Entry for the Wightman Prize in Clinical Medicine. 1936

Submitted by R. J. Dawson.

Wards 25 v 26 - 8th Course
A Report and Commentary on Six Cases showing Achlorhydria.
Case 1. Chronic Gastritis.

Mrs. Jessie Oliver, Aet. 42.
6 Lily Terrace.
Edinburgh.

Admitted: 30. 6. 35. to W. 25, R. 9. 8.
Discharged: 21. 6. 35

Complaint: - Pain in epigastrium.

Duration: 3 months.

History: Previously to six months ago patient had felt perfectly fit, and had been on a normal diet. Six months ago, however, she commenced to have frequent attacks of pronounced nausea, unaccompanied by vomiting or pain, and coming on very shortly after taking a meal. About three months ago, in addition to these symptoms she began to have intermittent attacks of pain, confined to the epigastrium, coming on about 1/2 hrs. after a meal, and partially relieved by taking baking soda or magnesia.

Constipation has been a constant feature: but there is no history of melena.

Patient has been losing some weight, and attributes it to the light milk diet which her doctor prescribed. She suffers from some flatulence and anorexia.

Previous Illnesses:

Sciatica - three attacks.

Hemorrhoids, which are still present.

20 years ago she was in W. 27 complaining of similar symptoms: she was in for 5 weeks and discharged as cured.
9 years ago she had another attack which was also cured.

Family History:
Nothing significant elicited.

Examination:
Patient is rather small, slender, and thin in build. Height 5ft. Weight 9st. 12lbs. She shows no evidence of marked cachexia or anaemia.

Alimentary System:
Patient is edentulous. Tongue is heavily coated. Abdomen is flat, with rather loose skin and little subcutaneous fat, and it moves freely. There is slight deep tenderness in the epigastrium, rather to the left of the mid-line, but no hyperaesthesia was elicited, nor was there anything abnormal palpable. The liver and spleen were not enlarged.

Functional Test Meal - low total acidity and low hydrochloric. No nucleus, except in fasting juice, which also contained lactic acid.

X-Ray (GA series) showed no evidence of a lesion in the stomach or duodenum.

Circulatory System:
Pulse is regular in time and force and of good amplitude. Rate 60/min. B.P. 140/80. The vessel wall is thickened and somewhat tortuous. There are no abnormal extracardiac pulsations to be seen. Apex beat is localised and situated in the 5th intercostal space 3½ ins. from the midline. The cardiac borders are not displaced. Heart sounds are in all respects normal.
Hemopoietic System:

R.B.C. 4,610,000 / c.mm. Hb. 89%. C.I. 0.94.
W.B.C. 7,400 / c.mm.
Blood film showed no abnormalities.

Nervous System:

d. Intelligence average.
e. Motor functions unimpaired.
f. Cranial nerves normal.
g. Deep reflexes present and equal on each side.
h. Abdominal reflexes present. Plantar reflex gave flexor response on both sides.
i. Sensory functions unimpaired.

Locomotor System:

Muscular power is good. There are no evidence of sciatica at present.

Respiratory System:

No abnormalities found.

Urinary System:

No abnormalities found.

Diagnosis:

A history of dyspepsia in conjunction with the finding of achlorhydria is most commonly due to Gastric carcinoma or chronic gastritis, so long as it can be shown that the gastric symptoms are not secondary to disease elsewhere in the body. There was found, in this case, nothing to suggest these latter causes, and the diagnosis rested, therefore, between the two conditions mentioned. The long history of previous and similar gastric upset, the
Comparatively slight losses of weight and appetite, the negative X-ray examination, and, above all, the patient’s improvement as regards symptoms and gain in weight, as a result of treatment, were all in favour of a diagnosis of chronic Gastritis.

Treatment:

- Acid hydrochloride, dil. n. 88, t. i. d. with meals.
- Laxine 3 1/2, between meals.
- Lipo-diet. (3rd week).

Progress:

Except for some occasional nausea patient felt much improved as a result of treatment and her symptoms disappeared. She was discharged on 21.6.35, having gained 24 lb. in weight during her three weeks in hospital.

Prognosis:

See the discussion of this case.
Case 2  Primary microcytic Anaemia.

Effie STEWART  39.
Station Road
Armchair.  Occupation - Housemaid.

Admitted: 30. 11. 35. to W. 25. H. E.
Discharged: 2. 1. 36.

Complaint: General weakness and lassitude, with vague muscular pains.

Duration: Three years.

History: About three years ago patient began to notice a feeling of undue fatigue at the end of a day's work, although her work was not sufficiently heavy to warrant such a condition. This feeling grew increasingly worse, until she was forced to give up her work two years ago and has since led a very inactive life. About 2 years ago also her friends remarked on her increasing paleness. On her doctor's advice she had her teeth extracted because of dental caries, but she noticed no subsequent improvement in her general condition.

The feeling of lassitude still persists. Her ankles are occasionally swollen towards the evening, but this disappears on resting. Lately she has had some dysphagia, especially for solid foods.

Previous Illnesses:
Measles - aged 6 years.
Mumps - aged 10 years.
Slight rickets during childhood.
Gastro-enteritis for 2 weeks, the result of eating "mushrooms", aged 20 years.
Habits:

Her diet appears to have been ample and fairly well-balanced, both at home and at work. She has always lived and worked in healthy surroundings.

She has never indulged in any sort of narcotics.

Family History:

Nothing significant elicited.

Examination:

Patient is a pale, anaemic young woman, with poor bodily development, and having a rather depressed expression.

Height 5'3". Weight 6st. 7lbs.

Her muscular power is poor, and bilateral genu valgum is present, the result of rickets in childhood. She has koilonychia.

Lymph glands are not enlarged anywhere.

Haemopoietic System:

R. B. C. 3,240,000 / c.mm. Hb. 28%. C. I. 0.42.

W. B. C. 3,200 / c.mm.

A blood film showed marked hypochromasia, with some punctate basophilic and anisocytosis, the majority of the cells being microcytes with a few macrocytes. No immature red cells were seen. A differential white blood count showed no abnormalities.

Cardiovascular System:

The pulse is regular in time and force, shows slight tachycardia (90/min.) and the wave is normal. The artery wall is not palpable. S. P. 122/76.
Heart: Apex beat is not visible. There is some weak pulsation in the suprasternal fossa, and Jugular venous pulsation is present. By palpation the apex was found to be in the 5th left intercostal space, 3 ins. from the midline, and it was diffuse and rather feeble. The borders of the heart were not displaced, except the right one which was ½ ins. lateral to the right border of the sternum. On auscultation a soft, blowing, systolic murmur was heard in all areas, loudest in the pulmonary area where the 2nd sound was accentuated.

Alimentary System:-

The tongue is glazed and rather atrophic in appearance. Teeth are all artificial. The absence was of normal shape and moved freely on respiration. No pain or tenderness was elicited anywhere.

The spleen was not enlarged.

Liver - upper border 1½ space, lower border 4½ space in right mid-axillary.
Fractional list meal showed complete achylia.

Menstrual History:

Periods regular, lasting 7 days, with no accompanying pain or sickness. They are normal in quantity, though poor in colour.

Nervous System:-

a). Cerebral and mental functions normal.

b). Cranial nerves normal.

c). Motor functions normal.

d). Deep reflexes present, with exaggeration of the knee jerks.


g). Sensory functions normal.
Respiratory System:
Some suggestion of a bilateral Harrisson's Dulus being present. Otherwise, no abnormalities found.

Cardiovascular System:
No abnormalities found.

Diagnosis:
The failure to find any clinical signs of chronic haemorrhage, tuberculosis, a latent malignant growth, or any similar chronic condition, made it unlikely that the condition was one of secondary anaemia: the rarity of tuberculosis, and the absence of the typical skin colouration, excluded such a condition: and the absence of splenic enlargement, coupled with the response to the therapeutic administration of iron, made a diagnosis of Splenic Anaemia unlikely.
The condition was therefore considered to be one of Primary microcytic Achromytic Anaemia.

Treatment:
Rest in bed. Light varied diet.

Lecium Sulphate tabulo t. b.i.d.
Mannite. Campobol. 5 cc. i.m.i. twice weekly.

Progress:
The patient improved considerably under treatment. The blood count rose from R.B.C. 3,240,000/c.mm., Hb 28%, C.I. 0.42, to R.B.C. 4,1440,000/c.mm., Hb 41%, C.I. 0.46.

Since she was looking and feeling very much better, and was well able to continue the treatment as an outpatient, she was
discharged, though only partially cured. She was given the necessary instructions for continuing the treatment at home, and was told to report for a further blast count in two months' time—when she has not done.
Case 3  

Pernicious Anaemia.

Jan MARSHALL.  
23 Albert Street  
Leith.  
Occupation - Typist.

Admitted: 24. V. 35 to W. 25, R. I. C.  
Discharged: 4. VIII. 35.

Complaint: - General weakness and pallor.

Duration: - Two months. Patient has had to discontinuе her work during the last 3 weeks.

History: - Six months ago patient had an attack of acute diarrhoea which confined her to bed for about four weeks. From this she made a quick and fairly satisfactory recovery, being left with some residual anaemia, and she returned to her work. About two months ago she was noticed to be paler than normal, and began to be troubled with constant lassitude and weakness. These latter symptoms progressing until, three weeks ago, she was forced to stop her work as a typist (hours 8 a.m. - 6 p.m.).

Patient feels weak and anorexic, she has breathlessness and palpitation on exertion, and her ankles are occasionally swollen towards the end of a day.

