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ON THE PATHOLOGY OF PERNICIOUS ANAEMIA.

By WALTER K. HUNTER, M.D., B.Sc.

The word Anaemia, used as a general term, implies a deficiency of blood in the circulation. By that we mean not so much a defect in bulk, as in the constituent elements of the blood—the haemoglobin and the red blood corpuscles. Considering anaemia then, in this general sense, *i.e.* as a physical sign expressed in terms of the amount of haemoglobin and of the number of red blood corpuscles, we find that it may be produced in one of three ways: (1) By direct loss of blood, (2) by diminished production of blood, and (3) by increased destruction of blood. In the first group we include the anaemias following on haemorrhage, whether internal or external. The second group is more difficult to define; but any cause which impairs the nutrition of the tissues generally must also affect the healthy activity of the blood-forming organs. Thus, insufficient food, insufficient exercise, indigestion, lesions in vital organs, may all determine a certain degree of anaemia.

The increased destruction of blood of the third group may be brought about in several different ways. For example, the plasmodium of malaria causes destruction of many red corpuscles; and, indeed, in all the fevers and wasting diseases there is doubtless some destruction of blood, due either to the direct action of a poison in the circulation or to the leucocytosis resulting therefrom. Certain drugs,[1] too, are known to destroy red blood corpuscles, but they do it in different ways. For example, glycerine, when injected into the circulation, acts on the red corpuscles, separating them from their haemo-

[1] Hunter, *Lancet*, Vol. II., 1892.

globin, and produces thereby a typical haemoglobinuria. Toluylendiamin, on the other hand, confines its destructive action chiefly to the blood in the portal area; and the large increase of iron pigment subsequently found in the liver is due to the corpuscle disintegration which this poison produces.

These, then, are some of the causes of anaemia. But in investigating the pathological anatomy of a disease a consideration of the causes forms but the introduction to the inquiry, and it is the effects with which we are more particularly concerned. We have seen that anaemia implies some defect in the constituent elements of the blood. Now it is on the blood that the tissues depend for nourishment and aeration, so that ill effects must be looked for as a result of this defective blood supply. The most common of these is fatty degeneration, and it is found chiefly in the heart-muscle and liver-cells. The fatty changes in these tissues seem to depend on their defective supply of oxygen, the result of the diminished amount of haemoglobin, for this is the vehicle which carries the oxygen.

Another change is sometimes met with in the presence of a deposit of iron pigment in the liver cells. It is said to be a constant appearance in cases of pernicious anaemia, and it is, as we have seen, also found in animals after the administration of toluylendiamin.

But there are still other changes to be noted. We know that a loss of blood cannot take place without some effort on the part of the organism at repair. Evidence of this is shown in the increase in size and activity of the various blood-forming organs. For example, the change in the marrow of the long bones from a fatty to a red lymphoid tissue is nothing but the outcome of a demand for more red blood corpuscles. It is more difficult to say what the increase in size of the spleen and lymphatic glands so often met with may be due to. In some cases it is only the spleen or possibly one single group of glands that is found enlarged, while on the other hand there are cases where the whole of the adenoid tissues throughout the body seem to be involved. Most probably it is some poisonous substance in the blood or lymphatics which causes this hypertrophy of adenoid tissue. Certain of these poisons

would seem to stimulate the glands to growth, while others, in addition, to stimulate them so that they discharge the products of their growth (*i.e.* leucocytes) into the circulation.[1] This may explain why in some cases there is but slight increase of white corpuscles in the blood, while in others the white corpuscles are increased to such an extent as to be equal in number to the red.

The changes, then, which follow anaemia are not wholly confined to the general tissues and blood-forming organs; for the blood itself, besides a deficiency in haemoglobin and red corpuscles, presents other important changes which must not be overlooked. We know that following an haemorrhage of any considerable extent, as well as in many other cases of anaemia, nucleated and other forms of immature red corpuscles are to be found in the circulation. This is evidently due to there being such an urgent demand for a fresh supply of blood to make up for what has been lost, that red corpuscles are hurried into the circulation before being fully developed. These embryonic corpuscles seem to be of little use to the organism, and their presence in considerable numbers in the spleen in such cases suggests the idea that they are soon withdrawn from the circulation and destroyed. The increase of leucocytes, on the other hand, when not excessive, should be of much benefit to the organism on account of the phagocytic or protective properties which they possess. But when in excess there is reason to believe that their rapid formation causes many of them to enter the circulation immature, and as such, they more probably succumb to rather than counteract any poison which may be present. This unhealthy condition of the white corpuscles also explains why the vessel-walls so easily rupture, and why haemorrhages are so frequent in the group of diseases we are at present considering.[2]

Turning now from these general considerations to the subject with which we are at present more particularly concerned, the pathology of pernicious anaemia, we find, to begin with, that the term itself is used differently by different writers. For example, Dr. Stockman[3] maintains that pernicious anaemia is

[1] Spencer, Erasmus Wilson Lecture. *Lancet*, Vol. I., 1897. [2] *Ibid.*
Stockman, *Brit. Med. Jour.*, Vol. I., 1895.

