THE LETTSOMIAN LECTURES

ON

ANÆMIA:

ITS PATHOLOGY, SYMPTOMS, AND TREATMENT.

Delivered before the Medical Society of London.

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LECTURE I.

The Composition of the Blood.—The Plasma.—The Formed Elements.—The Red Corpuscles; their Sources, Life-history, and Fate.—The Seats of Blood Destruction.—The Colourless Corpuscles; their Sources, Functions, and Fate.—Blood Platelets.—Elementary Granules.—Hæmoglobin.—The Pathology of Anæmia.—Defective Hæmogenesis or Excessive Hæmolysis, or the two combined—Anæmia, Secondary and Symptomatic, or Primary and Idiopathic.

MR. PRESIDENT AND GENTLEMEN,—In choosing anæmia as the subject of these lectures I have been influenced by the following considerations:

1. Anæmia is a condition which we have to take into consideration almost every day of our lives, and has an interest, therefore, for those practising in every department of medicine. 2. It is a disease which has in recent years received a great deal of careful study at the hands of some of the ablest investigators in our own and other countries; and 3, because it is a subject to which I have myself devoted considerable attention. It has seemed to me that the time has come when the careful and detailed work which has been accomplished should be collated, and thus allow of our taking a comprehensive view of the whole subject. How imperfectly I have done this I am only too fully conscious, but I still hope that the bringing together the labours of many workers on a subject of great intricacy will not be without some value. I must apologise in the next place for some elementary details with which you are all acquainted, but with which I am obliged to preface the consideration of anæmia, for unless we define what we agree to consider the normal condition of the blood, we cannot point out what are departures from it.

Should the blood be regarded as an internal medium or as a tissue? The majority of writers and physiologists are inclined to follow Claude Bernard, that the blood is not to be regarded as a fluid tissue, but as an internal medium, bearing the same relation to the constituent tissues as does the external medium to the individual. If we take this view, it must, I think, be the plasma or lymph rather than the blood itself, which should be regarded as an internal medium, seeing that it is the plasma alone which penetrates into the intercellular spaces, bathes the cells with fluid, and thus constitutes what Dr. Harry Campbell has happily and aptly termed: "the internal cell environment."¹ On the other hand, arguments have been advanced in favour of regarding the blood as a tissue, especially recently, by Dr. William Hunter.² Whether regarded as a medium or a tissue, a mechanism exists which in all ordinary circumstances maintains a standard, within certain limits, both as regards its quantity and quality.

With regard to the quantity of blood, it has been shown to vary in relation to the body weight in different animals, and that in man it is about one-thirteenth of the body weight. The quantity of blood is liable to constant variations, whilst oscillating round an equilibrium, but unfortunately we have no means by which, clinically, we can estimate the quantity. The mere capacity and fulness of the superficial vessels teach us nothing of the volume of the blood, as we cannot at the same time estimate the amount of blood contained in the capillaries and small veins of the abdominal viscera.

The Composition of the Blood.—The normal blood consists of formed elements floating in a fluid—the plasma.

The Plasma or Liqueur Sanguinis.—The plasma is a clear fluid of a faint straw colour, consisting of fibrin, or fibrin factors, and serum. It is alkaline in reaction, owing to the presence of disodic phosphate and sodium bicarbonate. The reaction of the blood has received but little attention, but von Jaksch has shown that it is diminished in pernicious anæmia, leukæmia, and in fever;³ and Haycraft states that the reaction of the blood in different conditions may vary as widely as that of the urine. The specific gravity of the plasma varies from 1026 to 1029. The specific gravity of the blood as a whole varies from 1035 to 1068 (Lloyd Jones), or from 1045 to 1075 (Landois). Some valuable observations on the specific gravity of the blood have recently been made by Dr. Lloyd Jones.⁴ According to his observations, it is highest at birth, reaches its minimum between the second week and second year, and rises gradually to a point attained in the male between the ages of 35 and 45 (1058.5), and in the female after the climacteric (1054.5). It tends to be higher in the male than in the female, and is probably only the same in the two sexes at the extremes of life. The effect of pregnancy is to diminish the specific gravity to a slight extent within the limits of health. Solid and liquid food cause a fall in the specific gravity, if no alcohol is taken. Gentle exercise causes a fall, but violent exercise and free perspiration cause a rise. It is subject to "diurnal variation," tending to fall during the day and rise during the night's rest. These observations appear to me important, as the specific gravity of the blood is likely to cause an alteration in the red blood corpuscles. Ehrlich has shown that a change of the red corpuscles from the normal to that of degeneration, as displayed by staining with eosin-hæmatoxylin, can be demonstrated in simple traumatic anæmia a very short time after the bleeding. It thus appears, according to him, that the diluted condition of anæmic serum, as such, exercises an injurious influence upon many blood discs. In pernicious anæmia the specific gravity is usually between 1028 and 1038. With fibrin and its formation we shall not concern ourselves, merely remarking that the amount of fibrin seems to present remarkable variations in anæmic conditions. The serum consists of proteids—serum-albumin and paraglobulin (or serum-globulin) fats, extractives, salts, water, and a peculiar yellow pigment (choletelin—MacMunn), on which its colour depends. In anæmia, especially in its severe forms—such as hæmorrhage—there is a diminution in the solids and an increase in the water, so that, temporarily at least, a condition of hydræmia exists. The albuminous constituents, of which hæmoglobin is the chief, are greatly diminished. I do not propose to dwell on the chemical composition of the blood, which will be found very fully dealt with by Dr. Sidney Coupland in his Gulstonian Lectures.⁵

The Formed Elements.—The coloured or red blood corpuscles are biconcave discs of yellow colour. Their average size is 7.5 μ (micromillimètres) in diameter, but they range between 6.5 and 8.5 to 9 μ , with a thickness of 1.9 μ . The percentage of less or greater diameter varies in different individuals. In the newly born and very young child the range is very great, from 3.3 μ to 10.3 μ , and in certain diseased conditions there is a reversion to this embryonic or infantile type. In such cases the range between the smallest and largest forms may be from 2.5 μ to 14 μ . To these aberrant forms the terms microcytes and megalocytes have been applied (Osler). The red corpuscles consist of a framework or stroma composed of globulin, which is impregnated with a red pigment consisting of hæmoglobin, which is loosely associated with the stroma from which it may be separated. The stroma appears to have a spongy structure, which soaks up the hæmoglobin. The coloured corpuscles have no distinct membrane. The hæmoglobin may be split up into a proteid belonging to the globulin group, and into a pigment containing iron—hæmatin. The red corpuscles not only vary in size, but in colour, according to the amount of hæmoglobin they contain. This variation in colour, which can scarcely be observed in health, becomes very conspicuous in anæmia. Apart from the quantity of hæmoglobin in a corpuscle, there is no evidence of variations in its quality be-

¹ *The Causation of Disease*, by Harry Campbell, M.D. Lewis, 1889, p. 18.

² *Transfusion*, BRITISH MEDICAL JOURNAL, July 20th, 1889.

³ *Zetschr. f. klin. Med.*, xiii, 8, 350.

⁴ *Journal of Physiology*, 1887.

BRITISH MEDICAL JOURNAL, 1881.

yond the amount of oxygen combined with it, and which constitutes the difference between the bright scarlet colour of arterial blood and the purplish colour of venous blood.

