THE GULSTONIAN LECTURES

ON
ANÆMIA.*Delivered before the Royal College of Physicians.*By SIDNEY COUPLAND, M.D., F.R.C.P.,
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LECTURE I.—PART I.

Impoverishment of Blood with regard to Hæmoglobin the essential fact in Anæmia—This may be Quantitative or Qualitative—Analysis of Blood in Chlorosis—Methods of Estimation of Hæmoglobin—Malasses, Hayem, Gowers, Quinquaud—The Red Corpuscles: Variations in Number, Size, and Form; their Development, Destruction, and Renewal—Share taken by Lymphatic Glands, Spleen, Bone-Marrow, and Liver (?) in the work of Blood-Formation—The Hamatoblasts of Hayem.

MR. PRESIDENT AND GENTLEMEN,—In selecting as the subject of these lectures, which I have the honour of delivering before you, a condition so commonly and widely prevalent as Anæmia, I fear that I have undertaken a task which is not easy of fulfilment. For around this subject there clings much obscurity, owing to our lack of knowledge; and it would require far more profound analysis than I can hope to give to illumine its dark places. I do not bring you any original researches, and I cannot discuss the question in all its bearings; but if, by a simple exposition of what I conceive to be the directions in which the solution of its problems lie, I can fulfil an useful purpose, I shall be satisfied. For the subject is one worthy of attention; and in this College, where the memory of Harvey—the student of the circulatory mechanism—is ever kept green, it is surely fitting that we should now and again review our knowledge of those conditions in which the blood plays so prominent a part. It is a truism to say that the integrity of the blood is essential to the performance of healthy function; and, as disease is in great measure only disordered function, it is plain that such disorder may be determined by, as it must determine, changes in the circulating medium itself. There are some diseases in which defects in the blood stand out in sharp relief; but, the more deeply the nature of disease is inquired into, the more clearly is it manifest that the blood—the mobile tissue pervading every part of the organism, and essential for its proper working—must be modified by any departure from the normal. The modification thus induced may be almost infinitesimal: it may be, in a sense, simply necessary to maintain the life of the individual when placed under abnormal conditions; or it may be so profound as seriously to interfere with the vital processes, and be the ultimate, if not the proximate, cause of death. Thus, in anæmia, we pass insensibly over the margin of health to disease—to the very confines of the latter's territory—the limit placed by death.

Naturally the greatest interest—for here lies the deepest obscurity—centres in the etiology of this condition; and my object to-day will be to consider facts concerning the blood and the part it plays in the economy, with the view of illustrating the varied manner in which the anæmic state may be brought about. Without attempting to give a definition of anæmia other than that it is a condition of the blood in which its composition is so defective that it cannot sufficiently fulfil its respiratory and nutritive functions—implying, that is, a lowering of its standard composition in those elements which are destined to promote oxidation, to accelerate tissue-change, and repair tissue-waste—I must, in the first place, say a little concerning the blood itself, and, in doing so, must crave indulgence for venturing to repeat facts so well known.

The blood consists of the fluid part or plasma, and the formed elements or corpuscles; the latter forming rather more than one-third of the whole by weight. The corpuscles contain about fifty per cent. of water, their main solid constituent being the albuminoid crystallisable substance hæmoglobin, associated in the coloured corpuscles with a minute quantity of iron, between 0.4 and 0.5 per cent. The serum, on the other hand, is composed of ninety per cent. of water, eight to nine per cent. of proteins, and two to one per cent. of fats, extractives, and saline matters (Foster). Then there is the curious circumstance in the inorganic constituents—viz., the preponderance of potash-salts and phosphates in the corpuscles as compared with a parallel excess of soda-salts and chlorides in the serum. (See Tables I and II.)

TABLE I.—Mean Chemical Composition of Blood.
(Becquerel and Rodier.)

	IN HEALTH.		IN CHLOROSIS.	
	Adult Male.	Adult Female.		
Water	780	791	828.2	
Solids	220	209	171.8	
Fibrin	2.2	2.2	3.4	
Albumen	69.4	70.5	72.1	
Corpuscles	149.0	127.2	86.0	
Extractives and Salts	6.8	7.2	8.8	
Fatty matters	1.6	1.9	1.5	

TABLE II.—Plasma. (Schmidt.)