not in itself a disease but rather an extreme degree of anaemia following on internal capillary haemorrhages. Dr. William Hunter,[1] on the other hand, holds that it is a distinct pathological condition in which none of the ordinary causes of anaemia are to be found and in which the post-mortem appearances are more or less distinctive. With the one, the anaemias for which no visible cause can be found have the same pathology as those resulting from considerable haemorrhages; with the other, the two are quite separate conditions. There are, however, many cases on record which would not seem to include themselves in either of these definitions, or possibly to occupy a position midway between them. Clinically, they present all the features of pernicious anaemia; and while an haemorrhage may seem to be their starting-point, the amount of blood lost, being temporary or small in amount, seems quite inadequate to explain such profound and progressive anaemia. The post-mortem examinations, too, give confirmation to this view, that in some of these cases at least the anaemia is not due to the haemorrhages.

It is with these various considerations before us that I have collected together and examined the tissues of fifteen cases, in which, during life, anaemia was a prominent symptom. The cases were very different. In some the anaemia seemed undoubtedly primary, in others it accompanied other well-defined diseases.

It is by comparing the tissues in this variety of cases, regarding them in the light of their clinical histories, that I propose to pursue the inquiry into the pathology of pernicious anaemia.

For permission and encouragement to publish these cases I am indebted to Dr. Lindsay Steven, a former pathologist, and to Dr. Workman, the present pathologist to the Royal Infirmary. The notes of the clinical histories and of the post-mortem macroscopic appearances are taken from the post-mortem room journal. I myself am responsible for the microscopic examination of the tissues.

Case 1. Mrs. M., *aet.* 31. Died May 21, 1896. A case of profound anaemia, commencing with signs of dyspepsia and

[1] Hunter, *Lancet*, Vol. II., 1888.

being characterized by increasing weakness, pallor, oedema of the feet, shortness of breath. Duration of whole illness about five months. Evidence of cardiac failure, of fluid in both pleural cavities, of albumin in the urine. Haemorrhages in the fundi of both eyes. Blood "very pale," red corpuscles 15 per cent., no excess of white corpuscles.

Post-mortem examination.—Pericardium and pleurae contained a large quantity of clear serum. Heart (10½ ozs.) pale and soft, valves normal, no evidence of fatty degeneration on microscopic examination; small haemorrhages in the substance and on the surface of heart-muscle. Lungs slightly oedematous, otherwise healthy. Liver (52 ozs.) presented appearances of passive hyperaemia and fatty degeneration; microscopically, fatty changes found chiefly at centres of lobules. Spleen normal in size and structure. Kidneys showed signs of commencing interstitial nephritis; considerable congestion in the capillaries. Stomach dilated, its mucous membrane pale and in places atrophied. Intestines showed patches of congestion and in places small haemorrhages. Marrow from femur deep red in colour and semi-fluid in consistence. Microscopic examination of marrow showed no trace of fat cells, these being completely replaced by blood corpuscles of various kinds and sizes. These corpuscles presented no very definite arrangement and consisted of (*a*) leucocytes with single oval nuclei and clear plasma (marrow cells). In some cases the plasma contained coarse oxyphile granules, giving the corpuscles the appearance of the eosinophile corpuscle normally found in the blood. (*b*) Large numbers of nucleated red blood corpuscles, ranging in size from that of an ordinary red disc to the very large corpuscles (giant cells) which often contained several red blood corpuscles in their interiors. Nuclei usually single; sometimes two, sometimes three in number. Some corpuscles contained coarse granules, making them look like eosinophile cells; if they were such, they were nucleated red blood corpuscle eosinophile cells, and not eosinophile cells of the leucocyte class. (*c*) Large numbers of red blood corpuscles. (*d*) Lymphocytes (small mononucleated leucocytes), sometimes solitary, sometimes collected into small groups.

Sections from various organs were treated with potassium

ferrocyanide and hydrochloric acid, so as to demonstrate any deposit of iron pigment that might exist. In the liver this deposit was considerable, both in the capillaries and in the liver cells. In the capillaries it appeared as small dark blue masses and in the hepatic cells in a much finer state of division. This pigment was most abundant in the cells at the outer parts of the lobules. In the spleen only a very few cells contained pigment, and the same applied to the epithelium of the kidneys. In the bone marrow there was a moderate deposit of iron, but it was impossible to state in what cells it was contained.

Case 2. Mrs. S., *aet.* 30. Died Feb. 2, 1895. A history of gradually increasing weakness, pallor, emaciation, vomiting, diarrhoea. Duration of illness about one year. Urine contained a trace of albumin. Blood, (*a*) a month before death—red corpuscles 30 per cent., haemoglobin 35 per cent.; (*b*) a day before death—red corpuscles 16·3 per cent., haemoglobin 17 per cent.

Post-mortem examination.—Pericardium contained 3½ ozs. clear serum. Heart (11½ ozs.) had no external fat, muscle presented no appearance of fatty degeneration. Lungs, emphysematous and oedematous. Liver (49 ozs.) presented no fatty change. Spleen (3¾ ozs.) normal. Left kidney markedly cirrhosed, right kidney showed commencing cirrhosis. Suprarenal capsules normal. Mesenteric glands slightly enlarged. No specimen of bone marrow.