Nucleated red corpuscles are found in the embryo, but never, as far as I am aware, in post-embryonal life in conditions of health. As regards the number of red corpuscles in healthy blood, 5,000,000 per cubic millimetre is generally accepted as the average; but, as Hayem,⁶ Laache,⁷ and others have pointed out, the residents in towns may have only 4,600,000 or 4,500,000 per cubic millimetre when in good general health. The number 5,000,000 per cubic millimetre may be exceeded, and taking the two sexes together the range of health may be said to extend from 5,500,000 to 4,000,000 per cubic millimetre; or, taking the sexes separately, in men the range is from 5,500,000 to 4,500,000, and in women from 5,000,000 to 4,000,000. In this country, where the estimations are usually made by Gowers's very convenient hæmacytometer, the corpuscles are expressed in percentages of the normal—the normal = 100. Expressed centesimally, the range of the two sexes is from 110 to 80; or of the sexes separately, that of men ranges from 110 to 90 per cent., that of women from 100 to 80 per cent.⁸

The Sources of the Red Blood Corpuscles—Hæmogenesis.—At an early stage of embryonal life, when blood makes its appearance, it is a colourless fluid containing only white corpuscles (each with a nucleus), which are derived from certain cells of the mesoblast. These white corpuscles change into red ones, which become flattened, and their protoplasm gets homogeneous and of a yellow colour. All through embryonal life new white corpuscles are transformed into red ones. In the embryo of man and mammals these red corpuscles retain their nuclei for some time, but ultimately lose them. New nucleated red blood corpuscles are, however, formed by division of old red corpuscles.⁹ Such is a concise statement by Dr. Klein of the development of the red corpuscles during embryonal life, and no differences of opinion practically exist on this subject. We see foreshadowed here the two modes of development of the red corpuscles believed by observers to take place in post-embryonal life, that is, from the colourless blood corpuscles and from pre-existing red corpuscles, each of which finds supporters. Whilst many histologists and physiologists believe that the red corpuscles are transformed leucocytes, of late a growing uncertainty has spread whether the evidence upon this point is conclusive. Practically all are agreed that a nucleated red blood corpuscle is the immediate precursor of the fully developed non-nucleated red blood corpuscle. The seats of origin of the red corpuscles are generally believed to be the bone marrow, the spleen, and the lymphatic glands, whilst some believe the thyroid body has blood-producing powers.

The tendency of all recent researches following the teaching of Neumann has been to narrow down the birthplace of the red corpuscles in man to the marrow of the bones, but we shall have to pass in review the evidence in favour of the other asserted sources. That the marrow takes a very active share, or the chief share, in blood production is now universally admitted, but the details of the development of the red corpuscles are still much disputed. The evidence that the marrow is concerned in the production of the red corpuscles is mainly that nucleated red corpuscles are always found in this situation, and that their numbers are enormously increased when blood formation is in a state of high activity. Moreover, when hæmogenesis is very active, the yellow marrow of the diaphyses of the long bones and the cancellous tissue of the flat bones disappears, and is replaced by red marrow, having the colour and consistence of raspberry jelly.

The development of the red corpuscles being admitted to take place in the marrow, there are differences of opinion as to the mode in which it occurs. It is believed by many that the red corpuscles arise from the parenchyma of the marrow, either from marrow cells (Neumann, Osler, etc.), or from leucocytes (Kölliker, Fuhrner, Malassez and Gibson), and that

their mode of origin is *extravascular*, whilst Bizzozero and Torre, and more recently Denys,¹⁰ believe that it takes place within the lumen of the vessels, that is, that it is *intravascular*. Bizzozero has modified his original opinion in the light of his further observations. At one time he believed that the red corpuscles developed out of colourless corpuscles, the latter passing out of the marrow pulp into the veins of the marrow before assuming hæmoglobin (Gibson). Bizzozero and Denys further agree in recognising an early or immature stage of the red corpuscles in certain cells within the vessels which they call "erythroblasts," but they differ in one important particular in that Denys believes the erythroblasts are transforming leucocytes, whilst Bizzozero maintains that the erythroblasts are young red blood corpuscles containing hæmoglobin.

We owe so much of our knowledge of the structure and functions of the marrow to Bizzozero's investigations, and his latest paper¹¹ appeared to me to place the facts so clearly and capable of verification that I have obtained the assistance of Dr. James Galloway to carry out a research on the marrow on Bizzozero's lines. These confirm in all essential particulars the conclusions arrived at by Bizzozero, and I have the opportunity, thanks to Dr. Galloway's help, of illustrating the mode of development of the red corpuscles.

In only one particular have we been unable to follow Bizzozero, and that is on the condition of the marrow in animals rendered anæmic by bleeding, and this is owing to the restriction which is placed on experimental research on animals in this country. I have not had the time to obtain the necessary licence by which we are fettered in this country. The observations we have made have been on fowls and pigeons, as Bizzozero and others have found that the marrow of birds is peculiarly favourable for the study of blood development, the ovoid shape and nucleated condition of the red corpuscles rendering confusion between them and other cells more easily avoidable. Indeed, one may go so far as to say that the marrow of birds should be previously studied before one enters upon the investigation of human marrow. Neumann, Malassez, Geelmuyden, and Gibson believe the red corpuscles originate from marrow cells, though the former at one time thought they arose from leucocytes in the bone marrow.

Gibson, whose paper¹² is a valuable contribution to medicine, from which I have gained much information, has described very fully and carefully the changes that take place in their development from marrow cells. He describes a thin ring containing hæmoglobin at the periphery of the cell; this gradually increases so as to fill the whole space between the cell envelope and the nucleus, and as the hæmoglobin-tinted perinuclear substance increases in amount, the nucleus appears to become smaller and to retreat towards the centre of the cell, the cell as a whole at the same time becoming smaller. He believes that the nucleus is the active agent in attracting the hæmoglobin to the cell, and that when its function is fulfilled—that is, when the cell is fully charged with hæmoglobin—being of no further service, it disappears. He believes also that nucleated red blood corpuscles arise in the marrow from white blood corpuscles, and that the white cells which are transformed into nucleated red cells in the bone marrow are not necessarily all produced there, conjecturing that many of them are produced in the lymphatic glands and carried to the bone marrow, there to enlarge and pass through the various stages of transformation.

Osler¹³ also believes that the nucleated red blood corpuscle is derived from the clear-bordered narrow cell, there being, in his opinion, no essential difference between the protoplasm of the two cells. He further thinks that the colourless marrow cells are derived from small lymphoid elements resembling free nuclei ("primary lymph cells," "protolucocytes"). The transformation of the nucleated red cell into ordinary red blood corpuscle is brought about by the gradual disappearance of the nucleus. Osler, too, believes in the development of red corpuscles within the large myeloid plaques, and in the elongated cells of the stroma of the marrow, in the

⁶ G. Hayem, *Du Sang*. Paris: G. Masson, 1889.

⁷ *Die Anæmia*, von S. Laache, Christiania, 1883.

⁸ The percentage may be expressed in millions per cubic millimetre by multiplying by 50,000; or millions per cubic millimetre as percentage, by dividing by that number.

⁹ Klein's *Elements of Histology*, p. 14.

¹⁰ *La Structure de la Moëlle et la Genèse du Sang chez les Oiseaux*, *La Cellule*, tome iv, fasc. 1.

¹¹ *Archiv für mikroskopische Anatomie*, Band xxxv, Heft 4, July, 1890, S. 424.

¹² J. Lockhart Gibson, On Blood-Forming Organs and Blood Formation, *Journal of Anatomy and Physiology*, vol. xx, 1886.

