TABLE III.—Average Annual Rate of Mortality from all Causes at Different Ages to 1,000 living during the Ten Years 1891 to 1900.

District.	All Ages.	Under 5.	5-	10-	15-	20-	25-	35-	45-	55-	65-74.
Manchester	26.3	99.4	6.7	3.8	5.5	6.7	10.3	19.0	30.8	50.9	79.3
Whitechapel	31.5	87.7	8.6	6.7	8.4	9.0	16.5	30.7	45.7	66.9	95.0
Strand	30.8	115.3	10.7	7.9	8.8	9.6	15.4	28.9	40.9	55.6	85.8
Stepney	22.3	104.9	6.9	3.3	3.4	3.4	5.1	10.5	15.5	27.3	52.3
Pontypridd	20.6	80.9	5.2	2.6	4.8	5.9	7.3	10.2	17.3	36.9	72.6
Liverpool	33.2	114.5	8.9	4.4	6.1	8.1	14.8	26.8	41.8	65.5	107.0
Salford	24.2	91.9	6.6	3.3	4.3	5.8	7.8	15.1	26.0	49.0	90.2
Middlesbrough	20.3	69.9	4.9	2.7	4.9	6.1	8.3	13.0	20.9	40.4	77.4
Wigan	21.8	73.0	5.3	2.7	4.0	5.7	6.8	12.0	20.2	41.5	86.1
Bedwellty	21.0	74.2	5.8	2.3	4.1	5.8	6.8	11.7	18.8	40.3	84.9
Leyburn	15.1	27.5	2.1	1.5	3.3	3.7	5.0	8.4	8.7	24.6	57.9
Hartismere	16.9	31.8	2.5	2.2	3.5	4.7	5.6	7.6	10.4	20.9	51.6
Aylsham	16.2	36.7	2.6	2.2	2.1	5.2	4.8	6.3	5.7	18.8	42.6
Aberayron	19.5	33.8	4.6	2.9	6.1	9.5	8.9	10.3	10.2	21.6	50.0
Depwade	15.7	31.9	2.3	1.9	2.8	4.7	4.9	6.4	9.5	18.1	51.7
Guilthcross	15.6	31.1	2.9	2.0	2.2	3.1	5.2	6.6	8.9	18.4	48.9
Sedbergh	15.3	27.6	3.0	2.4	2.9	5.6	3.8	9.5	10.3	23.0	56.8
Dunmow	16.5	23.7	3.4	2.4	3.5	5.0	5.3	5.8	11.9	20.6	50.8
Droxford	13.6	28.25	2.6	1.3	1.9	3.2	4.7	4.9	9.4	16.4	45.6
Hoxne	15.3	31.5	2.6	1.5	3.3	4.3	4.5	6.7	8.4	17.9	45.0
Leeds	—	74.8	5.7	3.0	4.7	5.2	7.4	12.6	21.5	41.9	82.6
Crediton	—	32.6	3.2	2.6	3.5	5.8	5.5	6.9	10.2	22.3	54.5

essential in inquiries into the incidence of certain diseases, has appeared to me inapplicable in this particular inquiry.

I would submit that it may be concluded:

1. That there is a very remarkable disparity of longevity in different districts of England and Wales.
2. That this disparity is closely related to density of population.
3. That mere movement of population from country to town, whilst probably tending to make the disparity appear greater than it really is, has on the other hand probably no very considerable effect upon the figures.

THE DIAGNOSIS AND TREATMENT OF SEVERE ANAEMIA.*

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The title of my paper is, perhaps, somewhat too extensive for the ground that I shall be able to traverse—a more correct description would be the differential diagnosis and treatment of pernicious anaemia—and since in the diagnosis and treatment the examination of the blood is of crucial importance, I shall have a good deal to say on the features of the blood in pernicious anaemia and in other cases of severe anaemia which may so resemble it as to give rise to difficulty in diagnosis.

The main symptoms of pernicious anaemia are simply those met with in any severe anaemia—great breathlessness on slight exertion, faintness or actual syncope, great muscular weakness, and palpitation of the heart. All these may be present in severe anaemia from whatever cause, and are in no way characteristic of pernicious anaemia, but there are certain other features which may be present, though by no means always so, which afford further clinical evidence of the disease. These are the peculiar yellow colour of the skin, suggestive of a slight

degree of jaundice; the presence of numbness and tingling in the hands and feet, the result of the lesions in the peripheral nerves and spinal cord, which are almost always found if these are examined *post mortem*; and the presence of small ulcerations and red patches about the tongue, lips, and gums, of soreness in the oesophagus and stomach, vomiting, and occasional attacks of diarrhoea, with the passage of pale, clayey and sometimes frothy stools. These symptoms of an infection of the alimentary tract are not always present, but if present they are most characteristic.