Her appetite is fair, and she has no digestive symptoms. There is no history of purpьric spots on the skin, of epistaxis, or of melana. Menstruation commenced 6 months ago; she has 3 normal periods, and for the
last 3 months there has been amenorrhoea.

Previous Health:—Nothing other than the usual slight ailments of childhood. She has only had one attack of rhinitis; no previous sore throats or growing pains.

Habits:—The appetite is quite good, and she takes a well-balanced mixed diet.

Surroundings:—Satisfactory, both at home and at work.

Examination:
Patient is a small though well-built girl, who looks only about 15 years old instead of her actual 19. Lips and conjunctivae are very pale, but there is a well-marked malar flush. She is bright and of average intelligence.

Haemopoietic System.

<table>
<thead>
<tr>
<th>Blood count</th>
<th>W.B.C.</th>
<th>R.B.C.</th>
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<tr>
<td></td>
<td>4,000/</td>
<td>960,000/</td>
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<td>4.6</td>
<td>28%</td>
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<td></td>
<td>C.I.</td>
<td>1.3</td>
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A blood film showed hyperchromasia, marked poikilocytosis, and many megalocytes. Megaloblasts were very scanty, and no normoblasts were seen.

Fragility test—no increased fragility.
Van den Bergh reaction—Positive delayed indirect.
Price Jones curve—see graph on opposite page.

Circulatory System.

Pulse rapid (120/min.), regular, not firm and force, and poorly sustained. B.P. 120/70.
There was visible fluid in the suprasternal area and over the jugular veins.

Apox. beat in the 5th intercostal space, 4 ins. from the mid-line, localized and rather weak.
The left border was displaced slightly outwards, and the right border was 1/2 ins. from the mid-line.
There was a soft blowing systolic murmur in all areas, and the 2nd sound in the pulmonary area was accentuated.

Alimentary System:

Tongue was glossy and atrophic, but there were no foetions in it. Taste good.
Abdomen was flat and muscular, and moved freely on inspiration. No pain or tenderness was found. The liver and spleen were not enlarged.
Stools: Benedict's test negative.
Tracelnic test meal showed complete achlorhydria.

Nervous System:

Omarhal Nerves - no abnormalities detected.
Table was no history of tingling in the limbs, of muscular weakness, or of changes in the gait.
Sense of position, and muscular coördination, good.
No sensory impairment for heat, cold, pain, or touch.
Slight impairment of vibration sense over the right ulna.

Sleep reflexes present but sluggish.
Plantar reflex - flexor response on both sides.

Urinary System:

No abnormalities found, except that urine contains leukocytosis (Leukocytosis's list).

Respiratory System:

No abnormalities found.
Diagnosis:

In this country the most common high column index anaemia associated with megaloblastosis is Pernicious Anaemia, but in this particular case it was decided, in view of the patient's age, that such a diagnosis should be firmly established having especial regard for the possibility of the condition being an aplastic anaemia. With this in view, there are two tests which assume great importance — the Price-Jones curve, and the response to liver therapy.

The Price-Jones curve has suffered severe criticism on the score that its margin of experimental error is too large to allow of its being of any real value. Briefly, these sources of error are:

1. Variations in fixing and staining methods, which affect the size of the erythrocytes.
2. The source of light.
3. The properties of the substage condenser.
4. The quality, and especially the aperture, of the objective.
5. The fineness of the observer's pencil point.
6. The thickness of the graduations of the micrometer.
7. The boredom and personal equation of the observer.

Thus it really seems to consist of two superimposed curves — that of the actual diameter and that of the normal curve of error.

In this case, however, all three curves were done by myself (i.e. one observer), using in each case the same instruments, technique, and standards, and no attempt was made to find the actual true size of the erythrocytes, since it was found that such an attempt
would involve a considerable increase in the experimental error present. The curves were therefore constructed using quite arbitrary units, and are thus comparable with each other, although not with any other curve.

This being accepted, it will be seen that the curve shows two features — anisocytosis and megalocytosis — to a degree which is uncommon in an aplastic anaemia, and this, in conjunction with the finding of marked perikilocytosis and a few megaloblasts in the blood film, makes the latter diagnosis unlikely.

In addition, the response to liver therapy is characteristic of Pernicious Anaemia, and although it could occur to a lesser extent in a commencing aplastic anaemia, it would hardly be maintained, as this one has, for almost a year.

The anaemias following EITHER or Bothicophalus infection simulate Pernicious Anaemia very closely, being also due to deficiency of the haemopoietic factor, but they are very uncommon in this country and still more so in people such as the patient who have never been abroad.

**Treatment.**

*vide Graph II.*

25. 3. 35 — 1. 6. 35. 5 c.c. Permanon daily by i. v. i.

The immediate reactions of hypotension and partial syncope were fairly severe on giving the first three injections.

15. 6. 35 — 15. 6. 35. 4 c.c. Camporolin bi-weekly by i. m. i.

15. 6. 35 — 29. 6. 35. 2 c.c. Camporolin weekly by i. m. i.

19. 6. 35 — 29. 6. 35. Mist: Sami. et Ammon. 6 h. 3 30. e.i.d.
Progress:

For blood changes, vide Graph II.

The pulse rate dropped from 120/min. to 70/min. during the first seven days, and thereafter remained fairly steady about the latter level.

On discharge the cardiac murmurs had disappeared with the exception of a faint systolic one in the pulmonary area.

2.9.35. R.B.C. 4,620,000/c.mm. Hb. 98%. C.I. 0.05.
Fractional last meal — Complete achlorhydria.

Given ophthal, to take 6 capsules daily.

2.9.35. R.B.C. 4,550,000/c.mm. Hb. 96%. C.I. 0.94.
2.12.35. R.B.C. 4,150,000/c.mm. Hb. 95%. C.I. 0.91.
3.2.36. R.B.C. 5,200,000/c.mm. Hb. 90%. C.I. 0.84.
Mrs. Roseann Kidd. alt. 56.
Falkirk Road.
Livingston. Housewife.

Admitted: 21. 9. 34. to W. 25. B.P.

complaint: Weakness and a feeling of pins and needles in arms and legs.

Duration: Five months.

History: Patient's manner is dissociated from her surroundings, she is nervous and agitated, and she cannot give a satisfactory account of her illness. Apparently she has been in a poor state of health for many months, and has worried excessively over domestic troubles. Five months ago she first noticed the weakness and the feeling of pins and needles in her limbs, and these symptoms, especially the weakness, have got progressively worse. She has lost some weight and she feels generally tired and listless.

Previous Illnesses: She has had influenza many times. Menopause is now established, but she is uncertain as to when that occurred.

Family and Social History.
Three children: two alive and well: one died from scarlet fever aged 15.

Husband died four years ago - cause unknown. Her household is hard, and her surroundings unsatisfactory. She neither smokes nor takes alcohol.
Examination.

Patient is a stout, pale, unhealthy looking woman, with a depressed outlook. Her attitude to others is apparently quite sane, and she has no delusions or hallucinations.

Nervous System.

Mental state - already referred to.
Sensory Nerves - no abnormalities detected.
Motor functions - slight but generalized weakness in arms and legs. All movements carries out. No incoordination present.
Sensory functions - Sense of touch, heat and cold present in both arms and legs. Vibration sense, and sense of position unimpaired, more especially the former.
Deep Reflexes - are all exaggerated in arms and legs, but no clonus is present.
Superficial Reflexes - Abdominal reflexes absent. Plantar reflex gave extensor response on both sides.
Organic reflexes present.
Wassermann Tachy (blood) - negative.

Haemopoietic System.

R.H.C. 3, 240,000 /c.mm. Hb. 82%. C.I. 1.3.
W.B.C. 8, 100 /c.mm.

Lumbar showed hyperchromasia, and only very slight aniscytosis and megalocyteiosis.

Alimentary System:

Subjective: - No symptoms. Appetite good and bowels regular.

Objective:

Tongue bad, some of them loose. Tongue clean and moist.
Abdomen is prominent and obese, particularly in
its lower part. There is no pain or tenderness, and nothing abnormal is palpable.
Liver and spleen are not enlarged.
\textit{Excretion Test Meal} – achlorhydria.

\textit{Circulatory System}:
\textit{Respiratory System}:
No abnormalities detected.

\textit{Urinary System}:
Urine contained no abnormal constituents.
Kidneys were not palpable, and there was no pain or tenderness along the renal tracts.
Blood Urea N. 24 mgns. %
Creatinine 2.5 mgns. %

\textit{Diagnosis}.
The clinical features of the disease were referable to a lesion involving the pyramidal tracts and the posterior columns of the spinal cord, of which the two commonest causes are disseminated sclerosis and subacute combined degeneration. In view, however, of the absence of many of the features of disseminated sclerosis, and of the presence of a blood picture suggestive of a mild Pernicious Anemia, the provisional diagnosis of subacute combined degeneration was made. The diagnosis to be confirmed by further investigation and by observation of the response to liver therapy. Unfortunately, the rapid deterioration of the patient’s health and her early death precluded this, but the confirmation was obtained at the post-mortem examination.

\textit{Treatment and Progress}.
27. 9. 34. Teeth extracted.
6. 10. 34. Liver therapy commenced.
9.10.34. Retention of urine occurred, and catheterisation became necessary.

10.10.34. Up to this point the patient's condition has shown but little variation, but she developed pyrexia, haematuria, and pyuria, and commenced to go downhill fairly rapidly. The organisms were later identified as Diphterococi and B. Proteus.

\[
\begin{align*}
\text{Hexamine} & \quad \text{gr. } x. \\
\text{Sodi. Acet. Praep.} & \quad \text{gr. } xx. \\
\end{align*}
\]
\[t.i.d.

