CLINICAL LECTURE ON IDIOPATHIC ANÆMIA.

Delivered in the City of Dublin Hospital.

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CASE III. *Profound Anæmia following upon Uterine Hemorrhage: Irregular Febrile Action: Absence of Dyspepsia: Constipation: Abnormal Characters of Blood: Treatment by Arsenic: Death.* [Reported by EDMUND SHACKLETON, L.K.Q.C.P.I.]—Sarah G., aged 54, was admitted to hospital under my care on March 2nd, 1879. She is a mother of five children.

History.—She had enjoyed good health, and had led an active life as general in-door servant up to five years ago, when her health became impaired. This ill-health she attributed to the effects of a mental shock produced by the sudden and unexpected news of a rupture of a close family tie. Hemorrhage from the womb was brought on at the time, though as to whether it was profuse was not noted. The menses had quietly and regularly ceased full twelve years before this bleeding. Since 1874, she had never been strong, and, year by year, her weakness and pallor had gradually increased.

On admission, her appearance was remarkably anæmic, differing from that of simple anæmia on the one hand, and chlorosis on the other, in being not so much white or green, as of a pale lemon colour. The bloodless look of the hands and fingers was very evident when examined against the light, not a shade of red being visible along the line of contact of the fingers. You are aware, doubtless, that, in a healthy hand, such line of contact similarly examined exhibits a blood-red colour, and that the absence of any colour in these situations is looked upon by some authorities as a sure evidence of the cadaveric state. She was not aware of any loss of blood by the bowels or kidneys; she had had no epistaxis nor sponginess of the gums; and she had never been exposed to malarious influences.

There was no emaciation, but quite the contrary; as the thorax, mammae, and abdomen were thickly covered with fat. The face was also full, but this was in part due to œdema. The legs were swollen up to the knees, but, after a few days' rest in bed, this swelling became less. The patient complained of a sensation of fullness and sometimes of pain in the epigastrium, accompanied by pain on pressure over this place, as well as over the right hypochondrium. For some months, she had had occasional pains in her shoulders, hips, and knees, and recently, for nearly six weeks, she experienced excruciating pain in one knee. There was, however, no evidence of thickening of the joints. There was nothing abnormal to be made out by examination of the abdominal viscera, and the kidneys seemed healthy, the urine being of natural colour, specific gravity 1017, and free from albumen and bile. There was no evidence of valvular cardiac disease, nor of arterial degeneration; the first sound was weak and short, the impulse feeble, and the pulse compressible, 80 in the minute. In the neck, venous murmurs were present, being very intense, and audible even in the recumbent posture. Over the pulmonary valves and in the direction of the pulmonary artery, there existed a soft systolic hæmic murmur. The temperature was above normal, though subfebrile, averaging in the morning 99.7°, and in the evening 100.6°.

The blood, when examined under the microscope, was characteristically similar to that of Cases I and II. There were, however, fewer microcytes than in Case I. There was no increase of white corpuscles (*vide diagram*). Unfortunately, I omitted to examine the eyes.

Recognising the case to be one of idiopathic anæmia, with most probably fatty disease of the heart, I put her upon arsenic and iron, thus: *Liquoris ferri perchloridi* ℥xv; *liquoris arsenici hydrochlorici* ℥iii; *infusi calumbæ* ʒi: to be taken three times daily. The bowels, which were habitually constipated, the patient going for nine days at a time without a motion, I kept regular with pills of iron and aloes.

This treatment was steadily pursued till March 12th, when, owing to a slight rise of temperature, and to sickness of stomach, it was stopped. During the next night, her bowels were moved several times, and her condition, at best but low, because now alarmingly prostrate.

Were it not for the great promptitude exhibited by Mr. Line in giving her two hypodermic doses of ether at short intervals, I doubt not she would have died before morning. At my visit at 9 A.M. on the 13th, her state was one of the gravest anxiety. She was a little restless; if possible, she was further blanched; her pulse was small, compressible, 110; and the temperature had run up to 103°. The first sound of the

a. Normal red Corpuscles in clusters, not rouleaux. b. Large. c. Small. d. Irregular Corpuscles.

heart was short. Digitalis, sulphuric ether, and aromatic spirit of ammonia were directed to be taken every second or third hour, and an astringent mixture of chalk, opium, and catechu after each motion. The temperature rose in the evening to 104° (*vide table*).

