normal

- Liver
- Haemoglobin
- Small intestine
- Large intestine
- Urobilinogen (Urobilinogen) in faeces
- Urobilinogen in urine
- Spleen (breakdown of cells)

**Fig. 2.** Retention Jaundice

- Liver
- Haemoglobin
- Spleen
- Urobilinogen
- Faecal urobilinogen: Dark stool
- Urobilinogen: Dark yellow urine

**Fig. 3.** Regurgitation Jaundice

- Liver
- Haemoglobin
- Block
- No urobilinogen in gut: Pale clay stool
- Cholesterol in urine: Dark brown-green urine
noted a slight discomfort across the epigastrium region after food. During the last 5 or 6 months this feeling has been replaced by a definite pain.

This pain comes on half an hour after taking food. It is acheing in character and associated with a weak feeling. It gradually disappears and has gone in an hour or two.

There has been no variation of the pain; no pain is felt in any other situation. There is no nausea or vomiting associated with it. She has occasional flatulence.

The bowels have always been regular without aid.

There has been no diarrhea or pain.

The motions have been pale lately.

The patient has been losing weight steadily for 2 years; this has occurred more rapidly during the last 6 months during which time she has lost about 4 stone.

About 6 or 7 weeks ago she was told her skin had a yellow tinge. Since then the yellowing has steadily deepened, with no intermission.

The skin over the lower abdomen has been itchy during the last 3 weeks.

The urine has been very dark in colour for 3-4 weeks and there has been some frequency of urination and dysuria for 4-5 weeks.

**Previous Health:** no illnesses of any significance.

**Social conditions:** For 11 years the patient has lived alone.

Her diet has consisted of 1 pint milk per day otherwise chiefly bread and tea.

**Family History:** Nothing significant.

**Examination**

**A. General.**

The patient is lying flat, quite comfortable and in no pain. She is exhausted but anxious to co-operate. Her voice is a mere whisper.

She is poorly developed, shows much muscle wasting and an extreme loss of subcutaneous fat. Her skin is deep yellow, wrinkled, dry and inelastic.

Lips and conjunctiva moderately pale.

Temperature 98.0°. Pulse 88/min. Respiration 24/min.
B. Systematic examination

Alimentary System.

Mouth: mucous membrane: pale but healthy; tongue: moist, with yellowish fur; under-surface is stained with yellow; teeth: all artificial - used for eating; faeces: clean, healthy

Abdomen:

a) Inspection: the abdomen is more full than was expected, considering the general loss in weight. Contour normal; no dilated veins; movement little or no respiration.

b) Palpation: Skin is loose, dry, non-elastic. There is slightly increased resistance in the right hypochondrium, and a mass was felt as indicated in diagram; this mass felt slightly nodular in contour.

On deep palpation, tenderness was elicited over the mass which was difficult to feel owing to strong contraction of the R Rectus muscle.

No masses.

Nothing else abnormal found.

c) Persussion: Confirms position of lower edge of liver. Upper edge is in 4". intercostal space - normal. Liver margin is 2-3 fingers below costal margin. Dullness found on percussion over the mass.

Special Examinations:

a) Barium meal: Negative.

b) Stool:

(i) Bacteriuric negative, repeatedly.

(ii) Biochemical exam:

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urobilin</td>
<td>negative</td>
</tr>
<tr>
<td>Total fats</td>
<td>37.7%</td>
</tr>
<tr>
<td>Split fats</td>
<td>84.0%</td>
</tr>
<tr>
<td>Unsplit</td>
<td>16.0%</td>
</tr>
</tbody>
</table>

[Total fat content is normally 10-12%]
c) Estimation of Blood Coagulation Time as a test of liver function:

This was carried out by means of capillary tubes on 12/2/42. Estimations were made on:

a) patient's blood
b) normal person's blood

Using blood from a finger-prick, under similar conditions.

Results:

Patient's coagulation time was 14.5 min +

Normal 4.5

This, along with the jaundice, indicates a disturbance of liver function. The test was repeated later, on several occasions.

Cardio-Vascular System:

Arteries: Pulse: Rate 88/min. Volume good;

frequent extrasystoles; vessels well palpable and positions.

B.P. 154/80

Veins: N.A.D.

Capillaries: 

Heart: Apex beat in 4th space in mid-clavicular line;
dominant a-systole; No thrill.

Sounds: 1 good quality; Apical diastolic murmur;

E.C.G.: "Normal sino-atrial rhythm with left axis shift."

Respiratory System: N.A.D.

Urinary System: No tenderness in renal angle, or near

Kidneys or bladder.

Urine: Dark green-brown; SG. 1014; Alkaline;

Trace 1 albumin; no sugar;

Bile ++ [tested with weak hydrogen peroxide]

Urobilinogen negative:

Nitr. +:

Renal Function Test: Blood Urea Nitrogen 11 mgm.

Nervous System: N.A.D.
Haemopoietic System:

No palpable spleen. No purpura or ecchymors.

Blood:

- R.B.C. 4,2 million /cm. mm.
- Hb 70 %
- W.B.C. 5,800
- C. Index 0.8
- W.R. negative

- Gesmin Index 167
- Van den Bergh biphasic

Coagulation time 14.5 min (3 x normal)

Diagnosis:

Referring back to the notes on types of jaundice, it will be seen at once that this is a jaundice of the regurgitation type, evidence for this being the bile-bilirubinaemia, the absence of faecal bilirubina.

In an elderly patient, whose jaundice has been steadily progressive, one differentiates jaundice of the cause of the duct blockage starts to a type of neoplasia, related or unrelated to the biliary system.

To clarify the issue, let us consider causes of biliary blockage in general.

Rich holds that regurgitation jaundice is essentially due to rupture of the bile canaliculi in the liver; ultimately this is caused by any of the following -

1. Necrosis of liver cells, due to toxic agents such as chemical, vegetable or bacterial poisons, or to severe anaemia or fatembolic disease.

There is nothing in this patient's history to suggest this as a causal factor in her jaundice.

2. Obstruction of bile ducts by:
   a) plugs with calculi, inflammatory exudate, parasites or neoplasms;
   b) stentiation from scarring or neoplasms;
   c) pressure, from inflammatory masses in the liver or pancreas, pancreatic masses, vascular tumours, neoplasms or enlarged hepatic lymph nodes.
We can exclude, on the basis of the history, previous inflammatory lesions, parasites, and calculi. The possibility of an aneurysm cannot be excluded but is much less likely to be the root of the trouble than is a neoplasm.

The patient's age, appearance and rapid loss of weight are all suggestive of neoplasm.

As to the location of the neoplasm: in this case it was not thought to be in the liver, because:

a) a neoplasm in the liver is usually secondary to one in the alimentary tract, and if this there is no sign of primary neoplasm, liver is very rare.

b) Neoplasm of the gall bladder is usually associated with a previous history of gallstones + of vomiting pain and flatulence; but it cannot be excluded.

c) Neoplasm of the head of the pancreas and chronic pancreatitis are both associated with deep progressive jaundice and are very difficult to distinguish from one another.

The former is often associated with chronic epigastric pain, especially after meals; a large hard liver, and rapid wasting or loss of weight. The latter does not show these phenomena.

In this case the evidence of the presence of fat-splitting enzymes in the gut was taken as sufficient to exclude chronic pancreatitis; in any case it is a much rarer condition than the neoplasm.

The final diagnosis therefore was made of carcinoma of the head of the pancreas.

**Prognosis.**

If the above diagnosis is correct, this is hopeless. The patient will live a month or two at the most.

**Treatment and Progress**

The patient remained extremely weak and exhausted.

10.2.42

The lesion indexed is now 222.

Cystitis has developed and is refractory; the organisms are B. Proteus and non-hemolytic staphylococci.
Patient was transferred to a surgical ward for laparotomy, and palliative drainage of gall-bladder. The pain was not gone, also the skin itch.

Surgical notes:

Pre-operative: Kapilon 5 mgm was given intramuscularly daily for 3 days before operation, and on the day of operation, to control the hemorrhagic tendency.

19.2.42

Operation: Cholecystectomy was carried out. The gall-bladder was not dilated. Contained no stones, but thick, tenacious bile. The head of the pancreas and the lymph glands in the neighbourhood were very hard, but no metastases were seen in the piece of liver exposed. The fundus of the gall bladder was drained.

20.2.42

Another 5 mgm Kapilon given. Patient went onto local glucose-saline.

22.2.42

Still very extended. Bile draining at rate of 15 cc per 24 hours.

23.2.42

Daily coagulation tests were done - see p. 11

23.2.42

Patient almost comatose.

3.3.42

Patient died at 2.30 am.

On 2.3.42 several investigations were made by Dr. Seabrook, the results of which are given below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howell Recalcification Time</td>
<td>4 min</td>
<td>1.5 min</td>
</tr>
<tr>
<td>Leucin Difference</td>
<td>8</td>
<td>40 % reduction</td>
</tr>
<tr>
<td>Total plasma proteins</td>
<td>5.35 gm%</td>
<td>7.0 gm%</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>0.55 mg%</td>
<td>0.33 mg%</td>
</tr>
<tr>
<td>&quot; albumin</td>
<td>2.35 gm%</td>
<td>4.0 gm%</td>
</tr>
<tr>
<td>&quot; globulin</td>
<td>3.0 %</td>
<td>2.8 %</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>266 mgm%</td>
<td>150 - 200 mgm%</td>
</tr>
<tr>
<td>Glucose index</td>
<td>150</td>
<td></td>
</tr>
</tbody>
</table>
A short series of Dry bleeding times was also done. These are recorded on the graph below, along with the writer’s coagulation time results and the icteric indices.
Pathology and Etiology:

We have already dealt with the pathology of the circumscription of the bile pigment which has occurred in this case, and have considered the immediate etiology of the block in the duct system.

Penetrating more deeply, the etiology of malignant disease is unknown, but there are certain factors which predispose to it, which may be divided into two groups, internal and external.

A. Internal factors:

1. Heredity: not illustrated here, but a definite factor in some cases.

2. Age: cancer is a disease of middle and old age, and this case is evidence for this. The reason may be that the carcinogenic etiologic factor must act for 10-15 years before it can produce a tumor.

3. Intracellular enzymes: it is believed that cancer cells liberate enzymatic substances which can incite continued growth and which act on normal cells causing them to become malignant. In this sense, therefore, the cause of cancer is the tumor cell itself.

B. Extrinsic Factors:

1. Irritation: cancer in some areas is thought to follow prolonged irritation (e.g., carcinoma of tongue after a chronic tooth etc.) but in this case there is no evidence of this; there is no such predisposing factor known in carcinoma of the pancreas.

2. Hormonal stimulation: stimulation of cell growth by the sex hormone of the ovary is well known but is not likely to be a causative factor in a patient of 74.
At operation there was no removal going part of the mass in the head of the pancreas and thus the type and structure of the growth is unknown.

As a rule this neoplasm is primary, and may be an adenocarcinoma or a seimious growth; there are usually secondary deposits in the regional lymph nodes and liver. None were demonstrated here.

Clinical features correlated with the underlying pathology:

A. Alimentary System

1. The enlarged firm liver is due (at least in part) to the fact that it is congested with bile. There was nothing found at operation to explain the nodular feel of the liver edge, but only a tiny part of the organ was exposed, and there may have been secondary deposits where they could not be seen.

2. The mass in the epigastrium is the tumor in the head of the pancreas.

3. The rapid loss of weight is due partly to a poor intake of food, partly to deficient absorption of fats since there is no bile in the intestine, and partly to the fact that malignant tissue competes very successfully with normal tissue for any nourishment that is available.

B. Cardio-Vascular System

1. The apical diastolic murmur is probably caused by an aortic-reumatic process affecting the aortic valve.

2. The basal systolic murmur may be haemolitic, or due to atheroma of the aorta. The thinning of the intimal layer suggests the latter.

3. The frequent extrasystoles may be due to the toxic action on the heart of the bile salts in the blood; but are more likely in this case to be caused by degenerative changes in the myocardium.
One expects bradycardia in a case of deep jaundice, due to the presence of bile salts in the blood; here however, the pulse is relatively rapid. This fact in association with the history of dyspnoea suggests a failing myocardium.

C. Urinary System

1. The presence of cholebiurin in the urine has already been explained (see introduction).

2. The pyuria and symptoms of frequent painful micturition are due to cystitis.

In my case infection the prevalent organism is usually B. Coli as in this case, and the condition predisposing to the transport of B. Coli from colon to urinary tract via the blood are:

a) basis of urine
b) a lesion or abnormality in the colon e.g. constipation, ulceration, carcinoma.

In this case no predisposing factor could be found, therefore the condition was treated with alkalies and sulphonamides, without much success.

The patient had been catheterised before admission to hospital and this may have been the start of her infection.

D. Haemopoetic System

1. The low haemoglobin and low white cell count may be due to the presence of a neoplasm, or merely to the patient's poor dietary history and exhausted condition.

2. The jaundice has been explained already.

3. The biphasic Van den Bergh is due to the fact that there is both haemo- and choledobilin in the blood; haemobilin goes on being produced but the damaged congested liver cannot
Take in the normal amount, therefore it gets diverted into the bloodstream along with the regurgitated cholecystic bile.

(4) The rise in blood cholesterol occurs because of regurgitation into the blood (along with the cholesterol) of cholesterol normally excreted into the intestine.

(5) The prolonged coagulation time of the blood gives rise to some interesting speculation.

In order that sheet blood may clot, there must be present four substances—calcium, prothrombin, thromboplastin, and fibrinogen.

The reaction is as follows:

a) Calcium + prothrombin + thromboplastin $\rightarrow$ thrombin
b) Thrombin + fibrinogen $\rightarrow$ fibrin.

If there is a prolongation of the coagulation time, there is presumably an abnormality or deficiency of one or more of the above factors.

Prothrombin is stored in the liver; its precursor is vitamin K (or at least K is necessary for its formation).

Vit. K is a fat-soluble vitamin and is not absorbed in case of obstructive jaundice because of the absence of bile salts in the intestine.

In this case, therefore, we expect the plasma prothrombin to be low, and in all such cases this is blamed for the haemorrhagic tendency noted in such jaundices; therefore Vit. K in the form of Kaphirin is usually administered routinely before operation, as was done here.

