produced artificially, it is accompanied by a, at any rate, closely corresponding rise in the number of the blood corpuscles—Hayem states that the specific gravity depends on the corpuscular richness of the blood¹—the difference possibly being caused by the passage of a certain amount of plasma into the lymph spaces. On the other hand, we find that while the density remains unaltered, even under abnormal circumstances, the number of the corpuscles is practically unaffected also.

These experiments, then, taken together, afford evidence in favour of variations in the number of corpuscles in the blood being largely concerned in bringing about differences in its specific gravity, particularly as certain other of our experiments, which cannot be quoted here, have similarly shown a fall in the number of corpuscles associated with a similar fall of specific gravity. But pathologically, at any rate, the problem is evidently more complex than would be inferred from the foregoing statements. Thus, in a severe case of pernicious anæmia which was in St. Thomas's Hospital, under the care of Dr. Bristowe, a few months back, the specific gravity of the blood was found to be 1027 only, while the number of red corpuscles in a cubic millimetre was slightly over 500,000. Now normal human plasma or serum has a specific gravity of 1028, about the same, or a little higher, than that of the entire blood in this case. The specific gravity of the red corpuscles is also, normally, so much higher than that of the blood, and more particularly, therefore, of the plasma, that even supposing that in this case their density was considerably lessened, as may be inferred from the ease with which, as I have shown elsewhere, the corpuscles break down or their hæmoglobin diffuses out, still we are driven to the conclusion that for the blood to show so low a density as the case in point, the specific gravity of the plasma must be lower still. It was unfortunate that it was not possible, at the time, to determine accurately the specific gravity of the liquor sanguinis in this instance.

Under certain circumstance, also, we have been able to lower the specific gravity of the blood for a length of time, from 25° to 30°, without a corresponding fall in the number of the corpuscles present in it, so that in these experiments also, an account of which is about to appear in the *Journal of Physiology*, it would seem that a considerable dilution of the plasma had been brought about. Christison, moreover, has shown by the older methods that the density of the blood serum is sometimes considerably lowered, more particularly in the early stages of kidney disease, when the specific gravity may be 1020 or even 1019. It would appear, then, that a rise of specific gravity in the blood may be the result of the formation of new corpuscles, or of a draining away of a certain part, particularly the watery portion of the plasma, such as occurs in cholera, or, to a much less extent, after the use of saline purgatives, while a lowering of specific gravity, particularly if marked in extent, will always have a pathological significance, although the cause may be a somewhat complex one; since, as we have seen, it must be the result of diminished specific gravity either of plasma or of corpuscles; of a large decrease in the number of the corpuscles; or, as is most probable, of all these factors combined.

¹ *Du Sang*, 1889, p. 400.

PORTSMOUTH (Population, 141,254).—*Scarlatina of a Mild Type: Pet Dog attacked by a Diphtheritic Affection.*—With a very favourable death-rate (18.1 per 1,000), a small prevalence of zymotic disease, and a good record of sanitary work, Dr. Mumby's report for 1889 bears satisfactory comparison with those of former years. Scarlet fever, though widespread through the district, was of so mild a character as to cause only 11 deaths, but whooping-cough and diarrhœa caused a greater mortality than usual. Small-pox was three times introduced into the borough. Two cases proved fatal. Diphtheria, though not remarkably prevalent, was of a fatal type. Many of the cases were associated with sanitary defects and dampness. In one household, where 5 cases occurred from drinking impure water, a pet dog was also taken ill and had to be killed. On making a *post-mortem* examination, Dr. Mumby found a distinct false membrane attached to the pharynx.

THE LETTSOMIAN LECTURES

ON

ANÆMIA:

ITS PATHOLOGY, SYMPTOMS, AND TREATMENT.

Delivered before the Medical Society of London.

By STEPHEN MACKENZIE, M.D., F.R.C.P.,

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LECTURE II.

Secondary Anæmia. Paroxysmal Hæmoglobinuria. The Symptoms of Anæmia. Oligæmia. Oligocythæmia. Degrees of Anæmia. Alterations in the Blood Corpuscles. Hæmorrhages. Circulatory Organs. The Urine. The Alimentary System. Pyrexia. The Nervous System. Chlorosis. Pernicious Anæmia.

MR. PRESIDENT AND GENTLEMEN,—Before proceeding to describe the symptoms of anæmia, I had intended to review the nature of secondary anæmia. The extent of my subject, however, is so wide that I am obliged to omit what I had prepared, and only allow myself to discuss one form of secondary anæmia. This, which has important bearings on many of the debated points in the pathology of anæmia, is paroxysmal hæmoglobinuria. This particularly interesting and important disease is of a purely hæmolytic nature, which lends itself to the study of the blood changes. As is well known, the attacks are excited by cold. To Dr. Copeman we owe some exceedingly valuable information on the changes in the blood in this remarkable disease. He has shown¹ that in intentionally induced attacks there may be a loss of from 129,000 to 824,000 red corpuscles per cubic millimetre in the course of two or three hours; and that as many as 824,000 corpuscles per cubic millimetre on one occasion were destroyed in a quarter of an hour. At the same time the percentage of hæmoglobin fell from 53 to 49. Dr. Copeman calculates that the reduction of red corpuscles in an attack reached the extraordinary number of 4,032,000,000,000. The blood-forming powers in this disease are exceedingly active. In one attack, watched by Dr. Copeman, the corpuscles were reduced from 3,612,500 to 2,930,000, and at the end of six days had risen again to 3,540,000 per cubic millimetre. Still further important changes were observed in the arrangement and forms of the red corpuscles, and in the rapidity with which these changes took place. In the course of from half an hour to two or three hours, the *rouleau* formation was partially or entirely lost, and many red corpuscles had become pyriform or spindle-shaped, and some were nearly colourless. The specific gravity of the blood was also observed to fall about 5° in an attack. The fact that such rapid changes in the forms of the red corpuscles may take place by a process of hæmolysis is of extreme importance, and goes to show that the poikilocytosis met with in many other forms of anæmia may be due to destructive changes. As Dr. Hunter has pointed out² the appearance of hæmoglobin in the urine in the disease is due to the destruction of corpuscles taking place in the general circulation, whence the hæmoglobin is conveyed to the kidneys and excreted. In pernicious anæmia the destruction takes place within the portal circuit, and all the hæmoglobin is converted into biliary and urinary pigments, and none is excreted, as such, by the kidneys.³

