anaemia from carcinoma at the cardiac orifice of the stomach. Here there were occasional enormous red corpuscles that would have done credit to any case of pernicious anaemia, and others that were distinctly above the normal size. But these were exceptions, and the *average* size was much below normal, in keeping with a haemoglobin percentage of 18, a red count of 1,560,000, and a haemoglobin index of only 57 per cent. Even in a typical case of chlorosis I have come across large numbers of macrocytes, which at first sight strongly suggested pernicious anaemia, but the other corpuscles were small, and, in spite of the number of large corpuscles, the average size was below normal, as shown by the low haemoglobin index of 64.

Prognosis and Treatment of Pernicious Anaemia.

There is much error in regard to the prognosis; the disease is too commonly looked upon as inevitably and speedily fatal, and so no proper steps are taken to ensure adequate treatment. Now, although I do not for a moment deny the seriousness of the disease, it is my experience that no other of the more serious diseases responds so satisfactorily to prompt and efficient treatment; and that *if recognized early* some cases may be actually cured, while others may have several years of fairly comfortable life ensured to them.

Take, for instance, a case whom I had under my care in August, 1903. Her lowest red corpuscle count was 1,570,000 and the blood at that date had all the typical characters of pernicious anaemia. After two and a half months' treatment the red corpuscles had risen to 5,064,000 per c.mm., the haemoglobin was 92 per cent. and there was absolutely no abnormality to be detected in the corpuscles. I have had her under me since then from time to time and she has shown no sign of relapse.

Another case had only 1,210,000 red corpuscles in the c.mm. when he was admitted into the infirmary under Dr. Dreschfeld in 1899, and was in every way a typical case of pernicious anaemia. After five weeks' treatment his corpuscles had risen to 3,560,000 and had almost lost their irregularity in size and shape, and two and a half years later, when he was under my care at the Ancoats Hospital, they had risen to 4,180,000 and in appearance were perfectly normal. He died in 1906, but from consumption, not from pernicious anaemia.

Now as regards the details of treatment. Ever since Byrom Bramwell first demonstrated its value arsenic has been our sheet-anchor in pernicious anaemia. The mode of giving it is of the greatest importance. It is quite useless to give 2 or 3 minims of liq. arsenicalis as is too often done in a perfunctory fashion. It must be started at 4 or 5 minims three times a day and rapidly run up by increments of 1 minim per dose every day or every other day to a dose of 12, or, if possible, 15 minims. When these large doses are being approached, the blood should be again examined, and, if improvement is commencing, the dose should be dropped, and then again increased. The reason for this is that if improvement has started there is less need to push the drug and greater need to avoid setting up toxic symptoms, which might entail its being wholly stopped for a while, with consequent liability to relapse. I have emphasized this point particularly, because I have on more than one occasion had this account given me on asking a doctor how a patient that he had sent to me had gone on: "That he had gone on splendidly for some weeks with the continued full doses of arsenic, but then he had shown toxic symptoms, the arsenic had had to be stopped entirely, and he had rapidly gone to pieces." Of course, if the second examination of the blood shows no commencing improvement, the arsenic must still be pushed, and, in the hope of its eventually proving effective, the risk of poisonous effects must be taken. One is between the devil and the deep sea.

The natural history of a case under such treatment usually is that he improves rapidly after he has once started to pick up, gives up treatment, and before long relapses, and the successive relapses which may occur are usually each more severe and more difficult to cure than their predecessors. He feels so well as the result of treatment that nothing will convince him that he is not permanently cured, and too often his doctor falls into the same belief and sends him off for a long holiday, with most dire consequences. It is of the utmost importance that the patient should keep on with small doses of arsenic, even though feeling perfectly well, that he should never go longer than ten days or a fortnight without being seen by his doctor, and that if there is any suspicion of a commencing relapse a blood examination should be at once made, for the relapses, if detected early, may respond readily to treatment, but if overlooked (and their onset is nearly always most insidious) they prove more stubborn than the previous attack.

