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SOME CLINICAL ASPECTS OF PERNICIOUS ANÆMIA.

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Reprinted from the 'Transactions of the Medical Society of London,' vol. xxxii, 1909.

LONDON:
HARRISON AND SONS, ST. MARTIN'S LANE, W.C.,
PRINTERS IN ORDINARY TO HIS MAJESTY.

1909.

[*Reprinted from the 'Transactions of the Medical Society of London,' vol. xxxii.*]

SOME CLINICAL ASPECTS OF PERNICIOUS ANÆMIA.

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Introduction.

Gentlemen,—I have recently had occasion to read through the records of the cases of pernicious anæmia that have been in Guy's Hospital since 1890, and your Secretary has asked me to say a few words about them from the purely clinical point of view. Dr. Dudgeon has just spoken upon the pathology of the complaint. The main features of the disease are so well known that I need not refer to some of them at all; indeed, I propose to restrict my remarks to seven particular points, viz., the following:—

I. The temperature charts of pernicious anæmia cases.
II. Pigmentation of the buccal mucosa in pernicious anæmia.
III. The size of the spleen in pernicious anæmia.
IV. The nerve symptoms in pernicious anæmia.
V. The variability in the colour index in pernicious anæmia.
VI. The injustice of the epithet "pernicious" in some of the cases.
VII. The difficulty frequently met with in accurately dating the beginning of the illness, with some thoughts that this difficulty suggests.

Before proceeding to discuss each of these points in turn, I should like to say that my present use of the term pernicious anæmia is a decidedly restricted one; some remarks that I shall make at the end of this paper will indicate that I think the limitations may some day be shown to need relaxation, but meanwhile I do not include as pernicious anæmia any case that has not at one time or another exhibited oligocythæmia with a high colour index and no leucocytosis during life; and, should death occur, a definite Prussian blue reaction in the liver. Fifty-eight such cases passed through the wards of Guy's Hospital between the years 1890 and 1907. The cases previous to 1890 have been collected together and published in the Guy's Hospital Reports in papers by Dr. Pye Smith, Dr. Frederick Taylor, and Dr. Hale White.

I must ask your indulgence if you do not find the following remarks in any way new or original. They will, perhaps, serve to bring out a few clinical points upon which I think less stress is sometimes laid than should be, and I hope they will elicit a discussion.

I. The Temperature Charts of Pernicious Anæmia Cases.

(Oral Temperatures.)

First, let me refer to the temperature charts of pernicious anæmia cases. It is remarkable how constantly there is slight pyrexia. I have copied out the charts in all the cases I have been able to find, and three points about them stand out saliently, viz., first, that when the patient is ill enough to be admitted to hospital it very seldom happens that there is not a rise to something between 99° and 100° F. every evening; secondly, that pyrexia exceeding 101° F. is possible in pernicious anæmia, though decidedly unusual unless there is some intercurrent malady such as tonsillitis or pneumonia; and, thirdly, that there is little tendency to subnormal temperatures in the morning, especially if the records are made only at 10 a.m. and 6 p.m.

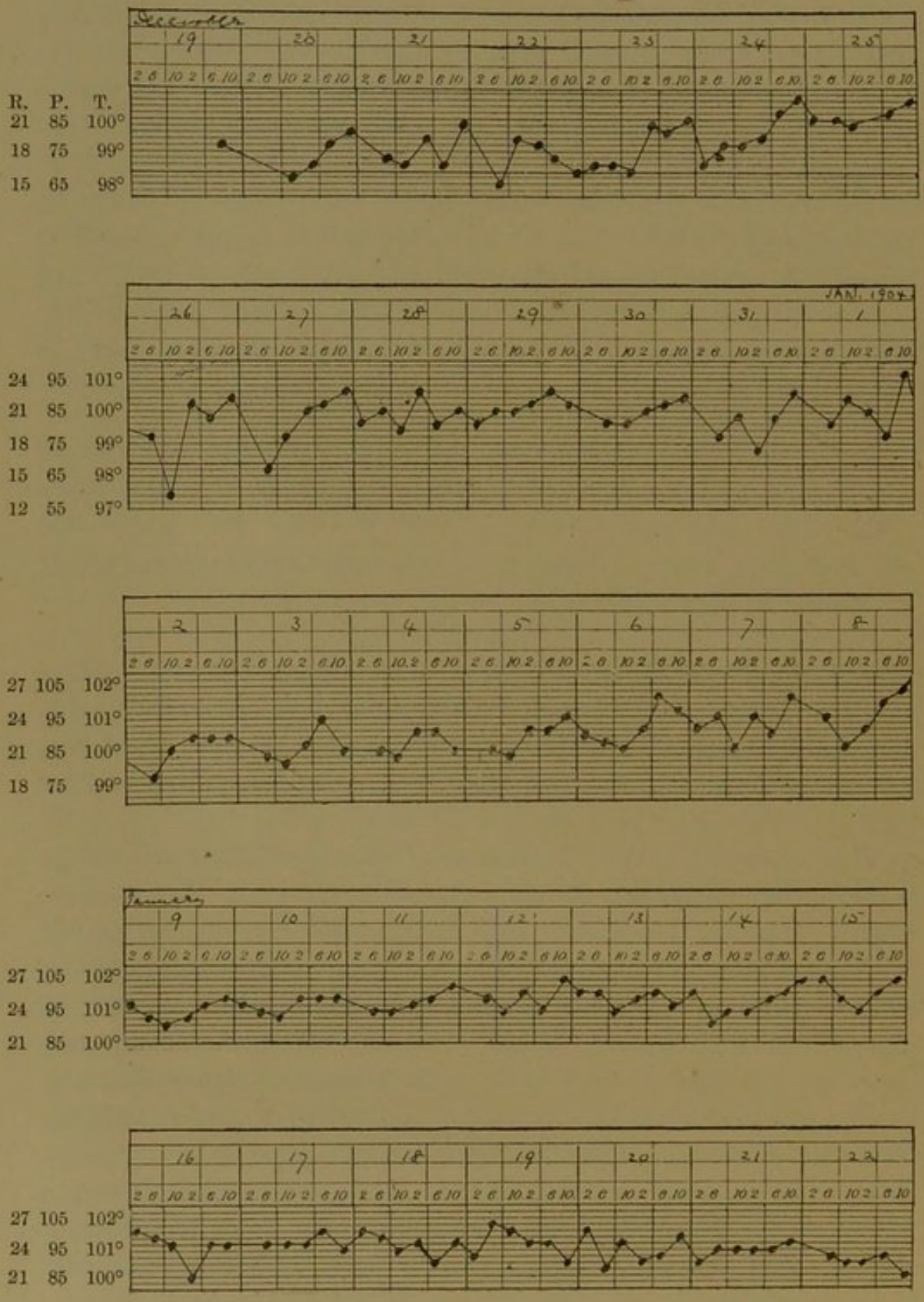
Judging from what happens in other asthenic conditions, such as those associated with chronic heart disease, for example, one would not have been surprised if the temperature in a severe case of pernicious anæmia had shown a tendency to be persistently subnormal; judging from what happens in cases of chronic sepsis on the other hand, one might have expected a moderate degree of

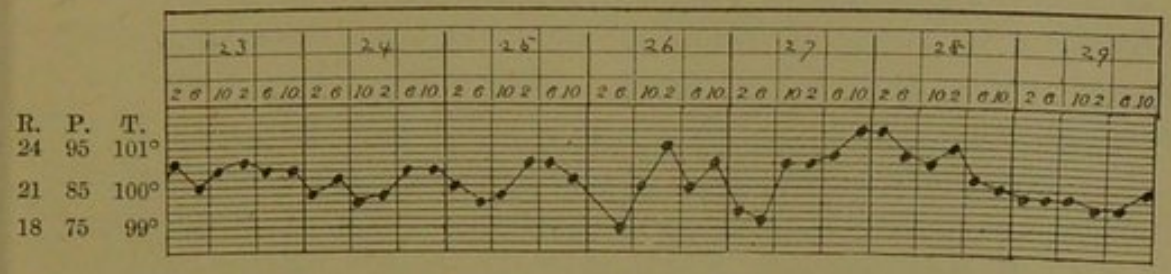
evening rise, but at the same time a considerable drop below normal in the morning. Neither of these types of temperature chart is at all like that of most cases of pernicious anæmia, however; in this disease it may be roughly said that the more the general condition of the patient improves under treatment the less does the tendency to evening pyrexia become; but that when the patient is decidedly anæmic and ill the condition is not like that of the majority of pernicious anæmia cases unless the patient's temperature tends to rise to something between 99° and 100·5° F. every evening without any great fall below normal at 10 a.m. in the morning. Chart after chart taken from successive cases of pernicious anæmia shows this slight but persistent pyrexia. The smallness of the variation in temperature at different times of the day in some cases is well exemplified by this four-hour chart in the case of Louisa W. The notes of her condition are as follows:—

Louisa W., aged 43, a florist, was admitted under the care of Dr. Taylor on December 19th, 1903, and died on February 13th, 1904. She came in for weakness and vomiting. She stated that she had never been ill until six months previously, when rapidly increasing weakness compelled her to give up her work. She also suffered from pains in the epigastric region and from vomiting, especially after taking food. There had been a moderate degree of epistaxis on several occasions. The catamenia had been regular, but latterly the loss of blood had been considerable each time. The patient was so weak that she could not walk three steps without resting; at the same time she was not emaciated.