19.10.34. Patient's manner became childish.
Pyrexia intermittent in character.

20.10.34. Delirium, followed by coma and death with hyperpyrexia (107°2).

Post-mortem Examination.

Central Nervous System.

Brain: Was oedematous, and discoloured by post-mortem autolysis. On section, no gross lesion was found.

Spinal Cord: A few areas of apparent softening were present, chiefly in the posterior aspect of the lower thoracic and upper lumbar regions.

Genito-Urinary System.

Kidneys: Were of average size. They showed marked cloudy swelling, but no evidence of chronic pyelitis or of acute infection of the parenchyma.
The right pelvis was in a condition of acute pyelitis; and the right ureter was considerably dilated and inflamed. The left pelvis and ureter were perfectly healthy.

Bladder: Showed very marked acute cystitis, the mucous membrane being covered with patches of slough. There was also some degree of acute cellulitis in the loose tissues of the pelvis around...
the lower end of the right ureter. No signs of mechanical obstruction to the right ureter were discovered apart from this pelvic infection.

**Alimentary System.**

*Stomach:* Was small and atrophic. Its mucous membrane was thin and entirely devoid of rugae.
*Intestines:* Showed some slight atrophy of their walls.
*Liver:* Prussian blue reaction faintly positive.

**Haemopoietic System.**

*Bone marrow:* Was actively haemopoietic.
*Spleen:* Was enlarged, deep red, and soft.

**Circulatory System.**

*Heart:* Generalised dilatation. Myocardium pace and soft.
*Values, Aorta, etc.: Healthy.*

**Microscopic Examination:**

*Bone marrow:* Shows marked leucoblastic activity. There is an abundant supply of megaloblasts. The erythropoietic activity is moderately well-marked, and megaloblasts are numerous. The appearances are in keeping with that of a case of Pernicious Anaemia.

*Spinal cord:* Shows the typical findings of subacute combined degeneration. The posterior columns have an open sieve-like appearance, in the meshes of which are numerous fat-containing compound granular corpuscles. Myelin stains show that there is widespread demyelination in the posterior and lateral columns, the nerve roots show no change.
Case 5. Portal Cirrhosis.

Robert Kennedy. 60.
93 High Buckholme
Salashie.

Admitted: 15. 8. 34 to W. 26. R. D. E.

Complaint: Jaundice.
Yellowing of skin.
Loss of weight.

Duration: Three weeks.

History: Patient was quite well until three weeks before admission, when he began to notice some general weakness; in addition his whole body had begun to be itchy, especially during the night. These continued, and anaemia and troublesome flatulence came on. Jaundice appeared fairly slowly and insidiously. He has had no pain on vomiting, and his stools have not altered in colour, but he has tended to be constipated. He has lost a little weight during the last 3 weeks.

Previous Illnesses: Dysentery in Egypt in 1916.
Dysentery in 1918.

Family History.
Mother died at 65 and father at 39, both of dropy.
Brothers - 3 alive and well: 12 died in infancy.
Wife and children are healthy.

Surroundings: Good.

Habits: Satisfactory. No history of intemperance.
Examination:

Patient is a large and powerful man, who looks young for his years. The jaundice is only very moderate in intensity. Temp. 98° F.

Alimentary System:

Teeth, generally, are bad. Tongue is moist but slightly furred. Throat healthy.

Abdomen fairly prominent and obese; it moves freely. No tenderness or rigidity was elicited.

The liver was enlarged to 1 ins. below the costal margin; its surface was quite smooth; the gall-bladder was not detected.

The spleen was not enlarged.

Stools - normal in colour; contained no blood.

Fractional Test Meal - Hypochlorhydria.

Van den Bergh - Biphasic Response.

Laennec's Tolerance Test.

+ 100 mgms. % + 129 mgms. % + 120 mgms. % + 96 mgms. %

Wassermann Reaction - Anticomplimentary serum, and no reaction could be made.

X-ray Abdomen and Bar. Series: - Bile-ducts not seen.

Urine - normal.

Hemopoietic System.

H.B.C. 4,850,000/c.mm. W.B.C. 7,600/c.mm.

Ht. 95%. C.I. 0.98.

Urea, creatinine and uric acid normal.

Erythrocytes not abnormal.

Circulatory System.

Pulse 82/min. B.P. 110/60. No abnormalities.

Heart was not enlarged. There was a faint systolic murmur in the mitral area, not propagated.

Other sounds normal in all respects.
Urinary System:
The urine contained bile but no other abnormal constituent.
The kidneys were not palpable, and there was no renal pain or tenderness.

Respiratory System:
No abnormalities found.

Nervous System:
No abnormalities found.

Treatment and Progress:
Light diet, with low fats. Mild aperients.
For itchiness: Laxd and Balsam lotion, Balsamamine lotion. Chaw bathes, and Bicarbonate baths were all tried without much effect.

In the course of these weeks the jaundice gradually grew less, and with it the itching.
10. 9. 34. Patient discharged.

10. 5. 35. Re-admitted to W. 26.

Since discharge from the R.S. E, the jaundice and itching have been constantly present, but for the last two weeks both have been much more intense, the skin irritation preventing him getting to sleep. As a result of this he has been getting very much weaker, although he has not lost much weight.
His appetite has been quite good: he has had occasional flatulence but no indigestion.
Stools vary in colour — sometimes normal and sometimes light: during the last two weeks they have been especially light.
Examination:

Alimentary System:

Teeth are bad. Tongue is dry, with an atrophic surface and two large fissures in it.

The liver was found to be still enlarged 1 ins. below the costal margin, and to have an apparently smooth surface. The spleen was not enlarged.

No free fluid was detected in the abdomen.

Cranial Nerve Test normal - acrylumina.

X-ray Sir Lumia - no organic lesion demonstrated.

Stool - No blood found. Microscopic exam. by tol. Barig - No protozoa or ova found: 100.000.000. Escherichia coli Haemat crystals present: no increase in streptococci or cellular elements; and no ova of worms present.

Van den Burg reaction - Positive indirect reaction

Lactulose Tolerance Test. Fasting sugar 75 mgms.%. 94 mgms. %, 90 mgms. %, 87 mgms. %, 93 mgms. %, 79 mgms. %

Haemo poetic System.

R. B. C. 1,680,000/ c.mm. W. B. C. 8,400 / c.mm.

Hb. 41%. C. I. 1.2.

Blood film showed hyperchromasia, anisocytosis, and megalocytes. No immature forms of leucocytes were seen.

Differential count: Polymorphs 70%. Small lymphocytes 6%. Large lymphocytes 23%. Eosinophils 1%.

Wassermann Reaction - anticomplementary serum.

Urinary System.

Urine contained bile and a trace of albumen. Otherwise, nothing abnormal found.

Circulatory System.

Respiratory " Notting abnormal found.

Nervous "
Treatment and Progress.

Light diet. Mild aperients.

For itching, menthol, camphor, 9 % borane hydrate.

20. 5. 35. Put on Camphor 5 cc. by i. m. i. every 3rd day.

21. 5. 35. Reticulocytes crisis - 39%.

25. 5. 35. Ascites, which had been slowly gathering,

was now marked, and 18 pints of bile-stained fluid

were removed by paracentesis.

29. 5. 35. Patient becoming markedly drowsy, with

temperature and pulse rate rising (102°7 + 130/min.)

No physical signs indicative of a pathological lesion

in the chest were found.

R.B.C. 3,100,000/c.mm. Hb. 49%. C.I. 0.9. Reticulocytes. 2%.

1. 6. 35. Patient had a severe haematemesis.

Temperature dropped by crisis, but he remained comatose.

3. 6. 35. Patient had another severe haematemesis

and died very suddenly.

Post-mortem Examination.

Serous Sacs: The peritoneal cavity was distended

with clear serous fluid. The pericardium and left pleural

sacs were obliterated by fibrous adhesion.

Alimentary System:

The veins at the cardiac end of the esophagus were

dilated and tortuous, and a bleeding point was

present in one of them.

The stomach contained fluids, blood and blood clots.

The duodenum and remainder of the intestines were

healthy.

The Liver: The organ was slightly reduced in

size, abnormally hard in consistence, and presented

a nodular appearance. On section it presented the

typical naked-eye appearance of diffuse nodular

cirrhosis. The Russian blue reaction revealed the

presence of iron both in the rounded liver masses

and in the interspersing connective tissue.
Spleen: Slightly enlarged and congested. Reaction positive.
Face, head, and face of the neck - healthy.

Respiratory system:
Both lungs congested and edematous. No pneumonia.
Cardiovascular system:
Mycardium pale and flabby. Tricuspid valve dilated.
cArteries showed a slight degree of arteriosclerosis.

Urinary system:
Kidneys showed some congestion. Russian blue reaction positive in the cortex.

Microscopic Examination:
Liver: The normal topography has been lost, the liver cells being arranged in groups of varying size and shape, and these groups having either an eccentric central vein or, more commonly, none at all. The stroma of the portal tract is greatly increased in amount, and has extended in an irregular manner between the trabeculae of liver cells. Within this stroma is a well-marked lymphocytic infiltration, and there are signs of active regeneration of bile ducts. The liver cells themselves show an abnormal amount of variation in size. No actual area of necrosis is to be seen, but there are places where fatty infiltration of the liver cells has occurred.

The condition is, therefore, one of a fairly fine subacute hepatic cirrhosis.

