PERNICIOUS ANAEMIA:

A Study of One Hundred and Seventy Cases with special reference to Complications.

By

THOMAS ALFRED MacGIBBON,

M.B., M.R.C.P. Edin.

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University of Edinburgh.

C O N T E N T S.

PART I.

INTRODUCTION.

During my tenure of office as Resident House Physician in the Royal Infirmary of Edinburgh I had ample opportunity of seeing cases of pernicious anaemia. From twelve to twenty cases under maintenance treatment reported every week and as the great majority report once a month I had the opportunity of seeing eighty cases. Nearly all of these had been in-patients and by the kindness of Dr Goodall I was able to study the records which, along with similar records of cases no longer in attendance, are the basis of this thesis.

Until 1926, pernicious anaemia was regarded as an incurable disease. Its duration was commonly less than one year, seldom more than two years, and a few cases of longer standing were published as curiosities. As the disease was usually in itself fatal in a short time, complications and associated conditions were of comparatively slight importance. To-day, thanks to the experimental work of Whipple (1) and others and the clinical work of Minot and Murphy (2) the pathology of pernicious anaemia is better understood and a therapeutic key has been provided.

In 1928 Naegeli and Gloor (3) after an extensive enquiry, concluded that treatment fails in ten per cent of/

of cases.

Many haematologists have thought this figure too high. Goodall (4) was prepared to accept it, if failure due to complications or to inadequate or delayed treatment be included. It is probable, however, that further developments in treatment, improvement in therapeutic preparations of liver, and in the technique and earlier use of transfusion have combined to lower the proportion of failures.

It is therefore a matter of some importance to study the complications of pernicious anaemia since these may influence prognosis either per se or by an adverse effect on the anaemia.

The complications may be purely fortuitous. They may be a result of the anaemia or may be associated with it so frequently that the conclusion is inevitable that they have a common cause or close relationship in pathology.

It seems impossible however to maintain such a classification in all cases.

There is no doubt that pregnancy would be considered a fortuitous complication, and little question that postero-lateral degeneration of the cord is an allied condition but the problem becomes very difficult when we come to deal with such cases as Hodgkins disease (described by Davidson (5)) myxoedema and scurvy, and seems at present almost insuperable when we meet with cases where the diagnosis may be complicated by the possibility/

possibility of such conditions as cirrhosis of the liver, achrestic anaemia, acholuric jaundice, cases which have a reticulocyte response to liver and promptly relapse, aplastic anaemia and others.

The present discussion will be confined to those in which the diagnosis was not in doubt.

PART II.

ANALYSIS OF PUBLISHED REPORTS OF CONDITIONS COMPLICATING PERNICIOUS ANAEMIA.

PREGNANCY.

The history of the association of pregnancy with pernicious anaemia is a tragic one. In the reported cases the anaemia has usually appeared either in the later months of gestation or in the puerperium. In some of the latter, sepsis was apparently either a causal or complicating factor and in the pre-liver era the result was almost invariably fatal.

Pregnancy ensuing on pernicious anaemia has apparently occurred with some frequency since liver treatment was instituted (6) and some such cases have come under my own notice, but as far as I know only one account of successful full time pregnancy in an old-standing case has been recorded, (Goodall (7)) and as this case came under my own observation I refer to it later. Goodall also refers to a case of a twin pregnancy ending at the eighth month. The infants only survived a few hours.

DISEASES ASSOCIATED WITH PERNICIOUS ANAEMIA.

One of the fullest accounts is given by Wilkinson(8) who has published an account of the conditions associated with pernicious anaemia in 370 cases.

His list is as follows:-

DISEASES CO-EXISTING WITH PERNICIOUS ANAEMIA IN A SERIES OF 370 CASES.

	Males	Females	Total	Percentage of 370.
Pulmonary (20)				
Asthma and bronchitis	7	6	13	3.5
Pneumonia	3	3	6	1.6
Tuberculosis	1	0	1	0.27
Cardiovascular (17)				
Hyperpiesis	4	4	8	2.6
Angina	3	0	3	0.8
Hemiplegia	0	2	2	0.5
Phlebitis	1	1	2	0.5
Fibrillation	0	1	1	0.2
Pericarditis	0	1	1	0.2
Endocrine (16)				
Exophthalmic goitre, hyperthyroidism	1	5	6	1.6
Simple thyradenoma	0	3	3	0.8
Myxoedema	1	2	3	0.8
Diabetes mellitus	2	2	4	1
Dermatoses (13)				
Acne rosaceae	2	1	3	0.8
Psoriasis	2	1	3	0.8
Urticaria	1	2	3	0.8
Eczema	1	1	2	0.5
Leukoplakia	0	1	1	0.2
Pruritus vulvae	0	1	1	0.2

Urinary (9)	Males.	Females.	Total.	Percentage.
Albuminuria	2	2	4	1
Nephritis	1	0	1	2
Cystitis	1	2	3	0.8
Haematuria	1	0	1	0.2
Malignant Disease (8)				
Buccal Epithelioma	2	1	3	0.8
Cervix and vagina	0	2	2	0.5
Stomach	1	1	2	0.5
Colon	0	1	1	0.2
Syphilis (6)	3	3	6	1
Gastro-intestinal (2)				
Ulceration	2	2	4	0.5
Cerebro-spinal (excluding P.L.D.)	2	1	3	0.8
Migraine	0	1	1	0.2
Parasites	0	2	2	0.5
Abscess	1	0	1	0.2

The nervous cases were post-encephalitis, paralysis agitans and anterior poliomyelitis.

This Series gives a fair idea of the incidence of complications and it is obvious that the majority of them are fortuitous. The large proportion of thyroid diseases - particularly in respect of excessive activity is unusual. There are conditions, however, which have an important influence on expectation of life although they have no direct connection with the anaemia, and some of these are common enough to require consideration. There are also the conditions which appear to be directly connected with pernicious anaemia. It is sometimes impossible to say which is the more appropriate class. The more important complications are considered further under their respective headings.

TUBERCULOSIS.

A fair number of cases of tuberculosis complicating pernicious anaemia has been published. In many of these the reason for publication has been the rarity of the combination.

Only one case, and that rather doubtful, occurred in my own series.

The combination would therefore appear to be entirely fortuitous.

SYPHILIS.

At one time syphilis was regarded as a causal condition. This view is no longer held. Only 6 cases are reported in Wilkinson's Series and the relationship seems to be incidental.

OTHER INFECTIONS.

Infections such as influenza and sepsis are regarded as serious. The effect of influenza is undoubtedly of grave import in a patient who already suffers from a debilitated condition.

Sepsis was at one time regarded by many writers as the cause of the disease. There is still a large body of opinion that sepsis plays an important part in delaying improvement under liver treatment.

Goodall (4) indicates that sepsis is not necessarily a bar to improvement, and quotes two cases:-

Case 1.- Female, aged 68, was admitted with a red cell count of one million, and a large parotid abscess. She died in seven days of septic poisoning but before she died there had been a reticulocyte response to liver of 30 per cent and her blood count had begun to rise.

Case 2.- This was a woman who suffered from pernicious anaemia and a foul discharge from a vaginal carcinoma. Her corpuscles rose from one to four millions before she died of toxaemia.

Davidson and Gulland (9) refer to the case of a man, aged 59. His red corpuscles numbered 680,000 and his haemoglobin percentage was 15. He was transfused and given liver extract and although "every tooth was in a shocking state of sepsis" he had a reticulocyte response of 52 per cent and within 3 weeks his corpuscles numbered 3 millions.

MALIGNANT DISEASE.

No suggestion has been maintained that there is anything more than an accidental relationship between pernicious anaemia and malignant disease except in the case of carcinoma of the stomach and of the bone marrow.

CANCER OF THE STOMACH.

Since it became known that the intrinsic haemopoietic factor is produced in the stomach several enquiries into the possible relationship of pernicious anaemia and gastric carcinoma have been made.

Connor and Birkeland (10) reviewed 638 cases of pernicious anaemia at the Mayo Clinique. In eleven there was also carcinoma of the stomach. In two of these, anaemia had preceded the carcinoma: in two, carcinoma was found before pernicious anaemia was detected: and in seven cases the incidence of the two conditions was almost simultaneous.

Washburn and Rozendaal (11) in a review of reported cases of gastric carcinoma indicate that its occurrence in pernicious anaemia is higher than would be expected on the basis of coincidence. If factors involved in the genesis of pernicious anaemia predispose to the development of malignant change in the gastric mucosa, a gradual increase in the number of cases of gastric carcinoma associated with pernicious anaemia would be expected as a result of more adequate treatment of pernicious anaemia and its favourable effect on life expectancy.

They reviewed a series of 906 cases of pernicious anaemia.

Gross lesions were found in 24 cases.

In 16 cases gastric carcinoma was found - an incidence 1.76 per cent.

In 8 other cases benign polypoid lesions were found.

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CANCER OF BONE MARROW.

Various suggestions of a speculative nature have been made concerning the relationship of this condition to pernicious anaemia. It has even been suggested that pernicious anaemia is a manifestation of cancer of the bone marrow. On occasion, carcinoma of the marrow has given rise to a blood picture similar to that of pernicious anaemia but so far as we know at present cancer of the marrow definitely following pernicious anaemia has not been described.

GASTRIC CONDITIONS OTHER THAN CARCINOMA.

Various lesions of the gastric mucous membrane have been from time to time reported.

In 1903 Faber and Bloch (14) found that if the abdomen were injected with formaline immediately after death, the described conditions had been due to post-mortem change.

These observations were confirmed by Gulland and Goodall (13) two years later.

More recently, however, Meulengracht (17) and Magnus and Ungley (20. p.6) have found that whereas the body of the stomach shows atrophic or gastritic changes the pyloric glands are relatively well pre-

served/

preserved and Brunner's glands appear normal. Menlengracht considers that the apparent contradiction between the pathology and anatomy of the stomach can only be explained on the ground of a disturbance in function. It is suggested that a hormone which normally stimulates the pylorus is absent in pernicious anaemia.

In this connection it may be noted that Votila (14) has claimed success in treating pernicious anaemia with desiccated intestine.

Jacobson (15) states that the anti-anaemic activity of the alimentary canal corresponds closely with the distribution of argentaffine cells. These granules stain black with silver solutions and are fluorescent in ultra-violet light.

In man they appear in the cardiac glands, are almost entirely absent in the fundus, are common in the pylorus, abundant in the duodenum and less abundant in lower parts of the intestine.

Jacobson found that these granules were absent in 12 cases of pernicious anaemia and in 2 cases of sprue, but were little altered in other forms of anaemia.