The liver was palpable, smooth, and decidedly tender; the spleen was palpable 2½ inches below the costal margin. The cardiac impulse was in its normal position, but there was a loud hæmic bruit in the pulmonary area. The patient's teeth were in particularly good order, and the mouth was clean. The nervous system appeared to be natural. There were decided hæmorrhoids, and they bled considerably each day. Indeed, the first diagnosis made in the case was that the anæmia was secondary to hæmorrhage from the piles. The blood counts and the *post-mortem* findings, however, indicated pernicious anæmia. The pulse rate varied from 88 to 108, the respiration rate from 20 to 32. The temperature chart showed a typical evening rise to about 100° F. The urine had a specific gravity of 1010; on one occasion only did it contain

Temperature Chart of Louisa W.

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R. P. T.
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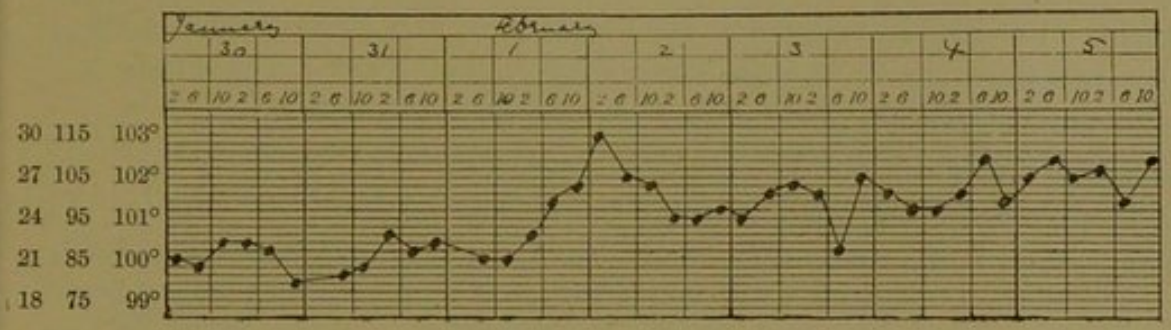
21 85 100°
18 75 99°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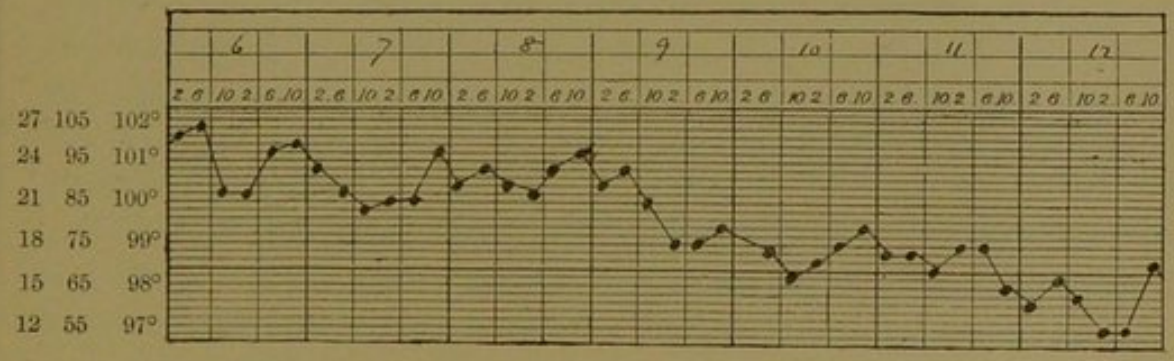
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18 75 99°
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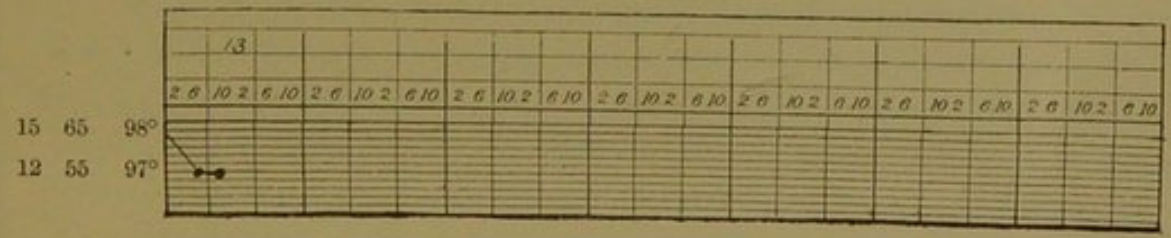
12 55 97°


13
2 6 10 2 6 10 2 6 10 2 6 10 2 6 10 2 6 10 2 6 10 2 6 10 2 6 10
15 65 98°
12 55 97°

albumen; there was no hæmaturia; uric acid crystals were deposited spontaneously; urobilin was not mentioned.

Arsenical treatment was tried, but there was great difficulty in continuing it owing to vomiting and diarrhœa, both of which became very severe before death. The latter came about by exhaustion.

The chief points noted at the *post-mortem* examination were: that the lungs were healthy, the heart presented much sub-pericardial fat, with obvious tabby-cat striation in the muscle, particularly in the musculi papillares of the left ventricle. The liver was large and pale, and gave an even more marked Prussian blue reaction than usual. The spleen was moderately enlarged, and gave a fairly good blue reaction, less in degree than that in the liver. The kidneys were pallid, and one of them was scarred from former impacts; they were not tested for the Prussian blue reaction.

The blood counts made during life were as follows:

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.	Leucocytes per cub. mm. (Thoma-Leitz.)
Dec. 20, 1903...	2,050,000	41	35	0·853	8,000
Jan. 5, 1904 ...	1,339,000	27	25	0·926	—
Feb. 2, 1904 ...	787,500	16	24	1·500	6,532

A differential leucocyte count in December, 1903, showed:—

	Per cent.
Small lymphocytes	27·2
Large ,, ...	2·4
Polymorphonuclear cells	66·6
Coarsely granular eosinophile cells ...	3·8

For nearly seven weeks her temperature never touched normal once.

So marked a pyrexia might readily lead to difficulties in diagnosis. For example: if diarrhœa were a prominent symptom, and the spleen were palpable, as is often the case in pernicious anæmia, typhoid fever might easily be simulated, and in more cases than one pernicious anæmia patients have given the history that their illness resulted directly from an attack of something

obscure that was regarded as typhoid fever. It may well be that the supposed typhoid fever in some such cases was really the pernicious anæmia itself with its pyrexia. A case in point will be referred to presently.

Here is another four-hourly chart from a pernicious anæmia case (Hannah H.), exhibiting a more remittent type of temperature, it is also an example of the way in which the slight evening rise gradually dwindles off, and finally ceases as the patient's blood condition and general health improve. I need not read the following notes about her. She was a typical case of pernicious anæmia.

Hannah H., aged 31, a housewife, was admitted under the care of Dr. Hale-White on October 1st, 1903, for general weakness and for loss of weight of six months', and for vomiting and nausea of three months' duration.

She stated that for two months past she had been dyspeptic, and that six months ago, without any apparent cause, she began to ail. Her menses became scantier each month, and she gradually became weak. She suffered from alternate anorexia and bulimia. Headaches and noises in her head came on, and palpitations on the slightest exertion. Latterly there had been bleeding per anum, oozing of blood from the gums, and streaks of blood in the vomit.

