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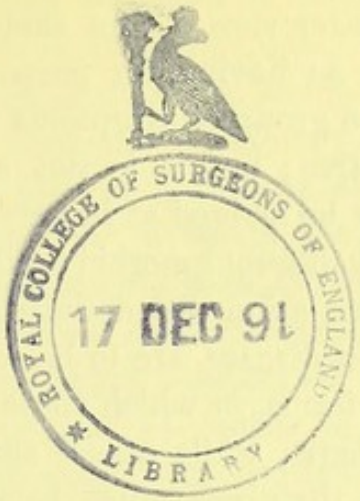
WILLIAM HUNTER, M.D., F.R.S. EDIN.



IS PERNICIOUS ANÆMIA A SPECIAL DISEASE?

BY WILLIAM HUNTER, M.D., F.R.S.EDIN.

John Lucas Walker Student of the University of Cambridge.

THE author has for some time been engaged on a series of investigations, pathological and experimental, on the nature of the disease commonly described as *pernicious* or *progressive pernicious anæmia*. The detailed results of these investigations will be published elsewhere: in the present paper it is proposed to discuss the preliminary question—Is pernicious anæmia a special disease? Are its features, clinical and pathological, sufficiently marked off from those of other apparently similar conditions to justify us in classing it apart from them?

According to Quincke,[1] and others who have followed him, pernicious anæmia is merely an extreme condition, differing from other forms of anæmia only in its intensity: it may arise in many different ways, it may be the result of various morbid conditions: loss of blood, long-continued discharges, defective nutrition, provided they are of sufficient intensity or duration, may all be factors in its production. Any anæmia may according to this view become progressive and pernicious provided on the one

[1] *Med. Times*, ii. 1876, 374, 428: *D. Archiv f. klin. Med.* xx. (1877).

hand it grows steadily worse, and on the other proves not to be amenable to treatment and terminates fatally.

According to a later view of the same observer,[1] pernicious anæmia is regarded as having, for purposes of classification, a *clinical* existence, the group of symptoms it presents being fairly uniform and distinctive; but it is not a separate *pathological* entity, seeing it may be arrived at in very various ways and may be dependent on very different morbid conditions. Some forms of it being found in association with definite structural lesions, such as those of malignant disease, are to be regarded as *secondary* to these lesions; other forms, in which these lesions are absent, are *primary* in their nature; while others again, and these perhaps the more frequent in their occurrence, belong to neither category, and can only be described as *intermediate*.[2]

To decide on the proper answer to the questions thus raised is not an easy task; its difficulty may be gauged by the fact that within the last few weeks so high an authority as Dr. Bristowe [3] has affirmed that "it is impossible at the present time to lay down any trustworthy distinction between the chlorosis of young girls and pernicious anæmia, except such as depend on the age and sex of the patient, and on the effects of treatment;" at the same time he expresses his belief that some fundamental difference between the two conditions must exist. That fundamental difference it has been the object of these researches to discover.

From the clinical standpoint Biermer's name for the disease—progressive pernicious anæmia—is, it must be confessed, a somewhat unfortunate one, and is probably accountable for much of the confusion which exists on the subject. The terms *progressive* and *pernicious* are apparently used in different senses by different observers. Any anæmia, whatever be its true nature, is by some described as *pernicious*, if only it is sufficiently profound; and it is described as *progressive* merely on the ground that the

[1] *D. Archiv f. klin. Med.* xxv. 579.

[2] See with reference to these and collateral points the able and interesting papers—among others—of Byrom Bramwell, *Med. Times*, ii. 1877, 323 and 429; Andrew, *Med. Times*, i. 1877, 471; Stephen Mackenzie, *Lancet*, ii. 1878, 797, 834; Coupland, *Lancet*, i. 1881, 531, *et seq.*; Pye-Smith, *Guy's Hospital Reports*, xxvi. 1883, 219.

[3] *British Med. Journal*, i. 1888, 1149.

patient does not recover. Whatever view, however, we hold as to the essence of the disease, there can be little doubt that though in the majority of cases it tends ultimately towards death, it is by no means uniformly fatal.[1] A sufficient number of instances have been recorded in which not only marked improvement, but even recovery has taken place.

From the point of view of pathology confusion has moreover arisen from the vague way in which the term *anæmia* is employed. Anæmia is constantly used as almost synonymous with *pallor*, and is hence applied indiscriminately to the most diverse conditions affecting the blood, whether the disorder be slight and involving little disturbance of health, or that associated with the severest forms of wasting or malignant diseases, or, lastly, that characteristic of the most pernicious form of "pernicious anæmia."

The underlying assumption in all these instances appears to be that the changes in the blood on which the *pallor* depends are always the same in kind, varying only in degree in different cases. This assumption is, I believe, groundless, and if it be cleared away, much of the prevailing confusion as to the pathology of "anæmia" in general, and of "pernicious anæmia" in particular, will disappear with it.