THE SYMPTOMS OF ANÆMIA.

Whenever hæmorrhage of any more than the most trivial degree exists, there must necessarily be diminution in the volume of the blood—oligæmia. The water is quickly replaced by the plasma from the lymphatic system, the deficient albu-

¹ Bristowe and Copeman, *Trans. Medical Soc.*, 1889, p. 256. Copeman, *Præct.*, Sept. 1890, p. 161.

² *Lancet*, vol. ii, 1888. An Investigation into the Pathology of Pernicious Anæmia.

³ I should have liked to allude to the detailed and careful observations of Dr. Rutherford Macphail, On the Blood of the Insane, *Journ. of Med. Science*, 1884 and 1885, had space permitted.

men and salts are soon supplied from the food, but the corpuscular deficiency remains for a time. In hæmorrhage it is the red corpuscles which are especially deficient, as owing to their "wall-loving" propensities fewer colourless corpuscles are shed; and, moreover, as Cohnheim points out, the lymph is an inexhaustible source for these. In experimentally induced anæmia in the dog, the number of red corpuscles continues to fall for some days after the hæmorrhage, and does not reach its minimum until eight or nine days. Successive hæmorrhages at intervals are more dangerous than a single hæmorrhage exceeding them in amount, apparently by interfering with the renovation of the blood. How great a loss of blood the human subject can bear is not ascertained, but dogs do not survive a greater loss than from one-nineteenth to one-fourteenth of their body weight.

Oligocythæmia.—In nearly all forms of anæmia the red corpuscles are diminished. The only form of primary anæmia in which this does not necessarily occur is chlorosis. The greatest reduction of the number of red corpuscles is in pernicious anæmia, in hæmorrhage and purpura, and in certain cases of malignant growths. In a case of puerperal hæmorrhage of Hayem's, which recovered, the corpuscles were as low as 850,000 (17 per cent.), and many of these were wanting in colour. Quinquaud has recorded a case of purpura with a corpuscular richness of only 740,000, Hérard one in which it fell to 620,000 on the day of death, and I have published a case in a child 11 months old in which the corpuscles were only 290,000 per cubic millimetre, or 5.8 per cent., just before death.⁴ What is the lowest number of corpuscles which may be reached without death resulting? With the exception of a case of Quinke's—to be subsequently alluded to—the lowest that I know of is one cited by Laache, a case of pernicious anæmia, in which the red corpuscles were reduced to 407,480 (8.1 per cent.), and later rose to 4,148,000 per cubic millimetre at the time of publication. I think we may fix 7.5 per cent. as the lowest which can be reached without being necessarily fatal.

It is convenient in practice to have some scale or measure of degrees of anæmia. For some years past⁵ I have been in the habit of using the following measure of the severity of the anæmia: Anæmia commences with red corpuscles at 80 per cent. It is moderate at from 80 to 65 per cent., first degree; it is decided at from 65 to 50 per cent., second degree; it is grave at 50 per cent., third degree; and usually fatal at about 10 per cent. (7.5 actually), fourth degree. My original scale was 65 per cent. moderate, 50 per cent. grave, 35 per cent. very grave, and 20 per cent. or thereabouts fatal. Increase of knowledge has compelled us to shift the last number to a considerably lower level. Though the diminution of red corpuscles is the most important element in diagnosis and prognosis, it is, of course, modified by the relative hæmoglobin richness. M. Hayem has given us a much more complete and valuable scale, which expresses the functional value of the blood. His estimation takes cognisance of the coloured corpuscles, the hæmoglobin, and the individual worth of the corpuscles, as well as the size of the discs.⁶ He also makes four degrees.

As Hayem points out, the anæmia is less grave when the same amount of hæmoglobin is distributed amongst a large number of small globules than amongst a smaller number of larger globules, as the former must facilitate the globular functions. All observers have noticed the fluctuations which take place day by day in the number and sizes of the red corpuscles.

Size of the Red Corpuscles.—In health we have seen the red corpuscles range between 6.5 and 9 μ . In anæmia the range is much greater, from 2.5 to 16 μ . The term microcyte is conveniently applied to corpuscles from 2.5 to 4 μ , and megalocyte to those whose dimensions range from 9 to 16 μ . Both these extremes, and gradations between them, are found in all varieties of anæmia—primary and secondary. Both microcytes and megalocytes are more common in pernicious anæmia than in other forms. Megalocytes, nevertheless, are found in chlorosis, in which disease a large number of corpuscles are smaller than normal.

Eichhorst's Corpuscles.—This term is applied to microcytes of

a deep colour and spherical shape, to which Eichhorst first drew attention.⁷ He believed at one time that they were diagnostic of pernicious anæmia; they are certainly common in this form of anæmia, though they are sometimes entirely absent,⁸ and they have been found in other forms. These corpuscles are from 3 to 4 μ , have not the usual biconcave aspect, and Eichhorst describes them as resembling "droplets of fat tinged with red."