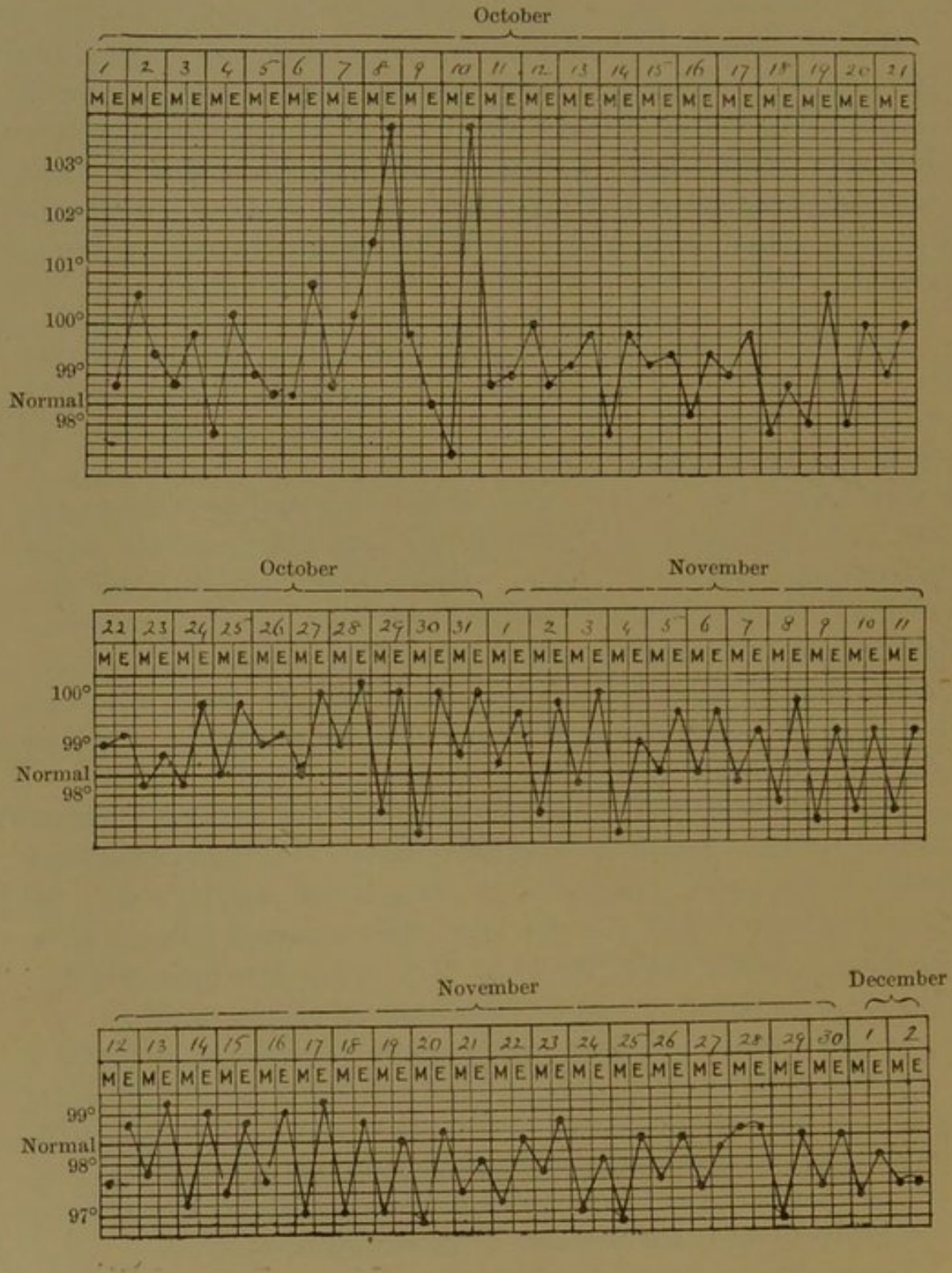
The teeth were much decayed. The face was extremely pallid, and dirty white rather than lemon yellow. The heart presented hæmic bruits, and a canter rhythm though the impulse was in its normal position. The abdomen was thin enough for the liver to be *seen* 1½ inches below the ribs. The spleen was just palpable. The urine contained indican in excess, but no obvious urobilin.

Arsenical treatment was adopted, but it was difficult to maintain on account of severe attacks of very foul diarrhœa. Various diagnoses were suggested, but that of pernicious anæmia was made obvious by the blood counts which are given below.

In this patient both knee jerks were extremely brisk, and there was ankle clonus in one foot but not in the other.

The retinæ were natural. The temperature was often 101° F. each night at first, and then as improvement took place it only rose to 100° F., and later to less still.

Temperature Chart of Hannah H.



She was discharged very much improved in health on December 10th, 1903, and she remained comparatively well for two months. She then began to lose ground again, the menses decreasing as before, weakness and palpitations increasing, the phlegm becoming streaked with blood, and vomiting taking place after food. She was re-admitted under Dr. Taylor on June 20th, 1904, and re-discharged, again relieved, on July 23rd, 1904. She was extremely pallid on admission, with tenderness of the shafts of the long bones. The liver was felt 2½ inches below the ribs; the spleen was not felt this time; there was pyrexia as before; the lung signs were natural; the heart was of normal size, but presented hæmic bruits in all areas, and there was a bruit de diable in the neck.

The urine had a specific gravity of 1015, and it contained neither albumen nor blood.

Arsenical treatment led to troublesome diarrhœa, but at the same time the patient's general condition greatly improved.

Upon inquiry at her old address it was learned, on August 15th, 1907, that: "Mrs. Hannah H. has been dead for over 12 months now," so apparently she survived her second rally for a year or more.

The following were the blood counts in her case:—

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.	Leucocytes per cub. mm. (Thoma-Leitz.)
1903.					
October 1 ...	987,000	19	29	1·526	5,000
„ 4 ...	750,000	15	25	1·666	—
„ 7 ...	650,000	13	25	1·923	—
„ 18 ...	700,000	14	28	2·000	5,000
„ 25 ...	900,000	18	28	1·555	—
November 1 ...	1,100,000	22	39	1·776	—
„ 8 ...	1,100,000	22	35	1·591	—
„ 14 ...	1,400,000	28	39	1·393	—
„ 20 ...	2,500,000	50	60	1·200	—
„ 29 ...	2,500,000	50	60	1·200	—
1904.					
June 22 ...	868,750	17	26	1·529	7,187
July 8... ...	2,500,000	50	58	1·160	—

Notes.—On October 1st, 1903, many poikilocytes and megalocytes

were present in films, and nucleated red cells to the extent of 1 to every 60 leucocytes.

On October 18th, 1903, the differential leucocyte count was "practically normal."

On June 24th, 1904, poikilocytes and megalocytes were numerous, and nucleated red cells were seen.

Differential leucocyte count:—

——	June 22, 1904.	July 8, 1904.
	Per cent.	Per cent.
Small lymphocytes	54	20
Large „	6	12
Polymorphonuclear cells	38·5	60
Coarsely granular eosinophile cells ...	1·5	8

Two more charts will be sufficient, I think, to emphasize my point.

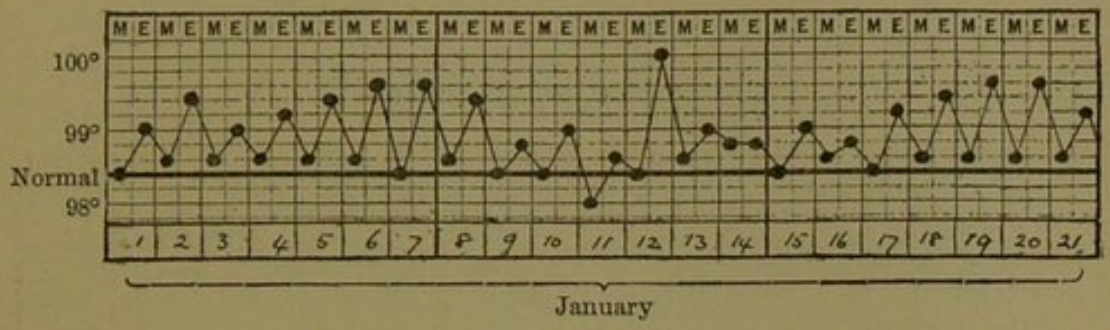
This one, from the case of Edward B., aged 53, is a very good example of what I should call the persistent slight evening pyrexia of pernicious anæmia.

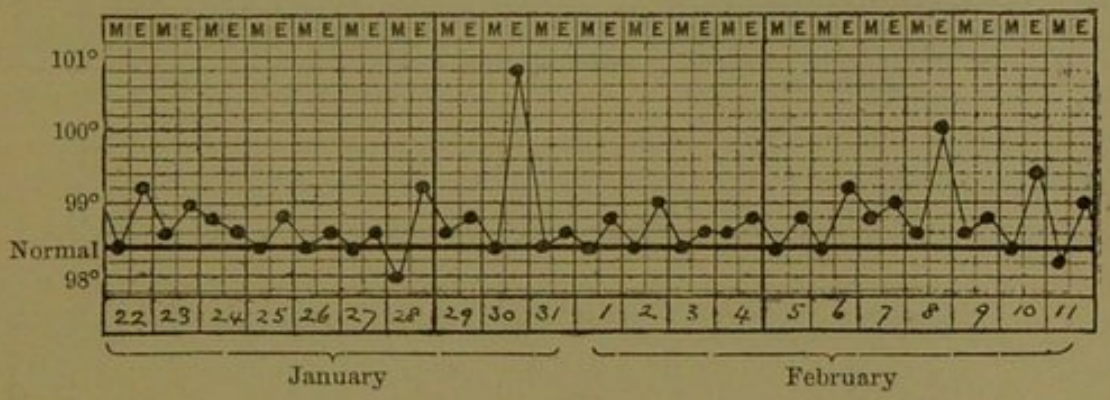
This other one, from a fatal case, Samuel D., aged 45, shows the increasing pyrexia towards the end of the disease, and a final drop to normal or below it just before death.

