Critical review : polycythaemia, erythrocytosis and erythraemia.

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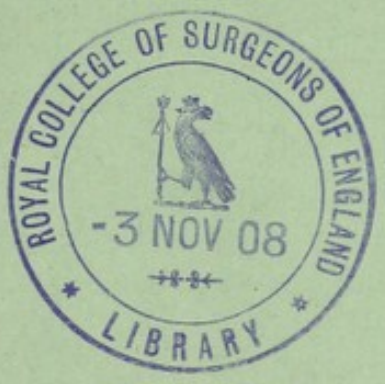

CRITICAL REVIEW

POLYCYTHAEMIA, ERYTHROCYTOSIS AND ERYTHRAEMIA

By F. PARKES WEBER

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PART I. POLYCYTHAEMIA.

Definition, &c. Polycythaemia or Polycythaemia rubra (French 'Polyglobulie') signifies a condition of the blood in which the number of the red corpuscles (erythrocytes) is decidedly above the average.

Slight physiological variations are connected with age, sex, and normal discharges (prolonged sweating, &c.) and probably also with atmospheric temperature; and greater physiological variations are connected with atmospheric pressure (living in high altitudes). In ordinary low altitudes the standard number of red cells in a cubic millimetre of human blood is taken as 5,000,000 for healthy males after the 'polycythaemia neonatorum' of the first few days of extra-uterine life has passed off. For women the average is slightly less than for men.

The purpose of the present article is chiefly to consider the form of polycythaemia known as 'erythraemia', but in order to limit and define the group of cases to which this term can be applied it will be necessary first of all to classify the other forms of polycythaemia and shortly to discuss the various conditions which are known (or may be supposed) to be capable of giving rise to polycythaemia.

Relative and absolute (true) Polycythaemia.

Polycythaemia may be (*a*) relative or (*b*) absolute (true).

(*a*) Mere *relative polycythaemia* is due to concentration of the blood, such as may be caused by choleraic diarrhoea or other excessive fluid discharges from the body (copious sweating). It is doubtless almost always of only temporary occurrence (possible exceptions occur in some cases of recurring night-sweats, &c.), and the diminution in volume of the blood-plasma, which causes it, is quickly recovered from when the normal osmotic conditions are re-established. Some degree of local relative polycythaemia can be induced (experimentally, as Cohnheim long ago showed, or by disease) in one limb or in one part of the body by obstruction to the return of venous blood from the

part in question; the explanation of this is that the delay of the blood-flow allows longer time for lymph to leave the blood-vessels, and so gives rise to local blood-concentration. As, however, will be afterwards pointed out, a condition of blood-stasis (impeded circulation) affecting a large portion of the body may probably sometimes give rise to a secondary (general) absolute polycythaemia as well as more directly to a (local) relative polycythaemia.

(*b*) In *absolute* or *true polycythaemia* (polycythaemia rubra vera) the total number of red corpuscles in the body is increased, and there is evidence, to which we shall later on refer, which shows that in most, if not in all, cases of absolute polycythaemia the total volume of blood in the body is increased as well as the number of corpuscles. It is quite probable that in certain patients with cardiac valvular defects, &c., a condition of absolute polycythaemia exists unaccompanied (owing to simultaneous relatively greater increase in the total volume of blood) by relative polycythaemia, but for our present purposes we need consider only those cases in which the presence of absolute polycythaemia is evidenced by the persistence of a relative polycythaemia discovered on making a blood-count in the ordinary way.

The possibility of cases of absolute polycythaemia being regarded as cases of mere relative polycythaemia (i. e. mere blood-concentration) is unlikely for the following reasons:—

(1) The absence of the recognized causes (diarrhoea, excessive sweating, &c.) of diminution in the total quantity of blood.

(2) The plethoric (full-blooded) or congested appearance of some of the patients.

(3) The persistence of the polycythaemia (merely relative polycythaemia, as already stated, is almost always only temporary).

(4) In some cases, moreover, as we shall subsequently point out, the total quantity of blood in the body can be estimated and proved to be in excess of the average.

In distinguishing cases of erythraemia from other forms of polycythaemia it is mainly or solely with the various classes of absolute polycythaemia that we are concerned.

Primary and secondary Hyperplasias of the Blood: Erythraemia and Erythrocytosis.

By analogy with cases of leukaemia and leucocytosis, cases of absolute polycythaemia have been divided into two main divisions:—(*a*) apparently primary cases of hyperplasia of the red cells, i. e. cases of erythraemia; and (*b*) secondary or symptomatic cases of hyperplasia of the red cells, i. e. cases of erythrocytosis.

In this way the term 'erythraemia', as proposed by W. Türk, H. Hirschfeld and W. Osler, is reserved for cases in which the increase in the number of red cells, or rather the excessive erythropoiesis of which the polycythaemia is the

expression, appears, as far as our present knowledge goes, to be the primary disorder, just as in leukaemia the increased formation of white cells appears to be the primary disorder. On the other hand the word 'erythrocytosis', as suggested by Hirschfeld, is applied to cases in which the polycythaemia is secondary and in which it generally appears to represent a conservative vital reaction, i.e. an effort on the part of the organism to compensate for some difficulty in the oxygenation of the blood and tissues of the body. Erythrocytosis is thus analogous to leucocytosis in the more recent sense of the latter term, namely as signifying a secondary or symptomatic (generally a reactive or conservative) increase of the white corpuscles, such as may result from streptococcal or other microbic invasions of the body.[1] Thus, in all cases of erythrocytosis there is as much cause for the hyperplasia of the red blood-corpuscles to occur as in cases of renal or valvular disease there is for the heart to become hypertrophied.

The best known forms of erythrocytosis are those connected with residence at high altitudes and diminished oxygen-tension in the inspired air and those due to imperfect oxygenation of the blood and tissues owing to circulatory disturbance in chronic cardiac and pulmonary complaints, especially cases of congenital stenosis of the pulmonary orifice of the heart.

The causes of Polycythaemia in cases of Erythrocytosis and in cases of Erythraemia.

In regard to the polycythaemia of chronic cardiac and pulmonary diseases there can now be no doubt that imperfect oxygenation of the blood and tissues is the exciting cause of the polycythaemia, in fact that deficiency of oxygen, as was many years ago suggested, stimulates the functions of the red bone-marrow so as to cause an increased formation of red cells. According to this view the polycythaemia is a 'conservative' or 'compensatory' vital reaction on the part of the individual, an automatic attempt to make up for deficient oxygenation of the tissues by increase in the number of the red blood-cells, which are the oxygen-carriers of the blood. Post-mortem examinations in cases of chronic cyanosis of cardiac or pulmonary origin help to confirm this hypothesis, for, in such cases, although the red colour of the bone-marrow of the shafts of the long bones is partly due, as I have satisfied myself, merely to engorgement with blood, evidence of abnormal haemopoietic activity is likewise obtained. It is surprising that in this respect very few exact observations have as yet been recorded, but E. Weil (1901), in post-mortem examinations on two children with congenital stenosis of the pulmonary orifice of the heart and chronic cyanosis, found that there was red transformation of the bone-marrow, microscopic sections

[1] It must, however, be remembered that the word 'leucocytosis' is still sometimes employed to signify a moderate increase in the number of white blood-cells, whether reactive in nature (constituting a 'leucocytosis' in the modern sense of the term) or arising as an early stage of leukaemia (the so-called 'leucocytic stage of leukaemia').

of which showed that all traces of the normal fatty tissue had disappeared. L. G. J. Mackey (1907) examined microscopic sections made by James Miller from the bone-marrow of a case similar to those of Weil and was able to confirm Weil's results. In a case of chronic cyanosis from pulmonary emphysema but without polycythaemia Mackey found the bone-marrow normal.

The polycythaemia of high altitudes,[2] which is now at last universally allowed to be an absolute or true polycythaemia, must be explained in the same way, as indeed F. Miescher suggested in 1893. It represents, in fact, a conservative vital reaction on the part of the individual (that is to say on the part of his bone-marrow) to compensate for the diminished oxygen-tension in the inspired air at high altitudes, i. e. to compensate for the resulting difficulty in maintaining proper oxygenation of the blood and tissues of the body. Animals when kept at high altitudes react by a polycythaemia just as men do, and the bone-marrow of dogs which have developed a polycythaemia from being kept at high altitudes, has been carefully, macroscopically and microscopically, examined and found to give abundant evidence of increased erythropoietic activity (Zuntz, Loewy, Mueller and Caspari). Jaquet and Suter's observations on the increase of blood-corpuscles and haemoglobin in rabbits when kept at Davos, the famous Swiss mountain resort, are well known, and will be referred to again later on. These observers found that the increase in red cells and haemoglobin was very striking. Jaquet obtained quite similar results (nearly parallel increase in the figures) by keeping rabbits in chambers, in which the atmospheric pressure was artificially reduced to correspond to a fall of 100 mm. in the height of the barometric column, which is equivalent to a rise of over 1,000 metres in altitude. Paul Regnard had already maintained that in animals an artificial atmosphere containing excess of oxygen reduced the number of red cells in the blood, and he had also increased the haemoglobin value of the blood by subjecting animals to an artificially rarefied atmosphere. But the value of his results was called in question owing to the artificial conditions to which the animals were subjected and the possibility of excess of carbonic acid playing a part in the latter experiment. Sellier (of Bordeaux) had likewise shown in 1895 that experimental reduction of the oxygen-tension in the air was sufficient to induce a polycythaemia in animals. Similar experiments had also been carried out by O. Schaumann and E. Rosenquist on dogs, rabbits, and pigeons. They were kept in an artificially extremely rarefied atmosphere, corresponding to an altitude of about 4,000 metres, and by this means not only were the red cells (erythrocytes)

[2] The extensive literature on this subject commences with Paul Bert's observation in 1882 that the blood of the Peruvian mountain-sheep (Llama), was capable of absorbing much more oxygen than the blood of sheep living at low elevations. Then follow the writings of A. Muentz (1890), F. Viault (1890), F. Miescher (1893), F. Egger, A. Mercier, A. Jaquet, F. Suter, Campbell and Hoagland, Abderhalden, Armand Delille and Mayer, Buckmaster, Schaumann and Rosenquist, P. Regnard and many other investigators. For an account of all this literature see the elaborate work on the effects of high altitudes by Zuntz, Loewy, Mueller and Caspari (1906), Jaquet's (1904) and Buckmaster's (1906) monographs, and the short summary in H. and F. P. Weber's *Climatotherapy* (London, 3rd edition, 1907, pp. 60–2).

increased in number, but in the case of the dogs and rabbits nucleated red cells (erythroblasts), that is to say, young unripe forms of red cells, were made to enter the circulating blood from their normal home in the bone-marrow. Various observations quoted by Jaquet and others show that the changes in the quality and quantity of the blood which occur as the result of living at high altitudes and which can be experimentally produced by subjecting animals to an artificially rarefied atmosphere, cannot be explained as the effects of low temperature or increased light. As further confirmation of these views it may be noted that E. Kuhn by the use of his so-called 'suction-mask', that is to say by periodical artificial diminution of the oxygen-pressure in the lungs, has apparently been able in some persons to produce a decided increase of red cells in the blood.

Here we may mention a number of other (clinical or experimental) conditions, which by interfering with the proper oxygenation of the blood and tissues of the body, may give rise to a secondary polycythaemia (erythrocytosis), viz.:—Experimental stenosis of the superior and inferior venae cavae and artificial compression of the thorax (Reckseh); diminution of oxygen and increase of carbonic acid gas in the inspired air (Sellier, Palleri and Mergari); clinical or experimental stenosis of the trachea or larynx (Vaquez, Sellier, Labbé, Quiserne); clinical or experimental pneumothorax (Raybaud, Schlosser, Auscher and Lapicque).

In regard to the cause of the polycythaemia in cases of erythraemia nothing certain is at present known, excepting that, as the changes found in the marrow of the shafts of the long bones at necropsies and in one instance (G. A. Gibson) during life (i.e. for 'biopsy' purposes) have shown, it is brought about by increased activity in the erythropoietic functions of the bone-marrow. But an increased activity of the bone-marrow is doubtless also the immediate cause of the other classes of absolute polycythaemia, as I have already pointed out in regard to the polycythaemias dependent on chronic cardiac and pulmonary diseases, and on residence at high altitudes. There is no evidence that increased durability of the red corpuscles and increased resistance towards haemolytic agents plays any essential part in the causation of any kind of polycythaemia, but I shall have to return to this subject later on.

I think I have now sufficiently explained what appears to be the only tenable view in the present state of our knowledge regarding the origin of the various classes of absolute polycythaemia. In all cases the polycythaemia is due to an increased haemopoietic (especially erythropoietic or 'erythroblastic') activity of the bone-marrow, that is to say it is always myelogenous in origin; but although the exciting cause of this increased functional activity is recognized, as I have already explained, in regard to the secondary polycythaemia (erythrocytosis) connected with disorders of the circulatory system and residence at high altitudes, it remains unknown in regard to the 'myelopathic polycythaemia' or 'erythraemia'. In this last class of polycythaemia the excessive functional activity of the bone-marrow constitutes as yet the primary recognizable morbid factor, and that is the reason why, in 1905, I proposed the term 'myelopathic' (not merely myelogenous or myelogenic) polycythaemia for it.

The excessive formation of red blood-corpuscles in myelopathic polycythaemia may perhaps, as has already been mentioned, be regarded as analogous to the excessive formation of white blood-corpuscles in cases of leukaemia. It can likewise be explained as the result of a morphological and functional reversion to (or, in certain cases, persistence of) a past condition (normal in foetal life and early life after birth) in which the bone-marrow of the shafts of the long bones is red and still actively engaged in the formation of erythrocytes, instead of being yellow and fatty as most of it is in healthy adults. If the analogy to leukaemia proves to be appropriate, the term 'erythraemia' must be considered preferable to the term 'myelopathic polycythaemia' and the various other names which have been proposed, since it implies that the disease is one which in regard to erythrocyte-formation is analogous to leukaemia in regard to leucocyte-formation. In fact, if, as H. Ribbert believes, there is a form of 'myeloma' (that is to say of growth originating in the elements of the bone-marrow) which should be termed 'erythroblastoma', because the tumour-cells are related to erythroblasts, it seems possible that cases of erythraemia may bear a relation to cases of erythroblastoma similar to that which cases of leukaemia bear to cases of leucoblastic myeloma. It must, however, be remembered that Ribbert's case of 'erythroblastoma' is as yet the only one recorded and the existence of so remarkable a kind of tumour-formation certainly needs confirmation.

Objections to the view that the excessive formation of red cells in the bone-marrow is the primary pathological condition in erythraemia have been urged by F. Lommel, J. Bence and others; and it must be admitted that in several cases of clinically (that is presenting the clinical symptom-complex of) splenomegalic polycythaemia evidence of general or local blood-stasis (impeded circulation) has been ascertained, suggesting that the polycythaemia, at all events in the cases in question, was more or less reactive in nature and secondary to imperfect oxygenation in the whole or part of the body. According to Bence, the polycythaemia of splenomegalic polycythaemia can be diminished by oxygen-inhalation, just as he claims that the polycythaemia of cardiac origin and that due to high altitudes can be, but R. Stern and others obtained negative results by this method. I shall return to these subjects in the later portion of this article devoted to erythraemia.

