Chapter 6.

THE MODERN PERIOD. ——— II.
(1800 - 1939)

The History of the Blood.

The Physiological Functions of the Blood.

From ancient times the blood has been regarded as essential to life. Some physiologists have indeed regarded it as life itself and have used the words synonymously. During the early part of the nineteenth century a new conception regarding its physiological function came into existence. (236) Wilkinson (1804) expresses the view that the function of the red globules is solely to restore the continual losses the body suffers and the formation of new parts. He errs from an insufficient knowledge of the erythron. The true function of the red blood as a respiratory organ had, as we saw, come into being during the previous century, and had been elaborated upon during the first half of the next century. In 1845 (287) Dr. Simon observes that the greater part of the carbon exhaled from the lungs in the form of carbon dioxide arises from the red corpuscles and in this way, the production of animal heat became linked up with the oxygen consumption of the red cells. (288) (289) (290) Henle, Wagner, Wharton Jones, and Mr. Newport considered the red corpuscles as floating glandular cells, and according to Jones their special function is to convert albumen into fibrin. Dr. Carpenter objected to this and attributed this change to the white corpuscles. Neither their views were however received with favour by the medical profession for it was shown that serum freed of all cells could still coagulate, thus frustrating their argument.

A theory on the physiology of the blood that found considerable favour during the middle decades of the century was that of Prater (1842). He revived the earlier views that
the blood was alive, but adds that it is by this living property it possesses that the body is both formed and nourished. His views differed but little from those of Dr. Alison, who a few years earlier had attempted to show that the blood was endowed with a "living, or self-moving power inherent in itself" and that any increase or decrease of this power resulted in disease. Not far removed from these ideas are those postulated by Clement, professor of Physical Science Vevey, in a paper to the Academy of Sciences at Paris. He considers that the red cells are possessed of a vital force by which they resist destruction and putrefaction and which excites the movement of the heart and circulation. The same force, he also says, resides over the nutrition of the organs. The carbon dioxide, which combines with the red blood cells, partially narcotises them and thus gives them a rest in their arduous nutritional task.

The state of knowledge in 1863 may best be expressed (293) in the words of Dr. Bennett. He writes, "the blood circulating through the body may be regarded as a river flowing by numerous canals through a populous city, which not only supplies the wants of its inhabitants, but conveys from them all impurities which through various channels find their way into its stream. The chief supplies enter the circulation in the form of water and of blood corpuscles, from the primary digestion. These receive oxygen in the lungs where they become coloured, are sent all over the body, and in the ultimate capillaries yield up their oxygen, which combines with carbon and other chemical constituents of the tissues to form numerous combinations. After a time they are dissolved in the liquor sanguinis, which fluid they serve to elaborate. The blood also receives and holds in solution the products of the secondary digestion, so that it is a highly elaborated, viscous, and complex organic liquid. It is the blastoma from which the living molecules, nuclei, cells, and other elements of the tissues are continually attracting, on the one hand, new
matter to supply the place of what is lost, and on the other, old matter which has sufficiently served the purposes of the frame. In what manner this important fluid utilizes the various products it receives from both sources is as yet unknown. All that we can determine is that the whole is in incessant motion, rushing rapidly out from the heart through the arteries, divided into minute streams by capillaries in the tissues, returning more slowly by the veins—a circuit through the frame completed in half a minute—subjected to the constant collision of about two billions of semisolid corpuscles, incessantly undergoing chemical alterations when exposed to the peculiar action of every organ in the body; and while impairing one or more of its constituent principles in this or that tissue as it passes through it, at the same time absorbing those which have been worn out in the service of economy.

Blood, therefore, is a mixture of the histogenic and histolytic processes of the body. It is in the circulation they mingle together, and is it there constantly constantly we must look for an explanation of numerous morbid conditions which derangements in so nicely a balanced an organic fluid may be expected to produce."

Speaking broadly this may be accepted as the general view regarding the function of the blood, which prevailed throughout the nineteenth century. Decidedly there were numerous advances made in knowledge on the various elements of the blood, likewise there was progress in knowledge regarding the pathology of such elements; but the evolution of the idea that the red blood cells served the purpose of tissue respiration and that the blood is for the purpose of nutrifying all the cells of the body and removing their products of metabolism had been reached shortly after the middle of the nineteenth century. (294)

Within recent years Boycott has introduced the conceptions of the erythron (viz. the circulating blood and the organs from which it arises), and facilitated a better understanding of the whole problem of the physiological processes
of the organs of blood formation and destruction. This conception has thrown considerable light on the understanding of the nature of anaemia and its logical treatment.

It is not within the scope of this work to discuss the problem of blood physiology in all its historic detail. When the anaemias are considered, further references will be given where this becomes necessary.

Diagnostic Methods in the Examination of the Blood.

A brief review of the various techniques used in determining the chemical and physical properties of the blood is necessary if we are to understand the developments which occurred in the better diagnosis of the anaemias.

a). Estimation of the Volume of the Blood:

Various methods have been employed in order to determine the total volume of the blood. Those of Valentin (1838), Vierordt (1842), Buntzen (1879), and Thibauts (1894) are among the best known of the last century. The modern way of estimating the blood volume is by the dye or carbon monoxide methods. In the last named lower values are obtained. By the dye method of Keith, Rowntree and Geraghty (1915) the blood constituents are roughly estimated at 1/12 of the body weight, or about 6,000 cc. in the average adult.


Blix-Hedin's (1890) method was that of centrifuging the blood and so determining the proportion of red cells and serum. His results were erroneous since the fibrin was not considered. Gartner (1892) improved on his method, and this was later simplified by Koeppel (1893), and Rosin (1892).

Another method was that of Biernacki (1894), whose determination depended upon the sedimentation of the red blood corpuscles.
A more accurate method was introduced by the brothers Bleibtrau. They used the Kjeldahl technique to estimate the amount of nitrogen in diluted blood before the corpuscles had settled and again in the serum after this had occurred. By arithmetical deduction they arrived at their conclusions. (305) This method was improved upon by Hamburger (1893), (306) Ejkmann, and v. Limbeck.

c). The Cell Count.

Although various instruments for determining the number of cells in the blood had been used for many years, no accurate (307) one had been devised until Mantagazza (1867) introduced his new type of "Globulometer". With this he was able to give the number of red cells in a cubic mm. for the average male as 5,000,000.

Most of the methods of enumerating the corpuscles and platelets which have been devised depend upon the determination of the number of blood corpuscles in a very small portion of blood, which has been uniformly mixed with some preserving and diluting fluid. Various such fluids have been used. For the red cells the earlier workers favoured those of Pacini, Hayem, Gower, Potain, Mosso, Mayet, Löwet, Toisson, Bräber and Mallessez; and for the white cells that of Thoma and Toisson. Those of Hayem and Toisson are still much used.

For platelets the same instruments used in counting the white cells were found servicable. Among the best known of the fluids suggested for this purpose appear those of Pruss and Affanasien. (308) Zappert's method of counting the eosinophile cells was among the few which survived the nineteenth century. (309) Gower's (1877) "Haemocytometer" received a wide approval at the time it was first introduced, but that of Hayem (1889) later found greater favour among haematologists. These two instruments were the forerunners to the modern haemocytometer.
The technique of Wallassez (1872) and Aferow (1880) never became popular.

The errors of these older instruments were investigated and commented upon by various workers like Reivert (1891); Laache and Thoma. The last mentioned introduced a haemocytometer which today still enjoys wide recognition for its accuracy. The counting chamber of Bürker with double Neubauer ruling, the Hauser counting chamber and the "Bright Line Chamber" introduced by Spencer Lens Company are most popular in America at the present time.

The modern technique for the estimation of the blood platelets is that of Cramer and Bannerman (1930).

d). Histological Examination of Blood Corpuscles.

Ehrlich's work on the action of dye-stuffs on the cellular elements of the blood opened up a new field of research. The reaction of this enquiry was immediate and far-flung. He and his followers showed that certain empirical relations existed between the cells and a variety of the analine dyes. It thus became possible to identify and group the blood cells with greater accuracy than hitherto; a fact which intensified research in haematology. In 1878 he demonstrated and differentiated the granular and non-granular leucocytes.

It is impossible to enumerate the works of all those engaged in staining methods; let it suffice to mention some of their names and leave the ardent student to further enquiry: Nikiforoff (1890), Gabritschewsky (1892), Ehrlich (1892), Schwartz, Gollasch (1889), Ruber (1886), Flehn (1890), Aldehoff (1891), Feletti, Westphal, Rieder (1892), Chenzinsky, Klein, Romanowsky, Weiss (1892), Neusser (1894), Bremer (1894).

The method of demonstrating the supposed nuclei of mature erythrocytes before Ehrlich's discovery was the simple procedure of adding acetic acid to blood. Frequent reference to this is found in the older writings.
At the present time the Romanowsky stains are the best known and most widely used. The dye concerned is the compound which is formed when the watery solutions of medicinal methylene-blue and water-soluble eosin are brought together. In the modern formula these changes are brought about by treatment with alkalis, especially alkaline carbohydrates, as was first practised by Unna in the preparation of his polychrome methylene blue. The chief formulae based on Romanowsky's combination, are those of Jenner (1899), Leishman (1906), Wright, Giemsa, and today Graham's.

Another method of staining, first described by Ehrlich in 1880, is that of "vital staining". This procedure has its special applications and is of great service in work on the reticulo-endothelial system. The work was followed by Haves (1909), Chauffard and Feissenger, Biffi, Vidal, Abrami and Brulé, Biondi, Haves and Damashek (1926), Sabin (1923), (339) Cunningham, Sabin and Doan (1925), and Cunningham and Tompkins (1930).

It may be mentioned here that micro-photography, that important aid to the histological examination of the blood, was first used by Richard Norris in 1882. What stimulated him to undertake his extensive enquiries into blood morphology was the discovery in August, 1877 that there existed in the blood many corpuscles which had the same colour and the same refractive index as the serum, and had hitherto escaped notice. This discovery produced an unprecedented haematological upheaval.


It was early shown that when red cells were added to water they burst and liberated their haemoglobin. A saline solution of sufficient strength to just counterbalance the "haemoglobin-loosening" effect was termed by Hamburger "isotonic". To test the strength of such isotonic solutions we have the methods advocated by Landois, Famburger,
(1866 etc), Laker (1890), Maragliano (1887) and others. Recently there are the methods employed by Emmons (1927), Vallery-Radot (1928), Faden (1934) and Whitby and Rynes (1935), for the most part based on the Sanford technique, in which blood is added to a range of tubes containing different strengths of hypotonic saline, and observing at which point haemolysis occurs.

f). Investigation of Haemoglobin.

Quantitative Estimation:

Before the time of Gower crude attempts at estimating the amount of haemoglobin in the blood had been made. In 1878 he introduced a modification of the existing haemocytometer and thus opened up a new field of research in the pathology and therapeutics of the haemopoietic system. This date is important from the point of view of the histological investigations on anaemic blood.

The principle on which his haemocytometer works is that it compares defibrinated blood, diluted with distilled water, with a solution of carmine-picrocarmine gelatine, the colour of which corresponds to that of a 1 per cent aqueous solution of normal blood.

Hayem's (1889) haemoglobinometer or "Dosage d'hémaglobine" acts in the reverse way. Here a blood solution is compared with a colour scale of picro-carmine, corresponding to known numbers of red blood cells. He took five million as the normal number of cells per cu.mm. and calculated the percentage of haemoglobin from this.

Another instrument invented for this purpose was the Mallessez's "haemochrometer" (1876). It acts on a different principle. A prism filled with picro-carminate of ammonia is adjusted in front of a light, until the blood and water, which are in a bulb, shows the same colour as that passing through the prism. Fixed to the apparatus is a scale, the final reading of which can be interpreted in terms of
"adsorption capacity" and "amount of haemoglobin" in an accompanying table.

Hénocque (1886) utilised the spectroscope and the bands of oxyhaemoglobin to determine the percentage of haemoglobin in any given blood. The instrument he called the "haematoscope".