Poikilocytosis (*ποικίλος*, varying in shape, *κύτος*, cell), the name suggested by Quinke⁹ for the variously deformed red corpuscles, has been generally adopted, but Ehrlich has recently proposed to substitute for it "Schistocytosis." The shapes assumed by the corpuscles are very varied: ovoid, pear-shaped, battledore, rod-shaped, bent forms, and irregularly outlined shapes are met with.

Nucleated Corpuscles.—Nucleated corpuscles, similar to what are found in the blood of the embryo, and at all times in the marrow, are occasionally, though rarely, found in the blood in anæmia of different kinds, and are probably evidence of its severity rather than of its nature.

Remarkable fluctuations of opinion have taken place regarding the nature and significance of these abnormal forms. At one time considered as peculiar to pernicious anæmia, increasing observation has shown that they may occur in all forms of anæmia. They indicate that the blood elements have undergone a change, constructive or destructive, but the observations of Boas and Copeman in hæmoglobinuria show we must be cautious as to the inferences we draw regarding their origin. Copeman has pointed out how readily crystals of hæmoglobin are formed in pernicious anæmia, a proof of the increased fragility of the corpuscles.¹⁰

The Colourless Corpuscles.—In pure anæmia the leucocytes are not increased in number actually, nor in many cases relatively. Not infrequently, however, at the close of cases of profound anæmia, there is an augmentation of the colourless corpuscles.

Hæmoglobin.—In my first lecture I dealt with the variations which take place in the percentage of hæmoglobin in the chief varieties of anæmia. I will only add that in some cases of cancer the hæmoglobin is reduced disproportionately to the corpuscles. Thus I have recorded a case of cancer of the stomach where the corpuscular richness was 46 per cent., and the hæmoglobin 30 per cent., and, later, the corpuscles were 30, and the hæmoglobin 15, per cent.; in another case a corpuscular richness of 50 per cent., with 25 per cent. of hæmoglobin, and at the time of death the corpuscles were 33 per cent. and the hæmoglobin 25 per cent. The worth of the individual corpuscles was thus at one time not more than one-half of the normal. In most cases of purpura of which I have notes, the hæmoglobin deficiency has been below that of the corpuscles. In regeneration of the blood, as a rule, the corpuscles increase disproportionately to the hæmoglobin. This is usually well seen in chlorosis, but exceptions do occur.

Hæmorrhages.—In anæmia there is a liability to hæmorrhages, external and interstitial. Epistaxis, menorrhagia, and bleeding from the gums are the most common forms of external hæmorrhage, but hæmorrhages occur, also, from the stomach and bowels. Of interstitial hæmorrhages, extravasations into the retina are the most frequently seen, though I suspect, if we could see the brain, they would be found there equally frequently. Less common than retinal hæmorrhages are those into the skin—purpura. At one time retinal hæmorrhages were regarded as diagnostic of pernicious anæmia; but Quinke, Litten, myself¹¹ and others, have recorded cases where retinal hæmorrhages occurred in symptomatic anæmia. It may, I think, be now regarded as established that hæmorrhages in connection with anæmia are dependent upon its degree irrespective of its nature, and that the tendency to hæmorrhage occurs when the red corpuscles are below 50 per cent., and is more dependent on the deficiency in the number of corpuscles than in the amount of hæmoglobin.

Circulatory Organs.—In anæmia of moderate severity the

⁷ *Centralb. f. d. med. Wissenschaft.*, 1876.

⁸ Grainger Stewart (*BRITISH MEDICAL JOURNAL*, 1876, vol. ii, p. 40) and others.

⁹ *Deutsch. Archiv f. klin. Med.*, 1877, Band xx.

¹⁰ *St. Thomas's Hospital Reports*, 1887.

¹¹ *Ophth. Soc. Trans.*, vol. iv, p. 132.

⁴ *BRITISH MEDICAL JOURNAL*, 1883, vol. ii, p. 409.

⁵ *Lancet*, 1883, vol. ii, p. 1047; *Ophthal. Soc. Trans.*, 1884, p. 132.

⁶ *Op. cit.*, p. 407.

heart's impulse is often diffused and of a jarring character, but in extreme degrees it becomes feeble and often imperceptible. Increased area of dullness, indicating dilatation, is found in some cases, and there is no doubt that anæmia *per se* may give rise to enlargement of the cardiac chambers, as in a case of pernicious anæmia I have recorded.¹² Murmurs are frequently heard over the cardiac area. Dr. Kingston Fowler¹³ has given a very complete account of these, and with his observations my own in the main agree. Eichorst¹⁴ states that in three out of seven cases of pernicious anæmia examined by him a diastolic murmur was heard, and refers to other published cases. He states it may be transitory or persist till death, when the aortic valves may be found competent. Dr. Ernest Sansom thus explains such cases:¹⁵

"I have occasionally found murmurs in anæmic subjects closely resembling a double aortic—that is, systolic and diastolic. In such cases you will find that the systolic is the hæmic *souffle* heard at the aortic base, and generated either in the aorta, the subclavian artery, or in the pulmonary artery; and the seeming diastolic is really a continuous venous hum generated in the great veins of the neck. This continuous hum is overpowered during the systolic period by the arterial murmur, but it is audible during the diastole, so the murmur appears to and fro."