These argentaffine cells have been found to contain a complex purine body (pterine) and a similar substance has been found in liver extract.

The impression left by a study of the work on the stomach in pernicious anaemia is (1) that the relationship/

relationship to carcinoma remains a problem, probably more closely related to the pathology of cancer than of pernicious anaemia, and (2) that so many new problems have presented themselves that their interpretation must await the result of much further research.

INTESTINAL STRICTURE.

In 1895 Faber (16) described a case in which pernicious anaemia was associated with stricture of the small intestine.

In 1929, Meulengracht (17) collected 21 cases including 5 personally observed. One was due to a foreign body but most cases were attributed to tuberculosis.

In one case it was possible to demonstrate the presence of the anti-anaemic factor in the gastric juice which also contained free HCl.

Hanksley and Meulengracht (18) suggest that strictures impair gastro-intestinal functions in two ways - 1. by impairment of intestinal absorption: 2. by progressive gastritis, atrophy and failure of the stomach to secrete intrinsic factor.

Brock (19) reviews the subject and points out the resemblance between the blood picture in such cases and cases of idiopathic steatorrhoea and of the anaemia occurring among children of Mediterranean stock as described by Cooley (20).

CIRRHOSIS OF THE LIVER.

A few cases of pernicious anaemia following cirrhosis of the liver have been reported. It is probable that the cirrhotic liver is unable to elaborate or to store the haemopoietic factor.

There is no reason to suggest that cirrhosis occurs as a complication of pernicious anaemia except as mere chance.

CARDIO-VASCULAR DISEASE.

It is not surprising that in a disease whose incidence is chiefly in the later decades, cardio-vascular disease should be a common complication.

Wilkinson found it in 4.6% of his cases. High pressure is common. Angina and auricular fibrillation are frequently recorded. Coronary thrombosis has been described.

Stalker (21) gives a resume of the literature.

Steuart, Crane and Deitrich (22) discuss the circulation in pernicious anaemia. They made measurements of cardiac output, cardiac size, and related circulatory functions in five cases of pernicious anaemia, and compared them with similar investigations made during remission induced by liver extract when the blood was nearly normal.

They/

They found:-

1. At low haemoglobin levels, the stroke volume and minute volume output, cardiac rate, and O_2 consumption were, in all cases, elevated. The arm to tongue circulation time was decreased. Changes in the reverse direction occurred as the state of the blood approached normal.
2. In four instances vital capacity was moderately lowered during anaemia.
3. The venous pressure and electrocardiograms showed no significant alterations during the anaemic stage.
4. There was a rise in both systolic and diastolic pressure in all patients as the haemoglobin concentration increased.
5. Although the cardiac size was moderately increased in three cases, no significant change in size was observed as the haemoglobin concentration increased.
6. Left ventricular work, both per beat and per minute, was not increased during the anaemic stage: in fact, the work per beat was less than when the haemoglobin concentration in the blood was normal. It is suggested that the enlarged hearts found in this type of anaemia are due to myocardial anoxaemia, rather than to increased cardiac work. The elevated B.M. rates observed in these patients during the anaemic state were not due to increased cardiac work.

7. The amount of cardiac work done at rest, in anaemia was commensurate with the cardiac size.

8. From these observations it appears that during the anaemia of pernicious anaemia the heart is called upon to pump an increased amount of blood per minute, the amount appearing to be a linear function of the haemoglobin concentration. This is accomplished in part by increasing the heart rate, and in part, by maintaining a greater output per beat than may exist at higher haemoglobin levels. These alterations are reflected in a shortening of the circulation time: in short the red blood corpuscles, although fewer in number, move at an increased velocity and, as a consequence they are used more frequently in their O_2 carrying capacity. Shortening of the circulation time and increase in cardiac output as well as decrease in haemoglobin and increase in O_2 consumption also appear to have linear relationships so that an organ already working at an accelerated rate is put to the disadvantage of having to maintain a circulation sufficient for the requirements of an increased basal metabolic rate. With increase in the level of haemoglobin, changes in the reverse direction occur. Nevertheless, the hearts of these cases, without conjestive failure at rest, mechanically perform the work expected of them for their size.

PULMONARY CONDITIONS OTHER THAN TUBERCULOSIS.

The conclusion which may be drawn from published cases is that chronic bronchitis and asthma do not add to the severity of pernicious anaemia but the conditions merely combine to add to the debility.

Authors are agreed that pneumonia is a complication of the greatest gravity.

ENDOCRINE COMPLICATIONS.

THYROID.

In Wilkinson's Series twelve cases of pernicious anaemia gave a history of affections of the thyroid gland.

These were exophthalmic goitre in five instances, hyperthyroidism without exophthalmos in one case, adenoma in three and myxoedema in three. Where disease of the thyroid has been regarded as the primary condition, anaemia has very commonly been associated with it, but it has usually been of microcytic type.

On the other hand a number of case reports refer to cases with macrocytic anaemia.

THE BASAL METABOLIC RATE is commonly found to be normal or rather increased in pernicious anaemia.

Susman (23) found the B.M.R. exceeded 20% over the/

the normal in 18.5% of cases unaccompanied by cord affection and that it might be more than 20% under normal when cord involvement was present.

It seems impossible to explain these findings. There is no wasting - unless it be replacement of muscle by fat - to explain increased metabolism, and both myxoedema and hyperthyroidism have been described with some frequency.

There will be cordial agreement with the dictum of Davidson and Gulland (9) that "a plethora of biochemical facts tends to increase our difficulties".

ADDISON'S DISEASE.

It is a little remarkable that any connection between the Addison's disease of the suprarenal capsules and Addison's (pernicious) anaemia is to-day seldom mentioned. Indeed the only reference is to the possibility of a little pigmented case of Addison's disease being mistaken for pernicious anaemia, or of a pigmented case of pernicious anaemia being mistaken for Addison's disease.

Such a case is described in part 3 of this thesis. (p. 69)

DIABETES MELLITUS.

Parkinson (24) in 1910 described a case of pernicious anaemia associated with diabetes. Wilkinson found a description of 60 recorded cases.

Adams (25) found 3 cases of pernicious anaemia in 2000 diabetics and 3 diabetics among 1000 records of pernicious anaemia.

Joslin (26) found 88 cases of pernicious anaemia among 5086 diabetics:- 1.7 per cent. These represent the average recorded findings.

DERMATOSES.

Urticaria has been described in connection with pernicious anaemia. Wilkinson describes three cases relieved by the administration of dilute HCl and pepsin and the discontinuance of liver. A case of pigmentation will be described later. p.69 . There is nothing to suggest that the connection between pernicious anaemia and other skin affections is anything but fortuitous.

URINARY CONDITIONS.

Gulland and Goodall (13) in their histological study of seventeen cases found catarrhal or interstitial changes in every case.

Davidson/

Davidson, McCrie and Gulland (27) reported the occurrence of acute nephritis and uraemia following liver therapy.

Clinical evidence of nephritis was found in over 1.5 per cent of Wilkinson's cases.

DISEASES OF THE NERVOUS SYSTEM.

OPTIC ATROPHY.

Cohen (28) describes optic atrophy as the presenting sign in some cases. He points out that in pernicious anaemia disturbances of vision due to such conditions as retinal oedema and haemorrhage, thrombosis of the central artery or vein and chorioretinal degeneration and, rarely, haemorrhage into the optic nerve have long been recognised, but states that amblyopia as the first symptom had not been previously recorded. His first case had blurring of vision as the initial symptom. Pernicious anaemia showed clinically six months later and the eye condition began to improve only after the pernicious anaemia was treated.

His second case had nearly normal blood, but in view of the first case and a family history of pernicious anaemia and absence of gastric hydrochloric acid he was treated with campolon and the vision improved.

Cohen emphasises the following points:-

That/

That pernicious anaemia may give rise to nerve symptoms (1) by the anaemia itself leading to defective nutrition of nerve elements: (2) by loss of function followed by degeneration of nerve elements due either to a toxin present in pernicious anaemia or the absence of a specific substance essential to neural nutrition: (3) by areas of softening due to either haemorrhages or thromboses.

Box (29) also describes a case of optic atrophy as the presenting symptom. Examination of the blood led to a diagnosis of pernicious anaemia and treatment of this led to improvement of vision.

RETINAL HAEMORRHAGES.

In the older literature pernicious anaemia frequently appeared in lists of "bleeding diseases". This general statement has been dropped but retinal haemorrhages are still referred to. They certainly do occur but it seems doubtful whether they are not more likely to be due to arteriosclerosis than to the anaemia.

MENTAL SYMPTOMS.

Delusional insanity is also referred to in periodicals and text books.

Again I would suggest that arteriosclerotic changes are more likely to be the cause than the anaemia.

In my own experience patients suffering from pernicious anaemia as regards mental outlook and amiability compare most favourably with other patients and indeed with members of the general community.

PERIPHERAL NEURITIS.

Neuritis was frequently described some years ago when sufferers from pernicious anaemia were treated by arsenical poisoning. Neuritis still occurs. Numbness, tingling and feeling of cold are all common but it is difficult to say how much of all this is due to affection of peripheral nerves and how much may be due to early postero-lateral degeneration.

Greenfield and Carmichael's study (30) of the peripheral nerves in cases of postero-lateral degeneration seem to indicate that there is some degree of involvement of peripheral nerves.

POSTERO-LATERAL DEGENERATION.

I avoid the usual introductory adjectives, "subacute" and "combined" for the reasons that the first is seldom true and the second cannot be otherwise - if a person has posterior and lateral degeneration they/

they cannot be uncombined.

The term "subacute" was doubtless given by the neurologist who studied the "combined" degeneration while his patient was slowly dying of anaemia, and it still serves as a general heading which may include "acute fulminating" cases.

A study of the literature of the last ten years is of great historical interest.

There are contradictions between haematologists and neurologists and internal differences between members of each group. Even the extreme views, however, are important stepping stones across a morass of ignorance.

I propose to refer briefly to some of the more important contributions and make further reference to them as may seem desirable after giving a record of my own cases.

Ungley and Suzman (31) published an account of 61 cases of which 30 had been treated with liver. Care was taken to exclude cases with symptoms which might have been accounted for by peripheral neuritis.

Of the 30 cases 17 improved, 8 failed to improve and 5 died. Of the 17 improved cases, 8 were able to return to work.

Of the 31 cases which did not receive liver none improved/

improved and 28 died.

These results are often quoted as examples of improvement of the postero-lateral sclerosis but it seems obvious that a very large measure of improvement in health and strength must have been due to an increase in red corpuscles. This paper deals with previous literature.