Deposit of iron pigment in the liver cells was very marked Present also to a slight degree in the capillaries. No iron pigment in the other organs.

Case 3.[1] M. T., *aet* 52. Died May 7, 1892. Symptoms were progressive weakness, pallor, palpitation, breathlessness, oedema of feet, frequent attacks of vomiting. No albumin in urine, no history of haemorrhages. Duration of illness about two years. Red corpuscles 10 per cent., haemoglobin "showed a marked reduction."

Post-mortem examination.—Heart (16 ozs.) healthy except for a pretty considerable fatty degeneration of its muscle fibre.

[1] This case was reported by Dr. Gemmell and Dr. Steven at a meeting of the Glasgow Pathological and Clinical Society, May 9, 1892. (*See Glas. Med. Jour.*, October, 1892.)

Liver (75 ozs.) slightly enlarged, fatty degeneration of hepatic cells at centres of lobules. Spleen (6½ ozs.) soft, deep red in colour. Kidneys normal. Lungs oedematous. Ventricles of brain distended with fluid. Marrow of femur red in colour, semi-fluid in consistence.

Marked deposit of iron pigment in liver cells; deposit in capillaries slight. Practically no deposit in other organs.

Case 4. J. R., *aet.* 19. Died August 26, 1896. Case of profound anaemia with symptoms of headache, giddiness, breathlessness, pallor, prostration, constipation. Duration of illness about eight weeks: it seemed to start from an attack of acute tonsillitis. History of chronic purulent discharge from one ear. Blood corpuscles 21 per cent.; haemoglobin 18 per cent. No relative excess of white corpuscles.

Post-mortem examination.—Heart (14 ozs.) enlarged, pale, with appearances of fatty degeneration. Liver (45 ozs.) showed moderate fatty degeneration. Spleen (4 ozs.), kidneys, suprarenals, stomach and intestine practically normal. The marrow in the femur was red in colour and microscopically the same kinds of corpuscles as described in case 1 were seen. Here, however, the fat cells were considerably more in evidence, they not yet having been displaced by the invading corpuscles. There was also a fairly large proportion of marrow cells; but what struck one most was the large number of lymphocytes collected together in places so as to form distinct groups. There were almost none of the large cells containing yellow pigment masses, met with in some of the other cases.

Liver contained a considerable deposit of iron pigment, present in the capillaries but in much greater abundance in the hepatic cells. In splenic pulp some iron pigment both in the white corpuscles and in the spaces between them; none in kidneys or suprarenals.

Case 5. C. G., *aet.* 29. Died December 24, 1894. Illness had a duration of five months. It dated from a confinement during which there was a very considerable amount of haemorrhage. Symptoms were progressive weakness, pallor, oedema, vomiting, giddiness. Red corpuscles 20 per cent., they presented great irregularity in shape, microcytes were present; haemoglobin 21 per cent.

Post-mortem examination.—Pericardium and left pleural cavity each contained several ounces of clear serum. Heart (12¾ ozs.) increased in size and external fat much greater than normal; muscle wall soft and pale and the seat of extensive fatty degeneration; valves and coronary arteries healthy. Lungs oedematous. Liver (70 ozs.) enlarged, with marked fatty degeneration especially at centres of lobules. Spleen (6½ ozs.) soft, deep red in colour, malpighian corpuscles larger than normal. In intestine the solitary follicles near to ileo-colic valve unduly prominent. Glands of stomach slightly atrophied, with slight increase of the connective tissue round about them. Kidneys, suprarenals and pancreas all healthy. Marrow of femur reddish in colour and semi-fluid in consistence; appearances microscopically similar to those in case 1. Here, however, there was possibly a slightly larger proportion of marrow cells.

Deposit of iron pigment in liver considerable; more marked in hepatic cells than in capillaries. No deposit in any other organs.

Case 6. Mrs. F., *aet.* 31. Died March 18, 1897. Case of profound anaemia of several months' duration. History of increasing weakness, pallor, emaciation, dating from a confinement during which patient lost a considerable quantity of blood. On several occasions during the illness there were haemorrhages from the bowels. Blood examined a week before death—red corpuscles 16 per cent., haemoglobin 15 per cent., white corpuscles 1 in 44.

Post-mortem examination.—Pericardium contained 3 ounces of clear serum. Heart (9 ozs.) soft and flaccid; its muscle presented appearances of fatty degeneration. Liver (61 ozs.) pale and soft; fatty degeneration in many of the hepatic cells, especially those at centres of lobules. Spleen (8½ ozs.) considerably enlarged; pulp packed with blood corpuscles. Mesenteric glands enlarged, soft and pale, but structurally quite normal. Kidneys, suprarenals, pancreas, stomach and intestines presented normal appearances. Marrow from femur salmon-coloured and semi-fluid; microscopic appearances similar to those of case 5.

Deposit of iron pigment in liver very slight, less marked in

hepatic cells than in the capillaries. No pigment to be seen in other organs.