				Temperature.		Pulse.	
				M.	E.	M.	E.
March 7th, 1879	..	..	..	99.5	—	..	82
" 8th, "	..	..	..	99.1	—	..	78
" 9th, "	..	..	..	100.2	99.8	..	84
" 10th, "	..	..	..	100.0	100.7	..	86
" 11th, "	..	..	..	100.2	100.8	..	80
" 12th, "	..	..	..	100.2	100.8	..	82
" 13th, "	..	..	..	100.9	101.5	..	84
" 14th, "	..	..	..	103.0	104.0	..	110
" 15th, "	..	..	..	100.9	103.7	..	100

The following morning (March 14th), she expressed herself as better; the pulse and temperature had both fallen, to 100.8° and 100 beats respectively, and the diarrhoea was checked. In the evening, the temperature again rose to 103°. Unfortunately, through the night, the diarrhoea recurred, the bowels were moved three times within a short interval, and her strength ran down rapidly; the pulse became small, quick, and compressible, and she sank the following evening.

There was no blood in any of the discharges. In spite of all our efforts to obtain a *post mortem* examination of the viscera and bones, we were unfortunately frustrated, and thus lost a rare opportunity of confirming, or otherwise, the morbid anatomy of this disease.

REMARKS.—The foregoing cases have, I trust, made you familiar with the general outline and course of this interesting and rare disease. I shall now direct your attention, as shortly as I can, to the most prominent features, and afterwards we shall discuss what is known as the pathology, causation, prognosis, and treatment of idiopathic anæmia.

Before proceeding directly to this task, I wish to explain why it is that all through these lectures I have preferred to call the disease "idiopathic" to "progressive pernicious anæmia". My reasons are threefold: 1. The term "idiopathic" does not commit us to any name derived from pathological conceptions, when, as yet, its pathology is not accurately defined; 2. Although vague, it directs our mind at once back to Addison, to whom is due the credit of being really the first to establish it as a special and distinct form of anæmia; and 3. Because it does not, like

* Concluded from page 7.

that given it by Biermer, deal with the question of prognosis, nor presuppose a termination which, it is pleasant to think, does not always obtain.

The first and most prominent feature of the disease under consideration is naturally that from which it gets its name—the bloodless *pallor* of the patient. This pallor is not always of the same hue; in some, like Cases I and III, it is yellowish, and approaches that of jaundice, and so closely, that some of you actually did confound it with icterus. The diagnosis is, however, easy, as the tinge of skin is more of a lemon colour, like that of cancer and Bright's disease; and the conjunctivæ, as well as the secretions, are entirely void of any staining by bile-pigment. With reference to the eye, however, it should be borne in mind that, if subconjunctival fat exist in any quantity, it will probably be of a yellow colour in anæmia. Moreover, the mucous surfaces of the eyelids, lips, gums, and tongue share in the want of the normal blood-colour.

Physical examination of the heart and large arteries and veins reveal various murmurs, but they all are due to the feeble action of the heart and to the altered condition of the blood, common to all forms of great anæmia. In Cases I and II, the cardiac basic murmur seemed to be in the aorta. In Case III, its situation and direction was over the pulmonary artery. Occasionally, but very rarely, mitral murmurs are heard in this as in other forms of anæmia.

With this marked anæmia, it was surprising how little proportionate was the emaciation in any of the cases; and this persistence of *fat*, gentlemen, constitutes another of the prominent symptoms of idiopathic anæmia. Case III exhibited a marked increase of adipose tissue on the chest and abdomen; and, in Cases I and II, in spite of general muscular flabbiness and emaciation of the face and extremities, there was, nevertheless, a decided layer of fat under the skin of the abdomen. This symptom at once contrasts strongly with the anæmia of cancer or phthisis, and rather resembles the condition found in the chlorosis of young women.