There are many conditions which may give rise to anaemia so profound as to bear a close clinical semblance to pernicious anaemia. It would be impracticable to refer to them all, but the most important among them are these:

1. Diseases of the haemopoietic and lymphatic system, as leucocythaemia—spleno-medullary, lymphatic, or, more particularly, acute; Hodgkin's disease; leukanaemia, a condition probably closely allied to acute leucocythaemia; and primary aplastic anaemia.
2. Carcinoma of the stomach.
3. Repeated small haemorrhages.
4. Long-standing cases of septicaemia, in particular ulcerative endocarditis.
5. Severe chlorosis.
6. Chronic Bright's disease.
7. A number of secondary causes of severe anaemia, scurvy, malaria, syphilis, phthisis, infection of the intestine with *Bothriocephalus latus* or *Ankylostomum duodenale*.

All these conditions may cause severe anaemia which clinically closely resembles pernicious anaemia and accordingly they must be carefully borne in mind in examining a suspected case. It is a fatal tendency to place too sole a reliance on the blood examination. The examination may prove to one's satisfaction that a patient is suffering from pernicious anaemia, or it may as conclusively prove that he is not, but in this latter case the cause of the anaemia remains in doubt unless one has made inquiries as to other possible causes. So that when making the blood examination one must at the same time examine for any evidence of carcinoma of the stomach or for any history of haemorrhage, and a common form of the anaemia from haemorrhage is that which follows compara-

* An address to the Manchester Medical Society, November 4th, 1908, illustrated by a lantern demonstration of photomicrographs of the blood.

tively small but frequently repeated losses of blood from piles. Evidence of chronic septicaemia must be sought for and the heart examined, in the recollection that ulcerative endocarditis is very insidious in its onset, and that its symptoms frequently point to anywhere else other than the heart as the site of the mischief. Then the urine should be examined for albumen and other evidences of chronic nephritis, a condition which not uncommonly reveals itself by no other symptoms but those of anaemia. Other causes, with, as a rule, fairly obvious signs, such as scurvy, malaria, syphilis, and phthisis, must be borne in mind and examined for at the same time. Nor must it be forgotten that severe chlorosis may closely resemble pernicious anaemia, and that it may be met with not only between the ages of 18 and 25, but occasionally in older women, particularly in those that have suffered from it in their earlier years.

If, on a careful examination, none of these causes of severe anaemia can be recognized at present, there is a presumption that we have to do with a case of pernicious anaemia, but conclusive evidence can only be gained through the blood examination.

Blood Examination.

In pernicious anaemia the red corpuscles are greatly reduced in number; instead of 5,000,000 or more in the cubic millimetre we find only 2,000,000, 1,500,000, or they may be reduced to 1,000,000 or lower; that is to say, that there are only 40, 30, or 20 per cent. of the normal number of corpuscles. The haemoglobin is also reduced, but not to the extent that the corpuscles are; in a patient with 1,500,000 corpuscles (that is, 30 per cent. of the normal number) there may be 40 per cent. of haemoglobin, and the fraction formed by putting the percentage of haemoglobin above that of the red corpuscles is greater than unity, in the case supposed being $\frac{40}{30} = 1.33$, which, differently put, reveals the fact that each corpuscle contains 133 per cent. of the normal amount of haemoglobin, this figure, expressed either in relation to unity or per centum, being known as the haemoglobin index. The leucocytes are almost as constantly diminished from the normal 8,000 down to 2,000 or 3,000 or less in the c.mm., and as this reduction is almost solely confined to the polymorphonuclear neutrophils there is a relative excess of lymphocytes, these cells forming 60 to 70 per cent. of all the leucocytes present, instead of normally 15 to 20 per cent. On examination of stained films of the blood the most notable feature is the great diversity in the size and shape of the red corpuscles. There are many larger than normal, macrocytes, and, indeed, the average size is larger than normal, in keeping with the fact that each corpuscle contains, on an average, more than 100 per cent. of haemoglobin. The diversity in shape is an equally marked feature. In a normal blood the corpuscles are all approximately equal in size and with a correct circular outline, but in pernicious anaemia round corpuscles are in a minority, the majority are oval or elliptical or pear-shaped, or still more irregular—*poikilocytes*. We find, further, changes in the staining capacity of the red corpuscles, some are *polychromatophilic*—that is to say, they show an affinity not only for the acid eosin stain, as is normal, but also for the basic methylene blue, and so appear greenish or bluish; whilst some show the presence of granules which stain with methylene blue, the so-called "*granular degeneration*," or basophile stippling of the erythrocytes. In addition we may find *nucleated red corpuscles*, though I am inclined to lay much less stress upon them than upon the other features I have mentioned, and it is particularly the finding of the variety described as megaloblasts which is of such significance. Nucleated red corpuscles are not uncommon in many conditions of severe anaemia, but these are mostly normoblasts, corpuscles of about normal size, shape, and staining capacity with a small deeply staining nucleus. The megaloblasts which are met with in pernicious anaemia and in leucocythaemia are very different looking cells, and are characterized by three typical features—namely, the large size of the corpuscle, the large nucleus with well marked nuclear network, and the cytoplasm showing very decided polychromatophilia.