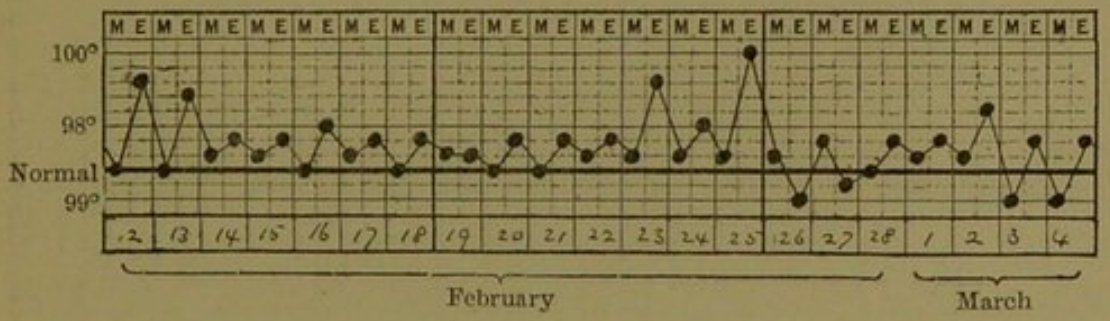
Edward B, aged 56, was admitted under the care of Dr. Goodhart on May 24th, 1893. He became relieved, and was discharged on July 22nd, 1893; he relapsed soon after, was re-admitted on November 28th, 1893, and died on June 9th, 1894.

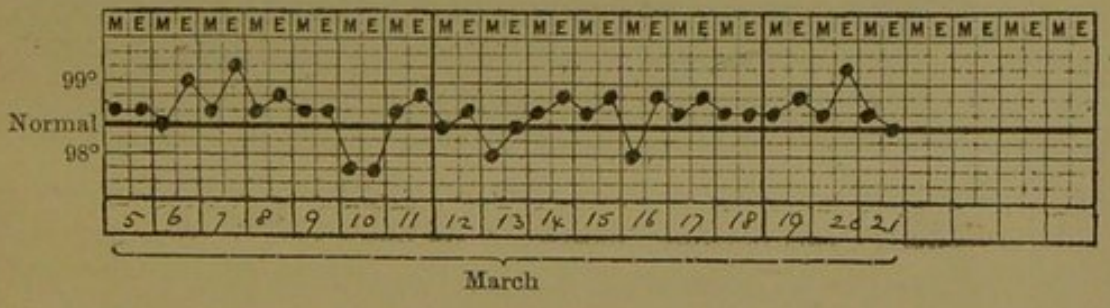
He gave the history that he was quite well until five years before his first admission, and that he then suffered a bad attack of diarrhœa during the summer, losing much blood per rectum at the time. Each summer since then he had had a precisely similar and very severe attack, lasting some weeks each time. In March, 1892, he first thought he was "jaundiced," and told his doctor so. In July, 1892, he was so much worse that he was laid up in Croydon Hospital for 22 weeks. After that he worked for eight weeks, but became progressively weaker and more ill. He had suffered from pains in the chest and abdomen, and from giddiness for over two years; these, together with prostrating weakness, were his main symptoms on admission.

Temperature Chart of Edward B.

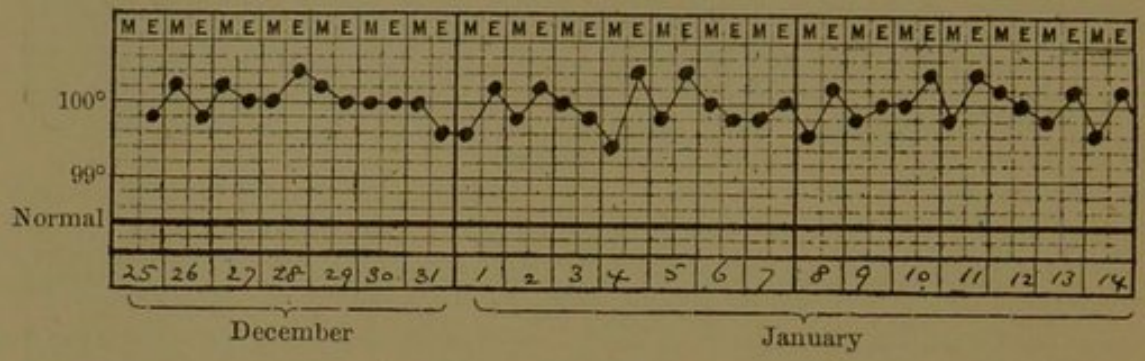


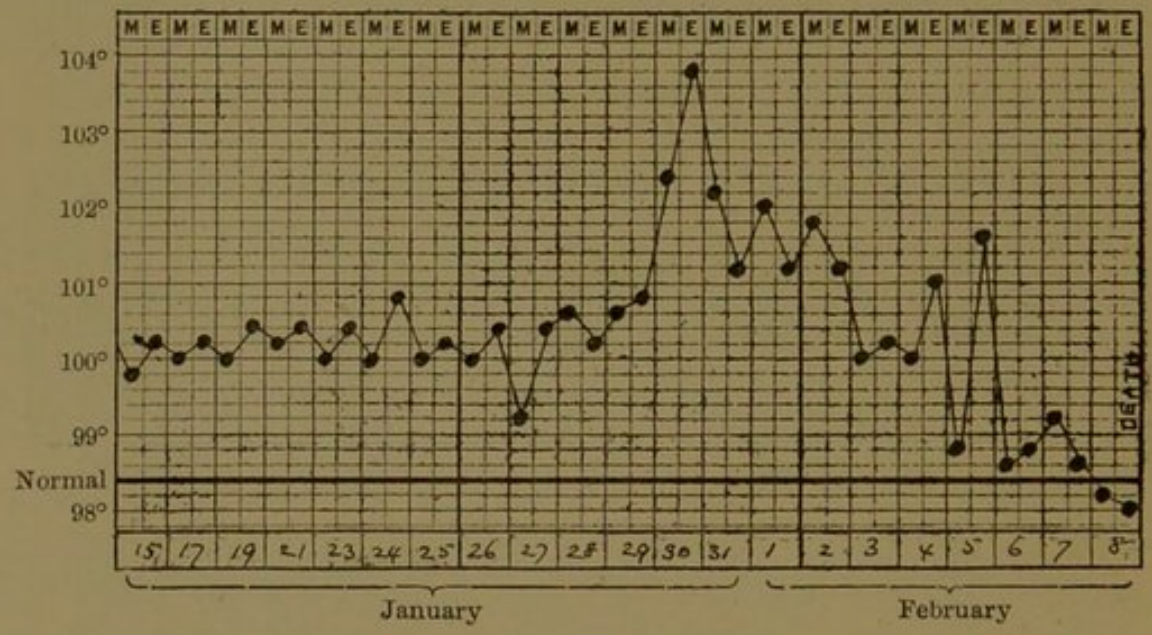






Temperature Chart of Samuel D.





He was the typical colour. There had only been slight loss of bulk, and he weighed 11 st. 1 lb. without clothes.

His temperature was always at least 99° F. at night, often it was 100° F., and sometimes 101° F. There were well marked retinal hæmorrhages and hæmic bruits. There had been œdema of the ankles, but this disappeared when he lay in bed. Appetite was poor, but there was no vomiting. The spleen was not palpable at first, but ultimately it became quite large. The liver was felt down to the level of the umbilicus, or lower. The urine had a specific gravity of 1010: it was constantly pale; it deposited uric acid crystals spontaneously; it was free from albumen except on one occasion, and from blood; it gave no urobilin band to the ordinary spectroscopic test. Epistaxis occurred spontaneously more than once, and at one time there were subcutaneous petechiæ upon the arms and diffuse purpuric blotches on the legs.

After the administration of arsenic there were one or two diarrhœic attacks, but there had been none before arsenic was given.

Itching of the skin was at one period a very troublesome symptom, though jaundice was entirely absent.

During the final relapse the patient became œdematous, and serous exudations occurred. Finally there was increased pyrexia with rigors, due to a terminal infective endocarditis, which was the immediate cause of death.

The *post-mortem* examination showed a well-nourished body, profoundly anæmic, but with very bright yellow-coloured fat. There was some œdema of the nether limbs. Each pleural cavity contained about three pints of serous fluid, the pericardium about 18 ozs. of a similar fluid, and the peritoneum 41 ozs. The lungs were very pale, and extremely œdematous. The alimentary canal looked normal. The heart was pallid, and the mitral and pulmonary valves œdematous, the former being incompetent and the latter bearing small recent granulations all along it near its free edge. The spleen weighed 19 ozs., and was dark and tough. The kidneys weighed 13 ozs., and the liver 80 ozs. Liver, spleen, and kidneys all contained a large excess of iron, and gave a well marked Prussian blue reaction.