Again, in very few instances is there any marked *dropsy*, such as occurs in the anæmia of heart or renal diseases. In the majority, there may be but œdema of the ankles and feet. As a rule, dropsy appears late in the disease, and is confined to the lower extremities. In connection with this symptom, it is interesting to notice how long the œdema persisted in Case I, remaining for several months after the disappearance of the anæmia.

In all my cases, and in particular in Case II, there were *pain* and *tenderness over the tibia*. I do not lay very much stress on this symptom, as, in delicate and frail people, any pressure, however slight, over the flat and exposed parts of the tibia, is attended by uneasiness and pain. It is, however, a symptom not lacking in significance, when you consider that certain changes to which I shall shortly advert have been found by Cohnheim and some other observers in the marrow of the long bones.

Dyspeptic symptoms are commonly present in cases of the disease we are considering, and may be so from the beginning to the end. Thus, in Cases I and II, they were prominent features; while, on the other hand, they were almost wanting in Case III. The patients also, as a rule, complain of pain either in the epigastrium, or extending across from one hypochondrium to the other. There are exceptions to this, since in some cases, like Case III, and a case recorded by Dr. Pepper (*American Journal of Medical Sciences*, October 1875, p. 323), pain was completely absent. This pain, with nausea and vomiting, when connected with anæmia, is in some patients so marked as to suggest the existence of gastric ulcer, simple or cancerous; and this view, you may remember, I was inclined to take of Case II, in the beginning in 1877, when first he was under my care; and it was on the same supposition entertained by other medical men under whose care he had afterwards been, that admission into the Hospital for Incurables was sought for him.

Diarrhœa or constipation, more usually the former, is another very common symptom. When attacks of diarrhœa occur, the patient's strength is rapidly and even fatally exhausted. Case III was thus brought to a rapid close, and Case I was on several occasions so prostrated by it as to be in a most precarious condition. Diarrhœa in so many instances seems to precede the development of the other prominent symptoms of idiopathic anæmia, that M. Lepine (*London Medical Record*, vol. v, p. 316), looking upon it as a cause of the disease, designates such cases as *anémie gastro-intestinale*.

On this point of diarrhœa, it is worth noting that, as Dr. Pepper remarks (*American Journal of Medical Sciences*, 1875, p. 313), while chronic diarrhœa and vomiting are by no means uncommon, hæmorrhage from the bowels has as yet not been noticed.

The *urine*, in the majority of cases, seems but little altered. It is free from albumen, bile, or sugar, and presents a normal reaction and colour. The amount of urea eliminated is usually diminished (Dr. Mackenzie,

Lancet, vol. ii, 1878, p. 835); but the deficiency is not more than may be explained by the small amount of nitrogenous food consumed, its frequent rejection by vomiting, and by the absence of all muscular exercise. In some cases, the urine was of a high colour. In connection therewith, Dr. Purser (*op. cit.*) suggests the idea that, the high colour being due to an increased pigment giving a distinct iron reaction, the *iron of the blood was eliminated by the kidneys among the products of the destruction of the corpuscles*. In order to test the accuracy of Dr. Purser's hypothesis (as he had himself made no analysis of the urine in this disease), I determined to have the urine of Case I examined for an excess of this metal. I should mention that Dr. Harley has demonstrated the existence of iron as a normal ingredient in healthy urine and in the extractive colouring matter (*The Urine and its Derangements*, p. 342). On the other hand, Vogel and others deny its presence, except as the slightest trace. A sensible quantity, therefore, was necessary to justify Dr. Purser's supposition. I think that there can be no doubt that, in the urine of Case I, such a hypothesis was thoroughly confirmed by facts. My friend Dr. J. Emerson Reynolds, Professor of Chemistry in the University of Dublin, not only gave me every facility in carrying out my investigations on this point, but most kindly undertook himself the laborious process of making a quantitative analysis of specimens of the urine of Case I. In order to avoid possible error, as well as for the sake of comparison, two analyses were made. The first was on February 20th, 1878, while the patient was taking large doses of iron (Blaud's pills, five three times a day). The urine on this occasion showed a very considerable quantity of iron, nearly three-quarters of a grain, viz.: total urine of 24 hours, = 55 fluid ounces; excretion of metallic iron in 24 hours, = .7485 grain metallic iron. The second analysis was made sixteen days later, and the iron treatment had been discontinued from the 22nd February previous. This analysis gave .308 grain of metallic iron in 72 ounces. This discovery of the excretion of iron in such a quantity in the urine of idiopathic anæmia seems to supply a missing link between the pathological condition of the liver and kidneys, described by Quincke and Purser, and the state of the urine. In five *grammes* of undried kidney, in which there was granular pigmentation of the cortex, Dr. Purser found 0.0176 *gramme* of metallic iron (*Dublin Journal of Medical Science*, No. lxxi, p. 420). Quincke has also demonstrated a considerable quantity of iron in the liver, pancreas, and kidneys. In one liver 2.1, in another 0.6, per cent. of the dried organ was found to consist of metallic iron, and, from the dried kidneys, 0.32 per cent. of iron. In Quincke's cases, there was the possibility that part at least of the iron was derived from medicine.