Schwald¹⁶ gives a somewhat similar explanation. The arterial tension, contrary to what would be expected, is sometimes increased in anæmia (Broadbent, Sansom, Bramwell), and Dr. Broadbent is inclined to attribute to arterial spasm a share in the production of the dilatation of the left ventricle often encountered.¹⁷ My own experience corresponds with that of Dr. Byrom Bramwell, that the arterial tension is only increased in cases of slight or moderate anæmia,¹⁸ or, I may add, anæmia of rapid occurrence. In profound anæmia the tension is low, and the artery is empty between the beats. The increase of tension occasionally met with is no doubt of nervous origin. Cohnheim¹⁹ has shown that anæmia is an exciter of the vaso-centre, and acts more vigorously in proportion to its degree and rate of progress. The low arterial tension in the late stages of pernicious and other grave forms of anæmia is probably due to the fatty degeneration of the left ventricle, and possibly to exhaustion of excitability of the vasomotor centre. To the former cause is also due the dropsy which usually occurs towards the close of severe anæmias, though an hydræmic condition of the blood no doubt favours it. The œdema of anæmia is slight in degree, and usually limited to the feet and legs. Nothing like anasarca is ever seen, but dropsical effusions of moderate amount are found in the serous cavities in many fatal cases. Œdema of the feet and ankles is not uncommon in chlorotics who are much on their legs, and disappears when they are put to bed—a proof of its dependence on cardiac feebleness. Palpitation and breathlessness are explained partly by the cardiac feebleness and in part by the deficiency of oxygen carriers in the blood.

Pyrexia.—Occasional and irregular pyrexia is common in anæmia of whatever nature. I have found it in traumatic anæmia in previously healthy persons and after hæmatemesis, and in my notes of cases of chlorosis I find slight degrees of pyrexia very common, "a mimic reproduction of the irregular 'anæmic fever' that appears in pernicious anæmia" (Coup-land). It is more pronounced in the latter than in other forms, but some cases of pernicious anæmia are throughout apyrexial. The fact that fever occurs in chlorosis is important, as its occurrence in pernicious anæmia, in concurrence with the exacerbations of other grave symptoms, has been regarded as evidence of blood destruction.

The urine supplies us with most valuable knowledge as to the changes which are taking place in the blood, and becomes our chief source during life of information as to whether

hæmolytic influences are at work. We shall deal with this more fully under pernicious anæmia. Albuminuria is not uncommon in the late stages of severe anæmia, and is best explained by Cohnheim's theory of degeneration of the glomerular epithelium due to the defective quantity and quality of the blood passing through the glomerular tufts.

The Alimentary System.—Functional and organic diseases of the digestive system are common in all forms of anæmia, and may stand in the double relationship of cause and effect. Anorexia, nausea and vomiting, and gastralgia are exceedingly common, the latter, sometimes associated with gastritis, being often very marked in chlorosis. Constipation is present in some cases, diarrhœa in others, the latter often being encountered in cases of pernicious anæmia.

The nervous system shares in the general disturbance. Sustained mental activity is rendered impossible, and an unstable condition or "irritable weakness" of the nervous centres is induced, which shows itself in hysterical phenomena in some cases of chlorosis. In profound chronic anæmia, as in the acute anæmia of severe hæmorrhage, delirium and convulsions may close the scene, or be followed by coma. In anæmia, especially in its primary, but not very profound, forms, neuralgic affections are very common, explained by the late Dr. Anstie, as "the cry of the nerves for healthy blood." Amaurosis, from optic neuritis and consecutive atrophy, occurs in some cases of anæmia, especially that following hæmorrhage.

We must now pass on to consider the principal species of idiopathic anæmia. In doing this, my object is rather to review the facts regarding them in relation to their pathology than to give a complete clinical picture, which the time at my disposal does not allow of. First of all we must consider

CHLOROSIS.

In this form of anæmia the observations of Duncan²⁰ in two cases, have in the main been confirmed by all subsequent observers, namely, that the essential feature in the blood change is a diminution in the hæmoglobin capacity—an oligochromæmia. In many cases the red corpuscles are scarcely at all below the normal, whilst the hæmoglobin is reduced to from 60 to 30 per cent. In other cases, the red corpuscles are also deficient, but in these also the hæmoglobin is disproportionately reduced. Thus, two categories of cases are found in chlorosis, to the first of which Laache²¹ would give the name "pseudo-chlorosis," while the second he would call "true chlorosis." What is common to both is that the corpuscular worth is diminished. Whilst, however, this is characteristic of chlorosis, it is not peculiar to it. In severe cases of chlorosis, the corpuscles undergo a notable diminution, constituting what some would designate chloro-anæmia. Thus Laache has published a case in which the corpuscles were as low as 2,440,000 (48.8 per cent.), (Coup-land a case with 2,090,000 (41.8 per cent.), Gowers a case with 26 per cent., whilst M. Hayem records a case in which the actual number of red corpuscles was 937,360 (18.7 per cent.). Another characteristic of chlorosis is the relatively large number of small red corpuscles of 3μ to 6μ , but they may be reduced to even 2.2μ (Laache). Though some large or even giant corpuscles are occasionally found in chlorosis, Malassez stands almost alone in stating that, as a rule, the corpuscles are increased in size in chlorosis. Poikilocytosis is sometimes present, as in the diagram exhibited, which is taken from a girl, aged 18, with 85 per cent. of red corpuscles, and 35 per cent. of hæmoglobin. In chlorosis there is little liability to hæmorrhage, which we have seen stands intimately related with severe degrees of oligocythæmia. This applies to retinal hæmorrhages, which, apart from inflammatory changes, are certainly rare. Papillitis and papillo-retinitis are, however, probably more common in this form of anæmia than in any other. Saundby and Eales²² found that, of fifty cases of chlorosis examined by them, 10 per cent. presented unequivocal evidence, and in a further, 8 per cent., there was evidence of some degree of neuro-retinitis. Hirschberg was the first to note the occurrence of optic neuritis in chlorosis. Gowers has recorded several cases, and cases of double papillo-retin-

¹² *Lancet*, 1878, vol. i, p. 13.