Bezzozero (1889) devised a "haemo-chromo-cytometer", which could be used either as a chronometer or a cytometer. In the former, that thickness of a solution of blood, of predetermined strength, which is sufficient to produce a certain depth of colour, is estimated; in the latter the estimation is that thickness of blood in an isotonic saline solution, which prevents the eye from seeing a particular light through it.

Fleischl's "haemometer" (1885) has a graduated, translucent scale deepening in colour from one end to the other, and is moved below a compartment filled with water, until the colour corresponds with that of a blood solution in another compartment. The percentage of haemoglobin is read off from the sliding glass scale. Miescher modified this instrument.

In 1891 v. Limbeck and Sadler investigated the relative values of the methods advocated by Gower, Hénocque, Fleischl and Bezzozero and showed those of Gower and Fleischl to be superior to the others.

Two years later Hoppe-Seyler (1893) made an instrument he called the "Calorimetric Double-pipette" to be used for the same purpose. This consists of a telescopic arrangement whereby haemoglobin is compared with carbon monoxide haemoglobin. It is, however, slow in comparison with the simpler methods of Gower and Fleischl, and thus did not become popular.

For spectro-photometric estimations of haemoglobin reference must be made to the papers of Vierordt, Elan, Otto and G. and A. Krüss.

Various other haemoglobinometers have been invented. Tallquist's (1900) is still in use. He compares the colour of a drop of blood on filter paper with that of a colour scale representing varying percentages of haemoglobin.
Oliver's (1896) "haemoglobinometer" works on the principle of the industrial and commercial "tintometer". Dare's instrument was popular in America. It consists of the comparison of a capillary tube, full of blood, with a rotating colour scale; the comparison being made within a camera-tube held in front of a light.

Among the more recent methods used for estimating the percentage of haemoglobin are those of Van Slyke (1921), which expresses the results in grams of that substance per 100 ccm. of blood; of Sahli, in which blood is mixed with a decinormal solution of hydrochloric acid, thereby converting the haemoglobin to acid haematin, and the brown colour matched with standardised brown-coloured glass; of Sahli-Welling, which is a modification of the above; of Newcomer, in which the principle is the same as that of Sahli; of Sheard-Sanford, in which a costly and complicated instrument, the photometer, which functions with a photo-electric cell and allows the haemoglobin to be directly read in terms of grams per 100 ccm. of blood.

For the qualitative examination of haemoglobin, which depends upon its chemical behaviour, the spectroscope, at an early date, came into prominence. Hénocque's apparatus, or Hering-Maschek's spectrosopes without lenses were favourites. References to the papers of Hoppe-Seyler, Jäderholm, Dittrich, Kuniyosi Katayama, and Dresses are appended.

The Density of the Blood and the Plasma.

This problem was undertaken by numerous workers from an early period. A complicated but accurate method, devised by Schmaltz proved to be the best for a long time. He used the "capillary pyknometer". Other methods, quicker but less accurate were devised by Fahraeus (1892), Roy (1894),
Hammerschlag (1890), Haycroft, and Siegl (1892).

h). Estimation of Coagulation Time.

Of the early methods those of Vierordt (1878) and Wright (1892) were the best. More recently Lee and White (1913) devised a simple method of placing 1 c.c. of blood in a test-tube, 8 mm. in diameter, and corking it. The tube is inverted at half minute intervals until coagulation has occurred. The time is then noted.

The capillary tube method of Wright (1921) appears to enjoy the greatest popularity today. Finally there is Howell's method.

i). Measurement of the "Osmotic Elasticity" of the Plasma and Serum.

The methods employed were mostly purely chemical or bacteriological. Numerous textbooks on the matter have been written. There were the so-called "plasmolytic" method of de Vries (1884), the "corpuscular method" of Hamburger (1906) and the freezing method discussed by Ostwald. The modern methods are those of Determann (1907) and Denning and Watson (1906).

j). Other techniques which are for the most part twentieth century innovations to the study of haematology are the "direct measurement of the red cell diameter" of Price-Jones (1927) and the "diffraction micrometer method", and the "substitute for the halometer" (Price (1929)).

Also the "estimation of red cells size by diffraction methods" using Eve's halometer, or the method put forward by the Association of Clinical Pathologists and modified by D.M. Price (1929), or Pyper's (1929) method.

For the determination of corpuscular volume there are the methods of Rahn (1931), and Minto (1932); while for the
"red cell sedimentation rate" Westergren's technique (1921, 1926), and those of Zeckwer and Goodall (1925), and Wintrobe (1933, 1935) are most widely used.

Finally the technique of bone marrow biopsy has been developed by Custer (1933) although as will be shown, this was attempted many years ago.

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The Chemical Properties of the Blood.

In 1815 J.A.F. v. Auërie and J.S.F. v. Bohnenberger of Tübingen carried out an analysis of the blood. They admirably summed up the knowledge of their time but added little to the stock of knowledge.

Lyon (1831) investigated the arterialisation of blood and came to the conclusion that this depended upon two factors. Firstly the presence of atmospheric oxygen and secondly the presence of "muriate of soda", found in the blood serum. He assumes that it is only the combination of these two which brings about the change.

Turner (1833), a few years later, worked on the same problem. He supported Steven's view and says: "The change from venous to arterial blood appears, contrary to the received doctrine to consist of two parts essentially distinct; one is a chemical change, essential to life, accompanied by the absorption of oxygen and evolution of carbonic acid; and the other depends on the saline matter of the blood, which gives a florid tint to the colouring matter after it has been modified by the action of oxygen."

Clanny (1834) invented a new and better method for collecting the gases obtained from the blood for the purpose of analysis. The only practical method of the time was that devised by Vogel, and this was not satisfactory. Clanny demonstrated that oxygen and carbon dioxide circulated in the blood in small quantities and that there was always a large
and uniform quantity of nitrogen in that fluid. "The theory", he says, "of Priestley and Lavoisier and after them, of Laplace, Crawford, Gren and Girtanner, viz---that the blood absorbs no air from the lungs but gives out hydrogen and carbon, which combine with the oxygen of the air inspired, form water and carbonic acid", he holds as untenable, since he proved that the lungs gave off no hydrogen and even if they did it would not combine with the oxygen at body temperature. He believed the carbon dioxide to be formed in the blood from the free carbon it contained, and which originated from the chyle only. By another experiment he found twice as much nitrogen in arterial as in venous blood.

The question of the quantities of gases in the blood had long been a problem of uncertainty. Magnus (1837) settled this matter fairly conclusively. His experiments gave the following results: Arterial blood per 100 cu. inches contains 6.5 cu. inches of carbon dioxide plus 2.4 cu. inches of oxygen plus 1.5 cu. inches of nitrogen (equals 10.4 cu. inches). Venous blood per 100 cu" contains 5.5 cu" carbon dioxide plus 1.2 cu" of Oxygen, plus 1 cu" of Nitrogen. (equals 7.7 cu"). The investigations also settled beyond all doubt that arterial blood contains carbonic acid as well as oxygen and nitrogen, but that it has more oxygen and nitrogen than venous blood.

Felix Boudet (1833) detected in the blood serum two entirely new principles and confirmed the presence of a third. From this he drew the general conclusion that if a sufficient quantity of blood could be examined it would be found to contain the characteristic principles of the different secretions, as cholesterine, urea, etc. The substances he isolated from the blood were an alkaline soap, cholesterine and a fatty substance, which he designated "seroline". An oily matter isolated by Le Cann, Boudet regards as partly alkaline soap and partly seroline and cholesterine.

In 1832 Hermann (1833) announced his discovery of acid in blood. In the presence of Dr. Stevens, at Moscow, he repeated
his experiments. He explains the difference between arterial and venous blood in terms of this acid. The acid in venous blood, mostly carbonic acid, he says, turns the colour black or dark. This can be quickly changed to arterial red when it is brought into contact with neutral salts, which in turn can be turned dark with any acids. He came to the conclusion that venous blood contains free carbonic acid, which can be removed, by exposure to air or even to hydrogen at ordinary temperatures.

Le Cann in his thesis estimated the blood to contain twenty-five substances. These he enumerated as free oxygen, nitrogen, carbon dioxide, extractive, phosphuretted fat, cholesterine, seroline, free oxalic acid, margaric acid, hydrochlorate of potassium, sulphate of potassium, hydrochlorate of soda, lactate of soda, hydrochlorate of magnesia, fatty acid salt, carbonate of soda, yellow colouring matter, carbonate of lime, albumin, carbonate of magnesia, water, fibrine, haematosine, globules.

In the substance haematosine he found iron, held within the red cells. This is well expressed by Rees in his Galstonian Lectures. The "iron", he says, "of the blood resides in the colouring matter dissolved in the liquid which is enclosed in the colourless envelope of the corpuscles. The serum of the blood contains no iron; the serum of the chyle contains iron in abundance. The crassamentum of the blood contains iron; that of the chyle only such a trace of it as may be accounted for by the adhering serum. Again the specific gravity is far below that of the liquor sanguinis. Hence, on the mingling of these fluids, an endosmotic transmission of iron in solution will take place into the corpuscles.

"It follows that if the specific of the liquor sanguinis be anyhow lowered, or that of the chyle much increased, the supply of iron to the corpuscles will be so far impaired."
Blood examination during this period made rapid strides due to the advent of organic chemistry. It was early realised that the inorganic analyses of the blood, carried out in the past were undoubtedly erroneous in many respects. This led to the investigation of this organically constituted fluid with renewed vigour. As an example of this enthusiasm we have but (404) (405) to turn to the works of Garrod (1843), Mulder, Lumas (1846-7), Richardson (1858), C. Schmidt and others. Garrod gives a formidable list of substances found in the blood among which may be mentioned globulin, haematine, and haemaphaein which constitute fibrin. Of the fats, in addition to those mentioned by La.Cann he notes cerebrate and oleic acids.

Berzelius had shown at a somewhat earlier date that the addition of sulphate of soda to freshly drawn blood prevented coagulation. This observation was later to assume greater prominence when blood transfusion became a recognisable and widespread therapeutic measure.

In 1850 C. Schmidt gave a general review of the chemical composition of the serum and mentions that their proportions are as follows:-

A thousand grams of serum of a healthy man of 25 years contains 908.84 grams of water.

Material not volatilised at 120°F.---91.16 gm

Albumen etc.---32.59 gm.

Inorganic material---3.57 gm.

Chlorine---3.566 gm  '  potassium sulphate---0.283 gm.

K₂SO₄ ------0.130 gm  '  "  chloride----0.362 gm.

Phosphoric ac.  '  "  sodium "  ----5.591 gm.

Potassium---0.317 gm  '  "  phosphate----0.273 gm.

Sodium ------3.433 gm  '  soda  ----1.545 gm.

Ca, phosphate0.30 gm  '  Calcium phosphate ----0.300 gm.

Magnesium --0.220 gm  '  Magnesium  "  ----0.220 gm.

Oxygen------0.458 gm

The alkaline carbonates of the blood were stated to be a portion of the soluble salts. Their existence were acknow-
leged by Marchand, Lehmann, Nasse, H. Rose and others, but denied by Enderlin and Liebig. These workers made elaborate tables showing the salts present in blood serum.

The important observation that urea was present in the blood was first shown by Prevost and Dumas, who also demonstrated its increase during certain diseases of the kidney, and in June 1847 Garrod found it in normal blood.

Millon had put forward the statement that copper and lead occurred in normal blood. This was refuted by Melsens (1848) in a communication to the Royal Academy of Belgium.

In 1850 C. Schmidt postulated that the knowledge of the chemical constitution of the blood was of subordinate interest so long as it is not known what proportion the particular components are divided between the blood and plasma. This statement was supplemented by v. Limbeck. He says, "An analysis of the whole blood does not give us the composition of the blood, nor is an analysis of single constituent parts sufficient. It is necessary to make first, a complete analysis of the whole blood, and then a similar one for a constituent part, e.g. the serum."

The initial study of alkalinity of the blood by Marchand, Lehmann, Nasse, Rose and others was followed up by the valuable work of Kühne, Liebreich (1868), Zantz (1867-68), Lassar, Landois (1895), v. Jaksch (1889), Winternitz, Kraus, Tanasz, C. Schultz-Schultzenstein (1894), Drouin, and v. Limbeck (1895); while the investigation of the blood acidity was undertaken by Kraus and Drouin.