In this case, however, the plasma prothrombin was not reduced. One wonders whether the apparent effect of the Kaphirin on the coagulation times, as seen on the chart on p. 11 is fictitious; or
whether it was low at that time, and later rose to a normal figure after bile drainage.

Trichinigen is one of the plasma proteins; it is manufactured and stored in the liver, thus in cases of liver disease it is reduced. In this case it was above normal.

It is said to be raised in acute liver disease and "almost" severe chronic.

Possibly the present case was not sufficiently prolonged to show this latter effect.

Thromboplastin is contained not only in the platelets, as used to be thought, but in all the body cells; therefore the blood can clot in the absence of platelets. It is therefore difficult to imagine a circumstance where there would be a deficiency of thromboplastin.

Calcium, the last factor to be considered, was, unfortunately not more estimated in the patient's serum, but clinically there was no evidence to suggest hypocalcaemia.

Calcium is present in the serum in 2 fractions:

a) about 40-60% is an ionizable salt, and diffusible
b) the remainder is connected with protein molecules, and is not diffusible.

Boyd states that the serum calcium is reduced in jaundice because it is bound by the bile pigment; Bodansky states that it is the non-diffusible part of the calcium that is reduced, since in jaundice the serum proteins are reduced and the non-diffusible calcium is associated with them.

In this case the plasma proteins are reduced so this factor may be operating in the calcium.

But there is a large body of opinion which holds that the serum calcium is never the deficient
member in a prolonged clotting time, so we must look elsewhere for the cause, since in this case all the usual factors in the reaction appear to be blameless.

There is a substance in normal blood to prevent its clotting in the vessels — this is Heparin. It is possible that in an unexplained long coagulation time there may be excess heparin present. It may be that some other substance acts as an antigen, and that heparin is the antibody produced, but this is all still extremely problematic.

It is worth noting that, in relation to the prothrombin factor, the method of estimating plasma prothrombin is said to be based on an "act of faith" and may not in fact be accurate. The assumption is made that if known quantities are present in vivo of all the substances necessary for clotting, except prothrombin which is unknown, then the rate of clotting will be proportional to the concentration of prothrombin; this is not yet justified.

The bleeding time (see chart p. 11) was also prolonged.

The bleeding time varies inversely with the platelet count, which is supposed to be reduced in jaundice of this type. Unfortunately no platelet counts were done.

The capillaries may also be at fault in a prolonged bleeding time. In this case a series of capillary resistance was done, and the results were low; so this may be a factor in the present case.

Plasma Proteins: the total plasma protein was reduced by 25%.

This may be due partly to a prolonged
low protein intake; partly to the inability of a damaged liver to manufacture the plasma proteins.

When the proteins diminish, the albumin is the first to be lowered; then the normal albumin:globulin ratio is inverted.

**Diagnosis & Prognosis/Treatment**

The prognosis in any case of malignant disease is very doubtful; in one like the present it is hopeless.

In several cases jaundice associated with malignant disease observed in the wards and heard of during the last year or so the whole course of the illness, from the beginning of symptoms until death, has been a matter of 4–6 months.

Had this patient not been operated on, she might have lived a similar length of time. The outlook, however, would have been worse, since the steadily deepening jaundice would have resulted in cholestasis with possibly coma and convulsions.

Also, the intercurrent urinary infection, present as it was, to chemotherapy would have made life a misery.

When operation was undertaken, it was not with any hope of curing the condition by removal of the primary tumour but in such cases relief can be given by a cholecysto-duodenostomy, done usually in 2 stages: 1) drainage and decompression of the liver (the past due in this case)

2) the maximin of gallbladder function to duodenum.

If the whole operation could have been completed, it would merely have relieved the jaundice and its accompanying discomforts; the patient would have died of the carcinoma just the same, and perhaps in a shorter time.

As it happened in this case, the time was shortened even more. When one considers the patient's age, condition of weakness, and the fact that she lived alone, with no living relatives, the more rapid termination of the illness was, on the whole, desirable.
Further discussion on this case will follow in the Commentary, after the second case has been described.

CASE II

Mr E. R.  age 60.  Housewife.

Admitted to the ward on 15.4.44.

Complaints:

Weakness  Fissured
   Pallor
   Breathlessness
   Swelling of ankles
   Tingling in hands  feet
   Increased pallor
   Tendency to jaundice
   Vomiting
   Staggering gait

1 year
2 months
4 weeks

History of Present Illness:

The patient was perfectly well until 2 years ago when she has felt herself getting tired and weak, and depressed.

About 1 year ago the tiredness became very noticeable and the patient noted that her complexion had become more pale. She got "green pills" at this time from her doctor.

At that time she had no digestive trouble, her appetite was good, bowels regular, no urinary symptoms, no cough, and she slept well.

Two months ago she noticed her ankles were swollen a little at night, and that she became slightly breathless on moderate exertion. Her previous tiredness and pallor were intensified, and she noticed a feeling of numbness in fingers
and does, along with occasional "pins and needles" sensations. There were no troublesome.

4 weeks ago she began to have attacks of vomiting, chiefly in the mornings, bringing up frothy greenish material. This occurred daily, and the patient's appetite diminished in association with these attacks.

She became so weak that she could hardly put on her clothes; she was "ashamed to go out because she was so pale."

When she did go out, her legs felt weak and she was inclined to stagger.

At this time she was greatly troubled by a buzzing in the ears, especially the left ear, which was continuous and worried her greatly.

She has not to her knowledge lost any blood before or since the onset of her illness.

Of late the bowels have been regular with daily medicine. The stools have been fairly dark in colour. She has not taken any "green pills" lately.

She has had no urinary symptoms. Her weight has kept quite steady.

She has not had pain in her chest or palpitations.

No headaches or sore throat.

She has had a few small ulcers on her tongue;

"... cracks at the corners of her mouth;"

"... slight "grittiness" and watering of the eyes;"

bruises easily.

Previous History:

Gynaecology at age 28.
Occasional colds.

Family History:

Nothing significant. No jaundice or meningitis.

Social Conditions:
The patient is Irish, from Dublin, and before the war used to go home
every year. Of late this has been impossible and she is suffering from acute anaemia, with consequent aggravation of her symptoms.

Her home here is not congenial; she has been alone for 6 years since her family grew up, and she dislikes her neighbours, believing that they deliberately try to worry & frighten her.

**Diet:** She used to take her main meal at the day at a restaurant but plate has given this up (quarrelled with the restaurant keeper) and now does not bother to cook much.

Her diet for the last 2 months has been almost exclusively bread & margarine and tea, with an occasional egg. She never touches potatoes or other vegetables.

**Examination.**

**A. General**

The patient is lying comfortably, flat in bed. She is very pale, with a yellowish tinge in skin and sclera - rather biscuit-coloured than yellow. She is very well-covered - well developed.

Mentally, she is confused and rambling, and facts are elicited with the utmost difficulty.

Temperature 99.0°  Pulse 100/min. Respir. 20/min.

**B. Systematic.**

**I. Alimentary System.**

- **Mouth:** Buccal mucous membrane very pale but clean and healthy.
- **Tongue:** Clean, pale, moist, not excessively smooth.
- **Teeth:** Upper artificial - worn for eating; lower - 1 or 2 cavious.
- **Gums:** Clean and healthy.
Abdomen
   a) Inspection - well covered, misogyny freely on inspiration.
   b) Palpation - soft all over. No spleen or liver enlargement palpable. No induration or rigidity.
   c) Percussion - no ascites.

Special examinations:
   a) Examination of stool: Bengali negative on 3 successive occasions.
      Stool moderately dark in colour.
   b) Test Meal: Histamine - fast achlorhydria with mucus in large amount and evidence of a slow-emptying stomach.
   c) Evidence of liver disease:
      i) Conjugated bile pigment (venous) 2.5 min. normal.
      ii) Albumin index 17 (normal about 8)

Haemo poetic System

- No pleura or lymph gland palpable.
- No purpura or ecchymoses.

Hep's test of capillary resistance is negative.

Blood:
   R.B.C. 1,800,000 / cm. mm.
   Hb 4.4 g
   W.B.C. 6,800
   C. R. 1.2

Film: Gross macrocytosis, anisocytosis, poikilocytosis.
      Occasional cells, thin, polyblastosia.

Differential white cell count:
   - Polynuclears 60%
   - Lymphocytes 38%
   - Monocytes 2%

Reticulocytes 3.1%
Platelets 565,000 / cm. mm.
Bloodling time
(119 method) : 1.5 min. (Normal up to 4 min)
Coagulation time
(venous blood) : 2.5 min. ( ... 4 up to 7 )

Olecran Index : 17
Van den Bergh : indirect positive (indicating
haemobilin in plasma)

Stomatid Puncture
(20.4.44) : Typical megaloblastic reaction.

Red cell fragility test : Patients cells gave same
(24.4.44) result as normal control.
Sedimentation rate : 30 mm per hour.

Nervous System.

Patient, as was stated already, is garrulous and a
poor witness. There is evidence from her
conversation that she is anxious, and tends to
be suspicious of everyone.

Cranial nerves - N.A.D.
Motor functions - muscle tone in the limbs is
poor, equally so on both sides.
Abdominal muscles also flabby.
Muscle power diminished also, on both
sides.

Reflexes
a) superficial - abdominal reflexes doubtful;
plantar " flexor.
b) deep - biceps, triceps, diminished equally
supinator on both sides.
Knee, ankle present and equal.

Sensory functions : Diminished vibrational sense in both
legs. No other abnormally detected.
Cardio-Vascular System

Arteries:  Pulse rate 100/min. Regular in time space. 
Volume good. Well not palpable. BP 140/95.

Veins:  

Capillaries:  Very slight venous pulsation.

Heart:  Apex beat in 5th space, just outside mid-clavicular line. Weak & diffuse. Sounds pure and closed at apex; soppy systolic murmur at base.

X Ray:  The heart shadow is displaced to the left. There is some left ventricular hypertrophy and tortuosity of the aorta.

Urinary System

Urine:  The only abnormality found was excess uricinogen. Urine gave a pink reaction with rhodobilaldehyde reagent.

Respiratory System

Evidence of Dietary Deficiencies associated with the anaemia:

1. Skin  - soft, pale; no pigmentation or roughness
2. Eyes  - no vision, cataract, corneal injection, photophobia, Brittle spots; no vision at corner of eye.
3. Mouth  - no ulcer on tongue or inside of mouth; no "raw-beef" or "magenta" tongue; very slight cheilosis.
4. Intestinal  - no diarrhea; appetite if no medicine; loss of appetite.
5. Cardio-Vascular  - slightly enlarged heart; slight oedema; palpitation and dyspnoea on exertion
6. C.N.S.  - Mental disturbance
Parasites
7. General  - Weakness and weakness.
Of these, Nos 1 and 2 suggest that there is no deficiency of Vit. A.
There is no gross deficiency of Vit. B₂ or B₁, but Nos 4-7 could all be produced by lack of B₁, as well as by anaemia.
This will be discussed further, later on.

**Diagnosis**

The diagnosis was made of Permanent Anaemia.

This was suggested, on careful examination, by:
1) anaemia in an elderly patient with
2) good state of nutrition;
3) slight jaundice;
4) acroparasthesia.

It was confirmed, later, by:
1) Peripheral blood picture
2) Megaloblastic reaction of bone marrow
3) Evidence of haemolysis:
   a) icteric index
   b) Van den Bergh reaction
   c) urobilinogenuria
4) Achylia gastrica
5) Response to liver therapy.

In the differential diagnosis we must consider:

1) Other causes of achylia gastrica with anaemia - the chief being carcinoma of stomach.
   In this case the fractional test meal result, the absence of weight loss, and the repeatedly negative Benzinie reaction of the blood exclude this condition.

2) Other causes of excessive haemolysis, giving a positive indirect Van den Bergh reaction:
   a) Where cells are abnormally fragile e.g. macrocytic anaemia other than P.A.T. acholuric jaundice, sickle cell anaemia etc.
b) Where the cells are acted upon by bacterial toxins, parasites, or drugs [e.g. haemolytic streptococci, malaria parasites, sulphonamides, etc.].

In this case there was nothing in the history or examination to suggest group (b); in (a) alcoholic juvenile is a disease of young persons, familial, and gives rise to a higher reticulocyte count than occurs here. There is no evidence to suggest any of the other members of the group and we therefore hold to our original diagnosis of pernicious anaemia.

**TREATMENT and PROGRESS.**

The patient remained in the ward for 1 month. On the 9th day after admission liver therapy was begun; Anaehaemia was the type employed, and was given intramuscularly in doses of 2 cc.

She had, in all, 5 doses of Anaehaemia, with intervals ranging from 3 to 5 days between doses.

Her temperature for the first 7-10 days after admission was unsettled, averaging 98.4°-99°. After the first injection fever it rose to 100.5° at night, and this was accompanied by a certain amount of mental disturbance which necessitated the use of morphine g x 1/4.

This was the only untoward reaction to liver. During the second fortnight, the patient's pulse and temperature settled to within normal limits.

The response of the blood to liver is seen on the chart. What cannot be charted, but what was most impressive was the daily improvement in the patient's colour and behaviour. Each day there was a noticeable
diminution in the yellow tinge, and an increase of normal pink in the cheeks. The mental state improved greatly and the patient herself felt stronger daily. The buzzing in her ears, which had worried her so much, disappeared, to her great joy.

The urobilinogen disappeared from the urine; the icteric index fell from 17 to 8; the BSR from 30 mm/hour fell to 9 mm/hour; and the blood picture was practically normal when the patient was discharged, although the ideal of 100% Hb and 5 million RBC cells had not been attained.

The blood changes are collected together on the chest in the next page. They will be discussed later.

The patient was discharged on 11.5.44 with instructions to attend her own doctor for further injections and iron therapy.

**Commentary**

**Pathology and Etiology**

Here, as in case I, we have dealt with the type I jaundice present, and the mechanism of its production. We have also decided that the immediate cause of the excess haemoglobin-aemia is the production of immature and therefore abnormally fragile red blood cells, which are destroyed in large numbers by the reticulo-endothelial system. The earlier stages in the pathology must now be considered.