¹³ *On the Origin of Anæmic Murmurs*. Churchill, 1884.

¹⁴ *Die progressive perniciöse Anæmie*, 1878, s. 224. Since this was in type I have seen an important paper by Dr. Handford in the *Intern. Journ. of Med. Sci.*, December, 1890, "On the Condition of the Heart in Anæmia," which deserves attention.

¹⁵ *Diagnosis of Diseases of the Heart*, p. 134.

¹⁶ *Deutsch. med. Wochens.*, 1889, No. 21.

¹⁷ *The Pulse*. Cassell and Co., 1890, p. 160.

¹⁸ *Diseases of the Heart*.

¹⁹ *Lectures on General Pathology*, *New Sydenham Soc. Trans.*, vol. 1, p. 428.

²⁰ *Sitzungsbericht d. k. k. Acad. d. Wissensch. in Wien*, Bd. lv, 1867.

²¹ *Op. cit.*, s. 86.

²² *Ophth. Rev.*, i, p. 303.

itis have been recorded by Mr. R. Williams²³ and myself.²⁴ In my own case, which is one of several I have seen, the corpuscular richness was 80 per cent., and the hæmoglobin only 30 per cent.

The existence of hypermetropia, as first pointed out by Gowers,²⁵ increases the liability to inflammatory changes. Cardiac murmurs and venous hum in the neck constitute part of the clinical features of chlorosis with which all are familiar, and with them are associated palpitation and breathlessness on exertion. In speaking of the symptoms of anæmia in general, I have remarked that pyrexia is by no means uncommon in chlorosis. In some cases the pyrexia is considerable, constituting what has been called "febrile chlorosis." Hayem stated that chlorosis only assumes a febrile form when the globular richness, expressed in healthy corpuscles, is below 1½ million. With regard to the urinary system, most authorities state that it is normal in amount, pale in colour, of low specific gravity, and contains but little urea and uric acid, and my own experience agrees with this. Dr. Hunter has shown that the urine in chlorosis in three cases he examined contained only 1.76 milligrammes of iron, whilst that of health averages 5.65 milligramme per diem.²⁶ Further observations on the urine in chlorosis, clinical and chemical, are greatly wanted. The alimentary system very frequently, though not invariably, shows signs of disturbance, and sometimes these are so pronounced that some would make a variety, "dyspeptic chlorosis." How far they are caused by the anæmia and how far by the conditions that give rise to chlorosis are much debated questions. Constipation is exceedingly frequent, and is believed by many to be causally related to chlorosis. Its absence in many cases, and the frequency with which constipation occurs in young people who are not anæmic, make the dependence of chlorosis upon constipation very doubtful, and I believe its importance has been considerably overrated. The nervous disturbances—"the irritable weakness"—of chlorosis are very characteristic phenomena, and to be explained partly by the anæmia and in part by the conditions that give rise to it. The age at which it occurs and the sex of the sufferers imply a highly sensitive and mobile, if not unstable, condition of the nervous system. As well known, chlorosis is frequently associated with menstrual irregularities, especially amenorrhœa; but it also occurs in those whose catamenia are regular, if somewhat scanty, and may coexist with excessive menstrual discharge. Leucorrhœa is very common in chlorosis, disappearing with its subsidence.

Chlorosis occurs almost exclusively in women, though occasionally cases are met with in young males. It is met with, especially between the ages of 14 and 24. All are familiar with Niemeyer's oft-quoted statement: "According to my observation, obstinate chlorosis attacks all young girls without exception, in whom the menses have appeared in the twelfth or thirteenth year, and before the development of the breasts and pubes."²⁷ It is occasionally hereditary, and possibly congenital. The narrowing of the aorta, the thinning of the arterial tissues and irregularities of position of the arterial branches, described by Virchow, though not invariably present, point to developmental defects. The character of the blood, its poverty in hæmoglobin, comparative richness in other albuminates, the markedly renovating influence of iron, all indicate a defective hæmogenesis, a "hypoplasia" of the blood as well as that of the blood vessels (Immermann). Moreover, there is little or no evidence, clinical or pathological, of excessive hæmolysis. There is no drain upon the system other than that of menstruation, and this, in many cases, is suspended. On all of these grounds we are justified in regarding chlorosis as due to defective blood formation, often associated with, and possibly in some cases due to, disturbances in the generative system. Most probably both are due to some inherited or acquired developmental feebleness of the blood-forming organs rendering them unequal to the calls made upon them, which, treated promptly and properly in most cases, is of transitory duration, but which, more pro-

found in degree or imperfectly treated, may prove a lifelong complaint.

PERNICIOUS ANÆMIA.

I have already given reasons which appear to me sufficient for adopting this name for another variety of idiopathic anæmia. First described by Addison in his lectures in 1843, which were published in 1853, a knowledge of the disease was confined to a few until Gusserow in 1871 and Biermer in 1872 (the latter calling it "progressive pernicious anæmia") drew attention prominently to the subject. Since then a large number of writers at home and abroad have contributed to our knowledge of the disease.