Baker, Bardley and Longcope (32) discuss results of liver treatment in postero-lateral degeneration. They find, as others do, that cases with ataxic symptoms usually respond better than spastic cases. Their statement of results of treatment suggests that they are inclined to "damn it with faint praise".

They give the following table.

	Cases	Well	Improved	In Statu Quo.	Worse	Not followed
Numbness and tingling	34	6	11	12	2	3
Absent Vibration Sense	16	1	1	10	-	4
Diminished sensibility	16	2	3	6	1	4
Weakness	44	4	36	3	1	-
Ataxia	19	1	12	2	1	3
Romberg's Sign	15	2	3	8	-	2
Disturbed position sense	14	1	2	8	-	3
Spasticity	9	1	1	5	-	2
Increased reflexes	7	-	1	2	-	4
Diminished reflexes	8	1	1	3	-	3
Extensor Plantar reflex	9	2	-	5	-	2
Disturbed cutaneous sensation	7	2	1	3	-	1
Sphincter disturbance	6	2	3	1	-	-
Psychic disturbance	7	4	2	-	-	1
Loss of Potentia	5	3	1	1	-	-
Total Observations	216	32	78	69	5	32

Sargant (33) suggested massive doses of iron in the treatment of postero-lateral degeneration but no other observer has obtained satisfactory results from its use.

Goldhamer and Colleagues (34) investigated 461 cases of pernicious anaemia and noted evidence of postero-lateral degeneration in 89.2 per cent and cerebral symptoms in 64 per cent. They conclude that anti-anaemic therapy has no curative effect on spinal cord degeneration, but contributes indirectly to the improvement of symptoms by increasing muscular power.

Grinker and Mandel (35) are equally gloomy and find that any improvement in nerve symptoms is due to cure of the anaemia. They suggest that it is useless to give larger quantities of liver than are necessary to maintain a normal blood count.

Their opinion, however, is considerably diminished in value since they seem to hold that a count of 4,000,000 is evidence of adequate treatment.

Mellanby (36) discussing the effects of Vitamine A deficiency finds it difficult to escape the conclusion that postero-lateral degeneration is nutritional in origin, and that the responsible defect involves a mechanism in which Vitamine A is concerned. It is difficult, however, to agree that Mellanby's experi-

mental/

experimental results in young rabbits are relevant to the clinical findings in pernicious anaemia.

Russell (37) found benefit in postero-lateral degeneration following the injection of Vitamine B 1 (Binerva) but found the improvement was greatest when there was evidence of affection of the peripheral nerves.

Ungley (38) states that it is probable that more potent material is required to improve cord lesions than to supply the needs of blood formation and that it is difficult by oral administration to maintain a sufficiently high intake. He contests the view that postero-lateral degeneration is due to vitamine deficiency. Treatment with concentrates of Vitamines A and B has given disappointing results, and highly purified extracts of liver such as anahaemin containing neither of them, have proved as successful as more crude extracts in the treatment of postero-lateral degeneration.

It is obvious that the difference in experience and opinion is acute and apparently neither reconcilable nor explicable.

The subject will be further considered after the account of cases.

PART III.

PART III.

A STUDY OF 170 CASES WITH SPECIAL REFERENCE TO COMPLICATIONS.

Tables have been prepared showing the sex, and age of the patient on admission to hospital, the haemoglobin percentage on admission and on discharge or the latest date afterwards on which the patient reported.

The order in which the cases are arranged is chiefly alphabetical as the notes have been filed in that way. No great advantage would have followed re-arrangement since patients are usually very indefinite in statements concerning the duration of illness.

The last sixty cases on the list are those who had reported as late as June or July 1940. Many of them have been long under observation.

In the columns headed treatment the following contractions are used for the chief measures or preparations employed.

A. Anahaemin.

B. Boots' Extract by mouth.

C. Campolon.

E. Examen.

H. Hepatex.

L./

L. Whole liver.

M. Marmite.

P.f. Pernaemon forte.

P.v. Pernaemon intravenously.

S. Stomach or Stomach preparations.

T. Transfusion.

V. Valentine's liver extract.

v.b. Vitamine B (Binerva).

The tables are supplemented by notes of the more interesting or important cases.

These are indicated by N.

The following contractions are frequently used:-

R.B.C. - Red Corpuscles.

Hb. - Haemoglobin.

P.L.D. - Postero-lateral degeneration.

Numbers of red corpuscles are given in millions per c.m.m.

P.A. - Pernicious anaemia.

A. PATIENTS WHO HAVE NOT RECENTLY REPORTED.

	Sex.	Age.	Admitted	Hb.	Complications and Notes.		Treatment.	Last seen.	Hb.
1	F	66	6.33	54	Numbness.		P.f.	6.33	80
2	F	60	2.31	23	Died, pneumonia.		T.	3.31	65
3	F	50	7.35	40			P.f.	8.35	70
4	M	47	1.33	38	Numbness. Glossitis		B	1.34	80
5	M	59	5.33	32			P.f.	6.35	86
6	M	55	3.29	17	Died, Cancer of Stomach.	N.	T.L.	7.33	90
7	M	59	3.28	34			L.	3.28	60
8	FS	57	5.30	33	Died. Cancer of uterus		S	6.30	60
9	M	50	11.34	40	Rodent ulcer of cheek		P.f.	8.36	90
10	M	68	6.35	26			T. P.f.	10.35	90
11	F	46	10.28	24	R.B.C. 0.95		A.	11.28	88
12	F	65	10.34	25	Died. Ventricular fibrillation.		P.f.	6.35	90
13	F	80	12.32	30			V.	2.33	70
14	F	68	1.33	32			T. P.f.	3.33	70
15	M	72	3.34	25			L.M.	4.34	70
16	M	56	2.30	32	Died. Lymphadenoma	N.	T.	2.30	30
17	M	49	11.29	45	Numbness and Tingling		B	4.31	72
18	FS	45	10.34	33			P.f.	1.35	78
19	M	58	10.31	51	P.L.D. B.P. 200/100		L.M.	5.34	70
20	Fs	51	4.33	25			B.	3.33	62
21	F	79	3.33	28	Numbness. Lost ankle jerks.		B.P.	5.33	70
22	F	50	12.35	50			P.	1.36	72
23	M	66	6.31	23	Died. Oedema of lungs.		T.L.	10.31	64
24	F	55	8.35	24			P.v.P.f.	1.36	80
25	M	55	4.34	52			P.v.	5.34	80
26	F	68	11.29	28	Died. Parotitis.		T. P.f.	11.29	30
27	F	45	8.34	35	Metrorrhagia. 4 years.		P.	9.34	63
28	F	60	4.33	43			B.	5.33	70
29	M	61	5.32	42			P.v. M.	6.32	95

S = single.

	Sex.	Age.	Admitted	Hb.	Complications and Notes.		Treatment.	Last seen	Hb.
30	M	58	1.34	28	P.L.D. Knee jerks absent.		P.	11.36	77
31	M	53	6.31	22	Died. Marrow partially aplastic.		T.B.	9.31	18
32	F_S	26	8.33	46	P.L.D. Jerks increased.	N.	P.v. B.	5.35	90
33	F	49	12.32	38	"Aplastic" case.	N.	T.P.	1.33	12
34	M	58	4.31	40	Arthritis of Spine		L.P.	1.39	100
35	F	49	3.34	37			L.	4.34	100
36	F_S	46	2.32	40	Migraine.		E.	3.32	90
37	M	74	10.37	22	Died. Nephritis. Pneumonia.		T.E.	10.37	22
38	F	27	6.35	32	Followed premature labour.	N.	T.P.v.	7.35	75
39	M	41	1.33	25	Fish liver failed.		T.E.	3.34	100
40	M	57	12.35	77	P.L.D. Spastic.		P.f.	2.38	86
41	F_S	73	3.39	40	Myxoedema.		P.v.B.	4.36	70
42	F	31	9.32	60	Caesarean Section	N.	L.	10.32	80
43	F	49	6.30	12	Pneumonia. Died.	N.		6.30	12
44	F	60	8.31	20			L.	10.31	72
45	M	45	11.33	40			P.	12.33	90
46	M	55	6.29	35	Hb. fell to 12%.		T.B.	8.30	97
47	M	55	11.36	40	D. Mitral. Had P.M.A.	N.	E.	1.38	86
48	M	51	3.29	50	Inoperable gastric Carcinoma.		B.	8.30	78
49.	F.	42	2.32	48	B.P. 180/120.		P.f.	11.33	90
50	M.	59	12.30	62	P.L.D. Acute mania.		-	12.30	62
51	M.	54	3.31	54	Pyloric Stenosis		P.f.	10.33	110
52	F.	72	10.33	52	Became maniacal.			10.33	52
53	M.	48	1.30	38	Numbness. Had syphilis.		P.f.	7.30	90
54	M.	50	11.32	34			P.v. M.L.	8.33	95
55	M.	63	6.33	36	Pigmentation.	N.	P.v. B.	5.34	77
56	F.	60	7.33	40			P.v. B.	7.33	70
57	M	53	9.33	40	Albuminuria.		P.v. B.	9.33	82
58	F	58	9.28	30			T.B.	10.28	62
59	M	69	1.35	58	P.L.D. Spastic. B.C. 165/100		P.v.	3.35	80
60	M	66	12.33	62	Knee jerks increased.		B.	2.34	70
61	F	37	1.30	23	Onset during Pregnancy.		L.	3.30	58
62	F_S	42	9.34	25			P.B.	11.36	80
63	F	65	5.36	27	Admitted comatose. Died.		T.E.	6.36	27
64	M	49	2.30	40			S.	7.31	90
65	F	58	11.32	32	Fish liver useless.		B.	12.32	70
66	M	61	8.32	15	Died. Chronic Osteomyelitis	N.	T.B.	11.32	18