1000 parts contain:		viz.	
Water	901.51	Pot. chlorid.	0.569
Solids	98.49	Sod. chlorid.	5.546
		Sod. sulph.	0.251
		Sod. phosph.	0.271
		Sod. carb.	1.532
		Calc. phosph.	0.298
		Mag. phosph.	0.218

Corpuscles. (Schmidt.)

1000 parts contain:		viz.	
Water	618.63	Pot. chlorid.	3.679
Solids	381.37	Pot. phosph.	2.943
		Pot. sulph.	0.132
		Sod. phosph.	0.693
		Sod. carb.	0.134
		Calc. phosph.	0.094
		Mag. phosph.	0.060

Analyses show, therefore, that the corpuscular elements form the greater part of the solids of the blood, and it follows that the hæmoglobin is by far the most abundant of its albuminoid constituents.

True anæmia, of course, implies a diminution in all these blood-constituents—a condition only obtaining, and that in a transitory manner, after profuse and sudden hæmorrhage, the quantity of fluid lost being made up by a rapid osmosis of water from the tissues. The blood in that case becomes hydræmic, as it may do in the later stages of a chronic anæmia where there has been loss or destruction of the albuminoids of the serum. The consideration of such rapid and extreme forms of anæmia as those produced by sudden and severe hæmorrhage does not enter into my programme, except as serving to illustrate the various phases of anæmia, whether primary or secondary. The most marked fact in such anæmia is the impoverishment of the blood in its albuminous constituents, especially in the hæmoglobin—an impoverishment which may be owing to an actual diminution in the quantity of this substance, but which is also very probably due to a qualitative change in it, whereby it is rendered unable to subserve its chief office, that of conveying oxygen to the tissues. At present, there is but little known concerning this latter modification.* Attention has been mainly directed to the alterations in amount of hæmoglobin and of the albuminoids; and it is found that the diminution in these constituents is accompanied to a definite, but a comparatively small, extent, by an increase in the saline matters, and generally also by an increase in the water of the blood. I have placed before you (Tables III and IV) certain

TABLE III.—Mean Composition of Blood (1000 parts).

	IN CHLOROSIS. (Andral & Gavarret.)	
	IN HEALTH. (Lecanu.)	
Water	790.0	Incipient. Fully developed.
Solids	210.0	801.0 853.2
Fibrin	3.0	199.0 146.8
Corpuscles	127.0	3.5 2.9
Solid resid. of serum	80.0	106.8 56.7
		88.0 88.0

TABLE IV.—Anæmia with Amenorrhæa. (Beale.)

	(Treated by citrate of iron.)		
	Fifth Day.	Thirty-fifth Day.	Sixty-fifth Day.
Water	865.28	836.46	829.49
Solids	134.72	163.54	170.51
Fibrin	2.52	1.28	2.69
Corpuscles	49.29	78.73	85.79
Solids of serum	82.91	83.53	82.03
	(Salts, 7.54.)		(Salts, 8.203.)

analyses of blood in chlorosis, which show that in that form of anæmia, at any rate, the reduction of solids is mainly in the corpuscular part of

* It has been lately argued with much force by Drs. M. P. Jacobi and White (*Archives of Medicine*, 1880), that, in anæmia, the organised albuminoids of the body, including the corpuscular hæmoglobin, are all functionally inactive, and are rendered unable to condense oxygen and to store albumen in sufficient quantity for the needs of the organism. This is the most explicit statement I know of the view that the change in the hæmoglobin may be not simply a quantitative, but a qualitative, one.

the blood, and not in the serum; and there are abundant analyses made in more recent days which show that the reduction is almost entirely that of the hæmoglobin. The contrast between this deficiency and the normal, or even excessive, amount of serum-albumen in this disease, has been adduced as evidence of the essential difference between this form of anæmia and other forms. It seems doubtful, however, whether it is wise to base the distinction upon such a narrow ground as this, seeing that, in the all-important feature of anæmia—that of deficiency of hæmoglobin—chlorosis takes the chief place.