It is impossible to allude to the work of most of these in the time at my disposal, but I must mention the service Dr. Pye-Smith has done to medical literature in his articles in the *London Medical Record*, 1877, and in *Guy's Hospital Reports*, vol. xxvi, in which will be found historical and critical reviews of the literature, and valuable original observations and pathological teaching. I must also allude to Dr. F. Taylor's paper in *Guy's Hospital Reports*, and since this was in type to a paper in a forthcoming number of the same *Reports* by Dr. Hale White, of which he has allowed me to see a proof, to Dr. Sidney Coupland's able and complete Gulstonian lectures on anæmia in 1881, and to Dr. William Hunter's numerous and valuable contributions on the subject. Dr. Hunter's clinical, chemical, pathological, and experimental investigations, carried on over a series of years, have, by the ability with which they were conceived and the exactness with which they have been carried out, added more to our knowledge on the subject than those of any individual worker since Eichhorst's valuable treatise in 1878.

Pernicious anæmia manifests itself insidiously by increasing pallor and weakness. In a large proportion of cases disturbances of the alimentary canal (nausea, vomiting, diarrhœa, etc., and not infrequently stomatitis) precede or accompany the onset of the disease, and such disturbances are of common occurrence throughout its course. The patient, whilst losing colour and strength, maintains, as a rule, his flesh. Since Addison's time the details of the anæmia which is so striking to the naked eye have been most carefully investigated by means of modern instruments of precision.

I have already pointed out that the specific gravity of the blood is reduced from 1038 to 1028, and that its alkalinity is lessened. In this form of anæmia the solids of the plasma are greatly diminished. Great attention has naturally been devoted to the red corpuscles, and there have been noted the following alterations:—(a) Their cohesiveness is modified; normal *rouleaux* formation is rarely seen; usually the corpuscles are arranged singly, or collected into clumps, consisting of a few red corpuscles irregularly grouped together. (b) The reduction in the number of the corpuscles is remarkable, and only equalled by cases of hæmorrhage and rare cases of malignant growths, and only exceeded by cases of fatal spontaneous hæmorrhage—such as purpura with epistaxis. At a time when the disease is recognisable, the number is below 50 per cent., and generally at or below 30 per cent. (2½ to 1½ millions per cubic millimètres). In fatal cases the numbers at the close of the case are extraordinarily low. Thus Lépine has recorded a case with 378,000 per cubic millimètre (7.5 per cent.) the day before death, Worm-Müller with 360,000 (7.2 per cent.) Quinke has published a case in which the corpuscles were reduced to 143,000 (2.8 per cent.) without death resulting, but all Quinke's numbers read much lower than those of any other observer. It may be stated that in fatal cases the corpuscles generally sink to about 18 to 16 per cent. before death, and, with the exception of Quinke's case, no case has been known to recover in which the corpuscles have fallen as low as 7.5 per cent. It will thus be seen that nearly all cases have reached the stage which I have called "grave anæmia" (50 per cent.) when first recognised, and nearly all to Hayem's fourth degree of anæmia, or "*aglobulie extrême*" before death. (c) Poikilocytosis, though, as has been shown, not peculiar to this form, is more constant, and carried to a more extreme degree than in other varieties of anæmia. The most remarkable alterations in the forms of the corpuscles are sometimes observed. (d) Their size presents great variations. Many microcytes (Eichhorst's corpuscles) are usually seen, and, though not peculiar to, are most common in this form of anæmia. On the other hand, megalocytes are also

²³ BRITISH MEDICAL JOURNAL, 1884, vol. i. p. 10.

²⁴ *Ibid.*, 1885, vol. i. p. 328.

²⁵ *Medical Ophthalmoscopy*.

²⁶ *Med. Soc. Trans.*, vol. xiii.

²⁷ *Textbook of Practical Medicine*, American translation, 1876, vol. ii. p. 743.

present. What, however, is especially characteristic of pernicious anæmia is the large number of red corpuscles above the normal size, but not so large as to really deserve the name of megalocytes—corpuscles of from 8 to 12 μ . Nucleated corpuscles have been found by many observers, but are not always present. (e) The vulnerability of the corpuscles is increased. This is shown by the manner in which the colouring matter separates from the stroma, as pointed out by several observers,²⁸ and, as Copeman has shown, by the readiness by which blood crystals form from them without the addition of any reagent. (f) The hæmoglobin capacity of the corpuscles is generally increased, so that the percentage of hæmoglobin exceeds the percentage of corpuscles, and the worth of the individual corpuscles is increased, often to 1.25, and occasionally to as much as 1.75 (1.0=normal).

I have, however, recorded a case²⁹ in which the worth of the corpuscles was as low as, on one occasion, 0.75, and, on another occasion, 0.26. In the great majority of cases the worth is increased, so that, as pointed out by Osler, the anæmia is less than is indicated by the deficiency of corpuscles. The fact, however, that the majority of the corpuscles are larger than normal neutralises to a great extent any advantage accruing from the increased worth of the individual corpuscles, as the same amount of hæmoglobin distributed amongst a smaller number of large corpuscles must expose a smaller superficies than distributed in a larger number of small corpuscles. The colourless corpuscles are not, as a rule, increased in pernicious anæmia, but a marked leucocytosis has been observed by Litten, and Gottlieb, and myself as a premortal phenomenon. Hæmorrhages are more common in this form of anæmia than in any other, especially due, as I have pointed out, to the oligocythæmia. Retinal hæmorrhages are almost invariably present, and petechiæ are not uncommon. External hæmorrhages, especially epistaxis, bleeding from the gums, and metrorrhagia are common, and other hæmorrhages not rare. After death hæmorrhages into the brain and its membranes have been found in several cases, and minute extravasations beneath the serous membranes are not uncommon. In one case I found small hæmorrhages in the liver. The troubles in the circulatory system, characteristic of anæmia, are pronounced, but do not call for special remark. Pyrexia is present in the majority of cases. It is irregular in its course and duration. The temperature often runs up to 101° or 102°, and may be even as high as 104°. It does not remain high long. Exacerbations of most of the symptoms have been noticed to accompany a rise of temperature in some cases, but this is not invariably the case, and some cases of pernicious anæmia are non-febrile throughout their course. I have already alluded to the disturbances in the alimentary system. The skin acquires a peculiar tint—a “faded leaf,” or discoloured wax, or a lemon tint, which is very characteristic. The interpalpebral conjunctiva is often yellow, but in some cases is pearly-white. The “lemon tint” has been found to vary from time to time, and an increase to occur at periods when the urine becomes darker and more bile is passed by the fæces; in one case the pyrexia being at the same time increased. In some cases the yellow colour is more marked, and Bartels has collected eleven cases, and added a twelfth of his own,³⁰ in which it amounted to a true icterus. In these cases no disease accounting for it was found in the liver; and Bartels attributes the jaundice in such cases of pernicious anæmia to a more acute course than usual; in other words, to an unusual activity of destruction of red corpuscles. Dropsy, to a slight degree, about the feet and ankles, is common towards the close of the disease, but never anything amounting to anasarca.