Characters of the Blood and Blood-forming Tissues in Absolute Polycythaemia.

Before proceeding further it will be well to consider certain features common to erythraemia and erythrocytosis. We have already given our reasons for believing that in all cases the *essential change in the blood-forming tissues is an increase in the erythroblastic elements of the bone-marrow.* We have now to consider *certain characters of the blood probably common to all classes of absolute polycythaemia.*

The degree of relative polycythaemia in cases of absolute polycythaemia. In all classes of absolute polycythaemia, but especially in erythraemia, the increase in the number of red cells is sometimes very remarkable. In cases of congenital heart disease, with more or less chronic cyanosis, blood-counts of seven to eight million red cells to the cubic millimetre are not at all unusual, as in the case of a girl, aged seventeen years, whom I showed at the Clinical Society of London in 1907, and whose red corpuscles had varied from 6,375,000 to 7,352,000 in the cubic millimetre. Many much higher counts are referred to by Quiserne. Some authors formerly thought that in chronic cyanosis connected with heart disease the red corpuscles never exceeded eight millions per cubic millimetre of blood, but in congenital pulmonary stenosis and more complicated forms of congenital heart disease the following counts prove the contrary:—9,447,000 (Banholzer, 1894); 8,470,000 (G. A. Gibson, 1895); 10,540,000 (Variot, 1897); 9,860,000 (Audry, 1902); 9,084,000 (Babonneix, 1902); 9,800,000 (Fromherz, 1903); over 10,000,000 (Friedel Pick, 1904, and J. H. Drysdale, 1905); 8,320,000 (Batty Shaw, 1907). In a child aged two months with congenital heart disease, in which a subsequent necropsy showed also that the spleen was congenitally absent, Gardère (1908) found the red blood-cells 9,000,000, and the white cells (chiefly mononuclear forms) 25,000. Recently at the Clinical Section of the Royal Society of Medicine (November 8, 1907), Murray Leslie showed a woman aged 22 years with congenital heart disease, who had cyanosis and clubbing of the fingers from birth, and whose blood was found to contain over 11,000,000 red cells to the cubic millimetre; and even this is not the highest count recorded in congenital heart disease.

In three patients at the German Hospital, London, with cyanosis connected with chronic pulmonary emphysema and circulatory insufficiency, we obtained blood-counts of respectively 6,350,000, 6,850,000, and 6,870,000 red cells per cubic millimetre, and in a fourth case the counts on various occasions were 6,930,000, 8,230,000, and 9,357,000.

In normal persons the 'polycythaemia of high altitudes' (including that of residence at localities 6,000 feet and more above sea-level) may reach seven to eight million red cells per cubic millimetre of blood.

In cases of erythraemia counts of nine to ten million red cells and over have been fairly common, with haemoglobin-values up to 160 to 180 per cent. of the normal standard, and even higher. If samples of such extremely polycythaemic blood (in which coagulation has been prevented by the addition of citrate or tartrate of potassium) are allowed to stand in a cylindrical glass vessel until the corpuscles have had time to settle down, it will be found that the corpuscular sediment occupies over nine-tenths of the whole column, the blood-plasma forming only a thin layer on the surface; whereas in normal human blood the corpuscular layer and the layer of blood-plasma are about equal in volume. It has indeed been supposed that there is not 'standing room' for more than about 13,000,000 red cells to the cubic millimetre, as R. Hutchison has expressed it. In cases of polycythaemia with cyanosis and splenomegaly

blood-counts of 12,000,000 have been registered by Cabot, 12,500,000 by Reckzeh, and 13,600,000 by Koester, whilst haemoglobin-values of 190 to 200 per cent. (Sahli's methods) have been recorded by both Rosengart and Koester. The latter states that the haemoglobin value (estimated by Sahli's apparatus) in his case was on one occasion 240 per cent. (misprint ?) of the normal. In haemoglobin measurements there are, however, greater sources of error than in blood-counts.

The degree of polycythaemia may of course vary to some extent according to the part from which the blood is taken, as Malassez long ago insisted. Obstruction to the return of blood from a limb increases the proportion of corpuscles in the affected part (local relative polycythaemia), as Cohnheim proved experimentally in animals; and vasomotor influences (constriction or dilatation of vessels) affect the relative erythrocyte-count by altering the local concentration of the blood, as experiments by Grawitz, Cohnstein and Zuntz, and Chéron have shown. In a patient whose case was recorded by Reckzeh (his third case), in whom there was progressive obstruction to the blood-flow in the superior vena cava, the cyanosis and polycythaemia were for a long time limited to the portion of the body chiefly affected by this obstruction.

Though the blood used for blood-counts is practically always capillary blood it must not be forgotten that in polycythaemia the increase of red cells is generally not quite uniform in the arteries, capillaries and veins, at all events when the polycythaemia is secondary to impeded circulation. Thus G. A. Gibson on one occasion in a boy, aged 16 years, supposed to be suffering from mediastinal pericarditis, found the erythrocytes in the arterial blood to be 7,000,000, in the capillary blood 8,500,000, and in the blood from a vein 10,000,000. Palleri and Mergari in a case of congenital pulmonary stenosis counted the red cells in capillary blood from the finger at 6,650,000, in venous blood from a vein in the arm at 6,400,000, and in arterial blood from the temporal artery at 5,950,000. Ascoli, however, in a case of (clinically) splenomegalic polycythaemia made the erythrocyte-count from the radial artery 6,100,000 when the capillary blood from the lobe of the ear only gave 6,000,000 (? admixture of serum from the subcutaneous tissue). Geisböck in 'hypertonica polycythaemia' found almost the same number of cells in arterial as in venous blood. On one occasion in one of his patients with high blood-pressure the red corpuscles were counted in blood from the radial artery, in capillary blood from the finger, and in venous blood from the median vein; and the resulting figures were respectively 10,530,000, 10,695,000, and 10,775,000.

The viscosity of the blood in polycythaemia and its relation to the blood-pressure. The blood-viscosity is always raised when the number of red corpuscles per cubic millimetre is much increased. This can be demonstrated, as I have myself found, in specimens of blood from patients with polycythaemia and chronic cyanosis of cardiac or pulmonary origin. So also in two cases of splenomegalic polycythaemia I found the viscosity of citrated specimens of the venesection-blood to be more than twice the normal. Supposing the viscosity

of normal human blood to be about 5·1 to 5·3, that is to say 5·1 to 5·3 times that of water (when the temperature of both is 38° C.), Lommel found the viscosity to be over 11·0 in two cases of polycythaemia with splenomegaly (in one patient the splenomegaly was only temporary), whilst Bence in another case obtained figures varying from 15·9 to 20·9, and Münzer in another case showed that the figures varied between 12·0 and 23·0, partly according to the special form of viscosimeter which he employed; in Löw and Popper's first case the viscosity of the citrated blood (by Hirsch and Beck's method) was 10·4; in Saundby's case of 1907, J. H. Watson (by Denning and Watson's method) estimated the viscosity at 9·4. In three cases of cyanosis in heart disease, and in one case of bronchitis with emphysema, Bence obtained viscosity-values of between 6·9 and 8·2. Determann has shown that the viscosity of the blood is increased, like the number of erythrocytes is, at high altitudes. In some rough experiments made in 1904 with J. H. Watson on citrated horse's blood, we showed that the variations in viscosity generally depended mainly, though of course not entirely, on the proportion of the blood-corpuscles to the volume of blood-plasma. It was found, for instance, that horse's blood-plasma, artificially mixed with two millions of red corpuscles to the cubic millimetre, took 84 seconds to pass through the bulb of the 'viscosity-tube', whilst a sample containing four million red corpuscles to the cubic millimetre took 110 seconds to pass through the bulb of the same tube. All observers who have investigated the subject have found that increase in the number of red corpuscles raises the viscosity of the blood, but we may especially refer to the early work of A. Czerny (1894), the experiments of C. Jacob (1901), and Sherrington and R. J. Ewart (1904), and the elaborate papers on the subject by Determann (1906) and Denning and Watson (1906). On the whole subject of human blood viscosity we would refer also to the writings of Burton-Opitz (1900), Trommsdorff (1900), Hirsch and Beck (1901), J. Bence (1906) and W. Hess (1907).

In spite of the excessive viscosity of the blood, the blood-pressure in polycythaemia, though usually, is not always high, and in most cases the left ventricle of the heart is not greatly hypertrophied. Evidently the difficulty in circulation caused by the abnormal blood-viscosity is to a great extent avoided by compensatory dilatation of blood-vessels. This is just what some of the experimental work on the relation of artifically increased blood-viscosity to blood-pressure (Jacobj) would lead one to expect, but all observers are agreed that artificial increase of blood-viscosity does tend to raise the blood-pressure in spite of compensatory dilatation of blood-vessels.

The haemoglobin-value of the blood in absolute polycythaemia. The haemoglobin-value may be very greatly raised, but it is seldom increased to the extent corresponding to the increase in the number of red cells. Thus generally the colour-index of the red cells is below 1·0. It seems probable that the red cells may in some cases be numerically increased as a kind of compensatory reaction to make up for their deficiency in haemoglobin. Thus in some cases of syphilis, &c., a secondary polycythaemia (erythrocytosis) seems to be associated

with a subnormal haemoglobin-value, constituting a blood-state which may perhaps be termed a 'polycythaemic anaemia'.

The specific gravity of the blood and blood-serum in absolute polycythaemia. The specific gravity of the blood seems usually to be raised, but apparently often not in proportion to the degree of polycythaemia. The specific gravity of the blood-serum, however, is probably never raised when the polycythaemia is absolute. In erythraemia Weintraud found it below normal. According to Askanazy the specific gravity of blood-serum is normally 1028–1032. Weintraud found it only 1025–1026 in two of his erythraemia cases and Geisböck in one of his patients with 'polycythaemia hypertonica' made it 1025–1028.

The dry residue of the blood and blood-serum in absolute polycythaemia. The percentage in normal blood-serum is said to be 9·21 to 10·50. In two of Weintraud's cases of splenomegalic polycythaemia it was found to be 9·30 and 9·28 respectively, whilst in a similar case Senator gives it as 10·72. In a case of 'polycythaemia hypertonica' Mohr found it 10·1, and Geisböck in one of his best marked examples of the same condition made it 9·0 to 9·9. The estimation of the dry residue and specific gravity of the blood-serum in polycythaemic patients is of course of some value in excluding the possibility of blood-concentration. (I do not know that this point has been investigated in regard to the erythrocytosis of high altitudes in human beings.) The percentage of dry residue in the blood as a whole is doubtless rather above than below the normal in all forms of polycythaemia. In three erythraemia cases Weintraud obtained figures between 22·6 and 29·0 per cent., and in similar cases Senator found the percentage 27·2, and Löw and Popper 27·3, whilst Askanazy estimated the percentage in normal men as 20·3 to 22·8.

Iron and albumen in the blood of absolute polycythaemia. The amount of iron is probably raised in proportion to the increase in haemoglobin. In regard to the percentage of albumen in the blood-serum it is worth mentioning that both Weintraud and Senator found it in erythraemia cases decidedly below the normal (8·8 per cent. according to von Jaksch) for healthy adults; in one such case Weintraud also estimated the percentage of albumen in the blood as a whole and found it slightly below the normal (22·6 per cent. according to von Jaksch).

The coagulability of the blood in polycythaemia. The blood-coagulability appears to vary independently of the richness of the blood in red cells and haemoglobin. It may be raised or lowered in polycythaemia just as it may be in oligocythaemia.

Increased haemolysis in absolute polycythaemia. As the rate of production of the red cells in these cases is increased it may be concluded that the rate of their destruction is likewise probably increased, unless the cells are unduly resistant to haemolysis or otherwise peculiarly durable so as to have an abnormally long life. For this latter supposition there is certainly no evidence, although Fick (quoted by G. Schroeder) at one time was inclined to explain the 'polycythaemia of high altitudes' as due to a hypothetical increase in the

life-duration of the red cells. In two cases of erythraemia (Parkes Weber, Saundby) the resistance of the red cells to haemolysis (methods employed by Wright or Ribierre) was found to be about normal, and in one case (Vaquez and Laubry) it was found to be unduly low; these observations are opposed to any theory of increased durability of the red cells. Abeles in two cases of polycythaemia found the excretion of iron in the urine to be above the normal, an observation which as far as it goes supports the view that increased haemolysis accompanies absolute polycythaemia. In this connexion it may be added for what it is worth that the total excretion of urobilin has been estimated in three or four cases of (clinically) splenomegalic polycythaemia; in a case reported by Lommel it was found to be above the average and in Senator's two cases it was about normal, whilst Löw and Popper in their first case found it slightly raised. Evidence by microscopic examination after death regarding the amount of phagocytosis in the spleen in absolute polycythaemia is very scanty. In one case of erythraemia in which the spleen was microscopically examined H. Hirschfeld found very many cell-containing phagocytes present, but in another case he found very few. Owing, however, to the large size of the spleen in Hirschfeld's two cases it seems probable that in at least one of them the total phagocytosis of red cells was very greatly increased.

The total blood-volume in absolute polycythaemia. It is probable, as I have already mentioned, that in absolute polycythaemia the total volume of blood in the body is generally, if not always, above rather than below the normal average, that is to say the quantity which should correspond to the body-weight. In 1900 J. S. Haldane and Lorrain Smith published their 'carbon-monoxide method' of estimating the total volume of blood in the body, a method which made it clinically possible to recognize the presence of true plethora, and in 1906 C. G. Douglas tested this method in animals and found that the results obtained by it agreed fairly closely with those obtained by the old Welcker's method in which the blood had to be extracted from the tissues after the death of the animal. Oerum of Copenhagen, in a recent account of Haldane's carbon-monoxide method, points out that the importance of ascertaining the total blood-volume when examining the blood is something like that of estimating the total daily output when examining the urine. The carbon-monoxide method has been already employed in various cases of true polycythaemia in man. Lorrain Smith and H. L. McKisack, in the case of a boy, aged 12 years, suffering from adherent pericardium and chronic cyanosis, not only showed that the proportion of red cells to blood-plasma was excessive (relative polycythaemia), but also demonstrated by the carbon-monoxide method that the total volume of blood was far beyond the normal standard, so that there was undoubtedly a condition of true plethora present. The number of red cells in the cubic millimetre of blood was 6,340,000, and by the carbon-monoxide method it was ascertained that the total volume of blood in this boy's body was nearly double that of the normal standard. In the case of splenomegalic polycythaemia which I described in 1905, the total volume of the patient's

blood was estimated in the same way by Haldane himself, and was found to be greatly in excess of the normal. In fact, with a blood-count of between eight and nine million red cells to the cubic millimetre, and with a haemoglobin-value of about 150 per cent. of the normal standard, there was likewise a great excess of the total blood-volume, that is to say, a condition of true plethora was also present. This is exactly what one would suppose from the plethoric look of such patients and from the engorged state of their visceral blood-vessels as revealed at the few post-mortem examinations which have as yet been recorded. I have Dr. T. D. Acland's permission to state that in an as yet unpublished case of splenomegalic polycythaemia under his care at St. Thomas's Hospital, Dr. Haldane made a clinical estimation of the total blood-volume by the carbon-monoxide method, and showed that it was about two and a half times the normal. Dr. R. Hutchison also kindly informs me that in two typical cases of splenomegalic polycythaemia (accounts of which have not yet been published) at the London Hospital Dr. A. E. Boycott determined the total blood-volume by Haldane and Lorrain Smith's method and found it in both cases very much increased; in one of the two cases, indeed, it appeared to reach the extraordinary figure of 10,750 cubic centimetres, that is to say, probably more than three times the volume normally corresponding to the patient's body-weight. Quite recently, in another patient, Boycott and Douglas determined the total blood-volume by the same method and again found it greatly increased, as it was in all the other cases.