The blood counts made during life were as follows:—

Date.	Red corpuscles per cub. mm.	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal.	Colour index.
1893.				
May 24	800,000	16	30	1·875
June 5	1,250,000	25	35	1·400
„ 20	2,100,000	42	50	1·190
July 7	1,850,000	37	45	1·216
„ 21	2,750,000	55	60	1·091
1894.				
January 15 ...	500,000	10	18	1·800
„ 28 ...	1,150,000	23	—	—
February 6 ...	900,000	18	20	1·111
March 7	1,000,000	20	20	1·000
„ 22	900,000	18	18	1·000
April 10	1,250,000	25	20	0·800
May 4	1,600,000	32	15	0·469
„ 29	2,000,000	40	30	0·750
June 8	1,850,000	37	19	0·512

NOTE.—There was no leucocytosis and films were typical of pernicious anæmia.

Samuel D., aged 45, was admitted under the care of Dr. Hale White on December 23rd, 1893, and died on February 9th, 1894.

He gave a history of having been dangerously ill six years previously, with symptoms which were diagnosed as "cholera," though he had never been abroad. He recovered after some while, and enjoyed fair health on and off for five years. He then began to get progressively weaker, to lose his appetite, to suffer from very troublesome diarrhœa, and from breathlessness on ordinary exertion. He had been continuously under medical treatment from August, 1893. His height was 5 feet 5 inches, and his weight 8 st. without clothes.

His skin had the primrose-yellow colour of pernicious anæmia. There were hæmic bruits in the mitral, aortic, and pulmonary areas, and in the neck. Neither liver nor spleen could be felt. The urine was dark, and contained both indican and uribilin, but neither albumen, blood, nor sugar. The optic discs and retinæ were at first natural, but later they developed hæmorrhages.

Much diarrhœa interfered with arsenical treatment. There was a very slight improvement for a time, then a relapse, and the patient

lay semi-comatose for some days before he died. There was no œdema. The lungs and pluræ were natural except for old adhesions over the latter, and for petechial hæmorrhages both beneath the pluræ and in the substance of the lungs. The heart weighed 12 ozs.; the valves were natural, but the muscle exhibited tabby-cat striation.

The stomach and intestines all looked quite natural; there were not even any enlarged follicles in the colon. The liver was pale brown, and gave a fairly good Prussian blue reaction with the potassium ferrocyanide and hydrochloric acid test. The spleen weighed 7 ozs., and was firm and dark. The kidneys together weighed 9 ozs., and they were pallid but otherwise natural.

The blood counts during life were as follows:—

Date.	Red corpuscles per cub. mm. (Thoma-Zeiss.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Oliver.)	Colour index.
December 24, 1893	1,000,000	20	17	0·850
January 1, 1894 ...	1,200,000	24	20	0·833
„ 19, 1894 ...	1,450,000	29	24	0·827
„ 26, 1894 ...	850,000	17	25	1·470

There are doubtless cases of pernicious anæmia in which there is no such slight evening pyrexia, but I would submit that this is when the patients have rallied and have improved considerably in health. Pyrexia in pernicious anæmia has been recorded again and again, of course, but I do not think that enough stress has been laid, as a rule, upon the fact that in nearly every case of the disease in which the patient is moderately or severely ill there is a slight but definite and often long-continued evening rise to somewhere between 99° F. and 100° F., or even 101° F.

II. Pigmentation of the Buccal Mucosa in Pernicious Anæmia.

In the next place I should like to recall to memory the remarks made by Dr. Hale White before the first meeting of the Association of Physicians of Great Britain and Ireland, upon a case of pernicious anæmia in which there were abnormal pigmentary deposits, not only

in the skin, but also in the buccal mucosa. It is well known that Addison's disease and pernicious anæmia may present such similar symptoms that it is sometimes difficult to be sure which malady the patient is suffering from. It was formerly a generally accepted opinion that the presence of pigmentary deposits beneath the buccal mucosa inside the lips or cheeks would be decisive in favour of Addison's disease in such a case. Unfortunately this can no longer be maintained, for in the two following cases of pernicious anæmia, in which the diagnoses were confirmed by *post-mortem* examination, at which the suprarenal glands were normal to the naked eye, there was well marked pigmentation of the buccal mucosa. The first of them was the one in which Dr. Hale White himself observed the phenomenon ; the other is a hitherto unpublished case.

Frederick V., aged 33, a shoemaker, first came under Dr. Hale White's care in 1904, and was in the hospital from August 2nd to December 15th. There was a long and indefinite history of increasing weakness and unfitness for work, and upon examination the chief point that attracted attention was the colour of the skin. The man was not emaciated, though tall and spare ; the lips were pale, but the skin, instead of being primrose or lemon-yellow, was an unhealthy sallow tint, and upon closer inspection it became clear that there was an abnormal pigmentation in it, partly diffuse and partly in small localised dark brown freckle-like spots over the body. Addison's disease at once suggested itself as a diagnosis, and at first sight this seemed to be confirmed by the presence of well marked sepia-coloured pigmented areas and streaks within the mouth, particularly on the inner aspect of the cheeks, precisely as in Addison's disease. The difficulty was rendered greater, perhaps, by the variations in the colour index of the blood, which was sometimes low and sometimes high. Dr. Hale White adhered to the diagnosis of pernicious anæmia, laying much more stress on the high colour indices than upon the low ones.

Arsenical treatment was adopted, but without great relief, and later suprarenal extract, iron, and bone marrow were all tried. The patient went out a little better than when he came in, but was twice re-admitted in 1905. He rallied again, and lingered on until 1907, when he finally died, and the *post-mortem* examination showed that pernicious anæmia was the correct diagnosis, and not Addison's disease.

The blood counts during life were as follows :—

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.	Leucocytes per cub. mm.
1904.					
August 5 ...	2,100,000	42	44	1·048	2,400
September 3 ...	2,260,000	45	36	0·800	—
,, 6 ...	2,470,000	49	34	0·694	3,125
October 3 ...	1,450,000	29	37	1·276	2,656
,, 14 ...	2,060,000	41	34	0·829	2,188
,, 20 ...	1,350,000	27	34	1·259	2,810
,, 28 ...	1,760,000	35	35	1·000	2,030
November 12 ...	1,650,000	33	36	1·091	1,800
,, 20 ...	1,650,000	33	36	1·091	2,500
December 10 ...	2,200,000	44	37	0·841	2,000
1905.					
January 20 ...	1,731,250	35	36	1·029	—
February 3 ...	1,350,000	27	27	1·000	1,250
December 2 ...	1,750,000	35	45	1·286	1,800
,, 14 ...	1,750,000	35	26	0·743	4,375

NOTES.—In this case both plantar reflexes were persistently extensor, though there was no ankle clonus and no increase in knee-jerks. There was also paræsthesia of the legs to electrical stimulation, the strongest shocks being scarcely felt, though other sensations seemed natural.

On February 3rd, 1905, 7 nucleated red cells seen in counting 100 white cells. On February 3rd, 1905, the differential leucocyte count was as follows:—

	Per cent.
Small lymphocytes	68
Large ,, ...	2
Polymorphonuclear cells	27
Eosinophile cells	3

Annie B., aged 33, a housewife, had been in St. Thomas's Hospital from November, 1905, to January, 1906; she then came into Guy's Hospital under the care of Dr. Taylor, from May 19th, 1905, to August 3rd, 1906, when she was discharged relieved, only to relapse at once and be re-admitted to St. Thomas's Hospital in September, 1906, dying there in November, 1906.

She was a married woman who had had one child and no mis-

carriage. Her illness started eight months before her first admission to St. Thomas's Hospital with an increasing general weakness. She had also noticed puffiness of her ankles and feet, especially on walking; loss of appetite; dyspepsia; and a ringing in her ears.

On admission she was a typical case of pernicious anæmia. The heart was a little dilated, and there were generalised hæmic bruits and a bruit de diable in the neck. The liver came 1½ inches below the ribs in the right nipple line. The spleen was not felt. There were no retinal hæmorrhages. There was widespread pigmentation of the skin, both in specks and spots and in bigger patches, in addition to which there was *decided pigmentation in or beneath the buccal mucosa on the inner aspects of the cheeks.* This was confirmed at autopsy.

The pigmentation was not known to have ante-dated arsenical treatment. The urine was high coloured, of specific gravity 1012; it contained neither albumen nor blood, but gave a well-marked urobilin band spectroscopically. The patient's temperature was often 99° to 100° F. The pulse rate was 88 to 100 and the respiration rate 20 to 24. There were curious subjective sensations of paræsthesia, particularly in her thighs, which seemed to her at all times to feel "too hot inside and too cold out," in a way which struck her as being both abnormal, inconvenient, and different to her sensations in other parts of the body and limbs.

The behaviour of the knee-jerks is noteworthy. They were present on admission to St. Thomas's Hospital, but they had disappeared on December 21st, 1905, when liquor arsenicalis was being given in 9 minim doses. The medicine was stopped, and the knee-jerks had returned on December 27th. Liquor arsenicalis in 3 minim doses was again given and the knee-jerks were again absent on January 3rd, 1906. They had returned by the time of her admission to Guy's Hospital in May. They were again absent in September, 1906.