Until the latter end of the nineteenth century it was thought that the constituents of the corpuscles were fairly constant, but Hamburger and Lehmann showed that the substances in solution in the cells are undoubtedly subject to variations, owing, among other things, to respiration. The variations were first accurately investigated by v. Limbeck.
The earlier researches on the chemical constituents of the red cells by C. Schmidt, Hoppe-Seyler (1881) and Jüdell were inferior to those of Bleibtreu, or those analyses which investigated the red corpuscular pulp rather than the whole clot. Aronet (1887) pointed out that the first objection to methods of isolating the corpuscles from the fluid was that they were not obtained intact. This applies particularly to the methods of Jüdell and Hoppe-Seyler, and in lesser degree to those of v. Jaksch and Biernacki.

By the close of the last century the following substances were supposed to enter into the composition of the red cells: haemoglobin, lecithin, cholesterin, and an albumin which is allied to globulin and coagulates at 75°C. The inorganic constituents were taken to be: potassium, sodium, calcium, magnesium, chlorine, phosphoric acid, carbonic acid and water. The general opinion at the time was that the plasma consists of serum and fibrin-forming material. The serum contained serum-albumin and serum-globulin, fats, sugar, urea, uric acid, creatin, carbonic acid, lecithin, cholesterin and a colouring matter—lutein. Its inorganic components were chlorides, phosphates, sulphuric acid, sodium, potassium, calcium and magnesium.

The chemistry of the white corpuscles and platelets was deficient by the end of the nineteenth century owing to the inability to separate them from the blood. Crude attempts were made by Lilienfeld who examined pus; by Hoppe-Seyler, who examined leukaemic blood. This work was continued without much advance by Salomen, Nasse, Woroschiloff, Meischer, Obermeyer, A. Kossel (1894), Ranvier (1891), Bizzozero, Löwit (1886) and Lilienfeld (1891).

The albumens of the serum received special attention during the close of the last century from Chabrie (1891), who claimed the discovery of a substance he called "albumon"; but Drechsel (1894) and Brunner (1896) showed this to be a substance not present in blood within the living body, and
was only produced by the coagulation of albumen and globulin. 

Kamarsten (1895) found the total amount of albumen in human serum to be $7.619\%$ per cent and that it remained fairly constant relative to the other substances in the blood. Boserup and Rodier had as early as 1835 made a large number of examinations of serum in health and disease and summed up the findings in the following words: "The albumen of the serum diminishes appreciably in three special conditions, viz.: Bright's disease, certain diseases of the heart with dropsy and puerperal fever". Some workers like v. Jaksch estimated the amount of serum-nitrogen and from this calculated the albumen content. Fick and v. Limbeck (1894), however, found this method inaccurate. It was shown that the two albumens—the serum-globulin and serum-albumen, although relatively stable with regard to their total amount in the blood, varied considerably in their relative proportions. The early literature on this subject is confusing, and it is not without a feeling of dismay that one reads the conflicting views of men like Howells and Salvioli, Bruckhardt, Tiegel, Emmerich, "stelle", Hoffman, Halliburton, Nya and Viglezio, Hans Buchner and Castellino.

With regard to the nitrogenous substances in the blood urea was shown to be the most important. Active workers in this field were Gescheidtens (1881), Garrod (1879), Salomon, etc.

Of the salts in the blood Biernacki and others suggested that a decreased amount of potassium generally means an increased amount of sodium, and gave the following examples:

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of r.b.cs</th>
<th>Potass.</th>
<th>Oxid.</th>
<th>Sod.</th>
<th>Oxid.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy man</td>
<td>5.03 millions</td>
<td>0.175%</td>
<td></td>
<td>0.216%</td>
<td></td>
</tr>
<tr>
<td>Anaemia graviditas</td>
<td>0.905</td>
<td>0.024%</td>
<td></td>
<td>0.346%</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis anaemia</td>
<td>1.426</td>
<td>0.056%</td>
<td></td>
<td>0.347%</td>
<td></td>
</tr>
</tbody>
</table>

He suggested sodium as the most valuable constituent of the blood. He further showed that a loss of phosphoric acid seems to go parallel with a loss potassium, viz. with a loss of red corpuscles.

The normal amount of iron in the blood was found by
v. Limbeck to be somewhere between 0.056 and 0.058 per cent, being a little less in females. The relation of iron to potassium, due to their connection with the red cells, was determined by many workers. Biernacki quotes the following figures of Fleischl:

<table>
<thead>
<tr>
<th></th>
<th>Potassium Oxide</th>
<th>Iron</th>
<th>Haemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal blood</td>
<td>0.164 %</td>
<td>0.0551 %</td>
<td>105 %</td>
</tr>
<tr>
<td>Chlorosis</td>
<td>0.164 %</td>
<td>0.0461 %</td>
<td>60 %</td>
</tr>
<tr>
<td>&quot; (severe)</td>
<td>0.061 %</td>
<td>0.0223 %</td>
<td>25 %</td>
</tr>
</tbody>
</table>

The historic review of the carbohydrates of the blood is an essay in itself. The early works that should be consulted are those of Hofmeister, Hamburger, v. Mering, Chauvean and Kaufmann, Seegen, Cavazzani, Trinkler, Kraus, Cantani, Hoppe-Seyler, Lépine, Arthur, Saikowski, Araki, Zielessen, Sauer, Gabritschewsky, Czerny, Trambusti, Bial, Barral and Gumprecht and v. Jaksch.

Space does not permit of a review of the chemical analyses of the blood carried out during the last three decades. A modern table of the chemical constituents must suffice as a comparison with those of the last century (1937):

Chemical Constituents (Yracke and Garver):

- Non-protein nitrogen: 25-30 mg. per 100 cc. of blood.
- Urea: 12 -15 mg. per cent.
- Uric acid: 1-3 per cent.
- Creatinine: 1-2 per cent.
- Sugar: 80-120 mg per 100 cc. of blood.
- Chlorides:
  - In plasma: 570-600 mg. per cent.
  - In cells: 285-300 mg per cent.

Calcium: 9-10 mg per cent in the plasma of adults; slightly higher (10-12 mg. per cent) in that of children.

Serum protein, total: 6-8 Gm per 100 cc. of blood.
- Albumen: 4.5-5.5 Gm per cent.
- Globulin: 1.5-3.0 Gm per cent.
Carbon dioxide combining power of the plasma: 55-80 of carbon dioxide per 100 cc. of plasma.

Cholesterol: 150-200 mg. per 100 cc. of blood.

With regard to haemoglobin compounds reference to the extensive works of Bancroft (1923) on the subject should be made.

The Physical Investigation of the Blood.

The physiological and pathological variations in the specific weight of the blood, as shown by means of simple methods adapted for clinical use, were subject of much discussion towards the end of the last century. The older workers on this subject were Davy, Nasse, Vierordt, Becquerel, Rodier and Landois, and later Roy (1834), Lloyd Jones, Devoto Hammerschlag (1830), Schmaltz (1831), Peiper (1831), Scholhoff (1832), Siegl Hock and Schlesinger (1843), Glogner (1894), Menicanti Grawitz, Lyonnet, and Moell (1894).

All the authors found a relatively smaller specific weight in women after puberty. Lloyd Jones, investigating the influence of age on the density of the blood in health, found the specific gravity to be highest at birth (1066) in both sexes; between the second week and second year the density sank to a minimum (boys 1043 --- girls 1050); it then gradually increased, reaching its highest point in males between the 35th and 45th years (1059.5), and in females after the climacteric (1054.5).

The period of childbirth was found to be characterised by a relatively low specific gravity. It increased in old age in both sexes, until the initial density of birth was again reached.

V. Limbeck summarises this knowledge as follows: "The density and the amount of water of the blood in physiological conditions undergo considerable variation. The tissues and their power of absorption have an intimate connection with the quantity of water in the blood. The action of the vaso-motor centre has a considerable effect on the density. The most important point in pathological cases, so far as the density is concerned,
is the amount of plasma in the circulation."

With regard to the volume of the blood-corpuscles and plasma in the blood v. Limbeck tells us that "the total volume of the red corpuscles is certainly of great importance to the metabolism. The volume of the white cells, on the other hand is of secondary interest." As early as 1842 C. Schmidt showed that variations in the amount of water of the blood affected both the plasma and also the corpuscles. Pathologists were loth to take this view that variations of corpuscular volume occurred. This is instance in the writings of Daland (1831) and others, but Gärtner (1892) strongly supported Schmidt and showed the possibility of variations in individual cells. Friedheim (1893) confirmed this and showed that the total volume of the corpuscles was independent of their number and of the amount of haemoglobin. The first to investigate this matter under pathological conditions was Herz. Numerous workers found an increased volume of red corpuscles in certain severe anaemias. Herz, Daland, Friedheim determined this by centrifugal methods and by enumeration. Biernacki and v. Limbeck proved the same fact by sedimentation, and from this v. Limbeck deduces that some relation exists between the volume of the corpuscles and the increased amount of salt within them observed by Biernacki.

The study of the osmotic relations of the blood had its origin in the work of De Vries, who was the first to investigate in plants what he called the "isotonic" state of the fluids within and without the cells. Donders first applied this to animal cells, especially the red corpuscles, and his pupil Hamburger pursued the subject in a long series of investigations. A new field was thereby opened to physiologists and pathologists. v. Limbeck appears to be the first to estimate the isotonic coefficient in pathological cases. In health he found it to be about 0.46 per cent sodium chloride, and in anaemia to be diminished, but increased, as an exception, in
The Haemoglobin and the Colour of the Blood.

By the end of the eighteenth century and during the first few decades of the nineteenth the opinion generally held was that the red colour of the blood was due to the peroxide of iron. It had its supporters but it also had its opponents, the most ardent of whom, among the early workers, were Stevens, Brande and Scudamore.

Berzelius found that $\frac{1}{160}$th part of the blood globules was iron united with phosphoric acid. Mr Brande was unable to confirm this and found only a trace of iron. He attributes the colour to "the removal of a portion of carbon and hydrogen from that fluid" and the differences in colour to "modifications of animal matter, and not to different states of oxidizement of iron". Scudamore (1824) after experimentation also arrived at this conclusion.

Physiologists began to enquire more earnestly into the form in which this metal occurred in the blood. Sage and Gren conceived that it existed as a phosphate, and Deyseux and Parmentier were led soon after to infer, that in whatever form it occurred, it was the free alkali of the blood which kept it in solution. Dr. Wells at a later date disproved this, and states that no metallic compound loses its colour at 212°F. as blood does; and that if iron is the real colouring matter of the blood, it must exist in the form of a salt, which he thinks impossible, for it cannot be detected by the liquid reagents used to test for the presence of iron. He, therefore, infers the red colour to be due, not to the iron, but a peculiar arrangement of the organic elements of the colouring matter. This led to a division of opinion.

In 1803 Brande made the observation that the use of Pyrmont mineral water, or ferruginous remedies in general, increased the quantity of the red globules of the blood. At
this time Emmert and Reuss, and Vanquelin found protophosphate of iron in the chyle and lymph, and they consequently inferred that this salt, which is colourless, became the red perphosphate when the chyle is changed into blood.

Imhoff (1819) in a thesis published at Göttingen states that there is iron in the blood which may be detected by a magnet. Engelhart (1825) and Rose (1826) regarded this as an improbable assertion. To Engelhart goes the credit of first demonstrating, beyond all doubt, the presence of iron in the red blood corpuscles, by liquid analysis. He also showed that the dark venous blood may be made more florid by agitation with oxygen as well as with air, whereas hydrogen, nitrogen, carbonic acid, nitrous oxide, and olifient gas have no action at all. By passing chlorine through the blood he was able to remove all its colouring matter. This colourless fluid he found possessed iron, which could be demonstrated by using liquid reagents. In serum alone he found no iron.

In his nicely performed experiments he included the investigation of the quantity of iron in the blood and found that 50 Gm. of ox blood yielded 0.246 Gm of oxide of iron or 0.492 per cent, and in sow's blood 0.526 per cent, the mean of which is very similar to Berzelius' findings some years previously.

