REMARKS ON THE NATURE AND TREATMENT OF PERNICIOUS ANÆMIA.

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In this paper I shall endeavour to show that pernicious anæmia is not a disease in itself, but is a high degree of anæmia usually following on numerous remote or predisposing causes, all of them well recognised as tending to produce the anæmic state; that in certain individuals the anæmia induced by these causes tends to bring on degenerative changes in the blood vessels, which lead in turn to the occurrence of numerous capillary hæmorrhages all over the body; and that it is the persistent and long-continued duration of these small internal bleedings, assisted often by larger external ones, which confers on certain cases of anæmia the fatal, or "pernicious," or "progressive" character of the illness.

The most obvious symptoms which a typical case of pernicious anæmia presents result largely from long-continued deficient supply of oxygen to the tissues, due to an excessive diminution of red corpuscles and of hæmoglobin. It is hardly necessary to enumerate them at length, but stated broadly they are as follows: The patient, usually stoutish though sometimes emaciated, presents an extremely pallid appearance with a yellowish tinge of the skin; there is excessive languor, debility, and apathy, with dyspnoea and palpitation on the slightest exertion, and some degree of subcutaneous œdema, these last symptoms resulting from cardiac feebleness. Gastric dyspepsia, diarrhoea, and irregular febrile attacks are also prominent features. The urine is abundant, sometimes pale, at other times high-coloured, occasionally contains a little albumen, and usually a greatly reduced amount of urea, although sometimes this constituent is either normal or slightly in excess. The amount of urea is probably of comparatively little significance, as it depends on the amount of food which the patient is able to take and digest, hence the recorded variations. In the majority of cases, though by no means in all, retinal hæmorrhages are present. The red blood corpuscles are greatly diminished in number and altered in size and shape (poikilocytosis), the hæmoglobin being usually proportionately diminished in amount. As previously stated, it is to this blood condition that the clinical symptoms are for the most part immediately referable. The patient usually dies after a more or less prolonged illness, and on *post-mortem* examination nothing may be found beyond extreme general anæmia, marked fatty degeneration of the heart and other viscera, and numerous minute hæmorrhages or larger ecchymoses scattered all over the body. The red bone-marrow may or may not be hypertrophied, and deposits of iron-containing pigment are usually found in the liver, spleen, and kidneys. Other gross lesions have been described, to which I shall return later on.

Before developing my own views it is necessary to examine the current opinions regarding this condition, which may be most conveniently done under three headings, although it is rather difficult to separate sharply the second and third. These are:

1. Is pernicious anæmia a distinct disease?
2. What cases are to be regarded as pernicious anæmia?
3. The immediate cause of the condition.

I.—IS PERNICIOUS ANÆMIA A DISTINCT DISEASE?

There has been a large amount of discussion as to whether the clinical condition constitutes a disease in itself, "a morbid entity," or whether it is simply an extreme degree of bloodlessness secondary to numerous other conditions. Undoubtedly in reading over the published reports of cases, especially those of more recent date, one gets the impression that the condition is generally regarded as a distinct disease; but, on

consulting the papers and memoirs of those who have devoted most attention to the subject, it is at once apparent that there has existed, and still exists, very great divergence of opinion on this most important point. To go a long way back, the earliest and one of the fullest and most excellent accounts of pernicious anæmia which I have come across is by Dr. J. S. Combe,¹ of Edinburgh, whose introductory remarks are perhaps worth quoting at length. He says:

"It appears to me entitled to still further attention and to a more minute detail, as exhibiting a well-marked instance of a very peculiar disease, which has excited little attention among medical men, and which has been altogether overlooked by any English author with whose writings I am acquainted.....and while some may be disposed to regard the peculiar characteristics from which it derives its denomination of anæmia as constituting a morbid state *sui generis*, others may consider the defect of the red circulating mass as an accidental and occasional circumstance denoting some peculiar change in the assimilative powers, the primary stages of which we have been unable to detect. Doubtful myself which of these opinions may be the most correct, I shall do little more than state correctly the phenomena of the case and minutely describe the appearances presented on dissection. One remark only I may at present offer: that if any train of symptoms may be allowed to constitute anæmia a generic disease, the following may be considered an example of it in its most idiopathic form."