In regard to the polycythaemia of high altitudes there is less evidence of associated polyaemia (true plethora) in human beings, but Jaquet and Suter found that in rabbits kept at high altitudes (Davos) a very striking increase occurred, not only in the number of red corpuscles and richness in haemoglobin per cubic millimetre of blood, but likewise in the total quantity of blood (and haemoglobin) which could be extracted from the body. Guillemard and Moog, from their observations on rabbits at the summit of Mont Blanc, also conclude that the total blood-volume is increased at high altitudes.

The relation of increased total blood-volume (polyaemia, plethora vera) to absolute polycythaemia. Not many years ago the possibility of the persistence of a condition of plethora was denied by most authorities. R. von Limbeck, in the second edition (published in Germany in 1896, English translation, 1901) of his *Clinical Pathology of the Blood*, wrote: 'The doctrine of plethora, formerly a dogma, has received its death-blow, owing to the growth of experimental investigation. It was especially due to the works of von Lesser, Worm-Müller, and Cohnheim that the possibility of the persistence of a condition of plethora came to be denied.' In 1900, J. Lorrain Smith, by the 'carbon-monoxide method' previously referred to, proved that in the so-called anaemia of chlorosis the total volume of the blood was in reality greatly increased (in proportion to the severity of the disease), and now, as we have already pointed out, it appears that true (absolute and persistent) polycythaemia is always, or almost always, accompanied by a condition of true plethora (polyaemia).

Are there any experimental observations which throw light on this association of true plethora with polycythaemia? Yes, I think there are some, and, curiously enough, they are the very experiments of Worm-Müller (1875) on which Cohnheim based his assertion that plethora could not exist. These experiments and those of von Lesser (1874) did, indeed, prove the impossibility of suddenly producing a persistent plethora by the experimental transfusion method, but, at the same time, they wonderfully well illustrate the manner in which a condition of persistent polycythaemic plethora may arise under certain pathological (chronic cardiac disease, &c.) or physiological (residence at high altitudes) conditions. I shall, therefore, shortly describe the experiments in question as given in von Limbeck's work already referred to. When von Lesser and Worm-Müller tried to produce plethora artificially by transfusion of blood into an animal, the blood-vessels were at first enlarged to receive the excess and the blood-pressure was augmented, but a portion of the injected blood quickly began to leave the vessels, the lymph-stream increased, and the increase in the blood-volume gave place to an increase of blood-corpuscles (polycythaemia), which in its turn gradually disappeared. No bad symptoms were observed when the quantity of blood transfused amounted even up to approximately 80 or 100 per cent. of the (estimated) normal total blood-volume in the animal's body. Within half an hour after the transfusion half the injected fluid had already, according to Worm-Müller, left the blood-vessels, though the cellular elements remained, giving rise to a polycythaemia. In the case of a rabbit transfused for fifteen minutes from another rabbit, the red corpuscles counted before the experiment were 5,160,000 to the cubic millimetre, but twenty-two minutes after the transfusion they were 8,280,000 to the cubic millimetre. In these experiments the polycythaemia did not last long. Worm-Müller found that the number of corpuscles was reduced to the normal in two days. Similarly, in the case of a dog in which the quantity of the blood was much increased by transfusion, the number of red corpuscles in the cubic millimetre of blood was found to be greatly in excess thirty minutes after the experiment, but here again the polycythaemia was only transitory, disappearing some days after the transfusion, though of course less quickly than the artificial plethora did. From all these experiments it is clear that the circulatory system finds it much more easy to get rid of a superfluous quantity of blood-plasma than to free itself of a superfluous number of corpuscles, but why the 'plasma-plethora' in chlorotic patients is not got rid of remains a problem to be solved.

In no such experiments have the conditions prevailing in the various classes of polycythaemic polyaemia (plethoric polycythaemia) (plethora vera) of human beings been fulfilled. In all these cases in human beings the polycythaemia, as we have explained, arises from increased activity in the haemopoietic functions of the bone-marrow, and the increased activity of the bone-marrow is in its results practically equivalent to a gradual persistent transfusion of blood into the vessels. In other words, the bone-marrow in these cases is constantly

engaged in producing excess of blood,[3] and forcing all of it into the blood-stream. The increased total quantity, and polycythaemic quality, of the circulating blood are both therefore the natural result of the persistent increased formation of blood in the bone-marrow, and a similar condition of persistent polycythaemia would be obtained in Worm-Müller's experiments on animals, were it possible (which of course it is not) to modify his experiments so as to make the transfusion of blood a gradual persistent process, lasting, not for a few minutes, but for days, weeks, months, and years.

Possible causes of Secondary Polycythaemia (Erythrocytosis) other than Chronic Cardiac and Pulmonary Diseases and Residence at High Altitudes.

We have already discussed erythrocytosis connected with residence at high altitudes (diminished oxygen-tension in the inspired air) and erythrocytosis due to imperfect oxygenation of the blood and tissues in chronic cardiac and pulmonary complaints. These probably afford the most typical examples of secondary polycythaemia, but we shall now have to consider other occasional causes of polycythaemia, because a case cannot be classed as one of erythraemia (primary absolute polycythaemia) until all adequate causes for secondary polycythaemia (and indeed relative polycythaemia) have as far as possible been excluded.

Erythrocytosis secondary to blood-stasis (impeded circulation) not of cardiac or pulmonary origin. Lommel and Reckzeh have especially urged the view that polycythaemia, and indeed polycythaemia with splenomegaly, though cardiac and pulmonary disease be absent, may, nevertheless, be secondary to impeded circulation, possibly more or less local in origin, for instance, extreme passive congestion in the portal system. In many cases presenting the symptom-complex of splenomegalic polycythaemia it must be admitted that evidence of more or less vascular obstruction has been found during life or at the necropsy, e.g. thrombotic changes in the spleen and other organs, cirrhosis or great engorgement of the liver, and disease of blood-vessels in the limbs. In two cases of polycythaemia with splenomegaly (van der Weyde and van Ijzeren's case and Lommel's first case) the necropsy showed that there had been chronic obstruction and final thrombosis in the portal vein. In those cases the polycythaemia may have been at all events partly due to the impeded circulation. Cases of polycythaemia with chronic cyanosis and splenomegaly may indeed be explained in this way when there is undoubted evidence of greatly impeded circulation and when there is likewise some adequate cause for the splenomegaly, but it must be remembered that chronic passive congestion of cardiac or cardio-pulmonary origin seldom gives rise by itself to clinically obvious

[3] It may be taken that the blood-plasma is in some way or other so dependent for its existence on the blood-corpuscles that the formation of blood-corpuscles in the bone-marrow is practically equivalent to the formation of blood.

splenomegaly; obvious splenomegaly is nearly always absent in cases of polycythaemia secondary to congenital or acquired cardiac disease.

Polycythaemia and erythrocytosis of toxic origin. Toxic conditions interfering with the proper oxygenation of the blood and tissues of the body sometimes give rise to a polycythaemia, probably to some extent reactive in nature, though doubtless often partly due to blood-concentration. The polycythaemia caused by acute phosphorus poisoning (Taussig, von Jaksch, R. Silbermann) only lasts for the first two or three days. Taussig, who was the first to discover its occurrence, counted 8,650,000 red cells to the cubic millimetre of blood in one case. According to Silbermann's statistics it is well marked in about 54 per cent. of all cases. More or less polycythaemia is frequently present in carbon-monoxide poisoning (von Jaksch, von Limbeck, G. Reinhold). Reinhold in one case found the red cells increased to 11,200,000 in the cubic millimetre, but a most striking feature in these cases is that in spite of the increase in the number of red cells the haemoglobin-value of the blood may be actually diminished, so that the condition may be termed one of 'polycythaemic anaemia'. Thus, in Reinhold's above-mentioned case, when the red corpuscles numbered over eleven million to the cubic millimetre, the haemoglobin-value of the blood (measured by Sahli's method) was only 90 per cent. of the normal, so that the colour-index of the red corpuscles was only 0·4, if we can rely on haemoglobin measurements in these cases of carbon-monoxide poisoning.

It is possible that the coal-tar derivatives, antipyrin, phenacetin, acetanilide (antifebrin), &c., which give rise to methaemoglobinaemia and cyanosis when taken in excess, may occasionally produce polycythaemia, though they usually cause oligocythaemia. Anyhow, the destruction of red cells in these cases is followed by a remarkable erythroblastic reaction, and in Stengel and White's case of chronic acetanilide poisoning with 'cyanotic anaemia' and splenomegaly the blood contained an extraordinary number of nucleated red cells. It seems that the haematoporphyrinuria of chronic sulphonal poisoning may sometimes be associated with a very decided increase in the number of red cells in the blood (see case of A. Fells in Appendix B.)

In regard to the artificial production of toxic oligocythaemias and toxic polycythaemias it appears certain that a toxin which in ordinary quantities will give rise to oligocythaemia may in some individuals, when given repeatedly in very minute doses, give rise to a polycythaemia. The explanation, in my opinion, is that in the former case the oligocythaemia is the expression of the (prevailing) 'action' of the toxin, and in the latter case the polycythaemia is the expression of the 'reaction' on the part of the organism being more powerful than the action of the toxin (cf. F. P. Weber, 'A Note on Action and Reaction in Pathology and Therapeutics,' *St. Bart.'s Hosp. Reports*, London, 1903, xxxix. 139).

As an exceptional and striking example of polycythaemia provoked by the direct 'action' of an 'agent' rather than as a 'reaction' towards it, we may

instance the work of Paul Carnot and Mlle. Cl. Deflandre on the effects of 'hemopoiétine' on the blood and bone-marrow. These observers found that an absolute polycythaemia could be artificially produced by the injection of serum from an animal in which an erythroblastic reaction was in progress. In one rabbit Carnot by this means was able to raise the number of red cells from 5,465,000 to 11,900,000 in the cubic millimetre of blood. After 14 days the count was still as high as 7,595,000. Comparison of the blood in the arteries, veins, and capillaries, and examination of the bone-marrow, left no doubt that the increase in the number of red cells produced by 'hemopoiétine' was an absolute increase, that is to say, not due to altered distribution of the corpuscles or to concentration of the blood, but to an increased production of red cells in the bone-marrow. On the other hand, as an example of polycythaemia provoked as a 'vital reaction' on the part of the organism towards a toxic agent, we may instance the results of Belonovsky, of St. Petersburg, who claims to have increased both the number of corpuscles and the amount of haemoglobin in the blood of anaemic persons by the injection of minute doses of haemolytic serum.

In this connexion a case recorded (1907) by Pel, of Amsterdam, is of great interest. In an officer, aged 66 years, suffering from attacks of paroxysmal haemoglobinuria, Pel found that there was decided polycythaemia (six to nine million red cells in the cubic millimetre of the patient's blood). It is very interesting also to know that J. McFadyean (1888) found a condition of great polycythaemia accompanying attacks of haemoglobinuria in horses. McFadyean (1893) stated that in horses an erythrocyte-count at the beginning of an attack might in some cases show nearly double the normal number of red cells. The blood-viscosity must therefore have been greatly raised. He suspected the presence of a dietetic factor in the aetiology of such cases, and we may call to mind that Burton-Opitz (1900) by means of a meat diet in dogs increased both the number of red blood corpuscles and the blood-viscosity.

It seems also reasonable to suppose that equal doses of a particular toxin when used in different individuals may give rise to oligocythaemia in some individuals and polycythaemia in others, according to their body-weight, age, and temporary state of reactive power. It is quite possible that there are various unknown toxaemias (of intestinal origin, &c.) which may sometimes cause oligocythaemia, sometimes polycythaemia and plethora.

Erythrocytosis in Chronic Infectious Diseases. An increase in the number of red corpuscles is sometimes met with in tuberculous, syphilitic, and probably also in old malarious cases, quite apart from the polycythaemia occasionally caused by great sweating, diarrhoeal discharge, &c. This increase in the red cells (like the more frequent diminution) is probably due to toxins circulating in the blood or to the local presence of the pathogenic microbes in the bone-marrow. As we have just explained, 'agents' of similar quality may sometimes give rise to oligocythaemia and sometimes to polycythaemia, according to quantitative conditions on the side of the 'agent' and 'reactive' conditions

on the side of the affected individual, so that it is not surprising that a disease like tuberculosis or syphilis, frequently causing oligocythaemia, may occasionally give rise to polycythaemia.

A slight polycythaemia, doubtless reactive in nature, has sometimes been observed in early cases of tuberculosis. Mircoli regards it as the effect in particularly constituted individuals of (or what I should call an expression of the reaction of the haemopoietic tissues towards) the circulation of minute amounts of tuberculin in the blood, and Rebaudi and Lionello succeeded in inducing an increase in the number of red cells by injecting minute quantities of tuberculin. Geisböck observed an increase of the red cells to 6,200,000 in a young girl with miliary tuberculosis. The polycythaemia sometimes found in quiescent or obsolete pulmonary tuberculosis, especially in patients under favourable conditions (for instance, under prolonged sanatorium treatment), is probably often compensatory to the fibrotic changes in the lungs. Whether primary splenic tuberculosis really induces the great polycythaemia, which in some cases it has been supposed to, is a question to which we shall again refer in Part II, but we may here mention that Lefas and Bender produced polycythaemia in animals by intrasplenic injection of attenuated cultures of human tubercle bacilli.

Syphilis, though it often leads to oligocythaemia, may occasionally give rise to slight polycythaemia, with which, however, there may be diminution (as in chlorosis) of the haemoglobin-value, so as to give rise to a kind of 'polycythaemic anaemia'. Geisböck has observed considerable temporary polycythaemia (6,100,000 to 8,700,000 red cells) with low blood-pressure during attacks of influenza in three young persons who attracted special attention owing to the red or bluish-red colour of their faces.

Polycythaemia of suprarenal origin. It would be interesting to know whether the cyanosis and 'plethoric type of obesity' which have sometimes been observed in connexion with hypernephroma, notably in children (Bullock and Sequeira, L. Guthrie), are ever accompanied by polycythaemia, but unfortunately the blood has seldom, or hardly ever, been examined in such cases from this point of view. Increase in the number of red blood-cells has been experimentally obtained in animals as a result of 'suprarenin' injections, but this may be a merely relative increase, not an absolute erythrocytosis (*vide* O. Hess, 1904).