¹³ *BRITISH MEDICAL JOURNAL*, 1886, p. 862.

latter case thus supporting the contention of Schäfer¹⁴ that red corpuscles may develop within connective tissue corpuscles.

To return to Bizzozero's observations and our own. Bizzozero advises that the fresh marrow should be teased and examined in its natural fluid, and in a simple solution of sodium chloride (0.7 per cent.), and preparations of fresh marrow hardened in various ways should be examined unstained, and stained with various reagents. Each of these methods is necessary as a control to artificial changes which may be occasioned by the modes of treatment. It appears to me particularly necessary that sections of marrow, suitably hardened, should be always examined, as in teased preparations it is difficult or impossible to determine whence cells which are taken to be developing blood corpuscles come from, whether from within the blood vessels or from the parenchyma of the marrow. When a section of marrow (fowl's) is examined with a low power, it is noticed that the vascular network in the long bones consists of a few arteries running in the long axis; from these a few small arteries are given off at an acute angle, which course thence towards the periphery of the marrow, whence they lose themselves in a few narrow capillary vessels. These arterial capillaries open into a close network of very wide venous capillaries which, anastomosing with one another, wander through the whole marrow in a centripetal direction, and empty themselves into large veins which run parallel with the arteries in the long axis of the marrow. The arrangement may be compared to a wheel, the arterial and venous trunks corresponding with the axis and the venous capillaries with the spokes. The great disproportion between the calibre of the arterioles and venules, which is very striking, occasions as a necessity that the blood stream must be peculiarly slow, and therefore favourable to changes taking place within the venules. Moreover, when anæmia is produced, the fat cells are absorbed, allowing of an increase in the parenchyma (lymphatic tissue) and dilatation of the venules. Bizzozero and Denys assert that these capillaries have distinct walls, their outlines being mapped out by a regular border, interrupted here and there by oval elongated nuclei. We can confirm this statement, which is an important one. Some observers believe these venous capillaries have no walls, but are simply tunnelled out of the parenchyma, so that no boundary exists between the parenchyma and the venules.

In extreme degrees of anæmia the venules become so much dilated that they are in many places actually in contact with one another. With sections of marrow hardened in Müller's fluid or in corrosive sublimate, and stained with picric acid, alcohol, and hæmatoxylin, it can be ascertained that there are no hæmoglobin-containing cells external to the blood vessels. Within the arteries and venous trunks blood corpuscles of the usual type found in the blood elsewhere are seen, but in the venous capillaries there are found young embryonal forms of red corpuscles undergoing division. Even in the marrow of healthy animals one observes a tendency of the corpuscles in the venules to arrange themselves in the following manner. In the centre of the lumen are red corpuscles fully developed and deeply stained with hæmoglobin. In the peripheral part of the vessel are found near to, or in contact with, the wall of the vessel a varying number of leucocytes, and in the intermediate area, or middle zone, are a number of cells undergoing mitosis, and which are composed of a spherical nucleus, which is surrounded by an envelope of hæmoglobin-containing protoplasm. These are the young red corpuscles undergoing indirect division, to which, following Löwit, the name of "erythroblasts" has been applied by Denys and Bizzozero. In animals made highly anæmic by bleeding Bizzozero describes (1) the venous capillaries are markedly widened at the cost of the parenchyma; (2) in the parenchyma is seen an atrophy of the fat cells and a hyperplasia of the leucocytes; (3) the lumen of the venous capillaries is filled out in a most marked manner by young red blood cells and leucocytes; the fully grown red blood cells form narrow streaks in the axis of the vessels; the leucocytes, as well as the young red blood cells (the latter in greatly the preponderating quantity) increase in number actively by the process of mitosis. So far Denys and Bizzozero travel together, but

regarding the nature of the erythroblasts they differ. Denys maintains that the erythroblasts are developmental forms free from hæmoglobin between the leucocytes on the one hand and the fully developed red blood corpuscles on the other hand. Bizzozero, on the contrary, asserts that the erythroblasts always contain hæmoglobin, and that they arise from previously existing hæmoglobin-containing cells by a process of karyokinesis. He points out that Denys's observation that the erythroblasts contain no hæmoglobin has been caused by the influence of corrosive sublimate upon the hæmoglobin, and that by examining fresh marrow, marrow hardened in Müller's fluid, and by processes of staining recommended by H. F. Müller and Foa—one may satisfy himself that the youngest forms of red cells already contain a trace of hæmoglobin. Many of these are dividing by mitosis, and he asks, "Can there well be a younger element than a cell which is not yet independent, as it still forms part of another cell from which it takes origin?" Dr. Galloway's and my own observations entirely confirm those of Bizzozero that the erythroblasts at all stages contain a greater or less amount of hæmoglobin.

Bizzozero's conclusions may be briefly summarised by the following statement—That in the marrow of birds: (1) owing to the great disproportion between the calibre of the arteries and venous capillaries, the blood must circulate in the latter with extraordinary slowness; (2) that in the venous capillaries, the blood is different to what is observed in the vessels of any other part of the body, in that the fully developed red blood cells occupy only the axis of the lumen; around them are situated quite up to the vessel wall two sorts of elements; leucocytes are to be found in larger quantities than is usually the case in other parts of the body, and red blood cells which are to be recognised as young red blood cells (erythroblasts) by their round or slightly oval shape, the characters of their protoplasm and their nucleus. Moreover, a certain number of erythroblasts are seen in a state of indirect division. The vessels of the marrow are the only regions of the organism of birds, in their adult condition, in which erythroblasts and their developmental forms are found; in these vessels alone is one able to locate the source (herd) of the red blood cells. (3) In anæmia the venous capillaries are enormously dilated at the expense of the parenchyma, especially the fat cells, the lymphoid tissue increasing, and the leucocytes showing more active mitosis. In the lumen of the vessels, the number of leucocytes increase as well as the erythroblasts, which almost completely fill up the lumen of the venous capillaries; the fully grown red blood cells occupy only a small space corresponding to the axis of the vessel. The number of leucocytes which are found in a state of mitosis is considerable, but that of the erythroblasts is great. (4) On account of the characteristics of its structure, the network of the venous capillaries of the marrow is distinguished from all other networks of the body. It subserves the production of two morphological elements of the blood, namely, the leucocytes and the red blood cells. In the manufacture of the first are associated with it many other organs of the body, and among them also the parenchyma of the marrow itself; in the production of the latter, on the other hand, the marrow is alone concerned. (5) The vascular network of the marrow may, therefore, be considered as a true endovascular organ—a gland which secretes morphological elements. Bizzozero and Torre,¹⁵ in 1884, showed that the blood development in the marrow is the same in all vertebrata as in birds, but the former states he has not found blood corpuscle-containing cells in the marrow of birds. The three main points appear to me to be quite certain, at least as regards the marrow of birds: (1) that development of red corpuscles takes place entirely within the vessels (venules); (2) that the young red corpuscles arise from pre-existing red corpuscles; (3) that the young red corpuscles are formed by a process of indirect division (karyokinesis).

Thus, whilst all observers are agreed that the nucleated red blood corpuscle is the immediate precursor of the fully-developed non-nucleated red corpuscle, they are divided into three camps as regards the origin of the nucleated red blood corpuscle: (a) Those who believe that they arise from marrow cells; (b) those who believe in their derivation from colour-

¹⁴ Creighton has described the development of red corpuscles in blood cysts by a process of budding from embryonic cells lining their walls.