Pernicious anaemia is due to absence of an intrinsic factor, which is secreted by the pyloric
segment of the stomach, the duodenum, and in diminishing degree possibly by the remainder of the intestine. It is generally held that the intrinsic factor is a ferment which reacts with an extrinsic factor in the food to produce the "specific anti-anemic factor" or S.A.F.

The intrinsic factor is quite distinct from pepsin or remain. The nature of the extrinsic factor is not known but it is present in any well-balanced diet. S.A.F. is absorbed from the small intestine and since chiefly in the liver. S.A.F. is essential for normal blood formation and the nutrition of the spinal cord; in its absence the bone marrow undergoes megaloblastic degeneration.

The lesion which abolishes secretion of the intrinsic factor almost always supersedes the secretion of HCl and pepsin by the body of the stomach. Achylia is, therefore, a cardinal symptom of P.A. The lesion in the stomach is not known, but is probably a degenerative change associated with advancing years and favored by hereditary vulnerability.

[It will be realized that a P.A.-like picture will be given by the blood if
1) there is failure to take in intrinsic factor
2) there is failure to absorb the S.A.F.
3) there is destruction in the liver
4) there is destruction of S.A.F.
but these do not concern us now.]

Blood

The normal sequence of events in the maturation
of a red corpuscle is as follows:

Erythroblast
Normoblast
Reichshofer
Erythrocyte.
If the S.A.F. is lacking, the development from erythroblast to normoblast does not occur; instead, if the normoblast there appears a large nucleated red cell called a megaloblast. This cell eventually loses its nucleus and becomes a megalocyte.

Erythroblast  Megaloblast  Megalocyte.

The tendency, therefore, in P.A. is for the cells to revert to a more primitive or embryonic type; for the essence of the disease is a failure on the part of the red cells of the marrow to mature sufficiently quickly. The megaloblastic reaction of the marrow, and the megaloblastic or macrocytic type of anaemia are evidence of this tendency.

**Conclusion / Clinical Features with Pathology.**

**A: Haemopoietic System:**

1. The jaundice has been dealt with already. It is due to excess haemoglobin in anaemia from breakdown of fragile red cells.

2. The pallor is associated with the low red cell count (1-8 millions/cumm) and Hb (44%) 

3. The W.B.C. count is not so low as one would expect in P.A. but the differential white count is typical; there are relatively few polymorphs, and a corresponding increase in lymphocytes. A very low white count in P.A. is a bad prognostic sign, suggesting an imminent aplasia of the marrow.

4. The platelets are usually reduced in P.A.; here they are nor. This may be associated with the relatively high white counts.
The high colour index is typical of P.A. indicating a hyperchrome macrocytic anaemia.

The finding of polychromatic cells, and occasionally me with punctate basophilia, also 3-1% echinocytes suggest an abnormally large number of immature red cells in the peripheral blood. These phenomena are all part of the same process.

Normal bleeding time is quite consistent with P.A.

It was on the short side here, which agrees with the increased number of platelets found.

Normal coagulation time is to be expected here, in contrast distinction to that in a regeneration type of jaundice.

Sedimentation rate is raised (normal is about 5) and this is due to the relatively low proportion of cells to plasma in the blood. It is interesting to note how it fell to normal as the blood improved.

Cell fragility test showed no deviation from the normal. [The condition which gives a definite increased fragility is oedemic jaundice]

---

Nervous System.

The ataxia and loss of vibration sense suggest a lesion in the posterior columns of the spinal cord.

The cord, in a severe case is swollen, and shows translucent patches first in the posterior columns, then in the lateral. These lesions coalesce and form a ring of degenerated tissue around the grey matter.

There are many such patches which coalesce; the disease begins in the dorsal region and spreads up and down.

These lesions cannot be attributed to the effect of the anaemia, since they may develop before the anaemia. Melanocyte has suggested that there may be two accounts; one for blood, the other for spinal cord anaemia.
It is possible that the cause factor may be vitamin B.

(2) The anaemia - numbness and tingling in the hands and feet - suggest a mild peripheral neuritis; this may be due to the anaemia, or to a deficiency of Vit. B, which is highly probable in this case (see the dietary history on p.)

(3) Renal emphysema and peculiar are due to cerebral anaemia; the patient's behaviour altered strikingly as her blood improved.

C. Cardio-vascular System

Breathlessness, weakness, oedema, pruritus, enlarged heart may all be due to the anaemia; they could also be attributed to a deficiency of Vit. B.

D. Urinary System

The excess uricobain in the urine was explained in the introduction - illustrated in Fig 2.

E. Alimentary System

Vomiting, loss of appetite and tendency to constipation could be due to anoxaemia of the mucous membrane of the intestines, and anaemia. They could also be due to B, deficiency.

Discriminable Treatment & Prognosis

As soon as the diagnosis of P. A. is made, liver therapy should be begun, using a preparation known to be potent and not liable to cause reacim. The patient should stay in bed until the haemoglobin reaches 50%.

No drugs are generally used at this stage, but dilute hydrochloric acid may be used to improve the appetite - 3 1/2 spp. in a tumbler 1 lemonade with the meal b.i.d. or t.i.d.
Liver Therapy:

Give 4 cc 1 cc. Anabrenin intramuscularly and repeat this in the first week.
Or, as in this case, 2 cc every 3 or 4 days.
and keep on until

\[ \text{Hb is 100%} \]
\[ \text{R.B.C. are 5 million /cm.m.} \]

Iron must be given to supply the new cells with
haemoglobin.
Give as FeS\(_{2+}\) or \(\frac{3}{4}\) t.d.

If there should be anaphylactic reactions to the liver, change the preparation; or have the patient desensitized by an expert.

It is better to use, if available, the crude liver preparations since they contain the Vit B complex.

If this cannot be done, Vit B should be given in the form 1 year 1 oz per day, or
maximum, as much as desired.

If for any reason, parenteral liver therapy cannot be carried out for long, hog's stomach can be used to maintain the blood at its correct level.

In this case it will be seen that liver therapy caused the reticuloocytes to rise to 25% (their highest level) on the 4th day after treatment began.

The reticuloocyte crisis may be any time between the 3rd and 7th days with parenteral therapy.

The Hb rose steadily until the 9th day, then the curve flattens slightly; this may be an indication that iron was required at this stage.

Vitamin C and even Thyroid may be required in some cases to achieve a normal count and Hb.

In all cases, after restoring the blood to an optimum level, it must be kept there by regular injections and blood examination. If this is done, the prognosis is excellent; if not, gross spinal degeneration may occur, severe
relapses of the anaemia, and an aplastic anaemia may be the terminal stage.

All these complications may be avoided if the patient co-operates, and the doctor is convinced about the regular examination of the blood.

In the present case there was, as reported, a most striking improvement when the blood had reached 75% Hb and 3.8 million red cells.

There is no reason why this patient should not live happily and in perfect health for very many years if both she and her doctor determine that she shall do so.

SUMMARY.

Two cases of jaundice in elderly female patients have been described. The types of jaundice manifested by them have been contrasted, and the mechanism of the production of jaundice described.

The clinical features of each case have been correlated with the underlying pathology, and for each the etiology, prognosis and treatment have been reviewed.
Cases 3 and 4

Obesity
Two Cases of Obesity.

Introduction, and statement of the problem.

Obesity, or adiposity, is defined as the excessive deposition of fat in the subcutaneous tissues. Of this condition there are various types:

1. Exogenous obesity, due to over-eating;
2. Obesity due to endocrine symptoms e.g.
   Flashing's syndrome
   Cushing's "
   Adrenogenital
   Acromegalic disease
   Obesity following castration or the menopause
   Obesity associated with hyperinsulinism
3. Obesity due to hypothalamic lesions
4. Idiopathic constitutional obesity.

The eating of excess food may be due to habit, greed or anxiety; but there is also a centre in the hypothalamus, a lesion of which appears to produce pathological hunger as seen in certain cases of brain tumour. This lesion may also be operative in apparently idiopathic obesity.

But the mere eating of excess food is probably not the only factor, since anxiety states producing excess hunger may yet be associated with leanness and an inability to put on flesh.

On the other hand, the majority of cases of idiopathic obesity cannot be ascribed to excessive intake of food, and it cannot be doubted that
If two people on similar diets, or if two children in the same family having similar food, one may be short and the other thin.

In addition to the calorie factor, the role of the peripheral times must be considered. If hormones which normally excite oxidative processes in the cell are unable to act on organs usually thus influenced (because of a physico-chemical disturbance in these organs) the local result is inhibition of oxidation and the accumulation of fat.

Disruption of the water and salt affinity of the times is found in many obese patients. The changed colloidal condition of the cell due to its increasing inhibition of water must correspond to changes in its reaction to hormonal influence.

Thus, even with a normal food intake, and a healthy condition of the endocrine glands, if the peripheral times react abnormally, obesity will result.

The following two cases will illustrate methods of investigation of cases of obesity. There are many points of resemblance between them, and neither is clear-cut as regards etiology, but one is of especial interest in relation to progress made under treatment.

[The writer is much indebted to this last-mentioned patient for the loan of photographs taken to show the various stages of recovery.]
CASE I

Mrs A.P. aged 30. Housewife.
Admitted to hospital 25.8.42.

Complaints:

- Headaches 15 years
- Vomiting 2 "
- Diarrhoea 6 months
- Headaches 5 "
- Breathlessness 5 "
- Headaches 2 "

History of present illness:

The patient was perfectly well until age 15 except that she had amenorrhoea. She was operated on at that time (?) imperfect hymen after which menstruation commenced and continued thereafter somewhat irregularly; the periods lasting 7-14 days.

At age 17 she married and had already become fairly stout.

" 18 her first pregnancy occurred, accompanied with hyperæmias.

" 20 Second pregnancy — also hyperæmias.

" 22 Third " — Normal.

" 24 Fourth " — terminated because of severe hyperæmis.

She had albuminuria at this time but no oedema.

Periods were quite regular.

" 27 Fifth pregnancy — vomiting, thirst, albuminuria and possibly hyperæmis.

No oedema.
From September 1938 onward, the sequence of events in her history is interesting:

Sept. '38: Patient had a mental shock due to finding her aunt dead in bed. After this she had extra work, since she undertook the care of the aunt's business.

July '39: Her 5th baby was born. She began to have pains in the chest; these occurred first at night, later during the day, and were like "something sharp passing through the chest."

At this time she was troubled by nocturnal frequency: she was up 3-4 times a night. Periods quite regular.

January '41: She felt tired, listless and unable for work, and suffered from sleeplessness.

The baby died of meningitis.

Her husband went abroad, and she felt very lonely, and rumors of air-raid. The neighbours were ungenial.

Feb. '41: Patient's younger sister, unmarried, became pregnant; the patient was extremely worried about the possible reaction of the family.

August '41: She began to have skin eruptions; wet pimples came out in crops on arms, legs and neck, and were very itchy.

Dec. '41: She had a severe cold which did not clear up, and had severe nausea with it.

Jan.-Feb. '42: Felt very tired and unable for nothing.

Headaches are very severe, especially behind the eyes and on top of the head.

These occur 2-3 times per day and are severe enough to make her weep.
There is a constant tickle of discharge down the back of the throat, from the nose. Periods very irregular again.

March '42: Patient had her eyesight tested. Normal result.
A specimen of urine showed much albumin. She noticed her face puffy in the mornings, and felt sick every morning on rising.

From the end of March onwards she was in bed off and on; she had to sleep propped up as she was afraid of choking. She was breathless even in speaking, and had flushings.

April '42: She began to have fits of shaking which affected the whole body. These came on at first when in bed at night, and kept her awake; later they occurred during the day and were so bad that she could do no work. She felt nervous and irritable, laughed and cried easily. She was sleepless at night and drowsy during the day.

June '42: She noticed herself to be awkward and fumbling in her movements; she dropped things and was inclined to fall.

July '42: She had diarrhoea for 5-6 weeks before admission to hospital, also slight swelling of the ankles. Her appetite was poor, and she complained of flatulence and epigastric pain which was especially severe at night, and made her sweat and vomit.

August '42: Admitted to hospital for investigation.
Previous History:
Age 5: Scarlet fever - 3 weeks ill.
Age 6: Diphtheria - 16 " " , with paralysis of tongue, eye muscles, slower".

Family History:
Mother age 50 - died very young after youngest child born in 1920. Now weighs 20 stone.
Sisters: a) Age 29 - both inclined to be stout.
       b) Age 22 -

No obvious serious physical defects in family.

Social Condition:
Patient has had a good deal to do - her own homework as well as the aunt's business (a shop) to manage.

In the last 5 months she has been on a milk and fish diet but in fact has had little fish, never any meat, and no vegetables. She does not eat much at any time.

Examination:
A. General
The patient is a huge woman, weighing 19 stone 10 lb. Height 5' 6".
She is sitting up quite comfortably in bed, and is mentally extremely intelligent and cheerful, and not conspicuously emotionally unstable.

Her obesity is distributed chiefly in the trunk and proximal parts of the limbs; the legs, arms, feet and hands are quite slender.

[ The photograph dated June 1941 gives a good idea of her appearance at the time of examination; she had not changed much in a year. ]

T. 98.6°  Pulse 80/min  Respiration 20/min.
B. *Systematic Examination.*

**Cardiovascular System.**

Arteries: Pulse 80/min. Regular in time and volume. Weak and not palpable. BP 130/85.

Veins: N.A.D.

Capillaries: No oedema.

Heart: Apex beat not palpable. Sounds very faint; pulse mark closed in all areas.

ECG: Normal sinus rhythm; left axis deviation.

**Respiratory System.** N.A.D.

**Alimentary.**

Mouth: Tongue clean moist. Tastes healthy. Teeth good.

Abdomen: N.A.D. Ribs, fat, tendons, pubic and iliac crests.

**Urinary System.**

Urine: The only abnormality was albumin. 1.5 gm%. Microscopic exam negative.

Renal Function: Blood urea nitrogen 14 mgm%.

**Nervous System.** N.A.D.

Fields of vision: normal.

X-ray of skull (27.8.42) shows no evidence of a pituitary tumour.