Local processes affecting the nutrition of the bone-marrow in regard to the occurrence of polycythaemia. It is of course well known that disturbances of nutrition in the bone-marrow, such as those caused by toxins circulating in the blood, by the presence and local growth of pathogenic microbes and tumours, and by widespread gelatinous degeneration, may produce obvious morphological changes in the blood. F. Müller ligatured the nutrient artery supplying the marrow of an animal's long bone, and (as a result, he thinks, of deficiency of oxygen in the bone-marrow) after three or four minutes many erythroblasts were found in the blood obtained from the efferent vein. In regard to the possibility

of polycythaemia being sometimes due to direct excitation of the bone-marrow, it may be mentioned that Byrom Bramwell in a case of osteitis deformans (Paget's disease) obtained a blood-count of 6,700,000 red cells to the cubic millimetre with a haemoglobin-value of 105 per cent. Patients with 'angina cruris', 'intermittent clandication,' or actually commencing gangrene from arterial obstruction in one of the lower extremities, manifest occasionally (though rarely, as far as my experience goes, and I have private notes of several cases in which the blood was examined) some degree of polycythaemia. I am indebted to Dr. J. Galloway for showing me a typical example of this combination. His patient was a man over 50 years of age, with typical angina cruris from chronic arterial ischaemia in one leg. Whenever his red blood-cells were counted the number was found to be considerably above the normal, about 7,000,000, for instance, on one occasion. This man had had syphilis, and afterwards became hemiplegic and died, probably from cerebral vascular disease on a syphilitic basis. Geisböck mentions a man, aet. 64, with high blood-pressure and arteriosclerotic gangrene of the right foot, whose blood was found to contain 10–11 million red cells in the cubic millimetre (haemoglobin-value 156 per cent.). Lommel refers to a man, aet. 46, with severe pain and commencing gangrene in the right foot from arterial disease; the blood-count in this man gave 9,700,000 red cells, and the haemoglobin-value was 150 per cent. Erythromelalgia-like symptoms, probably connected with more or less organic vascular changes in the affected limb, have been recorded in several cases of erythraemia (see Part II). In all these clinical observations, however, the exact relation of the vascular disease to the polycythaemia is not quite clear.

Action and Vital Reaction in regard to Erythrocytosis.

In previous paragraphs I have already referred to the question of the same 'agent' at one time giving rise to oligocythaemia, and at another to polycythaemia. Just as infective 'agents' of like nature in different cases excite very different degrees of leucocytosis, or none at all, so also with regard to the red cells similar agents excite an erythrocytosis in some cases and not in others. Chronic cyanosis of cardio-pulmonary origin may in some cases induce a very marked erythrocytosis, whilst in other cases, in spite of the cyanosis, the number of red cells in the cubic millimetre of blood may be below normal. Doubtless much depends on the 'dose' and duration of action of the 'agent', for, whereas ordinary doses of haemolytic serum cause an oligocythaemia by direct destruction of red corpuscles in the blood, repeated minute doses may actually increase the number of the erythrocytes. In the former case the direct effect of the haemolytic 'agent' predominates, but in the latter case the vital 'reaction' of the bone-marrow is more powerful than the haemolytic 'action' which calls it into play. So also with regard to tuberculin, very minute amounts (in some individuals) may induce an increase instead of a decrease in the number of red blood-corpuscles. In the balance of 'action' and 'vital reaction' much must

depend on the condition of the patient's organism, due to age, sex, habits, the quality of his bone-marrow, and the temporary state of his general health. Reaction on the part of the bone-marrow may be affected by changes in its substance or in the blood-vessels which supply it with nutrient material and oxygen. Besides these obvious factors in regard to the degree of reaction there is the possible occurrence of obscure individual peculiarities or idiosyncrasies to be remembered. Thus, there are some persons whose red blood-corpuscles always show a peculiar susceptibility towards haemolytic agents (A. Chauffard, &c.). We still want information, however, in regard to the possible occurrence of persons congenitally endowed with red blood-cells that manifest a special durability or abnormally great resistance to haemolytic agents.

In regard also to individual peculiarities, one may suppose that, if the activity of the bone-marrow be greatly increased from any cause, erythroblasts or myelocytes more readily escape into the blood-stream in some subjects than in others. This might account for the presence of nucleated red cells in the blood in some cases of erythraemia but not in others. It might also account for the exceptional occurrence of erythroblasts in the blood in the 'polycythaemia of high altitudes' and other forms of erythrocytosis.

Individual peculiarities of reaction may perhaps help to explain the fact that splenomegaly connected with (or actually caused by) obstruction in the portal vein (phlebitis spleno-portalis) may in some individuals be associated with oligocythaemia so as to simulate splenic anaemia, Banti's disease, or Hayem's splenomegaly with chronic jaundice (Oettinger and Fiessinger, Dock and Warthin, &c.), and may in other individuals be associated with polycythaemia so as to give rise to the symptom-complex of splenomegalic polycythaemia (van der Weyde and van Ijzeren, Lommel's first case).

Probably the great differences between different cases of erythraemia in regard to blood-pressure may likewise to some extent be explained as dependent on individual peculiarities of reaction.

Cases of Polycythaemia of Uncertain Nature.

In Appendix B short notes of various obscure cases are included. Particularly worthy of mention are the cases of polycythaemia in young persons, mostly associated with splenomegaly, of which comparatively few examples have as yet been recorded. These cases are, I believe, by no means so rare as has been supposed.

In regard to the whole subject of polycythaemia, what we now most require is the careful and unbiased study of individual cases, as to their commencement and progress, as to evidence of obstructed circulation not of cardiac or pulmonary origin, as to the presence or absence of chronic toxaemic conditions, and as to the oxygen-capacity of the blood.

PART II. ERYTHRAEMIA.

Synonyms:—'Splenomegalic polycythaemia', 'Myelopathic polycythaemia', 'Polycythaemia with chronic cyanosis', 'Erythrocytosis megalosplenica' (Senator), Vaquez's disease, Osler's disease.

Definition of Erythraemia. A disease or morbid condition characterized by well-marked persistent relative and absolute polycythaemia (increase in the number of red blood-corpuscles) due to an excessive erythroblastic activity of the bone-marrow, which appears to be the primary morbid factor in the condition; it is characterized likewise by persistent increase in the viscosity and total volume of the blood, and usually by a cyanotic appearance of the patient and by enlargement of the spleen.

Although the term 'splenomegalic polycythaemia' is included amongst the above-mentioned synonyms of 'erythraemia', it is preferable to employ the term (splenomegalic polycythaemia) in a clinical sense merely, that is to say, as signifying a clinical symptom-complex characterized by a polycythaemia not obviously secondary to blood-stasis and by a splenomegaly for which no local cause (such as obstruction in the splenic and portal veins) is suspected. The results of post-mortem examinations (Reckzeh, van der Weyde and van Ijzeren, Lommel), however, make it certain, as we shall subsequently point out, that in some of these cases the polycythaemia has been more or less secondary to blood-stasis. Such cases, therefore, are not pure examples of erythraemia according to the definition just given, though clinically they are cases of 'splenomegalic polycythaemia'.

History. In 1892, H. Vaquez, of Paris, described a peculiar form of cyanosis accompanied by excessive and persistent polycythaemia ('hyperglobulie'), and in a supplementary note (1895) Vaquez drew attention to the existence of splenomegaly and the absence of cardiac lesions in his case. Other early cases of polycythaemia associated with splenomegaly are those recorded by Rendu and Widal (1899), Moutard-Martin and Lefas (1899), R. C. Cabot (1899 and 1900), Cominotti (1900), McKeen (1901), Saundby and Russell (1902), and W. Türk (1902–1904). In a prefatory note to Russell's description of Saundby's case in the *Lancet* the condition was characterized as a 'clinical entity', but it was probably the appearance of two papers by W. Osler (1903 and 1904) that widely drew attention to the subject in England and America. Important papers have been published on the subject in Germany by Rosengart, Weintraud, Lommel, H. Hirschfeld, Senator, and others. L. G. J. Mackey, in 1907, was able to collect over forty cases from the literature. Reports of many more exist, and the writer knows besides of several as yet unpublished cases.[4]

[4] Owing to the kindness of various medical friends, especially Dr. R. Hutchison (3 cases), Dr. Purves Stewart, Dr. T. D. Acland, Dr. H. H. Tooth, Dr. A. F. Voelcker, and Dr. E. Cautley, he has had the opportunity of himself seeing and examining quite a number of published or

Erythraemia cannot be quite so rare as it has been supposed to be. There have been several post-mortem examinations; the first complete one was published by Weber and Watson in March, 1904. In former times cases of erythraemia were probably classified under various headings, such as plethora, general venous congestion with cyanosis, &c. Cuffer and Sollier's two cases (1889) of 'congestive venous diathesis' were perhaps examples of erythraemia.

Signs and symptoms. The patient may complain of lassitude, headache, migraine (ophthalmic migraine with 'rainbow-scotoma' or 'teichopsia' in G. Koester's case), vertigo, sensations of fullness in the head or of rush of blood to the head, abdominal pains (especially in the left hypochondriac region), dyspepsia, constipation, distressing thirst, menorrhagia, epistaxis, bleeding gums. Other recorded haemorrhages in erythraemia have been from the stomach, intestines, kidneys, and into the pleural or peritoneal cavities or into the brain. Subjective symptoms may at first sometimes be almost wanting, but usually for some years before the polycythaemia or cyanosis has been observed the patient has suffered from feelings of tension or pains in the left hypochondriac region, pain or sensation of congestion in the head, and loss of strength or lassitude. The vascular engorgement and redness or cyanosis of the skin, most obvious in the face and ears, vary much in different cases and in the same patient at different times. True cyanosis is sometimes quite absent; none was observed in Parkes Weber's second case. Exposure to cold and emotional influences may intensify the cyanosis of erythraemia, just as they sometimes act in other forms of cyanosis. Osler, in his recent 'clinical lecture', points out that a warm room and mental excitement may occasionally cause blueness of the face in these patients to give place to redness. The vascular engorgement is of course not limited to the skin, but may be observed likewise in the mucous membrane of the mouth, fauces and larynx, in the conjunctivae, and by ophthalmoscopic examination in the interior of the eyes. Especially characteristic is the bluish-red appearance of the tongue. Sometimes cutaneous pigmentation, mostly only slight in degree, has been observed. Osler in his recent case drew attention to the fact that a typical so-called 'white line' could be produced by cutaneous irritation, a sign which some French authors have recently supposed to be connected with functional insufficiency of the suprarenal capsules. The spleen can generally be felt moderately or considerably enlarged and hardened, and the liver not rarely reaches below the costal margin. Considerable variation in the size of the spleen from time to time has been observed in one or two cases, and in one of Weintraud's cases the splenomegaly disappeared whilst the patient was under observation. The urine may be either pale and abundant or highly coloured and containing excess of urobilin (Weber and Watson, Türk, &c.), as evidenced, for instance, by spectroscopic examination without concentration of the fluid. It often contains a little

unpublished cases besides his own. Dr. Purves Stewart's case at the Westminster Hospital in 1903 was the first one recognized in London. Dr. Acland's case at St. Thomas's Hospital in 1904 was the first one in which the total blood-volume was estimated.

albumen and sometimes hyaline and granular tube-casts. Occasionally much albuminuria has been recorded, as in Münzer's second case and in Cautley's case, but in the latter considerable organic renal disease was found at the necropsy. Here we may mention that the total excretion of urobilin from the body was found to be slightly above the average in a case of (clinically) splenomegalic polycythaemia reported by Lommel and in Löw and Popper's first case, but it was about normal in two cases reported by Senator. The blood-pressure is frequently, but not invariably, above the normal. In a few cases organic renal disease has doubtless had something to do with the high blood-pressure. In cases of so-called 'hypertonia polycythaemica' (see later on) the brachial systolic blood-pressure, as measured by the Riva-Rocci method, may, according to Mohr, even reach 320 mm. Hg.

Blood-changes. The most important signs are of course those yielded by examination of the blood. The red cells are increased in number, generally to between 7 and 12 millions in the cubic millimetre, and on the average they are generally rather increased than decreased in diameter (as Vaquez was the first to point out), but very little attention has, I think, been devoted to ascertaining the average volume of the red cells by J. A. Capps's method. Though the erythrocytes are usually normal in appearance, in Begg and Bullmore's case (a doubtful case, however—see Appendix B, No. 12) they showed poikilocytosis, and marked polychromatophilia; Türk likewise mentions having met with polychromatophilia and slight poikilocytosis. The degree of polycythaemia has in some cases been observed to vary greatly from time to time. The highest erythrocyte-count seems to have been 13,600,000 in Koester's case. In regard to the white cells the only quite constant feature is the excessive proportion of the polymorphonuclears (not rarely up to 80–85 per cent. or higher). The number of white cells is, however, nearly always increased, often up to 20,000 to 30,000 per cubic millimetre. In one case (Parkes Weber) the minimum count was only 4,000, but a still lower figure, namely 1,080, has been noted by Geisböck (Appendix B, 11), unless there was a misprint. Weintraud has recorded as high a count as 54,000. A few normoblasts and one or two myelocytes have occasionally been noted. In Blumenthal's case in which the white cells numbered 16,300, as many as 36 per cent. of them were myelocytes. The haemoglobin-value may reach even to 170 or 180 per cent. or even higher (the 240 per cent. recorded on one occasion by Koester is scarcely conceivable), but the colour-index is often below 1·0. Nothing abnormal has been found by cryoscopic examination of the blood (Senator, Parkes Weber). The specific gravity of the whole blood is probably always raised, and in Glaessner's case it reached 1,083, but further observations in this respect are required. The dry residue of the blood is doubtless also somewhat increased, whilst the dry residue and specific gravity of the blood-serum seem to be usually diminished (see Part I). The amount of iron in the blood is probably raised in proportion to the excess of haemoglobin. The viscosity of the blood is increased, more or less in proportion to the degree of polycythaemia (see in Part I, the paragraphs on the

Viscosity of the Blood in Polycythaemia). The blood-coagulability is probably sometimes greater and sometimes less than normal. The resistance to haemolysis was found in one case (Vaquez and Laubry) decreased, and in other cases (Parkes Weber, Saundby) about normal. The total blood-volume, as estimated during life by Haldane and Lorrain Smith's 'carbon-monoxide method', is greatly above the normal (as we have already dwelt on in Part I), and this clinical finding is confirmed by the appearance of the viscera as seen at post-mortem examinations (see Appendix A). It is worth mentioning (though the significance is by no means clear) that in two cases of (clinically) splenomegalic polycythaemia Senator found increased activity in the respiratory gas-exchange, and so also did Lommel in the second of his cases.

Complications. As occasional complications we may mention jaundice (Türk, Geisböck), hepatic cirrhosis (see Appendix A, 11, 13), renal disease (Appendix A, 10, 23 and 25), ovarian tumour (second case of Parkes Weber), a certain amount of pulmonary emphysema (Appendix A, 7, 12, 24), bronchitis (W. Pfeiffer), bronchiectasis (Kikuchi), slight valvular lesions of the heart (Appendix A, 6, 12), myocardial fibrosis (Appendix A, 15), arteriosclerotic changes, thrombotic infarction of the spleen (Appendix A, many cases), the results of vascular disease in the brain (Appendix A, 4, 15, 22, 23, 25), erythromelagia or erythromelagia-like pain (Türk, Parkes Weber, Cabot, Collins, Lommel, Weintraud), angina cruris of ischaemic origin and arteriosclerotic gangrene of a foot (see Lommel's case and also one of Geisböck's cases of 'hypertonia polycythaemica', abstracts in Appendix B, Nos. 16 and 17), gastric ulcer (Appendix A, 12, 19), pigmentation of the skin, Ménière's attacks, tabes dorsalis (Glaessner), uncontrollable impulses (Cassirer and Bamberger), and insanity (Weber and Watson). Splenic tuberculosis was found in two cases, and in two other cases pulmonary tuberculosis was the cause of death.