Literally speaking, the word *anæmia* may designate any condition in which some degree of pallor or "bloodlessness" exists. But we must distinguish between (1) anæmia that is only symptomatic of disease elsewhere than in the blood, and (2) anæmia in which the changes in the blood are the chief or characteristic feature. In the former the changes in the blood are not more marked than corresponding changes in other tissues not the seat of the primary disease. In the latter the blood-changes are the most marked changes found in the disease, if they are not actually the disease itself. In all wasting diseases such as malignant disease, phthisis, chronic suppuration, &c., there is undoubtedly a degree of bloodlessness, of anæmia in the broad sense; for there is less blood in the body, and that of poorer quality than in health. But other tissues of the body are likewise wasted, the muscles, the adipose tissue, and so on, and the wasting of the blood simply corresponds to this general loss

[1] Pye-Smith, *Guy's Hospital Reports*, xxvi. 1883, 219; Padley, *Lancet*, ii. 1883, 811.

of substance in the parts not specially affected by the primary disease. The general disturbance of nutrition affects the blood and the other tissues simultaneously, and in the majority of cases proportionately. As regards the muscles indeed, on whose condition the appearance of the patient so much depends, we may find that the changes in them are qualitatively and quantitatively more marked than the changes in the blood; and this occurs even in patients whose anæmia, as judged by the pallor only, is apparently profound enough to be called *pernicious*, or if the case ends fatally, *progressive* and *pernicious*. But if the marked pallor is alone sufficient to identify such a case as one of pernicious anæmia, to be consistent we should also class it as one of "progressive muscular atrophy," the changes in the muscles being even more marked than those in the blood. We are prevented from so describing it simply by the knowledge that "progressive muscular atrophy" is not the result of general malnutrition, however profound, but is due to changes in the nutritional centres of the muscles which lie in the anterior horns of grey matter in the cord. We have hitherto had no such definite knowledge of the pathological changes in the blood which underlie pernicious anæmia, and hence the term has come to be applied to forms of bloodlessness having, as I hope to show, as little in common with each other as the muscular wasting of phthisis or œsophageal cancer with true progressive muscular atrophy.

Classification.

That some essential difference exists between certain forms of anæmia has of course long been known, and various provisional classifications have accordingly been proposed from time to time. Thus, as has been hinted above, anæmias have been spoken of as *primary* or *secondary*, according as the blood-changes constitute the chief or the sole character of the disease, or are consequent on the existence of demonstrable disease elsewhere. Chlorosis is an example of the former, the anæmia of Bright's disease or of cancer of the latter. For ordinary purposes of clinical description such a division may be useful: and it serves to distinguish broadly two apparently distinct types of anæmia. But such terms as "primary," and "secondary," are

at best vague and inapt, and they have no pathological significance. In no case can a condition of anæmia be really primary; in every case it must be secondary to changes in some organ or organs, whether these changes are manifest as in wasting diseases, or obscure and difficult of recognition as in chlorosis. And even from the clinical point of view the distinction is useless, when the question is to determine the separate existence of such a form as pernicious anæmia, or to give grounds for referring a given case to its true position. To one observer the anæmia in a given case will appear primary, since he finds no morbid condition sufficient to account for it; to another it will appear secondary, if malignant disease is suspected during life or discovered after death.

The classification proposed by Dr. Sidney Coupland in the Gulstonian Lectures[1] of 1881, is deserving of more attention. He distinguishes two great classes of anæmia, the *symptomatic* and the *idiopathic*. Broadly speaking the former would correspond to the secondary, the latter to the primary forms just mentioned. Of symptomatic anæmia he distinguishes two varieties—the *simple*, in which the anæmia is slight; and the *pernicious* in which it is profound, as in wasting diseases generally. Of idiopathic anæmias he also distinguishes two varieties —the *simple*, including such conditions as chlorosis, in which the anæmia though distinct, and constituting in itself almost the whole of the disorder, is by no means dangerous to life; and the *pernicious*, including those forms of disease considered in this paper, which from their clinical characters and their tendencies deserve the titles of "pernicious" and "progressive." This classification has, according to Dr. Coupland, the merit of distinguishing between the two great varieties of pernicious anæmia which he believes to exist—varieties "destined like the simpler forms to be merged again into one when etiology shall be perfected." This forecast is based on the assumption that the anæmic process is identical in the two varieties, the forms it takes differing one from another only in their intensity—"the symptoms of pernicious anæmia proper being those of simple anæmia aggravated and intensified, its effects those of simple anæmia carried to an extreme degree."

[1] *Lancet*, i. 1881, 571.

This classification I regard as faulty in that it recognises two varieties of anæmia each entitled to be called "pernicious." These varieties, as I hope to prove, have really little in common as regards their pathology, and are capable of being distinguished clinically. The classification in fact tends only to perpetuate the prevailing confusion as to the clinical and pathological existence of the disease as a distinct form of anæmia.

I would venture in some measure to clear up this confusion by defining as clearly as our knowledge permits the meaning of the terms *idiopathic* and *symptomatic* as applied to anæmia. The term *symptomatic* is doubtless open to the objections urged against the terms *primary* and *secondary*,—anæmia, whatever its nature or its intensity, must always indicate the existence of pathological changes somewhere, and is so far always "symptomatic," whether for example it be the anæmia of chlorosis or that attending malignant disease. But nevertheless the division into symptomatic and idiopathic varieties, broadly speaking, is not without advantage from a clinical standpoint, and I propose for the present to retain it.

I begin for clearness' sake with the definition of the term *idiopathic*; for any form of anæmia not coming under this head may then be regarded as *symptomatic*. The term *anæmia* I use in the widest sense to include every condition, whether local or general, in which the blood is either qualitatively or quantitatively impaired. *Idiopathic anæmia* is therefore a condition resulting either from loss of blood, or from diminished production or increased destruction of it, the latter disorders of hæmogenesis or hæmolysis being unaccompanied by any corresponding changes in other tissues of the body.

Before we can describe a given case of anæmia as truly idiopathic it must comply with the following conditions:—

(1) That the changes in the blood (as determined by actual examination) must not only apparently but actually constitute the most marked feature of the disease.

(2) That the other chief symptoms of the disease must in great part at least be referable to the altered condition of the blood.