**Haemopoietic System.**

R.B.C. 4.5 million/cu.mm  
Hb. 94%  
W.B.C. 5,600  
Differential white count:  
- Polymorphs: 47%  
- Lymphocytes: 51%  
- Monocytes: 2%  

Plasma Proteins: Alb. 3.94  
Glob. 2.03  
S. 1%.
Endocrine System.

According to Zondek in "Diseases of the Endocrine Glands" the following points should be noted:

a) Adiposity:
   (i) Amount - excessive
   (ii) Distribution - on trunk, hips, shoulders, sparing distal parts of limbs.

b) Bone Skeleton: Normal growth.

c) Hair: Fine, thin; has been coming out.

d) Skin: Soft fine texture; warm; not moist; no rash or pigmentation.

e) Expression: Round, rather childish face (see photograph) with slit-like eyes.

   Alert, cheerful expression in conversation.

f) Voice: No abnormality.

g) Circulatory System: N.A.D.

h) Blood: Slight relative lymphocytosis

i) Eyes: Fundi and fields of vision normal.

j) Skull: N.A.D.

k) Urine: Oliguria and albumin

l) B.H.R.: 7:1

m) Menstruation: Irregularity up to 1934.

Regular from then until 5 months ago.

Periods last 2-3/24 days.

The following further investigations were made:

1) Urea Range

   | Specimen | Vol. | S.G. | Urea |
---|---------|-----|-----|------|
   | 6 am    | 10 oz | 1020 | 2.3  | 5 " |
   | 7 "     | 8 "   | 1007 | 1.2  |
   | 8 "     | 8 "   | 1005 | 0.4  |
   | 9 "     | 4 "   | 1010 | 1.3  |
Gynaecological examination — Prof. Johnstone

(28.10.42)

Patient had complained of a heavy feeling in the pelvis as though something were dropping down.

No prolapse found. Two small polyps were removed. A discharge of watery and bloody nature from the vagina.

No pyaemia. There is a mild degree of gonococcal infection. Recommend a douche of 1% boric acid 3 x 20 ml to the great gums and water 3 times a week.

Urinary Hommes

20.11.42

A Z. test negative

Voblas's Water Excretion Test

2.9.42

The result is given on the chart on next page. Normally after drinking a litre of fluid the individual excretes the whole fluid in about 2 hours. In this case only 66% was excreted in 4 hours which shows a definite tendency to water retention.

NaCl Excretion Test

10.9.42

Results appear on p. 11.

Before the administration of the 10 gm NaCl the patient was excreting about 3 gm. of chlorine per day in the urine; the normal chlorine excretion is 6-9 gm. per day, thus she showed chlorine retention to that extent.

The day following the administration of the NaCl she excreted a total of 9.5 gm chlorine. This result is considered to be a satisfactory response and the verdict therefore was, finally, that she has no definite chlorine retention.

But Zundek holds that this test is in fact not reliable.
Volhard's Water Excretion Test

2. 9. 42

Mrs. A. P.  Case I

After emptying bladder, 1 litre of water taken at 5 a.m.

cc. of urine
spec. gravity

% of ingested water excreted after 4 hours = 66.7%
At the beginning of November '42, the writer described the case to Dr. Parkinson of the Physiology Department who was working at that time on a case of pituitary disorder. As a result, 24-hour specimens of the patient's urine were collected, concentrated, and tested by animal experiments for the presence in the urine of a) a pressor substance and b) an anti-diuretic substance.

These investigations will now be described.

**Preparation of urine for injection:**

The 24-hour specimen was concentrated down to a volume of about 8 cc and neutralised with alkali. Two 24-hour specimens were used in the 1st experiment, representing the total output for 2 consecutive days. These are named P_1 and P_2.

2) In this experiment, the urine of a known hypertensive patient was also used for purposes of comparison; also Infusion - a posterior pituitary extract.

The animal used was a cat, anaesthetised with chloroform. A cannula was inserted into the left common carotid artery, to record the blood pressure. The various injections were given into the left femoral vein.

An indication of the type of results obtained in this first experiment (to determine the presence of a pressor substance in the urine) is given on the next page. The diagrams are only roughly accurate - sufficiently so for our present needs.
0.5 units Infusion.
Back to base line in 7 min.

P1 urine 0.5cc injected rapidly.
Back to normal in 30 sec.
Result resembles that following the injection of any foreign protein.

Hypertensive urine 0.5cc
(Not fully neutralised with alkali)
Back to base line in 20 sec.

P1 urine 1cc run in slowly over 1 minute.

Hypertensive urine 1cc, fully neutralised, run in over 1.5 min.

Normal saline 1cc, acidified with acetic acid, run in over 55 sec.
No change.

Hypertensive urine 2cc run in over 75 sec.

P2 urine, 1cc, over 40 sec.

Infusion 0.5 units, injected rapidly.
Response in 5", maximum in 20".
Back to normal in 8 min.
Commentary on these results:

Infusions (poisonous plant extract) appeared to have a definite pressor effect. In both cases when it was used there was an immediate rise in B.P., which was sustained for several minutes. Hypertensive urine had a variable effect. In one no. 5 when it was fully neutralized it had a very slight, but maintained, pressor effect.

P1 urine and P2 urine had depressor effects, whether injected rapidly or over a period of 60 seconds.

The conclusion is that in the urine of Irish A.P. there is no substance which exerts a pressor effect under the circumstances described.

In the second experiment, to determine the presence of an anti-diuretic factor in the patient's urine, the urine was concentrated and prepared as before.

The animal employed was a dog, with catheter in bladder. The dog drank 250 cc water at the commencement of the test; thereafter at 15 min. intervals the urinary output was measured - the total output for each 15 min. being collected in a beaker.

After an hour, when the maximum output seemed to have been achieved, an injection was given of 1 cc concentrated urine. The result is shown on the graph acrossleaf. The immediate result was a diminution in output, but as this was on the low-grade in any case it is not very conclusive evidence.

The commentator remarks would probably have been given as a response to any foreign protein.

There is, therefore, no definite evidence of an anti-diuretic factor in the patient's urine.
18.11.42. Mrs A.P. Anti-diuretic Test.

Urine output in cc.

Dog drank 250 cc. water.

Minutes

0 10 20 30 40 50 60 70 80 90 100 110 120
Diagnosis.

The foregoing investigations point definitely to the endogenous type poisoning, but less definitely to the cause. All factors considered, the patient resembles most closely the type called by Zondek in "Disease of the Endocrine Glands" as the "Cerebro-Pituitary-Peripheral" or Water-Salt Obesity. Differential diagnosis, and reasons for the present diagnosis will be discussed in the commentary, after Case II has been described.

TREATMENT and PROGRESS.

The patient remained in hospital from 25.8.42 until 28.11.42. During these 3 months she kept well, except for occasional sick and faint spells about the beginning of October, shortly after commencing mercurial therapy.

She was all the time on a 1000 Calorie diet.

On 25.9.42 she began mercurial treatment to lessen the occult oedema thought to be present.

She had 2 cc mersylyt intravenously with excellent diuretic results.

1 cc mersylyt was repeated 2 days later.

After these injections she was not sick; it was decided therefore, in view of the slight persistent albuminuria, to stop mercurial therapy, and use instead Ammonium Chloride as a diuretic.

14.10.42 Ammon. Chlor. gr xv t.i.d. began.

This was continued for 10 days with fairly good results.
29.10.42 After a break of 3 days, Ammon. Chlor. was resumed, gr. XV t.i.d., continued for a fortnight.

7.11.42 Patient began a course of physiotherapy — exercises of various types, including breathing, abdominal contraction, trunk rotation, elevation, shrugging, and shoulder circling; hip & knee exercises etc.

11.11.42 Thyroid begun — gr. t. i. d.

29.11.42 Patient was discharged home, having lost in all 3 x 5 lbs. since admission. New weight 16s. 5d.

A record of therapy, urinary output and weight loss is seen on the chart overleaf.

On discharge she was given a diet of 1100 cals.,
and a prescription for Ammon. Chlor. gr. t. i. d.
(which she was to take for a fortnight)
and for Thyroid 8F gr. t. i. d. (which she
would take for the second fortnight each month)

Report of further progress:

The patient kept faithfully to her diet and
drugs, and reported at regular intervals.

28.12.42 Weight 15st. 11lb. She feels well, but
still has chilly feelings in back at night. This
usually occurs during the first days before her
period is due. After the period is over she
feels much better.
She has had slight headache.
Still some albuminuria.
She was given a prescription for phenobarbitone gr. nov.
Weight 16 11 lb.

Sleeping poorly. Has phenobarbital 1/2 hour.

Headache has been worse lately.

Periods not quite regular. No sickness.

Urine normal. Digestion good.

Slightly irritable; apt to weep easily; tendency to claustrophobia in strange places.

To stop Ammon. Chlor. and take Hypnot.

1/2 t.i.d. for 3 weeks each month, stopping just before the menstrual period was due.

November '43. Weighs 13 6 1/2 lb.

May '44. 12 31 7 lb.

Now looks and feels extremely well. Rarely her headaches. Does not pass much urine.

Periods regular. Can manage with very little sleep and her abundant energy.

She is not now keeping so strictly to her diet but is still steadily losing weight.

Still on Hypnot. 1/2 t.i.d.; also takes phenobarbital 1/2 t.i.d. — if not she feels she would be very nervous irritable.

Record of weight since admission to hospital.

180 170 160 150 140 130 120 110 100

Photographic Illustrations of

the patient's progress.

Mr. A.P. has very kindly lent the following photographs in order to illustrate the stages in her progress. The very obvious improvement, both mental and physical, needs no comment.
CASE II

Mr J. M., aged 62, Housewife.
Admitted to Hospital 12.6.43.

Complaints:
- Shortness
- Breathlessness
- bouts of sickness
- Weakness

40 years
many years
6 weeks.

History of present illness:
The patient has had bouts of sickness for years; they last a day, but there is residual abdominal tenderness for a week.

She had a severe attack 6 weeks ago with sickness and pain in the left side for one night.

After this she was in bed for 2 weeks, and had very little food. Since getting up she has felt weak and short of breath on exertion.

She began to get short after the birth of her first baby 40 years ago; in the last 2 or 3 years she has put on weight more rapidly.

Her appetite is usually good. Bowels are regular. She is troubled with flatulence.

She had headaches until 2 years ago; when she woke in the morning the headache was present on one or other side of the head. Associated with this she seen lights in front of the eyes and occasionally was sick. The headache usually lasted all morning.

She had frequent dizzy spells 2 years ago;
at that time she had extra work to do but has been taking things more easily of late.

Since her pregnancy, she has been troubled by frequency of micturition (i.e., for 21 years) and has had to pass urine every hour. There is no urgency. She has to rise 2-3 times per night to pass urine.

She has had a "pain at her breast" intermittently for 6 weeks; it is worse on walking, and when she lies on her left side. If she sits down when the pain is on, it disappears in about half an hour. Heat relieves it.

Previous Health:
Rheumatic fever 36 years ago
Swelling of face 1 year ago
Brachitis every winter

Family History:
Her mother and one of her daughters are small and stout. No other evidence of endocrine disorder in the family.

Social Conditions: Nothing to note.

Examination:
A. General: The patient is an extremely short woman, weighing 17 st 13 lb. Height 5'6".

She looks flushed. The skin is of average texture with evidence of growth of hair on the chin, which has been shaved.

She has a broad chest and neck, a rather phlegmatic in appearance.

Nasal development is good.

T. 98.0°  P. 75/min.  R. 20/min.
Systematic

Cardio-Vascular System

Arteries: 75/min; irregular in time space; volume good; well pulsatile; B.P. 205/155

Veins: No dilated veins

Capillaries: No oedema

Heart:
1) Inspection - no apical beat or pulsations visible
2) Palpation - pulsation palpable
3) Auscultation - faint, short, heart sounds
   Suggestion: tic-tac rhythm

E.C.G. Anomalous fibrillation with left axis deviation

X-Ray: Enlarged left ventricle

Respiratory System: N.A.D. Expansion poor

Alimentary System

Mouth: Teeth all felt; tongue, healthy

Anus: Clean and moist

Abdomen: N.A.D. Pendulous masses, jet not tender

Nervous System

Abnormalities discovered were:
1) Slight diminution in temporal fields, normal fields
2) Ankles jolt, hard to elicit

X-Ray: Skull 26.6.43: Enlargement of pituitary fossa with thinning of sella turcica
   Suggests pituitary tumour

X-Ray: Skull shows considerable thickening

Urinary System

Urine: S.G. 1.008
   Albumin 2 gm per litre
   Otherwise N.A.D.

Catheter specimen - no growth or culture
Haemopoietic System:

Hb 103 %
RBC 5.8 million / cmm.
C.I. 0.9
WBC 8,000.

WS: negative.

Endocrine System:

a) Adiposity:
   i) amount: excessive
   ii) distribution: chiefly on trunk, shoulders, hips, but arms legs are not
   substantially slender in comparison.

b) Bone Sclerosis: normal. Some thickening 1 small
   1 skull: seen by X Ray.

c) Hair: average texture.

d) Skin: normal. Hair on chin.

e) Expression: stoical, slow to respond.

f) Voice: mild abnormal.

g) Circulatory system:

h) Blood:
   High RBC. and Hb.

i) Eyes:
   Slight? bilateral hemiopia.

j) Skull:
   X Ray evidence of pituitary tumour.

k) Urine:
   Low S.G. Albumin 2 g.p.lime.

l) BMI: -5.2

m) Menstruation:
   Periods stopped at age 50.

The following further investigations were made:

<table>
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<th>Specimen</th>
<th>Vol.</th>
<th>S.G.</th>
<th>Urea</th>
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<tr>
<td>10 pm - 6 am</td>
<td>100 cc</td>
<td>1024</td>
<td>2.45 g.%</td>
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<tr>
<td>6 am</td>
<td>30</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>300</td>
<td>1017</td>
<td>2.2</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>0.7</td>
<td></td>
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</table>
Gynaecological Examination - Dr. Hamilton (17.6.43)

Report: The patient's frequency of menstruation is probably due to trignitis.

The uterus is enlarged and retroverted, there is possibly a cyst lying behind a small uterus.

Vollhans' Water Excretion Test

See result on next page.