Morbid Anatomy. There have been post-mortem examinations made in several cases, and an abstract of the results in all these cases is given in Appendix A. Evidence of increased erythroblastic activity in the bone-marrow has been found in almost every case in which the bone-marrow from the shafts of the long bones was examined after death, and in one case G. A. Gibson obtained similar evidence by exploring the condition of the bone-marrow during life. Much of the marrow of the shafts of the long bones which is normally of the yellow fatty kind has been found converted into red (active blood-forming) marrow, so that the total amount of erythrocyte-producing marrow in the body must have been enormously increased, though the red marrow normally present may not have been much altered. A striking feature in Weber and Watson's case (Appendix A, 12) was the large proportion of non-granulated mononuclear cells of the large lymphocyte type (probably to be regarded as 'non-granulated myelocytes' or 'myeloblasts') seen in sections of the altered marrow, doubtless signifying excessive leucoblastic activity. In Blumenthal's case (Appendix A, 21) the marrow contained very much more leucoblastic than erythroblastic tissue; in Westenhoeffer and Hirschfeld's case (Appendix A, 22) likewise the

leucoblastic were in excess of the erythroblastic elements of the marrow. For the most probable explanation of these facts, see later on under 'Pathology and Aetiology'.

The spleen has been almost always found enlarged and engorged with blood, but (in the cases carefully examined) this organ showed little (see Appendix A, 15), if any, erythroblastic transformation; in two cases (Appendix A, 16, 22) Hirschfeld found a certain amount of myeloid change, but this was leucoblastic, not erythroblastic. In this connexion it may be mentioned that in Ascoli's case the spleen was punctured with the consent of the patient during life, and the splenic juice obtained from the puncture was searched for erythroblasts with a negative result. In many cases the spleen contained anaemic infarcts, apparently of thrombotic origin. In one or two cases no enlargement of the spleen was found either during life or after death (Herringham, Blumenthal). The lymphatic glands seem hardly ever to be affected, and when examined microscopically (H. Hirschfeld) they have not presented the least signs of erythroblastic transformation. The enlarged lymphatic glands in Blumenthal's case showed vascular congestion and fibrosis. The extreme vascular engorgement of the liver noted in some cases is quite distinct from that found in 'nutmeg' livers. The liver has been found at most necropsies not to be much altered excepting in regard to vascular engorgement, and in Löw and Popper's first case the relative functional integrity of the organ was confirmed by dietetic tests during life.

In every case examined post mortem the distension of the visceral blood-vessels has been very striking, the mesenteric venules presenting sometimes the appearance of having been forcibly injected for purposes of anatomical demonstration (see Weber and Watson). Amongst occasional findings (see Appendix A) have been a certain amount of pulmonary emphysema, arterio-sclerosis, fibrosis of the cardiac muscle, slight changes in the cardiac valves, hepatic cirrhosis, renal disease, and the results of disease of cerebral blood-vessels. Primary tuberculous nodules in the spleen were reported in two cases (Moutard-Martin and Lefas, Rendu and Widal) in which it was scarcely possible that anaemic infarcts could have been mistaken for tuberculous caseous masses. In Scharold's case of primary splenic tuberculosis, confirmed by post-mortem examination, there was cyanosis, but no blood-count was made, and it cannot be taken for granted that polycythaemia was present. In view of the greatly increased blood-viscosity the absence of very much cardiac hypertrophy in most polycythaemic cases is remarkable.

Pathology and Aetiology. Explanation of erythraemia as a primary disease of the bone-marrow. Most of the signs and symptoms of erythraemia may be accounted for by the increased formation of red blood-cells in the bone-marrow, which is evidenced not only by the results of post-mortem examinations, but during life by the high percentage of the polymorphonuclear leucocytes and the occasional presence of erythroblasts and myelocytes in the circulating blood, and in one case (G. A. Gibson) by direct examination of the bone-marrow of

a long bone ('biopsy' method). The results of this excessive erythroblastic activity of the bone-marrow may be compared to what would be the consequences of persistent slow transfusion of blood into the veins of an animal. Experimental sudden transfusion of blood in animals (von Lesser, Worm-Müller) leads to temporary plethora followed quickly by polycythaemia, and it is reasonable to suppose that a slow transfusion of blood, lasting not for a few minutes only but for months and years (were it possible from the experimental point of view), would give rise to a condition of persistent absolute polycythaemia associated with true plethora, such as is met with in cases of erythraemia (see Part I, sections on the Cause of Absolute Polycythaemia and on the Blood-Volume in Absolute Polycythaemia). Dilatation of capillaries and venules would necessarily follow, and probably in most cases, for a time at least, there would be increased arterial blood-pressure. Ultimately degenerative changes in the vascular system would be likely to occur, leading to true passive congestion, cyanosis, bleeding from the gums, thrombosis in various organs, and local circulatory disorders. The excess of the total erythroblastic activity in cases of erythraemia may be supposed to be the primary change giving rise to the clinical symptoms. It may be regarded as analogous to the increased leucoblastic activity in leukaemia, or as a return of the marrow to the condition of foetal activity. In a few cases it appears as if the bone-marrow had never lost its foetal characteristics, and as if the polycythaemia was the result of this 'infantile' (or rather 'foetal') condition of the blood-forming organ (see Blumenthal's case and other cases of polycythaemia commencing in early life—in Appendix A and Appendix B).

That increased leucoblastic activity nearly always accompanies the increased erythroblastic activity in the bone-marrow is evidenced during life by the usually large number of white corpuscles, especially polymorphonuclears, and by the occasional presence of myelocytes, in the circulating blood. At necropsies the examination of the marrow of the shafts of long bones has shown that a decided increase of leucoblastic tissue (see Appendix A, Nos. 12, 22) does accompany the increase of erythroblastic tissue, and probably in most cases the leucoblastic elements occupy more space in the bone-marrow than the erythroblastic elements do. This feature of the bone-marrow seems to have been exaggerated in Blumenthal's case (Appendix A, 15), in which during life 36 per cent. of the white cells of the blood were found to be myelocytes; after death the leucoblastic elements of the bone-marrow were found very greatly to exceed the erythroblastic elements. In fact, Blumenthal's case appears almost to represent a link in a chain, which future observations may discover, connecting erythraemia with myelocytic (myeloid) leukaemia. We fully expect in the future to read of cases showing conditions of the blood and bone-marrow more or less similar to those in Blumenthal's case described as examples of 'Blumenthal's disease'.

It is not quite clear why in erythraemia more of the bone-marrow should consist of leucoblastic than of erythroblastic elements. I think the most probable explanation is that in the marrow of these patients (and probably also in that of healthy individuals) the red cells are much more rapidly produced than are the

white cells by their respective 'parents'. Hence even when the bone-marrow consists chiefly of leucoblastic tissue the red cells far outnumber the white cells in the blood. Moreover, the average life-duration of red cells perhaps exceeds that of white cells.

The enlargement of the spleen which is found in most cases of erythraemia seems to be due partly to engorgement with blood, the organ acting as a kind of elastic blood-reservoir, and partly to hyperplasia of the splenic pulp, possibly connected with the increased haemolysis (see the paragraph in Part I on 'Increased haemolysis in absolute polycythaemia') which must necessarily accompany all conditions of absolute polycythaemia; unless indeed the erythrocytes are specially long-lived, but there is certainly no evidence in favour of the red cells being endowed with special durability (I shall return to this subject later on). The splenic enlargement can certainly not be accounted for by the partial myeloid (leucoblastic, not erythroblastic) transformation that has been found in some cases (Appendix A, 16, 22), and still less so by the presence of erythroblastic foci detected by Ledingham after careful search in one case (Appendix A, 15). Thrombotic infarcts, past malaria, or tuberculosis (see later on) may sometimes partly account for the splenomegaly, and in one or two cases in which great vascular degenerative changes constituted a striking feature there may have been a syphilitic element present. At future necropsies great care should also be taken to examine for changes in the splenic and portal veins. Both splenic infarcts and obstruction in the splenic and portal veins may give rise to more or less splenomegaly. And, though it must be remembered that the presence of disease in the splenic and portal veins in cases of splenomegaly does not necessarily signify that the enlargement of the spleen was entirely secondary to venous obstruction, splenic enlargement in certain cases supposed during life to have been examples of splenic anaemia or Banti's disease (Dock and Warthin, Oettinger and Fiessinger, &c.) has, after death, been found to be connected with obstruction in the splenic vein; so also in two cases characterized clinically by polycythaemia with splenomegaly (van der Weyde and van Ijzeren, and Lommel's first case) the necropsy showed the presence of chronic obstruction in the portal vein.

Erythraemia affects persons of either sex chiefly between the ages of 35 and 50, but has been observed in persons after 60 and several times before 30 years of age; according to the observations of Blumenthal and Ambard and Fiessinger (Appendix A—see also some cases in Appendix B) it may sometimes possibly even be congenital. Nothing is known as to the relation of the condition to climate (atmospheric temperature) and race.

Nervous excitement or mental worry has been suggested as the exciting cause in some cases. According to various theories the abnormal activity of the bone-marrow (giving rise to the polycythaemia) is due to a state of toxaemia having its source in the spleen, lungs, or alimentary canal, or, it is suggested, the polycythaemia may be regarded as the result of a compensatory reaction towards some hypothetical disturbance in the gas-exchanging functions of the blood,

which disturbance might in its turn be of toxaemic (for instance, alimentary, digestive, or metabolic) origin.

The results of post-mortem examinations make it appear that the increased erythroblastic activity of the bone-marrow which gives rise to the polycythaemia cannot be regarded as secondary to blood-stasis (impeded circulation) in most cases of 'splenomegalic polycythaemia', though, as we shall presently have to admit, blood-stasis may occasionally give rise to the same symptom-complex (that is to say, may give rise to polycythaemia with splenomegaly). The increased blood-viscosity (see Part I) necessarily accompanying polycythaemia must, however, favour the *development of a secondary condition of blood-stasis*, whether there be a compensatory increase in blood-pressure (as there usually is in erythraemia) or not. Delayed circulation in its turn favours the occurrence of thrombosis[5] in the various viscera, and the occurrence of thrombosis further hampers the circulation. Again, delayed circulation, and congestion, in the blood-vessels of the lungs and bronchi promote the development of chronic catarrhal changes, which induce cyanosis and throw extra work on the right side of the heart. So that in erythraemia an elaborate *vicious circle* is established; the polycythaemia in various ways tends to impede the circulation, and the blood-stasis thus produced favours cyanosis and increases the circulatory difficulty by giving rise to a further (compensatory secondary) polycythaemia in addition to the primary (myelopathic) polycythaemia.

Blood-stasis (impeded circulation) in regard to erythraemia and erythrocytosis. It must be remembered that the blood-stasis and chronic cyanosis resulting from cardiac and pulmonary diseases (especially congenital pulmonary stenosis) sometimes give rise to a secondary polycythaemia (erythrocytosis) quite equal to that observed in many cases of erythraemia (see Part I), and Lommel has endeavoured to show that most cases of erythraemia are really due to blood-stasis (impeded circulation). We believe that the signs of more or less impeded circulation undoubtedly present in many cases of erythraemia are secondary to the polycythaemia in the way we have just explained, and we do not believe that the presence of a certain amount of blood-stasis by any means necessarily signifies that impeded circulation is the chief cause of the polycythaemia. Moreover, although the presence of increased arterial blood-pressure is no sure sign of the absence of any blood-stasis of cardiac or pulmonary origin, the fact that in some cases of polycythaemia with high blood-pressure (the 'hypertonia polycythaemica' or 'polycythaemia hypertonica' of Geisböck and Hess) the number of red corpuscles is almost as great in the arterial as in the venous blood forms a strong argument against blood-stasis playing a large part in the

[5] In some cases of polycythaemia the coagulability of the blood appears to be diminished; the diminution of coagulability in such cases, although it would partially neutralize the tendency of the delayed circulation to favour thrombosis, can scarcely without further evidence be regarded as an automatic vital compensatory change analogous to the compensatory increase in the number of red blood-corpuscles in cases of congenital heart disease and chronic blood-stasis.

causation of the polycythaemia in the cases in question. It must, however, be admitted that blood-stasis, especially when due to chronic obstruction in the portal and splenic veins, may, at least in some individuals,[6] give rise to polycythaemia with splenomegaly, that is to say, may give rise to the clinical symptom-complex 'splenomegalic polycythaemia', which may be mistaken for true erythraemia. The cases of Reckzeh, Lommel, and van der Weyde and van Ijzeren (described in Appendix A) are probably, as Lommel insists, to be explained in this way, and such cases of clinically 'splenomegalic polycythaemia' should not be included as examples of erythraemia according to our use of the latter term, as defined at the commencement of Part II.

We have now considered the prevailing theory of erythraemia, which regards the polycythaemia in these cases as due to a 'primary myelopathy', and we have likewise considered the most important rival theory, which regards the polycythaemia as secondary to blood-stasis, but there are several other theories which have been brought forward, and, though by some writers they have been set up to be knocked down again, we must now shortly consider them.

Other possible theories of erythraemia:—(*a*) *Increased durability of the red blood-cells.* There is no practical clinical method for measuring the average life-limit of the red corpuscles. H. Quincke in experiments on animals ascertained the time taken for the blood to return to its normal state after the artificial production of plethora. By his observations he estimated the normal average duration of life of the red cells at two to five weeks, but G. Froin by other methods of observation has estimated it at a much higher figure. Fick (quoted by G. Schroeder) suggested that the 'polycythaemia of high altitudes' was due to an increased durability of the red cells resulting from residence in mountain resorts. But, as pointed out in Part I, it is almost certain that this polycythaemia of high altitudes is due to a genuine increase of the erythroblastic activity of the bone-marrow. Certainly in regard to the polycythaemia of erythraemia there is no evidence forthcoming that it is due to increased life-duration of the red cells, but on the contrary there is some evidence pointing to the total haemolysis in the body being increased, as one would expect it to be, in all cases of absolute polycythaemia. We have already dealt with this subject in Part I, under the heading 'Increased haemolysis in absolute polycythaemia', and need not add anything further to what we have already stated there.

(*b*) *Diminished oxygen-capacity of the haemoglobin,* that is to say, diminution in the amount of oxygen that the haemoglobin will take up as compared to the amount taken up by the haemoglobin in normal blood. Bence and von Koranyi suggested that absolute polycythaemia might in some cases be the result of a compensatory reaction towards some impairment in the quality of the haemoglobin which diminishes its oxygen-capacity. Mohr and Lommel have likewise paid attention to this question. Mohr actually found decided

[6] As already explained, the erythropoietic reaction towards blood-stasis appears to vary much in different individuals. See Part I, Section on 'Action and Vital Reaction in regard to Erythrocytosis'.

diminution of the oxygen-capacity of the haemoglobin in a case of congenital pulmonary stenosis with secondary polycythaemia (erythrocytosis). It must be remarked, however, that in cases of methaemoglobinaemia and sulph-haemoglobinaemia, in which the oxygen-capacity has been lowered owing to some of the haemoglobin in the erythrocytes becoming changed into methaemoglobin or sulph-haemoglobin, no secondary polycythaemia has been observed, and in a few cases of erythraemia (Saundby and Russell, Tooth, Herringham) the presence in the blood of methaemoglobin or sulph-haemoglobin has been excluded by spectroscopic examination. Moreover, in cases of polycythaemia with splenomegaly, whether actually cases of erythraemia or not, the oxygen-capacity of the haemoglobin has never been found notably reduced. In two cases of Lommel and one of Mohr it was found to be at the lowest level within normal limits. Nor was Bence's suggestion supported by Senator's results or by two cases (referred to by Parkes Weber, 1906) in which A. E. Boycott examined the oxygen-capacity of the blood.