(3) With regard to *post-mortem* appearances, that the changes

in the blood, whether alone or in association with changes in the blood-forming (hæmogenic) or blood-destroying (hæmolytic) organs, constitute the characteristic morbid feature of the disease.

The diagnosis of idiopathic anæmia *during life* will therefore rest upon (1) the detection of certain definite changes in the blood, the changes being more marked than the concomitant change in any other tissue; and (2) the demonstration of a definite relation between these changes in the blood on the one hand and the remaining clinical features on the other: and *post-mortem* upon (3) the demonstration that the special morbid phenomena present can be referred only to disorder of the great processes, hæmogenic and hæmolytic, on which the condition of the blood depends.

Let me illustrate these propositions by reference to the anæmia of phthisis as compared with that of chlorosis or leucocythæmia. In phthisis, the blood-changes, however profound the pallor, do not by any means constitute the most marked clinical feature of the disease; while the other symptoms, the night-sweats, the fever, the cough, the expectoration, cannot be explained by reference to those blood-changes, nor are these dependent on hæmogenic or hæmolytic disorder. The condition of the blood, in fact, throws no light either on the nature of the disease or its seat. The anæmia of phthisis is therefore rightly classed as symptomatic.

In chlorosis however the blood-changes, especially the great diminution in hæmoglobin in comparison with the slight diminution in the number of red corpuscles, constitute the chief clinical feature (as in this case also the chief pathological feature) of the disease; they suffice in themselves to account for the remaining clinical characteristics—pallor, debility, giddiness, breathlessness, palpitation, &c., and, lastly, the blood-changes themselves can be shown to depend on disordered blood-formation or hæmogenesis. It is unnecessary here to stop to discuss at length the nature of the dependence of the blood-change on the constipation and gastro-intestinal disturbance generally associated with chlorosis. A single reference may suffice. Bunge[1] has satisfactorily shown how the excess of decomposition-products in

[1] "*Ueber die Assimilation des Eisens*," *Zeitschr. f. Physiol. Chemie*, 1885, 49.

the intestine, naturally accompanying the characteristic constipation, will by breaking up the organic iron compounds of the food, tend to prevent the due absorption of iron in the only assimilable form, and so lead to impaired blood-production. Chlorosis in girls is, in fact, an idiopathic anæmia, hæmogenic in its origin, and is due to a deficient supply of assimilable iron at a time when the recent onset of menstruation has removed a certain proportion of the already small supply of that element present in the body.

So too in leucocythæmia the blood-changes—the abnormal increase in the white corpuscles, and the more or less marked diminution in the red—constitute the chief clinical feature of the disease; they serve to account for the other symptoms, the debility and so on; and they, in conjunction with the alterations in the blood-forming organs, the spleen, lymphatic glands, or bone-marrow, constitute the chief morbid changes discoverable after death. What the exact relationship between the blood-changes and the changes in these organs may be is another question, and one which need not here be discussed; but that it exists is an undoubted fact. Leucocythæmia therefore I must regard as a special form of idiopathic anæmia.

Let us now apply these considerations to the case of pernicious anæmia. Here the blood-changes certainly constitute the most marked clinical feature of the disease. They suffice in themselves to account for, at any rate, most of its other features—the extraordinary pallor, the debility, breathlessness, and palpitation, the fatty degeneration of the vessels with the attendant hæmorrhages, and all this without any characteristic emaciation. At this point however a distinction appears to arise between pernicious anæmia and *e.g.* chlorosis, considered as alike forms of idiopathic anæmia. What relationship exists between the blood-changes and the remaining characteristic features of the former disease—viz. the peculiar lemon-coloured, sometimes icteric, tint frequently observed, the occasional attacks of jaundice, the gastro-intestinal troubles, such as dyspepsia, occasional vomiting, marked constipation, or (what a careful review of the literature proves to be nearly as common) diarrhœa, the recurrent pyrexia usually followed by aggravation of all the previous symptoms, and, lastly, the persistent tendency of the disease to a fatal issue, in

other words its *perniciousness?* In chlorosis or leucocythæmia we have succeeded in referring the various symptoms to the blood-changes; in pernicious anæmia we have hitherto been only partially successful in proving the relationship of the blood-changes to the clinical features just recited. Up to the present we have not been able to explain why most if not all of the features regarded as characteristic of pernicious anæmia should sometimes be found associated with malignant disease, such as cancer of the stomach, or with other equally distinct organic morbid changes—while in other instances the same features, with a degree of anæmia far in excess of that ever observed in malignant disease, should occur in the absence of any recognisable organic lesion or disease. This gap in our knowledge I have endeavoured by clinical and pathological observations, to fill up; I have sought to prove that, like chlorosis and leucocythæmia, true pernicious anæmia is a form of idiopathic anæmia, and that it is to be regarded as having a definite existence, pathological as well as clinical. I have satisfied myself that not only some, but all of its features, including the fever, the jaundice, and the perniciousness, are referable to changes in the organs and tissues concerned in blood-formation or blood-destruction, and to no others.

Various Anatomical Changes found associated with the Features of Pernicious Anæmia.

Before proceeding to the consideration of the changes in the blood, I must briefly refer to the relation, above alluded to, between certain definite organic diseases, such as cancer, and the symptoms of pernicious anæmia occasionally associated with them. The digression is the more necessary as it is largely from this association that the existence of pernicious anæmia as a symptomatic condition has been inferred.