As in Case 1, only a proportion of the ingested water was excreted in 4 hours: 56.6%.

This shows a tendency to water retention.

Examination at Eye Department - Dr. Cameron - 8.7.43

Report: definite diminution in both temporal fields.

Blood Chemistry 9.7.43

a) Blood Chlorides (NaCl) 440 mgm % [normal 450-530]

b) Serum Potassium 16 " 18-21"

c) Blood Sugar Curve: sluggish response compared with normal.

d) Serum Sodium (20.7.43) 34.3 mgm % [normal 325-350]

[Graph of Blood Sugar curve with types of normal blood-sugar curves shown.]

50 Gms Glucose

<table>
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<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gm. %</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
<td>350</td>
<td>400</td>
<td>450</td>
</tr>
</tbody>
</table>
Volhard's Water Excretion Test
28.6.43

Mrs. J. M. D.

28.6.43

After emptying bladder, 1 litre water drunk at 5 am

- Excr. urine in ce.
- Specific gravity

Total water excreted after 4 hours = 56.6% of that ingested.

<table>
<thead>
<tr>
<th>cc</th>
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<tbody>
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<td>300</td>
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</tr>
<tr>
<td>350</td>
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<tr>
<td>200</td>
<td>1.005</td>
</tr>
<tr>
<td>100</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Chart:
- X-axis: 5:00 - 9:00 am
- Y-axis: cc
- Graph lines for urine and water.
17.7.43.

Animal Experiment.

A test, similar to that in Case I, to determine whether or not a pressor element was present in the patient's urine was carried out by Dr. Pickford.

Cat's B.P. responses recorded below:

1.0 units Infundin

11 cc iv.

Had not regained base line after several minutes.

Normal urine 3 cc iv.

Slow fall over 11 sec. then more rapid rise to normal base line.

HCl. urine 3 cc iv.

Slow rise - maximum after 19 sec.

No subsequent fall.

Atoxin 2 mgm. iv.

Rise for 14 sec. then immediate rise.

Normal urine 3 cc iv.

Fall over 8 sec., then rapid rise to normal level.

HCl. urine 3 cc iv.

Slow fall over 8 sec., then rapid rise to base line.

1.0 units Infundin

Rise for 6 sec. No subsequent fall.
The results are inconclusive:

Infundin as in case I produced a rise in B.P.
Normal urine consistently caused a fall in B.P.
similar to the reaction to a foreign protein.

MED. (the patient's) urine on the first occasion caused
a rise similar to that produced by Infundin;
on the second occasion it caused a result
similar to that of the normal urine.

That is therefore no evidence that her urine contains
a foreign substance.

Urinary Hormones. 30.7.43.

On the basis of the slight suggestion of virilism
presented by the patient, it was decided to estimate
the function of the suprarenal glands.

So this end an examination was made of the
urine by Dr. Hain.

Report: (i) 24 hour specimen contains 13 mgm. of

  17-Ketosteroids.

  [The normal average is 3.5 - 14.6
   " mean is 7.4
   A small or large woman may exceed this.]

(ii) 24 hour specimen contains 3-4 mgm. Pregnenolone.

In the case of adrenal hyperplasia, the results would be

(i) more than 20 mgm. 17 Ketosteroids per 24 hrs
(ii) and 10-30 mgm. Pregnenolone

... in this case there is no evidence of such a lesion.
Sodium Amalgal Test. 6.8.48.

The patient showed a raised blood pressure, both systolic and diastolic.

To determine if possible whether the rise in diastolic pressure was due to organic disease or spasm of vessels of the renal, the above test was carried out.

Ideally, several B.P. readings should be taken in order to get a reliable base line before commencing the test. Then the patient, lying down comfortably, is given Sok. Amalgal gr. iii by mouth. The pressure is thereafter readed half-hourly. The sodium amalgal may be repeated at hourly intervals until three doses (gr. iv) in all have been given, if the patient is not fully asleep.

B.P. note are taken half-hourly until the readings again normalise, or the patient is awake; usually there synchronises - if not the B.P. is taken still back to normal, if circumstances permit.

The results are given hereafter.

In this case a satisfactory base line does not appear; the initial reading is much lower than that obtained on admission, but reference to the progress chart shows that the B.P. had been falling steadily. On 28.7.43 it was 175/100

Therefore the initial reading in the test is probably correct.

The sodium amalgal did not cause a very significant fall in either systolic or diastolic B.P.
Results:

Dialytic hypotension may be due to the following causes:

A. Renal Dysfunction
   i) exclusive vascular disease
   ii) primary renal
   iii) renal reflect - obstructive to outlet.

B. Extrarenal
   i) Neurological
   ii) Endocrine
   iii) Perinurinal

A positive result with Sodiocyan Amalgad (a definite fall in D.B.P.)
is often obtained in group B, especially in nos. (i) and (iii).

These patients are thus singled out from those with organic vascular changes which do not alter during nuresis.

The patient in this case has probably got arteriolar damage
with super-added spasm, since the D.B.P. did fall but
not so strikingly as in a case of pure arteriolar spasm.
As in Case I, there also seems in no clear-cut reason for the severity.

There is a mixture of exogenous and endogenous.
The latter is possibly partly pituitary (basophil adenoma) in nature.

Further discussion of the diagnosis will appear later.

TREATMENT and PROGRESS.

The patient was in hospital for almost 2 months, from 12.6.43 until 6.8.43.

She was given a 1000 Calorie diet, and on this alone her weight fell 11 lbs in 3 weeks.

On 7.7.43 the addition of thyroid 0.25 gr per day was made and during the next 3 weeks the combination of diet and thyroid caused a weight loss of another 3 lbs. Thereafter there was no further fall.

The next of weight, urine output etc. is seen below.

On 6.8.43 the patient was discharged, her weight being now 16 st 8. (On admission 17 st 13½)

She was instructed to continue the thyroid 0.25 gr per day for a fortnight, then a fortnight 0.1 gr in each mouth.

This patient has never reported back, so given any indication of her further progress. This is in striking contrast distinction to Case I.
**DISCUSSION**

of the two foregoing cases.

**Differential Diagnosis**

The possibilities regarding type of obesity are, as was noted in the introduction,

1. Exogenous: due to excess eating
2. Endogenous: endocrine and hypodermic
   - **Cushing's syndrome**
   - **Bernard's disease**
   - **Fröhlichs syndrome**
   - **Water-salt obesity**
3. Idiopathic or constitutional.

1) Exogenous factors can be definitely excluded in Case I.

2) In both cases, the slow response to dietetic treatment indicated an endogenous element.

**Endogenous types:**

In Case I, no definite glandular or endocrine lesion or a clear-cut "text-book" character was found.

- **Primary:** Skull X-ray normal
  - Feet: normal
- **Secondary:** No evidence of Cushing's syndrome, with hypertension, stipe, virilism etc.

Thyroid: BMR normal

On the other hand, the distribution of the adipose tissue, taken together with slender hands and feet strongly suggest a primary origin. The fact that no evidence of primary tissue was seen in the X-ray does not exclude the possibility of a lesion existing in the infundibulo-hypothalamic region, of neoplastic, inflammatory or degenerative character.

Also, the oliguria and evidence of water retention (Volhard's test) suggest a type of being called by
H. Zondek "Cerebro-Pituitary - Peripheral" Obesity, or "Water-Meat" Obesity. [True, there was no evidence of salt retention (see p. 11) but according to Zondek this particular test is not reliable.]

This "cerebro-pituitary - peripheral" obesity may arise from disease of the anterior pituitary; decrease of the thyroid; damage to the hypothalamus; damage to peripheral organs in which the hormones act; or from attention interfering with the physiological interplay of these factors, e.g., abnormal excitability of the autonomic nervous system.

In this type of obesity the fat is "girland" in distribution, sparing the limbs; headache is common; there may be disturbed menstruation or amenorrhea; there is oliguria; a normal B.M.R.; occasional mental peculiarities, and the heart shows dilatation of the left ventricle.

The above phenomena are all present in Case I, and one is inclined to place him in this category. The underlying cause was a growth causing cerebral compression and a consequent compression of the diencephalon; or there might be straining of C.S.F. fluid in the 3rd ventricle due to a process compressing the aqueduct.

As for Case II:

The etiologic factor cannot be excluded. "Endogenous" is suggested by his appearance.

Re Adnen: pro: Raised B.P., hirsutism, high blood count and Hb; con: Negative results of urinary hormone analysis.

Psychia: pro: Rather slow mentally. con: B.M.R. normal.

Pituita: pro: X-Ray suggests a tumour; signs suggestive of adenoma; bilateral diminution of visual fields.
Pancreas: Hyperinsulinism—occasionally associated with obesity. The blood sugar curve of this patient is definitely abnormal (see p. 25) but there were no symptoms to suggest a permanent hypoglycemia.

This effect, resembling hyperinsulinism, may be produced by a lesion in the islet of Langerhans or due to a somatic lesion in the anterior pituitary causing defective control over the pancreas.

In this case there is evidence greater abnormality also, but the average output of urine is better than in Case I.

It is obvious that the diagnosis of the exact lesion in this case is extremely difficult if not impossible. It is difficult to imagine a pituitary lesion sufficient in extent to produce the X-ray picture found here, (which presumably is a basophil adenoma type in view of the patient's appearance) which does not at the same time cause increase of the appropriate hormones in the urine, since this type of pituitary lesion causes adrenal hyperplasia.

A point against a "Cushing's syndrome" diagnosis is the type of blood sugar curve; in a case the subject's basophil adenoma is hypoglycemic with a sustained high blood sugar after the administration of glucose.

It may be after all that this patient is primarily an exogenous obesity case, with secondary hypertension; and with traces of endogenous obesity of uncertain origin.

No definite conclusion was arrived at.
Pathological Processes underlying some Clinical Features common to the two cases:

1. Excess Weight:

   This may be due to:
   
   a) fat in the tissues,
   
   b) fluid

   a) Fat results from failure of the body to balance intake of energy; this may result from:

   i) failure of hormones in their duty, either because of lesion of the submaxillary gland concerned, or a failure in the conveyance of the hormones, from a healthy gland to normal tissues.

   ii) failure of peripheral tissues to react to the influence of the hormones, by carrying out their normal processes of oxidation.

   b) Fluid can cause increase in weight by:

      i) retention of fluid in the tissues in the form of subcutaneous edema.

      ii) abnormal water-retention causing a disturbance in cell metabolism and hindering the normal oxidizing process; which hindrance causes the laying down of fat.

In both our present cases there is evidence of water-retention on the basis of the Volhard test. In Case 1 there is also oliguria, unusually severe. We must now consider why this water-retention should occur.

Factors causing diminished output of urine:

A. Renal:

   1. Glomerular:

      i) filtration pressure

         air pressure

         capillary pressure

         glomerular filtration

         rise of urine

         venous pressure
ii) Collodion osmotic pressure

iii) Proportion of active glomeruli

iv) Permeability of glomerular membrane

2. Tubule:

i) Change in composition & contents tubule

ii) Changes in the activity of cells lining tubules, e.g., the anti-dilute factor of the posterior pituitary increases reabsorption processes in the tubule.

B. Peripheral

The manner in which water exchange between the capillaries and the interstitial fluids is regulated is still not completely understood; indeed there is usually less difficulty in accounting for the occurrence of oedema than in explaining its avoidance under normal conditions.

Oedema occurs when there is an abnormal accumulation of extracellular fluid at any site. Generalised oedema can be produced by cardiac and renal disease, hypoproteinaemia, and increased capillary permeability due to other factors.

In neither case is it clear why water retention should occur. Neither nephrosis from low blood pressure or urinary obstruction; the other factors are less easy to exclude. Both patients had a slight degree of albuminuria; there was no associated signs from disease. It has been noted however that albuminuria is frequently associated with lesions of the pituitary in animals, where it is thought to be due to alterations in capillary permeability of unknown etiology.

In both patients there may be an excess of the anti-dilute factor circulating in the blood; this cannot be proved or disproved.

Other things being equal, the total amount of fluid in the body depends on the total quantity of

---
salt and water ingested is administered.

The largest quantity of fluid will be retained if the salt and water form an isotonic solution with the body fluids. Any tendency for excess fluid to accumulate in the tissue spaces will be greatly exaggerated by administration of sodium chloride or bicarbonate, or both, if sufficient water is made available to produce for the production of interstitial fluid.

Excess intake of salt alone will not cause oedema; water will.

If salt and water will tend to produce oedema.

The kidney does not seem to be affected so much by a change in the volume or body fluid as by a change in its composition. If excess water is drunk, it is normally rapidly excreted, along with a little salt from the tissues; if excess hypotonic saline is drunk, it is likewise rapidly excreted, plus a little water from the tissues; if, however, excess normal saline is taken, it tends to be retained, since it has produced only a minimal alteration in the composition of the serum.

One hypothesis regarding water balance is that the secretion of urine is continually braked by the presence in the blood of a substance (e.g. post-pyretic anti-diuretic factor) the formation and secretion of which is inhibited by the administration of water to the body. There may be conditions (e.g. a cystic tumour of the mid-brain) in which the secretion of this factor is excessive; Case I may be an example of this.

Action of Anti-Diuretic Hormone: - There are 2 theories:

1. That it acts extra-nervously, causing a redistribution of water between the blood and the tissues; for this there is little evidence;

2. That it acts by decreasing tubular reabsorption of water.
In animals, the result of injecting A.D. hominis seems to depend on the amount of water in the body available for, or demanding excretion. This is obvious in animal experiments after the animal has taken a large drink of water.

In man, A.D. hominis cannot accelerate the renunciation of water in the tubules if the concentration of salts in the urine is high, i.e., it does not prevent a salt diuresis. This is seen in Case 1 who reported well to administration of 10 gm. Nall and to the ammonium chloride diuretic treatment.

It is found that the anti-diuretic hormone is excreted in part in the urine, but its concentration in the urine does not vary as the concentration in the blood. Case 1 therefore could have had a high blood concentration of A.D. substance, and yet her urine could have the indefinite or negative anti-diuretic effect on the animal as recorded on p. 15.

Headache is another feature common to both cases.