(*c*) *Possible toxic and infectious causes.* In regard to the possibility of polycythaemia resulting from various toxic and infectious causes we must refer to the paragraphs in Part 1, on 'Erythrocytosis of Toxic Origin' and 'Erythrocytosis in Chronic Infectious Diseases'. In cases of erythraemia, or at all events of (clinically) 'splenomegalic polycythaemia', chronic toxic or infectious conditions have not rarely been present, for instance, disorders of the digestive canal accompanied by a coated tongue, tuberculous nodules in the spleen, bronchiectasis (Kikuchi) and otorrhoea (Ascoli). Kikuchi in his case thought that the bronchiectatic trouble might be acting on the bone-marrow as it acts on the bones in the cases in which it gives rise to Marie's so-called 'pulmonary hypertrophic osteoarthropathy'. In one or two cases of (clinically) splenomegalic polycythaemia there has been clubbing of the fingers, a condition generally supposed to be often partly toxaemic in origin, though often partly due to local blood-stasis.

Syphilis and malaria, like tuberculosis, have been suspected in some cases, but there is little to be said in favour of any one toxic or infectious condition playing an important part in the aetiology of erythraemia. Possibly they may in some cases act as exciting causes, that is to say, as giving a starting stimulus to the bone-marrow, just like in other cases the erythroblastic reaction following a haemorrhage or the disturbance caused by the fracture of a rib or long bone might be supposed to do. There is scarcely more to be said in favour of toxaemia connected with chronic constipation and gastro-intestinal disorders as the cause of so rare a condition.

Splenic tuberculosis, though present in two cases (Rendu and Widal, Moutard-Martin and Lefas), was absent at all the more recent necropsies, and many patients have been submitted to the tuberculin test (Preiss, Weber, Horder, Löw and Popper's first case) with negative results. Primary tuberculosis of the spleen was found by Scharold (1883) at the necropsy on a man aged 25 years, in whom a peculiar alternating redness and cyanosis of the face

had been observed during life. No blood-count was made, and the presence of polycythaemia can scarcely be taken for granted in Scharold's case, especially as in a case of acute miliary tuberculosis of the spleen recorded by D. D. Stewart (1901) examination of the blood showed complete absence of any polycythaemia, in spite of a tendency to cyanosis having been noted. Moreover, tuberculosis of the spleen is by no means always accompanied by polycythaemia (Bayer). Altogether, the theory that the typical symptom-complex of chronic splenomegalic polycythaemia in human beings can result from splenic tuberculosis needs confirmation, in spite of the experiments by Lefas and Bender on animals, who produced polycythaemia by the intra-splenic injection of attenuated cultures of human tubercle bacilli. However, it must be admitted that local tuberculosis may cause splenic enlargement, and that small amounts of tuberculin (see Part 1), whether produced by tubercle bacilli in the patient's own body or injected therapeutically, may, in specially constituted individuals, give rise to a secondary polycythaemia. Therefore splenic tuberculosis must be admitted as a possible occasional cause of both splenomegaly and a certain degree of polycythaemia, if not of the typical symptom-complex, chronic splenomegalic polycythaemia.

In one or two cases of erythraemia pathogenic organisms have been searched for (Herringham, Hutchison and Miller), in the blood during life or in the tissues after death, with negative results.

Subdivision of cases of erythraemia. We have already excluded certain cases of (clinically) 'splenomegalic polycythaemia' as being probably due to blood-stasis and therefore not coming under our definition of erythraemia (given at the commencement of Part II). The remaining cases of splenomegalic polycythaemia, and erythraemia without splenomegaly, may be subdivided into different groups according to whether the blood-pressure is very much raised or not, or according to whether the spleen is enlarged, as it usually is, or apparently not enlarged (Herringham, W. Pfeiffer, &c.). We may provisionally class in a group by themselves the cases of absolute polycythaemia with high blood-pressure and without obvious splenic enlargement, that is to say, the cases of 'hypertonia polycythaemica' or 'polycythaemia hypertonica' of Geisböck and Hess. Needless to say, in regard to the high blood-pressure in such cases the question of the presence or absence of organic renal disease must always be taken into account. Equally worthy of a special place is a group of cases commencing in early life. These two groups we shall now shortly consider.

Polycythaemia hypertonica without splenomegaly. F. Geisböck, in examining the blood of patients with increased blood-pressure, found that the number of red corpuscles was in some cases increased up to 8–11 millions in the cubic millimetre of blood, and his observations have been confirmed by O. Hess and others. This polycythaemia was nearly as well marked in the arterial as in the venous blood. The patients were beyond middle age, mostly between their fiftieth and sixtieth years, and were red in the face, suggesting the 'habitus apoplecticus' of older medical writers. There was apparently no evidence of splenomegaly. Most of the cases showed a little cardiac enlarge-

ment; in several the urine contained a trace of albumen; in a few there was distinct arteriosclerosis or renal disease; several of the patients had suffered from apoplectiform attacks; and one of them (a man aet. 64) had arteriosclerotic gangrene of the right foot. One patient (a man aet. 55) was much improved by long-continued treatment with iodothyrin. Of another case, decidedly relieved by venesections, and very carefully investigated by Geisböck, we must quote some details. The patient was a man, aet. 54, whose father had died from cerebral haemorrhage. He denied ever having had any venereal disease, but had been accustomed to drink a good deal of beer and smoke much tobacco. He suffered from headaches and occasional giddiness. His skin was red, but not cyanotic. The heart was very slightly enlarged (as shown by percussion and by orthodiascopy with Röntgen rays). The systolic brachial blood-pressure (Riva-Rocci apparatus) was 200–210 mm. Hg. The liver and spleen were not enlarged. The urine, rather abundant and of somewhat low specific gravity, showed an occasional trace of albumen, but no tube-casts. The blood-count gave between ten and eleven million red cells to the cubic millimetre. The haemoglobin-value was 140 to 185 per cent. The specific gravity of the blood-serum and the amount of its dry residue were not increased, showing that the polycythaemia was not due to blood-concentration. Moreover, on one occasion Geisböck was able to compare specimens of this patient's blood taken at the same time from the radial artery, the tip of the finger and the median vein respectively, and he found very little difference between the three specimens. The erythrocyte-count of the arterial blood gave 10,530,030; of the capillary blood 10,695,000; of the venous blood 10,775,000.

Congenital erythraemia and erythraemia commencing in early life. We have already alluded to this group in the Section on 'Pathology and Aetiology'. Short abstracts of Blumenthal's, and Ambard and Fiessinger's cases, of which post-mortem records have been published (very incomplete in the latter case) are given in Appendix A; and in Appendix B we have included short notes on cases of Minkowski, Nichamin, and Hann. In such cases it is possible that the bone-marrow of the shafts of the long bones may early in the patient's life have reverted to its foetal erythroblastic activity, or indeed this foetal character may never have been entirely lost (as it normally should be early in extra-uterine life). Blumenthal's case, which was fully examined after death, is further remarkable for the extraordinary leucoblastic activity, which accompanied and relatively greatly exceeded the erythroblastic activity (in this respect, however, compare post-mortem results, Appendix A, cases Nos. 12 and 22). This leucoblastic activity, the existence of which was confirmed after death by the large amount of leucoblastic marrow present in the shaft of a long bone, was manifested during life by the count of about 5,868 myelocytes in the cubic millimetre of circulating blood. The case, therefore, to some extent, as already stated, appears to connect erythraemia with myelocytic (myeloid) leukaemia.

In connexion with these cases of erythraemia in early life the question

may be asked, Do they perhaps represent an extreme degree of what may be roughly termed the congenital plethoric tendency normal to some individuals, in other words, the 'plethoric type' of person whose food is popularly said 'all to turn into blood'?

Diagnosis of erythraemia. The plethoric or cyanotic appearance of the patient, the presence of splenomegaly of uncertain origin, erythromelalgia-like symptoms (as in my second case), or other circumstances, may lead to examination of the blood. The diagnosis of erythraemia then depends, as we have already pointed out, on the recognition of a condition of persistent absolute polycythaemia and the absence of obvious cause for any considerable 'erythrocytosis' (secondary polycythaemia). Splenomegaly, due to causes other than erythraemia, such as passed malaria, syphilis, or chronic obstruction in the splenic or portal veins, if it occurs in association with some form of secondary polycythaemia (erythrocytosis), may doubtless give rise to great difficulties in diagnosis. As a matter of fact, however, the spleen can seldom be felt below the ribs in patients with congenital or acquired cardiac disease. In polycythaemic cases I consider that enlargement of the liver, if present without obvious enlargement of the spleen, is a point somewhat in favour of the increase in the red cells being secondary to blood-stasis.

Prognosis and Course. Some cases seem to be almost non-progressive, or seem to improve, at all events for a time, with or without special treatment. Some have died (see Appendix A) in a sudden exacerbation of cyanosis (Herringham, Weber and Watson). Others have died from complications due to vascular disease in the brain (Cabot, Westenhoeffer, Cautley, Hutchison and Miller, Löw and Popper), or from tuberculosis (see Appendix A, No. 1) and intercurrent causes.

Treatment. Subjective improvement seems to have followed spontaneous haemorrhages (Weintraud), and treatment by an occasional copious blood-letting has been carried out with at least temporary relief of symptoms in an as yet unpublished (splenomegalic) case by Dr. T. D. Acland. In two or three other splenomegalic cases also, including Cautley's case and an unpublished one kindly shown me by Dr. R. Hutchison, venesection has been tried with apparently temporary benefit. Moreover, in one of Geisböck's cases of 'polycythaemia hypertonica' without splenomegaly (already referred to) great relief was obtained by venesections. On the other hand, in a case of polycythaemia with low blood-pressure (see Appendix B, No. 11) Geisböck observed no improvement worth mentioning from a bleeding of 260 c.cm. (Treatment in that case at Carlsbad had a better result.)

In a case of moderate polycythaemia (with history of malaria), reported by Schneider, excision of the enlarged spleen was resorted to, and the number of red cells decreased, but shortly after the operation the patient developed progressive pulmonary tuberculosis. In Comminotti's case death from sepsis occurred six weeks after the operation. In another case the operation of splenectomy was fatal from internal haemorrhage (Axel Blad). In van der Weyde

and van Ijzeren's case of (clinically) splenomegalic polycythaemia splenectomy was followed by the patient's death 25 days after the operation. Derüschinsky's case, in which no alteration in the blood followed successful removal of an enlarged spleen, though often quoted in this connexion, was never polycythaemic. We may here note that in one case (Lauenstein) of removal of the normal spleen for traumatic rupture of its capsule the number of red corpuscles in the blood at first fell, but then rose, so that 5 weeks after the operation 5,800,000 were counted in the cubic millimetre. Lauenstein's case is, however, probably only an example of temporary polycythaemia following splenectomy, of which other examples are known, but in Schupfer's recent case of removal of the spleen for primary splenomegaly (see Appendix B, No. 18) the patient 3 years after the operation showed cyanosis of the extremities and polycythaemia with 6,270,000 red cells in the cubic millimetre of blood. Before the operation his red cells were counted at 2,880,000 to 4,920,000.

The application of Röntgen rays did no good in my second case, nor did it improve the general condition in a case (with low blood-pressure) mentioned by Geisböck (see Appendix B, No. 11), but I have heard of apparent improvement from their use in a case under Dr. H. H. Tooth's care at St. Bartholomew's Hospital, and of a decided benefit in a case of which Dr. T. J. Horder has kindly given me details (see Appendix B, Case No. 12; there is, however, some doubt as to the nature of the case). Arsenic, quinine, thyroid substance, vaso-dilators (erythrol tetranitrate or sodium nitrite), and a variety of drugs have been tried, but generally without any satisfactory effect. One of Geisböck's patients with 'polycythaemia hypertonica' (see Appendix B, No. 14) was greatly improved by a long course of iodothyrin. Begg and Bullmore recorded improvement in their case (a doubtful case, see Appendix B, Case No. 12) from quinine and inunction of iodide of mercury ointment. Bence thought that the polycythaemia could be reduced by oxygen inhalations, but Stern was not able to record any such result. In Münzer's second case inhalation of oxygen failed to reduce the blood-viscosity.

On general principles one would, as far as possible, avoid mental fatigue, excitement, and impure air, prevent constipation, caution against excess of tea, coffee, tobacco, and stimulating meats and spices, prohibit alcohol owing to its action on the blood-vessels, chalybeate drugs owing to their effect on the erythroblastic tissues, and coal-tar products such as antipyrin, phenacetin and acetanilid, which by their action on the haemoglobin in the blood occasionally produce cyanosis. The plentiful use of German 'sour milk' or some similar preparation, on account of the effect on the flora of the large intestine, might be worth a trial in some cases, and a lacto-vegetarian diet (Stern), or one rendered as poor in iron as possible (P. Ehrlich), has likewise been suggested.

APPENDIX A

Necropsy Findings in cases of Erythraemia and cases clinically characterized by Polycythaemia with Splenomegaly.

(1) H. Vaquez (1892 and 1895).—A man, aet. 40, with chronic cyanosis and polycythaemia. Red cells over 8,000,000. Haemoglobin (by Malassez's method) 165 per cent. Spleen and liver both greatly enlarged. He died of acute tuberculosis, and the necropsy confirmed the presence of enlargement of the spleen and liver and the absence of cardiac disease.

(2) Rendu and Widal (1899).—Man, aet. 30. Illness commenced with feeling of discomfort in the left hypochondrium several years before his death. The spleen reached downwards to the ilium. Liver somewhat enlarged. Much cyanosis. Red blood-cells, 6,200,000; later on only 5,250,000. Increase of dyspnoea and death. At the *necropsy* the spleen was firmly attached by old adhesions to surrounding structures; it was fibrotic, and contained caseous masses. There was tuberculosis of other viscera. The bone-marrow was thought to show evidence of over-activity.

(3) Moutard-Martin and Lefas (1899).—Woman, aet. 49. Red blood-cells 8,200,000. White blood-cells 31,400. No cyanosis. Splenomegaly. Slight enlargement of the liver. Death with vomiting and diarrhoea. At the *necropsy* the enlarged spleen showed scattered caseous nodules, apparently tuberculous.

(4) R. C. Cabot (1899).—Woman, aet, 46, masseuse. About 7 years before her death she had an attack of temporary loss of consciousness. 4 years later she suffered from periods of mental and muscular debility with cyanosis and congestion of the face. Spleen apparently not enlarged. Red cells over 10,000,000. Haemoglobin 150 per cent. She died of middle meningeal haemorrhage, and the post-mortem examination (as far as it went) showed nothing beyond this, except great congestion of the viscera.