Case 7. A. M., *aet.* 41. Died Dec. 28, 1896. Case characterized by progressive weakness, breathlessness, palpitation, oedema of feet and legs, pallor of skin and mucous membranes—all of about twelve months' duration. Enlargement of cardiac, hepatic and splenic areas; evidence of mitral incompetence, trace of albumin in the urine, haemorrhages into fundi oculorum. Three months before onset of illness a severe attack of diarrhoea, with blood in the motions, lasting for three weeks. For a time great improvement under treatment, as seen by examinations of the blood:

(*a*) Five months after onset of illness, red corpuscles 21 per cent., haemoglobin 18 per cent.
(*b*) Three months later, red corpuscles 65 per cent., haemoglobin 70 per cent.
(*c*) Three months later still, red corpuscles 27 per cent., haemoglobin 25 per cent.
(*d*) A week before death, red corpuscles 16 per cent., haemoglobin 12 per cent.

Post-mortem examination—Heart (17 ozs.) enlarged, with sub-pericardial fat slightly in excess. Both ventricles dilated and left somewhat hypertrophied. Muscle tissue pale and soft, the seat of considerable fatty degeneration. Mitral valve had some vegetations along the edges of its curtains. Lungs oedematous and bronchial mucous membranes congested. Liver (78 ozs.) enlarged, soft, pale, with fatty degeneration in the cells at centres of lobules. Spleen (13½ ozs.) much enlarged; structure quite normal. Kidneys, pancreas and stomach all healthy. Mucous membrane of intestines was pale, and a superficial ulcer was to be seen near to the ileo-colic valve. Bone marrow from one of the ribs bright red in colour.

Liver showed but slight deposit of iron pigment, and that almost entirely confined to the capillaries. Kidneys had a very slight iron deposit in their convoluted tubules. Other organs were free from this pigment.

Case 8. T. R., *aet.* 60. Died Dec. 14, 1893. Symptoms were progressive weakness, pallor, drowsiness. Oedema of feet

and signs of fluid in both pleural cavities. Patient had suffered for twenty-six years from bleeding piles. Blood examined three weeks before death—red corpuscles 23 per cent., haemoglobin 25 per cent.

Post-mortem examination.—Considerable serous effusion into pericardium, both pleural cavities and into abdominal cavity. Heart (16½ ozs.) enlarged, external fat very much increased; muscular tissue pale and flabby, having undergone considerable fatty degeneration. Lungs oedematous. Liver (44½ ozs.) small and pale; considerable fatty degeneration of the hepatic cells. Spleen (2½ ozs.) quite normal. Kidneys, suprarenals, stomach and intestines also normal. Marrow from femur semi-fluid and red in colour; microscopic appearances similar to those described in case 5.

Deposit of iron pigment in the liver, though quite distinct, was by no means abundant. It was more marked in the capillaries than in the hepatic cells, in which it appeared more as a diffuse stain than as a finely granular deposit. In the kidneys there was a distinct deposit in the epithelium of convoluted tubules; practically none in any of the other organs.

Case 9. J. M., *aet.* 45. Died July 30, 1894. Case of anaemia of four years' duration, characterized by progressive weakness, pallor, breathlessness, palpitation, oedema of feet and eyelids. Trace of albumin in urine. Patient had been subject to chronic bronchitis for twenty years. Blood examined shortly before death—red corpuscles 18·6 per cent., haemoglobin 20 per cent.

Post-mortem examination.—Pericardium, left pleural cavity and abdominal cavity each contained several ounces of brown-coloured serum. Heart (10½ ozs.) soft and flabby, external fat increased, but muscle fibres free from fatty changes. Lungs oedematous. Liver (60 ozs.) showed moderate fatty degeneration. Spleen (12 ozs.) much enlarged, soft, in structure quite normal. Both kidneys slightly enlarged, with slight increase of the connective tissue elements, suggesting a commencing interstitial nephritis. Bronchial lymphatic glands enlarged and the seats of minute extravasations of blood. Stomach showed atrophy in many of the gastric glands. Nothing special to note in pancreas, suprarenal capsules or thyroid

gland. Brain very pale, its ventricles distended with brown-coloured serum. Marrow from femur had semi-fluid consistence and bright red colour; its fat cells had been entirely displaced; there was a fair proportion of marrow cells, and otherwise the appearances were similar to those in case 6.

Liver contained a considerable deposit of iron pigment both in the capillaries and in the hepatic cells. Slight deposit in renal and intestinal epithelium as well as in the lymphatic glands.

Case 10. Mrs. B., *aet.* 26. Died June 11, 1896. A case of cardiac failure with signs of mitral incompetence; albumin and blood in urine, considerable fluid effusions into pericardial, pleural and abdominal cavities. There was great pallor and nutrition generally was much impaired. Bleedings from gums, bowels and air passages. Small ecchymoses in the legs. The condition of blood was not noted.