	Sex.	Age	Admitted	Hb.	Complications and Notes.	Treatment.	Last seen	Hb.
67	F	56	10.33	18	Cystitis.	E.	5.38	95
68	M	59	6.31	23		L.	7.31	82
69	M	60	6.34	30	Atheroma. Haemoptysis. N.	L.T.	9.34	25
70	F	41	6.33	25	Tendon jerks absent.	P.	7.33	60
71	M	52	2.28	38	P.L.D. N.	Varied	7.33	86
72	F	59	7.30	30		S	12.30	65
73	F	58	8.31	42	Cystitis.	M	2.38	95
74	F_S	67	9.31	88	P.L.D. Spastic.	L	10.31	88
75	F	78	10.33	48	Tingling. Died Cancer of Stomach.	P.f.	10.37	45
76	M	63	6.34	48	P.L.D.	P.f.v.b.	1.36	95
77	F	51	4.33	28		L.B.	5.33	62
78	M	66	11.34	48	Knee jerks increased. Died Cancer of rectum.	A	4.38	92
79	M	67	12.26	30	B.P.180/128. Cerebral haemorrhage.	Various	3.88	88
80	F	66	2.37	52	Huntington's Cholera.	E.	3.37	78
81	F	45	3.37	32		C.	5.37	74
82	M	54	6.33	54	Died influenza and jaundice.	H.T.	6.40	100/20
83	F	70	8.37	40	Wassermann + .	P.f.	10.37	50
84	F	71	2.35	28		P.B.	5.39	96
85	M	52	3.35	38		P.f.	7.38	86
86	M	68	7.35	32		P.f.	12.38	100
87	F	37	6.29	8	P.L.D. Haemorrhage. N.	T.B.	5.37	70
88	M	43	1.35	33		P.f.	6.37	93
89	M	57	9.36	65	P.L.D. Ataxia. Tremors & wasting	H. v.b.	12.38	92
90	M	59	7.31	35		A.	6.40	104
91	M	66	7.36	25	Alcoholic.	T.H.	6.39	84
92	M	30	12.32	45	Tingling.	E.v.b.	3.39	106
93	F	45	9.38	47		C.	4.39	96
94	M	45	11.35	50		E.	8.39	96
95	F	40	2.38	46	Epileptic dementia.	C.	3.38	54
96	M	57	10.36	38	Cholecystitis.	P.f.	4.39	108
97	M	56	3.31	40		A.	5.37	88
98	M	61	5.38	40		T. P.f.	2.39	76
99	M	74	9.35	55	Tingling. Tobacco Amblyopia.	E.	7.38	90
100	M	61	12.38	42		A	3.39	95
101/								

	Sex.	Age.	Admitted	Hb.	Complications and Notes.		Treatment.	Last seen.	Hb.
101	M	46	11.37	38	Tingling.		P.f.	6.39	104
102	F_S	30	1.31	16			T.P.v.	4.37	92
103	M	50	5.36	64			E.	11.38	110
104	M	59	3.36	42			E.	10.39	92
105	M	34	4.38	78	Numbness and Tingling. Laparotomy.	N.	P.f.	6.38	92
106	M	53	9.33	40	P.L.D. K.J. absent.		P.f.	9.37	95
107	M	50	8.35	40	B.P. 180/100		P.f.	3.37	92
108	F	82	6.38	30	R.B.C. 0.9		P.f.	11.38	90
109	M	56	5.38	40	Scurvy.	N.	Diet P.f.	5.38	104
110	M	56	10.30	58	Phlebitis.. Numbness.		S.	4.39	102

B. CASES CURRENT.

111	F	61	3.36	48			A.	6.40	90
112	M	57	8.33	36	Numbness and Tingling.		M. P.f.	7.40	100
113	F	75	8.35	36	B.P. 180/82		P.f.	7.40	94
114	F	52	3.35	38	Haemorrhoids. Glossitis.	N.	E.	6.40	102
115	M	59	4.31	32	Tingling. Mitral disease.		P.f. E.	6.40	100
116	M	61	1.37	32			E.Thyroid.	7.40	114
117	F_S	62	6.30	28	Numbness. Rheumatoid Arthritis	N.	M.Pf. v.b.	7.40	110
118	F	38	4.40	40	Uterine prolapse.		P.f.	7.40	74
119	F	36	12.33	35	Impaired Sensibility.		P.f. C.	7.40	112
120	F	37	7.34	25			M. P.f.	7.40	100
121	F	48	3.33	24	B.P. 200/130.		M.E.	7.40	96
122	F_S	36	4.34	30			A.	7.40	98
123	M	31	8.35	30			P.f.	6.39	99
124	F	68	9.38	28			P.f.	6.40	100

No.	Sex	Age	Admitted	Hb.	Complications and Notes.		Treatment.	Last seen.	Hb.
125	F	51	3.37	30			E.	6.40	97
126	F	27	5.33	26	Twins. Abortion.	N.	A.	7.40	100
127	F	63	11.37	28			T. E.	7.40	99
128	F	40	5.36	40	Toxic Goitre.		E.	7.40	104
129	F	65	6.29	22	Tingling. B.P. 170/126		E. v.b.	6.40	100
130	F	49	5.39	49			P.f.	7.40	100
131	M	62	3.38	62			P.f.	7.40	100
132	F	28	4.37	50	Healthy infant July '40.		A.	7.40	85
133	M	50	4.38	51	Oxaluria.		E.	7.40	101
134	F	69	8.36	44	P.L.D.		E. v.b.	7.40	92
135	M	27	10.33	36			T.L. P.f.	3.40	90
136	F	55	6.38	25	Tingling.		P.f. v.b.	7.40	80
137	M	60	12.29	56	No treatment for 5 years from '34.		M.L.	12.39	110
138	M	56	5.37	48	P.L.D.	N.	E.	7.40	92
139	F	52	7.39	22			A.	7.40	98
140	F.	38	4.40	30	Followed Puerperal fever after 13th child.		P.f. A.	7.40	78
141	F_S	48	8.36	20	Cystitis.		E.	7.40	94
142	M^S	58	2.35	19	B.P. 160/90	N.	P.v. A.	6.40	100
143	M	47	10.37	48	Haemorrhoids.		P.f.	7.40	98
144	F	45	2.36	36			P.f.	6.40	88
145	F	57	1.36	30	P.L.D. ataxia. B.P. 216/90	N.	E. b.v.	7.40	100
146	M	68	2.39	34	Numbness.		P.f.	2.40	100
147	M	66	9.35	40			P.f.	7.40	95
148	F	50	7.36	55	P.L.D. tremors, wasting.	N.	T.E. b.v.	7.40	88
149	F	63	11.39	48	Biliary & renal colic. Epilepsy	N	Various	7.40	90
150	F_S	54	3.33	40			P.f.	7.40	82
151	F	34	10.30	30	Pigmentation. Pregnancy.	N.	P.f.	7.40	90
152	F	66	4.36	40	K.J. increased. B.P. 210/100		A.	6.40	92
153	M	76	8.37	40			C.	7.40	95
154	F	61	6.38	30	P.L.D. B.P. 150/85		P.f. v.b.	7.40	98
155	M	59	3.32	30	Tingling and numbness.		M. P.f.	7.40	90
156	F	58	11.35	40	B.P. 182/80		P.f.	7.40	90
157	M	35	7.35	40			P.f.	4.40	97
158	F_S	50	3.37	46			E.	5.40	84

159/

No.	Sex.	Age	Admitted	Hb.	Complications and Notes.	Treatment	Last seen.	Hb.
159	F_S	62	1.37	30	Tingling and numbness.	H.	7.40	96
160	M	69	11.39	45	Senile deafness.	P.f.	6.40	88
161	F	60	8.35	50	P.L.D. spastic. B.P. 170/100.	E.	7.40	90
162	M.	50	5.38	52		E. P.f.	7.40	92
163	M.	48	12.35	50	W.R. + .	P.f.	6.40	74
164	F	53	4.35	16	R.B.C. 0.560. Oedematous. N	A	7.40	84
165	M	65	12.38	55	B.P. 190/100	P.f.	7.40	96
166	F	34	9.33	36		A.	2.40	80
167	F	47	6.38	54		P.f.	7.40	82
168	F	43	5.39	42		P.f.	4.40	80
169	F	46	3.33	46	Knee jerks increased.	M. P.f.	7.40	98
170	M	62	3.30	30		T.L.P.	6.40	110

GASTRIC CARCINOMA.

CASE 6.

A.B. Male, aged 53 was admitted in March 1929 with breathlessness, nausea and vomiting and a red count of 730,000 with 17 per cent of haemoglobin.
Films typical. No HCl in the stomach contents.
He was transfused and treated with liver.
He improved rapidly and left hospital in May 1929 with 94 per cent of haemoglobin. He remained fit for four years.
On June 29th 1933 he had R 5.46 and Hb. 95.
On that date, however, he complained of weakness, loss of appetite and nausea. He was breathless and had palpitation. He looked in poor physical condition with a slight yellow tinge. The heart was not enlarged but there was a soft, blowing systolic murmur.
Nervous system seemed healthy but knee jerks could not be elicited. The urine was normal.
Later, he began to complain of pain under the right costal margin and gastric distension and flatulence.
The abdomen became distended with flatulence, abdominal pain increased and death occurred on 7th July 1933.

A post-mortem examination revealed a large quantity of blood in the peritoneal cavity.
On the lesser curvature in the pyloric antrum there was a shallow carcinomatous ulcer about 2 inches in diameter.
There/

There was no evidence of gross bleeding from this. There were a few secondary growths on the peritoneal surface of the bowel in the pelvis and there were large masses of glands invaded by secondary growth along the lesser curvature, hilum of the liver and along the aorta.

Gall bladder, bile passages and pancreas showed no abnormalities. The spleen was firm and slightly enlarged. The kidneys and suprarenals showed no gross abnormality. No actual bleeding point was discovered to account for the large intra-peritoneal haemorrhage. The epicardial fat was gelatinous. The myocardium was fatty. Coronary vessels and aorta showed slight atheroma.

The centre of the shaft of the femur contained some bright red marrow mixed with the fat.

The appearances were not those typical of severe untreated pernicious anaemia but suggested that some reaction was taking place.

The Prussian blue reaction was not marked in any of the organs.

COMMENT.

This case is of outstanding interest since there was definite pernicious anaemia with a red count of only 730,000 more than four years before the patient's death. There was moreover a complete remission before the/

the fatal illness began.

The case raises the questions:

(1) Does the red marrow in the shafts of the long bones revert to the normal in a long-standing remission in pernicious anaemia?

(2) Do the deposits of iron pigment disappear in a long-standing remission?

As far as the case goes, both questions appear to be answered in the affirmative.

LYMPHADENOMA.

CASE 16.

M. 56. Admitted almost moribund.

Had suffered from lymphadenoma for over a year.

It was impossible to ascertain which condition came first.

R. 7.8. Hb. 20.

Patient was transfused but did not respond and died in two days. There was no post-mortem but the blood changes were characteristic of pernicious anaemia and an excised gland showed typical lymphadenomatous changes.

CASE 32.

F. single 26, admitted 2nd August 1933 complaining of some tingling and numbness in toes and occasional vomiting.

The patient's age and enlargement of spleen to the costal margin suggested the possibility of acholuric jaundice while increased reflexes, Romberg and Babinski signs pointed to disseminated sclerosis. Spherocytes were not numerous. There was no increased fragility, and no reticulocytes were present till pernaemon was administered. Acholuric jaundice was thus excluded. Absence of nystagmus and the presence of abdominal reflexes besides sensory phenomena seemed to exclude disseminated sclerosis.