(5) V. Cominotti (1900).—Woman, aet. 33. Her father died of spinal caries. She suffered from pains in the situation of the spleen, epistaxis, and headaches. Cyanosis. Splenomegaly. Some enlargement of the liver. Splenectomy was performed and the patient died of sepsis about 6 weeks after the operation. The red blood-cells were about 7 million to the cubic millimetre before the operation; after the operation the number sank to 6,000,000 and then to 5,300,000. It is remarkable that even with the high counts before the operation the haemoglobin-value was estimated at only 80 per cent. The spleen was large and showed fibrous increase. At the *necropsy* in addition to the septic changes in the abdomen caries of the dorsal spinal column was discovered.

(6) Saundby and Russell (1902).—Man, aet. 48. Red cells 7 to 9 millions. Chronic cyanosis. Slight jaundice and increasing drowsiness before death. At the *necropsy* the heart showed slight old mitral valve disease, and there was some hypertrophy. The bronchial tubes contained a good deal of muco-purulent secretion. The spleen was enlarged, but is stated to have been of normal consistence on section; apparently no microscopic examination was made. The bone-marrow of the femur was described as normal to naked-eye inspection. Russell saw the patient with an enlarged spleen several years before any cyanosis was observed. The records of several cases, however, and notably Parkes Weber's second case, show that cyanosis by no means always accompanies erythraemia; the absence of cyanosis cannot therefore be accepted as necessarily signifying the absence of polycythaemia.

(7) W. Osler (1903).—Man, aet. 46. For 20 years slight cough off and on and headaches. Failing strength last 6 years. Cyanosis 4 years. Some

cutaneous pigmentation. Spleen not felt. Red blood-cells 8,250,000. Death occurred after a few hours' drowsiness deepening into coma. The cyanosis in this case rivalled that of congenital heart disease ('morbus caeruleus') so that the patient was known as the 'blue baby'. At the *necropsy* the heart was about normal, the lungs were moderately emphysematous, and the spleen was a little enlarged; but full notes were not available.

(8) A. J. van der Weyde and W. van Ijzeren (1903).—Woman, aet. 44. Chronic cyanosis. Some enlargement of the heart. Great enlargement of the spleen. Blood examined for methaemoglobin with negative results. Red blood-cells 7,600,000; white cells 12,800 (of which 84·7 per cent. were polymorphonuclear neutrophiles). Splenectomy was performed and the patient died 25 days after the operation. The *necropsy* showed great dilatation of the veins in the portal circulation, thrombosis of the portal vein, and thickening of the hepato-duodenal ligament from old inflammation. The spleen was found to have undergone a kind of fibrosis. The kidneys were normal. In this case it is remarkable that with the increase in erythrocytes the haemoglobin-value was estimated at only 90–95 per cent.

(9) R. Breuer (1903).—A woman, aet. 52. Chronic cyanosis with enlargement of spleen and liver. Slight albuminuria and cardiac enlargement. Death was due to internal haemorrhage after removal of a large uterine fibromyoma. At the *necropsy* the bone-marrow of the long bones was found to be in a state of haemopoietic over-activity. The spleen apparently gave no evidence of there being any erythrocyte-formation in progress (no groups of erythroblasts were seen) but it contained great quantities of eosinophile cells.

(10) W. Türk (1904).—Woman, aet. 43. Erysipelas 3 years ago. Phlebitis in left leg 5 months ago. Right facial paralysis. Attacks of temporary aphasia. Neuro-retinitis on both sides. Much cyanosis. Red blood-cells 7½ millions. Urine contained albumin with epithelial and other tube-casts. She died comatose. The *necropsy* showed nephritis and hypertrophy of the left cardiac ventricle. Extreme engorgement of the viscera with blood. The spleen was enlarged and contained multiple anaemic infarcts.

(11) W. Türk (1904).—Woman, aet. 35. Headache and pain in right hypochondrium 1½ years. Enlargement of the liver and spleen. Jaundice. Excess of urobilin and a little bilirubin in the urine. Wasting. No cyanosis or special redness of the face. Red blood-cells about 8 millions; white cells about 10,000; a few erythroblasts and a few myelocytes present. Death with increase of jaundice and haemorrhage from the nose and alimentary canal. The red blood-cells diminished in number to 5,160,000 before death. The *necropsy* showed cirrhosis of the liver with regenerative changes (multiple adenomata). The spleen was large, adherent to the liver, and of firm consistence. The bone-marrow in the long bones was dark red in colour and of fairly firm consistence.

(12) F. P. Weber and J. H. Watson (1904).—The patient was a man aged 58 years, who had always been very ruddy in the face, though strictly temperate with regard to alcohol. He had apparently usually enjoyed fair general health, though always inclined to 'indigestion' and constipation. A tendency to blueness of the nose and extremities had been noticed during the last 6 or 7 years. Latterly he had been subject to feelings of giddiness and prostration which prevented him from following his employment. At the end of 1903, some time after an injury (fracture of ribs), he began to suffer from delusions and had to be sent to a lunatic asylum, where, in spite of apparent mental improvement, he seemed to get weaker. Red blood-cells 9 to 11 millions. White cells 7,500 to 12,000, of which about 82·4 per cent. were neutrophile polymorphonuclears. Haemoglobin-value about 170 per cent. Brachial blood-pressure increased. Urine showed excess of urobilin. The patient died

suddenly of syncope during a period of increased cyanosis. The *post-mortem examination* showed the presence of a certain amount of pulmonary emphysema, slight old disease of the aortic valves of the heart, and an ulcer of the pyloric region of the stomach, but these changes were quite insufficient to account for the enlarged spleen, and for the polycythaemia, and the other symptoms observed during the patient's life. Moreover, the liver had not the typical 'nutmeg' appearance of chronic passive congestion, as it would have had if the enlargement of the spleen had been due to pulmonary emphysema and cardiac disease. On the other hand, the examination of the patient's bones showed that almost all the ordinary yellow (normal) marrow of the shafts of the long bones was in this patient replaced by red marrow from which fat cells were nearly absent, in other words, the amount of erythrocyte-forming tissue in this man's body was immensely greater than in the bodies of ordinary persons. It became, therefore, obvious that even if the formation of red blood-corpuscles had not been particularly active in any one part of the bone-marrow, the total production of red cells in the patient's body must have been very greatly above the average, owing to the great excess of the tissues engaged in manufacturing them. The enlargement of the spleen seemed to be due merely to increase of the splenic pulp and engorgement with blood. The organ was certainly not the site of any active erythropoietic or myeloid change. A striking feature in microscopic sections of the bone-marrow was the large proportion of non-granulated mononuclear cells of the 'large lymphocyte type', probably to be regarded as 'non-granulated myelocytes' or 'myeloblasts'. In the light of later researches there can be no doubt that the bone-marrow in this case was the site of excessive leucoblastic as well as erythroblastic activity.

(13) Axel Blad (1905).—Woman, aet. 34. Pains in epigastrium and left hypochondriac region. Face congested. Splenomegaly. Liver felt below ribs. Red blood-cells 11,000,000. The spleen was excised and death occurred a few hours after the operation. The *necropsy* showed that death was due to profuse internal haemorrhage. The spleen contained some small infarcts, and microscopical examination seemed to show that its enlargement was due to simple hyperplasia. The liver was slightly enlarged, and microscopic examination showed early cirrhotic changes. The condition of the bone-marrow is not stated.

(14) P. Reckzeh (1905).—Reckzeh's third case of polycythaemia with chronic cyanosis and splenomegaly was that of a man aged 24 years, in whom there was progressive compression of the vena cava superior by a malignant tumour of the thymus. The cyanosis and polycythaemia were limited to the territory of the superior vena cava till towards the end of life. On May 2, 1904, the red cells in blood from the upper part of the body were 6,200,000, and from the lower part of the body, 5,100,000. On May 24 the respective counts were 7,100,000 and 6,800,000, and on May 30, 6,500,000 and 6,000,000. With increase of weakness and mental stupor the patient died on June 5. The *necropsy* showed that the tumour of the thymus had extensively involved the right lung, and there were metastatic growths in the brain, kidneys, pancreas and elsewhere in the body. In regard to the cause of the final general polycythaemia in this case it should be noted that the right lung was extensively involved by the tumour and that the right bronchus was compressed by an infiltrated and enlarged lymphatic gland. The substance of the enlarged spleen was soft in consistence and deep red in colour. The bone-marrow was apparently not examined.

(15) R. Hutchison and C. H. Miller (1906).—Man, æt. 45. Red blood-cells 7½ to 11 millions. White cells 17,160 to 22,000. Cyanosis. Spleen extended to umbilicus. Death with coma and hyperpyrexia. *Necropsy*:—Thrombotic softening in occipital lobes of brain. Myocardial fibrosis. The viscera extremely congested. The enlarged spleen was connected by dense adhesions to surround-

ing structures, and contained necrotic patches apparently due to thrombotic infarction. The splenic pulp was carefully searched for the detection of erythroblastic foci, and a very few minute clumps of proliferating nucleated red cells were observed, but in view of their small size and number J. C. G. Ledingham (in his special report) concluded that the spleen had not been exercising any important function as an erythrocyte-forming organ. The bone-marrow from the shaft of the left femur was red in colour, and Ledingham reported :—'One could not conclude from a single section that red blood-cell formation was actively proceeding, but when one reflects that large tracts of marrow were in a similar condition one must infer that the polycythaemia is to be explained by a general increase of the erythroblastic functions of the marrow.'

(16) H. Hirschfeld (1906).—Man, æt. 51. Left-sided haemothorax. The blood was not examined during life. At the *necropsy*, in spite of the large pleural haemorrhage, the viscera were found to be extremely engorged with blood. The bone-marrow in the long bones was mostly red, and microscopic examination showed proliferation of the cellular elements, notably of the normoblasts and giant-cells, but not of mast-cells. The spleen was enlarged and contained a big cyst with sero-sanguineous contents. The splenic substance showed a partial myeloid transformation, which was, however, almost entirely leucoblastic (granulated cells) not erythroblastic; very many cell-containing phagocytes were present.

(17) K. Glaessner (1906).—Man, æt. 44. Syphilis 20 years ago. Pain in the left side of the abdomen 14 years. Dyspnoea seven or eight years. Tabes dorsalis. General cyanosis. Red blood-cells 10 to 11½ millions. Death with right-sided hemiplegia and great dyspnoea. The *necropsy* (apart from the changes in the nervous system) showed the characteristic extreme engorgement of the viscera with blood. The long bones contained areas of bluish-red marrow (erythroblastic marrow) replacing fatty marrow. The spleen was large and showed scattered yellow nodules.

(18) F. Lommel (1906).—Man, æt. 42. Great injection of superficial veins. Splenomegaly. Liver somewhat enlarged. Red blood-cells 8,230,000 to 8,600,000. Haemoglobin (with the lowest erythrocyte figure) 140 per cent. by Sahli's method. The illness had commenced three years ago with headache and feeling of congestion in the head and of pressure in the abdomen. There were frequently recurring pains in the abdomen. Venesection (150–200 c.cm.) was repeatedly performed with temporary subjective relief. Unusually severe abdominal pains were followed by collapse, vomiting, melaena and death. The *necropsy* showed extreme congestion of the portal tributaries (accompanied by angioma-like formations), apparently due to chronic obstruction in the portal circulation. Great thickening of the hepatoduodenal ligament. Recent thrombosis of the portal, splenic and superior mesenteric veins. The substance of the spleen was harder than normal. The bone-marrow (humerus, sternum and ribs) was deep red in colour, and no fatty marrow was seen.

(19) N. Schneider (1907).—Man, æt. 51. He had formerly suffered from malaria. In April, 1901, he was found to have polycythaemia (6,000,000 red cells, 22,000 white cells) and splenomegaly. The spleen was removed in May, 1901, and was found to contain some anaemic infarcts and the capsule was thickened from old perisplenitis, but no careful microscopic examination was made. In June, 1901, the blood-count showed 4,500,000 red cells and 16,000 white cells. Signs of pneumonia in December, 1901, were followed by progressive pulmonary tuberculosis. In April, 1902, the number of red cells was again above the normal, but then decreased until the patient's death, which occurred in October, 1902. On the day of death the red cells numbered only 1,385,000; the white cells numbered 55,400, of which 87·8 per cent. were polymorphonuclears and 1·4 per cent. were myelocytes; there were about twice as many nucleated red

cells (normoblasts) present as white corpuscles. The *necropsy* showed advanced pulmonary tuberculosis, dilatation and hypertrophy of both sides of the heart, with myocardial fibrotic changes in the walls of the left ventricle, aortic atheroma, chronic indurative nephritis, and an ulcer of the pyloric region of the stomach. The bone-marrow of the shafts of the long bones was red. It is not quite clear that Schneider's case was one of erythraemia according to our definition of the term (Part II).

(20) L. Ambard and N. Fiessinger (1907).—A woman, rather beyond middle age, corpulent, plethoric-looking, and very cyanozed. She had been cyanozed and dyspnoeic as a child as if she had congenital heart disease. Her general condition had much improved on the commencement of menstruation, but at the menopause she again became cyanozed and dyspnoeic. Red cells 7,800,000; later on (a month before death) 5,615,000. Dropsy. Death. The *necropsy* showed chronic interstitial nephritis and hypertrophy of the left ventricle of the heart. No valvular disease except slight thickening of the aortic cusps. The spleen was not enlarged, and to naked-eye examination the splenic substance appeared normal. The liver was engorged with blood, but macroscopically and microscopically did not resemble a 'nutmeg liver'. The bone-marrow, owing to a mistake, was not examined.

(21) R. Blumenthal (1907).—Woman, æt. 31. From two years of age she was subject to attacks of paroxysmal dyspnoea, accompanied by severe headache and followed by copious expectoration. From the age of 21 years: cyanosis, debility, haemorrhages. Red blood-cells 11,450,000; white cells 16,300, of which 36 per cent. were myelocytes; no nucleated red cells; haemoglobin 110 per cent. The appearance of the patient's face somewhat resembled that of patients with Graves's disease, but in addition it was extremely congested. By ophthalmoscopic examination the retinal veins were seen to be tortuous and engorged with blood. The *necropsy* showed fibrous adhesions of the right pleura and bronchopneumonia of the lower lobe of the left lung. The bronchial lymphatic glands were very large and of reddish-brown colour. There was a remarkable varicose condition of the veins of the dura mater, and a small haemorrhage was found in the hypophysis cerebri. The heart was somewhat hypertrophied. The capsule of the liver was thickened in places. There was no disease of the kidneys. The bone-marrow from the shaft of the humerus was red and succulent, like foetal marrow; by microscopic examination the leucoblastic tissue was found to be markedly in excess of the erythroblastic. Microscopic examination of the enlarged lymphatic glands showed great richness in blood-vessels, congestion, and fibrosis. Microscopic examination of the liver showed passive congestion and some increase in the interacinous connective tissue. Microscopic examination of the spleen gave no evidence of erythroblastic or myeloid transformation. Blumenthal regards the case as probably of congenital origin. The case is remarkable for the excessive leucoblastic activity, evidenced by the large number of myelocytes present in the circulating blood, and by the results of microscopic examination of the bone-marrow after death. It should, however, be remembered that, though the leucoblastic was decidedly in excess of the erythroblastic tissue, yet, owing to the foetal-like condition of the marrow in the shafts of the long bones (normally occupied by fatty marrow), the total amount of erythroblastic tissue in the body must have been very greatly in excess of the normal.