Although these experiments definitely and undubitably showed the presence of iron in the blood, they did not settle the dispute as to whether it is the iron which imparts to the blood its red colour or not.

Dr. Stevens (1832) supported the views of Lyon previously mentioned. He showed that the addition of salt to dark clot caused it to become red. He held that the natural colour of the haematosine (colouring matter of the blood e.g. haemoglobin) is black, and that it becomes red when acted on by saline matter. Oxygen played no part in his scheme of things, except inasmuch as it removed the carbon of the blood by combining with it, and that the carbon dioxide then converts the haematosine to its inherent dark colour. These views were
favoured by Turner (1834) and Hoffmann (1833). Williams (1835) advanced a new theory that oxygen and salts cause the colouring matter to become more transparent and so more florid. Dr. Day concluded that neutral salts brightened the blood by separating the corpuscles so that they reflected more light; and that water, acids and other agents, darkened the blood by altering the form of the corpuscles and partially dissolving the colouring matter. He remarked that haematosine is black only in mass, and red when reduced to powder, or viewed in a small portion by transmitted light. It was argued by numerous workers that if the brightening of the blood arose simply from the action of certain agents such as oxygen and carbon dioxide, protoxide of nitrogen, etc, on the colouring matter, this substance, when separated from the corpuscles, would suffer the same change. This, however, was found not to be the case from the experiments of Mulder, Nasse, Schultz and Henle in 1843. In 1835 O'Shaughnessy christened the colouring matter of the blood "sub-rubrine". The introduction of this term did not result in a better understanding of its nature. Sheerer (1844) advanced a novel explanation for the red colour of the blood. He refers the whole of the difference between bright arterial blood and dark venous blood to a physical change rather than a chemical one, and says it depends upon the different forms assumed by the corpuscles, and not due to the oxygen acting on the blood, for he found that in blood dissolved in distilled water, the passage of oxygen through it did not render it bright. Dumas (1846-7) arrived at a somewhat similar result and concludes that the colouring matter of the blood has the power of assuming the arterial tint only while it exists in the form of "globules" and that it is lost when they are dissolved. Although Dr. Stokes first proved the theory that the red colouring matter of the blood of the oxygen John R. Roberts (1863), two years earlier, anticipated this view in
his thesis. This is an important date for it marks the commencement of the modern view of the oxygen-carrying properties of the haemoglobin.

Hoppe-Seyler assumed from his investigations that the haemoglobin is not held bound within the stroma of the red blood corpuscles by mechanical means, but that its fixation may be due to a chemical combination.

By 1894 the place and manner of origin of the destruction of the haemoglobin in the body was almost entirely unknown. Ross in 1844 had put forward the view that the spleen was the organ which produced the haematosine and that from there it was carried through the thoracic duct and so to the lungs where it entered the corpuscles. This view was again advanced by A. Schwartz (1838) but was proved erroneous by Gürber (1891).

It was early found that a 100 Gm of human blood contains about 14 Gm of haemoglobin. The introduction of instruments for calculating the amount of this substance in the blood, particularly the hematocrit of Blix-Nedin, resulted in an avalanche of literature on the subject which for a while almost buried the other branches of haematology beneath its weight.

The outcome of this work was to show that haemoglobin, known also as haemoglobin and haemocrystallin, contained 96 per cent albumen and 4 per cent haemochromogen. Hufner and Külz showed that haemoglobin forms another and more stable compound oxygen, namely "methaemoglobin", than is usually the case with oxyhaemoglobin. Tschirkoff claims to have found it in Addison's disease, and Ruyter has recognised a very similar but not identical colouring matter in a case of "malignant oedema", where the colouring matter of the haemoglobin was also a brownish-red-black colour. Gamgee (1898) showed that oxyhaemoglobin is absolutely non-diffusible. Haemoglobin-aemia was first intensively studied by Lichtheim, Murri,
Haemosiderin, an amorphous iron-holding product of the decomposition of haemoglobin was shown to originate apart from any cellular activities by Perls, Thoma and Ziegler.

During recent years a number of blood values have come into use depending on the amount of haemoglobin present. Most of them are for clinical use both diagnostic and prognostic and for estimating the progress during treatment.

The values given below are those of Wintrobe; slightly different values are given by Haden, Price-Jones, Vaughan and Goddard. The values for infants and children have been given by Lippmann and Mackay.

Values for normal individuals:

Haemoglobin:

Men, 14 to 18 average 16 Gm per 100 cc. of blood.
Women, 12 to 16 average 14 Gm per 100 cc. of blood.

Volume of packed cells (Haematocrit):

Men, 40 to 54, average 47 cc. per 100 cc. of blood.
Women, 37 to 47, average 42 cc. per 100 cc. of blood.

Red cells:

Men, 4.6 to 6.2, average 5.4 millions/cu.mm. of blood
Women, 4.2 to 5.4, average 4.8 millions/cu.mm. of blood.

From the above data, red blood corpuscles per cubic mm., grams of haemoglobin and volume per cent may be worked out by the use of the following formulae:

For the calculation of Volume and Haemoglobin (colour) Indices.

Red blood cells equals 5.0 millions/cu.mm. equals 100 %
Haemoglobin equals 14.5 Gm per 100 cc. equals 100 %

Colour Index (C.I.) = \( \frac{\text{Haemoglobin per cent.}}{\text{Number of red blood cells per cent}} \)

Mean Corpuscular Volume = \( \frac{\text{Haematocrit per cent x 10}}{\text{Number of red blood cells in millions}} \)

(Normal = 30 to 94 cu. micra., average 83.7 cu. micra.)

Mean Corpuscular Haemoglobin = \( \frac{\text{Gm. Hb. per 100 cc. X 10}}{\text{Number of r.b.c. in mils}} \)

(Normal = 27 to 32 micro-micrograms, average 27.5)
Mean Corpuscular Haemoglobin Concentration (M.C.H.C.) =

\[
\frac{\text{Gm. Hb./100 cc x 100.}}{\text{Haematocrit per cent.}}
\]

(Normal 33 to 38 per cent., average 35 per cent.)

From these values it has become possible to distinguish four types of anaemia——Macrocytic, microcytic, normocytic and hypochromic. These will be discussed in due course.

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The Number of Cells and the Volume of Blood.

Opinions have varied considerably in regard to the average number of red blood corpuscles. The first to investigate the matter with any accuracy was Welcher (1854). He estimated that in a cu.mm of blood there are normally 5,000,000 red cells in men and 4,500,000 in women. His estimates were later shown to be the average of those of a number of other investigators like Vierordt, Cramer, Malassez, Hayem, Sörensen, Patridgeon, Bouchat and Dubrisay, Cutler and Bradford, Laache, Helling, Friderichson, Otto, De Renzi, Holla, Andreessen, Zälein, Neubert, Ziegler, Reinl, Gräber, Stierlin, Reinicke, and others. Individual workers, however, show considerable variations, thus Andreessen (1883) gives 7,000,000 as a maximum in males and Bouchat and Dubrisay (1878) give 3,306,500 as the lowest figure in normal females. It must, however, be remarked that Welcker's figures and the average of all the others are remarkably close to those of more recent workers, e.g. Price-Jones (1931), who gives the average male as 5,428,000 and the average female as 5,012,000.

Wintrobe's (1933) figures as we saw before are 5,500,000 and 4,200,000.

From the time of Welcker it has been observed that there are physiological variations of these numbers depending on the time of day, presence of menstruation and pregnancy.

With regard to the quantity of blood in the body the
early workers (before 1840) regarded the average man of 160 lbs, to have the following amounts:

Borelli—20 lbs,        Haller—30 lbs,
Blumenbach—33 lbs,      Young—40 lbs,
Dumas——25 lbs,         Fletcher—30 lbs.

Vierordt estimated it at 1/13th of the body weight. The limits of error in the methods of estimating the total quantity of blood, suggested by these early men, were later shown to be great, although many of the values they arrived at closely approximate the modern estimates. Haldane and Smith later determined the total quantity of blood in fourteen healthy subjects by a method based on the capacity of the blood to absorb carbon dioxide. They found it to vary between 1/13 th and 1/16th of the total body weight. The modern dye method, mentioned before, gives the value at 1/12th.

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Coagulation of the Blood.

We saw in a previous chapter that the eighteenth century workers Jurin (1719), Keill (1717), Langrish (1735), (503) (504) Boerhaave (1740), and Haller (1756) supposed coagulation to be merely a "running together of the red globules". We saw that the "buffy coat" was believed to be formed by the fibrin left at the surface of the clot after the red corpuscles had sunk to the bottom, and which occurred when clotting was delayed as in inflammatory conditions. This view had been adopted by Davies, Hewson (1780), and Davy (1768). (507) (508) (509)

Somewhat similar opinions had been expressed by Thomas Houlston (1767), George Fordyce (1768), William Hunter, James (510) (511) (512) (513) (514) Hakittrick (1772), George Levison (1776), James Gregory (515) (516) (517) (1782), Dr. Cullen (1789), Hugh Moises (1784), James Wilson (1819) and others. In addition we have also seen
that Harvey and Sydenham attributed the coagulation of the blood to the escape of its native animal heat or to the cold of the atmosphere. Fewson, however, had shown that cold even retards coagulation and that freezing prevents it, whereas at higher temperatures coagulation was increased.

He had wisely added that there are more factors than just cold and rest in the phenomenon. His experiments had shown further that though air may promote coagulation it is not the cause of it. Hunter reported that blood coagulates more readily "in vacuo". Dr. Davy could not confirm this. Sir Humphrey Davy in 1800 showed that coagulation was neither materially hastened nor retarded by nitrogen, nitrous gas, common air, oxygen, nitrous oxide, carbonic acid, or hydrocarbon. Dr. Davy's observations on the effects of carbon dioxide and oxygen are similar.

In 1818 Sir Everard Fume and Mr Bauer revived the discarded hypothesis of Sydenham, Queensay and Bordenave, that the fibrin of the blood is formed of the colourless matter of the red globules. Prevost and Dumas (1821), in France, brought forward a similar view, and were supported by Milne Edwards (1827). This theory was later adopted and further expounded upon by Dutrochet (1831) and Beclard (1827).

In Britain this theory never took root as may be evidenced from the contrary views in favour of Fewson's suggestions, by Gordon (1817), Wilson (1819), Babington (1830), Sharp (1833), Hodgkin and Lister (1827) and Grainger (1829). On the Continent too, there were antagonists to this theory---Burdach (1837) in Germany and De Blainville (1829) in France, who declared that such a structure (viz. fibres of decolorised red blood cells laid end on end) was seen only by the dupes of an optical delusion.

The term "fibrin", as far as could be gathered, was first used in its present sense by Fourcroy in his publication of 1801. That this fibrin is liquid in the flowing blood seems to be the claim of discovery of many men, especially
Berzelius and Lénis (1839). This cannot be true since even before the time of Boerhaave this view had already been expressed.

Scudamore (1824) tried to explain coagulation as follows: The fibrin, he says, can only remain fluid when intimately mixed with the red particles, serum and carbonic acid. The first essential step is the liberation of carbon dioxide, after which the fibrin coagulates by virtue of its innate characteristics.

Schwann thought all the fibres of fibrin to arise from a transformation of cells. Dr. Martin Barry (1842) propounded the theory that the fibrils originate from the interior of the blood discs and apparently grow out of them like so many flagellae.William Addison was the first to show under the microscope that in coagulation the fibrin is "precipitated in the form of molecular fibres, which, entangling the corpuscles together in a mass, so form the clot of the blood".

A very common view at that time was the assumption that coagulation produced a rise of temperature in the blood. One of the first to denounce this was John Davy, who failed to demonstrate that this was the case. He wrote a long article on the effects of chemical and physical agents on the coagulation of the blood. He introduces nothing new that is worthy of noting, and only adds to the fallacies of the time.

Black found that the intravenous injection of a number of substances prevented coagulation. Among these he mentions sodium hydroxide, sodium sulphate, ammonia, silver nitrate, zinc sulphate, phosphoric acid, arsenic, arsenious acids, ferrous sulphate, oxalic acid, infusion of galls and infusion of digitalis.