There is another line of treatment which may be combined with the arsenical, based on Hunter's theory that the essential cause of the disease is a chronic oro-gastro-intestinal infection. The removal of carious teeth, the use of antiseptic mouth washes and of gastric and intestinal antiseptics should never be neglected. Various internal antiseptics may be used. I have mainly employed salol, beta naphthol, mercury perchloride, and petroleum emulsion. The same rule applies to these as to arsenic—they should be continued in small doses during the well periods and in full doses on any suspicion of relapse.

Finally, I should like to say a word about the use of red bone marrow in the treatment of pernicious anaemia. I had seen so many cases in which various extracts had been used with absolutely no good result that I not unnaturally became very sceptical as to its value. Its use, too, was advocated on an imperfect analogy with the use of the thyroid substance in myxoedema. The action of the thyroid gland is a chemical one, and its secretion is a chemical product, but the action of the bone marrow in producing the blood cells is a purely vital one, which must cease as soon as its cells are dead. But comparatively recently Dr. Gullan has published some cases in which its use appears to have been effective. He suggests that in addition to the vital process of reproduction of red and white cells which goes on in the bone marrow there may be a chemical process—the production of an internal secretion. He supposed that when the red bone marrow is administered this internal secretion may be such as to stimulate the vital production of blood corpuscles in the patient's bone marrow, and also that it may act, as there is some experimental evidence to show that arsenic does, by increasing the resistance of the red corpuscles to the action of the haemolytic toxins which are looked on as the cause of the disease. Consequently I tried the effect of the red marrow on two cases, old standing cases, one of whom had been suffering for at least four years, and had relapsed several times. Both were proving resistant, as is the way with relapses, to the arsenic and antiseptic treatment, and I can say that the more rapid improvement in both dates from the addition of the red marrow to their dietary, and one, the worse of the two, has now kept well for six months on no other treatment, though I cannot say how long the improvement is likely to last. At any rate, I believe that combined with other methods it is one which should not be neglected.

PERNICIOUS ANAEMIA WITH PIGMENTATION OF THE SKIN AND BUCCAL MUCOUS MEMBRANE.

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These notes on two cases of pernicious anaemia which were under observation about the same time appear to me to be of interest on account of the unusual site of the pigmentation in the first case, and the early appearance of glossitis as a symptom in both.

Case I.

H. F., aged 52, a baker, was first seen on October 14th, 1908, complaining of general weakness of about five months' duration.

History.

Family history was unimportant and personal history good, he having had no illness of importance since childhood. There is a history of alcoholic excess at intervals over many years; he is a moderate smoker and has had no venereal disease.

Except for occasional attacks of biliousness—gastric discomfort and flatulence—he has always had good health. In May, 1908, he was able to carry on his business, which entailed early rising and long hours, without undue fatigue, and felt quite well. In the beginning of June he had an attack of diarrhoea without stomach disturbance after eating a quantity of new potatoes, and to this he attributes his present illness. The attack lasted two or three days. Some time afterwards he noticed that he had to take any exertion more leisurely on account of shortness of breath, and that his feet were slightly swollen at night. He suffered from pains in the legs at this

time, and occasionally noticed purple spots over his shins. During July the breathlessness became marked, and his friends commented on it and on his pallor. He became aware also of a decided loss of energy, feeling "done up" after his day's work, and of an excessive sleepiness. Owing to increased weakness and giddiness he had to shorten his hours, and finally by the middle of August to give up work altogether, as he had sometimes to be assisted home after fainting attacks. While his appetite and digestion seemed good, he has had at intervals, causeless and painless attacks of diarrhoea which ceased in a few days on a strict milk diet; and, occasionally, since the onset in June, a sore mouth and tongue which made chewing very painful. On each occasion he has "cured" this with borax and honey, and for the past six weeks it has not troubled him. For the last two months he has been mostly in bed; at times able to get up and go out; at others, shivery, languid, and liable to faint if he raises his head from the pillow. He has not been able to rise for two weeks past. His present complaint is of weakness and distressing noises in the chest and ears. He has never had pain in the stomach nor vomited. There is no history of any haemorrhage.