So important is this constituent that, in endeavouring to analyse the etiological side of anæmia, and to explain the effects of the condition, inquiry may be almost concentrated upon the variations of hæmoglobin to the exclusion of the other blood elements. Consequently, many methods have been devised for determining as accurately as possible the absolute and relative quantities of hæmoglobin in the blood. These methods severally consist in (1) the determination of the amount of iron in the corpuscles, it being found to be in constant proportion to the amount of hæmoglobin; (2) in the spectroscopic appearances given by solutions of hæmoglobin of various degrees of concentration; (3) in the absorptive capacity of a given quantity of blood for oxygen; and (4) in the comparative determination of the amount of colouring matter by contrasting a solution of blood of known strength with certain standard colours or coloured substances corresponding to the tint of a solution of normal blood. This last is the simplest and readiest of all the methods, although not quite as accurate as some of the others where larger quantities of blood are dealt with. It is to MM. Hayem and Malassez that we owe the introduction of these methods, and the simple apparatus devised by Dr. Gowers modifying the latter's method is before you. I have placed on the table specimens of blood of different degrees of anæmia, illustrating this method, where the standard of comparison represents the colour of 20 cubic millimetres of normal blood diluted 100 times. In that way, the percentage amount of hæmoglobin may be estimated, but the absolute quantity has been determined by some of the other methods. Of these, I may specially mention that carried out by Quinquaud, who, availing himself of the reducing properties of sodic hydrosulphite, was enabled to calculate the maximum quantity of oxygen capable of being absorbed by a given sample of blood. The mean capacity in health, he found, was 240 cubic centimetres of oxygen to every 1,000 grammes of blood; and as estimations by iron show that hæmoglobin contains 0.43 per cent. of that metal, and that 1,000 grammes of blood contained 0.53 grammes of iron, it follows that the quantity of hæmoglobin capable of absorbing the above amount of oxygen must be 128 grammes. (See Table V.)

TABLE V.—*Estimation of Hæmoglobin and its capacity for Oxygen. Mean of four observations. (Quinquaud.)*

	Amount of Hæmoglobin in 1000 cc. of Blood.	Amount of Oxygen absorbed by 1000 cc. of Blood.
Adult male	130 grammes	250 cc.
Adult female	114.2 grammes	225 cc.
Old man	105.8 grammes	205 cc.

M. Quinquaud has here assumed that hæmoglobin invariably has this absorptive capacity for oxygen, and has applied this method of determination to estimate the hæmoglobin in various diseases. In the main, his results accord with the older and more elaborate analyses, as well as with those obtained by the colour-methods. For example, he found that, in chlorosis, the hæmoglobin suffers absolute diminution to a greater extent than in any other disease, except pernicious anæmia and cancer, but that the solid matters of the serum were very slightly, if at all, reduced—a result similar to that I have recently quoted. The obvious objection to the method is, that it does not allow for alterations in the quality of the hæmoglobin of a given specimen of blood, which would alter its capacity for absorbing oxygen. Another difficulty arising in regard to most of the methods of absolute determination, lies in the discrepancies liable to creep in in the minute calculations they involve, a criticism which applies with equal force to all methods of blood-numeration and analyses of small quantities of blood. Thirdly, all these methods are imperfect, in that they, of necessity, tell nothing of the total amount of the blood, which may be much impoverished as a whole, but which, owing to alterations in density, may apparently yield a normal or even excessive amount of colouring matter and corpuscles. These points were well illustrated in a recent paper by Drs. Baxter and Willcocks (*the Lancet*, vol. i, pp. 361, 397, and 439, 1880), and enforce the lesson, that the results of these methods of estimation can only be dealt with in a relative sense; and that a very slight deviation may lead to very great error in the total result.

It is impossible, however, to deal with alterations in hæmoglobin without inquiring into the natural history of the red corpuscles themselves, which are so largely composed of this substance. This we may now proceed briefly to consider. We may expect to find variations in

the number, size, form, and evolution of those elements to be associated with the anæmic state; for, in general terms, this state depends either on a numerical deficiency in these corpuscles, to a deficiency in their hæmoglobin, or in both these directions.