The fact that blood remains fluid in the body Thackrah (1834) ascribes to the influence of the nerves acting directly on the blood. It is difficult to follow his reasoning for it is not made clear where the synapsis occurs.
important conclusion that it is the living blood vessels which inhibit coagulation and that when the vessels become devitalised coagulation is the result.

Gerhard and Hufeland showed that the continual passage of an electric current through the blood tended to keep it fluid. Scudamore's investigations however failed to confirm this. (542)

Prater (1832) found that all neutral salts suspended coagulation and that coagulation may be produced subsequently by the addition of water. He also found that minute quantities of all neutral salts hastened coagulation, whereas larger quantities prevented it. Dr. Simon (1845), quoting Hamburger mentions that carbonates and acetates in all degrees of concentration, prevent the coagulation of the blood, while the sulphates, tartrates and borates, in strong solution retard and in weak solution accelerate coagulation. Mr. Ancell (1839), working on the same problem, gives a lengthy table of the effects of various substances on the coagulation of the blood.

A view concerning coagulation was that put forward by Hunter (1837), in which he returns to the philosophical explanations of the Middle Ages. He believes that it occurs by virtue of its "living principle" and that without this living principle no coagulation can occur. Ample demonstration to the contrary has been supplied by Davy, Hewson, Gulliver, etc., who showed that blood may be coagulated after freezing and after drying and then redissolving the fibrin etc.

Richardson's opinion that coagulation occurred by the liberation of a volatile principle from the blood after it had been shed, and which he identified with ammonia, did not find many patrons.

Later in the century Alexander Schmidt gave evidence, in his famous researches on coagulation, that fibrin and a similar substance may be produced in the disintegration of leucocytes. F. Meischer, too, in a memoir, has described
the conversion of pus cells into a fibrinous clot, thus confirming an observation of Rovia. These investigations led (546) Wooldridge (1881) to perform a number of experiments upon the white cells, and his results were a confirmation of the earlier work of Schmidt, Neischer and Fano, of whom the last-mentioned investigated the action of peptone on the blood. He assumed that with the breakdown of the leucocytes or at least certain leucocytes, a "fibrin ferment" is liberated which is able to bring about coagulation by its action on the fibrinogen in the plasma. This ferment he associated with (547) lecithin. The destruction of the leucocytes, he states, is not merely passive resulting from death of the cells, but due to the destructive action of the plasma. Woolridge's work was confirmed in its entirety by Rauschenbach (548).

Woolridge subsequently modified his views, and he concluded that the fibrin ferment was potentially present in the serum as well as in the cells, and that in the case of the serum some body existed which had the power of liberating or producing this ferment. In other papers he expounds upon this theory.

Prior to 1885 Osler, Bizzozero and Fayem had respectively shown the presence of coarse granules, "Blutplättchen" or haematoblasts in the blood and had attributed to them the power of coagulation. Woolridge strongly contested these views in his Croonian Lecture on the "Coagulation of the Blood" delivered in April 1886, by saying he finds "that the plasma contains, in solution, everything necessary for coagulation;" and continues, by stating "I will not go so far as to affirm that the formed elements cannot exert any influence, yet it is very doubtful whether they play any part at all, and it is certain that they are not necessary". He divides the coagulable matter of the plasma into A-fibrinogen, which separates from the plasma on cooling or on adding a certain amount of magnesia, and which endows the plasma with spontaneous coagulability, by giving rise to the ferment in the plasma; B-fibrinogen, which forms
the bulk of coagulable matter of the plasma, does not precipitate out on cooling the plasma, but is precipitated by neutral salts or by acids, and consists of proteid and lecithin; C-fibrinogen, the fibrinogen of Hammarsten, which is either absent from the plasma or present in very small quantities, and clots readily with fibrin ferment, but does not clot with leucocytes. It is interesting to note that this A-fibrinogen is literally the same as the blood platelets, but that he regards them not as cellular elements but as a proteid precipitate.

These investigations set the pace for other workers in the same field. To enumerate their findings is not possible here. It may, however, be noted that of the modern theories (554) (555) those of Morawitz and Howell are the most widely accepted. Morawitz assumes that when blood is shed the platelets come in contact with a water-wettable surface. As a result the platelets disintegrate and liberate thrombokinase—a substance also liberated by the damaged tissue cells. The thrombokinase, together with the calcium ions of the blood react with the production of prothrombin in the plasma which is capable of forming thrombin, whilst the fibrinogen in the blood in the presence of thrombin forms fibrin. This may be expressed in the following equation:

Prothrombin + calcium ions + thrombokinase = Thrombin.

Thrombin + fibrinogen = fibrin.

Intravascular clotting according to this theory is prevented by the absence of thrombokinase, that is, by the absence of disintegrated platelets, and to a less extent by the absence of substances liberated from damaged tissue.

Howell's theory assumes that calcium ions by themselves are able to change prothrombin to thrombin without any action on the part of disintegrated platelets or tissue juices. Incirculating blood the change is prevented by an anti-prothrombin known as heparin, and which may be prepared from the liver by an elaborate method. This substance when added to
blood will prevent clotting for several days. There are many authorities who do not believe that there is a free circulating heparin. During the process of clotting the heparin is neutralised by the thrombokinase from the destroyed platelets. In equation form this is:

\[
\text{Prothrombin} - \text{Calcium ions} = \text{Thrombin}.
\]

\[
\text{Prothrombin} - \text{Calcium ions} - \text{heparin} = \text{no thrombin}.
\]

\[
\text{Prothrombin} - \text{Ca. ions} - \text{heparin} - \text{cephaline} = \text{Thrombin} \quad \text{(thrombokinase)}
\]

\[
\text{Thrombin} - \text{fibrinogen} = \text{fibrin}.
\]


At the beginning of last century Dr. Cullen said:

"The red globules have been considered as an oily matter, and from thence their distinct and globular appearance has been accounted for: but there is no direct proof of their oily nature; and their ready union with, and diffusibility in, water, renders it very improbable. As being microscopical objects only, they have been represented by different persons very differently. Some have thought them spherical bodies, but divisible into six parts, each of which in its separate state was also spherical; but other persons have not observed them to be thus divisible. To many observers they have appeared as perfectly spherical; while others judge them to be oblate spheroids, or lenticular. To some they have appeared as annular, and to others as containing a hollow vesicle. All this with several other circumstances relating to them, very variously represented, show some uncertainty in microscopical observations; and it leaves me, who am not conversant in such matters, altogether uncertain with respect to the specific nature of this part of the blood. The chemical
history of it is equally precarious; and, therefore, what has been hitherto said of the production and changes happening to these globules, we choose to leave untouched—. We suppose that the red globules, when viewed singly, have very little colour, and it is only when a certain number of them are laid upon one another that the colour appears a bright red: but this also hath its limits; so that when the number of globules laid on one another is considerable, the colour becomes of a darker red. Upon this supposition, the colour of the mass of blood will be brighter or darker as the colouring part is more or less diffused among the other parts of the mass; and we think this appears to be truly safe from every circumstance that attends the changes which have been at any time observed in the colour of the blood". Priestley disproved the last statement by showing that air acting on blood brightens it. Dr. Priestley believed this to be produced by the absorption of something from the air and not by the liberation of something from the blood.

A gradual change in the conception of the morphology of the red cell took place during the first few decades of the nineteenth century. Hume, for example, believed they were minute spherical bodies, consisting of a central globule (557) enveloped in a colouring matter during life. Young (1813) also maintained this to be the case and considered that the central "umbilicus" or prominence shown so clearly by Amici of Modena, was nothing but an optical illusion. Hodgkin and Lister (1827) showed that the cells were hollow on both sides but in addition they pointed out that some were flat and others even "swollen on the broad surfaces". Prevost, Dumas, Donné and Müller demonstrated by numerous experiments that the globules were composed of a central nucleus and a surrounding membrane filled with colouring matter.

M. Donné, in short, regards the bodies as minute bodies of a lenticular shape formed of a ground-work of fibrin, in
the interstices of which albumen and colouring matter are deposited. Müller's (1832) ideas may be summarised in his own words: "The globules of the blood", he says, "are composed of a colourless nucleus and red crust, which undergoes gradual solution in pure water, but not in salt or sugarised water. After the solution of the red crust in water the central nucleus remains, insoluble in simple water, but are dissolved in alkaline water. The most effectual mode of detaching these nuclei from their red capsules, is to mix a drop of acetic acid with a drop of blood from a frog, or any other animal, and to observe the effect microscopically. The red crust is instantly dissolved in the acetic acid, while the illiptical nuclei remain, and may be examined in their proper form."

These workers belonged to the so-called "Nuclear Theory", of whom Boudet was a keen supporter. Many of the early investigators like Dollinger (1819), Gruithuisen (1820), Oesterreichen (1826) and Wedemeyer (1828) held the view that the red blood cells are formed in part by globules detaching themselves from the parenchyma of the various organs of the body. They, therefore, believed that the blood is elaborated in the substance of the tissues. It is natural that the supporters of such a hypothesis would also adopt the view that the red cells were nucleated. There were, however, a group of observers who clearly differentiated between nucleated and non-nucleated red cells. Magendie (1833) was one of these. He says that there are two classes of red corpuscles, "those with and those without a nucleus. The former belong to reptiles and fishes, the latter to mammalia and birds". He continues by saying that "it has been advanced that the globules are composed of a sort of proper parenchyma. According to this view their superficies are formed of haemato-sine; the parenchyma itself of albumen; the central nucleus of fibrine; but the perfect solubility in water of the globules of mammalia and birds, makes me suspect the correctness of
In 1339 we still find the theories of Malpighi and Leeuwenhoek on the origin of the red blood cells. Schultz (1839), for example, in great detail describes the metamorphosis of the fat globules in the lymphatics into red cells. Another erroneous view he held was that the weight of the cells is proportional to its colour. Thus, according to him, the dark vesicles are heaviest and sink to the bottom of the container, the red ones are lighter and lie above the darker ones.

An interesting observation about this time was that of Emmerson (1836). He describes the visible motion of the red corpuscles. His description is certainly that of true movement. He says: "I witnessed the most unequivocal living action among the globules, moving about in all directions, sometimes actually appearing to coalesce, if such an expression may be admitted, and then separating; passing over, and on one side of each other, and continually altering their shape, position and appearance; and as they rolled over, there occasionally seemed to be organs obscurely perceptible under the highest magnifier." Probably he was observing no more than currents in a fluid suspension of the cells.

Still working under the impression that the red cells are active, living and nucleated Barry (1840) concludes that they propagate by division of their nuclei. In this he was supported by Müller, Edwards and perhaps by Rees (1841) and Lane. Opposing them were Bonn, Bernouilli and Keil who considered the vesicles to be simply little bubbles of air. Professor Schultze of Berlin took an intermediate position. According to him the red cell had a vesicular membrane and within was an "aeriform fluid" in the middle of which was a nucleus.

A very enlightening piece of work was carried by Donne. He arrived at the conclusion that the existence of the nucleated red cells in the adult is a fallacious observation, though he states that they be present in the young embryo. He also
adds that there is no difference between the globules of arterial and venous blood. His observations fell on barren soil for physiologists persisted in examining the blood of amphibians, in which the red cells are nucleated.

In 1854 David Tod postulated a revolutionary view regarding the origin and nature of the red cells. He is not satisfied to call them alive but creates a new word for them --- "haematozoa". He mentions that these haematozoa and the spermatozoa are merely the primary and secondary stages of the same being. By this statement he at one fell swoop attempts to destroy the labours of Schwann, Schleiden, Kölliker and Goodair; and also the work of Wagner, Miller and Henle on the formation of the "spermatophori". His views were novel and certain novelists succumbed to it. Dr. Paxton (1855) was one of these. In place of the "haematozoa" he calls the red corpuscles "haematids" or "haematic protozoa". The evolution of the blood, he says, "is fourfold, and comprehends:

1) the chylid. 2) the haematid. 3) The lymphid and 4) the liquor-sanguinis". Thus the chyle is converted directly into the living red cell, and in debilitating conditions the "lymphid" or white cells are produced and a leucocythaemia ensues.