Response to treatment by liver preparations made the diagnosis clear.

"APLASTIC" ANAEMIA.

CASE 33.

A married woman, aged 49, was sent from a gynaecological ward where "thick fleshy polypoid masses" had been removed by curetting. Early in July 1932 she had a profuse vaginal haemorrhage. Thereafter great weakness in the legs was noticed.

On admission the blood showed macrocytic anaemia, R 1.7: Hb. 38: L. 8.

Pernaemon was administered daily by intravenous injection and a tube of Boots' liver extract was given by mouth. On 12.12.32 Hb. had fallen to 28. She was transfused on the six following days. Haemoglobin reached 36 but fell again. On 21st January red corpuscles were 560,000 and Hb. 12. Reticulocytes never exceeded 6 per cent. Patient died.

Post-mortem, marked prussian blue reaction was present in the liver. "About 50% of the fatty narrow was replaced by blood-forming tissue, partly erythroblastic and partly leucoblastic. Many of the erythroblasts were megaloblasts although the nuclei were unusually pyknotic."

This case illustrates what has frequently been pointed out, that the marrow picture does not necessarily correspond to the blood picture. Here the narrow was active but the blood showed no signs of regeneration.

PREGNANCY.

CASE 38.

Mrs McG., aged 27, was admitted to a maternity hospital on 17.5.35 five weeks before full time on account of severe anaemia.

She was given 'Campolon'. On the 19th pains began and she was transfused. She was delivered the next day, and the day following was again transfused. She showed a local uterine infection which cleared up and she was given Campolon, 2 c.c. twice daily. There was but slight reticulocyte response and the haemoglobin did not exceed 40.

She was admitted to the Royal Infirmary on 22.6.35. It was ascertained that she had two previous pregnancies with no abnormal accompaniment and had two healthy children. No abnormal condition was found apart from the blood changes and resulting symptoms. She was pale. Blood pressure 108/78. R. 1.3: Hb. 32.: L. 6. Spleen enlarged to percussion.

She received three doses of pernaemon intravenously in six days. Thereafter she was treated for a month with Campolon 2 c.c. intramuscularly every second day.

On July 8th her haemoglobin had risen only to 54. Two doses of pernaemon forte intramuscularly were then given. She left hospital on 3rd Aug. with haemoglobin 75 and has not reported since.

PREGNANCY - CAESAREAN SECTION.

CASE 42.

Mrs N. aged 31. She had been under treatment for two years for pernicious anaemia but details could not be obtained.

On admission her blood showed R. 4.3. Hb. 64. L 11. Red Corpuscles showed remarkable anisocytosis. Many megalocytes were present but they were hypochromic. Both liver and iron were given but no improvement followed.

She was therefore sent to the Simpson Maternity Hospital where Caesarean Section was performed. The child died. On her return to the ward her blood showed R. 4.4: Hb. 60. She was then treated with liver only and was discharged with R. 5 and Hb. 80.

It is unfortunate that the blood counts are not convincing but the diagnosis of pernicious anaemia was originally made on good authority. The record had been mislaid.

CASE FOLLOWING PNEUMONIA.

CASE 43.

This case is unusual inasmuch as the patient stated she had been quite fit till she took pneumonia. She was 49 when she took pneumonia in February 1930. She went for a holiday in May against the advice of her doctor. She was admitted in a dyspnoeic condition with vomiting and diarrhoea on June 26th 1937. R. 635. Hb. 12. L. 900. She died next day.

A post-mortem showed typical prussian blue reaction in the usual organs and the marrow was typical. There were pericardial petechiae and large subperitoneal haemorrhages throughout the ileum.

CASE 47.

Male, aged 55, had suffered from weakness and palpitation for years.

Admitted 26.11.36 he had R.1.86. Hb. 40.

Treated with "Examen" his haemoglobin reached 90 on 24th March 1937.

By this time, however, auricular fibrillation had started.

His thenar eminences began to waste and fibrillar tremors were seen in the deltoid and arm muscles.

He died suddenly on January 18th 1938.

PIGMENTATION - ADDISON'S DISEASE.

CASE 55.

A miner, aged 63, was admitted on 13.6.33 complaining of shortness of breath, weakness and loss of weight.

His blood showed R 1.04: Hb. 25: L 4.6.

On pernaemon intravenously and Boots' extract it improved rather slowly and in May 1934 when he passed out of observation the Hb was 77.

He always had a low blood pressure, the last reading being 95/60.

He showed widespread areas of pigmentation. Face, neck forearms, back of hands, lower abdomen and extensor surfaces of the legs all showed a brown pigment.

There were also pigmented patches on the buccal mucous membrane. The palms of the hands showed a decrease in the normal pigmentation. The areola round the nipples were black.

There were no changes in the other systems except some fibrosis of the lungs seen on X-ray examination.

CHRONIC OSTEOMYELITIS.

CASE 66.

A night watchman, aged 61, was admitted on 11th March, 1932. He said he had been in good health till 2 years ago when he began to have headaches and sickness and was easily tired.

He added that he had trouble with his left leg at the age of 16 and that there had been a periodic discharge ever since.

It was noted that there were superficial crusts over the left tibia which was irregular in shape especially at the edges.

He had been treated in hospital for 5 weeks in November and December 1931, and again in March 1932 when he was transfused and treated with liver. He stopped this when he "ran away" but had been taking Marmite.

On admission his red corpuscles were 790,000: Hb. 15.

He was transfused with blood and 5 c.c. pernaemon.

For some time thereafter he had a daily intravenous injection of pernaemon but with little response. There was a persistent leucocytosis (12 to 15 thousand).

He had another transfusion in September. Marmite, liver and pernaemon were all given but reticulocytes seldom reached and never exceeded 4 per cent.

At the end of October daily injections of Campolon were given. There was no reticulocyte response and no increase in Hb. Leucocytes fluctuated from 14 to 22 thousand.

After consultation with Mr Struthers the left leg was amputated through the thigh on November 21st.
The man died the following morning.

A post-mortem examination showed a strong prussian blue reaction in the liver, a faint reaction in the spleen and a very slight reaction in the kidneys.
The heart showed fatty degeneration.
The marrow of the femur was a pale pink colour with scattered areas of deep red.

Microscopic examination of the bone-marrow showed that the reaction for the most part was myeloblastic. The majority of the cells were myeloblasts and myelocytes, very many being eosinophil. There were small islets here and there of primitive blood cells.
A few areas were seen showing definite megaloblastic reaction typical of pernicious anaemia but this was mostly masked by the myelocytic reaction.
The spleen showed congestion. The sinuses were packed with cells, a great number of which were white cells, chiefly polymorphs. A few nucleated red cells were also seen.
The main appearances were those of sepsis.

The interesting point seems to be that the marrow was not aplastic and that the sepsis appears to have stimulated the formation of leucocytes and directly or indirectly inhibited the formation of red corpuscles.

HAEMOPTYSIS FROM ARTERIOSCLEROTIC VESSELS IN LUNGS.

CASE 69.

An insurance agent, aged 60, complained that he became exhausted after walking even a few yards. He was admitted on June 6th 1934.

For nearly a year he had suffered from successive crops of boils. His habits were temperate and his work light. Heart was a little enlarged. Pressure 160/70. Sounds healthy. Nervous system seemed healthy.

R. 1.05: Hb. 30. He was given pernaemon 5 c.c. daily. Reticulocyte response was poor, not exceeding 4 per cent. On 3rd July his Hb. had reached 35 and he was transfused. Two days later it was 45 and this level was maintained for a week. Two months later it was 35, twelve days later it was 18 (24th Sept.) when another transfusion was given. The same night he had a slight haemoptysis. This continued until he died on Sept. 27th.

A post-mortem examination showed bone marrow hyperplasia of megaloblastic type. Degenerative changes in liver, kidneys and myocardium. Strong Prussian blue reaction in liver and spleen, not in kidneys. Arterio-sclerosis most marked in the pulmonary arteries.

CASE 71.

H. age 52. Admitted 22.2.28. Cellarman.
Complained of hot and cold feelings, shortness of breath, weakness and swelling of feet. Duration 3 months.
Patient served in Macedonia during the war and attributed his illness to malaria.
He had also suffered from dysentery.
His parents had died when over 50: his father of bronchitis, his mother of "paralysis".
Patient was rather stout and slightly yellow.
Appetite good. Some feeling of distension after meals.
Nothing abnormal on examination except an unduly smooth tongue and achlorhydria.
Heart and vessels showed no gross abnormality.
No disturbance of the respiratory system.
Urine normal.
The spleen was just palpable.
Red corpuscles 1.5 million: Hb. 38; Leucocytes 2 thousand. Red corpuscles macrocytic and hyperchromic.
Wassermann test negative.
Van den Bergh reaction, direct delayed. Icteric index 20.
No symptoms referable to the nervous system except hot and cold feelings.
No objective signs of disease.
Patient/

Patient was treated with lightly cooked whole liver. In two months his red Corpuscles had reached 4 million and Hb. 75 per cent: in 4 months 5 million with Hb. 80 per cent: in 6 months 5 million with Hb. 92 per cent. For the next five years he was treated at home chiefly with marmite alternating with liver. For 8 months he remained well on marmite alone with counts of 5 million or more, and 95 to 100 per cent of haemoglobin.

In November 1932 he began to feel numbness of the feet and legs and he was given "Pepsac", a preparation of gastric mucous membrane. This was followed by sickness and diarrhoea. He began to lose control of the bladder sphincter and to have some difficulty in walking.

He became delirious and was re-admitted on 5th Dec.1932. His counts were Red Cells 3.37: Hb. 82: Leucocytes 14,000. He was given Boots' liver extract and the blood improved.

On 2nd February 1933 the red corpuscles were 4.59 and Hb. 95.

On the contrary, nervous symptoms went from bad to worse and might have been described as "fulminating". He had partial loss of control of the bladder sphincter. There was partial anaesthesia on the median side of the right leg and great difficulty in distinguishing the application of sharp and blunt objects to both legs. The arms seemed to escape and the cranial nerves showed no abnormality. Abdominal reflexes were present. The plantar/

plantar reflex was extensor on both sides but knee and ankle jerks could not be elicited. Although the blood presented almost normal picture the patient was now a helpless cripple. He was removed to the Longmore Hospital for Incurables where he survived for several years.

HAEMORRHAGE.

CASE 87.