Post-mortem examination.—Large quantities of serous fluid in pericardial, pleural and abdominal cavities. Heart (16 ozs.) dilated in both ventricles; valvular structures healthy; muscle fibres free from fatty change. Passive hyperaemia and oedema of both lungs; large areas occupied with haemorrhagic infarctions not obviously of embolic origin. Liver (43 ozs.) presented a marked fatty degeneration, especially in the central parts of the lobules. Spleen (6 ozs.) much congested; microscopically its pulp was seen packed full of red blood corpuscles. Kidneys showed marked hyperaemia of their vessels. Intestines hyperaemic with submucous haemorrhages. Pancreas and suprarenals normal. Marrow from femur red in colour; its fat cells in some places quite intact, in others entirely replaced by blood corpuscles; a fair proportion of marrow cells and a considerable number of very large nucleated red corpuscles (gigantoblasts) noted; the rest of the tissue consisted of red corpuscles and nucleated red blood corpuscles.

A considerable deposit of iron pigment in the liver, most marked in the hepatic cells, especially those at the external two-thirds of the lobules; no deposit in any of the other organs.

Case 11. A. M. Died June 5, 1896. A case where the prominent symptoms were profound weakness, pallor, occasional

attacks of diarrhoea and bleeding at the nose. A less degree of anaemia had existed for some four or five years, dating from an attack of rheumatism, since which time there had been shortness of breath and other evidence of valvular disease of the heart. Red corpuscles 20 per cent., haemoglobin 10 per cent.

Post-mortem examination.—Heart (16 ozs.) considerably enlarged, its muscle soft and pale, with the appearances of fatty degeneration. Numerous minute haemorrhages were found scattered throughout its substance. The mitral and tricuspid valves were thickened and deformed, evidently the result of chronic endocarditis. Minute haemorrhages found on the surface of the lungs. Liver (60 ozs.) hyperaemic, considerable fatty change in the hepatic cells. Kidneys much congested; both had appearances of commencing interstitial nephritis. Spleen (7 ozs) enlarged and dark red in colour. Numerous areas of congestion in alimentary tract; in caecum several small ulcers, each about the size of a millet seed. Considerable atrophy in the glandular epithelium of the stomach. Suprarenals and thyroid normal. Marrow from femur red in colour; microscopic appearances much the same as those in case 6.

Deposit of iron pigment in liver very slight; absent in other organs.

Case 12. A. Z., *aet.* 57. Died Jan. 22, 1892. A case of heart disease (mitral incompetence), of at least two years' standing, following an attack of rheumatism. For some months before death signs of cardiac failure with increasing anaemia. Attacks of epistaxis frequent and a purpuric eruption was present on the legs. Red corpuscles 24 per cent., haemoglobin 22 per cent.

Post-mortem examination.—Subcutaneous fat abundant. Pericardium contained six ounces of clear serum. Heart (14½ ozs.) enlarged and its muscle tissue showed distinct signs of fatty degeneration. Liver (51 ozs.) pale, only slight fatty change in the hepatic cells. Spleen (4 ozs.), kidneys and suprarenal capsules were quite normal. Stomach enlarged; there was to be noted in its anterior a small ulcer which microscopic examination proved to be cancerous. Marrow from femur was a mass of yellow fat and contained none of

the corpuscular elements found in red marrow. Practically no deposit of iron pigment in any of the organs.

Case 13. M. F., *aet.* 55. Died Nov. 11, 1893. A case of syphilitic disease of the liver associated with chronic bronchitis and obstinate constipation, of some months' duration. Pallor of skin and mucous membranes very pronounced; considerable oedema of subcutaneous tissues. Red corpuscles 54 per cent., haemoglobin 17 per cent.

Post-mortem examination.—Abdominal wall contained a layer of fat two inches thick; peritoneum, mesentery and omentum likewise loaded with fat. Heart (13 ozs.) pale, but it showed no fatty changes. Liver (75 ozs.) considerably enlarged and on section seen to be studded with white nodules varying in size from that of a hazel nut to that of a split pea. Microscopic examination showed these to consist of inflammatory cells displacing and destroying considerable areas of hepatic tissue: the appearances strongly suggested syphilitic disease of the liver; fatty degeneration was noted in many of the remaining liver cells. Spleen (13½ ozs.) enlarged; it contained some nodules similar to those in the liver. Kidneys, stomach and intestines healthy. Marrow from femur semi-fluid and red in colour.

Amount of iron pigment in liver very slight; it was present in the capillaries as much as in the liver cells.

Case 14. J. B., *aet.* 35. Died Oct. 6, 1896. A typical case of Addison's disease of twelve months' duration. Red corpuscles 88 per cent., haemoglobin 70 per cent., slight increase in number of white corpuscles.

Post-mortem examination.—Some old tuberculous disease at apices of both lungs. Suprarenal capsules almost completely replaced by caseating tuberculous masses. Some of the abdominal glands also caseous. Heart (7 ozs.), liver (44 ozs.), spleen (7½ ozs.), stomach, intestines and kidneys all much congested but structurally normal. Marrow from femur slightly red in colour and microscopic examination confirmed the suggestion of a commencing "lymphoid" change. In places the fat cells were found quite intact, but in other parts of the sections these were becoming replaced by red corpuscles and nucleated red corpuscles. Not many marrow cells were in evidence, but there

were to be noted some much larger cells which contained opaque yellow masses. Whether these last were nucleated red corpuscles or marrow cells much enlarged, it was difficult to say.