¹⁵ *Vierteljahrsschrift der Naturforschenden Gesellschaft in Zürich*, Band xcvi.

less corpuscles (leucocytes, leucoblasts, erythroblasts)—they have not clearly indicated which of the several varieties of the colourless corpuscle is the parent of the red corpuscles; (c) those who deny altogether the development of red corpuscles from white corpuscles, and who believe that all red corpuscles arise from pre-existing red corpuscles by a process of indirect division (karyokinesis). Further, those who adopt the two first views believe in the extravascular origin of the red corpuscles; whilst those adopting the last believe it to be entirely endovascular. It is still a matter of uncertainty as to how the nucleus disappears. Some believe, with Rindfleisch and Ehrlich, that it passes bodily out of the cell; others, with Kölliker and Neumann, that it breaks down and becomes absorbed in the general cell substance. No entirely satisfactory explanation has been hitherto afforded of how the nucleated red corpuscle derived from a narrow cell or leucocyte acquires its biconcave form. That this very special characteristic of the fully-grown corpuscle is no accident we may feel sure, but evidence of a developmental tendency. If we accept the view that the nucleated red corpuscle is derived from a pre-existing red corpuscle no difficulty is experienced, as we have simply an instance of a cell reaching its ultimate and full development, just as a ciliated columnar cell is evolved out of a flat or spherical embryonic epithelial cell. On the other hand, great difficulties are presented in regarding the fully-developed red corpuscle reaching such a highly-specialised form from cells offering such wide differences as the colourless corpuscles and marrow cells.

Blood-forming Functions of the Spleen.—In the human subject the spleen appears to have a limited capacity of blood generation in extrauterine life. Neumann and Freyer have been led to the conclusion that the spleen is practically not a blood-forming organ. Bizzozero and Salvioli have demonstrated that it has decided, if not very active, blood-forming powers. Much of the difference of opinion that exists has arisen from the kind of animal that has been the subject of experiment, for the relative share taken by the cytogenic organs in blood formation differs considerably in different classes. Whilst caution must be exercised in inferences drawn as to the hæmopoietic functions of the human spleen from observations and experiments on animals, seeing how widely they differ amongst themselves, as far as the evidence afforded by the effects of removal of the spleen goes, it is in favour of the human spleen behaving in this respect like the spleen of the dog. A case of removal of the spleen, recorded by Credé,¹⁶ was followed by decrease in the red corpuscles—many of those present were of small size, and some nucleated—and by an increase, relative and actual, in the number of white corpuscles. The blood gradually changed to the normal again by the end of four months and a half. Bizzozero and Salvioli found in guinea-pigs and dogs, made anæmic by bleedings, nucleated red corpuscles in greater or less number. In dogs the spleen became “rose-coloured and very much swollen,” and, by simply looking at it, they could say “there will be nucleated red cells here” (Gibson). Dr Gibson¹⁷ has recently made some careful and important investigations on the hæmopoietic properties of the spleen, and concludes that the blood-forming action of the spleen is, in extrauterine life, a subordinate one, but that when the reserve blood-forming capabilities of an animal are called on its activity is increased. That the spleen gives rise to colourless corpuscles is generally admitted. They arise, partly by indirect division from other colourless corpuscles, and partly by budding from the cells of the stroma (Klein).¹⁸

Blood-forming Functions of the Lymphatic Glands.—It has long been held that lymphatic tissue, whether arranged as glands or occurring in patches of adenoid connective tissue (as in the agminated and solitary glands of the intestine), are the chief producers of colourless corpuscles. It is also thought they may have the power of transforming colourless into red corpuscles. That this power, if it exists, is very sparingly exercised in general is evidenced by the well-known characters of lymph. It is, however, possible that when lymph is delayed in its channels it may bring about the conversion of leucocytes into red corpuscles. This has, it

is believed by Gibson, been proved, where, after ligation of the thoracic duct (in a dog), a number of nucleated red corpuscles were found in the abdominal glands. The same results are believed by some to be brought about by the experiments of disease. In cases of chyluria, lymph scrotum, and elephantiasis, in all of which lymphatic trunks are obstructed, the fluid contained in the lymph vessels is said to be reddish, or even as red as blood, when unmixed with chyle. Dr. Gibson thinks that the normally scarcely existing powers of blood transformation in health may be called into greater activity by demands upon the blood-forming powers of the individual. Foà and Salvioli¹⁹ found red corpuscles forming endogenously within large protoplasmic cells in lymphatic glands.

Blood-forming Properties of the Thyroid Body.—It has recently been suggested that the thyroid body, if not in ordinary circumstances a blood-producing organ, may take on this function when all the latent capacity of blood-formation of the organism is called into play. The evidence on which this opinion is based has been shown by Gibson to be very meagre and inexact, and it may be accepted that the thyroid body has no hæmopoietic functions.

We have thus considered all the usually ascribed sources of blood-formation, and find that it practically amounts to this: That in postembryonal life the red blood corpuscles have their birthplace in the marrow, though a slight power of hæmogenesis may exist in the spleen, and possibly in lymphatic structures. We now turn to the other end of the life of the red blood corpuscles.

The Seats of Blood Destruction: Hæmolysis.—The life of every cell is limited, and the red blood cell is no exception to this universal law.

We have abundant indirect evidence of destruction of red corpuscles in the formation of bile, the pigment of urine, and other pigments derived from hæmoglobin. The average life of a red corpuscle has been estimated by Quincke at about two weeks. The most active destruction appears to take place in the portal system of blood vessels. In the spleen, marrow of bones, lymphatic glands (and in the liver of the embryo), are found large cells containing blood corpuscles. The corpuscle-containing cells may contain one or two, or even as many as ten or twenty, red corpuscles in their interior, in all stages of disintegration, from the almost normal red corpuscle to mere granules of blood pigment. From the occurrence of these blood corpuscle-holding cells in the organs of blood formation, one conjectures that by breaking down effete corpuscles they subserve the purpose of supplying the new corpuscles with the necessary raw material for the building up of hæmoglobin-containing protoplasm.

Osler has also described²⁰ “included corpuscles” in the blood stream, that is, colourless corpuscles containing one or more red blood corpuscles. They are very rare, and must be regarded as red corpuscles which have come to a premature end, and are being removed by predatory or proctorial phagocytes. In ordinary circumstances, when the red corpuscles are about to disintegrate, according to Quincke, they are taken up by the white corpuscles in the hepatic capillaries, by the cells of the spleen, and the bone marrow, and are stored up chiefly in the capillaries of the liver, in the spleen and in the marrow of bone. They are transformed, partly into coloured and partly into colourless proteids, which contain iron, and are deposited in a granular form or are dissolved. Part of the products of decomposition are used for the formation of new blood corpuscles in the marrow and spleen, and also perhaps in the liver, while a portion of the iron is excreted by the liver in the bile (Landois and Stirling). In pernicious anæmia the liver has been shown by Stahel, Quincke, Peters, Rosenstein, Mott, and others, to contain an excess of iron. It was at one time thought possible that this excess of iron was due to its administration; but the observations of Kobert, Cohn, and Gläveck have proved such not to be the case. Dr. William Hunter has worked out very completely and carefully the difficult problem of blood destruction.²¹ He describes it as of two kinds. (a) *Passive destruction*, which

¹⁶ *Langenbeck's Archiv*, Band xxviii, p. 401.

¹⁷ *Op. cit.*, p. 473.

¹⁸ *Quart. Journ. of Microscop. Science*, vol. xv, p. 369.