Condition on Examination.

He is a well-built, muscular man, inclined to stoutness, but with no sign of wasting. Expression is languid. Face is extremely pale and pigmented (see below), and skin over the rest of the body is slightly yellow in tint. Mucous membranes are of a dull white colour, and the ocular conjunctiva is slightly yellow. Temperature is 100° F.; pulse 110, regular and very compressible. Tongue is clean, pale, flabby, and unusually smooth. All the teeth are gone, except two incisors, two canines, and four molars, which are blackened and carious. Pupils are equal and normal. There is slight oedema of the chest wall, dorsum of feet, and eyelids, and tenderness on pressure over sternum and long bones. The slightest exertion, such as sitting up in bed, brings on a violent thumping pulsation over cardiac area, especially noticeable in the epigastrium, and evident in the vessels of the neck, and this pulsation he "hears painfully distinctly." The area of cardiac dullness is slightly increased to the right, and a soft blowing V.S. murmur is heard distinctly at the apex, less distinctly at base. Second pulmonic sound is accentuated. At bases of lungs behind there is deficient resonance to percussion, and a few fine moist râles are present. There is very marked dyspnoea on movement. Liver dullness extends about 1 in. below the costal margin, and the edge can be palpated there. It is not sensitive to pressure. Spleen is not enlarged, and there are no enlarged glands. Abdomen is relaxed and soft, and nothing abnormal can be detected there.

Urine is high coloured, acid, and specific gravity is 1018. A faint trace of albumen is present, but no casts. Knee-jerks are active, and plantar and superficial reflexes normal. Sensation appears to be undisturbed.

Fundus Oculi (Dr. Arthur J. Ballantyne).—There is abnormal pallor and transparency of the blood in the retinal vessels. In both fundi there are numerous flame-shaped haemorrhages and several soft-edged exudative patches. Some of the haemorrhages have the pale centre, sometimes described as characteristic of the haemorrhages of pernicious anaemia.

Blood examined on October 14th showed red corpuscles 1,230,000 (24 per cent.) per c.mm.; haemoglobin, 32 per cent.; index, 1.33; and white corpuscles, 5,500 per c.mm. The most noticeable feature in the stained slide was the very large size of a great number of the red cells, and on measurement 40 to 45 per cent. of them were over 9 μ. Most showed a tendency to oval in shape, and only a few were circular. There were numerous poikilocytes and microcytes. Polychromatophilia was marked, many of the red cells staining grey, brown, or purple in whole or in part (Erhlich-Biondi stain). Polymorphonuclear leucocytes were diminished in numbers to 50 per cent., and a small percentage of neutrophile myelocytes was present. Nine megaloblasts and two normoblasts were seen in differentiating 1,000 leucocytes.

On the arms and legs and lower abdomen, and to a lesser extent on the face and neck, a marked pigmentation of the skin is present. Over the face and neck pigmented patches are distributed, pale grey to pale brown in colour, with a distinct edge and irregular outline, but clearly marked off from the surrounding very pale skin. Similar patches are present on the lower legs, dorsum of feet, forearms, and backs of hands, and in those situations are of a dark brown colour. Scattered over those surfaces are also a number of discrete spots, light brown to chocolate in colour, varying in size from a pin's head to a sixpence, and mostly of circular outline. They are not elevated. Over thighs, flanks, and lower abdomen the skin presents a mottled appearance, due to the presence of a large number of discrete pale brown spots about the size of a lentil. A few spots are present on the front of the chest. There is no pigmentation of axilla or nipples.