The number of coloured corpuscles in a cubic millimetre of blood is, on an average, 5,000,000 for the adult male, and 4,500,000 for the female. These figures, originally calculated by Viorordt and Welcker, have been confirmed of late years by the process of numeration by means of the hæmocytometer invented by Hayem, and introduced into this country in a modified form by Dr. Gowers. Their precise accuracy has been questioned, some asserting that they are too high, others that they are too low—discrepancies depending partly, perhaps, on instrumental errors, and partly upon the variations which occur in the healthy subject in relation to food, to the greater or less concentration of the plasma, to the region from which the blood is taken, or the state of contraction of the vessel yielding it. At the same time, these figures represent sufficiently well the average of health, and serve well enough as standards of comparison. Mere numeration, however, is misleading as an indication of the blood-value; the hæmoglobin also must be taken into account; and we can hardly have a better example than in chlorosis, where, with a much diminished quantity of hæmoglobin, the number of corpuscles is often but slightly, if at all, below the normal. It has, therefore, been an object to determine the actual quantity of hæmoglobin falling to each corpuscle. Malassez especially has attempted this, so as to express the corpuscular richness in terms of hæmoglobin, and the hæmoglobin in terms of corpuscular richness (Table VI); and he has quite lately further perfected his method,

TABLE VI.—*Hæmoglobin and Corpuscles. (Malassez.)*

	No. of Corp. per cub. mm.	Qty. of Hgbn. per cub. mm.	Qty. of Hgbn. per Corpuscle.
Chlorosis	3,600,000	0.038	10.53 μ gr.*
Chlorosis	2,800,000	0.048	17.14 "
Ditto 1 month after treatment ..	3,300,000	0.062	18.78 "
Anæmia	4,000,000	0.086	21.56 "
Essential anæmia	1,830,000	0.033	16.66 "

* The sign μ gr. = $\frac{1}{1000000}$ of a gramme, and is employed to obviate the inconvenience of dealing with a large number of zeros in decimals.

whereby it can be clearly shown that the corpuscles in pathological conditions may contain a greater proportionate amount of hæmoglobin than in health, and the converse. He has shown also that the size of the corpuscle does not determine the amount of the hæmoglobin either in the animal series or in disease in man (see Tables VII and VIII).

TABLE VII.—*Hæmoglobin and Size of Corpuscles. (Malassez.)*

	Amt. of Hæmoglob. per Corpuscles.	Site of Corpuscles.	Amt. of Hæmoglob. per 1 μ cub. of Corp. Subst.
Man	30 μ gr.	72	0.416 μ gr.
Pigeon	52 "	125	0.416 "
Lizard	70 "	201	0.348 "
Frog	216 "	629	0.343 "
Proteus	1066 "	9200	0.115 "

TABLE VIII.—*Hæmoglobin and Size of Corpuscles. (Malassez.)*

	Richness in Hæmoglobin.		Diameter of Corpuscles.	
	Absolute.	Relative.	Absolute.	Relative.
Cancer	13 μ gr.	0.43	6.64	0.87
Chlorosis	22.7 "	0.75	8.29	1.09
Normal	30 "	1.0	7.60	1.0

Variations in colouring matter are seen whenever one calculates the number of corpuscles and estimates the percentage of hæmoglobin; but, although in one specimen 4,000,000 corpuscles with a percentage of 30 of hæmoglobin will be equivalent to 2,000,000 with 60 per cent., as regards the total quantity of colouring matter, it must be borne in mind that the respiratory or nutritive value—in other words, the functional value—of the one may be greater than the other, owing to the difference in the number of the elements, or to difference in their size.

The size of the coloured corpuscles (diameter of $\frac{3}{100}$ to $\frac{1}{200}$ of an inch or 7.7 μ) is a tolerably constant quantity in health; but in anæmic conditions it is common to find very many corpuscles much below the averages. The smaller spherical coloured elements, which have received the name of microcytes, are often abundant in anæmic blood. They may represent immature forms of the red corpuscle; and I shall have to mention yet smaller elements, upon the presence of which great stress is laid by M. Hayem, in speaking of the development of the blood. More than one authority has declared that the corpuscles in chlorosis are larger than those in health, and that in cancer they are plainly smaller—changes which, if occurring, might be related to the nature of the intimate substance of the corpuscle, where also may be found explanations for changes in form as well as size.