Up to the most recent times very little advance has ever been made on this. Combe quotes² a still earlier case, reported in 1684, entitled *Exanque fere Corpus*, to which the following commentary is made by the reporters: "*Quomodo sanguis, qui neque ante mortem neque post mortem effluit, perierit, difficile erit pronunciare*"—a commentary which has been repeated very frequently since.

Addison³ applied the term "idiopathic anæmia" to cases "occurring without any discoverable cause whatever: cases in which there had been no previous loss of blood, no exhausting diarrhoea, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease." Evidently he regarded it as a distinct disease, different from so-called secondary anæmias presenting similar clinical features. *Post mortem* he found only anæmia and fatty degeneration of the heart and other organs.

Biermer⁴ regards it as a condition of extreme anæmia secondary to many causes, such as diarrhoea, poor food, pregnancy, and hæmorrhage. Immermann⁵ considers it a disease *sui generis* owing to its rarity, the extreme anæmia, absence of emaciation, and the non-effect of treatment. Quincke⁶ says: "It is not a disease in itself, but pernicious anæmia, like anæmia generally, is the product of very different processes, and represents the highest possible degree of the anæmic condition." It is therefore, he thinks, difficult to distinguish from "simple anæmia," and many cases are on the border line, substantially the same opinions being held, so far as I can gather, by Dr. Bristowe⁷ and by Dr. Sidney Coupland.⁸

Dr. Andrew⁹ holds also that it is not a disease in itself, but is due to many causes which, however, we cannot always discover. Müller¹⁰ expresses practically the same views, while Eichhorst¹¹ thinks that some cases are "primary," "idiopathic" or "essential" (the disease beginning in the blood), and others secondary to pregnancy, loss of blood, and various exhausting conditions.

Lépine¹² regards the condition as following on causes generally recognised as predisposing to anæmia, but thinks there is superadded an individual debility in blood-forming power, and consequently that to a certain extent it is a specific disease.

Dr. William Hunter¹³ states definitely his opinion that "Pernicious anæmia is to be regarded as a special disease, both clinically and pathologically." His reasons for this opinion and various other points raised I shall discuss later.

II.—WHAT CASES ARE TO BE REGARDED AS "PERNICIOUS ANÆMIA?"

Here also great differences of opinion exist. Dr. Pye-Smith¹⁴ holds that cases of extreme anæmia after pregnancy, diarrhoea, hæmorrhages, etc., are not true cases of the "idiopathic anæmia of Addison," where no cause is discoverable,

and Dr. Hale White¹⁵ limits the disease in much the same way by saying: "For the case to be an example of the disease described by Addison, it is essential that there should not be present any of the usual causes or concomitants of the anæmic state." Our knowledge of the pathology, etiology, and clinical symptoms has, however, grown greatly since Addison's time, and this being so, it seems very undesirable to cramp ourselves by a definition formed many years ago from early and incomplete observations. Addison, exact and striking as his clinical picture of the condition is, had only seen comparatively few cases; he had no knowledge of the blood changes nor of many other important points, and in fact he himself throws doubt on the propriety of the term "idiopathic." Strictly speaking, no disease can properly be described as idiopathic; there must be some cause, although we may fail to recognise it, and hence the application of such a term simply denotes that we do not know the true cause. As a matter of fact, since Addison's time, fatal or "pernicious" anæmia has been definitely shown to follow on various causes, although it is freely admitted that the origin of certain cases is still mysterious. Thus out of 135 cases collected by Eichhorst, only seventeen are put down as "idiopathic" or "essential" (that is, where no cause is discoverable), the remainder being attributable to pregnancy, exhausting discharges, prolonged poor feeding, etc. But even if no sufficient cause can be made out from the history or *post-mortem* examination, this may result from our present insufficient knowledge or faulty observation, and we can scarcely conclude that the disease is in such cases idiopathic.