Another symptom, and that a remarkable one, was the occurrence of *pyrexia* at irregular intervals, without any assignable cause, and of very unequal severity. In general, the temperature is subnormal (see Case II); but, as in Case I, suddenly the thermometer may register 103°, 104°, or even 106°. In Case I, the latter temperature was reached—a degree higher than any hitherto recorded in a non-fatal case of anæmia (for Dr. Pepper gives one other instance of 106° being reached, but it was immediately before death); and in Case III, a like fever existed, reaching to 104° a day or two before death. The Case II contrasts well with the others, as, during the patient's stay in hospital, he was free from all fever. This fever seems to follow no regular type, the morning temperature being often higher than the evening, and the pulse is not commensurately accelerated. A satisfactory explanation of these sudden pyrexial outbursts is not forthcoming. Since like febrile conditions occur in leukæmia, in which the red corpuscles are few, we might be justified in connecting its occurrence with this oligocythæmia were it not that, throughout the whole course of some fatal cases of idiopathic anæmia, no such attacks of fever were met with.

The next, and perhaps the most remarkable and characteristic feature of the disease to which I direct your attention, is the *altered character of the blood*. The abnormal conditions are threefold: 1. Diminution of the number of the red corpuscles (oligocythæmia); 2. Want of colour (achroicythæmia); and, 3. Alterations of shape and size of the corpuscles (micro- or macro-cythæmia).

Dr. Mackenzie (*Lancet*, vol. ii, 1878, p. 834), to whose paper I am much indebted, has made some very valuable observations on the diminution of the coloured corpuscles in various anæmic states, but in none did he find so few corpuscles as in cases of this disease. In one of his cases it was so low as 13 per cent., or 0.650 million per cubic millimètre, while the average in eleven cases of phthisis given by Sorensen reached 4.35 millions per cubic millimètre, and in cancer (six cases) 3.66 millions. The want of colour is readily noticed as the blood is drawn, and under the microscope, with transmitted light, the red corpuscles are of a much paler tint than normal.

However remarkable the relative paucity of coloured corpuscles, and their want of hæmoglobin may be, the alteration of the corpuscles as

to size and shape is still more striking, and may be considered one of the pathognomonic features of this form of anæmia. The natural size of the red corpuscle is about 1-3500th of an inch; in this disease it may, on the one hand, not reach a quarter that size, some corpuscles being as small as a sixth; and on the other hand, many of the corpuscles may attain a size larger than that of the white cells. In health, the largest corpuscles have a diameter of 8.8 *micro-millimètres*, and in some cases of idiopathic anæmia, corpuscles of 10 and 14 *micro-millimètres* have been met (Mackenzie, *op. cit.*) The diagrams of the above cases exhibit these alterations of size, and in the microscopical examination of the blood, the combination of large and small cells at once caught the eye. Nucleation of some of the large cells has been noted by some observers, the nucleus being often at the side of the corpuscle, and of a deeper colour. Such a condition has been depicted by Dr. Byrom Bramwell (*Edinburgh Medical Journal*, November 1877) and Messrs. Mackern and Davy, of Guy's Hospital (*Lancet*, 1877, vol. i, p. 642).