¹⁹ Landois and Stirling, *Textbook of Physiology*, p. 10.

²⁰ *Loc. cit.*, p. 862.

²¹ Summary of Three Lectures on Transfusion, *BRITISH MEDICAL JOURNAL*, 1889, vol. ii.

is the ultimate destiny of the red corpuscles which live their allotted span and undergo a process of natural decay. This form is evidenced by the presence of pigment in certain organs of the body, chiefly in the spleen, capillaries of liver, and bone marrow. "The chief character of this pigment is the large and varying size of the individual pigment particles, and their irregular shape." It is never found within the liver cells, but always lies enclosed in leucocytes within the capillaries. (b) *Active destruction*, in which the hæmoglobin, instead of remaining within the red corpuscles, escapes from them into the plasma, and is in great part excreted by the liver as bile pigment. "The chief character of this pigment is the small uniform size and spherical shape of the individual particles. The assumption of this form by the pigment is independent of the action of the cells, but the conversion of the hæmoglobin into blood pigment is as much the result of cellular activity as in passive destruction." The pigment is formed from free hæmoglobin, and is found chiefly within the liver cells in the portal zone. In conditions of health no trace of blood pigment is usually found as the result of the breaking up in, and the excretion of this free hæmoglobin from, the body. But when, as in pernicious anæmia, excessive activity of blood destruction takes place, it is found abundantly in the liver cells. The amount of bile pigment formed is an index of the amount of active destruction. "It is greatest during digestion, and is most marked of all five or six hours after the ingestion of food. Since we cannot conceive," Dr. Hunter writes, "of an increased formation of bile pigment without a corresponding greater supply of hæmoglobin in the liver cells, we must conclude that the ingestion of food is followed by increased active destruction." It appears to me doubtful whether we need go quite so far as this latter statement with Dr. Hunter. As far as I can see there is some force in Voit's remark: "There is no reason why there should be a greater destruction of red corpuscles during digestion than during the fasting state." One can understand that bile pigment formed during fasting must be derived from destruction of red corpuscles, as there is no other source for the hæmoglobin; but in a diet containing flesh, when bile pigments are greatest, the hæmoglobin taken as food and converted into hæmatin is at least a possible source of bile pigment, without ever becoming organised into blood. According to Dr. Hunter, with whose conclusions on this point most physiologists are in agreement, the spleen and the gastro-intestinal mucosa are the most active seats of blood destruction.²² The effete and many vigorous red blood corpuscles undergo destruction there; their liberated hæmoglobin is carried by the portal blood to the liver, where it becomes converted into bile pigments. The bone marrow is (outside the portal circuit) the only other seat of blood destruction. The share of the spleen (or, at least, the importance of its share) in hæmolysis is not absolutely established. Schäfer has examined the blood from the splenic vein in a large number of animals, and the result of his observations is decidedly against the view that the spleen is an organ concerned in the destruction of red corpuscles.²³ Dr. Mott has shown that the spleen often does not give the iron reaction, and states that chemical analysis may show no excess of iron, although the liver may contain a great excess over the normal. Dr. Hunter, however, only regards the spleen as *one* of the seats of blood destruction, which goes on when the spleen is removed. Moreover, the presence of iron albuminates in the spleen and bone marrow may be explained by the peculiarities of the circulation in these structures, by the delay in the capillary veins caused by the disproportion between their calibre and that of the arteries discharging into them.²⁴

The Colourless or White Blood Corpuscles (Leucocytes).—Amongst the important advances in our recent knowledge of the blood is the recognition that the colourless corpuscles differ much amongst themselves, certainly as regards their morphological characters, and probably as regards their physiological functions. Speaking generally, the colourless cor-

puscles are larger than the red corpuscles, having an average size of 10μ , but varying between 4 and 14μ . The colourless corpuscle may be described as a globular mass of protoplasm containing one or several nuclei. They number in health about 6,000 per cubic millimetre (Hayem), but their numbers vary much at different times in the same individual in health, and still more so in disease. Max Schultze, Bizzozero, Heyl and Ehrlich, and others have pointed out important differences displayed by them. Ehrlich, especially, has started an important inquiry, which promises practical aids to our knowledge. He has shown,²⁵ not only that the granules he has described in them differ in their colouring by basic, acid, and neutral dyes, but also in their behaviour in solvent fluids, in their size and shape, in the influence upon them of high temperatures (100° to 180° C.), and in their distribution in the body of the cell. Space prevents my doing more than giving the results of his investigations which have some bearing on my present subject: "(1) In all acute leucocytoses only the mono- and poly-nuclear forms are increased, while the eosinophile cells are apparently correspondingly diminished. (2) An increase of eosinophile cells always indicates chronic changes in the blood-forming organs. (3) Decrease in the number of leucocytes and preponderance of the mononuclear forms, when associated, are a sure sign of defective nourishment of the system of long duration. (4) Severe traumatic anæmia always gives rise to poikilocytosis and the appearance of nucleated red blood corpuscles; frequently also to an increase of polynucleated, eventually of mononucleated, elements. (5) In leukæmic blood the absolute number of eosinophile cells²⁶ is always increased, often to a very great extent." Of the origin of the white corpuscles, all are agreed that they arise from lymphatic structures, the lymph glands, and disseminated lymphatic tissue, for which Dr. Pye-Smith has proposed the comprehensive and convenient name "lympharia," from the spleen and the bone marrow. Apart from their disputed share in the genesis of the red corpuscles, the active part they play in inflammation as established by Cohnheim, they have recently been shown by Metchnikoff, Ruffer, and others, to act as "phagocytes" or scavengers, whose function it is to remove from the blood and tissues micro-organisms and other deleterious matters. When their life cycle is completed, or under the influence of too powerful bacterial action, they undergo disintegration forming the "elementary granules" found in the blood.

Blood Platelets.—Besides the red and colourless corpuscles, the blood contains some smaller formed elements concerning the origin, nature, and functions of which there are as many theories as the bodies themselves have received names. There are the "hæmatoblasts" of Hayem, the "globulins" of Pouchet, the "Körnchenbildungen" of Max Schultze, the "Elementarkörperchen" of Zimmermann, and the "Blutplättchen" of Bizzozero. They are circular or oval in shape, with well defined margin, and consist of brightly refractile protoplasmic material of a light grey colour, and in the human subject are destitute of nuclei. They vary in size from 1μ to 1.3μ . Their numbers have been variously estimated. Hayem states that on the average there are 250,000 hæmatoblasts in the cubic millimetre. Osler has calculated them at from 125,000 to 300,000 per cubic millimetre, Fusari at from 18,000 to 250,000. Hayem and Pouchet regard them as embryonic red corpuscles, and believe they have been able to trace transitional forms between them and the fully developed red corpuscles. Neumann, Max Schultze, Riess, and Ehrlich, on the other hand, believe that they are the result of blood disintegration, though Osler says there is no corroborative evidence of this. Hayem has described them as tinted with hæmoglobin. Osler, on the other hand, denies that the largest platelets contain even a trace of colour, and Bizzozero also says that they contain no hæmoglobin. What appears at first sight to be an argument in favour of Hayem's view is the fact, generally admitted, that when blood regeneration is most active (as, for example, after hæmorrhage) they are most numerous in the blood. On the other hand, Neumann, Ehrlich, Riess, and Leube believe that in such circumstances

²² Klein has shown there are reasons for believing that the blood corpuscles are disintegrated by a destructive influence of the matrix of the spleen upon the corpuscles, and not in the manner usually described, the corpuscles being taken up by lymph cells. *Op. cit.*, p. 371.