That an association of this kind does (in certain cases, for example, of gastric cancer) exist there can be no doubt.[1] The frequency of the association has been probably over-estimated, partly owing to the loose employment of the term "pernicious,"

[1] Quincke, *D. Arch. f. klin. Med.* xxv. 579; Eisenlohr, *ibid.* xx. 499; Weigert, *Virch. Arch.* lxxix. 1880, 387; Grawitz, *ibid.* lxxvi. 1880, 353; Ehrlich, *Centralbl. f. d. med. Wiss.* 1880, 484.

which, as I have already said, is applied by some to any profound anæmia accompanied by cachexia and tending to death.

(1) When doubtful cases are excluded there remain a sufficient number of authentically recorded cases to prove that in the same patient *cancer* and the characteristic features of pernicious anæmia may coexist. The question arises—What is the nature of the connexion between them? Is it accidental or essential? Have the clinical features of pernicious anæmia been stamped on those of malignant disease without any further pathological changes than those implied in the latter? Or have pathological changes special to and characteristic of pernicious anæmia been added to those already and independently existing? In a case[1] of Eisenlohr's the latter supposition would seem to be the most appropriate; here the symptoms of malignant disease existed for two years, and then suddenly took on the features of pernicious anæmia. Most, if not all, of the instances of apparent association have as in this instance been cases of cancer of the stomach; yet there is no doubt that cancer of the stomach may run its course to the fatal termination without giving rise to more than symptomatic anæmia; and again, there is no doubt that the features of pernicious anæmia in its intensest form may be presented apart from malignant disease of the stomach or of any other organ. Such considerations induce the belief that even if malignant disease *in certain situations* may occasionally predispose to pernicious anæmia, the association of the two diseases in particular cases is rather due to an accidental coincidence than to any essential pathological relation.

(2) There is another group of morbid conditions, one or more of which have from time to time been found *post mortem* in association with the symptoms of pernicious anæmia: I mean certain *changes in the gastro-intestinal tract.* The frequency of gastro-intestinal symptoms in this disease has lent colour to the view, held by some, that it has no special pathology of its own, but is merely the outcome of a sufficiently profound disturbance of nutrition. And the view is apparently borne out by the fact that not uncommonly no other marked lesions but those of the gastro-intestinal tract have been detected at the autopsy. The lesions and changes so recorded are as various as they are

[1] *D. Arch. f. klin. Med.* 1877, xx. 499.

numerous, being rarely alike in any two cases. They include atrophy of the gastric mucosa and especially of the gastric glands;[1] cirrhotic contraction of the stomach with disappearance of the gastric glands;[2] interstitial inflammation of the gastric mucosa with partial or total atrophy of the glands;[3] ulcers of stomach and duodenum;[4] duodenitis;[5] degenerative changes in the abdominal sympathetic ganglia;[6] degenerative changes in the nerves and ganglia of the intestinal walls;[7] and lastly, the presence of intestinal worms.[8]

In no other system of the body have the morbid changes discovered in association with pernicious anæmia been so various or so frequent. But the very number and variety of these lesions make it difficult to assign essential importance to any one of them, as the pathological factor in pernicious anæmia. Some of them, on the one hand, such as atrophy or degeneration of various parts of the intestinal wall, may possibly be as much the result as the cause of the anæmia; while on the other hand similar or even more marked anatomical changes in the gastro-intestinal tract are frequently found unassociated with the features of pernicious anæmia. I am therefore unable to attribute great or essential pathological importance to these gastro-intestinal lesions, whatever may be their importance as predisposing or etiological factors. I shall elsewhere consider to what extent they may possibly determine the *form* and the *intensity* of the anæmia.

(3) One of the conditions above referred to—*the presence of worms in the intestine*—deserves a somewhat fuller consideration. Much attention has recently been directed to it by Continental observers. The anæmia of the workers in the St. Gothard Tunnel apparently presented all the features of pernicious anæmia,[9] and was associated with the presence in the intestine

[1] Fenwick, *Lancet*, ii. 1877, 1, 39, 77.

[2] Nothnagel, *Deutsches Arch. f. klin. Med.* xxiv. 353.

[3] W. Nolen, *Centralb. f. d. med. Wiss.* 1882, 767.

[4] Zahn, *Jahresb. üb. d. gesammte Med.* 1882, ii. 218; Litten, *Berl. klin. Woch.* 1880, 693.

[5] Homolle, *Centralb. f. d. med. Wiss.* 1879, 815.

[6] Banti, *Jahresb. üb. d. gesammte Med.* 1881, ii. 239.

[7] Sasaki, *Virch. Arch.* xcvi. 287.

[8] Bäumler, *Centralb. f. d. med. Wiss.* 1881, 560; Sahli, *Deutsches Arch. f. klin. Med.* 1883, xxxii. 421.

[9] Bäumler, *loc. cit.*; Sahli, *loc. cit.*

of *Anchylostoma duodenale*, often in large numbers; the anæmia moreover in general disappeared rapidly on their removal. More recently Reyher [1] and Runeberg [2] have traced a similar relation between the anæmia in some cases and the presence in the intestine of *Bothriocephalus latus*. The nature of the relation has not, however, in either case been satisfactorily explained. In the St. Gothard cases the anæmia was ascribed to the constant loss of blood from the intestinal walls; but this does not meet the fact that the anæmia is not always proportionate to the number of worms present, and that it is sometimes absent altogether even when they are very numerous.[3] Similarly with regard to *Bothriocephalus*, Runeberg's observations show not only that worms may be present without any pernicious anæmia, but that in Finland, where the parasite abounds, true pernicious anæmia occurs in patients not infested by it, and that these cases prove especially intractable. For these and like reasons I am obliged to conclude that, as with malignant disease so with intestinal worms, their presence alone cannot be held as accounting for the pernicious anæmia associated with them.