For the characteristic discoid shape (except in the case of the microcytes just mentioned) very little altered in the living state, although, after removal from the body, under the influence of reagents, etc., they

undergo many changes of shape. Considerable, and perhaps undue, stress has been laid upon the form-changes in corpuscles in the severe cases of idiopathic anæmia, of which they have been made almost a pathognomonic feature. In so far as they indicate a certain degree of instability, fragility, and proneness to decay of the corpuscles, or some altered relations between the plasmic fluid and the viscous globule, such curious alterations in shape may be suggestive of a profound blood-change. But more than this we are not warranted in saying.

Great interest attaches to these corpuscles in respect to their development in the embryo, their subsequent formation, destruction, and renewal; and it cannot be said that our knowledge is yet complete with respect to these matters. Their bearings upon the subject of anæmia are manifestly so important that I must not leave this part of my subject without alluding to them. The primitive blood-cells arise directly from the mesoblastic elements within the developing blood-vessels. These embryonic coloured corpuscles are nucleated, and in early fetal life the blood is largely composed of such nucleated corpuscles, which gradually disappear with the further development of the body. As soon as the liver and spleen are differentiated, the formation of these corpuscles takes place within these organs, although it is not confined to them, the connective tissue cells giving rise to red corpuscles formed out of their protoplasm (Schäfer). There seems no reason why this latter process should not go on in the growing organism after birth, together with the new formation of blood-vessels. In adult life, it is generally believed that the coloured corpuscles are developed from the colourless cells of the lymph, the transformation taking place partly in the general circulation, but largely in those organs which are specially devoted to the formation of the corpuscles of the blood—the spleen, lymphatic glands, bone-marrow, and liver. The splenic pulp contains cell-elements of different kinds, lymphoid corpuscles of various sizes, red corpuscles, intermediate forms, and certain peculiar blood-corpuscle-holding cells, which may represent a stage in the final involution of the red discs, or indicate their evolution from lymphoid cells. As to the lymphatic glands, their rôle is evident. The hæmatogenous function of the bone-marrow, first described by Neumann twelve years ago, is now generally admitted. It was founded on the resemblance of this tissue (especially in young subjects, where it is more vascular, redder, and less fatty than in later life) and its vascular supply to the splenic pulp, containing, as it does, lymphoid cells, cells with coloured nuclei, forming transitional elements between the lymphoid and red corpuscles. The relative abundance of this tissue in youth accords with a like degree of development of cytogenic tissue elsewhere in the body, and affords a contrast in the reparative power, after blood-loss at that period as compared with later ages. Hence an explanation for alterations in the corpuscular richness of the blood has been sought in changes in the bone-marrow, when the other organs of sanguification have appeared to be unaffected. The liver, which in the embryo undoubtedly is a source of the coloured corpuscles, is by many considered to play a part in blood-formation throughout life; but there does not appear to be yet sufficient proof of this.

One other point of interest concerning the formation of blood-corpuscles must be mentioned. M. Hayem, who has paid much attention to the subject, and whose observations include not only human blood, but the blood in all classes of vertebrata, has described "hæmatoblasts" of a somewhat different kind from those which are recognised in the marrow or spleen. These are small rudimentary blood-discs, furnished by the lymph together with the leucocytes, but so transparent and fragile as to escape observation, unless the blood be promptly examined at a freezing temperature, or "fixed" by reagents. They are faintly coloured, and in size vary from one-sixth to two-thirds that of the fully-formed corpuscles, to which they bear a tolerably constant proportion—viz., one to twenty, being thus considerably in excess of the leucocytes. The existence of small granular masses in the blood has long been noticed; and I have already mentioned the occurrence of smaller forms of red corpuscles, which are regarded by Hayem as intermediary between the very immature hæmatoblast and the completely developed corpuscle; but it is at least singular that these hæmatoblasts, so numerous as they are, should have been so long overlooked by histologists. I may add, that their discoverer not only attributes great importance to them in the development of the blood, and regards their presence in undue amount as evidence of incomplete evolution of the blood (as in chlorosis), but asserts that they play a leading part in the formation of fibrin.