(22) Westenhoeffer and H. Hirschfeld (1907).—Man, æt. 28, supposed to be suffering from meningitis. No blood-count was made during life. The *necropsy* showed cerebral haemorrhage, but not meningitis. The viscera were all extremely engorged with blood, and so was the bone-marrow, all the cellular elements of which were increased, the white cells more so than the erythroblasts. The normal fat had entirely disappeared. The white cells in the bone marrow could

be divided into two groups: (1) granulated and (2) non-granulated, the latter resembling the so-called 'Rieder's lymphocytes'. The normoblasts were mostly arranged around clusters of these lymphocytes, as if they were genetically allied to them. Although the nucleated red cells were not relatively in excess, it was clear that their total number in the bone-marrow of the whole body must have been enormously increased. The spleen was large, and this enlargement appeared to be due chiefly to engorgement with blood. The Malpighian follicles seemed rather smaller than the average. The slight myeloid transformation detected in the spleen was of the leucoblastic, not of the erythroblastic, kind; erythroblasts were present in only very small numbers, and so they may have been carried there in the blood-stream. Very few cell-containing phagocytes were seen. The lymphatic glands were examined macroscopically and microscopically, and showed nothing abnormal beyond the general hyperaemia.

(23) E. Cautley (1908).—Man, aet. 47. Tender swelling in the splenic region. The colour of the face varied from deep red to a cyanotic tint. Red blood-cells $7\frac{1}{2}$ to 10 millions. Albuminuria. Death occurred from cerebral haemorrhage. The *necropsy* showed granular kidneys and cardiac hypertrophy. The enlarged spleen was firmly adherent to the surrounding structures, and contained two infarcts; the soft splenic tissue was divided into lobules by fibrous bands. Cautley adds that most of the post-mortem appearances could be explained as the result of local thrombosis of the extremely viscid blood. Cautley does not think that the microscopic examination of the bone-marrow or of the various organs afforded any indication of the aetiology of the condition. I understand, however, that the bone-marrow from the shaft of a long bone was red in colour.

(24) W. P. Herringham (1908).—Woman, aet. 38. At one time she was said to be anaemic, but afterwards she was high-coloured and subject to attacks of shortness of breath with lividity. Red cells 7,630,000. Haemoglobin 120 per cent. She died in one of her attacks of dyspnoea and cyanosis. At the *necropsy* the lungs were emphysematous, but they were not of the large kind. There was no cardiac disease. The liver was congested but not enlarged. The spleen was not enlarged and seemed natural on section. The bone-marrow was not examined.

(25) J. Löw and H. Popper (1908). Their second case was a woman, admitted into hospital with right hemiplegia of 14 days' duration. Spleen much enlarged. Red blood-cells 9,300,000. White cells 23,000. Haemoglobin above the normal. Death 5 days after admission. *Necropsy and microscopic examination*:—Thrombosis of the left common carotid artery and of the artery of the left Sylvian fossa, with consecutive softening in the left cerebral hemisphere. Chronic interstitial nephritis. The spleen was engorged with blood and showed increase of reticular tissue; the splenic pulp consisted chiefly of red blood-corpuscles and leucocytes; only remnants of the Malpighian corpuscles were left. The bone-marrow from the right thigh was examined. It was dark red in colour and full of dilated blood-vessels; there were only a few fat vesicles left; the cells consisted of numerous neutrophile and eosinophile myelocytes, fairly numerous neutrophile and eosinophile polymorphonuclear leucocytes, fewer small and large lymphocytes, erythroblasts (medium quantity), giant-cells and erythrocytes; the giant-cells, namely megakaryocytes and (fewer) myeloplaxes were relatively increased in number.

APPENDIX B

Specially Remarkable or Obscure Cases with Polycythaemia

(1) R. G. Hann (1908). (?) *Erythraemia of early life. Improvement in the general condition accompanied by increase of the polycythaemia.*—Girl, aet. 18. Enjoyed good health till 13 years old. Bodily development since then somewhat retarded. Menstruated twice when 15 years old, but never since. During the last two years suffered occasionally from severe abdominal pains of uncertain nature. Spleen extended three finger-breadths below the left costal margin. Liver not enlarged. Red blood-cells between 6 and 7 millions; haemoglobin 110 per cent. In this case an inherited syphilitic taint was suspected. In August, 1908, Dr. Hann kindly informed me that since January (when I had had the opportunity of studying the patient), under treatment by potassium iodide, iodide of iron, and occasionally tincture of perchloride of iron, the girl's general condition had decidedly improved, but the splenic enlargement remained unaltered and the polycythaemia had slightly increased (7,270,000 red cells on August 12). In regard to the increase of the polycythaemia accompanying improvement of the general condition compare Appendix B, Case 12.

(2) Nichamin (1907). *Erythraemia of early life.*—Young woman, aet. 20. Chronic cyanosis, polycythaemia, and splenomegaly. The splenomegaly dated from early childhood, and the cyanosis from the age of 13 years. She commenced to suffer from various haemorrhages when she was 15 years old. At 17 years she acquired malaria. Her sister had likewise enlargement of the spleen from childhood.

(3) Minkowski (1905). *Erythraemia of early life.*—Man, aet. 22. Remarkably cyanotic from early childhood. No heart disease. Polycythaemia. Splenomegaly. Came under notice for a cyst in the capsule of the right kidney, a most unusual condition, which was operated on successfully.

(4) M. Ascoli (1904). *Polycythaemia with splenomegaly (? toxaemic factor).*—A carpenter, aged 20 years. History of malaria and double otorrhoea. Cyanosis of face. Pigmentation of abdomen. Spleen somewhat enlarged. The urine showed a trace of albumin, excess of urobilin and some tube-casts. Blood: red cells 7,200,000; white cells 15,000 (of which eosinophiles constituted 20 per cent.); no erythroblasts seen; haemoglobin only 95 per cent. Improvement occurred whilst he was in the hospital. On one occasion arterial blood taken from the radial artery gave 6,100,000 red cells, whilst capillary blood from the lobe of the ear gave only 6,000,000 (could this be due to admixture of subcutaneous serum ?). Comparison with other cases seems to me to suggest a toxaemic factor in Ascoli's case.

(5) P. K. Pel (1907). *Toxic polycythaemia and haemoglobinuria.*—Man, aet. 33. Syphilis 11 years ago. Polycythaemia; 6 to 9 million red cells; haemoglobin-value 110 to 140 per cent. Repeated attacks of paroxysmal haemoglobinuria. Pel suggests that both the polycythaemia and the paroxysmal haemoglobinuria may have been of toxic origin.

(6) A. Fells (1908). *Toxic polycythaemia with chronic sulphonal poisoning and haematoporphyrinuria.*—A woman, aet. 37, who had been long resident in India, and had suffered from sunstroke and many attacks of fever. In 1906 she had intermittent pyuria with pyrexia. The blood-count showed polycythaemia (6,500,000 red cells) without leucocytosis. The urine became of a clear port-wine colour and was reported to contain 'urobilin', but Dr. Fells kindly informs me (August, 1908) that a subsequent careful investigation showed the red colour was due to haematoporphyrin. The woman had been accustomed to take sulphonal for years, though none had been prescribed during the nine months

prior to her death. No splenomegaly could be detected clinically: there was no post-mortem examination.

(7) Guinon, Rist and Simon (1904). *Acholuric jaundice and splenomegaly with temporary (toxaemic?) polycythaemia.*—Girl, aged 10 years. Chronic jaundice of variable degree with urobilinuria and chronic splenomegaly. Transitory cyanosis and polycythaemia accompanied exacerbation of the jaundice. Red blood-cells 6,000,000 to 7,600,000. Two or three months later the number of red cells fell to 4,000,000, and a year previously the count had given only 3,400,000. The resistance of the red cells to haemolysis was above the average. This case may certainly be compared in some respects to Hayem's chronic splenomegalic 'acholuric' jaundice (with oligocythaemia).

(8) M. Mosse (1907). *Acholuric jaundice (no bilirubin in the urine), splenomegaly with polycythaemia.*—A man, aet. 58, with chronic splenomegaly, urobilinuria and chronic acholuric jaundice. Red blood-cells 6,750,000 to 7,825,000; haemoglobin 100–110 per cent. Mosse compares his case in some respects to cases of splenomegalic polycythaemia (erythraemia), in other respects to the cases described by Hayem under the heading 'chronic infectious splenomegalic jaundice'. In Hayem's cases there was likewise urobilinuria (without bilirubinuria), but there was oligocythaemia instead of polycythaemia as in Mosse's case. Mosse's case may likewise be compared to the preceding one (No. 7).

(9) F. Dronke and C. A. Ewald (1892). *Polycythaemia from use of iron and arsenic.*—These authors in one case observed great polycythaemia following the long use of Levico water (which contains iron and arsenic). On November 23, 1891, the red cells were 5,120,000; on December 14, 5,300,000; on January 23, 1892, 8,400,000. This last count was carefully controlled by a second count and found to be correct. It is, however, noteworthy that with so remarkable a polycythaemia the haemoglobin-value was found to be only 85 per cent. of the normal.

(10) H. Neumann (1894). *Polycythaemic reaction (a form of 'blood crisis') following oligocythaemia.*—Man, aet. 57. Supposed to have Addison's disease, of acute onset, accompanied by great anaemia. Then a gradual improvement in the man's general condition followed, and the oligocythaemia gradually gave place to polycythaemia. Afterwards the number of red cells fell again to the normal. The count of erythrocytes gave 1,120,000 on April 15, 1885; 3,330,000 on June 8; 5,490,000 on July 24; 6,500,000 on October 1; 7,700,000 on January 8, 1886; 6,590,000 on January 26; and 5,500,000 on July 6. It is probable that when cases of anaemia from haemorrhage and other forms of anaemia improve with or without special treatment, the anaemia may occasionally give place to a temporary polycythaemia, as if the normal level had been overshot by the reactive effort of the blood-forming tissues.

(11) F. Geisböck (1905). *Case of (clinically) splenomegalic polycythaemia with low blood-pressure. Unsuccessful treatment by Röntgen rays.*—Man, aet. 51. Apparent recovery from severe jaundice. Then headache, giddiness, and loss of appetite and weight. Face somewhat cyanotic. Slight goitre. No disease of heart or lungs. Blood-pressure 100 to 110 mm. Hg. Liver and spleen enlarged. Occasional trace of albumin and a few tube-casts in the urine. Red blood-cells 9,100,000. White cells given as only 1,080. Haemoglobin-value 200 per cent. Venesection of 260 c.cm. scarcely relieved his headaches, nor did the application of Röntgen rays to the spleen improve his general condition. Carlsbad treatment had a better effect. Geisböck thought the case resembled some of those described by Türk.

(12) C. Begg and H. H. Bullmore (1905) and T. J. Horder (1908). *Case of (clinically) splenomegalic polycythaemia. Good results from inunction of*

biniodide of mercury over the spleen and large doses of quinine. Afterwards good results from application of Röntgen rays to the spleen. Woman, aged 47 years in 1904, when she was treated at Bath by Dr. C. Begg. Red blood-cells 6,850,000. White cells 11,300 (of which polymorphonuclears 77·3 per cent.). Haemoglobin-value 100 per cent. Poikilocytosis and polychromatophilia were well marked, especially the latter. No myelocytes were seen. About four normoblasts were counted to a thousand white cells. Diminution in the size of the spleen and subjective improvement undoubtedly accompanied the treatment by quinine and inunction with biniodide of mercury (the part being exposed to artificial heat). It may here be noted that up to the age of 30 years the patient had suffered from frequently recurring 'liver attacks' with vomiting; after that age the attacks recurred less frequently. In May, 1906, she was first seen by Dr. Horder, who has kindly given me notes of her further progress. The spleen was very large, but under treatment with Röntgen rays (Dr. Horder and Dr. Lewis Jones) it decidedly diminished in size. The patient's general condition likewise improved, although the number of red blood-cells (5,400,000 before the Röntgen treatment) increased simultaneously with the improvement. It seems possible, as Dr. Horder suggests, that in this case the polycythaemia was in some way 'compensatory'. It may be noted, however, that in Hann's case (Appendix B, 1), increase in the polycythaemia likewise accompanied improvement in the patient's general condition. Dr. Horder, who is shortly going to publish an account of his observations, tells me that the subcutaneous tuberculin test gave a negative result on three occasions.

(13) Münzer (1908).—*Erythrocytosis probably from blood-stasis not of cardiac origin. Obesity. Thyroid treatment.* The first case mentioned by Münzer was that of an obese man with extreme tendency to fall asleep. Cyanosis. Red blood-cells 9,800,000. No enlargement of spleen or liver. There was distension of the neck, which Münzer supposed was connected with substernal fat or goitre. Under thyroid treatment the man's weight fell from 103·0 to 89·3 kilograms and all his alarming symptoms disappeared.

(14) F. Geisböck (1905). *Polycythaemia with high blood-pressure treatment with iodothyrin.* Man, aet. 55, a bank-director, overworked and very excitable. Little enlargement of the heart; slight irregularities in the cardiac action. No albuminuria. 'Rush of blood' to the head at times. Erythrocytes 6,100,000. Haemoglobin-value 108 per cent. Blood-pressure 170 mm. Hg. Improvement after the use of iodothyrin. The blood-pressure fell to 120 mm. Hg.

(15) F. Geisböck (1905).—*Slight polycythaemia with chronic interstitial nephritis.* Man, aet. 51. Admitted with cerebral haemorrhage. Red face. Some enlargement of the heart. Arteriosclerosis. Albumin and tube-casts in the urine. Red blood-cells 5,700,000. Haemoglobin-value 104 per cent. Blood-pressure 250 mm. Hg. The necropsy showed decided, but not extreme, chronic interstitial nephritis.

(16) F. Geisböck (1905). *Polycythaemia with high blood-pressure and arteriosclerotic gangrene of the foot.* Man, aet. 64. History of hard work and some indulgence in alcoholic drink. Red blood-cells 10,400,000 to 11,320,000. Haemoglobin-value 156 per cent. Brachial blood-pressure 150–160 mm. Hg. Trace of albumin in the urine. Arteriosclerosis. Gangrene of the right foot. Amputation. The dorsalis pedis artery of the amputated foot was extremely sclerotic.

(17) F. Lommel (1908). *Polycythaemia with 'angina cruris' and commencing gangrene of the foot.* Man, aet. 47, thin. Severe pain and commencing gangrene in the right foot with absence of pulsation in the right anterior tibiali artery. Pirogoff's amputation was performed in 1903. In 1906 Lommel detected

a considerable polycythaemia (9,700,000 red cells and 150 per cent. haemoglobin-value). There was clubbing of the fingers.

(18) F. Schupfer (1908). *Polycythaemia and chronic cyanosis following the operation of splenectomy for splenomegaly in Banti's disease.* In a man, aet. 42, the enlarged spleen was removed for supposed Banti's disease, and the progress of the case was followed for 3 years. The man's general health was improved, and the liver, which was enlarged before the operation, returned to its normal size. But polycythaemia and chronic cyanosis gradually developed. The red blood-cells 3 years after the operation were 6,270,000, whilst before the operation they had been only 2,880,000 to 4,920,000 in the cubic millimetre.

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