Pigment spots are also present on the buccal mucous membrane, situated on the palate, lips, and cheeks; on palate and lips being symmetrically placed, on cheeks irregularly and where the teeth are absent. They are thirty in number, the smallest being the size of a pin's head, and the largest $\frac{3}{8}$ in. by $\frac{1}{2}$ in. The colour varies from a light patchy brown to a deep homogeneous chocolate; they are irregular in outline, but have a distinct edge. The spots are not raised, nor affected by pressure, nor sensitive to touch.

On the ocular conjunctiva on the upper surface of the globe, situated at the extremity of the vessels, are dark, opalescent spots about the size of a pin's head.

There were no signs of haemorrhage on the mucous membranes or skin.

The patient could give no definite information about the spots on his skin, except that they had "become much worse lately."

After-History.

The patient became gradually weaker, though he had periods of apparent improvement, alternating with periods of apparent collapse. Temperature was irregular till he died, varying from 99° F. to 101° F., but never normal. Dyspnoea (which was not affected by posture) was very marked, and palpitation troublesome. On October 20th red corpuscles were 933,000 per c.mm., and haemoglobin 28 per cent. On the 21st he fainted on attempting to get out of bed; vomited considerably, and for the next two days was hardly able to move. On the 24th, he again fainted on attempting to rise. Red corpuscles were 614,752 per c.mm., haemoglobin rather under 20 per cent., and he had to be punctured several times before enough blood could be got to fill the pipettes. On the 25th he was unconscious all day, bowels and bladder acting involuntarily. Next morning he was sitting up in bed, having partaken of bread and porter. In the afternoon he became comatose, and remained so till he died, twelve hours later. *Post-mortem* examination was refused.

CASE II.

Mrs. H., aged 65, was seen in November, 1908, complaining of general weakness, giddiness, and palpitation, of eight months' duration.

History.

She had a history of ten years' indifferent health, having suffered from anaemia and shortness of breath, but otherwise no definite illness till two and a half years ago. Then, following a "sore tongue," she suffered from attacks of diarrhoea, and became gradually very weak, pale, and breathless. She was in hospital (August, 1906) for a time, and left much better. A similar turn took place in 1907; she was again in hospital, improved, and was better for some months. Eight months ago weakness and breathlessness gradually increased again; and since then she has suffered from bilious attacks (without vomiting or pain), which frequently left her skin yellow. These attacks were followed often by diarrhoea, and occasionally accompanied by a sore tongue. During the last month she has been completely confined to bed on account of weakness. There is no history of haemorrhage. There is a history of alcoholic excess for some years.

Condition on Examination.

The skin was lemon yellow in tint and ocular conjunctiva was slightly yellow. There was no marked wasting. There was slight oedema of the eyelids, pulse was 100, regular and soft, and temperature 99° F. Teeth were mostly absent and remainder carious, and the gums were spongy. Tongue was slightly furred, and on the left side of dorsum and tip a shallow ulcer, 1 in. by $\frac{3}{4}$ in., with red edges, and very sensitive to the touch, was present. Cardiac dullness was normal and a V.S. murmur was present all over the cardiac area. Liver was slightly enlarged, and the spleen could be palpated. There was tenderness to pressure over the stomach. Urine was pale, with a specific gravity of 1016, and contained a trace of pus. Knee jerks were active and superficial reflexes normal. Blood examination showed red corpuscles 1,800,000 to 1,660,000 per c.mm., haemoglobin 50 to 48 per cent., index 1.6 to 1.5, white corpuscles 4,400 to 5,400 per c.mm. More than 50 per cent. of the red corpuscles were over-sized. Poikilocytosis and polychromatophilia were marked. Differential count gave neutrophiles 42.5 per cent., small lymphocytes 43.7 per cent., large lymphocytes 9.7 per cent., eosinophiles 3.2 per cent., myelocytes 0.7 per cent. Two megaloblasts were seen in counting 400 leucocytes on one occasion, three on another, but no normoblasts.

A slight degree of pigmentation of the skin was present. On the face and neck, arms and backs of hands, legs, thighs, dorsum of feet, and lower abdomen small pale brown spots, fairly circular in shape and about the size of a lentil, were

Blood Examinations (Case I).