The spleen was the only organ with a deposit of iron pigment, but in it the amount was very considerable. The pigment granules were seen in the white corpuscles of the pulp as well as in large masses lying outside of these cells.

Case 15. Mrs. D., *aet* 34. Died March 9, 1897. A case of Hodgkin's disease of some two months' duration. There was enlargement of glands in the neck, armpits and groins; spleen and liver were likewise enlarged. There was albumin and blood in the urine, oedema at the ankles, bleeding at the nose and purpuric patches on the thighs. Red corpuscles 72 per cent., haemoglobin 50 per cent., white corpuscles 1 in 33.

Post-mortem examination.—Heart (12 ozs.) soft and pale, but otherwise normal. Lungs oedematous. Liver (109 ozs.) greatly enlarged; with the microscope it was seen to be infiltrated throughout with lymphoid cells, which, in places, especially round the vessels, were collected in such masses as to entirely replace the hepatic cells. Kidneys both enlarged; they also presented considerable infiltration with lymphoid cells. Spleen (36 ozs.) greatly enlarged and of a salmon colour. The pulp was full of cells like ordinary white blood corpuscles; malpighian bodies not increased in size. Lymphatic glands all over the body enlarged but structurally quite normal. Pancreas slightly infiltrated with lymphocytes. Suprarenal capsules, stomach and intestines normal. Marrow from femur was salmon-coloured; unfortunately there was no opportunity to examine it microscopically. No deposit of iron pigment in any of the organs.

We have, then, presented to us in these fifteen cases a variety of anaemias, and the difficulty which remains is their classification. It is with this before us that we now proceed to consider the meanings of the various morbid changes just recorded; and as the deposit of iron in the liver has specially attracted attention, we shall consider it first.

We have already seen how an excessive destruction of red corpuscles in the portal circulation produces a deposit of iron pigment in the liver cells. And we know that a precisely similar condition of the liver is recognized as being the characteristic, and possibly the only, constant morbid change met with in pernicious anaemia. It seems, therefore, quite reasonable to conclude—especially in absence of definite proof to the contrary—that pernicious anaemia is likewise due to excessive destruction of blood in the portal area. That this iron in the hepatic cells is not derived from internal haemorrhages is pretty certain; for the iron from extravasated blood is carried to the spleen rather than to the liver, and if any of it does appear in the liver it is as small masses in the capillaries and not as fine granules in the hepatic cells.[1]

A marked deposit of iron in the hepatic cells, then, indicates an excessive destruction of red corpuscles, by some poison passing into the portal circulation from the alimentary tract. According to this view the pathology of our first three cases is quite clear: in each of them there was the large amount of iron in the liver cells and in each there was no visible cause for the anaemia. They are what we might call unequivocal cases of pernicious anaemia.

The six next cases, however, are not so easily classified; for, while corresponding to the above in their symptoms and physical signs, they differ, either in the post-mortem appearances or in their having a history of some possible "cause" for the anaemia. Thus, cases 4, 5 and 9 resemble our first three cases in there being in all of them a very considerable deposit of iron in the hepatic cells. But in case 4 there was the history of an acute tonsillitis as the starting-point of the illness, in case 9 there had been chronic bronchitis for twenty years, while in case 5 the anaemia dated from an haemorrhage during childbirth. But, again, iron pigment in the liver cells means destruction of red corpuscles in the portal circulation, therefore these three cases must also have had this destruction of blood in their portal circulation. The tonsillitis, then, of case 4, the bronchitis of case 9, and the haemorrhage of case 5 must be regarded, not as the causes of these anaemias, but

[1] Hunter, *Lancet*, 1892.

simply as producing a debility favourable to the production in the alimentary tract of certain poisons; and it is to these poisons that we must consider the anaemia to be due. We might have discounted as "accidental" the "causes" in cases 4 and 9, and called them cases of pernicious anaemia; but this could not be so in case 5, which seemed so directly dependent on a profuse haemorrhage. Case 5 is just the kind of case that has been denied the name "pernicious," and so I quote it to show that an anaemia may be a pernicious anaemia in spite of having had a history of haemorrhage.

The other three cases in this group, numbers 6, 7 and 8, resemble case 5 in also having a history of some loss of blood; but in none of the three was there much iron pigment in the liver cells. The anaemia in these cases, then, must in the meantime be looked upon as due to haemorrhage. It is to be noted, however, that the hepatic cells in none of them were quite free from iron pigment. In case 8, indeed, the pigment was fairly well marked, and, although not nearly so abundant as in case 5, there was quite sufficient to suggest some relationship between the two. We have no explanation here, however, as to why, in some cases, a haemorrhage is the starting-point of a rapidly increasing anaemia—which is not "pernicious"—while in others an equal loss of blood produces little or no effect.

The six cases still remaining seemed undoubtedly to be secondary anaemias. Cases 10, 11 and 12 were cases of heart disease; but while 11 and 12 had practically no iron pigment in the liver, in case 10 the deposit was as considerable as in case 1. During life there was no thought of case 10 being a primary anaemia, as may be concluded from the fact that the corpuscles in the blood were not enumerated. The congested condition of the organs, too, and the haemorrhages all correspond to the diagnosis of cardiac failure. But then the large deposit of iron in the liver cells means an excessive destruction of blood in the portal circulation; and so case 10 must be considered a case of heart disease in which pernicious anaemia appeared as a complication. In the last three cases—cases 13, 14 and 15—there was no iron pigment in the liver cells.