The result of our enquiry so far is, therefore, that even if pernicious anæmia were not regarded as a special disease, but merely as an extreme manifestation of ordinary anæmic processes, we could not with our existing knowledge say definitely on what pathological condition or conditions it essentially depends; we could not explain why it is present under apparently unfavourable sets of conditions, and why it is absent under apparently favourable ones. None of the various lesions described, and it must be remembered that it is only in a minority of cases that even these have been found, would appear capable by themselves of explaining the true nature of the anæmia we are considering; none of them can be regarded as in any sense the essential or invariable pathological condition underlying it. In other words an examination of the evidence forces us to the conclusion that pernicious anæmia cannot be set down as a form of *symptomatic* anæmia in the above defined sense of the term.

[1] Reyher, *Deutsches Arch. f. klin. Med.* 1884.
[2] Runeberg, *ibid.* 1888.
[3] Sahli, *ibid.* 1883, p. 428.

Changes in the Blood.

Let us now enquire how far it conforms to the conditions laid down for an *idiopathic* anæmia; how far, in brief, its clinical and other features can be referred to the changes in the blood or to alterations in the hæmogenic or hæmolytic processes on which these changes are dependent. We shall first describe the principal changes met with in the blood, so far as they seem peculiar to pernicious anæmia; they are briefly the following:—

(1) The *marked oligocythæmia*, sometimes to a very high degree and far in excess of that ever found in symptomatic anæmia. This oligocythæmia is in certain cases at least entirely independent of the occurrence of hæmorrhage.

(2) The relative *richness in hæmoglobin*, in comparison with the high degree of oligocythæmia which is frequently met with.

(3) The presence in the blood of small yellowish globules or *microcytes*, distinguishable by their form and colour from the various other small coloured elements present in all forms of anæmia alike.

(1) First, as regards the oligocythæmia, the diminution in the number of corpuscles is sometimes extraordinary, and certainly constitutes one of the most marked of the changes in the blood. The degree of oligocythæmia varies much in different cases. In almost all, however, the number of corpuscles is reduced from the normal 5,000,000 per cubic millimetre (cmm.) to 2,500,000 or less; in not a few it falls to 1,000,000 or even to 500,000 per cmm. Sorensen[1] thought the latter number the lowest compatible with life, or at least with subsequent recovery. But Quincke records the case of a patient whose proportion fell to 143,000 per cmm., and who notwithstanding recovered, and therefore it is probable that Sorensen's minimum is too high. I can say from my own experience that it is not uncommon to find the proportion so low as 700,000 or 800,000 even when the patient first presents himself, and that without any urgent symptoms other than the extreme debility.

[1] *Virchow and Hirschwald's Jahresber.* 1878, i. 241.

The marked character of the oligocythæmia will best appear if we compare it with that found in other anæmic conditions, in which, if we were to judge by the *pallor* alone, the "anæmia" would be thought as intense as in pernicious anæmia.

In *chlorosis* the diminution in the number of corpuscles is by no means proportionate to the degree of pallor. In seven cases Sorensen found the average number so high as 3,790,000; Dr. Coupland found the average in seven cases to be 3,000,000; as the average of eighteen observations Hayem found the number to be 3,520,000. My own observations agree in the main with these results—the average obtained being about 3,750,000. Lower than this the number may fall, especially if the case be in any way complicated, as it not infrequently is, by the hæmorrhage, *e.g.*, from a gastric ulcer; but on the whole there is no feature of chlorosis more remarkable than the extraordinary disparity between the actual diminution in the number of corpuscles and the profound degree of pallor. The change in the blood in chlorosis is, as we all know, not so much an oligocythæmia as a poorness in hæmoglobin, the latter far in excess of what can be explained by the diminution in the number of corpuscles. In few cases of chlorosis is the diminution in this number so great as 30 or 40 per cent., while a diminution of 70, 80, or even 90 per cent., is not only possible, but not infrequently met with in pernicious anæmia.

In the anæmia of *malaria* Hayem[1] found the number of corpuscles so low as 1,182,700, and in a case of *purpura hæmorrhagica* even lower, namely 1,000,000.

In *leucocythæmia* Sorensen found the number of corpuscles in one case to be 1,150,000; in another, 2,160,000; and in one case, recorded both by this observer and by Quincke, the number was so low as 500,000.

It is in *wasting diseases* however that the most striking contrast with pernicious anæmia is presented; and this is all the more remarkable inasmuch as the anæmia in these cases, judged by the degree of pallor, is often so profound as to apparently entitle it to be termed pernicious; this variety of anæmia constitutes in fact that termed by Dr. Coupland the

[1] *Gaz. des Hôpitaux*, 1876, 892.

pernicious variety of symptomatic anæmia. Thus in *phthisis*, according to Malassez,[1] there is no regular or constant diminution, an observation which I can fully confirm, and it is also confirmed by Sorensen. The latter found as the average of eleven cases the number of corpuscles so high as 4,350,000, a diminution so slight as to be scarcely appreciable. Similarly in *malignant disease* the change is but little more marked. In six cases of carcinoma Sorensen found the average to be 3,660,000. In *lead-poisoning*, in which the pallor is generally marked, Malassez[2] found that the number did not fall below 3,200,000. Lastly, during *inanition*,[3] the result of starvation, the changes in the blood are relatively less marked than those in most other tissues of the body. So far from being diminished the number of corpuscles per cmm. of blood is often actually increased.[4]

The result of this comparison goes therefore to show that as regards oligocythæmia the changes in pernicious anæmia are far in excess of those found in the anæmia accompanying wasting and malignant disease. This difference is not merely one of degree, but seems to be radical and peculiar to pernicious anæmia; for the oligocythæmia which in all other forms of anæmia rarely reaches a diminution of 50 per cent., and is usually much less, in pernicious anæmia constantly reaches 80 per cent. or more.