Mrs D., age 37, admitted 19.6.29, semiconscious and almost pulseless. Her blood showed R.O.355,000: Hb. 8: L. 1200. No reticulocytes. She was immediately transfused. Great difficulty was experienced in finding a vein and in getting blood to flow into it when found. A pint of blood took 3 hours to flow into the vein and after it half a pint of saline was added. Next day she had improved and the history was elicited. She had suffered for many years from menorrhagia.
In January 1929 she had influenza and metrorrhagia.
In April she became very breathless and her feet began to swell.
She was also troubled with diarrhoea and sometimes vomiting.
Previously she had enjoyed good health.
She had two healthy children but her first and fourth pregnancies had resulted in still-births.

Further examination showed a typical blood picture and a slightly enlarged spleen. She was treated with lightly cooked whole liver. In a week corpuscles exceeded a million with 25% Hb. In a month the figures were R 3.3: Hb. 62; in two months R 4.2: Hb. 75.
She was never a very satisfactory patient.
In February 1935 she reported with Hb. 75.
In May 1937 she showed Rombergism with very slight knee jerks/

jerks, R. 2.04: Hb. 70.

She was advised to return for re-admission but possibly because the advisability of tooth extraction had been mentioned, she did not arrive.

LAPAROTOMY.

CASE 105.

Male, aged 34.

Full details of this case are withheld. On account of pallor, dyspepsia and achlorhydria he fell among surgeons and laparotomy was performed. He was admitted when his haemoglobin, after liver treatment, had risen to 78. Films were strongly suggestive of the real diagnosis. Numbness and tingling were present.
On discharge Hb. was 92.

SCURVY.

CASE 109.

M. 56. Bachelor. Poultry farmer. Admitted 5.5.38.

Patient complained of weakness and said he had great difficulty in carrying on his work for the last eight years. He did carry on for six years before seeking medical advice. By this time his legs had become discoloured. His doctor advised him to keep to bed and gave him an injection each month. The discoloration disappeared.

Two years before admission he came as an outpatient and pernicious anaemia was diagnosed.

His figures then (2/36) were R. 3.48: Hb. 85: L. 4.2.

It was noted that petechiae were present on his legs.

His teeth were artificial.

On admission he was found to have petechiae on abdomen and legs and haemorrhages into his calf muscles.

R. 1.7: Hb. 30: L. 1.3. Reds macrocytic but rather hypochromic. On pernaemon forte and a high Vitamin C diet he recovered rapidly and went home in less than a month with Hb. 104.

HAEMORRHOIDS. GLOSSITIS.

CASE 114.

Mrs B., aged 52, complained on 23rd March 1935 of feeling weak and tired and said her feet became swollen at night. She stated that her doctor had told her two years previously that she had pernicious anaemia and that she had been treated with liver. She had 38 per cent of haemoglobin and 2.3 million red corpuscles. Films were macrocytic but rather hypochromic and it was found that she was losing blood from haemorrhoids. She received pernaemon intravenously and had a reticulocyte response of 13 per cent on the third day.
On 16th April she had 90 per cent of haemoglobin and a week later an operation for haemorrhoids was carried out. From that time onwards she has had an injection of liver extract once a month. The chief preparation used was "Examen". Haemoglobin has always exceeded 80 and occasionally has exceeded 100. On 6th March 1940 she complained of a sore tongue, and a very acute glossitis near the point on the surface and all round the edges was found. An ointment containing essence of peppermint was applied and the condition which had been very acute subsided in ten days. When last seen she seemed in good health with a haemoglobin percentage of 102.

RHEUMATOID ARTHRITIS.

CASE 117.

Miss C. aged 62, came under observation in June 1930 when she had 28 per cent of haemoglobin, and 1.1 million red corpuscles. She was advised to take as much lightly cooked liver as she could. She had a rapid rise of reticulocytes to 20 per cent. and her blood condition improved. In three weeks she had 2.3 million corpuscles with 48 per cent of haemoglobin. Progress thereafter was slow but by September her count exceeded 4 million with 80% Hb.

Rheumatoid changes occurred in her fingers and in Dec. 1930 she began to take Marmite instead of liver. The expense kept her from taking it regularly and her blood had many ups and downs and her rheumatoid condition was getting worse. In July 1933 she had 70 per cent of haemoglobin and then failed to report for 2 months when she returned with 36%. Pernaemon 5 c.c. intravenously was given and a slow rise up to 80 per cent in October 1933 followed. The year 1934 saw another fall to 30% and a rise to 90. It was now realised that changed conditions and her rheumatoid fingers had practically ended the patient's career as a teacher of music, and that she had not taken the remedies advised but only what she could afford. By this time she had numbness and tingling; knee jerks sluggish, vibration and joint sense impaired. The rheumatoid changes in the hands had increased.

In/

In May 1935 she was started on depot treatment with pernaemon forte and vitamin B 1 was also injected once a month.

Throughout 1938 and 1939 her haemoglobin was well maintained - on one occasion reached 120. The postero-lateral symptoms had not increased and the rheumatoid condition seemed less acute.

This year there has been increasing difficulty in keeping the Hb. level above 70. Various preparations of B 1 have been given and neither the nerve condition nor the rheumatoid condition have deteriorated. The patient has however reached the age of 72 and the complacancy of old age seems to have mitigated her discomfort in spite of increasing frailty.

TWIN PREGNANCY.

CASE 126.

Mrs G. age 27. Complained on 27.4.33 of weakness of 4 months duration. A year previously she had suffered from cervicitis and dysuria.

There was pallor, glossitis and haemic murmurs.

Apparent loss of flesh and mental listlessness.

Red Corpuscles 1.4: Hb. 33: Leucocytes 9.4: Retics. 8.

She was treated with an experimental extract of liver and then with Boots' extract by mouth. Haemoglobin fell to 22 in 5 days and then increased. On May 6th it was 30, on May 15th 60, on 19th 64, and on 3rd August 90%. For the next four years patient's course was uneventful. She had a variety of liver extracts but from June 1936 she has had anahaemin 2 c.c. approximately once a month. In January 1937 she gave birth to twins weighing $1\frac{3}{4}$ and $2\frac{1}{4}$ lbs. She did not survive. Patient remained in good health. She had a miscarriage in May 1939.

Up to the time of writing she remains in good health getting only 1 c.c of anahaemin per month. She has become considerably stouter.

P. L. D.

CASE 138.

H. Male, 56, Boot machine operator, admitted May 11th 1938 complaining of weakness of the legs.
Stated he had suffered from pernicious anaemia some years previously but had given up treatment.
He was found to have 1.8 million red Corpuscles, Hb. 48. Leucocytes 3400.
There was numbness and tingling in hands and feet. Slight Rombergism. Sensibility not impaired. Arm reflexes unimpaired. Left knee jerk diminished. Right normal. Both ankle jerks absent. Both plantar reflexes extensor.
He made slow progress on the preparation first given but his haemoglobin reached 72 in 3 weeks. Thereafter he was given anahaemin and in another fortnight his haemoglobin was 104. His knee jerks now became increased and his legs rather spastic. On getting about, however, his legs became oedematous and although no cardiac lesion could be demonstrated his blood pressure was only 95/65. He has since improved and returned to work. He reports regularly every month and haemoglobin remains above 90.

A LOW COUNT.

CASE 142.

D.M. 58. Coachman-gardener. In 1921 began to get tired easily, and to suffer from indigestion which was relieved by an acid medicine.

No previous illness of importance.

Pale yellow and breathless. Blowing systolic murmur at all areas. Pressure 160/100.

No change in nervous system. No abnormal ingredient in urine. No HCl in gastric contents.

Red Corpuscles 980,000. Hb. 19. Leucocytes 4700.

Reticulocytes: 2 per cent.

Patient received an intravenous injection of "pernaemon" 5 c.c. on eight successive days. On the successive following days his reticulocytes were 3, 8, 15, 32, 36, 40, 31, 12, 4.

Five days after his injection, Haemoglobin was 30 and in ten days 50 per cent. Since that time different preparations have been given. For over four years he has had an intra-muscular injection of anahaemin 2 c.c. every four weeks. His haemoglobin observations have fluctuated between 80 and 100.

Except for the disability due to thickened arteries he has no symptoms.

ATAXIA: HIGH PRESSURE.

CASE 145.

Mrs F. M. aged 57. Complained on 17th January 1936 of attacks of sickness which had lasted at least 10 years, sore tongue for years, pains in the limbs and difficulty in walking.

She stated that the sickness had no constant relation to food. She never had vomited bile or blood. There had been tingling in the limbs for 3 years and for 4 years she had difficulty in walking as she did not know where her feet were and she was easily tired.

She said she had been treated for 2 years by liver injections but had not improved. She had eaten liver for years and was sick of it.

Has had dentures for years.

Her home is comfortable and she has no family. Blood pressure 120/74.

Has tingling sensations but no impairment of sensibility. Coordination tests performed well. Motor functions and reflexes all normal. Red Corpuscles 1.2 Hb. 30. L. 2.8.

She received an intravenous injection of pernaemon and a few days later an intramuscular dose of pernaemon forte. There was a reticulocyte response up to 18 per cent. and in a month Hb. was 70. There was no objective sign of nervous disease but in May the difficulty in walking/

PROGRESSIVE MUSCULAR ATROPHY.

CASE 148.

Mrs M., aged 50 admitted 21.7.36 complaining of pallor, lassitude and diarrhoea.

She stated that she always felt tired and for three years had spent more time in bed than out of it.

She had taken some liver on the advice of her doctor but did not continue on account of its expense.

In 1908, when 3 months pregnant, she suddenly lost the power of arms and legs. She made a partial recovery but a residual left hemiplegia was apparent and there was poor control of bladder and bowel.

On admission the spleen was palpable. Mitral systolic murmur. There were increased reflexes in left arm and leg: the left plantar reflex was extensor.

R. 2: Hb. 38: L. 2.

As patient was collapsed and delirious she received a pint of citrated blood. There was immediate improvement and in a month Hb. was 70.

She has reported every month since discharge.

In September 1937 she began to complain of tingling of the fingers and toes. There was wasting of the adductors of the thumbs with active fibrillar tremors. There were tremors of the arms extensors and wasting of the right deltoid. Arm reflexes all increased.

As far as motor functions were concerned the picture was one of amyotrophic lateral sclerosis but there were also/

also sensory phenomena. A variety of Vitamine B preparations have been given but there has been a steady deterioration.

Throughout 1938 there was little change.

In 1939 the usual Hb level was 90.

There was Rombergism, poor sensibility to heat and cold. All tendon reflexes increased and plantar reflexes extensor. In 1940 there appears to have been an improvement in general health but an increased nerve disability.