It is difficult to define exactly what constitutes "pernicious anæmia," seeing that the name has been given to a congeries of symptoms none of which are pathognomonic, but during the last twenty-five years many cases have been carefully reported as cases of pernicious anæmia by clinicians who have devoted special attention to the subject, and whose opinion may be regarded as perfectly final and conclusive, that in all respects their patients presented the typical clinical symptoms of the condition. In some of them no cause could be stated, but in the great majority very striking pathological changes were found either during life or after death, and there can be no reasonable doubt that the anæmia resulted directly or indirectly from these changes. Widely different as the causes may have been, it is a striking fact that they produce an identical clinical picture in all cases. Cases following on atrophy of the mucous membrane of the stomach have been very fully detailed by Fenwick,¹⁶ Brabazon,¹⁷ Nothnagel,¹⁸ Henry and Osler,¹⁹ and others. Curiously, the majority of such patients are described as being stout, and in appearance well nourished. Stengel²⁰ reports an instance in which the patient, after suffering for fifteen years from gastric dyspepsia, ultimately developed all the symptoms of pernicious anæmia, and on *post-mortem* examination cirrhosis of the stomach, with almost complete destruction of the gastric glands, was found. Prolonged diarrhoea, with or without intestinal ulceration, has also been noted very frequently as a forerunner (Wilks,²¹ Quincke,²² Fraenkel,²³ Stricker,²⁴ and many others).

Many cases undoubtedly follow on severe or prolonged hæmorrhage. Thus Habershon²⁵ had a case after repeated epistaxis; so had Quincke. Schepelern²⁶ describes several cases as brought on by long-continued metrorrhagia, and Finny²⁷ had a similar experience; Greenhow,²⁸ after menorrhagia, and I myself have seen a case from hæmophilic bleeding. The cases described as following on pregnancy (Gussow²⁹) and lactation are now extremely numerous, while typhoid fever (Rosenstein³⁰ and others) has also frequently been assigned as a cause.

Among other predisposing and anæmia-producing conditions may also be mentioned syphilis (Müller³¹ and Laache³²), yellow fever (Bramwell³³), and mental shock (Mackenzie³⁴ and Cortin³⁵). Chlorosis is sometimes the starting point, nine cases being recorded by Müller³⁶ and one each by Marshall Hall³⁷ and Coupland³⁸. Habitual poor feeding, especially if accompanied by hæmorrhage from any source, seems also to induce fatal anæmia, and Lépine states that immediately after the siege of Paris, cases brought on by starvation and diarrhoea were much more common than they have been there subsequently. It is well known that bile salts circu-

lating in the blood break down the red corpuscles, and, from the frequency with which jaundice has been reported (Habershon, Quincke, Bristowe, Mackenzie) as preceding or accompanying pernicious anæmia, I am inclined to think that it also may be reckoned among the predisposing causes. The monographs on "Progressive Pernicious Anæmia" by Müller, who reports 62 cases, many of them from his own observation, and by Eichhorst, who has collated 135, and reports 7 observed by himself, give a large amount of corroborative evidence.

Sarcomata and carcinomata also occasionally give rise to all the clinical symptoms of pernicious anæmia, although this must happen rarely. It seems, however, to be now very generally admitted, and Dr. William Hunter, after examining the evidence *pro* and *con.*, says, "Apart from these more doubtful cases, however, a sufficient number of cases have been recorded by competent observers to prove conclusively that all the characteristic features of pernicious anæmia may be presented by patients the subjects of malignant disease." I myself have never seen such a case although I have examined many patients suffering from malignant disease with profound anæmia, and in whom the corpuscles and hæmoglobin were reduced to one-half, or even to one-quarter of the normal, but the *tout ensemble* was never, in my experience, that of typical pernicious anæmia. Nothnagel,³⁹ however, states that he has seen two cases of cancer of the stomach develop into pernicious anæmia while under his care, and Eisenlohr⁴⁰ had a similar experience. Retinal hæmorrhages and altered bone marrow seem to be not uncommon in malignant cases. As regards sarcomata, Mosler and Gast⁴¹ relate a case in which the bones were found to be like ivory, the marrow quite gone, and sarcomata in nearly all the bones of the body; they attribute the extreme anæmia to non-formation of blood corpuscles in consequence of destruction of the bone marrow. Grawitz⁴² also records three cases in which there were numerous sarcomata involving the marrow. Such patients are generally stout, and have plenty of subcutaneous fat in spite of the malignant disease.