We have seen, then, that the anaemia of the first five cases

and of cases 9 and 10, is due to an excessive destruction of blood in the portal area, and in cases 6, 7 and 8—as far as we at present understand—to direct loss of blood through single or repeated haemorrhages. But in the five cases still remaining we must find another explanation, for in none of them was there any appreciable deposit of iron in the hepatic cells, and in none a history of haemorrhage. The cause of their anaemia must then have been due either to defective formation of blood or else to an increased destruction of blood brought about in a manner different from that caused by such a poison as toluylendiamin. In case 11, where the marrow of the femur was unaltered, the anaemia might have been due to defective formation of blood; but in the other four cases the change of the yellow marrow to red (which means an increased formation of red corpuscles) favours rather the view of an increased destruction of blood. It is quite readily understood why in certain diseases there should be this increased destruction of red blood corpuscles. In heart disease the circulation is defective and there is an increase of waste product poisons in the blood. Addison's disease and syphilis are in all probability also due to a poison; and it must likewise be some poison which causes the overgrowth of the spleen and lymphatic glands in Hodgkin's disease. These poisons in the blood must have an injurious effect on the nutrition of the red corpuscles, and we have already seen that unhealthy red blood corpuscles are soon removed from the circulation and destroyed. But this process of blood destruction is of a totally different nature from that in the cases of pernicious anaemia. It applies more or less to the whole circulation, it is slow and chronic, and indeed just a part of the general tissue destruction which takes place in most wasting diseases. In blood destruction of this kind there is no increased deposit of iron in the liver cells.

The deposit of iron pigment in the other organs was but slight. When found in the renal epithelium in cases of pernicious anaemia, it is explained as being an excess of pigment, which, passing through the liver, reaches the general circulation, and is in the process of being excreted by the kidneys.[1] The pigment in the renal epithelium of all our cases was

[1] Hunter, *Lancet*, 1892.

variable and small in amount, and we need give it no special consideration.

Before leaving the subject of the deposit of iron in the tissues, I wish to note that the method of its demonstration by ferrocyanide of potassium and hydrochloric acid is somewhat uncertain and liable to lead to error. I frequently found that sections from different parts, and sometimes from the same parts of a liver, did not show the iron reaction equally well, and I had to examine many sections in a case to be certain as to a negative result. The reaction under ordinary circumstances does not take place when the iron is intimately combined with the protoplasm of the cells, as for example in the red blood corpuscles and in the tissues generally. But in some of my sections I found the nuclei of the hepatic and renal epithelial cells stained a light blue colour, due doubtless to the iron of these nuclei giving the reaction. This was probably caused by the use of too strong reagents. I feel sure, however, that my positive results were not due to a reaction from iron in chemical combination in the cell protoplasm, for then the deposit would not have appeared granular and it would not have limited itself to the cells at the outer parts of the lobules. In the cells whose nuclei turned blue the appearance was not that of a granular deposit but rather of a diffuse stain, and there was no appearance of any iron reaction in the plasma of the cells.

As regards the relationship between the amount of iron in the liver and the deficiency of haemoglobin and red blood corpuscles in these cases, one cannot draw any definite conclusion. In the first nine cases—those we might call the primary anaemias—one is struck by the very slight difference between the percentages of haemoglobin and of red corpuscles. The difference in none of the cases is greater than might be accounted for by the methods of estimation. In none of the cases with iron in the liver cells was there the great excess of haemoglobin over corpuscles said to be found in cases of pernicious anaemia; and in none of the cases following haemorrhage was the deficiency of haemoglobin much greater than that of the red blood corpuscles. But why in cases of pernicious anaemia should there be an excess of red colouring

matter in the general circulation when, according to the pathology we have been considering, this excess is confined to the portal circulation? We have seen that before the blood reaches the general circulation most of the free pigment is absorbed by the hepatic cells, and in our cases this seemed to be so, judging from the proportion of haemoglobin in the blood and the amount of iron pigment in the renal epithelium. Further, if we accept the view advanced by Hunter,[1] that the microcytes found in the blood in pernicious anaemia are products of blood destruction and not stages in the evolution of the red blood corpuscles—if we take this view, we should expect the microcytes likewise to be confined chiefly to the portal circulation. This corresponds with my own observations, which go to show that microcytes are not nearly so often found in the blood as some would have us believe.

Comparing these first nine cases—the primary, with the last five—the secondary anaemias, we find that in the latter the normal proportion of haemoglobin to red blood corpuscles no longer exists, but that the haemoglobin, in almost all the five cases, falls considerably short of the corpuscles. This state of matters accords with the view that a deficiency of red corpuscles is much more easily made good than a deficiency in haemoglobin.

The proportion of the white blood corpuscles present in the blood has been noted in so few of the cases, that we can draw no conclusions.