In 1845 Wharton Jones recognised three phases in the development of the blood corpuscles; these he names the phase of the granular-cell, the phase of the nucleated-cell and the phase of the free cellaeform nucleus. All three phases he notes occurs only in mammals. The free cellaeform nucleus is the normal red cell. In the lymph occur the granular cells, nucleated cells and free cellaeform cells. According to him the lymph and blood are identical as regards corpuscles, except that in the former the free cellaeform nuclei have not yet attained their perfectly red stage.

This classification was adopted and modified by numerous workers. Rindfleisch's "granular cells" were the coarsely granular cells of Wharton Jones, a small number of the granular cells of Donders and Moleschott, and Valentin.
"amoeba" in the blood, and which were characterised by movement. Distinction between these cells and the lymph corpuscles was made by Leydig and Erb. They describe them as cells with a round, sharpe contour, isolated with acetic acid and possessing one or more nuclei which fill only part of the cells. The free cellaeforner nuclei were distinguished from the colourless lymph corpuscles (leucocytes) by Henle. Their magnitude he found was less than the lymph corpuscle and they were darkly cloudy. The nucleated cells he describes as faintly coloured and partly colourless, smaller than the lymph corpuscles and their nuclei distinctly visible without the addition of acetic acid.

The nucleated red cells Ecker calls "young blood corpuscles" and he represents them as oval with a normal red colour and round nuclei. This worker was the first to make specific mention of this cell (normoblast), though Nasse, Prayr, Wademeyer (1822), H. Meyer (1843), Köllicher and others had noticed them. Bealet's "old red blood corpuscles" appear also to belong to this category.

In 1863 Rindfleisch assumed that there is a gradual growth of the lymph corpuscles from immature to mature forms. He claims to be able to see them without trouble. This is remarkable since the cellular stains had not yet come into use. A truer statement is that of Kneutinger (1865), who was able to demonstrate the transitional stages only with great difficulty. These transitional stages were, however, not considered as such by Donders and Moleschott (1843), but as blood corpuscles in the process of resolution. Henle (1863) failed altogether to find Rindfleisch's intermediate forms.

Welcker found the size of the red cells to be 22.3 mmm in length and 15.9 mmm in breadth, while the thickness he estimated at 3.6 mmm.

Donders and Moleschott found that the relation of colourless corpuscles to red cells were 1:8, but they did not
distinguish the granular cell from the lymph corpuscle. (582)
Very similar proportions were obtained by Rindfleish (1863) and Knettinger. They were described by these workers as cells crowded with little molecules. The nucleus becomes apparent when acetic acid is added. They possess ameoboid movement, and occur in little clumps.

Wharton Jones was also the first to describe colourless and faintly coloured nucleated cells, scarcely visible, oval and sometimes round.

Certain pale blood corpuscles were first mentioned by Hensen (583). Later workers found them in starved frogs.

Transitional forms between the lymph and red blood corpuscles were seen by Henle (1863), but they were described later in greater detail by Rindfleish, Schultz, Wagner, Nasse, H. Müller, Frey and Beale.

Finally, round, dark-coloured blood corpuscles, not found in freshly drawn blood, were mentioned by Donders and Moeschott, who added that they were glittering and water resistant. Nasse defines them as non-nucleated cells and Meyer as small, dark-coloured blood corpuscles with a nucleus scarcely or not at all visible.

When these "white corpuscles" were first discovered is a matter for speculation but it is generally attributed to Hewson (1773).

In 1845 Virchow recognised them in the form of "weisses blut" (white blood). Davaine (1850) first lucidly described their amoeboid movement in human blood and in 1843 W. Addison, in 1846 A. Waller and in 1857 J Cohnheim demonstrated their powers of diapedesis. And important observation was that of v. Recklinghausen (1863) when he showed that certain pus cells are amoeboid and can ingest finely divided material. (586)

The blood platelets were first described by F. Arnold in 1845, and later at greater length by Max Schultz (1867), who christened them "haematoblasts"; Hayem adhered to this term, but since the time of Bizzozero (1882) they have been
known as blood platelets.

The original view that the red blood cells arose in the lymphatic vessels were becoming less and less tenable, although we still find this seat of origin mentioned by 1860-3 (588) (589) (Zimmerman (1860), Bennett (1863))

Our modern knowledge of erythropoiesis and morphology dates from Ehrlich's discovery of the tissue stains. The introduction of this gave breadth and importance to the subject of haematology. To him as much as any one in the past does medicine owe an eternal debt. From the middle of the seventies of last century the knowledge of the blood cells and their origin grew rapidly.

Rindfleish first called the red nucleated cells in the bone marrow "haematoblasts" and endeavoured to show that their role was the formation of red cells. He formulated the idea that the blood cells originated in the bone marrow. The name haematoblast was, as we saw, used by Hayem to indicate the precursor of the white cells, and were probably what we now designate the blood platelets. He struck away from the current view that an interdependence between the red and white cells existed. Norris (1882) supported Rindfleish's views with regard to the origin of the red blood corpuscles, while Bizzozero (1881) favoured the cancellous tissues of the bones as the place of origin. This worker and Torre found that erythropoiesis was confined to the blood vessels and leucopoiesis to the intervascular tissue, of the bone-marrow of birds.

This was confirmed by many workers and lately Doan, Cunningham and Sabin (1925) showed that it applied also to mammals.

It was the study of embryonic bone marrow that led to the idea that that tissue is the seat of haemopoiesis. Although we see in this an approach to the modern view, it must be realised that in 1880 there were still a number of theories (593) regarding the organs of blood production; these were the mesenteric glands, spleen, liver, muscles, cancellous tissue of the bones, bone marrow and peritoneum.
Another advance in the study of the blood cells was made by Metchnikoff, who working on the larvae of 'Echinoderms' demonstrated a phagocytic behavior of the embryonic mesoderm cells. This he intimated to Virchow at Messina. Later he discovered phagocytic blood cells in 'Diaphinae' infected with 'monosprora infestans'. These studies together with the original demonstration by v. Becklinghausen that cells took into their substance foreign matter, had their repercussions in the world of medicine and opened the door to a better understanding of the protective mechanism in bacterial infection, and of physiological phagocytosis.

The results of Ehrlich's researches and his nomenclature of the red cell elements of the blood, with regard to the changes in their form and size, constitute the basis of our knowledge of anaemia. According to him poikilocytosis (or "schisto-cytosis) is the most important evidence of degeneration in anaemic blood.

The following two tables by Norris will show at a glance the state of knowledge at the beginning of the twentieth century. Table one shows the development of thought concerning the morphology of the blood, especially that of the white corpuscles. The next table is also of interest in that it gives systematically the knowledge of the bone marrow cells simplified from the views of Pappenheim, Wolff and Türk.

(See next page)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Types of Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Muller</td>
<td>1838</td>
<td>Red bodies 'Lymph and Chyle'</td>
</tr>
<tr>
<td>Wharton Jones</td>
<td>1846</td>
<td>Nucleated Cells 'Finely granular' Cells</td>
</tr>
<tr>
<td>Max 'Schultze'</td>
<td>1865</td>
<td>Small 'Hyaline' Large 'Hyaline' granular Cells Cells</td>
</tr>
<tr>
<td>Hayem</td>
<td>1877</td>
<td>Small 'Amoeboid' 'Round' old 'Granular' Cells 'Amoeboid' Cells</td>
</tr>
<tr>
<td>Ehrlich</td>
<td>1877</td>
<td>Lymphocytes 'Neutrophil' Basophil' Eosinophil'</td>
</tr>
<tr>
<td>Metchnikoff</td>
<td>1892</td>
<td>Lymphocytes 'Mononuclear' 'Granular' Cells 'Leucocytes'</td>
</tr>
<tr>
<td>Sherring 'Chromocyte'</td>
<td>1893</td>
<td>'Large' 'Finely granular' Cells 'Hyaline' Cells 'Eosinophil' 'Granulated'</td>
</tr>
<tr>
<td>Kanthack and Farady</td>
<td>1894</td>
<td>'Lymphocytes' 'Hyaline' 'Finely granular' 'Eosinophil' 'Oxyphil' 'Basophil' Cells</td>
</tr>
<tr>
<td>Grawitz</td>
<td>1896</td>
<td>Type I</td>
</tr>
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<td></td>
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<td>Type II</td>
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<td></td>
<td>Type III</td>
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<tr>
<td>Erythroblasts</td>
<td>Lymphocytes</td>
<td>Granulocytes</td>
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<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>B Megaloblast</td>
<td>Myelocyte (Large) Mother-Lymphocyte Cell (fine neutrophil granules)</td>
<td>Myelocyte (course eosinophil granules)</td>
</tr>
<tr>
<td>O (young form)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Megaloblast</td>
<td>Türk's Stimulation Cells</td>
<td>Daughter Myelocyte (Eosinophil)</td>
</tr>
<tr>
<td>E (adult form)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M Normoblast</td>
<td></td>
<td>Daughter Myelocyte (Neutrophil)</td>
</tr>
<tr>
<td>A Normoblast</td>
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<td>Daughter Myelocyte (Basophil)</td>
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<tr>
<td>W</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B Erythrocyte</td>
<td>Mononuclear Leucocyte</td>
<td>Mast Cell</td>
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<tr>
<td>L</td>
<td>Polymorph Nuclear Leucocyte</td>
<td></td>
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<tr>
<td>O</td>
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<tr>
<td>O</td>
<td>Transitional Rieder's Lymphocyte Cells (old)</td>
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During recent years the morphology and physiology of the red cells has been greatly extended. (595)

Peskind's studies indicate that the red cells are enveloped by a haemoglobin-free layer composed of lecithin, cholesterin and nucleo-proteid.

With regard to their origin in the embryo Pander first noted their occurrence in isolated groups of mesodermal cells in the "vascular area" of the chick and which foci he termed "blood islands". The process was later more closely studied by His, Remak (1841), Kolliker (599) (1846), Wissosky (1877), Klein (1871), Stricker and others. From their studies it, therefore, appeared that the first blood cells of the vertebrates are formed by the appearance of haemoglobin in some of the cells of the mesodermal cord which go to form the first capillaries.

The theory of the endoglobular formation of the red cells was supported by Schäfer: This theory believed that the red cells were not cells in the true meaning of the word but were fragments of cells of endoglobular origin, while the nucleated red cells had a different significance, being formed by mitotic division of other nucleated cells. (602) (603)

This view was also held by Hanvier, Hayem and others. With the development of the lymphatic system and liver, this intracellular formation of red cells is said to cease, and few or no traces of it have been described in most mammals at birth. Kühnorn and Malassez, however, describe the formation of red cells in the late embryonic liver and marrow through germination of the giant cells in these organs. (604) (605)

Later workers (Spuler and Saxer) denounced this theory.

In late embryonal periods the process of development of the red cells has been found very similar to that in extra-uterine life. Bizzozero first stated that the nucleated red cells of the marrow multiply by indirect division of the nucleated red cells. He, however, claimed that the large
nucleated red cells of the adult bone marrow is the most primitive cell in the body capable of producing erythrocytes, believing that the intermediate stages between the embryonic wandering cell and the coloured erythroblast have been lost in late embryonic life. Later workers, however, satisfactorily demonstrated the origin of the red cell from a colourless precursor. Neumann, Rindfleisch, Obrászow, Malassez, Howell, Lowit, Müller and others agree that this primordial cell is a large mononuclear cell, larger than the erythrocyte and possessing a pale nucleus, and without haemoglobin. Opinion contrary to this has been voiced by Foa, who believes the erythrocytes are derived from the giant cells of the marrow, spleen and liver; Hayem on the other hand concludes that the red cells are derived from the blood platelets.

Most of the early workers were of the opinion that two colourless mother cells existed, one for the leucocytes and one for the erythrocytes. H.F. Müller and Pappenheim however, argued strongly in favour of a common parentage for these two cells.

The fact that the red marrow, in extra-uterine life, is probably the exclusive depot of formation of the red corpuscles was discovered almost simultaneously by Neumann and by Bizzozero in 1868. The other workers who, unlike the above two, regarded colourless cells as the progenitors of the erythrocytes, believed all lymphoid tissue to be probable sources of erythroblasts. Notable among these were Löwit and Müller, Gibson, Foa and Saxer.