Lastly, the clinical symptoms may be produced in every detail by certain intestinal worms, of which the best known are *Bothriocephalus latus* and *Ankylostoma duodenale*. Schauman⁴³ records 72 cases of tapeworm anæmia, 37 of which were observed by himself, and one has only to read his minute and careful clinical reports to be convinced that in every respect, even to the exacerbations and remissions, they resemble the classical non-parasitic form of the condition. It seems still to be a vexed question whether the worm induces anæmia by disturbance of digestion, or by the formation of a blood-destroying ptomaine which is absorbed from the intestine.

In *ankylostoma* anæmia the parasite directly sucks blood from the vessels of the intestinal mucous membrane, and thus it is due to direct loss of blood (Sahl⁴⁴, Leichtenstern,⁴⁵ Beaven Rake⁴⁶). Hirsch⁴⁷ and others have doubted if it be due to loss of blood, and prefer to call in the intervention of a ptomaine because the number of worms found is in some cases small. Lutz,⁴⁸ however, states that a very small number suffice to keep up the anæmia once it is established, and Neumann⁴⁹ that in dogs, when the malady has become chronic, only a few parasites are found, as they do not infest an unhealthy mucous membrane.

It seems certain, therefore, that pernicious anæmia is preceded in a large majority of cases by exhausting conditions, and that it results directly or indirectly from these conditions. It is easy to understand how blood loss, atrophy or cancer of the stomach, poor food, or the drain of pregnancy and lactation may bring on anæmia; a prolonged attack of typhoid fever or severe nervous shock may also do so in consequence of digestive disturbances, and impaired nutrition and vitality. The onset is very gradual always, and there is at first nothing to distinguish it from ordinary simple anæmia; nor is it in any way different, as the majority of such cases recover, but in a few degenerative changes in the small vessels occur leading to hæmorrhages and the more profound so called "pernicious" or "progressive" anæmia.

We must conclude, therefore, that "pernicious anæmia" is not a disease *sui generis*, but simply a collection of symptoms characteristic of the highest degree of anæmia.

REFERENCES.