Kidney: There is a slight degree of cloudy swelling in the tubules. Russian blue reaction is positive in the convoluted tubules.

Bone marrow: There is a greatly increased incidence of megaloblasts, which are seen in mitosis and in their varying stages of development. Erythroblastosis are relatively uncommon, and normoblasts even more so. Megaloblasts are fairly numerous.
Diagnosis:

The fact that the jaundice was painless and was toxic in type, indicating that it was due to a combination of an obstructive element and damage to liver tissue, narrowed considerably the range of possible causes.

When first admitted the case was considered to be one of icteric jaundice, due to the fairly typical symptoms and the improvement which occurred under appropriate treatment, but on readmission the intensification and persistence of the jaundice negatived this diagnosis.

Primary carcinoma of the liver was ruled out by the lack of pain; the more usual type is associated with more marked and irregular hepatic enlargement but it might possibly have been the diffuse form in which the liver is only slightly but regularly enlarged. There was, however, no evidence of the marked cachexia which one would expect, nor were there any signs of metastases in lymphatic glands or other organs of the body.

Secondary carcinomatous deposits were excluded by the regularity of the hepatic enlargement and the inability to find any evidence of a primary growth.

The jaundice was not due to Weil's disease since the case was afebrile in all but the terminal stages.

There was no history of having taken any drugs such as arsenic, and on these grounds such causes were excluded.

The regularity of the liver, the intensity
of the jaundice, and the lack of any history of close association with dogs made hydatid epig unlikely. In addition, the negative result of the examination of the faeces for amebae ranson ruled out the possibility of the condition being one of tropical abscess.

These remained, therefore, but one likely diagnosis — hepatic cirrhosis, and when the typical symptoms of portal obstruction appeared further confirmation of this view was obtained.

The anaemia which was present could not be definitely identified, although it was more like pernicious anaemia than anything else, owing to the absence of megaloblasts from all the blood films examined, but the diagnosis was confirmed at the post-mortem examination when the typical megaloblastic reaction in the bone-marrow was observed.
Case 6. Portal Cirrhosis.

William BURTON agt. 35.
1 Clapperhouse Place
Edinburgh.
Labourer.

Admission: 29.3.35 to W. 26. 8. 35.

Complaint: Increasing size of abdomen.
Pains in abdomen.

Duration: Six weeks.

History: About six weeks ago patient noticed that his abdomen was becoming progressively more swollen. In addition he was troubled with a feeling of fullness in the stomach, and a rather gripping pain situated around the umbilicus and coming on 3-4 hr. after meals. Latterly the pain has been less noticeable, but his abdomen has continued to increase in size. During the last week or two he has had some little dyspnoea on exertion, and slight swelling of the ankles, appearing towards evening.

Previous Illnesses: Intermittent or pyogenic glands in neck during childhood.

Jamaica in 1931.

For 18 yrs. patient had been a locomotive fireman, but 3 months ago he was forced to give this up on account of failing sight in the left eye.

Surroundings: Very poor - lives with his wife in a room and a kitchen, the roof of which leaks.

Habits: Dr. rumb MANUAL and smokes very little tobacco.
Family History: Nothing significant elicited.

Examination:

Patient, though small, is quite well developed. He has delicate venous stigmata on his chest, and his are deeply set. There is no jaundice or cyanosis. Height - 5ft. 2ins. Weight - 8st. There is slight oedema around the ankles.

Alimentary System:

Subjective: Appetite good. No digestive upset, except for flatulence. Bowels are regular, and have never been black in colour or shown red stools.

Objective: Tongue slightly furred. Gastric ulcers. Abdomen is tense and globular, moving slightly at all on respiration, and the umbilicus is prominent. There was no undue tenderness. Free fluid was present. The liver and spleen were not palpable.

Lactic acid Tolerance Test.

| T | 80 mgs% | ++ | 88 mgs% | ++ | 110 mgs% | ++ | 90 mgs% |

Cardiovascular System:

Pulse showed no abnormalities. Rate 80/min. B.P. 130/80. Heart was not enlarged, and the sounds were normal in all respects.

Respiratory System:

No abnormalities detected.

X-ray: - Diaphragmatic movements free, with no evidence of lung or pleural lesion.

Hematopoietic System:

R.B.C. 4,000,000/c.mm. W.B.C. 8,200/c.mm.

Ht. 92%. C.I. 0.85.
Urinary System:

Urine contained no abnormal constituents.
Kidneys were not palpable and there was no pain or tenderness along the renal tracts.
Blood Urea N. - 16 mgms. %.
Blood Cholesterol - 200 mgms. %.

Nervous System:

No abnormalities detected.

Laboratory Investigation:

Wassermann Reaction - negative on two occasions.
Acetic Fluid:

Filtrus showed a few polymorphs, lymphocytes, endotelial cells, and erythrocytes. No bacteria were found. No other organisms were seen and there was no growth on culture. Guinea pig inoculation test - no evidence of tuberculosis.

- Albumen . 0.81 gms. %
- Cholesterol . 3.2 mgms. %
- Globulin . 0.32 gms. %
- Total fat . 0.094 gms. %
- Urca N. 14 mgms. %
- Sugar . 59 mgms. %
- Chlorides (as NaCl) 6146 mgms. %

Treatment and Progress:

29. 3. 35. Paracentesis - 9½ pints milky fluid removed.
9. 4. 35. - 29 ¾ " " "
10. 4. 35. Guin Diuretia. gro. XV. t. i. d.
15. 4. 35. " gro. XX. t. i. d. Urinary output hardly affected, remaining at 20-30 oz/diem.
24. 4. 36. Paracentesis - 20½ pints removed.
25. 4. 36. Patient feeling much better; discharged to a convalescent home.
3. 5. 35. Re-admitted, complaining of re-accumulation of fluid in abdomen. Paracentesis was performed and 23½ pints of fluid removed.
9.5.35. Ammon. chlor. grs. XXX, t. i. d., followed, three
days later, by Salvarsan 1 cc. by i. v. i., twice weekly.
This raised the daily urinary output from about
15 z to 25-30 z.
16.5.35 – Paracentesis. 24 pints removed.
23.5.35. Discharged.
29.5.35. Re-admitted. Patient feeling quite
well except for abdominal fullness and slight
2.6.35. Paracentesis wound healing. Patient
was feeling quite well, and was preparing
to go home, when he rapidly became
collapsed, his pulse rising to 120/1 min. and
his temperature to 101° F. Cyanosis appeared
and became very marked. There was no pain,
and no abdominal rigidity could be detected.
In spite of Staphyanthin grs. 120 i. v. i., and Styphrex
grs. 2, patient did not rally, and died within
25 minutes of the onset of the attack.

Post-mortem Examination.
Serous Sacs: The peritoneum covering the
toils of intestines was acutely congested and covered
with fibrinous exudate which glued the coils together.
A large amount of turbid fluid was also present.
Pericardia and plural sacs contained small
quantities of serous fluid which was slightly bile-stained.

Alimentary System.
Oesophagus: The veins at the lower end were
dilated and tortuous.
Stomach & Intestines: – Were healthy.
Liver: The organ was reduced to about two-thirds
of the normal size, and definitely increased in
consistence. Its surface was nodular, the nodularity
being on the whole of a rather fine character.
The granules were yellowish in colour, the depressed areas reddish. Section of the organ showed that the liver substance was composed of islets of yellow tissue surrounded and separated by bands of connective tissue.

The condition was one of advanced cirrhosis of the liver.

Gall-Bladder:—Was healthy.

Spleen:—Was about three times its normal size, abnormally soft and, on section, presented the creamy-red, congested surface characteristic of a sptic spleen. The pulp was moderately difficult.

Pancreas:—Was normal.

Circulatory System:

Heart.—The myocardium was pale and soft, and all the chambers somewhat dilated.

Arteries.—Showed slight arterio-malacia.

Respiratory System:

Lungs showed local congestion and some oedema.

There was no pneumonia.

Genito-Urinary System:

Some congestion of Kidneys. Otherwise healthy.

Microscopic Examination.

Liver:—The section shows the irregular histology characteristic of portal cirrhosis: i.e.—the tissue is divided into islands of various shapes and sizes which are composed of trabeculae arranged in an irregular manner. There is no obvious relationship to inhaedra of veins or portal tracts. Separating the islets are bands of stroma varying much in breadth and variously infiltrated by small round cells. Many of the liver cells show vaculation from fatty change. This latter is probably associated with the progressive character of the cirrhosis and with the acute peritonitis.
Diagnosis:

The four main causes of ascites are, in this country, heart failure, tuberculous peritonitis, abdominal cancer, and hepatic cirrhosis. True was, in this case, nothing to indicate that the patient was suffering in any way from heart failure; the absence of typical symptoms and the progress under usual observation made cancer of one of the abdominal organs unlikely, although not definitely excluding the possibility; and there remained, therefore, either tuberculous peritonitis or hepatic cirrhosis. The comparative youth of the patient, the absence of jaundice or of any hemorrhages from the bowel, and the history of possible tuberculous infection during childhood, all inclined one to favour the diagnosis of abdominal tuberculosis, although so very direct evidence could be adduced, palpation after paracentesis being negative.

Shortly before the patient's death the report of the guinea-pig inoculation test was received, and in view of its being negative the final and correct diagnosis of hepatic cirrhosis was made. It is true that a tuberculosis tolerance test some weeks previously had indicated slight hepatic insufficiency, but with so much doubt being cast on the value of the test one was uncertain as to what interpretation should be placed upon its results. A correct diagnosis was made all the more difficult by the early age incidence of onset in this case, by the rapid and acute course of the disease as indicated by the onset and severity of the ascites, and by the absence of jaundice even as a terminal manifestation.
Commentary.