	Red Corpuscles.	Haemoglobin.	Colour Index.	White Corpuscles	Neutrophiles.	Small Lymphocytes.	Large Lymphocytes.	Eosinophiles.	Basophiles.	Myelocytes.	Megaloblasts.	Normoblasts.	No. Differentiated.
October 14...	1,230,000	32 %	1.33	5,500	50.1 %	39 8	3.8	4.7	0.1	1.5	9	2	1,000
October 20...	933,000	28 %	1.5	—	51.7 %	42.7	2.3	2.1	0.2	0.9	7	0	1,000
October 24...	614,752	20 %	1.6	5,000	50.1 %	47.0	2.0	0.4	0.0	0.5	22	1	1,000

distributed. On exposed surfaces the spots were darker brown in colour. There was no pigmentation of nipples, axillae, or mucous membranes.

These cases present some features of interest. The entire duration of Case I from the onset of distinct symptoms was five months, and the course, though showing the peculiar periodicity of the disease, was typically "progressive." Hunter[1] states those acute cases are the rarest form, and Cabot,[2] in an analysis of 1,200 cases, found 14 per cent. progressive. The patient definitely dated the onset to an attack of diarrhoea—in itself, as a cause, out of all proportion to the anaemia that followed—and his only previous complaint was of biliousness. It is interesting to note that he made no complaint of a sore mouth until particular inquiry was made on that point, though it had given him considerable pain and he had had recourse to treatment for it frequently. Both diarrhoea and glossitis appeared—according to his statement, when he was "quite well"—before any definite symptoms of anaemia had developed, and both recurred frequently during the course of the illness. In the second case the patient attributed the onset voluntarily to a "sore tongue" followed by diarrhoea. She had been anaemic for some years previously, but after this attack of diarrhoea her condition became rapidly worse. From her history she has had two relapses, and in each the gastro-intestinal symptoms were early and periodic.

These cases appear to me to agree with Hunter's conclusions. As a result of his prolonged experimental, pathological, and clinical inquiries he holds that pernicious anaemia is not merely a special form of anaemia, but that it is a specific entity. "The primary etiological factor is a specific haemolytic infection, giving rise to a specific infective glossitis, gastritis, and enteritis, with sepsis of the alimentary tract, as a potent predisposing factor." "A definite, specific, haemolytic, infectious disease, localized to the alimentary tract, with characteristic mode of onset, clinical features, and course; haemolytic and infective lesions."[1]

The appearance and symptoms of Case I at first suggested Addison's disease. The typical lemon-yellow tint of the skin was nowhere present, and the pigmentation of the face to some extent obscured the extreme pallor. N. S. Davis,[3] writing on Addison's disease, says "the symptoms of pernicious anaemia are so much like those of Addison's disease that the former might be suspected until the characteristic pigmentation appeared on some part of the surface"; and other writers refer to a possible confusion. In this case the widespread pigmentation of the skin, the presence of well-marked pigment spots on the buccal mucous membrane, with progressive asthenia, gastro-intestinal symptoms, and a tendency to syncope, made a diagnosis doubtful until the blood examination revealed the characteristic changes of pernicious anaemia, and further inquiry brought out the suggestive points in the history.

Pigmentation of the skin is an unusual feature in pernicious anaemia, and most of the textbooks do not refer to its occurrence. Cabot, in his analysis above referred to, found in 38 cases mention of a "brownish tint of the skin resembling sunburn, and usually attributed to overdosing with arsenic." Case II was possibly of this nature, as she had arsenic frequently and over long periods; but the resemblance of the spots in appearance and situation to those in Case I is suggestive. In Case I the administration of arsenic as a cause could be definitely excluded. A number of similar cases have been reported. Laache[4] noticed a dirty yellowish discoloration of the skin in several cases, which recalled Addison's disease; and Immerman[4] reported two cases in which a well-marked bronzing of the skin developed. Packhard[5] has reported a case in which areas of pigmentation were present over the face and body, with areas of leucoderma, and quotes Broadbent as having described a similar case.* Decastello[6] has reported three cases, in one of which the pigmentary changes corresponded with sensory nerve areas; and Fortune[7] a case in which well-defined brown patches and brown spots were present over body and limbs. It is noteworthy that in the cases which came to necropsy (Laache, Immerman, Fortune) the suprarenal capsules were found normal. On the other hand, Stanley[8] has described cases of anaemia (pernicious?) in which pigmentation of the skin occurred and in which at necropsy there were marked changes in the suprarenal bodies.