Towards the end pleurisy set in on the right side, and on November 11th, 1906, 3 pints of pleuritic fluid were withdrawn, followed on November 25th by another 4 pints. The patient collapsed, and died after the second aspiration.

Post mortem.—Prominent inflammation of the alveolar sockets, with looseness of all the teeth were noted, also pigmentation of the inner aspect of the cheeks. There were shallow circular ulcers of the skin around the left patella. Acute pleurisy had occurred on

both sides. The heart was not dilated; it was encased in the usual bright yellow fat; its valves were healthy; its muscle pale and soft. The liver was large and paler than normal, and gave a good Prussian blue reaction. The kidneys were markedly anæmic and gave a slight Prussian blue reaction. The spleen was large and pale red, and gave some degree of Prussian blue reaction. The marrow of the long bones was red. All other structures and organs, except for pallor, looked natural.

Microscopically the marrow showed well-marked megaloblastic changes. The heart exhibited pigmentary degenerations, fatty change, and slight monocular infiltration. The iron granules in the liver cells were chiefly at the periphery of the lobules. The spleen showed no fibrosis. The kidneys exhibited catarrhal changes in the tubules, and also iron granules in the epithelial cells.

For some of the notes of this case I am much indebted to Dr. H. C. Squiers.

Blood counts during life were as follows:—

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.
1905.				
November 18 ...	981,250	19	25	1·316
,, 30 ...	843,750	19	20	1·052
December 12 ...	1,100,000	22	25	1·136
,, 30 ...	2,231,250	45	40	0·888
1906.				
January 4	3,325,000	66	50	0·757
May 20	1,800,000	36	40	1·111
June 8	2,000,000	40	25	0·625
,, 19	2,040,000	41	35	0·854
,, 29	2,640,000	53	40	0·755
July 20	3,800,000	76	—	—
October 5 ...	679,687	13	20	1·532
,, 18 ...	1,178,125	28	25	1·087
November 11 ...	1,259,400	25	25	1·000

NOTE.—On many occasions typical poikilocytosis and megalocytosis were observed and many nucleated red cells. There was no leucocytosis.

It may well be asked what *rôle* arsenic plays in the occurrence of this intrabuccal pigmentation in pernicious anæmia.

I am unable to answer this question absolutely, but I think I am right in saying that in the Manchester epidemic of arsenical poisoning such pigmentation within the mouth was not observed. Moreover, it is known that pathological pigmentation of the skin may occur in pernicious anæmia even when no arsenic has been given. Nevertheless, arsenic had been employed in the treatment of both the above cases, and, therefore, although I can say that pigmentation of the buccal mucosa can occur in pernicious anæmia cases treated by arsenic, I am unable to say whether similar pigmentation can occur in pernicious anæmia cases in which no arsenic has been used.

I may, perhaps, add that the appearance of the buccal pigment is precisely similar to that seen in Addison's disease.

III. The Size of the Spleen in Pernicious Anæmia.

Passing next to a consideration of the size of the spleen in pernicious anæmia, I think it worth recording that, although the general statement that the spleen is not enlarged as a rule may be true, nevertheless there are quite a number of cases, on the other hand, in which the spleen is large enough to be readily palpated without any special expertness on the part of the observer. Clinically, out of 56 consecutive cases there were 18 in which the spleen was felt with ease. I would compare the degree of enlargement in these 18 with that which occurs in typhoid fever; in the greater number the spleen came below the costal margin for something between half an inch and two inches; in a few, however, the enlargement was greater, the spleen reaching down to below the level of the umbilicus in one. I need not burden you with the clinical details of these 18 cases, beyond, perhaps, mentioning that in 9 of them the liver was not palpable at the same time as the spleen, whilst in the other 9 it was.

It is of importance to add, however, that the clinical observation of splenic enlargement in so considerable a proportion of pernicious anæmia cases is quite borne out by the results of *post-mortem* examinations.

The actual weights of the spleens are known for 14 out of the 58 cases, and they vary from $3\frac{1}{2}$ ozs. or 105 grams, on the one

hand, to 26 ozs. or 746 grams, on the other. Eleven out of the 13 weighed more than normal, and it is noteworthy that 6 out of the 13 weighed no less than 10 ozs. or more. The existence of a spleen that can be readily palpated is, therefore, by no means unlikely in pernicious anæmia.

Weight of Spleen in 13 *consecutive Fatal Cases of Pernicious Anæmia.*

(Normal weight, 5 ounces, or 140 grams.)

Case.	Ounces.	Grams.	Case.	Ounces.	Grams.
1	3½	105	8	10	283
2	4	113	9	10½	306
3	6½	181	10	12	341
4	7	198	11	14	397
5	7¼	207	12	19	539
6	8½	248	13	26	746
7	8¾	255			

I am sure that the observations of many of you here will confirm this, and yet I think that it is a point that too little stress is laid upon as a rule.

The fact that pernicious anæmia may be a cause for definite enlargement of the spleen clearly increases the number of other conditions with which, under certain circumstances, it might become confused.

IV. The Nerve Symptoms in Pernicious Anæmia.

Dr. Gulland of Edinburgh has drawn attention to the fact that nervous symptoms may not only be prominent in cases already known to be pernicious anæmia but may also antedate the recognition of the blood disease by weeks or months or even years.

I have seen a case in which the patient attended for upwards of two years at a special hospital for nerve diseases for symptoms which were regarded as those of locomotor ataxy before the cord changes were recognised as being associated with pernicious anæmia.

It is not at all infrequent to find various degenerations in the spinal cord *post mortem*, particularly in the white matter, and when these are considerable the patient may have presented symptoms suggestive

of spastic paraplegia, ataxic paraplegia, locomotor ataxia, or simple ataxia, according to which parts of the cord were most affected. Peripheral neuritis may also occur, but it is difficult to say to what extent this may be due to the arsenic that is employed in the treatment of the disease.

It is less common, perhaps, for the complete signs and symptoms of any of the named diseases of the spinal cord to present themselves than for irregular nerve symptoms to appear, many of which are subjective, and, therefore, apt to be regarded as purely functional.

I shall presently read the notes of a case in which severe pains in the back, diagnosed as lumbago for lack of a better name, had been a prominent symptom for years before the pernicious anæmia was recognised. In other cases the nerve signs and symptoms—exclusive of headaches, gastric pains, giddiness, or buzzing in the ears, which are doubtless due to the anæmia directly—were as follows :—

Case (1).—"I could not be sure of my foothold owing to numbness in my feet, and when I tried to walk I stumbled about like a drunken man."

Case (2).—Paresis of the legs with ankle clonus on both sides.

Case (3).—Knee jerks sometimes present, sometimes not obtainable even with re-inforcement.

Case (4).—Paræsthesia of the thighs, with sensations in them described as their feeling "too hot inside and too cold out" quite unlike the ordinary sensations of the rest of the body.

Case (5).—Delusional insanity of a dangerous type. The patient talking restlessly but incoherently to himself about such things as "pice," "mines just over the hill"; mixed a number of native Urdu words with his English, confused identities, failed to recognise his wife or relatives, apparently retained no idea of time or place, neglected the calls of nature, and required much care and attention. It might, perhaps, be thought that such a case was one of ordinary insanity, but the appearance of the patient and the following blood counts showed that the mental symptoms were associated with pernicious anæmia :—

Date.	Leucocytes per cub. mm.	Red cells per cent. of normal. (Thoma-Leitz.)	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.
October 4	8,000	24	38	1·6
November 21 ...	8,000	71	78	1·1
December 12 ...	—	64	74	1·15

Case (6).—Ideas of grandeur and symptoms precisely similar to those of general paralysis of the insane.

Case (7).—Hallucinations of sight taking the form of a persistent notion that there was a large vase of flowers on the perfectly bare table; attributable, perhaps, to the position of the retinal hæmorrhages.

Case (8).—Persistently extensor plantar reflex on one side, flexor on the other, without ankle clonus.

Case (9).—Curious sensations in the thighs, knees, legs, and feet, compared by the patient, who was a Scandinavian, to a feeling "as though she were always walking in deep snow."

Cases (10), (11), (12), (13), (14), (15).—Numbness in the fingers and toes, hands and feet.

Case (16).—Tingling in fingers and toes.

Case (17).—Loss of power in both legs with increased knee jerks and ankle clonus upon both sides.

Cases (18), (19), (20).—Violent and severe sensations in the chest, compared sometimes to "tearing pains" and sometimes to a sense of the thorax being "tightly gripped and squeezed."

Case (21).—Severe pains in the back with paresis of legs.

Cases (22), (23), (24), and (14).—Absence of both knee jerks.

Case (25).—Absence of one knee jerk, the other being present.

Case (26).—Pains more or less all over the body, especially in the muscles, but without definite paresis.

Case (27).—Pains in the chest and abdomen with general itching of the skin.

Case (28).—Persistent extensor plantar reflex on both sides and scattered areas of marked paræsthesia in the legs, with sluggish knee jerks and no ankle clonus.