²³ *Proc. of Physiol. Soc.*, May, 1890, quoted by Mott.

²⁴ *Practitioner*, August, 1890, p. 81.

²⁵ *Zeitsch. für klin. Med.*, 1880, p. 553.

²⁶ The "eosinophile cell," whose normal and exclusive place of origin is the bone marrow, is a constant constituent of normal blood; frequently there are from 2 to 4 per cent., and their number may be as high as 10 per cent. *Charité Ann.*, xlii, 1888, p. 306.

the chemical changes and thinning of the blood exercise a deleterious influence on the red corpuscles, causing them to disintegrate, and thus give rise to the hæmatoblasts.

There have not been wanting observers who believe that the platelets are *arte facta*—the product of changes in the red corpuscles after they are shed. There is no doubt that similar bodies may be artificially produced, but there seems no real ground for this view of their ordinary production. They are present at the moment blood is withdrawn, and examined under the most favourable circumstances such as instantaneously fix the formed elements. Moreover, Bizzozero, Osler, Karl Laker have observed them flowing in the blood streams of living animals, after taking all precautions that the conditions did not interfere with the vascular contents. Their presence, therefore, whatever their significance, must be regarded as established, and of natural occurrence. Hayem believes they arise from lymph corpuscles while yet in lymph vessels; Pouchet, that they arise in the blood plasma itself by a process analogous to the precipitation of fibrin. Schmidt and others believe they are due to disintegrating colourless corpuscles, whilst Bizzozero is unable to decide whence they come. Recently, Gibson, who has examined into the question with great care and impartiality, believes that under the various names given to these formed elements are included two distinct elements, and that confusion between these accounts for much of the discrepancy in the statements of various observers. He prefers the term "microcyte" for them.

I am afraid it is impossible to choose a term free from all objections, but burdened as this subject is with multitudinous names for the same thing, it appears to me that we should try and agree upon one term. So high an authority on physiology as Dr. Michael Foster has adopted the term "platelet," and it would be a matter of general convenience if all British writers would follow his example. Substituting then the term platelet for microcyte, Dr. Gibson's views are put shortly as follows: ²⁷ There are (1) coloured platelets which, he believes, are simply fragments of broken-down red corpuscles, ²⁸ and (2) colourless platelets which correspond to the "Blutplättchen" of Bizzozero, and these, he believes, are mainly the escaped nuclei of the red corpuscles, though occasionally they may be derived from the nuclei of white corpuscles when these disintegrate. It will thus be seen that Hayem and Pouchet are the chief exponents of the doctrine that the platelets are developmental forms of red corpuscles. Whilst there are widely different views as to the nature and origin of the platelets, there is practically universal accord that they are active agents in the process of coagulation, and in the formation of coagula.

The Invisible Corpuscles of Norris.—These have been proved by the researches of Mrs. Ernest Hart ²⁹ and Gibson to be red blood corpuscles decolorised by the method of preparation.

Besides these definite forms, "elementary granules" have been described by Zimmerman and Beale. They are irregular bodies, much smaller than the ordinary corpuscles, and appear to consist of masses of protoplasm detached from the surface of leucocytes, or derived from the disintegration of these corpuscles or of the blood platelets. Others, again, are completely spherical granules, either consisting of some proteid substance or fatty in their nature. The protoplasmic and proteid granules disappear on the addition of acetic acid, while the fatty granules (which are most numerous after a diet rich in fats) dissolve in ether (Landois and Stirling).

Hæmoglobin.—The functional activity of the blood depends upon the amount of hæmoglobin contained in the red corpuscles. The hæmoglobin is estimated by various methods—in this country chiefly by means of Gowers's hæmoglobino-meter, which is extremely easy in employment, and gives sufficiently exact results for clinical purposes. Under conditions of health the red corpuscles contain a fairly uniform

amount of hæmoglobin, so that by estimating the number of corpuscles we have a tolerably accurate indication of the hæmoglobin richness of the blood; or, *vice versâ*, by estimating the hæmoglobin we may gauge the number of corpuscles. In anæmia, however, great variations may occur in the relative proportion of hæmoglobin and corpuscles, so that it is necessary to ascertain the functioning value of the blood to ascertain both the corpuscular richness and the hæmoglobin richness. Hayem recommends that the hæmoglobin richness should be expressed in terms of sound blood, which represents the functional value of the blood. If we divide the hæmoglobin richness expressed in healthy corpuscles by the actual number of red corpuscles, we obtain the value of the individual corpuscle. In dealing with percentages all we have to do is make the percentage of hæmoglobin the numerator and the percentage of corpuscles the denominator of a fraction. Osler has well summarised the variations which take place in the hæmoglobin contents of the red corpuscles:—

(1) In chlorosis, the hæmoglobin is reduced out of proportion to the reduction of the corpuscles, so that the individual worth of each red corpuscle in colouring matter may be very greatly lowered. Thus, the true anæmia (or functioning properties of the blood) may be very much greater than the number of red corpuscles per cubic millimetre would indicate.

(2) In ordinary anæmia from hæmorrhage or from organic disease the average worth in hæmoglobin of each corpuscle usually remains unaltered, and the percentage of colouring matter corresponds with the percentage of the corpuscles.

(3) In certain cases of pernicious anæmia, the interesting fact has been ascertained that the percentage of hæmoglobin is increased, and the anæmia is in reality not so great as the reduction in the number of corpuscles would appear to indicate.

Karl Laker ³⁰ has pointed out that the percentage of hæmoglobin (as tested by Fleischl's hæmometer) may be used as a diagnostic point between benign and malignant tumours. In the former the hæmoglobin is not diminished, whilst it is in the latter. My own observations show that in some cases of cancer (where there was no hæmorrhage or discharge) the hæmoglobin reduction was greater than that of the corpuscles.

Having now—I am afraid at wearisome length—considered the blood in health, we are in a position to discuss the departures from this standard, in so far as they relate to anæmia. Anæmia may be defined as a diminution in the quantity of the blood, of its corpuscles, or of its colouring matter. To the first the term *oligæmia* is applied, to the second *oligocythæmia*, and to the last *oligochromæmia*. Though these do not by any means necessarily correspond in all forms of anæmia, yet as a rule they are coincidentally modified. They all have this in common that they indicate "the poverty of the blood in normal functional red corpuscles" (Cohnheim), which is the criterion of the functional activity of the blood.

We have seen that blood corpuscles are constantly being used up in the production of bile, urinary colouring matters, and other pigments derived from hæmoglobin, and the other constituents of the blood are consumed in the processes of tissue metamorphosis and secretions, and that these losses are met by a continual process of blood regeneration, so that a balance existing between the income and expenditure of the blood, a normal though varying condition or equilibrium, is maintained. Anæmia, on the other hand, implies a want of adjustment between the gains and losses. To which end of the process are we to look for the explanation of anæmia? Is it due to defective hæmogenesis or to excessive hæmolysis? Until quite recently, this question, which was raised by every writer on the subject, was incapable of receiving a definite reply. So little was known of the details of blood formation and destruction that it was impossible to say what share modifications of each of these processes took in the bringing about of anæmia. Great advances have been made in the last few years in our knowledge of these processes, and though there are *lacunæ* to be filled up, we are reaching a position in which we can frame our pathology of anæmia on a logical basis. It

²⁷ *Op. cit.*, p. 107.