In Case 1 it might have been caused by

a) a space-occupying lesion not visible in X-rays (but no papilloedema)

b) sinusitis of the spheno-ethmoidal sinuses causing deep pain behind the eyes; she did have a long-standing nasal infection with post-nasal discharge;

c) some degree of cerebral oedema, associated with water retention

d) functional disturbance - she was restless, sick and not sleeping.

e) cerebral vascular spasm, due to action of the hypothalamic secretory secretion of post-eminent hormone.
In Case II it may be caused by

a) hypotension - there is a history of the pain being worse in the mornings. This is typical of hypotensive headaches.

b) space-occupying lesion - it is possible that there may be such a lesion in the region of the pituitary, which would give rise to the X-ray findings and yet cause no hormonal abnormalities. But such a lesion would produce more pain with the head down, whereas there is no history of this.

c) migraine - this is commonly associated with the "Cushing" type of syndrome, and the patient did complain of eye symptoms, associated with it.

Purulent Pain

This is probably partly of non-organic origin in Case I, associated with poor posture due to the obesity.

In Case II where there is evidence of head damage, the pain may be partly due to minor coronary infarction or to anginal attacks, since rest relieves it.

The pain which heat and change of posture relieves is probably fibrositis and postural in origin, due to the obesity.

Progress and Prognoses.

The two cases at this point differ enormously; it has been of very great interest to study the reactions of Case I throughout the last 2 years whereas Case II has faded completely out of the picture.

The treatment of cases of obesity of whatever type...
Consists primarily and essentially in a low-calorie diet, and it is here that diligent cooperation and self-discipline on the patient's part is essential. An intelligent grasp of the problem is a great assistance, and it was on this point that the first patient had the advantage over the second, besides being, on the whole, much more eager to be cured.

When the weight-chart curve has achieved a certain drop with diet alone, and is beginning to flatten out, thyroid may be added in doses adapted to the condition of the patient.

If water retention is suspected, diuretics are helpful, as in Case I.

In special cases, e.g., when definite cardiac disease or pain is present, surgery may have its place in therapy of obesity.

In either: in the average obese patient, the keynotes of treatment are diet and thyroid.

Prognosis depends on many factors: the type of obesity, the intelligence and cooperation of the patient, and the presence or absence of associated disease.

In Case I, the prognosis is good; she is now keeping her weight down while slowly increasing her diet, so is feeling well.

Case II is more gloomy; the fact that nothing has been heard of her for a year suggests lack of interest and cooperation. She may feel that the disadvantages of a diet outweigh the advantage of an elegant figure; and mine in any case she will have an easier life than the first patient. She may or may have given up the never-ending struggle with her obesity.
Cases 5 and 6

Disturbances of Circulation
Two cases of Hypotension

The following two cases have provided interesting material for investigation and speculation regarding the behaviour of the arterial blood-pressure and vasomotor mechanisms under various conditions, especially change of posture.

Introduction:

In order fully to understand the problem under investigation it is necessary first to consider the mechanisms underlying the maintenance of normal arterial pressure. Later on, when discussing the abnormalities found in these two patients, we shall be able to refer back to these points.

The average arterial S.P. of a young adult is about 120/80, and the factors which combine to maintain it at this level are as follows:

1. The pump action of the heart: This acts via the amount of blood it can discharge into the aorta per unit of time. When more blood is forced into the already filled arterial system it cannot escape at once from the system in the same amount as that in which it is thrown into the aorta, so the arterial walls become stretched. The pressure rises until the velocity of the flow through the arterioles is great enough to balance again the outflow with the inflow.

2. The peripheral resistance: This function resides in the arterioles and to a less extent in the capillaries. By far the greater part of the peripheral resistance of
the circulatory system is constituted by the arteries of the abdominal viscera - the splanchnic area. Stimulation of the greater splanchnic nerve causes constriction of these vessels and consequently a reduction in outflow from the arterial system. The pressure therefore rises until inflow and outflow are again balanced. Dilatation of these vessels, i.e., reduction in the peripheral resistance will naturally be followed by the opposite effect. When the splanchnic vessels are fully dilated they can accommodate all the blood in the body; in such an event the B.P. would be zero.

The quantity of blood in the arterial system:

In any closed system of rigid tubes fluid must fill it to capacity in order that a pressure can be developed within it. The arterial walls are not rigid but distensible and elastic, and a certain degree of stretching of these vessels occurs before any considerable pressure is created. The arterial system must actually be overfilled, and the greater the extent of this over-filling the greater will be the B.P.

The viscosity of the blood:
The greater the viscosity of a liquid the greater is the pressure required to force it along a length of narrow tube in a given time. The blood owes its viscosity to its colloids (plasma proteins) and its suspended corpuscles. Changes in the concentration of the blood, as a result of changes in the plasma proteins or in the number of corpuscles, will alter the viscosity. The viscosity is also altered by the chemical composition and gas content of the blood, e.g., CO₂ raises the viscosity; Oxygen lowers it. Hyperglycaemia, hypercalcaemia and acidoosis increase the viscosity; increase in temperature lowers it.
Elasticity of the vessel walls:
This is concerned mainly with the origin and maintenance of the diastolic blood pressure, and with sustaining the mean pressure at a higher level than would be possible in a rigid system under otherwise identical conditions. At the usual D.B.P. which exists, the arterial walls are stretched and by virtue of their elasticity tend to recoil against the distending force. In the arteries, the flow is pulsatile; beyond the arterioles, i.e., in the capillaries and veins, the flow is continuous. This change depends on the maintenance of a D.B.P. The elastic recoil of the arterial wall acts in a sense as a subsidiary pump to drive the blood onwards in a continuous stream between heart-beats. Otherwise the pressure would fall to zero after each systole.

Effect of variations in these 5 factors:

a) Change in heart-rate without alteration in any other factor will cause change in the D.B.P. but not much change in S.B.P. The D.B.P. will rise, since the period of diastole in the cardiac cycle is shortened. The fall in pressure during diastole is halted at a higher level by the earlier arrival of the next beat.

b) Change in the amount of blood discharged by the heart per minute, if other factors unaltered, causes a change chiefly in the S.B.P.

c) Change in peripheral resistance, with other factors unaltered, chiefly affects the D.B.P., since the peripheral resistance is so important in the maintenance of the D.B.P.

d) Change in viscosity affects chiefly the D.B.P.

e) Change in blood volume affects S. and D. B.P.

f) Reduction in the elasticity of vessel walls, e.g., in arterio sclerotic lowers the D.B.P.

But there is often an associated narrowing of the
peripheral vessels which more than compensate for the hardening of the walls of the larger arteries.

If the relaxin is confined to the larger arteries, the S.B.P. tends to rise, and the D.B.P. falls.

Now, before describing the cases, let us consider, lastly, the factors causing variations in B.P. under physiological conditions:

These factors are

1. **Age**: B.P. rises as age increases.
2. **Build**: The heavily built person has a higher B.P. than the slender, as a rule.
3. **Digestive**: After a meal the B.P. rises slightly.
4. **Emotion**: This especially affects the Systolic B.P. and the rise is due to
   a) Increased cardiac action;
   b) Change in the vessels through impulses playing on the cardiac and vasomotor centres;
   c) Release of adrenaline.
5. **Exercise**: Causes a rise in both S. and D. B.P. especially in the systolic.

During muscular effort, or even before it, i.e. at the instant the exertion is contemplated, the pressure begins to rise and the systolic reaches 150-200. Diastolic may reach 100-110, thus the pulse pressure is increased.

Immediately after exercise the pressure drops momentarily to normal, or even below. The final normal level is regained in 1-4 minutes.

The momentary drop, some think, is due to a sudden relaxation of the abdominal muscles; the blood is drained into the venous系统, the venae cavae and the abdominal muscles have their capacity increased, and the blood flow back to the
6. **Posture**

The **B.P.** is a little higher in the standing than in the sitting position, and lowest in recumbency. This occurs whether change in posture occurs actively or passively, and is a compensation for the effect of gravity.

The **S.B.P.** usually rises also, but less so than the **diastolic**.

In persons with an abnormally and habitually low **B.P.**, the **systolic** may rise in recumbency and fall on standing; but the **diastolic** is always higher in the erect position.

---

**CASE I**

Miss J.C., aged 32. Knitter in hosiery factory.

Admitted first in 4-2-43.

**Complaints**:

- Cough
- Pain in the chest
- Lassitude and weakness
- Haemoptysis

---

**History of present illness**:

Two months ago the patient had her tonsils removed. Since then she has been weak and tired, and off work. She has had a cough associated with copious yellow sputum, which has been occasionally tinged with blood.

Two days ago she coughed up, during 1 1/2 hours, about
a cupped p. blood.
She has had pain in the left side of the chest; it is worse on coughing and deep breathing. It developed 10 days after the mumps and lasted 3-4 weeks. During this time the patient was feverish.
Her appetite has been poor; she is very complaining. She has no breathlessness but feels choked when coughing. Nothing else to note.

Previous health

Swineflusis 5 years ago
Scarlet fever, measles, mumps as a child.

Family history

Nil to note.

Social

Good. Suitable and pleasant work.

Examination

General: Patient is plump, healthy-looking; skin flushed and moist.
T. 100.8° P. 96 R. 20
Weight correct for her height.

Systemic:

Respiratory system: Dull pulsation deep to L. scapula
Course carotid pulse at L. base.
Slight " R. "

Cardio vascular system:
BP. 110/70. N.A.D.

Alimentary

Nerual"

Uriney"

Hemopoietic
Hb. 90%
RBC. 4.5 million/cu mm.
WBC. 12,000
GSR. 110 mm/hr.

Further examination:
1. Chest X-ray
2. Bronchoscopy
**Diagnosis.**

The sputum was negative for tubercle bacilli. On the basis of clinical findings, history, and X-ray results, a diagnosis was made of lung abscess following smillectomy.

**Treatment & Progress.**

During the first 16 days in hospital, the patient ran an irregular temperature, with tachycardia 100-110/min, and respiration 20-30/min. The cough was very productive and purulent and much sputum which was bloodstained on one or two occasions.

On admission, the B.S.R. was 110 and W.B.C. 12,000.

In the next 10 days, the B.S.R. fell to 33 and W.B.C. rose to 16,000.

X-ray on 18.2.43 showed consolidation of left lower lobe with abscesses. Breathing exercises were started.

On 20.3.43, a lipiodol X-ray showed the bronchi in the left lower lobe to be displaced upward and laterally, and to be crowded together. Following the lipiodol examination, the temperature rose, and the B.S.R. rose to 125.

Blood culture was negative.

Chest aspiration on 25.3.43 produced foul pus—on culture there was growth of anaerobes.

At this time, blood fell to 58%.

The patient was transferred to a surgical ward on 2.4.43. There she had rib resection and drainage carried out.

She was readmitted to the medical ward on 30.4.43.

She improved steadily and on 3.5.43 she was discharged.

On discharge: B.S.R. 5; Hb 90%; W.B.C. 8,500.

4.8.43

Patient reported back to hospital.

The cough had recommenced after 4 weeks at home.

4 weeks ago, she coughed up 3 tablespoonfuls of blood.

She has been putting on weight but has no energy.

X-ray shows some consolidation remaining in mid-zone of left lung.
6.9.43    Patient again reported back.
The cough is still troublesome. Sputum is thick, yellow & foul.
Temperature is 100.4° and pulse is rapid.

10 days ago she had a fainting attack on rising in the morning.
She was readmitted to the ward.

Chest examination: { Coughed breathing in left lower lobe.
                  } Rhonchi over all areas.
Other systems:    N.A.D.

Blood:            { W.B.C. 12,000
                  } B.S.R. 22.

After admission her general condition improved but the
cough was very troublesome.

On 2.10.43 a kistitrodel X-ray showed a good deal of
dammed-up secretion in the left lung.

Potassium coughing was begun, resulting in considerable
elimination in sputum.

During this time in hospital her blood pressure
was consistently low, ranging from 110/80 to 105/70.

When she stood up she habitually felt faint, and
it was decided to investigate the effect of change of
position on the blood pressure, in case possible
hypotension should be the cause of her faintness.

**Blood Pressure Investigations.**

The following tests were done by the writer at the
suggestion of and with the advice of Dr. Gilchrist.
The patient performed all these tests in comparable
conditions; they were almost all done in the ward,
with the bed screened, and between 7 pm and
8:30 pm in the evening.

She was extremely cooperative throughout the whole
time, and reported intelligently on her sensations during
the tests.

In each case the patient was recumbent for some time
before the test started, and then was allowed to get a
reliable base-line of B.P. readings before any
attention was made in the conditions.

A control was made in the person of a healthy
young woman of 25 (medical student). Each of
the tests done on the patient was repeated with the
control in a similar condition as possible.

Graphs of the patient's and control's performance
are attached, labelled P. and C., with the number of the test.

Effect on B.P. of posture change: horizontal to vertical:

a) Patient: Rising to the standing position produced a
fall in both D.B.P. and S.B.P. of 15 mm Hg
and a rise in pulse rate of 25 beats/minute.
The extremities became very cyanosed but no cold.

On repetition of the test 20 minutes later,
the same results were obtained.

The patient experienced no abnormal feelings.

b) Control: Standing up caused a rise in S.B.P. of 30
and in D.B.P. of about 20 mm Hg; also a rise
in pulse rate of about 15/min.

This is the normal type of response to exercise.

Repetition of Test 1 with addition of light
Abdominal Binder and limb bandages:

This was carried out as it was thought that the
cyanosis of extremities might be a sign of venous
stasis elsewhere, especially in the splanchic veins.

Result: no improvement; very similar response
to that in Test 1.

The feet were still blue when patient was
standing up, and became pink on lying down. They
were quite warm throughout test.
Patient felt quite well.
Cyanosis of extremities especially feet.

Masked cyanosis of feet; not cold.

Pulse Rate v. B.P.

Patient lying down

Patient stood up
Standing record

Patient "lay down"
Lying

Patient "stood up"
Standing

Patient "lay down"
Lying
The chart represents a patient's blood pressure (B.P.) and pulse rate changes over time. The patient was lying down. When the patient stood up, their pulse rate increased. During the standing position, there was a slight decrease in B.P. and pulse rate. The patient then lay down, and the B.P. and pulse rate readings returned to the initial levels. Notes include:

- Patient was laughing, pulse rate rose.
- Patient lying down.
- Patient standing.
- Patient stood up.
- Patient lay down.