- ¹ History of a Case of Anæmia, *Trans. Med.-Chir. Soc. Edin.*, i, 194, 1824 (read May 1st, 1822). See also Dr. Kellie, *ibid.*, p. 119. ² From *Miscellanea Curiosa*, An. 7, Obs. xiv. ³ On Disease of the Suprarenal Capsules, London, 1855. ⁴ *Correspondenzbl. f. Schweiz. Aerzte*, 1872. ⁵ *Deut. Archiv f. klin. Med.*, xiii, 209, 1874. ⁶ *Volkmann's Sammlung klin. Vorträge*, 100, 1876. ⁷ *BRITISH MEDICAL JOURNAL*, 1888, i, 1149. ⁸ *Lancet*, 1881, i, 9. ⁹ *Medical Times and Gazette*, 1877, i, 471. ¹⁰ *Die progressive perniciöse Anämie*, 1877. ¹¹ *Die progressive perniciöse Anämie*, 1878. ¹² *Revue mensuelle de Méd.*, 1877. ¹³ *Lancet*, 1888, ii; *Practitioner*, 1888, ii. ¹⁴ *Guy's Hospital Reports*, xxvi, 219, 1883. ¹⁵ *Guy's Hospital Reports*, xvii. ¹⁶ *Lancet*, 1877, ii, 1, 39, 77. ¹⁷ *BRITISH MEDICAL JOURNAL*, 1878, ii, 134. ¹⁸ *Deut. Archiv f. klin. Med.*, xxiv, 353, 1879. ¹⁹ *Amer. Journ. Med. Sc.*, xci, 498, 1886. ²⁰ *Therap. Gazette*, 1894, 378. ²¹ *Guy's Hospital Reports*, iii, 203, 1857. ²² *Loc. cit.* ²³ *Charité Annalen*, iii, 283, 1876. ²⁴ *Charité Annalen*, ii, 1877. ²⁵ *Medical Times and Gazette*, 1876. ²⁶ *Schmidt's Jahrb.*, 1880, 186, p. 22. ²⁷ *BRITISH MEDICAL JOURNAL*, 1880, i, 43. ²⁸ *BRITISH MEDICAL JOURNAL*, 1871, ii, 613. ²⁹ *Archiv f. Gynäkologie*, ii, 218, 1871. ³⁰ *Berl. klin. Wochenschr.*, 1877, 113. ³¹ *Charité Annalen*, xiv, 253, 1889. ³² *Die Anämie*, 1883. ³³ *Edin. Med. Journ.*, xxiii, 408, 1877. ³⁴ *Lancet*, 1878, ii, 797, 894. ³⁵ *Philad. Med. Times*, 1885, 494. ³⁶ *Progress. pern. Anæm.*, 1877. ³⁷ *Theory and Practice of Med.*, 1837. ³⁸ *Loc. cit.*, Case 2. ³⁹ *Loc. cit.* ⁴⁰ *Deut. Archiv klin. Med.*, xx, 1877. ⁴¹ *Deut. med. Wochenschr.*, 1885, 447. ⁴² *Virchow's Archiv*, lxxvi, 353, 1879. ⁴³ *Zur Kenntniss der Bothriocephalus-Anämie*, Helsingfors, 1894. ⁴⁴ *Deut. Archiv klin. Med.*, xxxii, 421, 1883. ⁴⁵ *Deut. med. Wochenschr.*, 1885, 484. ⁴⁶ *Journal of Pathology*, iii, 107, 1894. ⁴⁷ *Lancet*, 1894, ii. ⁴⁸ *Volkmann's Sammlung klin. Vorträge*, Nos. 255, 256, 265. ⁴⁹ *Parasites and Parasitic Diseases of the Domesticated Animals*, English translation, 1892.

[To be continued.]

THE REMOTE EFFECTS OF SPINAL INJURIES IN MINERS.¹

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MINERS, from the nature of their occupation, are peculiarly liable to injuries of the spine and spinal cord. These generally result from falls of coal, stone, or rubbish, causing in the majority of cases what the miners describe as a doubling up of the body.

I wish to limit myself as far as possible to a consideration of the remote effects of spinal injuries, and only of those which are not dependent upon gross lesions such as fracture or dislocation of the spine, rupture of the cord, hæmorrhage upon or into the substance of the cord.

The great obstacle to the clear understanding of the surgery of the spine has been the loose and careless manner in which terms have been bandied about, and the retention of old-fashioned descriptive terms. It is difficult to steer clear of all the objectionable features of the older classifications, but I have ventured with some considerable diffidence to do so by dealing with my subject under the following heads:

1. The effects of spinal sprain.
2. The effects of injury to bone of a nature not sufficiently grave to constitute a gross lesion.
3. The effects of molecular disturbance of spinal cord in conjunction with sprain of spine.
4. The effects of molecular disturbance of the nervous system with or without those of sprain of spine.

I.—SPINAL SPRAIN.

From the first class, spinal sprain, I wish to exclude the spinal cord entirely. When one considers the anatomical relations of the cord, it becomes evident at once how admirably, safely and securely it is protected from external violence. Where nervous conditions have resulted after sprains these may readily be assigned to conditions quite independent of the cord. If we regard the spine for surgical purposes in the same light as we do any other joint, it will be clear that the condition of spinal sprain must obviously differ very greatly in extent and severity. In the mildest form the skin is stretched and the muscles damaged; in the more severe form, in addition to stretching and tearing of muscles, the ligaments of the spine are involved; they may be stretched, and are probably often torn.