The urine presents important changes in many cases which, according to some observers, have great diagnostic and pathological significance. Several observers (Fagge and Pye-Smith, Bristowe, Eichhorst) have remarked that in some cases the urine has a dark colour. This has been shown by Dr. Hunter³¹ to vary from time to time, with aggravations in the other symptoms. He states that the colouring matter is “pathological urobilin,” whilst in one case Mott found it was caused by normal urobilin. MacMunn’s observations go to

show that normal urobilin is, in all probability, derived from the hæmatin of the tissues, and perhaps from the hæmatin of the food, whilst pathological urobilin is derived, in all probability, from the bile pigments, and to a less extent from hæmatin. Connected as its appearance in the urine seems to be with increased secretion of dark bile, Dr. Hunter considers that the excretion of large quantities of pathological urobilin is valuable evidence of excessive destruction of red blood corpuscles. He has also found in the urine pigment granules in renal cells and casts in one case, whilst corresponding granules, which gave a blue reaction when treated with a solution of ferrocyanide of potassium, and afterwards dilute hydrochloric acid, in the epithelium of the convoluted tubes of the kidney in all the cases, twelve in number, of pernicious anæmia he had examined. Dr. Hunter has further shown that in pernicious anæmia there is a remarkable increase in the excretion of iron in the urine, a fact which has also been previously pointed out by Dr. Magee Finny, from analyses made by Professor Reynolds.³²

So much in the way of inference hangs on the condition of the urine, that I must raise the question whether dark urine, or urine containing an excess of normal urobilin or pathological urobilin, is invariably present in pernicious anæmia. In several cases of my own, with *post-mortem* examinations confirming the diagnosis, the urine was never noticed to be dark, being “amber” or “straw-coloured” throughout. I find also among recorded cases the urine is stated to have been “pale” in a fatal case by Byrom Bramwell, and by Mott (the latter only one examination); “very pale” in two cases (one fatal) by Bramwell; “natural” in colour in four cases (one fatal) by Bramwell and one by Musser.³³ My own cases, it is true, were not examined especially with reference to this point of colour, though the many observations made are against it being overlooked. The same remark possibly applies to the other published cases, with the exception of that by Mott, who was one of the first to call attention to the fact that the urine is often of dark colour in pernicious anæmia. Eichhorst, whilst recording a case in which the urine was of dark colour, states it is usually of bright-yellow colour, and that dark (*dunkel*) urine is exceptional—possibly by “*dunkel*” turbid is meant. In some of Laache’s carefully recorded cases the urine was pale in colour. It is possible that the cases in which the urine is dark may form a separate category from others in which this peculiarity is wanting, but I especially direct attention to the point that it may be cleared up by future observers.

Dr. Hunter, struck with the similarity of the hæmolytic process in pernicious anæmia with that induced in animals by the action of toluylene-diamine, more especially as regards the limitation of its action to the portal blood, was led to the conclusion that the blood destruction in the former is due to the action of a poison of a cadaveric nature, and that this is probably produced within the gastro-intestinal tract and absorbed from thence. Accordingly he instituted some investigations on this point, and these had as their result a demonstration that there is in pernicious anæmia a marked excess of aromatic sulphates in the urine, derived from the sulphur of the proteids of the food, and that this is indicative of increased but perverted gastro-intestinal activity and absorption. He has been able to obtain from the urine two ptomaines, identical with putrescine and cadaverine obtained from putrefying meat, and a third ptomaine which appears to be a special diamine body, distinct from putrescine and cadaverine. Dr. Hunter points out that ptomaines belong to the group of nitrogenous bases formed from proteids by the action of bacteria. Ordinary putrefactive organisms do not give rise to ptomaines in the urine, but they have been found in the urine and feces in cystinuria by Udransky and Baumann and by Brieger. Neither putrescine nor cadaverine possess any markedly poisonous properties, but they derive their importance from the fact that they are the common products of bacteria, differing widely in their pathological qualities. But the presence of even non-poisonous ptomaines, pointing to the existence of special micro-organisms in the alimentary tract, has a special significance, in the opinion of Dr. Hunter, as indicating the existence of one condition more than any other favourable to the production of other and more

²⁸ Byrom Bramwell, *Edin. Med. Journ.*, 1887; Mackern and Davy, *Lancet*, 1877, vol. i, p. 642.

²⁹ *Ophthalm. Soc. Trans.*, vol. i, p. 50.

³⁰ *Berlin. klin. Wochenschr.*, 1889, No. 43.