There is one factor however often at work in pernicious anæmia, and not always present in wasting diseases, which may play an all-important part in determining the degree of oligocythæmia, namely the occurrence of hæmorrhages more or less frequent and copious. I have hitherto purposely avoided any reference to this as one of the possible factors in bringing about the marked changes in the blood. There can be no doubt that frequent and copious hæmorrhages, especially when occurring in a patient already debilitated by disease, will do more than any other adventitious condition to bring about profound anæmia, pallor, and debility, closely resembling that found in

[1] *Le Progrès Méd.* 1874, No. 28.

[2] *Gaz. Hebdom.* 1873, 805.

[3] Boekmann, *D. Archiv. f. klin. Med.* xxix. 490.

[4] With special reference to these changes in the blood, see also Stephen Mackenzie, *Lancet*, ii. 1878, 834.

pernicious anæmia. And the difficulty of determining what is the part played by loss of blood in the production of the anæmia we term pernicious is all the greater inasmuch as the two conditions are so frequently found associated, and each is so apt to aggravate the other—the loss of blood intensifying the oligocythæmia and hydræmia, and this condition of the blood in turn inducing those degenerative changes in the walls of the capillaries on which the hæmorrhage depends. Cases of this sort are by no means uncommon, the diagnosis remaining uncertain to the end ; and it remains a question whether the patient died simply from the effects of repeated hæmorrhage, or whether the condition was really one of pernicious anæmia from the beginning, the fatal issue being merely hastened by the hæmorrhages. Now if the existence of pernicious anæmia as a distinct clinical and pathological entity is to rest on any firm basis at all, it is of the first importance to determine how far the features of the disease *in their entirety*, not merely the blood-changes, can be produced by repeated and copious hæmorrhage.

Opportunities for observing the effects of bloss of lood in man are not infrequently met with in the hæmatemesis of gastric ulcer, the epistaxis of Bright's disease, the hæmorrhage of malignant disease, or the metrorrhagia of malignant or fibromatous disease. A condition of the profoundest anæmia may in this way result, closely resembling in many of its features, especially those presented by the blood, the condition we term pernicious anæmia. At least this is true in part of the oligocythæmia, and also as we shall presently see of the changes in the form and size of the red corpuscles. But it is not true of the *extreme* degree of oligocythæmia, and still less of the other features which we have come to regard as almost equally characteristic, namely, the gastro-intestinal disturbances, the more or less marked jaundice, and the fever. I have found it impossible to produce in rabbits, even by repeated and copious bleedings, a degree of oligocythæmia in any way approaching that so frequently found in true pernicious anæmia. And this experience agrees with that of Hayem, who found it impossible in dogs to reduce the number of corpuscles even below 1,000,000 per cmm. without at the same time causing the death of the animal.

If we remember that in man life is often found quite compatible, and that for long periods of time, with an oligocythæmia measured by 700,000 or 800,000 per cmm., the result of these experiments in animals would seem to point to the conclusion that mere loss of blood, unattended by any other morbid condition, is not capable of explaining this feature of pernicious anæmia—a feature characteristically present even when no hæmorrhage has occurred. Of the occurrence of such an extreme degree of oligocythæmia apart altogether from loss of blood there cannot, I think, be a doubt; two such cases at least I have seen. The rapidity of its progress, and its intensity, are moreover such as cannot be accounted for by any assumed failure of nutrition however profound, or any defect in the blood-forming functions however marked.

On the double ground, therefore, of the results of these experiments on animals, and of the genesis of intense oligocythæmia in man apart altogether from hæmorrhage, I am compelled to conclude that the diminution in the number of corpuscles in pernicious anæmia is not *ab initio* the result of hæmorrhage; though it may be, and undoubtedly is, aggravated by its subsequent occurrence. While this is so, however, I am ready to admit that if, in a given case, the distinction to be drawn *during life* between anæmia resulting from loss of blood and pernicious anæmia had to rest solely on the relative degree of oligocythæmia possible in the two conditions, a great if not an insuperable difficulty might attend the diagnosis. I refer particularly to cases where the oligocythæmia is by no means so marked as in itself to be distinctive, and in which previous loss of blood has occurred perhaps in itself sufficient to account for it. Such cases would afford fair ground for the view that pernicious anæmia is merely an extreme manifestation of the anæmic process specially aggravated by loss of blood. But while this is admitted, it must be borne in mind that an extraordinary degree of oligocythæmia is really one of those features which points most strongly to the hæmolytic origin of the disease, a subject with which I propose to deal at length elsewhere.