In the worst forms, in addition to the foregoing lesions, we meet with rupture of nerves and hæmorrhage, often of a severe character, extradural or intradural, and often into the substance of the cord. But, as I have already stated, this is excluded from consideration.

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Amongst the miners who have come under observation many have suffered from the effects of the first and second forms, and, as we should naturally expect, the symptoms have varied very considerably both in extent and severity. The most prominent have been weakness, stiffness and rigidity of spine, varying degrees of immobility of spine, muscular rigidity, unilateral or bilateral, and local tenderness. All these, you will observe, are conditions which prevail wherever joints are sprained.

The effects of spinal sprain last for variable periods. Erichsen states that recovery from spinal sprain after railway accidents takes place generally in six months. In young miners, very few of whom have come under observation, the symptoms pass away in a few days or weeks, but in the older men they may persist for many months with such severity as totally to unfit them for work.

II.—INJURY TO BONE, NOT CONSTITUTING A GRAVE LESION.

I have placed here those cases which have presented signs and symptoms of caries of the spine. I have notes of three cases. In the large majority of cases of caries of the spine, we are able to elicit a history, clear or obscure, of traumatism, and patients will generally ascribe their diseased conditions to it. I do not support the proposition of direct causation by traumatism, although in the cases that I shall submit to you we were unable to obtain clear evidence of a tuberculous taint or diathesis. Perhaps the correct way of regarding these cases is to suppose that some vasomotor changes were set up in the bone as the result of the accidents, and that tubercle bacilli availed themselves of these changes to form for themselves a resting place and breeding ground. In two of the cases the disease confined itself apparently to the spine alone; in the third case, it appeared more than probable that the lung mischief was secondary to the spinal.

Briefly, the notes of the cases are these:—

CASE I.—J. J., aged 16. A large stone fell upon the lower part of his back. He walked home from the pit, a distance of half a mile, and then went to bed. He was in bed for a week, then got up and moved about the house. No symptoms prior to the accident. Two months afterwards he noticed a lump over the middle of his back, and he was put up in a plaster jacket, which he had worn up to the time of his examination. There was a well-marked posterior curvature of the dorsal spine.

CASE II.—C. R., aged 37, seen in October, 1888. A block of stone with debris fell upon his shoulders in December, 1887, squeezing him down to the ground and almost burying him. He was carried home, complaining of great pain in his back, more particularly in the lower dorsal region. A fortnight after the accident he was able with much difficulty to get about with the aid of crutches. He was obliged to use crutches for two or three months, and then he was gradually able to walk out a little, still complaining of pain in the back. He was not able to tell how soon after the accident he first noticed the lump in his back. There was a decided lateral and anterior posterior curvature of the spine, the most prominent point being at the lowest dorsal spine, and here he evinced great tenderness to pressure.

CASE III.—J. S. After a similar accident this patient developed spinal caries. At the time of examination there was also distinct evidence of lung mischief, which we were of opinion followed in point of time the appearance of spinal mischief, and was probably secondary to it. Unfortunately, in the notes there is no special mention of the true relations of accident and disease, but it was clearly our opinion, as the following note states that the spinal mischief was directly dependent upon the accident: "The spinal mischief was no doubt set in motion by the accident."

III.—MOLECULAR DISTURBANCE OF CORD.

I have adopted the term "molecular disturbance" in the third class to indicate a condition in which, to quote Erichsen's words "the intimate structure of the spinal cord is more or less deranged, by which its functions are greatly disturbed, and in which various symptoms indicative of loss or modification of innervation is immediately induced." I am quite aware that upon the pathology of this condition there will probably be a considerable difference of opinion, but I shall not enter upon a defence of my position, because this would be quite foreign to the object of my paper.

A history of modification of innervation I have been able to elicit in many of the cases which have come under observation. Generally it has assumed the form of temporary paralysis or paresis, temporary sensory disturbance in the form of numbness and tingling, or temporary interference with the process of urination. As far as I have been able to ascertain, motor disturbances are more frequent in their occurrence than temporary loss of control over the bladder.

Is this a common experience after spinal injuries? If it is then the following important question should not be difficult