Now let us turn to the characters of the blood in some of these other forms of severe anaemia that I have referred to. The more chronic forms of *leucocythaemia* only occasionally present any high degree of anaemia; and in

addition they present certain clinical features, the great enlargement of the spleen in the spleno-medullary form and of the lymphatic glands in the lymphatic form, which suggest the nature of the disease. A single glance at the stained film clinches the diagnosis, the great increase of leucocytes is at once apparent; a large proportion of these, 25 to 40 per cent., in the spleno-medullary form being *myelocytes* with a large single nucleus and neutrophile or eosinophile granules, whilst in the lymphatic form the great majority, well over 90 per cent., as a rule are *lymphocytes*. *Acute leucocythaemia* requires more circumspection. The anaemia is usually most profound, and not uncommonly there is no enlargement either of spleen or lymphatic glands, and it is impossible to pronounce for certain about a case until the blood examination is made, and in the absence of such examination there is little doubt that cases frequently go undiagnosed. But the appearance of the film is conclusive, and we find large numbers of lymphocyte-like cells, the larger forms usually preponderating. Of *leukaemia* I need say little; it is an uncommon, and as yet not quite clearly defined, condition. There is most profound anaemia, and the blood, while in many ways resembling pernicious anaemia, as in the high haemoglobin index, and the large average size of the corpuscles, bears also some resemblance to that in leucocythaemia. Though there may be no increase in the number of leucocytes (at times even a decrease), there are qualitative changes, consisting in the presence of a considerable proportion of *myelocytes* or of the large "*lymphoid*" cells that are met with in acute leucocythaemia, which distinctly bring it into the category of leukaemia-like diseases, and at times the number of leucocytes may greatly augment, so that the blood comes to be indistinguishable from a case of acute leucocythaemia.

Apart from these special conditions, the other forms of severe anaemia I have enumerated all show practically uniform blood changes which are on the whole the antitheses of those met with in pernicious anaemia. The red corpuscles are rarely reduced to the extent that they are in pernicious anaemia while the haemoglobin is proportionately more reduced than the corpuscles, giving an index of below 100, very often far below. The average size of the red corpuscles is smaller than normal, instead of being larger, and there is comparatively little variability in size or shape. Nucleated red corpuscles are less numerous; if present they are of the normoblast type, megaloblasts being practically unknown, whilst those which show polychromatophilism or granular degeneration are infrequent, except the latter in lead poisoning. I may say parenthetically that the anaemia of *bothrioccephalus* infection is an exception to this type. I have never seen a case, but the blood is said to be indistinguishable from that of pernicious anaemia, and the diagnosis depends on the discovery of portions of the worm or its ova in the faeces.

Let us consider one case, that of a man with severe anaemia, the result of long-standing loss of blood from bleeding piles. His haemoglobin was down to 28 per cent., a more profound anaemia than in most cases of pernicious anaemia. But the corpuscles were proportionately much less reduced, being 2,700,000, so that the haemoglobin index was as low as 52, each corpuscle containing barely half the normal amount of haemoglobin, whilst the corpuscles in the stained film appeared small and washed out, but fairly regular in size and shape. Another man had all the appearance and symptoms of a case of pernicious anaemia, and took his place among the patients at a university examination as such. But on examination the haemoglobin was found to be 20 per cent. and the red corpuscles 2,570,000, giving an index of 52, and the stained films showed all the characters of a secondary anaemia, and none of pernicious anaemia. I felt very strongly at the time that the slight gastric symptoms which he showed, and which had naturally been looked on as the gastric symptoms of pernicious anaemia, were due to carcinoma of the stomach—a surmise which subsequently proved correct, and was verified *post mortem*.

Occasionally in cases of secondary anaemia one sees so great an irregularity in size and shape of the red corpuscles that at a first glance a diagnosis of pernicious anaemia is suggested. In one such case, however, the index was found to be only 74, and a more critical examination of the film showed that the average size of the corpuscles was in keeping with this low haemoglobin index—decidedly below the normal—and so the superficial resemblance to pernicious anaemia vanished. Very occasionally one may get a few true macrocytes, as in one case of severe

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