²⁸ Osler, too, describes microcytes arising from the breaking down of red corpuscles, and, like Gibson, has watched their artificial production in the shed blood. The former states they are abundant in all forms of anæmia, chlorosis, splenic anæmia, leukaemia, pernicious anæmia, Hodgkin's disease, and in the anæmia of cancer, phthisis, and other chronic affections. They are most numerous in the primary anæmias, especially progressive pernicious anæmia. He adds they are certainly not always produced by post-mortem changes.

²⁹ *London Medical Record*, 1882.

³⁰ *Centralblatt f. d. med. Wissenschaft.*, 1887, p. 405.

is on this account that I have gone into such detail in what may be regarded as elementary matters, for as long as it was uncertain whether the histological changes observed in the marrow, the spleen, liver, etc., were to be regarded as the causes or the consequences of anæmia, no rational conclusion could be drawn as to its essential nature. We now have reached tolerable agreement as to seats and evidences of blood formation and blood destruction, and are now able to make these the basis of our pathology. We must, therefore, next proceed to discuss the share each of these processes takes in anæmia. It is obvious that, in simple hæmorrhage of all kinds, anæmia begins from excessive loss or expenditure. It is nearly equally certain that, in profuse discharges of pus or serum from the body, there must be a using up of blood, potential or actual, in the processes which bring these about. The blood-forming capacity of the individual may be in full integrity, but the drain may be such that it cannot keep pace with the demand, and anæmia is the result. Besides these obvious causes of blood expenditure, we have recently, from the closer study of certain forms of anæmia, been taught to recognise that an active destruction of red corpuscles may take place, not from an excess of physiological activity in the employment of the elements so destroyed, but by a process entirely pathological. On the other hand, without any undue calls upon it, blood formation may be defective, either in the quantity or quality of the red corpuscles, when again anæmia results. And, lastly, excessive destruction may be associated with defective formation, and thus each may exaggerate the effect of the other.

Some cases of anæmia are clearly connected with some definite morbid process which has primarily nothing to do with blood formation or destruction, but which stands in relation to the anæmia as cause and effect. It is a matter of practical and clinical convenience, as well as pathological propriety, to separate these cases from those in which no such causes can be ascertained with certainty; though I believe that the ultimate pathological standpoint in anæmia of all kinds must turn on the question of defective hæmogenesis or excessive hæmolysis. Yet if we do not adopt some such primary division, we shall have to group together conditions clinically widely different. How are we to estimate the activity of blood formation and destruction? By clinical observations and the revelations of morbid anatomy. Clinically, the activity or integrity of blood formation in anæmia is indicated, positively, by the character of the blood corpuscles, collectively and individually; and, negatively, by the absence of evidence of blood destruction afforded by secretion of faintly-coloured bile and pale urine. Excessive destruction, on the other hand, is evidenced by the dark colour of the urine and fæces produced by hæmolysis, and perhaps by the staining of the skin and other tissues by products of blood destruction. Morbid anatomy teaches us the actual condition of the blood-forming organs, and supplies us with evidence of whether blood destruction has or has not been excessively active in the organs where this is carried on. With the exception of the changes in the blood-forming and destroying organs, the remaining pathological alterations found in anæmia, the fatty changes in the heart and blood vessels, the hæmorrhages, etc., are the direct consequences of the anæmia, dependent upon its degree irrespective of its cause.

Defective blood formation may depend upon deficiencies in the quantity or quality of the food, in its want of variety, or imperfect preparation; upon failure of the powers of mastication, digestion, or assimilation; upon some defect, inherited or acquired, of the hæmopoietic viscera; or upon such unfavourable conditions as deficiency of light and fresh air, unsuitable temperature, and depressing and unhygienic surroundings. Excessive blood destruction depends upon an increase beyond the normal of those processes which cause active blood destruction, as by the processes of fever and inflammation, or the presence of deleterious substances in the blood. In many instances it is difficult to estimate the share which defective hæmogenesis and excessive hæmolysis play.

Anæmia thus depending on such a variety of causes, it becomes necessary to arrange the cases in some order, and the classification which naturally suggests itself, and which has been adopted by most writers on the subject, is into

1. Secondary and symptomatic anæmia; and
2. Primary and idiopathic anæmia.

In secondary and symptomatic anæmia, we have conditions in which the blood deficiency is not the essential feature of the disease, and in which the other symptoms present are not explained by the existence of the anæmia. In primary and idiopathic anæmia, on the other hand, the anæmia constitutes the main feature of the disease, and the other symptoms present are dependent upon it. Dr. Hunter has,³¹ in my opinion, very clearly indicated the criteria of an idiopathic anæmia, which he states should comply with the following conditions: 1. That the changes in the blood (as determined by actual examination) must not only apparently, but actually, constitute the most marked feature of the disease. 2. That the other chief symptoms must, in great part at least, be referable to the altered condition of the blood. 3. With regard to the *post-mortem* appearances that the changes in the blood, whether alone, or in the blood-forming or blood-destroying organs, constitute the characteristic morbid feature of the disease. Dr. Pye-Smith³² would make a third division of cases of anæmia "formed of all cases of anæmia associated with disease of the cytogenic organs, whether or not leucæmic." These, which undoubtedly form a natural and compact group, clinically and pathologically, should, I think, rather be included under idiopathic anæmia. In leucocythæmia we have not only an increase in the number of colourless corpuscles, but a great deficiency in the red corpuscles, and many of its symptoms are directly due to the anæmia. How is the latter produced in leucocythæmia? Is it due to excessive hæmolysis or to defective hæmogenesis? There is no strong evidence of the former, whilst the marked alterations in one or several of the blood-forming organs are suggestive of the latter. As long as the question of the origin of the red corpuscles from the colourless is unsettled, it is difficult or impossible to give a decisive answer to the question of how the defective hæmogenesis operates. If, as many believe, the red are transformed colourless corpuscles, an arrest of development is a ready explanation. If, on the other hand, all red corpuscles arise from pre-existing red corpuscles, this ready and inviting hypothesis is no longer tenable. I would merely draw attention to one point which appears to me to militate against the view of the deficiency of red corpuscles being caused by non-transformation of colourless into red corpuscles. This is the condition of the marrow in this disease. When red blood formation is active the venous capillaries become dilated at the expense of the lymphoid tissue, and the marrow becomes red. When, on the other hand, there is lymphoid hyperplasia of the marrow, this is at the expense of the venules, wherein the red corpuscles are produced; the consequence is there is defective formation of red corpuscles, whilst the eosinophile colourless corpuscles, which we have seen are formed in the lymphatic tissue of the marrow, are produced in excessive numbers. Ehrlich has, as I have pointed out, shown that the eosinophile colourless corpuscles are always increased in leucocythæmia. In "anæmia splenica" a similar difficulty arises in explaining the deficiency of red corpuscles. It has been attributed, with a good deal of plausibility, to the retention and accumulation in the spleen of large numbers of colourless corpuscles, which should normally be transformed into red corpuscles. This explanation assumes, what has not been proved, that the red corpuscles are transformed colourless corpuscles. Further, we have seen that the spleen has little share in the genesis of red corpuscles. If, moreover, as assumed, the colourless corpuscles are retained in the spleen, as long as the red corpuscle-forming process can be carried on, the lymphatic glands and marrow will furnish abundant colourless corpuscles for the manufacture of red corpuscles, if these really arise from them, as in cases of extirpation of the spleen. The same remarks apply to "anæmia lymphatica" (pseudo-leukæmia—Hodgkin's disease). The lymphatic glands, as we have seen, have little to do with the formation of red corpuscles, and the oligocythæmia must in this case be referred to failure of the function of the bone marrow. "Anæmia myelogenica," which stands very nearly related to idiopathic anæmia, differs from it in the fact that the marrow shows a lymphatic hyperplasia, which, as I have pointed out, must interfere with the blood-forming capacity of the marrow. That cases have begun as idiopathic anæmia, and later passed

³¹ Is Pernicious Anæmia a Special Disease? *Practitioner*, August, 1888.