Even in one's own short three years' experience of clinical medicine, one has noticed a slight though definite change in the general attitude taken towards the finding of achlorhydria in conjunction with certain pathological states. In reading certain of the less recent text-books, one is struck by the fact that the now constant association of achlorhydria with, for example, certain cases of hypochromic anaemia is carefully pointed out, but little or no further reference is made to its possible significance or otherwise. But of late the tendency has been, with increasing knowledge, to pay more and more attention to the complex functions of the stomach, for it is being more clearly realised that this organ has many more duties to perform than that of a mechanical gastric mill which it was formerly thought to be.

This series of cases, therefore, forms an interesting group for the consideration of the effect of achlorhydria on the onset and course of certain morbid states and, vice versa, the effect, if any, of these morbid states on the achlorhydria.

Before going any further it would be advisable if I were to define what, in this context, I mean by achlorhydria. It is that state in which no free hydrochloric acid is detectable, by means of Tofferi's reagent, in any of the samples from a fractional test meal; and it may therefore include those cases in which there is no free hydrochloric acid as ascertained by a fractional test meal, but yet hydrochloric acid is
secreted in response to the injection of histamine, since in no case was a histamine test near carried out. Thus the definition embraces both cases of true achlorhydria and cases of extreme hyperchlorhydria, but for the purposes of this discussion the limits are sufficiently narrow.

The natural outcome of the perfection of the modern methods of investigating the gastric secretions, and of the discovery of the constant association of achlorhydria with certain pathological conditions, was the investigation of the incidence of achlorhydria in people who were, by ordinary standards, quite healthy. This has been carried out by several investigators on a fairly large scale, and the results of their observations may be grouped in three ways:

1. Out of any hundred people — if a large enough number be examined — 80% will show a normal gastric secretion, 10% will show a tendency to hyperchlorhydria, and 10% will show hypochlorhydria.

2. Bemis and Yale, and others, investigating a large number of healthy young adults, showed the incidence of achlorhydria to be 4%.

3. The incidence of achlorhydria over all ages is 14%.

These last two observations show that the incidence of achlorhydria increases with advancing years, and while the figures themselves cannot be disputed, their significance is the subject of some controversy. As regards the first observation we are, at the moment, concerned only with the incidence of hyperchlorhydria, which is 10% of the population. Now an examination of this 10% was carried out by Hurst and Wilkinson,
and their work tended to show that hypochlohydria exhibited a certain familial incidence; and, moreover, in these hypochlohydric families, they found a further abnormal incidence of achlorhydric pernicious anaemia, subacute combined degeneration of the cord, and gastric carcinoma.

Considering for the moment only the subject of achlorhydria, the above facts would suggest that its incidence in apparently healthy people is the result of some inborn constitutional factor, leading to a functionally subnormal type of gastric mucous membrane having a tendency towards premature cessation of its secretory activity. Beyond these statistics of incidence, the evidence in favour of a Constitutional tendency is by no means clear cut. It is known that as age advances the mean acidity in both sexes tends to diminish, and with this fact in mind it is easy to postulate an increased and familial tendency towards early senescence of the gastric mucous membrane, but this has not been directly proved. The incidence of achlorhydria in the newborn suggests that a Constitutional factor is at work, but the evidence is equivocal. What has been put forward as the strongest evidence in favour of a true Constitutional achylia is the occasional discovery of a normal or almost normal gastric mucous membrane in patients having pernicious anaemia with achlorhydria; but against this one must remember that the true correlation between impaired secretion and the histology of the gastric mucosa has not yet been made.
Chronic Gastritis.

Further consideration of the theories of causation of achlorhydria is best taken in conjunction with a discussion of the case of chronic gastritis which has been described.

As age advances less and less importance can be attached to the hypochlorhydric body type which Burst describes as being the most likely to have hypochlorhydria, but in this case the patient has retained the fairly characteristic appearance to a certain extent. It is most unlikely that the achlorhydria is of recent onset; most probably it has been present for a number of years, and this superimposed attack of chronic or subacute gastritis is characteristic in that it succeeded, for no assignable cause, a fairly long period of freedom from gastric discomfort.

The presence of achlorhydria indicates that gastric function is subnormal; and any organ in a subnormal state is particularly liable to become the seat of a pathological process. Thus, while the patient's stomach may be able to fulfil its duties for considerable periods without giving rise to any symptoms, it is, to use the phraseology of heart disease, only just compensated — it has little or no reserve power — and so any mild dietary indiscretion will be sufficient to cause the onset of a further attack of gastritis. No doubt this is the reason why many people with achlorhydria do not have gastric symptoms very constantly; but, if a series of people with hypochlorhydria and a series with normal gastric secretions are observed, the former
will show a greater incidence of gastric disturbance.

A remarkable feature of this case, in common with many others of its type, is the improvement which follows the taking of a bitter stomachic before a meal and hydrochloric acid with a meal, although it is well known that the amount of acid which can be comfortably taken by mouth is far less in amount than that secreted by the normal stomach during the course of a meal. The only theory at which one has arrived in explanation of this phenomenon is this. In the achlorhydric patient the function of the oxyntic cells is so depressed that the psychic stimulus to activity fails to produce any response on their part; thus there is no acid liberated which can come into contact with the oxyntic mucosa in order to set free the hormone which is supposed to be responsible for the second flow of acid. But, if a bitter stomachic is taken, the psychic stimulus is exaggerated, and production of acid may result; or, failing this, the ingestion of hydrochloric acid causes, in the oxyntic, the liberation of the hormone necessary for further acid secretion, and so the acid secretion is augmented by the natural secretions, with the consequent marked improvement in the patient's digestive powers.

The cause of the achlorhydria remains yet to be discussed. The theory of familial constitutional hypochlorhydria, with its increased incidence of achlorhydria amongst these families, has already been examined and found to be, by itself, insufficient: and the tendency nowadays apparently is to ascribe the onset of achlorhydria to two causes — one the constitutional
hypochlorous diastris, and the other chronic or repeated attacks of gastritis. The mode of causation, therefore, in the light of this theory, is relatively simple. Any mechanical or chemical irritant leads first of all to an outpouring of excess mucus, which protects the surface of the stomach and exerts its feeble buffer action on the hydrochloric acid present, and, secondly, the irritant depresses the activity of or may destroy the delicate oxyntic cells, thus further decreasing the amount of hydrochloric acid secreted. Lastly, these two results of the irritant might produce a third effect, in that the sticky mucus may possibly block the mouths of the ducts of the oxyntic cells, leading to the atrophy of the oxyntic cells. That such factors could have been at work in the particular case under discussion is shown by the history of recurring attacks of gastric upset over a long period of years, but unfortunately one can only assume that she was originally one of the hypochlorous diastris type.

One of the many unfortunate results of the stress and strain of modern life is that the causes of gastritis have almost come to form part of the normal environment of the great bulk of the population. Such factors as improper mastication, either due to hurry, bad teeth, or ill-fitting dentures, or the habitual ingestion of tea, coffee, spices and condiments, alcohol or nicotine, or the taking of excessive roughage in the diet, are so common as to be almost universal, affecting all ages and classes, so that the prevention of gastritis in a patient who is constitutionally predisposedly susceptible to it
amounts almost to an impossibility.

Up to this point I have traced, to the best of my ability, the etiology and manifestations of achlorhydria. It now remains for me to discuss what is probably its most important aspect — its sequelae.

Up to the present this patient with chronic gastritis has suffered so disability other than periodic and temporary indispositions: these have been, so far, no permanent ill-effects. But with every passing year, at her age, she becomes increasingly liable to the onset of malignant disease in any one of its numerous sites and types, and the question is whether or not her gastric condition has rendered her more liable to become the victim of gastric carcinoma rather than of carcinoma in any other site. Such a question cannot, of course, be answered conclusively while we are as yet ignorant of the cause of cancer, but on two points at least we have the knowledge of general experience.

1. That the achlorhydria is always present prior to the development of the cancer, no case having been observed in which achlorhydria occurred subsequent to the development of carcinoma.

2. That carcinoma shows an increased tendency to become superimposed on any mucous membrane which is the seat of chronic inflammation. There are present here, therefore, the achlorhydria, and a mucous membrane which, while perhaps not altogether chronically inflamed, has at least been the seat of repeated attacks of inflammation, and the conclusions to be drawn from this are that the patient, in common with all other cases of chronic gastritis, while she will not necessarily develop gastric cancer, has a definitely increased tendency to do so, and on that account she should be carefully observed.
Primary Microcytic Anaemia.

Ten years ago, Primary Microcytic Anaemia formed a fair proportion of those cases grouped under the heading of "secondary anaemias of unknown origin," and its differentiation into a disease showing definite clinical manifestations and a fairly definite aetiology is due mainly to the work of Laber, who originally described the condition, and of Witee, who conducted extensive investigations into it. He collected a series of 117 cases, in which the blood changes were: a reduction in the number of erythrocytes 

and a low colour Index, often in the neighbourhood of 0.5; 
in addition, there were changes to be noted other than in the haemoipoietic system, namely, achlorhydria or severe hypochlorhydria, which was shown by 81% of the cases; glossitis, which was present in about 50%; dysphagia, present in approximately the same number; and koilonychia was found to be common. The particular case described in this series was chosen for its very exact conformation to type in respect of the clinical manifestations. It has occurred in a woman of the child-bearing age, with the typical blood-picture, who shows in addition achlorhydria, glossitis, dysphagia, and koilonychia.