Case (29).—Increased wrist jerks, elbow jerks, and knee jerks; ankle clonus and extensor plantar reflex on both sides and rigidity of the legs.

These are the various nerve signs and symptoms presented by 29 cases out of 58. The remainder did not spontaneously complain of anything similar, and nothing particular about the nervous systems attracted the attention of the ward clerks who wrote the reports. If 29 out of 58 cases present nerve symptoms, however, of degrees varying from subjective numbness of fingers and toes to definite spastic paraplegia it is clear that there is at least a possibility of a case of pernicious anæmia now and then being treated solely for nerve trouble unless some stress is laid upon the well known possibility of pernicious anæmia being associated with pathological changes in the spinal cord and peripheral nerves.

V. The Variability in the Colour Index in Pernicious Anæmia.

The final clinical criterion of pernicious anæmia at present is the occurrence of oligocythæmia with a high colour index and without leucocytosis. It is very important to realize, however, that the fact that the colour index proves to be low, or at least not high, when the blood is examined once only, or even more than once, is no proof that the condition is not one of pernicious anæmia, for when a series of blood counts are made at intervals in the same case it is comparatively common to find that there are periods when the colour index is less than 1 as well as other periods when it is greater than 1. Roughly speaking, the index tends to be highest when the patient is most ill and anæmic, and to become lower as the condition improves. This is no absolute rule, however, for a high colour index may persist even when much improvement has occurred, and on the other hand a low index is sometimes found when the patient is very ill.

It is astonishing how quickly the index may vary; even when the instrumental error is reduced to a minimum in the hands of skilled observers there may be a high colour index one week and a low one the next: such radical changes in the character of the blood have been attributed to derangements known as "blood storms."

Some of the series of counts already given, and these two additional ones that I give here, exhibit the fact that a pernicious anæmia blood may have a low colour index at times, and I think the point is one of great importance. It unfortunately adds to the difficulty of diagnosis, but it teaches that pernicious anæmia is not by any means to be excluded by a single blood count. I may add, perhaps, that the two last series of counts were made with a Thoma-Leitz's hæmocytometer, and a Haldane's hæmoglobinometer; moreover, the diagnosis was in each case confirmed by autopsy.

CHARLOTTE W., aged 49, Cook (widow). Died May 16th, 1902.

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.	Leucocytes per cub. mm. (Thoma-Leitz.)
1901.					
April 10 ...	650,000	13	26	2·000	7,000
May 15 ...	1,800,000	36	41	1·139	5,000
„ 26 ...	1,800,000	36	40	1·111	7,000
September 20...	1,800,000	36	60	1·666	—
„ 30...	1,600,000	32	42	1·312	—
October 2 ...	1,512,000	30	33	1·100	—
„ 7 ...	4,250,000	85	36	0·423	—
„ 11 ...	5,050,000	101	40	0·396	—
1902.					
April 3 ...	785,714	16	25	1·562	6,400
„ 23 ...	629,000	14	20	1·429	9,750
May 14 ...	876,000	15	10	0·666	4,800

NOTE.—Films were typical of severe pernicious anæmia.

The differential leucocyte count in April, 1902, was as follows:—

	Per cent.
Small lymphocytes	25
Large „	3
Polymorphonuclear cells	70
Coarsely granular eosinophile cells ...	2

CHARLOTTE R., aged 46, Housewife. Died on June 24th, 1903.

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.	Leucocytes per cub. mm. (Thoma-Leitz.)
1901.					
June 11 ...	1,466,666	27	39	1·444	11,428
July 5 ...	2,600,000	52	42	0·808	—
„ 18 ...	3,160,000	63	75	1·190	—
1902.					
November 29 ...	440,000	9	17	1·888	3,640
December 2 ...	752,000	15	21	1·400	3,800
„ 8 ...	1,284,000	26	32	1·230	3,400
„ 10 ...	1,294,000	26	32	1·230	2,800
„ 21 ...	2,334,000	47	—	—	4,600
„ 27 ...	3,296,000	66	58	0·879	4,600
1903.					
January 6 ...	3,864,000	77	60	0·779	7,032
June 6... ...	683,333	14	20	1·429	8,520

N.B.—440,000 red cells per cub. mm. is probably one of the lowest counts on record, particularly in a person who none the less rallied as above.

VI. THE INJUSTICE OF THE EPITHET "PERNICIOUS" IN SOME OF THE CASES.

I should now like to pass on to discuss an entirely different matter, and that is, the injustice of the epithet "pernicious" in some of the cases.

Pernicious, in its lay sense, is a very strong term, and I feel sure that its use leads the medical student to gather an erroneous idea of the prognosis in pernicious anæmia. It is true that hardly any patients in whom typical pernicious anæmia has developed ever become completely well again. It is also true that the fatal ending of the disease sometimes comes within a month or a few months of what seems to be the beginning of the disease. On the other hand, the average duration of pernicious anæmia from the time of its recognition until the patient dies is in a fair number of cases to be measured in years rather than in weeks or months; besides which

the illness is not one of continuous downward progress like that of carcinoma of the stomach for example, for nothing in medicine perhaps is so striking as the way in which, even if the rally be only temporary, a patient who may seem to be *in extremis* from pernicious anæmia, with his red corpuscles under 20 per cent. of normal, may recuperate not only once but sometimes several times. If one were condemned to suffer from a fatal malady, but were given the choice between malignant disease of the upper part of the alimentary canal, for example, on the one hand, or from pernicious anæmia on the other, it is clear that in either case one might be dead within the year; but that if one chose pernicious anæmia one would have a better chance, than with gastric carcinoma, of living for several years.

The intervals between the recognition of the pernicious anæmia by blood count and the time of death in the 40 cases in which, out of my total 58, the ultimate fate of the patient is known were as follows:—

1 year or less, 25—

Less than 1 month	5 cases.
1 to 3 months	8 cases.
3 to 6 months	5 cases.
6 to 12 months	7 cases.

1 to 2 years, 7—

12 to 18 months	3 cases.
18 to 24 months	2 cases.
1 to 2 years	2 cases.

2 to 10 years, 8—

2 to 3 years	3 cases.
3 to 4 years	1 case.
6 years	1 case.
8 years	2 cases.
10 years	1 case.

It will be seen that 25 cases died within the year, but that 15 survived for one year or more; 8 out of 40 cases lived for something between 2 and 10 years after the time when pernicious anæmia had been diagnosed beyond doubt. The word pernicious is, I think, rather too strong to be applied to a condition in which the prognosis is no worse than this. Lymphatic leuchæmia is far

more pernicious a complaint than is pernicious anæmia. I should like to see the older term, "Addison's anæmia" used instead.

It will be said that I have picked out a particularly favourable case when I give the following notes about Charles R. The allegation is true; but his story illustrates so well both the power some of these patients have of rallying, and also the length of time they may survive, and, further, the fact that their initial symptoms—lumbago in this case—may not seem to have any relation to a blood disease, that I beg leave to read this short account of him.

Charles R., aged 45, a bricklayer, was first admitted under Dr. Pavy in 1889 for mental irritability, weakness in the legs and pain in the back and loins. His colour at that time was not apparently abnormal, and the diagnosis made was "*Lumbago and paresis of the legs.*" The pains in the back were very acute and the patient had had three or four attacks of it each year for the previous 15 years. There was no hæmaturia nor other indication that the pains might have been due to renal colic, and lumbago seemed to fit the case. In view, however, of the subsequent course it seems at least possible that the pains were similar to those which other pernicious anæmia cases often complain of in one part of the body or another; for, less than a year later, in January, 1890, the patient was readmitted for loss of physical strength, failure of appetite, diarrhœa, and night sweating, and the skin was now pale and waxy, and had been obviously so for more than two months. There were no retinal hæmorrhages but occasional specks of blood were expectorated. There was no other bleeding. The urine was high coloured; it contained no albumen, blood, nor sugar. The blood count indicated pernicious anæmia. The patient was treated with pilula colocynthi et hyoscyami and mistura ferri et ammonii citratis and improved in general condition, though the blood count remained much the same.

By September, 1891, the patient was so weak, however, that he could not work, though he had worked between his discharge and then. He was re-admitted under the late Dr. Washbourn, and was in hospital from September 4th, 1891, to November 30th, 1891. The attacks of pains in the loins still continued, and they were very bad. There were neither enlarged glands nor spleen, nor vomiting, nor diarrhœa. Treatment was now by means of liquor arsenicalis, which was increased up to 9 minims three times a day, with material relief to the anæmia. The patient went out in November,

1891, and notwithstanding his "lumbago" remained well enough to work on and off for over four years before repetition of his old weakness and pallor compelled him to seek hospital treatment again. He was in from February 7th, 1896, till March 9th, 1896. He presented the typical pale yellow colour. His tissues were flabby, but not wasted. The urine sometimes exhibited a marked urobilin band spectroscopically, sometimes none. The temperature was typically up to 100° F. every night, and not below 98° F. in the morning as a rule. The nervous reflexes were natural. Arsenical treatment was adopted, and some relief ensued. The patient was discharged, able to walk about, but unable to do labourer's work. He slowly relapsed, and was re-admitted on March 1st, 1897. He seemed to get progressively worse, and yet he lived for two years after his discharge on May 20th, 1897. Mrs. R. writes on August 15th, 1907: "Mr. R. died two years after leaving Guy's Hospital, suffering from prostration and great pains in his head, it was indeed sad to see such suffering, and the brain very much affected."