(2) Another feature occasionally presented by the blood in this disease seems of special interest. I refer to the comparative rich-

ness of the blood in hæmoglobin, having regard to the number of corpuscles present. The percentage diminution in the number of corpuscles is often considerably greater than that of the hæmoglobin. The very opposite of the condition in chlorosis here obtains. Instead of a hæmoglobin-richness of 21 per cent. associated with 70 or 80 per cent. of corpuscles, a relation not infrequent in chlorosis, it is not uncommon to find in pernicious anæmia a hæmoglobin-richness equal or even greater, say 20 per cent. or 30 per cent., associated with a reduction in the number of the corpuscles to 12 per cent. or 15 per cent. of their original number. Thus in one case Coupland (*Lancet*, i. 1881, p. 571), found the corpuscles diminished to 10·6 per cent. of the normal number, while the hæmoglobin was reduced to 30 per cent. Quincke[1] found that in general the corpuscles were reduced to 10 to 12 per cent. of the normal while the hæmoglobin was reduced to 20 or 40 per cent. One observer, Laache,[2] has attached so much importance to this relation as to regard it as almost pathognomonic of pernicious anæmia. In what proportion of cases it is to be found remains a subject for future determination, but its presence in a certain number of cases is one of those features peculiar to this disease which has always seemed to me urgently to call for explanation. Its presence in any case would at once serve to distinguish between anæmia resulting from loss of blood and pernicious anæmia. The results of all my observations on animals after bleeding go to show, and the same conclusion applies to man, that the percentage diminution in the hæmoglobin after hæmorrhage is greater than that in the number of corpuscles, and that the return to the normal is always more delayed as regards the hæmoglobin than in the case of the corpuscles.

(3) The remaining changes in the blood I must now briefly consider. To the various changes in the shape and size of the red corpuscles, aptly described by Quincke under the generic term *poikilocytosis*, to which so much importance has been attached by various observers, I attach but little value: and I find that they are not characteristic of any one

[1] Quincke, *D. Arch. f. klin. Med.* xxv. 577.

[2] Laache, *Cent. f. d. med. Wiss.* 1883, 697; *Trans. Internat. Med. Congress of* 1884, ii. 4.

form of anæmia, but depend solely on the degree of hydræmia present. In pernicious anæmia indeed these changes are far more marked than in most other forms, but that is dependent more upon the greater hydræmia present in such cases than upon any other factor. It was a matter of special interest to me to determine how far they were common to the anæmia resulting from loss of blood and that resulting from the action of destructive agents, such as pyrogallic acid, injected into the blood. I found that though they could not be so readily produced by loss of blood as by the action of destructive agents, that was due solely to the fact that it was very much easier to produce a profound hydræmia by the latter than by the former method. The changes in the corpuscles were however in each case the same in kind, however much they might differ in degree. The *poikilocytosis*, therefore—the variations in the size and shape of the red corpuscles—so commonly met with in pernicious anæmia, testifies more to the degree of anæmia present than to its character; except in so far that in the absence of hæmorrhage it indicates the existence of a degree of hydræmia and oligocythæmia, in itself suggestive of the haemolytic nature of the disease.

Much attention has also been directed to the presence of so-called *microcytes*, that is of small, spherical, deeply-coloured corpuscles resembling minute red blood corpuscles, as being more or less characteristic. First described by Quincke, they were afterwards more particularly described by Eichhorst,[1] who claimed that they were almost pathognomonic. Hence has arisen the title "Eichhorst's corpuscles," sometimes given to them. The term *microcyte* is applicable to so many bodies discoverable in the blood that the use of it in any restricted sense only tends to confusion. These elements are certainly present in the great majority of cases of pernicious anæmia at some time or other during the course of the disease, although they vary[2] remarkably in their number, not only in different cases, but in the same case at different times. They are remarkable for their smallness, their diameter in some cases

[1] *Centralbl. f. d. med, Wiss.* 1876, 466.

[2] Eisenlohr, *loc. cit.* 1877, 496 ; Grainger Stewart, *Brit. Med. Journ.*, ii. 1876, 40 ; Wagner, *Berlin. klin. Woch.* 1879 ; Lépine and Germont, *Gaz. Méd. de Paris*, 1877, No. 18.

scarcely exceeding the fourth part of that of a red corpuscle; for their perfectly spherical form, whatever the shapes of the other corpuscles in the blood may be; and lastly, for their deep yellow colour, in this respect sometimes resembling droplets of oil rather than corpuscles. It is unnecessary for me here to discuss in detail their true nature and their significance. As regards their nature, opinion has as usual been much divided, some regarding them as stages in the evolution of the red corpuscles, and therefore as an evidence that blood-formation is at fault, others again regarding them as products of blood-destruction resulting from the breaking down of the red corpuscles. In favour of the former view is the fact that they have been described by two observers (Litten [1] and Lépine [2]) as occurring in anæmia resulting from loss of blood; on the other hand they were found to be absent by another observer (Eisenlohr [3]) in precisely similar conditions. The question is only of importance in so far as it concerns the value to be attached to their presence in pernicious anæmia, in which disease they certainly are more commonly met with than in any other. Their absence in any case cannot in my opinion be regarded as excluding the diagnosis of pernicious anæmia, since even when present they vary much in their number and may disappear for a time altogether. And as it is apparently possible for them to be present in other diseases (Afanassiew [4] found them in a case of typhoid fever), I conclude that although "yellow spherical microcytes" are not pathognomonic of pernicious anæmia, their presence in any case of doubtful nature, associated with marked oligocythæmia, affords a valuable indication as to the origin of the anæmia we are dealing with. It is in fact my purpose to show that they mark the anæmia as due to excessive destruction of blood and not merely to deficient formation,—that they prove it to be *hæmolytic*, not *hæmogenic*, in its origin.