The explanation of these signs and symptoms is difficult. Glossitis also occurs with fair frequency in cases of pernicious anaemia, and the two types of anaemia have two features in common — the anaemia
and the achlorhydria. The condition may therefore be of the nature of a toxic disturbance resultant upon abnormal nourishment as a result of the anaemia; on the other hand, it may be an outward expression of the achlorhydria—that is to say, the factors constitutional or environmental or both, leading to the production of achlorhydria in the stomach, may also cause a glossitis in the tongue; or the glossitis may occur reflexly as a result of the upset of gastric function, just as symptoms referable to the stomach may be present in lesions involving the appendix or gall-bladder. At present there would seem to be but little evidence either for or against any particular theory, although the fact that the glossitis tends to disappear as the anaemia improves suggests that the latter is indirectly its cause: but in order to elucidate which, if any, of the foregoing views is correct, it might be of value if a survey was taken of the incidence of glossitis in these cases of both types of anaemia which do not secrete hydrochloric acid, even if in small quantities.

A similar difficulty exists in regard to the dysphagia and koilonychia. They would apparently be more strictly confined to the Primary Microcytic Anaemia than is the glossitis, but in them again there is an almost complete absence of concrete facts on which to base one’s suppositions.

Let us now consider the aetiology of the disease and its relation to the achlorhydria which is such a common associated condition and is present in this particular case. In the causation of the anaemia these factors are at
work in varying proportions. They are
+ Impaired Iron absorption.
+ Deficient intake of Iron in the diet, and
+ The demands of menstruation and pregnancy on the Iron stores in the body.

Now it has been said that these three factors play a varying part, and probably the latter two assume their greatest importance in the less severe anaemia so common in women of the working classes, and to which attention has been specially drawn by Davidson. In the particular case I have described, however, these factors are probably of relatively minor importance, since the patient is unmarried, her menstrual loss is not excessive, and her diet apparently quite satisfactory from the point of view of Iron content. Thus the main aetiolog-ical factor is impaired Iron absorption.

The question of Iron absorption from the intestinal canal has resolved itself into a question of surprising complexity, in spite of the apparent simplicity of the various experimental techniques, this complexity being emphasised by a survey of the results of the various observers. One of the earliest of these, Burge, in 1895, concluded that inorganic Iron was not absorbed, but, if present in large quantities, might facilitate the absorption of organic Iron; whereas Aderhalden (1900) showed that administration of inorganic Iron greatly increased the rate of haemoglobin formation. Whipple, in 1918, found that administration of inorganic Iron was ineffective; whereas in 1920, in experiments lasting over a longer period, he concluded that it greatly increased haemoglobin formation if
given in large quantities.

As a result of the experience of therapeutic it is now generally admitted that the administration of inorganic iron does increase haemoglobin formation, but the anomaly still exists that whereas at least 1 Gm. of iron is necessary daily in treating the anaemia, only 30 mgs. at the most are required daily in producing the new haemoglobin during rapid recovery. Some explanation of this discrepancy between intake and utilisation amounts is afforded by recent experimental work on the behaviour and absorption of iron in solutions of varying acidity. It has been shown in vitro that the rapidity of solution of iron in dilute hydrochloric acid is greatly accelerated by the presence of an excess of iron; and, further, that while the same principle holds good in the case of organic acids, both processes are considerably slowed. This, therefore, explains the onset of primary microcytic anaemia, its being due to the acidosis, and the reason why the anaemia does not occur in all cases of acidosis probably depends on the varying iron contents of different diets. The experiment also shows the rationale of massive dosage of iron in treating such cases. Further confirmation of these results is obtained from those experiments in which iron was given orally in mixtures of varying acidity, when it was found that the maximal haemoglobin response was obtained with the higher acidities; and in those in which a cat’s intestine was rendered unduly acid by administering Ammonium Chloride or by tying the pancreatic ducts, when iron deposits
were found to form in the liver and spleen.

It cannot be denied that in this case the response to iron with regard to haemoglobin formation—which, under these circumstances is the important constituent of the blood—is rather disappointing, although this may be to some extent due to the comparative severity of the treatment as an in-patient, and to the fairly wide experimental error possible in blood counts done by those with only a moderate amount of experience in the technique. The patient was receiving iron in the form of Ferrous Sulphate Tablets—a proprietary preparation—in a dose of six per day. These 3 gr. tablets each contain Iron (ferrous state) 1.00 gr., Copper 0.01 gr., Manganese 0.01 gr., whereas St. Ferri. carb. (B.P.) contains 1 gr. of iron in 10 gr. of the pill. Now the minimum effective dose of St. Ferri. carb. is stated to be in the region of 45 grains per day, which is half as much again as the maximum pharmaceutical dose, and it is equivalent to 12 Ferrous Sulphate Tablets per day. Thus the patient was apparently ingesting sufficient iron. In addition there were two further factors favouring its absorption and utilisation—the hydrochloric acid which she was taking, and the copper which the tablets contained. The mode of action of hydrochloric acid in favouring the absorption of iron has already been referred to. Copper apparently plays a part in facilitating the absorption of iron, but would seem to have a specific action in causing more correct utilisation of iron which leads to haemoglobin.
formation, although haemoglobin itself does not contain copper.

It is unfortunate that the patient has not reported back for further blood examinations in order that one might have seen the effects of more prolonged treatment. But her deficiency is probably the result of the distance from Edinburgh at which she stays and her continued enjoyment of improved health.

The prognosis as regards this microcytic anaemia is, in this case, good, provided that the patient continues to take a quantity of iron which is in excess of that required by the normal individual, the exact amount of that excess being only determinable by trial and error.
Folicous Anaemia.

It is one of the many curious happenings in medicine that the first stage in the elucidation of the aetiology of folicous anaemia should have been the discovery of its cure; but it is nevertheless true that from the time of its recognition until 1926, when Minot and Murphy demonstrated the remarkable effects of liver therapy, the main advances which had been made were in the direction of increased accuracy in diagnosis; whereas, during the last few years folicous anaemia has become one of the simplest and easiest diseases to cure, and all but the final stage in its aetiology has been attained.

It was formerly thought that the association of folicous anaemia with achlorhydria was the result of lowering of the normal germicidal barrier to intestinal infection, with the result that toxins were absorbed from the increased and flourishing intestinal flora, and these toxins caused a haemolysis of the erythrocytes; but it is to the brilliant researches of bastel, especially that we owe the true and modern conception of the significance of the achlorhydria. He it was who showed that the haemopoietic factor contained in liver, to the presence of which its curative effect was due, was formed in the stomach by the interaction of an extrinsic factor, contained in lean beef, and an intrinsic factor, a hitherto unidentified element in the gastric juice. A resume of his experimental procedures is unnecessary, suffice it to say that a sufficient
number of experiments were carried out to eliminate the possibility of coincidence, and sufficient controls used to stifle the majority of the possible criticisms. These researches have been amplified by Wilkinson, who showed that the intrinsic factor was of the nature of an enzyme, and by Meulengracht, who showed that it was produced in the pyloric end of the stomach.

If being accepted, therefore, that pernicious anaemia is due to a deficiency in this intrinsic factor, what, if any, is the relationship of this factor to the achlorhydria? A number of observers, working along quite different lines, have concluded that the factor is quite separate and distinct from the other accepted gastric secretions — hydrochloric acid, pepsin, rennin, and mucus. Tastie, in his efforts to identify it, dissociated it from the other secretions: Wilkinson has collected several cases in which pernicious anaemia was present and yet hydrochloric acid was secreted in the stomach, and in some of these the absence of the intrinsic factor has been proved by biological methods: and Meulengracht claims that it is formed in the pyloric part of the stomach, whereas hydrochloric acid is secreted more in the body.

The aetiology of achlorhydria has already been discussed. It is generally taken that the diminution in functional activity affects the acid secretion primarily, then pepsin secretion, then mucus secretion, and, finally, the secretion of the intrinsic factor, and thus pernicious anaemia is an expression of the end-stage in the production of achlorhydria, and the
final explanation is that of the achlorhydria. In support of this theory one may quote cases reported both by Davidson and by Hurst, cases of pernicious anaemia with achlorhydria and gastritis, in which the gastritis was treated, leading to a return of the acid-secreting power of the stomach and a subsequent spontaneous cure of the pernicious anaemia. The case which I have described did not, unfortunately, come within this category, although its very early onset made one suspect the possibility of gastritis being the more important element in the production of the anaemia. A fractional test meal carried out some months subsequent to discharge from hospital showed persistence of the achlorhydria, and the withholding of milk extracts over a period of four months led to a steady diminution in the number of leucocytes.

The sporadic cases of pernicious anaemia in which acid-secreting power still remains constitute an objection to the theory of causation as it stands at present. In order to include them within the theory one must postulate an atypical sequence in the loss of function, a sequence in which the secretion of the intrinsic factor is entirely lost, while acid secretion has only reached the stage of impairment; and there is no evidence, either in favour of or against such a postulate, that it can occur as a result of gastritis superimposed on the constitutional factor already referred to. The final step, therefore, in the aetiology of pernicious anaemia will depend for its discovery, I think, upon further investigations into these atypical cases, in an effort to find some factor common both to
them and to those with achlorhydria. 