Incomplete as our knowledge is as to the precise manner in which the coloured corpuscles are renewed in the blood, it is even less certain as regards the manner of their destruction, and as to their duration as independent, functionally active elements. For their function is not simply that of carriers of oxygen to the tissues; they also furnish products to secreting glands, and in so doing must be considered to suffer

destruction, just as in certain glands—e.g., the mammary—the cells perish in giving rise to their peculiar product. Indeed, from analogy there would seem to be nothing peculiar in the continued destruction and re-formation of blood-corpuscles; for, although it may be true that a secreting cell often has a certain stability, and after yielding up its product is once more enabled to draw fresh material and convert it to its peculiar secretion; yet there must be a limit to cell life and a renewal of cells in place of those rendered effete by repeated acts of secretion. In the case of the blood, there is evidence of the rapidity of renewal of its elements in the increase in corpuscles following ingestion of food, in the diminution during fasting, in the repair of the blood after menstrual loss, or after profuse hæmorrhage, and, indeed, in recovery from anæmia of any kind. M. Hayem, finding the immature corpuscles, or hæmatoblasts, to stand in a constant numerical proportion to the fully formed corpuscles, sees therein evidence of continual change to maintain this ratio, whilst, on the other hand, Quincke, in some recent researches upon artificially induced plethora, has estimated the duration of a red corpuscle to be about two weeks. There are not, however, sufficient data to remove this interesting point from the region of speculation. We know that the material of the corpuscles is constantly being excreted from the body or deposited in the tissues; and we infer that this implies a destruction of the corpuscle. The actual seat of this destruction is not founded on much surer ground. The spleen has been long regarded as the place where such a regressive change takes place; its richness in iron, its peculiar nucleated cells containing colouring matter, suggest this; and yet the blood of the splenic vein is richer in corpuscles than its artery; so that, if the spleen is the seat of their destruction, it must also be the seat of their renewal; possibly building up new corpuscles from the relics of the old, besides sending forth also abundance of leucocytes, to undergo further transformation into the coloured elements. However this may be, there is less uncertainty as regards the liver, which seems to be the chief seat of the destruction of red corpuscles; for not only does the blood passing out of this organ contain comparatively fewer corpuscles than that entering it, but its cells are laden with pigment derived from the blood, which they excrete with but little modification in the bile, of which one pigment, the bilirubin, is identical with the iron-free hæmatoidin. Lastly, the urinary pigment must also be derived from the blood; but I do not know whether its precise seat of separation has been determined. [Under certain conditions, probably concerned as much with derangements in the circulation of the kidney as with any actual change in the blood itself, the hæmoglobin will transude into the urine unaltered. Such are the cases of so-called intermittent hæmatinuria, apparently sometimes associated with malarial influences. The appearance of indican, especially abundant in diseases of the alimentary tract, in the urine, has relations probably to imperfect changes in assimilation; but its occurrence in anæmia has also been declared, and is suggested to point to some relation with the deficiency of blood in colouring matter.] Lastly, in conditions of artificially induced plethora, and in pernicious anæmia, Quinquaud has found a great excess of iron taken up by leucocytes and gland-cells in the liver, kidney, and other organs.

Having dwelt at such length upon the red corpuscles, it will not, I hope, be concluded that I wish to ignore the other blood-constituents, or the part which their diminution plays in the production of anæmia. But it is because the essence of anæmia lies in the impoverishment of the blood in colouring matter, that I have said so little about the other constituents, nor do they need much exposition. The white corpuscles may have other functions than that of giving rise to the coloured corpuscles. They may take part in the renewal of other tissues and cells, but of this we have no concern to-day. In so far as they give rise to the coloured elements, any hindrance to their transformation, or arrest of it, must deprive the blood of its chief constituent. Dr. Cavafy's interesting research, which points to the leucocytes in leukæmia being incapable of further transformation, is suggestive of the link between this blood condition and that of pure anæmia.

Then as to the albuminates of the serum and the salts, I have before intimated that they suffer change in anæmic conditions; but I must reiterate my conviction that, as compared with the hæmoglobin, they play but a minor part in the symptoms or effects of anæmia. It is impossible to dissociate them from the condition, for their changes are certainly factors of importance in its etiology; and yet there may be, as in chlorosis, all the evidence of anæmia with no diminution, but even an excess, of those constituents of the blood.

[To be concluded.]

SUPERANNUATION.—Mr. Thomas Collingwood, late medical officer for the Wardleworth district and the workhouse of the Rochdale Union, has obtained a superannuation allowance of £75 per annum.