I failed, in the many examinations I made, to find a single nucleated cell, and others (including Dr. Purser) likewise met with none. Cohnheim (*Medical Times and Gazette*, vol. i, 1877) found them, after death, in specimens of blood from different parts of the body, although during the last week they were not visible. A peculiar interest, in a pathological aspect, attaches to such nucleated red cells, inasmuch as similar corpuscles have been found in the marrow of the bones by Cohnheim, Gardner, Osler, and Purser. It must, however, be borne in mind that the existence of such nucleated corpuscles is not confined to idiopathic anæmia.

An apparent nucleation occurred in several specimens of the blood of Case I, but this appearance was caused by the overlying of a small yellow corpuscle by a larger pale-coloured one (*vide* diagram 1). The small corpuscles were generally of a deeper colour, and their number varied in my cases, being fewer in the fatal case than in Cases I and II. Quincke and Eichhorst have drawn attention to these microcytes, the latter observer looking upon them as pathognomonic of idiopathic anæmia. On the other hand, several other observers have failed to record them, and their presence is expressly denied by Professor Rosenstein, Dr. Grainger Stewart, Dr. Bradbury, and Dr. Bradford (see Dr. Pye-Smith's review, *London Medical Record*, p. 438, 1877), while Lepine has noted that, in some cases, the chief feature is the increased size of the corpuscles. Moreover, Dr. Litten (*London Medical Record*, 1877, p. 120) has found microcytes in the blood in a case of phthisis, and similar small cells occur in splenic leukaemia and in cases attended with subcutaneous extravasations, such as scurvy.

The shapes assumed by the coloured corpuscles are very remarkable, and vary as much as their size. It is only the large cells which are thus altered. Case I exhibited most of these peculiarities, in which we found corpuscles, oval, egg-shaped, bowl-shaped, bifid, tailed, and crenated. The tailing of the corpuscles (and, presumably, the other shapes) can hardly be looked upon as a vital phenomenon; for, as Dr. Harvey and I were examining the freshly drawn blood, we saw some of these large corpuscles, as they slowly moved across the field, change their circular shape and become tailed. It seemed as though they were of an adhesive material, part of which became adherent to the glass, while the rest was drawn onward in the feeble current, and then, after momentarily clinging, the part was set free, and the corpuscle recovered its original circular or oval shape.

It must have occurred to you, while listening to the above description of the clinical characters and microscopical appearances exhibited in the interesting disease, to ask what can be its cause, and how far do *post mortem* revelations explain its nature? In reply, I may very shortly say that our knowledge of both the pathology and causation is as yet too immature and conflicting to enable us to lay down any very decided data, or to supply positive information.

Idiopathic anæmia seems (at least it is so in this country) to attack those placed in easy circumstances, equally with those suffering from privations; and males and females in about equal numbers. It is, however, more common at and after middle life, and, as was pointed out by Addison, it occurs somewhat more frequently in persons predisposed to be fat.

Post mortem examination of the viscera has not thrown much light upon its cause. In the majority of cases, though not in all (as Biermer would insist), the heart is the organ in which pathological changes have been most frequently observed. Its muscle is pale, and zig-zag striae of fat (tabby-cat mottling) are found on the walls or muscoli papillares. The spleen, liver, and kidneys are healthy, except for the excess of iron found in them, already referred to; retinal ecchymoses, either punctiform or striated, have been very frequently noticed, (in eight out of ten cases, by Quincke), and the walls of the stomach have been found (by Dr. Fenwick) thinned and pale. Yet I am of opinion all these

pathological changes are to be considered but the result of the profound anæmia and its consequence, malnutrition.