The other changes found in the general tissues as a result of anaemia were due chiefly to the defective blood supply. Fatty degeneration of the heart-muscle and liver-cells were the two most constant phenomena; and although these appearances were not found in all the cases, they were present in a very considerable proportion. There seems nothing to show why there should be this fatty change in some of the cases and not in others. I suppose we must fall back on the idea of a "predisposition" in the cases most affected.

We saw that in some of the cases there was atrophy of the gastric epithelium. This probably was also due to a defective blood supply, and the appearances suggested this rather than a destruction of the epithelial cells by an inflammatory process.

[1] Hunter, *Lancet*, 1892.

In four of the cases there was interstitial nephritis in greater or less degree. This nephritis may have been "accidental" or possibly due to the poison concerned in the production of the anaemia.

Of the changes in the tissues which are more intimately associated with blood formation, the most striking are those in the bone marrow. In case 2 the marrow was not examined and in case 7 only the marrow of the rib was seen; but in all the others, except case 12, the marrow of the femur showed, in a greater or less degree, the appearances of red marrow. In nearly all the cases this transformation of the yellow marrow into red was very complete, and the only cases in which any considerable number of fat cells persisted were cases 4, 10 and 14. This change in the marrow, however, is evidently not in direct proportion to the degree of anaemia. In case 14, where there was but little deficiency in the blood elements (red corpuscles 88 per cent., haemoglobin 70 per cent.), the fat spaces of the marrow were invaded to a very considerable extent by the red marrow cells. In case 12, on the other hand, where the anaemia was very pronounced (red corpuscles 24 per cent., haemoglobin 22 per cent.), there was no appearance of any such change. This surely means that in some cases the response to the demand for an increased supply of red corpuscles is much more ready than in others. Failure in blood formation would not then seem to be a frequent cause of anaemia. It may, however, be that treatment stimulates the bone marrow to a special activity and that this accounts for the temporary improvement, under treatment, in some cases of pernicious anaemia. When this activity is exhausted then the disease will rapidly get worse.

In considering the condition of the spleen in these fifteen cases we do not learn much, and it is very difficult to know what exactly determines its varying size. We say that poisons stimulate the leucocytes to multiply and that the spleen has to increase to produce them, or to store them. Theoretically, in pernicious anaemia, we should expect the spleen to be large; but this is not the case in the majority of our cases, and Hunter's[1] idea of the paroxysmal destruction of red blood

[1] Hunter, *Lancet*, 1892.

corpuscles is not a very convincing explanation of the small spleen so often found in this disease. Is it not more probable that while the poison of pernicious anaemia stimulates the white blood corpuscles to increase, it itself destroys the red corpuscles? It must surely at least affect their vitality, for otherwise no moderate leucocytosis would destroy them. In some of our cases enlarged lymphatic glands were found, but this has little bearing on the pathology of pernicious anaemia.

I have been endeavouring, then, in the foregoing pages, to point out that there is a certain relationship between all profound anaemias. They would seem to differ less in their physical signs than in their etiology, and it is the etiology which largely determines their pathological anatomy. Most of them are due in some measure to an excessive destruction of red blood corpuscles, and this in turn depends for its production and maintenance on a poison in some part of the circulation. The origin and nature of this poison have not yet been clearly defined, but we have seen that it differs in several respects in the different groups of cases. One of these groups is associated with, and probably the result of, certain wasting diseases, and its poison, which is in the general circulation, is slow and constant in its action. None of the iron liberated from the red blood corpuscles destroyed is deposited in the liver cells. In another group the poison seems to be absorbed from the alimentary tract and to be confined in its action to the portal circulation. In destroying the red corpuscles it liberates an iron pigment which is taken up by the hepatic cells, any small amount reaching the general circulation being deposited in the renal epithelium. There is yet a third group, in which, in physical aspect, the cases resemble very closely those last mentioned. They differ, however, in seeming to depend for their production on single or repeated haemorrhages and also in having little iron in the liver cells. The anaemia in some of these is doubtless due to the amount of blood lost; but in others, where a rapidly progressive anaemia follows one single haemorrhage, this explanation seems inadequate. It may be that certain cases have the capacity of recovery from an haemorrhage, while in others the efforts of the organism

altogether fail to make up the blood lost. It may be that, in these efforts of the organism at recovery, there lies the possibility of an increasing anaemia, for we have seen that following haemorrhage new blood corpuscles are sent into the circulation immature, and as such they readily succumb. If this goes on to any extent the anaemia will thereby be increased rather than diminished, for the products of corpuscle disintegration, in their turn, will act as a poison to other blood corpuscles.

The term "pernicious," then, as applied to anaemias is unsuitable. If we apply it only to those cases with an excess of iron in the liver cells, the term will be of no use clinically; for we have seen that of cases almost exactly similar (cases 5, 6, 7 and 8), one had abundant iron in the liver, while some of the others had practically none at all. If, on the other hand, we apply the term to the cases that are "progressive" it is equally unsuitable and indefinite. The classification of the anaemias is doubtless difficult, but in the meantime it would seem better to classify them as "primary"—those with their own "cause," and "secondary"—those which occur in the course of another well-defined disease. Even then some cases will be found having the features of both classes, and some, while starting in one class will pass into the other.