In the actual case described there are three difficult factors — the absence of any history of a familial tendency towards achlorhydria and its sequelae, the early age of onset, and the lack of symptoms referable to the achlorhydria per se. The lack of any history of a familial tendency would suggest that of the two causal factors in the production of the achlorhydria — gastric and the constitutional tendency — the former was in this case the more important; on the other hand, the early onset and the absence of symptoms of gastric dysfunction favour the view that the constitutional factor played the major role, but in the absence of further knowledge it is profitless to pursue the matter further.

There now remains the important question of prognosis. The anaemia can, as far as we know, be controlled indefinitely by means of liver therapy, given by any of the various methods of maintenance dosage, of which there are three main types. These are:

1) fortnightly intramuscular injections of 2-4 c.c. of buphenin or some similar extract of proved efficacy.
2) the "depot" system of giving large doses of extract intramuscularly at four or six week intervals.
3) the use of preparations of dried liver or dried stomach, given orally in doses approximately equivalent to 1/4 lb. of fresh liver daily, the exact amount required being determined by the results obtained by regular blood counts. In view of the pathological state of the gastric mucous membrane it is likely that the patient will be more prone to attacks of gastritis in later life than would be a normal patient; and on the same groundshurst considers such patients more likely subjects for gastric carcinoma. The question of the possible snar...
of subacute combined degeneration of the cord is one which might well be considered along with the discussion on that condition.

Subacute combined degeneration
of the
spinal cord.

The case in question is not just as typical, perhaps, as one could wish for in a discussion such as this, chiefly on account of the association of a certain amount of neurosis, of its relatively short history, and of its fatal termination. It has one advantage, however, in that there can be no question as to the accuracy of the diagnosis, and it has three features very typical of the condition—the association with achlorhydria and with a macrocytic anaemia, and the fact that death was not due to the subacute combined degeneration, but to an intercurrent infection.

The constant occurrence of achlorhydria, pernicious anaemia, and subacute combined degeneration in the patient has inevitably led to the presumption that they have all some aetiological factor in common, and as regards the first two, this matter has already been discussed. Davidson and Rolland state that the order of onset in the majority of cases is usually for the achlorhydria to appear first, then the subacute combined degeneration, and lastly the pernicious anaemia, and that when this order obtains
it is usual for the subacute combined degeneration to be more marked than the pernicious anaemia; alternatively, this may be partly reversed. The pernicious anaemia precede the subacute combined degeneration in a certain number (usually stated to be about 5%) of cases; and, finally, as apparently occurred in this particular case, their onset may be more or less concurrent and the conditions of approximately equal severity. Now, as has been said above, subacute combined degeneration does not occur in every case of pernicious anaemia: but if macrocytosis is taken as the criterion of pernicious anaemia, then pernicious anaemia is present in almost every case of subacute combined degeneration, as also is achlohydro. There are, however, exceptions to this, for subacute combined degeneration occasionally occurs in the absence of either pernicious anaemia or achlohydro; its presence has been noted in association with gastric cancer, and it also may occur as a manifestation of pellagra and scrofulous; and it is an interesting fact that in problems such as these the exceptions to the rule sometimes provide the clue to their solution.

Any discussion of the aetiology of subacute combined degeneration at the present moment is fraught with so little difficulty, for much of the knowledge which at present we possess is contradictory, and since each group of facts is fairly well authenticated. The contradictions at the moment cannot be reconciled. It is to be hoped that in the light of fuller knowledge, however, such will
be possible, just as the two theories in the causation of rickets — malnutrition and lack of sunlight — were eventually shown to be both correct. One of the chief contradictions is this, that while subacute combined degeneration occurs as one of the manifestations of pellagra and polyneuritis occurs in beri-beri, both are notably rare in any of the “pernicious-like” anaemias occurring, mostly in the tropics, due to loss of the extrinsic factor, which is said to be or to closely resemble Vitamin B. In the present state of our knowledge of the various factors which comprise Vitamin B, one is rather shy of separating them, but it is more or less generally accepted that pellagra is due to Vitamin B deficiency, beri-beri to Vitamin B2 deficiency, and that the extrinsic factor of pernicious anaemia is closely allied to Vitamin B2 although the truth of this latter is questioned by Davidson.

Hurst explains the onset of subacute combined degeneration by postulating the existence of an enzyme in the gastric mucosa, an enzyme produced by the same glands and acting in the same way as the intrinsic factor of pernicious anaemia, and which is essential for the normal nutrition of the central nervous system. Its absence, he says, leads to degeneration of the posterior and lateral columns of the spinal cord and thus subacute combined degeneration is usually, although not invariably, associated with pernicious anaemia. Now if these two intrinsic factors are so closely associated, might not subacute combined degeneration be dependant
upon an extrinsic factor also closely associated
with that of pernicious anaemia? Might it
not be that the haemopoietic factor is dependent
upon the interaction of an extrinsic factor
(allied to Vitamin B,) and an intrinsic factor,
just as the haemopoietic principle is dependent
on the interaction of a substance resembling
Vitamin B2 and Baste's intrinsic factor. On
such an assumption the apparent contradictions
already referred to can be reconciled with
each other, for pellagra becomes equivalent
to the anaemia due to loss of the extrinsic
factor and thus, in their pure forms, neither
is complicated by the manifestations of the
other.

In this country anything more serious
than a mild Vitamin B deficiency seldom,
if ever, occurs, and therefore the examples
of subacute combined degeneration which we
meet with, including this particular one,
are due to loss of the intrinsic factor
consequent upon impaired functional activity
of the glands secreting it. This is explained
the common, although not invariable,
association of the condition with achlorhydria,
and the final aetiology, therefore, under
these circumstances is that of the gastritis
which converts the achlorhydria into
achlorhydria.

Such theorising, however, is almost
as easy as it is valueless, and it seldom
leads to anything of any definite worth:
but it does suggest two methods by which
it might be confirmed or disproved.

7. The stomach extracts used in the treatment
of pernicious anaemia contain Baste's intrinsic factor, and therefore they should also, if the theory be correct, contain the neurospastic intrinsic factor. If, therefore, a sufficiently large series of cases of pernicious anaemia without subacute combined degeneration were taken over a long period of time, the incidence of subacute combined degeneration in those treated with stomach extracts and those treated with liver extracts could be compared, although the objection to this is that there is no proof that the neurospastic factor is not also stored in the liver.

II. Alternatively, patients with pernicious anaemia but no subacute combined degeneration might be fed on meat artificially digested by normal gastric juice, in a manner similar to that employed by Baste during his investigations on pernicious anaemia.

Both ideas, however, suffer from the defect that they are either too ambitious or too impracticable for present resources, and the whole question is made more difficult by the fact that we are dealing with the central nervous system, where the old saying that "prevention is better than cure" applies with all the greater emphasis, since in that system there can be no sure by means of which results may be more easily gauged, and the therapeutic value of any measure must be judged by its effect on statistics over a long period of time.

The duration of subacute combined degeneration is often of many years. Why, therefore, did this particular case last only
six months? The answer is probably to be found in two special circumstances— the functional nervous disorder, and the loss of control over the urinary sphincters muscles. Functional nervous phenomena may bear two relationships to organic disease—they may be secondary to it or they may predispose towards it, from lowering of the general vitality of the body. In this case both factors were probably at work, and each only to a certain extent. A mild tendency to what was apparently a neurosis or manic depressive state was intensified as a result of the organic disease: and the intensification of the mental upset reacted secondarily on the general bodily resistances by tending to exaggerate the susceptibility to an intercurrent infection. Secondly, the loss of control over the urinary sphincters made infection of the urinary tract very difficult, if not impossible, to prevent, and, when it did occur, added to its severity. Thus death occurred characteristically not as a result of the subacute combined degeneration per se, but as a result of a supervening secondary infection.

If she had lived the patient would probably have shown a fairly marked improvement, most noticeable in her general health, due to an improvement in the state of her blood, but also to a certain degree, in her nervous manifestations. They were in part due to the remission which occurs in the earlier stages of subacute combined degeneration, and these yield to treatment with liver, probably owing to the improved nutrition as a result of the amelioration of the pernicious anaemia.
The symptoms due to spinal cord involvement could not have been cured, but adequate anti-anemic treatment would have prevented their progression, and re-educative exercises would have made an invalid life unnecessary.

This is an appropriate stage at which to consider the prognosis of the case of pernicious anemia - B.A. Irwin. Price states that subacute combined degeneration never occurs in a case of pernicious anemia which is under observation and treatment; Davidson and Eulund, however, while admitting that the majority certainly do not, assert that some 5% of all cases of pernicious anemia will later develop subacute combined degeneration. We have at present no method of determining which cases will and which will not develop subacute combined degeneration, and the prognosis in this case therefore can only be expressed as a probability - that the chances are twenty to one against it developing. The question as to whether or not anything can be done to mitigate the likelihood of its onset is still sub judice. Many of the foremost authorities state that the best preventive treatment is intensive liver therapy, the ideal being to keep the erythrocyte count above 5,000,000/c.mm. There is probably but little rationale for such a proceeding other than clinical results, and while it is as yet early to draw conclusions from these, the results are encouraging. According to the theory of etiology and prophylaxis of subacute combined degeneration formulated on a previous page, such treatment would be most effective if the therapeutic agent were the desiccated stomach, and it is interesting to note that Wilkinson advises the use of such a preparation, although one is not aware on what grounds he favours it in particular.
Liver Cirrhosis

Cirrhosis of the liver is one of the most obscure of the many diseases affecting the human body; its pathology we know; its diagnosis offers considerable difficulties; its treatment is almost hopeless; and of its aetiology we are almost completely ignorant.