³² *Guy's Hospital Reports*, vol. xxvi.

into leukæmia, lends, I think, support to the view I take. These blood diseases associated with changes in the cytogenic organs, have, as Dr. Pye-Smith has pointed out, much in common with idiopathic anæmia. Many of the symptoms—the frequency of hæmorrhages, irregular pyrexia, their severity and ingravescence, the resistance to preparations of steel, and the more or less marked influence of arsenic, and the almost invariably fatal issue—are common to both.

Thus I consider all cases in which anæmia is not symptomatic should be regarded as idiopathic. The term “idiopathic anæmia” was, as is well known, first employed by Addison for that particular form of anæmia of which he gave such a masterly description. Others besides myself³³ have urged that it should be restricted to the class of cases described by Addison. The progress of our knowledge, however, in my opinion, now renders it advisable to enlarge its meaning so as to embrace all primary anæmias, and to use it as a generic term, including several species. Of these species two are well defined—chlorosis, and the form described by Addison, which has by common consent come to be called “pernicious anæmia,” and which name, I now think, it is useless to oppose. Probably, besides these two species, there are other distinct forms of idiopathic anæmia to which I shall have to allude in subsequent lectures.

ON REMOVAL OF THE UTERUS FOR CANCER.

By THOMAS KEITH, M.D., F.R.C.S.Ed.

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A MARRIED lady, 55 years of age, daughter of perhaps the most well-known provincial surgeon of Ireland, was sent to me by Dr. Smith, of Belfast, in the end of July last. Though never strong, her general health was always good. She lost her only two children in giving birth to them, on account of some narrowness of the pelvic outlet that required instrumental interference. The periods had ceased for four years without any unusual disturbance. Twelve or fourteen months ago, after some fatigue or exertion, she first noticed slight red discharge. This soon developed into a hæmorrhage, which gradually increased in severity. She lost flesh, became anæmic and feeble, and her general health gave way.

There was too easily recognised epithelial disease of the cervix, extending into the cavity of the uterus. As I was just leaving town for a holiday, I destroyed at once the whole of the sprouting bleeding surfaces by potassa fusa. After a few days' rest in bed the patient went north to Forfarshire, in the hope that the bracing air of the Grampians would recruit her failing health. The house was high above the sea level, and the weather was cold and wet. Finding that after three weeks she was losing rather than gaining ground, she returned south to Ramsgate, where her health improved. She looked better, though still feeble, when I saw her again in the last week of September. Though there was no hæmorrhage whatever since the caustic potass was used, it was too evident that the disease had spread during the last two months. The vaginal surface was still untouched. The uterus was high in the pelvis, as is generally the case in stout people, and there was a little narrowness of the outlet. In other respects the local conditions were not unfavourable for extirpation.

After two days' rest, the uterus, which contained a small fibroid, was removed by the vagina. As the uterus was drawn downwards the ligaments were tied in small portions. When possible, catgut ligatures were used, silk only to the upper and firmer part of the broad ligaments, which contained the round ligaments and Fallopian tubes. The ovaries and tubes were quite healthy, and were not interfered with. The large wound into the abdominal cavity was closed by horsehair sutures. No drainage tube was used. Some trouble arose from protrusion of intestine, and some pieces of appendices epiploicæ were always in the way, notwithstanding the presence of several flat sponges. The only anxiety after operation arose from the feebleness of the patient; yet she was up and was moved into another room in sixteen days, and left London on the twentieth day after operation.

³³ *Lancet*, 1878, vol. ii, p. 797.

The first time I performed vaginal hysterectomy for cancer was in the Edinburgh Infirmary in 1881. The same principles guided me then as in the above case, except that I brought down the fundus of a very large uterus through the posterior opening, having first washed away thoroughly a quantity of putrid discharge that had escaped from the uterus into the vagina. This bringing down of the fundus is an unnecessary proceeding. I do not think that it helps the tying of the broad ligaments, and it may be not free from danger. I have not done this again. In this case, from the size of the uterus, the opening was very large, and ten horsehair sutures were needed to close it—one-half this number is generally sufficient. It is nine years since this operation was performed; there has been no symptom of return, and the patient is in the best of health.

I have often wondered why vaginal hysterectomy is so seldom performed in this country. It has for years been a recognised operation in America, in Germany, and in Italy, where it is frequently performed by the galvanic cautery. One reason may be that here it has fallen through between the surgeon and the gynecologist. I am one of those who believe that we shall ere long see this operation, as well as all other abdominal work, pass into the hands of the regular surgeon, of one whose daily work it is to stop hæmorrhage and close wounds. It was not till ovariectomy was undertaken by a hospital surgeon (then Mr. Wells) that confidence in that operation was established.

The total removal of the uterus for malignant disease must, as a rule, be a better operation than the partial removal of the organ. No one nowadays thinks of removing a bit of a cancerous mamma. To remove as much of the uterus as is possible without opening into the peritoneal cavity, and then to follow up the disease of the cavity by the free use of the cautery, seems to me to be monstrously bad surgery. If the disease be confined to the lips it may be sufficient to stop at the internal os, but even this is not free from some danger. I have again and again opened into the peritoneum in my early efforts, though I have not seen any harm arise from this.

A few weeks ago I saw a lady in whom this accident happened, and on whom I operated nearly ten years ago. She had already been operated on several times before I saw her, and she is one of the few who have kept well. Now, I would never hesitate between the partial and complete removal, for from all we know there may be cancerous nests in the very fundus, even though the disease may seem to the eye quite local and limited. On this point it is refreshing to have the opinions of the German surgeons at the international meeting at Berlin in August last; Martin, Hegar, Olshausen, and many others gave no uncertain sound. Be the method of operation what it may, the great thing is that the principle of operation for total extirpation of a cancerous uterus is now established. There is no difficulty in the operation. It requires care, and there is seldom any trouble in applying the ligatures. There seems to be no reason why it should be attended with a large mortality. Its immediate risks are not great. I have not yet had the misfortune to lose a patient after it.

The two things to be attended to are the careful stopping of all bleeding, and the most rigid antisepsis or cleanliness, as some call it. Drainage is not necessary; indeed, there is little to drain if the wound be carefully closed, and it should be as carefully closed as any other abdominal wound. I prefer strong horsehair to anything I know. These sutures cause no irritation; they may remain in any length of time, and are easily removed. Possibly catgut may be better, but I have had a long experience of horsehair, and am satisfied with it. Many years ago an old medical friend came for me in haste to stitch up a badly torn perineum and rectum in the case of a lady whom he had just delivered by forceps. Some weeks after he called to tell me that she had done well, and was leaving town that afternoon. I asked when he had taken out the stitches; there were seven or eight of them. He had never thought of them, for he supposed I had used catgut sutures. He made some excuse for making an examination before she left, but he found no trace of the sutures, and he has confined her since without accident.

The practice of securing the broad ligaments by strong locking forceps, or even by specially constructed clamps, and