In addition to the characters of the blood just considered—the marked oligocythæmia, the comparative richness in

[1] *Berlin. klin. Wochen.* 1877, No. 1, No. 19.
[2] *Union Méd.* 1877.
[3] *Loc. cit.* 502.
[4] *D. Archiv. f. klin. Med.* xxxv. 1884, 233.

hæmoglobin, the poikilocytosis, the occasional presence of yellow spherical microcytes,—there are certain others which must be mentioned, though some of them are not peculiar to pernicious anæmia. These are the absence of the formation of *rouleaux* in the blood when drawn, and the occasional presence of nucleated red corpuscles.[1] In connexion with the peculiar richness of the blood in hæmoglobin, we find that many of the red corpuscles, especially the larger ones, are abnormally deep in colour, while hæmoglobin-crystals may often be very readily obtained from the blood on desiccation, as Copeman [2] has recently shown. As regards the colourless elements we have to note the absence of any increase of white corpuscles, or increase of the granular elements, and blood-plates,[3] such as is so common in phthisis and other wasting diseases; while as to the plasma the points of importance are—its extraordinary wateriness (hydræmia) in many cases, and its very low specific gravity in general (Quincke found it in one case to be 1028 compared with a normal sp. gr. of 1055). These changes in the blood, taken collectively, constitute the characters which I regard as peculiar to pernicious anæmia; and to complete its pathological differentiation it remains for me to establish their correlation with the other features of the disease.

From the above considerations it will, I think, be evident that on clinical grounds alone there is good reason for accepting the existence of a special form of anæmia, differing essentially in its nature from any that is usually regarded as symptomatic, and entitled to be described as *pernicious*, if not necessarily *progressive*. In another paper I shall show that this view is fully borne out when we take into consideration the pathological changes which characterise the disease. While in the symptomatic anæmias, namely those associated with ordinary organic disease, the blood-changes are but little, if at all, more marked than the changes found in other tissues, and are primarily referable to defective nutrition, to failure in *hæmogenesis*, in pernicious

[1] Bramwell, *loc. cit.*; Ehrlich, *Berl. klin. Woch.* 1880, 405.

[2] Copeman, *St. Thomas's Hospital Reports*, 1887.

[3] Eisenlohr, *loc. cit.*, 495; Osler and Gardner, *Cent. f. d. med. Wiss.* 1877, 258; Riess, *Berlin. klin. Woch.* 1879; Leube, *ibid.* 1879.

anæmia the changes in the blood are essentially *hæmolytic*. They are due to excessive destruction of the blood, while hæmogenesis is so little interfered with that it is generally in excess of the normal.

The practical question remains, How are we to determine whether a given doubtful case is one of pernicious anæmia or not? The difficulty of directly answering this question depends in some measure on the fact that, with perhaps the single exception of the disproportionate richness of the blood in hæmoglobin, there is scarcely one feature of the disease which is peculiar and characteristic, unless indeed in degree: each of its features may in some degree be singly presented in other conditions. But this is no longer true when we find these single features combined in a certain association. It is this combination or association which constitutes the clinical disease; and the diagnosis in a given case must have regard to all the features, and to their relation one to another.

From *chlorosis* pernicious anæmia may be readily distinguished. In the former the corpuscular richness of the blood is far in excess of the richness in hæmoglobin. In the latter this condition is in general reversed: the percentage of hæmoglobin is not only relatively high, but the degree of oligocythæmia is usually far more marked than in chlorosis.

From the anæmia symptomatic of *wasting diseases*, whether malignant or not, pernicious anæmia is distinguished by the greater degree of oligocythæmia it presents. In symptomatic anæmia, uncomplicated by hæmorrhage, the number of corpuscles is rarely reduced below 3,000,000 per cmm.; while in pernicious anæmia, even in the absence of hæmorrhage, it is often reduced to 1,000,000, 800,000, or even less. If, therefore, there be *no hæmorrhage* in question, a more or less rapid diminution to, say, 2,000,000 per cmm. points to an anæmia of *hæmolytic* origin, that is practically to pernicious anæmia, and that whether malignant disease already exists or not. The only other conditions in which, apart from hæmorrhage, an oligocythæmia of this intensity is possible, are perhaps *malaria* and *leucocythæmia;* and it is of interest to note that in both of these conditions increased hæmolysis probably plays an important part in determining certain at least of the characteristic changes in

the blood. These conditions are however easily differentiated from pernicious anæmia.

Where hæmorrhages have already occurred, the general question becomes more complicated, and the value to be assigned to the above figures may require modification. Each case must be discussed on its own merits, but we are not without general principles which aid us in arriving at a sound diagnosis. In the first place we must enquire whether the hæmorrhages have been sufficient to account for the degree of oligocythæmia present. It must here be kept in mind (1) that a diminution below 1,000,000 per cmm. is rare as a result of hæmorrhage alone, unless it is repeated and copious; (2) that oligocythæmia resulting from loss of blood is in most cases accompanied by a corresponding diminution in the percentage of hæmoglobin; (3) that in *hæmogenic* anæmias (and that resulting from hæmorrhage may be so described) we do not usually find in the blood the small yellow microcytes, perfectly spherical in form and deep in colour, which point to an anæmia of *hæmolytic* origin. Apart however from these changes in the blood, it is in such cases especially that we must in diagnosis have regard to the symptoms in their entirety and not to any one in particular. A profound anæmia due simply to hæmorrhage, such as results, for instance, from long-continued metrorrhagia, though associated with intense pallor and debility, is not necessarily accompanied by the peculiar lemon tint, by the gastro-intestinal disturbance, by the jaundice, by the pyrexia, &c., which are generally associated with hæmolytic or pernicious anæmia. Even in the presence of hæmorrhage, therefore, the presence or absence of the latter group of symptoms will in general suffice to determine the question whether the anæmia with which we have to do is referable to the hæmorrhage alone, or whether it must be classed as a manifestation of the special disease—pernicious anæmia.

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