It never became clear why she had been "paralysed" or why she had a hemiplegia. Cardiograms were normal and blood pressure not excessive. There seems now no doubt in view of the wasting and fibrillar tremors that she has an affection of the anterior horns.

Case 148. Hands and forearms.

EPILEPSY. CALCULI.

CASE 149.

Mrs P. aged 63. Admitted 1.11.39 with a history of debility for 5 years. Hb. 48%.

Treated with "Examen" she made a rapid recovery and Hb. has remained about 80.

Her complications are fortuitous but interesting.

1. She informed us that she used to take fits but had not had one for twenty years. On two occasions since she has taken a fit while visiting the Clinique.

2. Owing to a complaint of pain in the right hypochondrium she was examined by X-rays. The report dated Nov. 15th was as follows:- There are numerous facetted calculi in the gall-bladder and a very large staghorn calculus in the right kidney".

PREGNANCY.

CASE 151.

Mrs P., aged 34. This lady's case has already been published (7). She was admitted on 4.10.30 complaining of weakness. She was in good health till 2½ years before - some months after marriage. It was then noticed that she had a yellowish-brown complexion which has remained. She also had occasional small painful spots on her tongue and transient feelings of tingling and numbness in fingers and toes.

On admission she had R. 1.5: Hb. 31: L. 5.2.

Treated with liver she soon improved and on 20.11.30 was discharged with Hb. 70.

On 4.5.31 she had a miscarriage.

Throughout 1931 she was treated with marmite. Hb. was rather variable ranging from 64 to 92. At this time her husband was unemployed and sometimes she was short of both medicine and food - a state of affairs which lasted till 1934. She then got liver plus 2 tubes of Boots' liver extract weekly.

In April 1935 she became very deeply pigmented especially round the nipples but no other symptom was noted. B.P. 125/80.

She started Pernaemon forte and there was considerable improvement. In 1936 she changed to anahaemin and had a great year, especially as her husband had got a job.

Early/

Early in 1937 periods were absent for 9 weeks and her home doctor thought she had a miscarriage.
In 1938 the improvement in health and prosperity was obvious. In August a positive Ascheim-Zondec test was obtained and a healthy female infant was born on 1st January 1939. The patient was now 43 and the confinement was a bad one. Haemoglobin fell to 45. She was treated with pernaemon forte and iron and soon picked up. The infant, now walking and talking, is a fine specimen whose blood has shown no abnormality.
The mother is in good health. Pigmentation varies very greatly. Friends remark on her "sun-burn" but the nipple region and the abdomen are deeply pigmented.

Mrs P. and infant at age of 4 mos.

A LOW COUNT.

CASE 164.

Mrs W., aged 53, admitted April 1935 complaining of loss of strength and swollen ankles of over two years duration. Although exertion made her breathless she had continued her household duties.

Patient was rather spare. Tongue smooth with red papillae at the margins. The spleen was just palpable. A systolic murmur was heard at all the cardiac areas. Urine was normal and there was no involvement of the central nervous system. The red cell count was 560,000: Hb. was 16%: Leucocytes 1,400. These figures naturally excited some interest and were verified by experts.

It was argued that as the lady had carried out her household duties with 16 per cent of haemoglobin she might safely stay in bed at the same level. Transfusion was therefore withheld. She received an intravenous injection of pernaemon on five successive days and then Campolon intramuscularly for ten days. Reticulocytes rose from 0.8 to 6 per cent. on the 4th day, and to 30 per cent on the sixth day.

For over five years she has attended for an injection of liver extract every fourth Wednesday. Her haemoglobin has remained steadily between 85 and 98 per cent. except for one reading of 102.

PART IV.

PART IV.

COMPLICATIONS - INCIDENCE.

PREGNANCY.

Pregnancy preceding pernicious anaemia, whatever the relationship between the two conditions may be, is not a complication of the anaemia. One such case, a woman of 37, occurred in this series.

Five cases of pregnancy following pernicious anaemia are included. In one case, twins were born 4 years after the onset of pernicious anaemia and a miscarriage occurred later.

In another, a healthy infant was born 8 years after pernicious anaemia had been discovered.

One woman was delivered by Caesarean Section.

Details of the cases are given (Pp.43,44,61,69).

The fifth case was found to have pernicious anaemia three years ago. She has now given birth to a healthy son and is herself in good health.

COMPLICATING DISEASES.

The complications met with in this series were the following:-

Syphilis (two cases with positive Wassermann reaction and no other symptoms).

Rheumatoid arthritis. F 62. M 58.

Influenza.

Pneumonia (fatal) F 60.

Parotitis (fatal) F 68.

Osteomyelitis M 61.

Malignant Disease.

Gastric Carcinoma:- M 55, M 51, F 78, F 57.

Carcinoma of Rectum:- M 66.

Rodent Ulcer:- M 50.

Digestive Diseases.

Glossitis. F 52 (note p.58) M 47.

Biliary Colic F 63, M 57.

Pyloric Stenosis M 54.

Cardio-vascular Disease.

Valvular. F 65, M 55.

Thrombo-phlebitis M 56.

INCREASED BLOOD PRESSURE.

Males.		Females.	
Age	Systolic Pressure.	Age	Systolic Pressure.
58	160	75	180
65	190	48	200
58	200	65	170
69	165	57	216
67	180	66	210
		58	182
		60	170
		42	180
		50	180

ENDOCRINE DISTURBANCE.

Myxoedema F 51 F 73

Toxic Goitre F 40

Pigmentation (probably Addison's disease)

M 63
F 34
F 34 (see p. 69.)

URINARY CONDITIONS.

Nephritis M 74, M 53.

Cystitis F 48, F 56, F 58.

Oxaluria M 50.

NERVOUS AFFECTIONS.

Slight postero-lateral degeneration or neuritis.

Males.		Females.	
Age	30	Age	36
"	34	"	37
"	46	"	41
"	47	"	46
"	48	"	55
"	49	"	62
"	50	"	62
"	53	"	65
"	56	"	66
"	57	"	66
"	66	"	78
"	66	"	79 - 12
"	74 - 13		

= 14.7%.

Definite postero-lateral degeneration.

Males		Females.	
Age	30	Age	26
"	34	"	37
"	46	"	50
"	51	"	57
"	52	"	61
"	53	"	63
"	56	"	67
"	56	"	69 - 8
"	57		
"	58		
"	59		
"	63		
"	66		
"	69		
"	74 - 15		

= 13.5%

VARIOUS OTHER NERVE AFFECTIONS.

Epilepsy F 63, F 40.

Migraine F 46.

Mania M 59, F 72

Huntington's Cholera F 66.

Progressive Muscular Atrophy M 55, F 50, M 57.

Paralysis of Cranial nerves M 67.

Nerve Deafness M 69.

MISCELLANEOUS CONDITIONS.

Pregnancy 27, 28, 38, 42, 31 (Caesarean Section)

Metrorrhagia 37, 45.

Haemorrhoids M 47, F 52.

Haemoptysis M 60.

Aplastic anaemia M 53, F 49.

Lymphadenoma M 56 (died)

Scurvy M 56.

Alcoholism M 66.

Tobacco Amblyopia M 47.

On a general view we find 40 different conditions associated with 170 cases of pernicious anaemia.

The total number of complications among the 170 cases was 119 but a few patients had more than one complication.

No case of tuberculosis was found. Wilkinson found only 1 in his series of 370.

One case of pneumonia accords exactly with Wilkinson's finding, as do two cases of syphilis.

One instance of parotid abscess, one case of chronic osteomyelitis and two cases of rheumatoid arthritis occurred.

Malignant disease includes 4 cases of gastric carcinoma and two of malignant disease elsewhere.

There was no case of gastric or intestinal ulceration but one case of pyloric obstruction, probably cicatricial, was noted.

Glossitis as a complication or late symptom was noted twice.

Biliary Colic was seen twice. It is not recorded in Wilkinson's series.

Cardio-vascular disease (10%) greatly exceeds Wilkinson's figures (4.8), and this in spite of the fact that only pressures of 160 and over have been included as abnormal.

ENDOCRINE DISTURBANCES.

Affections of the thyroid are in insignificant numbers.

Addison's disease with its interesting association with pernicious or Addisonian anaemia is seldom seen in connection with pernicious anaemia. It does not appear in Wilkinson's list.

One case occurred in this series.

In two other cases there was a pigmentation so intense and of such distribution that a diagnosis of Addison's disease on that ground might have been justified. The absence of asthenia and low pressure, however, failed to support that possibility.

A few cases of dense pigmentation in pernicious anaemia have been demonstrated at medical meetings from time to time.

No case of diabetes occurred in this series.

URINARY CONDITIONS.

The small incidence of albuminuria in this series as well as in published records is remarkable since it is unusual to see healthy kidneys at post-mortem examination of cases of pernicious anaemia.

Other urinary conditions seem to be entirely fortuitous.

NERVE AFFECTIONS.

The nerve complications other than P.L.D. are an interesting miscellany.

Among the ten cases are two instances of mania which is not uncommon among published cases.

Progressive muscular atrophy is an interesting occurrence, - seen in three cases. Wilkinson refers to one case, but his total of nerve cases is only three, exclusive of Postero-lateral degeneration.

Postero-lateral degeneration is referred to later.

MISCELLANEOUS CONDITIONS.

It is notable that haemorrhage (from three different sources) was a feature of five cases. Needless to point out, it is a complication of great gravity, which should be promptly dealt with whenever possible. One case was remarkable - haemoptysis from sclerotic branches of the pulmonary artery.

Lymphadenoma in one case seemed to follow the anaemia.

Details of an interesting case of scurvy have been given.

COMPLICATIONS - SIGNIFICANCE.

PREGNANCY.

Considering the usual age incidence of pernicious anaemia this problem is not likely to be a very common one.

The subject of the anaemias of pregnancy is outside the scope of this thesis. Our present interest is in the pregnancies of pernicious anaemia. There seems no doubt that a woman suffering from pernicious anaemia, if adequately treated may give birth to a healthy infant without great risk to herself.

The case of a woman, aged 42, published by Goodall is noted on page 69 . An authentic history of pernicious anaemia for 8 years is given. The child is healthy.

Another satisfactory case occurred after a history of pernicious anaemia for three years.

A third case after Pernicious anaemia for 4 years is also noted. Unfortunately the lady had been too ambitious and her twins did not survive.

The fourth case was not a satisfactory patient. She survived Caesarean Section but the child died.

It may be concluded that pernicious anaemia is still a dangerous complication of pregnancy, but pregnancy is no longer a dangerous complication of pernicious anaemia.

DISEASES./

DISEASES.

As already pointed out the great majority of the complicating diseases are fortuitous. Some, however, gain significance by their frequency, some by a possible connection in pathology, and others because of an association which may be regarded as proved.