The chart is labeled with specific points indicating changes in the patient's condition.
Cough very troublesome.

Patient felt slightly dizzy on standing up; not cold. Cough better.

Toes slightly blue.

Toes blue, blanching time 5".

Toes normal, blanching in 3".

Feet warm, pink.

Pulse

P.b.r.

Patient lying down

Application of binder + bandages

Patient stood up

Standing

Patient lay down

Lying

Removal of binder + bandages

NB: Patient felt nothing, coughed less, breath more normal. Patient felt warm, feet pink.
It was now decided to test out the patient's postural B.P. response after administration of a drug of the sympathomimetic type i.e. one which might reasonably be expected to maintain the B.P. level if its previous fall were due to a deficiency in the sympathetic innervation of the vascular mechanism. The drugs chosen were ephedrine, phenoxyline and mephedrine.

3) Effect of Ephedrine on B.P. with change of posture:

a) Patient: In this test, results were not quite satisfactory as owing to circumstances beyond our control there was not sufficient time to get the usual base line before changing the conditions.

Ephedrine gr. ½ was given by mouth.

On standing, the D.B.P. was maintained, and S.B.P. fell 5 mm Hg

pulse rate 40/min (to 132.)

The patient felt cold, but not faint.

After a little exercise (walking about 25 yards) both S. and D.B.P. fell still further and pulse rate again shot up, from 105 to 135.

b) Control: The ephedrine caused very little change in the recumbent B.P.

On rising, the results were similar to the normal, in test (1), except that the pulse rate increased more in this test.
Patient felt heart beating faster.
Pulse irregular in force.
Patient felt cold, but not faint.
Pulse irregular in time and force. Quality of B.P. sounds varied greatly.

↑ Ephedrin q.3
↑ Patient lying down

↓ Standing
↓ After walk to end of work
Repetition of 3 using Phlebitone (20 mgm i.m.)

instead of ephedrine.

[The proprietary preparation used was "Shinabone."]

a) Patient:

The drug achieved its maximum effect on the resting B.P. in 6 minutes.

On change posture, it had no effect in maintaining the B.P. Both systolic and
diastolic fell:

\[
\begin{align*}
\text{S.B.P.} & \quad \text{fell by } 60 \text{ mm Hg} \\
\text{D.B.P.} & \quad 20
\end{align*}
\]

and Pulse rose by 55 beats/min.

On lying down, exactly the reverse happened.

While standing, the patient suffered from a slight
degree of palpitation (pulse was 135) and
felt cold. The feet were purple in colour,
the hands slightly less cyanosed but cold.

b) Control:

Drug achieved maximum effect in 9 minutes.

On rising up, the D.B.P. showed no change

\[
\text{S.B.P.} \quad \text{a gradual decline}
\]

Pulse rose jerkily from 85 to 120.

Lying down caused a sudden drop in pulse rate
from 120 to 65; the B.P. very slowly
attenuated to its original level.

While standing, control felt slightly cold
and looked pale. Her colour improved
as soon as she lay down again.
Pulse Rate + B.P.

BP sounds became louder →

BP sounds very loud: Patient cold + shivery
Feet + hands blue + cold
Slight palpitation: cold →

Feet purple + cold →
BP sounds very loud → "Silent period": 140-110"

Feet pale: hands red →
Coughing + sputum →

No abnormal sensations reported except cold (as)

Standing
Lying down
Standing
Standing
Patient felt slight palpitation.

Patient rather pale; felt cooler, but not shivery or faint.
Pulse had marked sinus arrhythmia.

Patient's colour normal.

Lying down

Standing

Lying down
5) Repetition, using Methadone i.m.

a) Patient: 5 mgm. given intramuscularly.

Drug achieved maximum effect in 15 minutes.

On standing, the B.P. and pulse responses were felt
and not respectively as usual, but to a
much greater extent.

S.B.P. fell from 130 to 90
D.B.P. .. 74 to 55
Pulse .. 180 to 175/min.

The patient felt cold, weak and dizzy.

She was pale and sweating and the pulse
was very strong; in fact, she suffered from
shock and collapse.

On lying down, these symptoms disappeared.

S.B.P. rose from 85 to 152
D.B.P. .. 56 .. 90
Pulse fell .. 168 to 80/min.

Just after the patient lay down she coughed up
about 2 teaspoons of blood. She felt
rather weak, still had palpitations 10 min.
later.

b) Control: 15 mgm. given i.m. (3 times the dose
given to the patient)

The recurrent B.P. and pulse were:

S.B.P. from 102 to 130
D.B.P. .. 60 .. 75
Pulse .. 56 .. 80.

On standing up, the B.P. remained unchanged, but
the pulse rose to 120/min.

Lying down caused no change in B.P. Pulse fell to 55.

Repetition of standing: pulse rose from 64 to 112
Lying: pulse fell .. 108 to 60

again no change in B.P.

Patient felt cold, "gone flabby" and "foggy".
Pulse Rate and B.P.

- Patient felt well except for any irritating cough.
- Coughing a good deal.
- B.P. sounds stronger.
- Patient felt palpitations.
- Patient stood up.
- Pulse felt cold, weak, and rather dizzy. Face pale, hands, and feet cold, and blue; sweating.
- Pulse thread-like.
- Hemoptysis: about 3/8
- HR: 170
- Patient lay down.
- Patient still feeling rather weak and having palpitations.

- Patient lying down.
- Methedrine 0.25 cc. 5 mgm.

- Patient lying down.
Repetition of Test 5 with Methylene blue, doing red cell counts and haematocrit estimation at intervals throughout the test.

This performance was carried through with the co-operation of two colleagues (medical students) one of whom did the red cell counts and the other the venepunctures for the haematocrits.

These 2 estimations were done at the same moment on 4 occasions throughout the test:

i) while patient lay quietly recumbent;
ii) when Methylene blue had achieved its maximum effect on the resting BP;
iii) while the patient was standing up;
iv) after... had lain down again.

[Three red counts were done on each occasion, and the mean taken for reading on the chart]

It will be noted from the record that the response of both systolic and diastolic BP to change of posture is much less abnormal than that resulting from the previous methylene test, 3 weeks previously.

There was, indeed, a gradual decline in both D.B.P. and S.B.P. while the patient remained on her feet, and on when she lay down there was an immediate rise of both.

The patient still felt shaky & cold when she stood up, and much better on lying down. Extremities were blue.

After the methylene injection, both haematocrit and red cell count showed a definite rise.

Haematocrit - red cell layer rose from 41.5% to 44%

R.B.C. count .... 3.9 mill. to 5.3 mill. per c.mm.

These increases are statistically significant.
Patient lying down

Methedrine 14.5mm

stood up.
Felt shaky. Cold sweating.
Hands feel blue.
Shaking stopped.
Lay down.
Feels quite well.

Hematocrit 45

Millions RBC/μL

0 1 2 3 4 5 6 7 8 9 10

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150

90 80 70 60 50 40 30 20 10
By the end of October 1943, when she was discharged, the patient had improved greatly. Her general condition was better, and she felt much less pain on assuming the erect posture. Her resting B.P. was still hypotensive — 110/70.

She has not reported to the ward since then.

[Further details will follow the description of the next case.]

CASE II

Mrs A. M.G. Housewife. Aged 39.

Admitted to ward on 23.8.43.

Complaints:

Pain in the legs 3 years.

History of present illness:

Three years ago the patient began to have pain in her legs. These pains occurred in both hot and cold weather; they are not very severe, and resemble a feeling of "heaviness".

The pain is almost continuous when the weather is cold, and the legs become reddish-purple in colour. The patient has tried to relieve this by bathing the legs in hot water, but is doubtful as to the results.

In hot weather the feet become painful, especially after walking, and the patient finds she can walk further in wet weather since the feet are cooler.

This pain resembles that brought on by cold, and the legs go the same red-purple colour as they are when cold.

In summer the pain is not continuous, and is relieved by resting the feet. Standing still is
not enough; the patient has to sit down before the pain is relieved.

Occasionally the pain comes when the feet are warmed up in bed, but no relief is obtained by getting out on the cold floor.

The hands give trouble only in winter; when cold, they go bluish and are painful. Both hands are affected. The sensation is relieved eventually by heat but this in itself is a painful process.

The patient has never had footbath. She does not date the onset of symptoms from any particular occasion or disease.

She has lost about 2 stone in weight in the last 3 years. Otherwise she has been well.

Her vision is good. She has had a few colds and one throat but has no chest troubles.

Appetite good; occasional flatulence; bowels regular.

No urinary symptoms. Periods regular.

Previous History

She has been subject to chilblains of the hands and feet since childhood. When she was younger the chilblains used to burst, but lately they have not done so.

No history of intermittent claudication, rheumtis, diabetes, pain in chest or any other parallel condition.

She has varicose veins.

Family History

Husband alive now. Miner.

No familial history of varicose disease.

Mother a.p.w. Varicose veins.

Father — age 65

Children — has had 5; 3 died of pneumonia. remaining 2 alive now.
Examination

General: A well-developed, slightly under-nourished woman, rather excitable, in no pain or discomfort. She is ½ stone underweight.

T. 98° P. 70 R. 20.

Systematic:

I. Cardio-vascular system:

Arteries : Pulse 70/min. regular; volume good; well no palpable; 130/120.

Heart : Apex-beat in 5th space inside mid-clavicular line. Sounds, pure & closed in all areas.

Examination - vasomotor phenomena.

Hearse : N.A.D.

Feet : A. dorsalis pedis difficult to feel but present on both sides.

Colour reddish-purple over toes and for 1" up the foot.

Feet are cold even after being in bed for some time.


Respiratory System : N.A.D.

Alimentary : " "

Urinary : ... Blood Urea Nit. 13 mg %.

Nervous : " "

Reflexes all brisk and equal.

Haemorrhagic :

R.B.C. 4.6 million
Hb. 80 %
W.R. 6,400
W.R. negative

Semen Calcium 7.6 mg %
Further Investigations:

1. 25.8.43  
   X Ray showed bilateral cervical ribs.

2. 27.8.43  
   Temperature Test:
   Right leg was kept outside bedclothes for 1 hour. This caused slight cyanosis in the left leg.

3. 28.8.43  
   Gravity Test:
   a) Measurements: circumference of right knee 12 3/4", ankle 8 1/2".
   b) Right leg was kept dependent for 1 hour.
   c) Subsequent measurements: right knee 12 1/2", ankle 8 1/2".

   There was no oedema.

4. 29.8.43  
   Blushing and Cold Press Tests
   BP at start of test: 110/66.
   The right hand was placed in ice-water:
   at start of test 6th fingers were normal, rest blue-red.
   After 24 minutes the feet were almost normal and no definite Raynaud phenomenon was noted.
   After 1 hour the right hand was red,
   " left " unsupported.
   BP at end of test: 140/98.

   There was thus a marked praeor effect from the minutes of the ice-water, but no definite Raynaud manifestations.

   Blushing times were measured on the left 2nd toe: results are seen on the chart.
   Pressure is made for a standard length of time, and the length 1 mm taken for the colour to return to the blanched area was measured.

5. 5.10.43  
   Serum Calcium 9.3 mg%.
   [ Cf. pre-operative level 7.6... ]
Blanching time

- R. hand in ice water
  - Both hands normal
  - Feet bluish-red

- Feet almost normal
- Great toes - red, blue patches
- No definite Raynaud phenomenon

- 2nd toe the most blue of L. foot
- 2nd toe is blue
- R.

- R. hand red - not blue
- L. " unaffected

- 8/21 10/66
- 14/07/48
**DIAGNOSIS.**

A diagnosis was made of Acrogeria, with
Raynaud's phenomena in addition.

[ Differential diagnosis appears later in the discussion ]

**TREATMENT and PROGRESS.**

The patient was referred to a surgical ward for
operative treatment.

6.9.43  Operation Notes  Prof. Leamnuth

[ Spinal Anaesthesia ]

a) The patient was placed in the left side with kidney rest
in position. A hockey-stick-shaped incision was
made, extending from the 11th rib downwards and
forward towards the anterior superior spine. The
free edge of external oblique was retracted forward, and
iliacus, ilio-scarci, backwards. A self-retaining
retractor was inserted and the 12th rib removed.

The sympathetic chain was then exposed. The
greater and lesser splanchnic nerves were divided and
amputated. The lumbar chain was isolated and
removed down to below the 3rd lumbar ganglion.

The wound was closed.

Summary: right lumbar sympathetic + splanchnicotomy.

b) 20.9.43 The same operation done on the left side.

Summary: left lumbar sympathetic + splanchnicotomy.

The patient made an excellent recovery and was
re-admitted to the medical ward on 1.10.43.
Blood Pressure Investigations

This patient, like our first, had always had a low pressure, averaging \( \frac{110}{60} \). There was no difference between the pre- and post-operative average B.P.'s.

As this patient had had a bilateral sympathectomy and resection of the splanchic nerves, it was decided to carry out with her some of the tests done on Case 1, to see the effect of abolition of the vas-constrictor impulses to the lower limbs and abdominal vessels.

**Effect of Position change - horizontal to vertical:**

On rising to her feet, this patient showed a B.P. and pulse change almost identical with that of Case 1:

- S.B.P. fell, from 160 to 78
- D.B.P. " " 75 " 62
- Pulse " " 68 " 120

And all these happenings were immediately reversed when the patient lay down.

The feet and legs were flushed and warm.

The patient experienced no abnormal sensations.

**Test (a) repeated, with Ephedrine \( \frac{1}{2} \) only:**

The drug prevented any D.B.P. fall, and the Systolic B.P. fell only 8 mm and very gradually.

The pulse rate rose from 85 to 132/min.

On lying down the pulse fell immediately to 75/min but the B.P. again, was not much altered.

No abnormal symptoms were experienced, unless later on at night when the patient complained of sleeplessness, palpitation,
B.P. & Pulse rate

10-10-43

No dizziness experienced.

Feet, toes, and outer aspect of leg very pink and warm.

Patient lying down

Stood up

Lay down

Sister & Doctor passed around ward.

Patient speaking emotionally about home.