Of late years, however, very remarkable changes, to which I have already alluded, have been found in the marrow of the bones. The following is abstracted from Cohnheim's description, with which, in most points, the majority of subsequent observers agree.

"The marrow of all the bones, the flat as well as the long, was of an intensely red colour. Under the microscope, there was an absence of the usually abundant fat cells, but in its place were seen (1) colourless corpuscles, like lymph corpuscles, but of a large size, with one or two bladder-like nuclei and a few multinucleated giant cells; also (2) an equal number of coloured cells, consisting of a few blood-corpuscles, spherical red corpuscles without nuclei, the size of, or twice the size of, a colourless corpuscle, and nucleated spherical or oval cells of variable size, with one or more nuclei."

Such as we might be inclined to look upon these changes in the medulla of the bones as a direct contributory cause of idiopathic anæmia, seeing they are presumably an imperfect formation, and, as Cohnheim, Osler, and Purser would have us believe, cause increased destruction of the blood-corpuscle. It is but right that we should accept such a theory with caution, since Dr. Bradbury failed to discover any medullary change in a case of idiopathic anæmia, while Newman, Litton, and Orth have found similar changes in wasting diseases, such as cancer and phthisis, and are of opinion, such marrow-changes are to be considered not a cause of idiopathic anæmia, but a consequence of anæmia, however produced (Mackenzie, *op. cit.*)

It is evident to you from what I have told you, that as yet the pathology of this disease is by no means a settled question; and, for the present, we must rest contented with the feeble ray of light let in upon so obscure a subject, with the earnest hope that ere long, research in a daily widening field of observation may result in a sound scientific etiology and pathology.

I shall not detain you with any dissertation on the question of *diagnosis*. From what we have observed together, you cannot but recognise that it is beset with difficulties, and yet that the difficulties are not such as cannot be overcome by careful analysis, aided by microscopical examination of the blood.

What shall I say as to *prognosis*? It cannot be other than most guarded, seeing that the majority of cases have ended fatally. Yet, while thus the title of Biermer seems fairly justifiable, we cannot but hope that in time therapeutics will sanction the withdrawal of not only the epithet "progressive", but also that of "pernicious". Already instances of, not arrest only but, recovery, are on record, and to that list, though a short one, we are able to add two more.

The *treatment* which has been found to answer best in this disease is not that to which the indications most strongly point. This indication is plainly iron, and yet iron fails altogether to produce any curative effect, to improve the colour or to increase the number of the blood-corpuscles. This was well exemplified by Case I, for in it I employed the metal in every form, in every dose, and in every combination. The only effect of the tincture of perchloride of iron was to induce diarrhoea. Dr. Pepper's (*loc. cit.*, p. 344) remarks on this point are so pertinent, that I shall quote them: "Iron would naturally suggest itself as the most appropriate remedy in view of the intense and progressive anæmia. It is found, however, that in some cases it is not well borne, and that, even when given in larger doses, it exercises no curative effect. The entire failure of the preparations of iron must be regarded as one of the marked features of difference between this form of anæmia and chlorosis."

I shall not tax you with the list of medicines which have been employed by various writers, but simply give my opinion that it is to arsenic we can look with most confidence for good results. This medicine you have seen me use with benefit in cardiac anæmia and in glandular sluggishness. It is also well recognised as possessed of influence for good in leukaemia. It was this which led me to employ arsenic in Case I, although at the time I was not aware how successful it had proved in the practice of Dr. Byrom Bramwell (*op. cit.*). It was administered by him in three out of eight cases of idiopathic anæmia, and in all of these convalescence took place; one other case, not treated by arsenic also recovering. Although it has failed in some cases, I cannot but look upon it as one of our surest tonics to the blood-making organs. How remarkable were its effects in Case I I need not remind you. It was also successful in Case II. In Case III, I cannot but regret that the patient was not sooner subjected to its influence, as, had her strength been better able to have battled with the attack of diarrhoea and fever, to which she unfortunately succumbed, I had hopes that this medicine might have produced in her like good results to those obtained in others.