³¹ Observations on the Urine in Pernicious Anæmia, *Practitioner*, 1889 and 1890.

³² *BRITISH MEDICAL JOURNAL*, 1880, vol. i, p. 44.

³³ *Proc. Phil. Co. Med. Soc.*, 1885.

poisonous ptomaines. The symptoms in one case of pernicious anæmia of Dr. Hunter's appear to support such a conclusion. Exacerbations occurred from time to time presenting the nervous phenomena of toxic poisoning. Dr. Hunter, therefore, feels justified in drawing the conclusion that the special factor required to initiate the symptoms peculiar to the form of anæmia is the presence, under certain favourable conditions, of micro-organisms of specific nature within the gastro-intestinal tract; and these favourable conditions he conceives to be such as have been met with—malignant disease and such other organic changes as have been found in association with this disease, or functional disturbances of the mucous membrane of the stomach and intestine induced by the presence of intestinal parasites, or by prolonged bad nourishment. Dr. Mott, in a valuable communication to which I have already several times alluded, does not believe that there is always a relation between the pyrexia, the diminution of corpuscles, and the colour of the urine. He points out, as Dr. Hunter has done, that ulceration in the intestines may exist in which the whole contents of the bowel must swarm with micro-organisms of many kinds, with everything to favour absorption of their contents without pernicious anæmia occurring. Further, that though constipation and anæmia may concur, and the latter may be benefited by curing the former, in such cases of fecal poisoning, the corpuscles are not broken down, but insufficient colouring matter is found.

The morbid changes found after death in pernicious anæmia indicate three processes: 1. The effects of the anæmia, in the bloodless condition of all the organs, with the exception in some cases of the spleen; and in the fatty and degenerative changes, especially marked in the heart and blood vessels. 2. The activity of the cytogenic organs, especially the bone marrow, which is usually red and vascular (and containing enormous numbers of developing red blood corpuscles) where it is normally yellow and fatty. 3. The signs of excessive hæmolysis and of the process of removal of the broken down corpuscles; the former, as demonstrated in the liver and spleen, by the evidences of active destruction of the red corpuscles; the latter, in the presence of blood pigment containing iron in the kidneys. Thus the evidence goes to show there is excessive blood destruction and its consequences, which the blood regeneration, however active, is unequal to compensate for. Dr. Hunter's pathology is so coherent, and supported by so much direct evidence, that I am convinced of its adequacy and correctness in some at least of the cases regarded as pernicious anæmia. For cases in which the urine is pale throughout, containing no pathological urobilin and no excess of normal urobilin, and no increase of iron—if such should be proved to occur—another explanation must be found; some different evidence of blood dissolution must be found, or unequivocal evidence afforded of defective hæmogenesis. Ehrlich remarks: "Degeneration and regeneration course side by side in uncomplicated anæmia; it depends upon the preponderance of one or other process whether this simple anæmia ends in a cure or in the progressive pernicious form."³⁴

THE HISTOLOGY AND PATHOLOGY OF THE FALLOPIAN TUBES.

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PATHOLOGY.

When it is stated that a comparatively small number of the tubes examined showed absolutely normal appearances, it will readily be understood that a brief notice of some of the most interesting pathological specimens is all that is possible in the limited space and time at disposal. The pathological

conditions selected for special consideration in this paper are:—First, tubal hypertrophy; secondly, the cystic conditions known as hydro-, hæmato-, and pyosalpinx; thirdly, certain malformations and displacements of the tubes; fourthly, tubercular disease; and fifthly, cancerous affection of the Fallopian tubes.

Fig. 4.—Hypertrophy of the Fallopian tube $\times 40$ diameters; A, areolar and peritoneal layers; B, circular and longitudinal fibres greatly hypertrophied and mingled; C, tubular and elongated structures lined by non-ciliated columnar epithelium and closely resembling gland acini; D, submucosa greatly thickened.

Hypertrophy of the Fallopian Tubes.—Whilst a few of the specimens showed the physiological tubal hypertrophy of pregnancy, one specimen exhibited a condition resembling great hypertrophy, which calls for a detailed notice. The uterine appendages were removed by Professor Simpson from a girl in whose history there was a strong suspicion of gonorrhœal infection. The tube was in all its extent manifestly enlarged, being about the size of the thumb, and was covered by old inflammatory adhesions which brought it into close relation to the ovary. The ovary, which was but slightly enlarged, showed on section one or two pea-sized cystic cavities. The peritoneal coat, as defined in the first part of this paper, was not at all enlarged. The loose areolar tissue connecting this coat with the middle muscular coat contained a number of isolated hypertrophied longitudinal and circular muscular fibres, and was very vascular. The muscular layer of the tube wall was greatly hypertrophied, and the longitudinal and circular fibres were so blended together that two separate layers could not be recognised, although the longitudinal fibres were somewhat more marked on the outer side and the circular on the inner. A few longitudinal fibres were seen entirely to the inner side of the circular lying in the submucous tissue. The inner coat of the tube was enormously thickened, and consisted of round and spindle-shaped cells, some of which had one, others two or more nuclei, and others, again, were simple granular cells, and between them ramified a few delicate fibrils of connective tissue. These cells at parts invaded the muscular layer separating the fibres from each other. The tubal plicæ, at some points nine, at others twelve in number, were simple and compound, and consisted of the same structural elements covered by a single layer of non-ciliated columnar epithelial cells. Tubular-looking structures lined by a similar layer of cells were everywhere visible in the mucous and submucous tissue and in the substance of the plicæ, and these structures were round, oval, or irregular in shape. We hesitate to regard this case as one of simple hypertrophy of the tube, for the appearances seen are