It has been shown that in pathological conditions the spleen in the human adult may resume its embryological function of red cell formation, as indicated by the presence of many nucleated red cells. (Bizzozero, Neumann, Howell). Under similar conditions it has also been shown that an extension of the red bone marrow may occur. (Neumann,
According to the authorities of the late nineteenth century the leucocyte had its origin from the so-called primary wandering cells, of mesodermal origin, which are found principally in the loose connective tissue of the early embryo. Their development was traced by H.E. Ziegler to masses of mesodermal cells surrounding the cords from which the capillaries are formed. The view soon therefore arose that the parent leucocytes lie originally outside the vessels, and that it is only by virtue of their amoeboid movement that they enter the circulation. Stohr and Gulland put forward an opposing opinion, namely that the cells multiply principally within the vessels and subsequently wander out at certain localities, where they collect to form lymph nodes.

Although the primary wandering cell was generally accepted as the phylogenetic origin of the leucocyte, Schmidt, Bonnet and others claimed that it originated from the capillary endothelium. An isolated view was also taken by v. Davidoff, Maurer and Beard who believed that the leucocytes are directly derived from the epithelial cells, principally of the intestine.

That different mother cells for the leucocytes and erythrocytes were assumed seems to be largely due to the fact that most early workers were concerned more with embryonic blood than that of the adult.

It is generally taken that the formation of the leucocytes occurred principally in the blood forming organs but since many young forms have from time to time been demonstrated in the circulating blood there arose a school of thought which accepted the view that these cells actively multiply by mitosis and more frequently by amitosis. (Sponk and Prins, Löwit, Wertheim).

With regard to the origin of the blood platelets opinion has been more divided than in the case of the
red and white blood cells. They were first described by Donne, in 1842, who regarded them as particles of globulin derived from the red cells. Its history through Schultze, Rokitansky, Ranvier and Bizzozero we have noted. In normal blood they were found to vary from 180,000 to 500,000 (Pruss ). Their numbers were found to be highest in afebrile anaemias, leukaemia and haemorrhages, and lowest in febrile diseases, malaria and after the administration of various poisons (Affanissien, Limbeck, Fusari and Pizzini ). (632)

Howell, Gibson and Flava regarded the blood platelets as fragments of the nuclei of disintegrated leucocytes. (633) On account of their chemical composition Lilienfeld assumed that they consist of nuclei of broken down leucocytes. Czermak, Mondino and Sala believe them to be the fragments of the nuclei of the hyaline cells. (634) The studies of Klebs, Engel, Bremer, Wlasson, Arnold, Maximow give strong support to the theory that the chief source of the blood platelets is from the red cells by the extrusion from them of masses of chains of globular material, which give many of the reactions of the nucleoproteids.

The most widely accepted view today with regard to the origin of the blood platelets is that put forward by Wright. He suggested that the thrombocytes are detached portions of cytoplasm of bone marrow megakaryocytes. Further work on this subject has been done by Naegeli and Olf . (635) (636), (637) (638)

To go into all the details of investigation on the development and morphology of the blood cells during the past few decades cannot possibly fall within the compass of this work. The main object is the history of anaemia, and it must therefore suffice to only indicate as briefly as possible what the modern view is regarding this problem. The theories which today hold sway are the Monophyletic Theory and the Polyphyletic Theory. They are offshoots
of the views which originated during the last century. The
former theory comes from Pappenheim and Maximow and adheres to
the idea that a single polyvalent cell, the "lymphocyte" or
"haematoblast", is present in all adult haemopoietic tissue
and that it is capable of giving rise to all other cellular
elements in the blood.

The following tables given by Kracke and Garver
will show at a glance what the modern conceptions are:

(644)

<table>
<thead>
<tr>
<th>Reticulo-endothelium</th>
<th>Haemocytoblast</th>
<th>Granulocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblast</td>
<td>Erythroblast</td>
<td>Erythrocyte</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Downey modifies this concept and assumes the presence of two
stem cells, one for granulocytes and one for lymphocytes,
both of which, however, are derived from a lymphocyte---
the haematocytoblast:

<table>
<thead>
<tr>
<th>Reticulo-endothelium</th>
<th>Haemocytoblast</th>
<th>Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblast</td>
<td>Erythroblast</td>
<td>Erythrocyte</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
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</tr>
</tbody>
</table>

The Polyphyletic Theory was championed by Ehrlich and
more recently by Naegeli who believe in two post-natal mother
cells, first the myeloblast from which comes the Erythrocytes,
Granulocytes and Monocytes, and secondly the Lymphoblast
which gives rise to the Lymphocytes. Naegeli denies the
existence of megaloblasts in post-natal life.

In diagramatic form this is:

<table>
<thead>
<tr>
<th>Reticulo-endothelium</th>
<th>Lymphoblast</th>
<th>Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblast</td>
<td>Granulocytes</td>
<td></td>
</tr>
<tr>
<td>Erythroblast</td>
<td>Monocytes</td>
<td>Erythrocytes</td>
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</table>

<table>
<thead>
<tr>
<th>Reticulo-endothelium</th>
<th>Myeloblast</th>
<th>Granulocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroblast</td>
<td>Monocytes</td>
<td>Erythrocytes</td>
</tr>
</tbody>
</table>
Tiney's view is somewhat different and is as follows:

---Lymphoblast-----Lymphocytes

Reticulo-endothelium-----Myeloblast---Monocytes.

Erythroblasts

Erythrocytes.

The most widely accepted theory is that of the trialist school which proposes a separate phylogeny for each blood cell, which indicates that in ante-natal life they have different sites of origin. In Kracke and Garver's words: "For example, in the bone marrow the myeloblast acts as a progenitor for the granular leucocytes; in lymphoid tissue the lymphoblast is the parent of the lymphocytes; and in the connective tissue the monoblast is the specific ancestor of the mature monocyte. Thus, for the first time, there are recognised these respective stem cells for the three types of leucocytes. According to Sabin and his associates these three leucoblasts arise from a primitive free cell which is present in all leucopoietic tissue and which in turn arises from the reticular cell of the reticulo-endothelial system. The trialists further separate the development of erythrocytes by tracing their origin from the endothelium lining and vascular system of the bone marrow. This concept is summarised in the following diagram.

---Lymphoblast-----Lymphocyte.

Reticulo-endothelium-----Monoblast------Monocyte.

---Myeloblast------Granulocyte.

Megaloblast

Erythroblast

Erythrocyte.

(Abnormal haemopoiesis will be discussed along with the anaemias).
Aetiology.

Various aetiological views for this condition have from time to time been put forward. For the most part chlorosis has been regarded as a symptomatic anaemia, holding the peculiar clinical characters of the disease as the result of the age and constitution of the patient in whom it occurs. Thus in 1803 Dr. Cullen writes: "The cause of chlorosis is thought to be an atony of the muscular fibres of the alimentary canal, especially of the stomach, joined with a similar atony of the perspiratory vessels over the whole surface of the body, the whole depending on an atony of those small arteries which pour out the menstrual blood. This atony may be occasioned by the same causes which bring on dyspepsia and hypochondriasis, but very frequently arises from love and other passions of the mind." This view is supported by Ploitisnky and Virchow and more recently by Paltauf, Ortner Fraentzel. Another aetiological factor first suggested by Hoffmann is intestinal intoxication. This theory has been favoured on various clinical and pathological grounds by Duclos, Nothnagel, Clark, Bouchard and many others. Jenner considered such a theory wrong and attributed the intestinal stasis to the anaemia. Bunge's theory, however, added force to the autotoxic theory for a while, since he maintained that as blood obtains iron solely from the nucleo-albumins, the iron in combination with sulphur as the result of intestinal putrefaction becomes non-absorbable. V. Noorden, Rethers, Morner and Lipman and Wulff later showed that no intestinal putrefaction occurs in chlorosis, nor is there any increased excretion of the derivatives of haemoglobin. This work considerably minimised Bunge's views.
In 1832 Blaud says that medical men of the past and present have been far too circumscribed in their view of the chlorotic diseases, by regarding them simply as symptoms, or as the signal and result of amenorrhea. He says "The real and specific cause of chlorosis, under all its Protein forms, is a vicious and imperfect sanguification; the blood being defective in crassamentum and colouring matter, and, in consequence becoming less capable of imparting functional energy to the body. Four weighty reasons are adduced in proof of this doctrine.

1). Chlorotic maladies are almost always brought on either by whatever interferes with, or deranges the assimilation of food and its conversion into the "pabulum sanguinis", as by living on unwholesome, and in nutritious food, or by breathing a corrupted atmosphere, etc.; or secondly by whatever enfeebles the system of the ganglionic nerves, which, we know, regulate, and keep in health the organ destined to form and to circulate the blood; such as all depressing emotions of the mind, masturbation, excess of venery, sedentary employment, etc.

2). The doughy, waxy whiteness of the skin, the pale lips and gums, the scanty and serous discharges from the vagina, nose, etc., and the watery state of the blood when drawn;

3). is denoted by an utter want of power and activity in the organic functions of the body, arising no doubt from a deterioration of the fluid, wherein, it is said, that life resides.

4). The efficacy of steel medicines, which have the power of restoring to the blood the excitive properties which it has lost, and which chiefly depend on its colouring matter."

There have been many physicians who have attributed chlorosis to functional disturbances of the nervous system. Murri supposes that the organ of gestation are the chief cause of circulatory changes and alterations of the blood chemistry. This theory was the outcome of the opinions of the older physicians like Trousseau. According to Meinert gastroptosis is a feature in chlorosis and is the aetiological factor in that it produces irritation of the abdominal sympathetic system.
Kruger, Fuhrer, Scharlan, Chvostek, Clement, Grawitz, Rummo, and Dorri believed that increased destruction of haemoglobin is the cause of the disease and the splenic enlargement.

Grawitz took chlorosis to be a vasomotor neurosis. In this he had numerous supporters.

Among the causes of chlorosis Ardland mentions obstruction of the bowels, a "sluggish languid motion of the blood, whether natural, or acquired by ease, indulgence, or want of exercise".

"Finally, it may proceed from a longing desire after the enjoyment of some person; or, in general, for a violent inclination to exchange a single life for the state of matrimony.

We saw that in the eighteenth century most writers confused chlorosis with amenorrhoea, and in many cases they were used almost synonymously. Ashwell (1836) attempts to show that chlorosis is the primary disease and the commonest cause of amenorrhoea. He shows, by quoting cases, that where chlorosis is complicated by amenorrhoea it is of long duration, and tends to produce "functional disturbances, at least, of the nervous, vascular, respiratory and digestive systems: and that if the disease terminate fatally, it will frequently, if not generally be in phthisis." He assumes that an idiopathic form of the disease exists "where puberty either has not been established at all; or so imperfectly, as that menstruation has has not been the result." He recognises a similar condition which may exist in boys about the age of puberty, and also points out that chlorosis is rare in country girls in whom it is "not considered a gross violation of good breeding to sport and play with activity." This opinion was shared by Samuel Fox (1839). After pointing out that amenorrhoea is only a symptom he states that its true origin is the derangement of the functions of the liver, and the digestive economy, and limited to any period of life. In the greatest number of cases he takes this derangement to be primary. He strongly opposes the view of Cullen, Mason Good and their followers that chlorosis is due to suppression of the menses.
Trousseau (1845) did not agree with the general opinion that phthisis is common in chlorotics; on the contrary, he states that the one has an inhibitory effect on the other.

Chlorosis as the result of shock has also been mentioned. In fact many physicians regarded it as a common cause for (664) all forms of anaemia, for example Fothergill writes that "anaemia may be associated with some profound impression made upon the nerve-centres; or the nerve-centres may be the parts most seriously involved in the general anaemia. The most obdurate case of anaemia ever brought under my own notice was that of a very healthy girl--healthy both in herself and her family history--whose father dropped down dead at her side at a market. He was a strong, hale man, and nothing could have been more unexpected. The shock so affected his daughter that she became markedly pallid and anaemic in a brief time; and no combination of remedies, nor perseverance in their use, ever produced any effect, worth speaking of, in this girl."