Posture - Change effect on B.P.

Note: Patient does not appear to be experiencing any discomposure or discomfort.
Patient lying down

Ephedrin gr 2 orally

Nurse came with medicine & patient talked & laughed

Feet pink but less so than with no drug

Felt heart going a little faster

Did not feel heart

Stood up

Lay down

Patient, just before coming to

Patient felt perfectly well throughout

Patient slept quietly several hours

Patient felt perfectly well, without anything

Patient slept without disturbance for about 2 hours, kept her own

Patient slept perfectly well next night.
Patient felt nil abnormal

Pulse irregular in force
Face flushed

Face flushed

Patient feels well.

Patient felt quite well throughout last few days.

No Nausea.
Test repeated, using Pholadine 20 mgm i.m.

The result of this test was a response very similar to that of the first patient:

The drug has its maximum effect in 12 minutes.

When the patient then stood up:

S.B.P. fell from 170 to 88 (over 15 minutes)
D.B.P. 
Pulse rate

There were no unpleasant sensations.

On lying down there was an immediate change:

S.B.P. rose from 90 to 140
D.B.P. 
Pulse fell

All these had regained the resting level in 30 minutes.

Unfortunately, there was no opportunity to use methadine on this patient before she went home.

She derived great benefit from her operation; the pain in legs and feet had disappeared before she was discharged, and she experienced no faintness on changing from the horizontal to the vertical position. The feet are now always warm and pink.

She has not reported to hospital since her discharge home on 13.10.43.

Discussion of both cases:

Both cases described above showed the condition known as hypotension i.e. they had arterial blood pressure (systolic) consistently at or about 110 mm Hg.

Case I showed hypotension throughout the entire time that she was under observation, although it was only
during the last 3 months that she experienced
symptoms caused by it.

Case II showed hypotension both pre- and post-operatively
and had no symptoms at all.

Hypotension is of various types:

1. It may occur without any cause discoverable—i.e., primary
   hypotension.

2. It may occur as a temporary or persistent phenomenon in
   many conditions, e.g., hemorrhage, shock, anesthesia,
   peritonitis, or any long-continued debilitating illness.

   It may also occur as a result of vascular dilatation in
   acute fever; from myocardial failure; in certain
   disorders such as myxodema and Addison's disease.

3. Orthostatic hypotension is an unusual condition in which
   the reflex mechanism, normally operating to maintain
   the B.P. against the effect of gravity, are apparently
   in abeyance, or their sensitivity greatly depressed.

   In this condition the following phenomena occur:
   a) A profound fall in B.P. occurs when the patient stands,
      e.g., to 40/0. The patient feels dizzy and may
      faint.
   b) There is absence of sweating
   c) " " a failure of the pulse rate to rise
   d) " " pallor of the skin

   These phenomena all suggest a fundamental abnormality
   in the sympathetic nervous system, and sympatheo-
   minetic drugs usually relieve the condition.

Case I showed the B.P. fall, but none of the other signs
of a faulty S.V.S. mechanism, and the more powerful
sympathetic-minetic drugs caused less immediate
than relief, owing to the exaggerated pulse rate
they produced.

Her hypotension is probably type 2, as we shall
see later, and not a true orthostatic hypotension.
The cyanosis of the extremities, which was observed while the patient stood up, suggests venous strain; this in all probability was not confined to the limbs but involved also the splanchic veins, causing a massive stagnation—pooling of blood with a consequent diminished return to the heart.

The fact that the abdominal binder and bandage did not produce any marked improvement is probably not significant; it was difficult to get them fixed on really tightly, single-handed.

The results with phentolamine—shivering, preternatural cyanosis—suggest that the fault here is that the drug exaggerated a normal sympathetic rise in pulse rate but failed to compensate for a deficiency in the venous return. It caused a certain amount of constriction to the arterioles, causing coldness, but did not act on the veins.

Methadone had a minor effect. The last test with methadone, giving results of increased red cell count and haemoglobin readings, suggests that methadone may act partly by increasing the blood volume (which in turn is a factor in raising the blood pressure, as we have seen), the increase being in cells as opposed to plasma.

For this last test to be satisfactory, there should have been 3 others to supplement it:

1) The same test done without change of posture
2) The test done on a normal catherized with posture change
3) Without

All these tests, however, seem to indicate that the most likely cause for the patient's symptoms is a poor venous return to the heart, which in turn will cause poor cardiac output and consequent cerebral anemia. The patient herself has noticed that she feels better if
she wears a tight corset; this would to some extent prevent splanchine and venous stasis.

The next question is - what is the physiology of this venous stasis?

The factors influencing venous blood flow are:

1. Contraction of the left ventricle, i.e., the "left urge". This drives the blood through the arteries and veins and back to the right atrium. By the time it reaches the right atrium, the energy has been almost entirely dissipated in overcoming the frictional resistance offered by the vascular channel.

2. Quantity of blood flowing through the arteries in relation to the capacity of the capillaries and veins. Generally, the more blood received from the arterial side, the greater will the capillary and venous pressure be.

But it is to be noted that the veins and capillaries are under nervous control, and the capacities of these vascular regions are therefore capable of adjustment to the amount of blood received from the arterial system.

3. The sub-atmospheric pressure in the thorax. This expansile, the thin-walled intrathoracic veins, and the venous blood is sucked into the thorax. A similar effect but of less degree is exerted on the walls of the arteries.

Also, the descent of the diaphragm during inspiration compresses the abdominal contents, increases pressure in the inferior vena cava, and thus augments the flow of blood towards the heart.

4. Action of the right side of the heart: if the blood is not pumped on by the right side of the heart as fast as it is carried in, there will be a damming-back-up of blood, with subsequent back-pressure.

5. Muscular effect of the muscles: the intermittent pressure which is brought to bear on a column of blood by the contraction of the limb muscles aids in propelling the blood along the veins. The valves in the veins direct the blood towards the heart, and the muscles
in fact act on the veins as the heart acts on the arterial system, i.e., as a pump.
During exercise, much more blood enters the venous side but is usually compensated for by the increased muscle effect of the respiratory movements. Most of the abdominal wall also contracts during exercise to lend support to the abdominal veins and prevent over-distension.

Gravity: the hydrostatic factor, or weight of the blood column, comes into play when the erect posture is assumed.

[above the heart level, this factor helps veins, hinder arteries];
[below " arteries, " veins.]

It is through the venous system that the effects of gravity on the circulation are more prominently displayed. This is because of the lower venous pressure, greater distensibility of venous walls, and the fact that the height of the blood column which must be raised against gravity is much greater (from feet to heart) than that of the arterial blood column (heart to brain).

In man, the mechanisms for counteracting the effect of gravity on the venous system are very efficient and include:
factors which help to do so are (mostly already mentioned)
a) impulses of left ventricle;
b) abdominal and limb muscles, replaced if necessary by binder and bandage;
c) respiratory muscles and pump;
d) veno-pressor and capillary tone mechanisms.

If any or several of these fail, venous stasis in the dependent parts will occur, as for example in a patient long bed-ridden, with poor muscles, and the tone of the venous mechanism lowered.

Even a healthy person will faint if kept standing immobile for long, owing to the lack of messaging
achin in the veins of the lower limbs.

In the case of our 1st patient there is no cardiac weakness but probably a considerable amount of muscle weakness owing to her long stay in bed. [There may also be in her case, a deficient thoracic muscle and pump action since one lung has been damaged and one side of the chest does not expand well. But this is of much less importance than the other cause.]

The fact that during the last B.P. test the response to standing was much better than the same test 3 weeks before (during which time she had been up and about) lends support to this theory.

There is every probability that this patient, as she gets about and her general health improves, will have fewer and fewer symptoms - low pressure. Should these still be troublesome, our investigations showed that ephedrine was the drug I most benefit to the blood pressure, without producing the excessive toxicity of the other drugs; this may be used really in half a grain dose, or at the particular time required, remembering that it takes about half an hour to achieve its maximum effect on the B.P.

In the second patient, the effect I change of position on the B.P. is probably partly due to the relaxing of the lumbar sympathetic chain, and the splanchnic nerves. We regret not having had an opportunity to do a postural test before the operation. This operation is said to double the blood flow in the vessels of the denuded area; the venous capacity must therefore be considerable.

In this patient the question of venous strain did not arise, as the extremities were pink and warm throughout all the tests.
The important in Case II was, however, not the hypotension, but the vaso-motor disturbance.

The vaso-motor mechanism is as follows:

a) The muscle in the wall of a blood vessel has a double nerve-supply, vaso-constrictor and vaso-dilator fibres.

b) The vaso-motor centres which send out constrictor and dilator impulses are situated in the floor of the 4th ventricle, and the constrictor centre is connected also with reticular centres in the spinal cord.

c) The highest vaso-motor centres are in the hypothalamus and central areas.

Vaso-motor tone and its regulation: that is, as has already been stated, a high degree of vaso-constrictor tone, since section of the splanchnic nerves causes doubling of the flow in the abdominal and lower limbs vessels.

Vaso-motor tone is dependent on:

a) afferent nervous impulses, received from various organs and regions of the body by the vaso-motor centres, as well as impulses from other nervous centres;

b) the chemical composition of the blood.

Vaso motor Reflexes.

The components of the reflex are:

1. afferent fibres in a peripheral nerve
2. vaso-motor centres
3. afferent vascular nerves, constrictor or dilator.

In man, peripheral nerve stimulation can readily elicit pressor and depressor reflexes. Warmth to the feet causes vaso-dilatation in remote parts. But if the temperature is applied to the extent to which it becomes painful, vaso-constrictor results.

Stimulation with cold usually causes vaso-constrictor; this is exemplified on p. 17 when it was noted that
this patient's blood pressure rose from 119/66 to 140/98 after immersion of one hand in cold water.

Vasodilatation in the extremity resulting from the immersion of another in warm water is not due to the stimulation of afferent nerve endings in the heated limb, but to the warmed blood acting on the vasomotor centre.

Response to cold is due partly to this mechanism and partly to afferent nerve impulses.

Excitation of psychic centres and the liberation of adrenaline are additional factors which play an important part in the press response resulting from painful stimuli. In example, in this patient's case, the rise in BP could not be totally accounted for by peripheral dilation: atheriosclerotic: in that case, the hands, feet would have been pale; there was, in all probability, a generalised splanchic vasoconstriction due to adrenaline release.

So far, then, we have determined that in Case II we see manifestations of a hypersensitive vasomotor reflex with respect to cold. This finding suggests a possible differential diagnosis between Raynaud's disease and Acrocyanosis.

In Raynaud's disease the fingers, toes and ears are the seat of periodic attacks of vasomotor spasm, induced by exposure to cold, usually symmetrical. The affected part becomes blue + cold, later pale + numb, the colour change beginning at the tips and spreading proximally. As the attack passes off, the part again becomes cyanotic, then red + hot, the numbness being replaced by a burning pain.

Lewis suggests that the spasm involves the digital arteries, and that the fault lies in the vessel wall;
the other view is that it is due to a vasomotoric hyperactivity and it is certainly a fact that section of the sympathetic chain relieves symptoms.

In acrocyanosis the hands, and less commonly the feet, are persistently cold, blue and sweaty. Exposure to cold intensifies the cyanosis but there is usually no pain.

In the hands, the cyanosis begins about wrist-level and deepens as it is traced towards the fingers.

The milder forms of this disease are closely allied to chilblains, according to Lewis.

The disorder is due to increased tone of the cutaneous arterioles resulting from hyperactivity to cold. The cutaneous circulation is slowed as a result of arteriole constriction; the partial asphyxia causes capillary dilatation and an increase in the quantity of blood in the skin. The slower blood flow, by allowing the haemoglobin to give up a greater part of its oxygen store, is responsible for the cyanosis; the depth or intensity of the colour depends on the fullness of the vessels.

The sluggish blood flow, along with capillary dilatation, may also render the capillary walls anaemic and more permeable, thus causing some degree of oedema in dependent parts.

In this patient's case, cold stimuli "produces in the hand, blueness and pain" according to the history. But this was not seen in the ice-water test, therefore she cannot be classed as a typical Raynaud's disease.

The fact of the occurrence of the present condition with childhood chilblains, suggests a congenital acrocyanosis.

But it must not be forgotten that the patient has bilateral cervical rise, which may affect the circulation to a greater or less extent.
In cervical rils, the subclavian atery tends to be compressed between the bone and the subclavian atery, with consequent reduction in the volume of the pulse. But the peripheral vascular disturbance, as due, it is thought, mainly to the pressure of the extra ribs upon the vasa communis fibro in the lower trunk of the brachial plexus.

In this case there were none of the clinical features suggestive of cervical rils — wasting, paralysis, etc., and the rils presumably played only a minor part, if any, in the existing vascular disturbance.

Another point to be noted in this patient's history is the fact that in warm weather the legs felt "heavy," burning, and were reddish-purple in colour, all of which phenomena were relieved by rest.

This suggests the condition known as erythromelalgia, a state of affairs possibly due to excess vaso-dilatation, or excessive response to the vaso-dilator centre to warmth.

Lewis suggests that the condition is a hyperexcitability of cutaneous pain fibres to heat or tension.

The pain which the patient has occasionally experienced in the feet and legs after getting warmed up in bed suggests the type met with in Obiterative vascular disease, due to the fact that the peripheral vessels cannot follow the general vaso-dilatation.

This patient, then, presents a multiplicity of vascular symptoms, suggesting numerous diagnoses. The general impression obtained after considering the whole clinical picture was that there was hyperactivity or vaso-constriction, and that she would probably benefit from sympatheticom. As we have seen, this prognosis was true.
It cannot be promised that the relief from symptoms will be permanent; after lumbar sympathectomy it is said that the increase in the blood flow through the femoral artery lasts several months, but this will vary with the individual.

One last point of interest in this case is the difference between the pre- and post-operative levels in the serum calcium:

- Pre-operative: 7.6 mg/dL
- Post: 9.3 mg/dL

This has been noticed in such cases, but no explanation has been found to account for it.

These two foregoing cases, though admitted to hospital and treated for very different complaints, have both provided a stimulus to the investigation and study of some aspects of the mechanisms underlying blood circulation; it is for that reason that they have been presented together.