In the first category are the cardio-vascular conditions. In the second is cancer of the stomach. To some extent this has been discussed in Part II.

The difficulty in diagnosis between pernicious anaemia and cancer of the stomach before haematological methods and X-ray diagnosis were elaborated has doubtless given the alleged association of these conditions an importance greater than it deserves.

Any increase in carcinoma of the stomach in cases of pernicious anaemia which may have occurred in recent years is doubtless due to improved treatment of pernicious anaemia so that cases live longer and live to an age when cancer is most common.

In the third category comes the very important feature of the disease - postero-lateral sclerosis.

CARDIO-VASCULAR CONDITIONS.

The incidence of valvular disease has not been greater than might be expected among the general community of similar age.

ARTERIO-SCLEROSIS AND INCREASED PRESSURE.

If a visiting physician were asked to guess the main complaint among the patients in the waiting room of the clinique his answer would be arterio-sclerosis.

It is regretted that when I collected the data concerning blood pressure I included only those pressures of 160 and over.

The addition of systolic pressures of 150 to 159 would almost certainly have doubled the length of the list. This might be inferred from the figures recorded, since 10 of the 14 cases show readings of 180 to 216. The incidence of arteriosclerosis is probably the main factor in stabilising the numbers attending the clinique. In spite of constant additions its numbers vary very little. As will be noticed later, these patients do not come into hospital to die. We may assume that sudden heart failure, coronary thrombosis and cerebral haemorrhage must be their common ending, but curiously enough there is only one record of such a happening among the 170 cases studied.

It may be repeated, as was stated in Part II, that many of the nervous and mental symptoms and retinal haemorrhages may be due to arteriosclerosis.

POSTERO-LATERAL DEGENERATION.

This feature of pernicious anaemia is by far the most distressing. Patients who have been in attendance for years with satisfactory haemoglobin readings begin to complain of weakness, numbness and tingling and from that stage they progress to increasing helplessness.

It is exceedingly difficult, probably impossible, to say whether the initial symptoms are those of neuritis or of postero-lateral degeneration nor is it possible to say when the conditions (if they are ever different) meet each other. My own impression is that the overwhelming majority of cases are cord lesions from the outset. This appears to be the view of Goldhamer and Colleagues (34) who found evidence of postero-lateral degeneration in 89.2 per cent of cases and also found treatment by anti-anaemic measures to be useless. In the cases I have quoted the distinction between the early cases with numbness, tingling and weakness and the later cases with changes in the reflexes has been rather arbitrary.

It is possible that as the result of anaemia there may be an element of neuritis which is recoverable but it would be remarkable if a true degeneration of neurons which never recovers in other circumstances should recover when it is due to the deficiency of pernicious anaemia.

I/

I agree with Baker (32) and Colleagues that any improvement we meet with occurs in the ataxic and not in the spastic cases. In judging of improvement in this respect we are more in the hands of the patient in the ataxic cases than in the spastic, and improvement in general health and in amount of haemoglobin doubtless improves the patients' subjective symptoms and strength but are not so likely to minimise spasticity.

I agree with Grinker and Mandel (35) that it is probably useless to give more liver than is necessary to maintain a normal blood count. I agree also with Russell (37) that some improvement may be obtained by giving Vitamine B 1 as well as liver. I have never seen any improvement without it - even with massive doses of liver.

DURATION.

It is almost impossible to make any statement about duration of life in sufferers from pernicious anaemia. There is usually a long history of illness or poor health when patients first complain.

Hospital patients from a distance may never return to report.

Of the 170 patients under review from 1929, 55 were known to be alive at the end of 1939. Thus -

Year	(1929)	1930	31	32	33	34	35	36	37	38	39
Number first reported.	(2)	3	1	1	8	2	10	8	9	8	6
Number still alive.		3	4	5	13	15	25	33	42	50	56

This statement is not of great statistical value since there is no information nor, indeed, reason for thinking that any large proportion of the remaining 115 patients are dead; but ten years ago anyone who claimed to have seen 56 cases of pernicious anaemia who had survived for periods between 1 and 10 years would not have been believed.

A few cases of long duration were reported as curiosities in pre-liver days, but doubtless such cases will become common.

DEATHS.

It is remarkable that in a series of 170 persons whose average age was 48 and all admitted on account of grave illness only 10 or 5.8 per cent died. All the others had greatly improved before leaving hospital.

The following table gives the sex and age of the patient, the cause of death and the last haemoglobin reading.

		Hb.
F 60	Pneumonia	-
M 59	Carcinoma of stomach	90
F 65	Ventricular fibrillation	90
F 78	Carcinoma of stomach	45
M 66	Carcinoma of rectum	92
M 61	Chronic osteomyelitis	18
M 60	Haemoptysis	25
M 56	Lymphadenoma	32
M 53	Marrow partially aplastic	18
F 65	Admitted comatose	27

It will be noted that only the last five cases had a serious degree of anaemia at death. In two of the five anaemic cases the cause of death was sepsis and haemoptysis respectively. Even in the three cases who died of pernicious anaemia there were complicating factors/

factors in two, and possibly in the third.

The high proportion of cases of cardiac and vascular disease in this series suggests that many deaths must be due to cerebral gaemorrhage or heart failure.

It is also probable that the end results of postero-lateral degeneration are not commonly seen in general hospitals and many of the fatal cases may be ascribed to various forms of "paralysis".

It is difficult to say whether aplastic anaemia is a result or a complication of pernicious anaemia. It certainly may follow pernicious anaemia but in my own moderate experience it more frequently does not.

It would appear that pernicious anaemia so long as well treated is not now a very fatal disease. It is the complications that kill and probably the most serious of these complications is old age.

TREATMENT.

The recent history of the treatment of pernicious anaemia is almost a romance.

The discovery that liver contains a haemopoietic substance and that this substance is elaborated from an intrinsic factor in the stomach combined with an extrinsic factor in food has been an amazing one.

The attempts to treat patients with raw liver have unfortunately not entirely ceased. An interesting series of observations was made with liver cooked in various ways, with fish liver and with yeast preparations such as marmite.

Preparations of gastric mucous membrane are still available but are seldom used.

The manufacturing chemists now supply a number of liver preparations which are almost exclusively used. A few are available for oral administration, and in cases where a patient is unduly sensitive about the use of a needle or is to be temporarily away from the care of his doctor they are of use.

A potent and reliable extract is supplied by Boots.

When a patient is desperately ill, intravenous injection is often efficacious and may be combined with transfusion. It will be found that a reticulocyte response generally occurs a little earlier after an intravenous/

intravenous than after an intra-muscular injection. A word of warning about these preparations is necessary. They should never be given intravenously unless expressly intended for such use. Very nasty reactions may follow the intravenous administration of a preparation intended for intramuscular use.

PRESENT PRACTICE.

The great standby for the maintenance treatment of pernicious anaemia has come to be intramuscular injection of liver extract. The adult dose varies with the degree of concentration and purification of the preparation supplied by different manufacturers. As will be seen in the tables on pp. 31-36 many preparations have been used. As these are put up in sterilised containers containing suitable quantities for one dose it has been found convenient to use the dose stated and to vary the intervals between doses as may be indicated. We find that in the overwhelming majority of cases this interval is four weeks. A few patients come every six weeks and a few come every three weeks, and very few indeed come at greater or shorter intervals. The attendance is influenced a little by factors outside mere haemopoietic necessity. Patients arrange to get leave from work once a month. There is also a blood brotherhood and sisterhood. The patients like to see their old friends and "feel strange" when/

when they come on the wrong Wednesday. The baby referred to on page. 70 , now walking and talking, is an attraction to patients.

There seems to be little difference between the majority of the liver preparations. Only one or two seem to be poor. There are considerable differences in price and these do not all correspond to quality, and there are curious differences in the reaction of patients.

Taken all over, the most reliable preparation is thought to be "pernaemon forte". It has been found, however, that its use is followed by more frequent reactions, but possibly this is because it has been most frequently used.

The next favourites in the Clinique are anahaemin and examen.

Very rarely are other measures called for.

The indications for transfusion are simply those for any other bloodless patient, except that the pernicious anaemia patient will survive a degree of anaemia which would be incompatible with life in any other condition.

Dilute hydrochloric acid may sometimes be employed but is never given as a matter of routine. Some degree of thyroid deficiency is common and should be treated. Iron may be called for when corpuscles are rising rapidly in number and "run away from their haemoglobin".

SUMMARY AND CONCLUSIONS.

A resume of recent literature dealing with the complications of pernicious anaemia is given.

Tables have been compiled showing the sex, age, haemoglobin percentage when first and last seen, complications and treatment in 170 cases. Of these, males numbered 84 and females 86. The average age on admission was males 49, females 46.

Notes of cases of special interest are included.

The incidence and significance of complications is discussed.

Postero-lateral degeneration in some degree occurred in 28 per cent of cases and to an advanced degree in 13 per cent.

Notes on duration, mortality and treatment are given.

The question is raised whether the red marrow in the shafts of the long bones and the iron deposits in the liver revert to normal during remissions. (Case 6).

Attention is called to the occurrence of glossitis occurring during remission of the anaemia. (Case 114).

Three cases showed fibrillar tremors and muscular wasting in addition to symptoms of postero-lateral degeneration.

Among/

Among the points of interest that emerge from this study are the following.

1. Since the introduction of liver therapy pregnancy in cases of pernicious anaemia is no longer rare. It occurred in 4 of the 86 female cases. While pernicious anaemia is a serious complication of pregnancy, pregnancy is not a serious complication of well-treated pernicious anaemia.

2. Cases of pernicious anaemia now live to have numerous complications. Forty different conditions were associated with the 170 cases studied, and some complication was present in 70 per cent of the cases. The most common and debilitating is postero-lateral degeneration.

3. The great majority of the associated conditions are fortuitous but some of these, notably arteriosclerosis, are important on account of their frequency, and effect on expectation of life.

4. Expectation of life has greatly increased:- Thus,
   (a) Of the 170 cases seen in the course of ten years 55 are still under observation and 10 are dead, but nothing is known of the others - many had come from a distance.

   (b) Of the 170 cases admitted to hospital only 10 are known to have died and only one of these of uncomplicated pernicious anaemia.

(c) It is probable that many cases die of vascular or nervous complications or may be killed by motor cars.

(d) It would appear that pernicious anaemia, so long as well treated, is not now a very fatal disease. It is the complications that kill, and among the most serious of these is old age.

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A list of references to Pernicious Anaemia and Gastric Carcinoma is given after the Section dealing with the subject. (page 11).