The two cases described illustrate the two main forms in which the disease may take— one form in which jaundice is the predominant feature, and the other in which ascites occurs. In the case with jaundice, pernicious anaemia was also present, and in both there was schistocytosis. The question is, therefore, is there any connection between these facts.

The marked dissimilarity between these two cases from a clinical viewpoint at once suggests that different processes were at work, but this is not borne out by the post-mortem examination, in which it was found that the primary lesion in both was the same—namely, the so-called portal cirrhosis. Why, therefore, should one be characterised principally by jaundice and the other by ascites? Amongst the great confusion and lack of unanimity which exists in regard to the nomenclature and aetiology of hepatic cirrhosis, there is one fact which is agreed upon by almost all observers—namely, that the cirrhosis as seen at a post-mortem examination is the end-result of a long-continued process of damage to liver parenchyma, followed by
repair in which both parenchymal and structural elements participate, more damage and more repair, and so on; and further, that this damage does not seem to show any pronounced predilection for any particular zone in the liver lobule, but would appear to exert its influence more or less indiscriminately. It is possible, therefore, that in one case the damage may be more commonly situated in the neighbourhood of the central veins of the lobules, giving rise to a process which tends to end in early obstruction to the portal circulation with consequent ascites; whereas, in another case, by a process rather difficult of explanation, the damage leads to interference with the excretion of bile, so making jaundice the more prominent feature; but it is probable that this latter is not the whole explanation, for it does not explain the intermittency of the obstructive element in the jaundice, as shown by the variations in the colour of the faeces and the fact that the Van den Berg reaction, when done, gave only an indirect response.

The association of one of the cases with pernicious anaemia is very interesting, and has been reported in several instances in the last few years. (Br. Jour. med. Sc. 1935) for example, having collected a series of 51 cases in 23 of which the colour index of the blood was greater than unity. There are three possibilities regarding its occurrence.

1. The liver cirrhosis may affect the storage and supply to the marrow of the haemopoietic factor.
The two diseases may be quite separate and have no connection with each other.

They may both be the result of the action of the agent responsible for the achlorhydria. Had the diabetes been diagnosed earlier it might have been possible to eliminate the first possibility by determining biologically whether or not the patient's stomach was secreting the intrinsic factor. If, by such methods, it had been found that the intrinsic factor was being secreted by the stomach, while a pernicious anaemia might admittedly have developed as a consequence of faulty storage of the haemopoietic factor in the liver, it would probably have been mild in character and fairly stationary, whereas in actual fact the anaemia was severe (H.C. 1,600,000/c.mm.) and was also progressive, since it was the patient's increasing pallor in spite of the masking effect of the jaundice, which prompted an examination of the blood and led to the discovery of the presence of the pernicious anaemia. Since this theory, while by no means disproved, has serious objections to it.

It is not too much to say that coincidence might lead to the occurrence of hepatic cirrhosis and pernicious anaemia in the same person as separate entities. But the former is a relatively rare condition, and the number of cases reported in which there was an associated macrocytic anaemia must form a percentage of the total cases too great to be dismissed on the plea of coincidence.
There remains, therefore, the third possibility, and there is more clinical evidence in its favour than for either of the other two. First, during the patient's first visit to hospital his stomach was still secreting hydrochloric acid, and there was no suspicion of a macrocytic anaemia being present. Secondly, when readmitted some nine months later his general condition was much worse, suggesting that the cirrhotic process in the liver was subacute and progressive (a supposition borne out by the post-mortem findings), achlorhydria was by then established, and pernicious anaemia was severe. Now if only this case had had a history of long-standing intemperance the explanation would be easy, for alcohol is supposed to be one of the causal agents of cirrhosis, and, in addition, an alcoholic gastritis might easily lead to the onset of pernicious anaemia. But unfortunately there is no such history, as so often happens in cases of hepatic cirrhosis, and has in fact occurred in both of these cases. Under these circumstances, therefore, one is forced to regard the achlorhydria and pernicious anaemia as being due to their usual causes, while the cirrhosis is the result of toxins gaining entrance to the portal circulation owing to absence of the antiseptic barrier normally furnished by the gastric hydrochloric acid — a very lame explanation which is really no explanation and does not advance us one whit.

And now there remains another question.
Why was it that the ascitic case, which also had achlorhydria, did not develop pernicious anaemia? It could hardly be that one case managed to store the haemopoietic principle in the liver and the other did not, for the pathological changes in both livers were similar, except for the fact that in the case in which case pernicious anaemia did not develop the liver had less liver tissue remaining. This case, however, had a rather shorter history, and it is possible that the achlorhydria is of comparatively recent origin so that, on the analogy of the case with jaundice, the patient might have developed pernicious anaemia had he survived longer. It was exceedingly unfortunate that peritonitis should have supervened, but in a markedly debilitated patient requiring repeated paracentesis it is a not unlikely complication. It had, in this case, much in common with a post-operative peritonitis in that it was not accompanied by any pain, but only by an increasing morbidity of the patient.

The aetiology of hepatic cirrhosis stands in much the same position as did that of pernicious anaemia twenty years ago — we are at the stage of postulating the existence of unidentified toxins of unknown origin gaining entrance to the body as a result of the operation of unknown factors and producing the characteristic changes in the liver. Certain vague poisons derived from alcohol have for long been such popular culprits that portal cirrhosis
still flourishes under the aliases of gin-drinkers' liver and alcoholic cirrhosis, but an examination of the literature on the subject leaves one with considerable doubts as to the exact part played by alcohol in the production of the condition. One authority, while admitting that there are a few cases not caused by alcohol, states that an alcoholic history is obtainable in the vast majority; another authority admits that a few cases have a history suggestive of alcohol being an aetiological factor, but contends that cirrhosis in the great majority of cases is not due to chronic alcoholism, quoting in support of his statements the comparative rarity of cirrhosis in communities where spirit-drinking is popular, this, in many cases, being Scotland.

Whichever be the finer statement, there was certainly no history of alcoholism in the two cases which have been described, and practically the only other thing which they had in common was the achlorhydria. Has, therefore, achlorhydria any significance in hepatic cirrhosis? Wright, in the series of 51 cases already referred to, did gastric analyses on 26 of them, and, of these 26, 14 had achlorhydria and 3 extreme hypochlorhydria — an incidence too great to be the result of chance. Thus there would apparently be some connection between the two conditions, but the question is whether the achlorhydria precedes the cirrhosis and has therefore some aetiological significance in regard to it; whether the two
Conditions occur concomitantly and have a common etiological factor; or whether the ascites is secondary to the cirrhosis and merely a manifestation of it. The fact that the ascites, in the case with jaundice, developed during the course of the disease suggests that either the second or the third supposition may be the correct one. Now for an organ such as the liver to suffer extensive parenchymal damage the causal toxin must be brought to it by the blood-stream, most probably that of the portal circulation, and the only viscus drained by the portal circulation which shows a constant deviation from the normal is the stomach. It is natural, therefore, to assume a connection between these two and, in view of what has been said above, that the two conditions develop more or less concomitantly, it might appear that the causal agent damaged the stomach while on its way to create its effects in the liver. It is probably to the admirability with which alcohol fits in with such a theory that it owes its popularity as the cause of cirrhosis, for it is a substance which is absorbed in a large measure by the stomach; which circulates for long periods in the blood-stream during the relatively slow process of breakdown and excretion; in chronic alcoholism it has a direct and deleterious action on the gastric mucosa; and the stomach and liver are the two organs which do not participate in the geneae although slight
increase in tolerance towards it. Considering also the non-alcoholic cases, however, the theory does nothing more than describe a small section of the probable route followed by an unknown agent of unknown origin, and is therefore as useless as it is vague.

The conclusion is, therefore, that while admitting a probable connection between hepatic cirrhosis and achlorhydria, one can find no definite factor common to both or which, in conjunction with one might cause the other.
Conclusions.

It has been my aim in discussing these six cases to endeavour to establish a definite connection between them, and to show the significance of this common factor in each case. As regards the first three this aim has been more or less successful; but as regards the others knowledge has not yet advanced sufficiently to allow of the process being carried much further than mere surmise. The series might have been more complete had it included examples of those other conditions characterised by achlorhydria, namely, gastric carcinoma, achlorhydria occurring after certain types of gastrectomy, and that occurring in apparently perfect health, but lack of suitable material and the restriction on the number of cases to be described have precluded this.

There remains one interesting question. Why, amongst a number of people, all having achlorhydria, should one develop gastritis, another microcytic anaemia, a third subacute combined degeneration of the cord, and so on? And why is it so seldom that one sees a combination of two or more of the possible conditions occurring in the same person, excluding, that is, the common association of pernicious anaemia and subacute combined degeneration of the cord? The case of gastritis, for instance, although advanced in years, had so suffic
cancer or pernicious anaemia: and, similarly, the case of pernicious anaemia, even on close questioning, would admit to no history suggestive of gastritis. Achlorhydria and all its sequelae, including hepatic cirrhosis, have been shown to have a familial tendency, but we cannot as yet foretell which particular manifestation will occur in any given case. It may be that the answer is to be found in the varying damage suffered by different parts of the stomach, as a result of variations in the severity of the inborn tendency towards achlorhydria and in the multitude of agents responsible for the gastritis. Or perhaps the impaired gastric function is not the whole tale, but in each case another factor, peculiar to one disease only, is at work, and on it depends what disease will appear. Of one thing we can be certain, however. Great as the advances are which have been made, the whole secret still eludes our grasp, and much research yet remains to be done before the final elucidation of these problems is attained.