During his last stay in hospital his temperature was again typically between 99° F. and 100° F. each night.

The spleen, formerly not felt, now came 2 inches below the ribs, and the liver came 1 inch below the costal margin in the right nipple line. Ophthalmoscopic examination revealed neither optic neuritis nor retinal hæmorrhages.

The blood counts were as follows:—

Date.	Red corpuscles per cub. mm.	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal.	Colour index.
1890.				
February	2,400,000	48	53	1·104
March	2,400,000	48	55	1·148
1891.				
September 18 ...	1,400,000	28	28	1·000
„ 25 ...	1,100,000	22	25	1·136
October 5... ...	1,800,000	36	35	0·972
„ 19... ...	2,100,000	42	35	0·833
„ 26... ...	1,800,000	36	36	1·000
„ 29... ...	1,800,000	36	40	1·111
„ 31... ...	2,000,000	40	40	1·000
November 2 ...	2,900,000	58	50	0·862
„ 9 ...	3,350,000	67	60	0·895

Date.	Red corpuscles per cub. mm.	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal.	Colour index.
1896.				
February 7 ...	1,250,000	25	30	1·200
„ 13 ...	1,500,000	30	35	1·166
„ 18 ...	1,500,000	30	35	1·166
„ 24 ...	1,250,000	25	30	1·200
„ 27 ...	1,200,000	24	30	1·250
March 9	1,000,000	20	25	1·250
„ 19	800,000	16	25	1·562
April 8	700,000	14	20	1·429
„ 22	1,500,000	30	30	1·000
May 2	2,150,000	43	32	0·744
„ 9	2,750,000	55	38	0·691
1897.				
March 1	3,000,000	60	30	0·500
„ 22	1,900,000	38	25	0·659
April 5	1,050,000	21	15	0·714
„ 12	659,000	13	16	1·231
„ 27	709,000	14	26	1·857

There was no leucocytosis. Poikilocytosis and megalocytosis were well marked, and at times nucleated red cells were seen.

VII. The Difficulty Frequently met with in Accurately Dating the Beginning of the Illness, with some Thoughts that this Difficulty Suggests.

I have just referred to the length of time that elapses in different cases between the recognition of the pernicious anæmia and the death of the patient. The recognition of the disease is chiefly by means of blood counts; but I should like to lay great stress upon the fact that in the majority of cases the blood-count recognition by no means coincides even with an early stage of the disease, much less with its actual beginning. When one reads through the impartial histories of these cases as recorded by medical ward clerks one is struck again and again by the fact that symptoms have been present for months, years, or even many years before the anæmia itself becomes pronounced. I quite grant that there are a few cases which seem to be acute; in most cases, however, the onset is quite insidious, and in quite a number the earlier symptoms are attributed to some entirely different malady, typhoid fever, for

example, or English cholera when diarrhœa was a prominent symptom; a chronic nerve disease, as in Dr. Gulland's cases; functional disorder of the stomach is another type of case; and so on. I hope to publish the notes of all these cases in the 'Guy's Hospital Reports'; it is clear that I cannot read them all here.

The 58 consecutive cases themselves dated their illness back for at least the following lengths of time prior to its recognition :—

For less than 1 month in 2 cases.
Between 1 and 3 months in 12 cases.
Between 3 and 6 months in 6 cases.
Between 6 and 9 months in 3 cases.
About a year in 11 cases.
Between 1 and 2 years in 9 cases.
Between 2 and 3 years in 4 cases.
Between 3 and 6 years in 7 cases.
For over 5 years in 4 cases.

I should like to recall the case of Charles R., quoted just now, to illustrate what I mean; I see no lack of continuity in the history of his case, from the original attacks of what appeared to be "lumbago" 16 years before pernicious anæmia was diagnosed, to the patient's death from the latter disease eight years after it was recognised by blood counts.

I could give many other examples of similar difficulty in deciding when the pernicious anæmia really began, but I will content myself with one more only, viz., the following :—

Amelia P., aged 50, a ship stewardess, married but childless, was admitted on January 11th, 1905, and was discharged on February 24th, 1905. Her husband writes on August 19th, 1907 : "After leaving Guy's my wife went to a convalescent home, from which she left very weak and ill. She rallied slightly when at home, some days comparatively well, others ill and depressed. She had a very bad colour, coppery shade. She suddenly lost consciousness, and finally died on April 1st, 1905."

When admitted she gave a history of increasing debility with vomiting, diarrhœa, and "indigestion" extending over four years and dating from an attack of "enteric fever" contracted at Naples. There had been many alternate remissions and exacerbations in

her symptoms, which sometimes kept her in bed for weeks at a time.

Her spleen could be felt 1 inch below the ribs. The heart was a little dilated. There was marked numbness in the fingers and toes. Pyorrhœa alveolaris was present, and was attended to by the dental house surgeons. There was the typical evening pyrexia up to 99° F. or 100° F. Arsenical treatment was adopted, and although diarrhœa was a troublesome symptom at times the patient's general condition improved for a while. The improvement was short lived, however, as has been noted above.

The blood counts in this case were :—

Date.	Red corpuscles per cub. mm. (Thoma-Leitz.)	Red corpuscles per cent. of normal.	Hæmoglobin per cent. of normal. (Haldane.)	Colour index.	Leucocytes per cub. mm. (Thoma-Leitz.)
1905.					
January 11 ...	1,856,000	37	55	1·486	4,200
February 7 ...	1,940,000	39	50	1·282	—
„ 22 ...	2,020,000	40	55	1·375	4,000

On enquiring into the nature of the "typhoid fever" in this case, it transpired that the symptoms were mainly diarrhœa and pyrexia, and that the patient was kept in bed for it for only four days. It seems clear, I think, that some name had to be given to an obscure febrile illness, and that typhoid fever seemed to fit it at first, but time showed, I think, a direct continuity between that illness and undoubted pernicious anæmia.

It might be urged that pernicious anæmia was not really present at the time of the "enteric" attack, but that the latter predisposed to it and was in a way its cause. I think, however, that our clinical knowledge of the disease is more likely to be advanced if we allow that the lumbago in the case of Charles R. and the diarrhœa and pyrexia in that of Amelia P. and other symptoms in other cases were really the earliest symptoms of a disease of which the later stages are characterised by profound anæmia, a high colour index, and a Prussian blue reaction in the liver. If this be so then pernicious anæmia is the name but for a late phase of a more general disease, which is at present unnamed. I would

suggest a comparison between it and phthisis in this respect. It is not so very many years since it was impossible to diagnose early phthisis, and consumption was regarded as essentially fatal, because it was only recognised when it had already passed beyond the stage when it was curable. The end of a phthisical person may even now be very rapid by galloping consumption, comparable to the acute cases of pernicious anæmia, or the end may be gradual with periods of recovery and relapse extending over months or years, comparable to the course of ordinary pernicious anæmia as we now understand that term; on the other hand, if recognised at a stage at which our grandfathers would have denied the existence of phthisis altogether, consumption may be completely cured; healed phthisis is found in a large proportion of *post-mortem* examinations at a general hospital in patients who may never have been suspected to have had phthisis at all. I feel sure that pernicious anæmia as we know it is but a late stage of that which may be much commoner than we think, recovering spontaneously, perhaps, in many cases as phthisis does in others, breaking out into an acute phase in others, running a subacute or chronic up and down course in yet others. We are now able to recognise phthisis early, by bacteriological and other means, in a way that our forefathers could scarcely have believed possible. I hope that similar early recognition of pernicious anæmia will also become possible as time goes on. It is recognised far earlier now than it used to be, and, perhaps, if it were thought of and diagnosed earlier still, some at least of the patients might be cured.

Conclusion.

In conclusion the points that I have tried to bring out in this paper are: First, that slight evening pyrexia is seldom absent in pernicious anæmia cases that are decidedly ill; secondly, that pigmentation within the mouth of precisely similar character to that seen in Addison's disease may occur in pernicious anæmia cases treated with arsenic; thirdly, that the spleen is to be felt in about one-third of the cases, and that it is really enlarged; fourthly, that nerve symptoms are not at all uncommon in pernicious anæmia; fifthly, that the colour index, though typically higher than 1 when an advanced stage of the disease has been reached, is not always nor continually high, especially during a period of improvement in the patient's condition, when it may be

actually low; and lastly, that pernicious anæmia as we now know it is very possibly only a late and almost incurable stage of a disease which it is to be hoped will some day be recognisable early enough to be cured.

HARRISON AND SONS, Printers in Ordinary to His Majesty, St. Martin's Lane.