With the exception of its presence in Addison's disease, buccal pigmentation does not appear to be of common occurrence. It has been reported as having been found, without any very evident cause present; in chronic gastric conditions; in abdominal conditions (Schultze[9]); in Graves's disease (Sibley[10]). It does not seem to occur as a result of the prolonged use of arsenic.

With regard to its occurrence in pernicious anaemia, I have found very little reference in the literature. Hale White[11] showed a case of pernicious anaemia with pigmentation in the buccal mucous membrane at a meeting of the Association of Physicians of Great Britain and Ireland (May, 1907) of which I have seen no report. Lazarus[4] reports a case in which "on the tip of the tongue and on the mucous membrane of the cheeks, were circumscribed reddish-brown, mahogany-like discolorations, of punctate to dime size, which were undoubtedly the sites of hyperaesthesia, and probably represented haemorrhages into the mucous membranes."

In the present case the spots were on the palate, lips, and cheeks, but absent from the tongue; insensitive to touch; and no signs of haemorrhage were observed.

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TWO CASES OF CARDIAC DISEASE.

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THE following notes of two cases of cardiac disease who were under my care at Llangammarch Wells, during the summer of 1908 may be of interest.

CASE I.

A youth, aged 16, who had had a weak heart for several years. His history showed that he had scarlet fever at the age of 6 years, and he also had subsequently several attacks of influenza. In 1902 he had a severe fainting attack, and consulted a specialist, when a cardiac lesion was first observed. A short time before his arrival at Llangammarch he had evidently strained himself by running when at school.

When I saw him in July he was somewhat feeble, being thin and tall; his height was 6 ft. and his weight 9 st. 3 lb. The heart was considerably enlarged. At the apex, which was in the nipple line, the sounds were normal, but at the right base there was a systolic murmur, which was also heard behind. The pulse was regular, 72, and the tension 130 mm. by Potain's manometer. There was extensive granular pharyngitis.

He was placed on a strict course of treatment, which he carried out very faithfully. He drank a glass of barium water three times daily, and he had daily either a barium bath or massage. At the commencement he was, owing to his feeble condition, restricted in his exercise, but after a short time he was encouraged to undertake a little hill climbing. His diet was carefully regulated, and he had a short rest every afternoon. The pharyngeal granulations were destroyed by the galvano-cautery.

He soon began to improve; he gained in weight and strength, and was able to ascend a fairly steep hill slowly without any marked acceleration of the pulse, and without any signs of dyspnoea. This treatment, after the method suggested by Oertel, I find to be of considerable value, and at Llangammarch there are special facilities for carrying it out. It is only used in selected cases.

After six weeks' treatment I found the patient much improved; the area of cardiac dullness had diminished, the apex beat now being distinctly felt half an inch inside the nipple line.

I heard from my patient a few weeks ago, and he reported that he felt very well, had gained in height, and had no cardiac symptoms to trouble him.

CASE II.

A young man, aged 19, had had rheumatic fever at the age of 11, and a second attack in 1907. He was also subject to chorea.

He was anaemic, he stooped considerably, and breathed chiefly through the mouth. The chest was flat, the area of cardiac dullness enlarged, the apex being in the nipple line, where there was heard a loud systolic murmur, which was conducted outwards and heard behind. The pulse was regular, the rate being 68 and the tension low. There was no dyspnoea