Pathology

The specific gravity of the blood was shown to be reduced in uniform ratio with the loss of haemoglobin. This was illustrated by many workers like Devoto, Hammerschlag, Schmaltz, Siegel, Hock and Schlesinger, Menicasiti, Stintzing and Biernecki. On the other hand the bulk of the blood was shown to be increased (Lloyd Jones; Marsh (1846)).

Babington found the specific gravity of the blood to be 1.055, that of the serum 1.027.

Mr. Jennings observed that there was a deficiency of considerably more than half of the red corpuscles and more than corresponding augmentation of 80 to 90 parts in 1000 of water.

Ancell says "the morbid condition of the blood in this disease whether we regard it as a deficiency of red corpuscles, only, or, together with that of an impoverishment of the liquor sanguinis, accounts for the pallor, the waxy
appearance; the amenorrhoea, the diminished temperature of the body, the oedematous tendency and, in fact, all the symptoms."

He goes on to say "the iron of the blood is a component part of the haematosin, its quantity therefore depends upon the colouring matter; it is greatly deficient in chlorisis; and there can be no rational doubt that the well-established beneficial effects of this element in the blood, in its various preparations, is directly attributable to its absorption and assimilation by the vital fluid."

The pathological changes underlying chlorisis, Fox says is a congestion of the capillary extremities of the biliary vessels, producing chronic derangement of the liver, and generally disordered health with resultant improper "chylification of the blood" and sallowness.

(668) Duncan was the first to count the corpuscles and at the same time to estimate the amount of haemoglobin present; he characterised the condition as one with approximately the normal number of red blood corpuscles but with a deficiency of haemoglobin. This was confirmed by Graeber (1888). Nevertheless numerous investigators have shown the number of red blood corpuscles to be diminished. Reinert (1891) gives a comprehensive table of the findings of many workers illustrating this point.

(671) Otto demonstrated that as the disease improved under treatment the red blood corpuscles first increased in number and later the haemoglobin rose.

Other blood abnormalities which were demonstrated were nucleated red blood corpuscles in large numbers, (Neudörfer (1854), while microcytes, poikilocytes, megaloblasts and the signs of degeneration described by Maragliano and Castellino (673) may be found in sever cases. Hammerschlag, Graeber, and Drouin (674) found the alkalinity increased but Krauss proved that it was normal.

Modern workers find little opportunity to study this disease. In a modern textbook of medicine a description of it
occupies at the most only a few pages. This is thought to be of better nutrition in modern diets, coupled with the greater freedom of young women to partake of a vigorous and healthy life.

This decrease in chlorosis has been steadily and universal since 1903 (Campbell (1923)).

The haemoglobin has been found by most observers to be reduced. Bramwell has reported values as low as 10 per cent. A contrary opinion was held by Eichhorst, Zumpf and especially Biernacki who found the haemoglobin to be normal or even increased.

Bramwell, Cabot, Hayem, Limbeck and others have all quoted low values for the number of red blood corpuscles per cubic mm., and varying from 937,360 (Hayem) to 4,000,000 in mild cases.

Poikilocytosis is usually quoted and Maragliano and Gabritschewsky noted what they called polychromatic degeneration.

The leucocytes have been shown to vary but little in the average case (Graeber, Grawitz).

A condition called pseudochlorosis came into existence towards the end of the last century and indicates a condition in which the clinical features are those of chlorosis but the blood does not reveal any abnormality with regard to haemoglobin percentage and colour index. Lloyd Jones believes that they are cases of anaemia with "oligoplasma" in which the diminution of serum masks the underlying anaemia. This view was supported by Biernacki.

**Clinical Features.**

These are generally described with completeness by all the writers of the early part of the nineteenth century. (875) The description given by Fothergill cannot be improved upon. In his Practitioner's Handbook of Treatment we read that chlorotic girls are often very fat. "At the same time
there is much lassitude, drowsiness, muscular inertia, defect of secretion, and general loss of tone. Every organ feels the lack of arterial blood; especially does the brain feel it. With the large amount of blood normally in the encephalon and its rapid flow, a condition of anaemia, with defective circulatory force, is soon felt by the contents of the cranium. The sense of energy, so delightful to all, is gone; and languor takes its place. The person is drowsy when up, and feels as if he (or rather she) never could sleep enough. In bed, however, the rest is broken from the blood flowing more freely into the brain when the head is laid upon the pillow. Consequently it is no uncommon thing for such patients to sleep almost propped up in bed. There is a great tendency to neuralgia, which may be cranial, facial, or intercostal. 'Pain is the prayer of a nerve for healthy blood', wrote Romberg; if very commonly it is so. When the pain is intercostal it is usually found in the sixth or seventh intercostal nerve of the left side in women. When so found it is generally associated with suckling or with discharges from the genitals, and usually with leucorrhoea.---Neuralgia, or, in others, pain in the vertex of the head, are scourges of anaemic women.

"Palpitation is a very common occurrence in states of anaemia and arises chiefly from nerve disturbance. The roots of the vagus nerve are imperfectly supplied with blood, and consequently, the vagus cannot exercise its wonted controlling, or inhibitory action over the heart. As the bulk of blood increases the palpitation vanishes. Haemorrhagic murmurs, either aortic or pulmonary, are very common; but ought rarely to be mistaken for the murmurs of organic change. The veins often give out a hum, the bruit de diable, which is commonly regarded as the most marked physical sign of anaemia.

"Breathlessness upon exertion is a very common phenomenon in anaemia." It is due to "the diminished amount of red corpuscles, and the impaired chemical interchanges resulting
therefore. The supply of oxygen is too imperfect for exertion and effort; and if these are attempted breathlessness follows. Upon this condition of diminution of blood-corpuscles and defective oxygenation depends also the fatness so often found in the anaemia, especially in the chlorotic. These pallid, pasty creatures often become very obese; becoming paler, more languid, from lack of blood corpuscles to supply oxygen to burn their hydrocarbons, and the fuel becomes deposited as fat. As they recover from their anaemia and regain their bloom of health, their stoutness diminishes, until they once more possess their pristine symmetry. Not uncommonly the colouring matter of the corpuscles dissolved in the hyaemic blood, is deposited in the areolar tissue, as in the dark suborbital patches of anaemia, and the general staining of the skin in chlorosis; or passes away in the urine as urohaematine.

"When anaemia is very marked it not uncommonly happens that there comes on oedema of the lower extremities," most marked at night and least on rising. "The oedema is due to fullness of the venous radicles and atony of the circulation." (676)

Bristowe informs us that chlorosis is rarely fatal and rarely leads to tuberculosis or other organic disease except gastric ulcer. Recovery he says is generally within a few weeks or months, but relapses are liable to occur. (677)

In 1830 Dr. Marshall Hall mentioned a number of cases of chlorosis. Two of these appear very similar to cases of pernicious anaemia. In the one, he says, "death occurred suddenly; the patient after being confined to bed a few days, and immediately after being in better spirits than usual, having sat up for a quarter of an hour, became faint, gasped and expired." In this case there was "a degree of icteric complexion." There were effusions into the ventricles, the pericardium and left pleural cavity, the lungs were gorged, heart was large, and so too the liver. The hand had an ivory colour. There was much adipose tissue and the ankles showed slight oedema.
To the list of symptoms Dr. Aitken (1866) adds the following: reduced body temperature with consequent coolness of the breath, lips, nose, ears, hands and feet are cold. Often, he adds, there is vertigo, headache, recurrent tinnitus aurium, especially of the right ear, sparks before the eyes, spinal irritation and convulsions or a "heaviness for sleep"; sometimes morbid sleep with frightful dreams. Mania may lead to suicide.

Although chlorosis is generally regarded as a non-fatal disease Dr. Hall (679) states that he has seen four deaths from this complaint within eight years, and adds: "I need scarcely add the remark, that chlorosis must not be viewed as totally free from danger. When anasarca has supervened to great pallor, there is a fear of effusion into the encephalon, and of a fatal result, which is sometimes of the most insidious, sometimes of the most sudden kind."

Certain complications to which chlorotics are particularly liable are mentioned by Marsh. "Chlorotic patients," he writes, "are liable to various incidental affections of the lungs. Acute bronchitis and acute pneumonia are not of very common occurrence; nor is bronchial haemorrhage or pulmonary apoplexy. These are more likely to occur in cases of anaemia produced by antecedent haemorrhage or wasting disease, than true chlorosis. I have, however, occasionally seen chlorosis complicated with circumscribed chronic pneumonia, and frequently with chronic bronchitis, terminating ultimately and remotely in tuberculous phthisis."

Treatment.

The treatment of chlorosis as it stood at the beginning of the nineteenth century may best be summed up in the words of Dr. Cullen as follows: "purgatives may be made use of; those which stimulate the rectum, especially aloeics, are useful by also stimulating the vessels of the uterus; and
for this reason indulgence in venery has sometimes been said to produce a cure, particularly with love-sick maids. The cold bath is also extremely proper.

"Cuperous emetics and gentle stomach purges, with medicines of the chalybeate and strengthening kinds, will most avail."

The following will often succeed extremely well:

Pill Rusi
Pill e. gumine
Ferri vitriol
Rubig. ferri ppt. ana drams ij
Gl. succin. rect. gtt. m xx
Syr. croci, q.f. ut ft. pill.

No. xii e. dram i. fumend. ij vel iv mane et vesp.

Or

Tinct. ferri muriati drams ij
Tinct. aloes ounce 1

Dram i three or four times daily with any vehicle".

Adland in 1817 introduced certain hygienic rules such as good air, moderate exercise and sleep—retiring for the night at least two hours after supper—and tranquility of mind.

Although the value of iron remedies had become generally recognised by this time, there were still workers who attributed little value to it. Wöhler in 1824 advanced the view that iron is not absorbed from the alimentary tract and therefore serves no useful purpose as a therapeutic agent. He based his conclusions, fallaciously, on the fact that he discovered none of the metal in the urine after large doses had been administered. This caused much confusion among certain medical men, and their opinions differed widely with regard to the therapeutic activity of the metal.

Kletzinsky (1854), in part, supported Wöhler's view, since he found, in an experiment upon himself, that as much iron as he had taken orally could be recovered from the faeces.

Although such observations tended to minimise the value of iron in chlorosis the majority of physicians believed it to be of benefit.
With regard to the form in which iron is most active (633)
Blundell (1823) mentions the carbonate and sulphate in
powder form. He was particularly fond of the compound mixture
of Myrrh (Friffith's mixture)

It is worthy to note that although iron was widely used, (684)
the doses for the most part were small. Dr. Blaud was
among the earliest to advocate bigger doses. Though he does
not claim to introduce this medicine for the first time he
deplores the timidity with which it is used, and the improper
forms in which it is administered. His favourite formula
is:

\[
\text{Ferri sulphatis} \\
\text{Potasse subcarbon} \text{ ana half an ounce}
\]

To be divided into 48 pills.
The dose is at first a pill night and morning and
increasing to four pills three times a day.

He gives a long list of cases treated successfully
by this means. To quote one case: "A.M. aged 21, had been
remarkably pale ever since her birth; but the dirty waxen hue
of the skin had increased for the last three years. The cata-
menia were regular, but very scanty and exceedingly light
coloured. The health, however, was tolerably good; and neither
the appetite nor the plumpness had decayed. By taking the
steel pills in augmented doses for a month, she obtained bloom
on her cheeks, lustre in her eyes, and vermillion in her menses." His catalogue includes several cases of chlorosis in men.

He wisely points out that all cases of pallor must not
be treated with iron and only "those that show no organic
cause for the chlorosis."

An unusual form of iron medication was that introduced
by Derouet-Boissière (1841). He treated chlorosis with
"ferruginous bread" (lactate, acetate and protocarbonate of
iron---3½ oz. bread contained 3 or 4 gr. iron salt) in the
belief that the iron along with the food would easier enter
the circulation. The Commission of the French Academy
investigated the matter and found the bread to be of value
in chlorosis.

The effects of iron therapy in cases with dilated hearts and chlorosis is mentioned by Duckworth (686). Trousseau believed iron to be sometimes dangerous in chlorosis. To support this he mentions a case who died as the result of iron medication.

A rather disconcerting observation on the effects of iron treatment was made by Lorrain Smith (1900). He showed that in cases successfully treated with iron preparations the total haemoglobin is the same as that of untreated cases. This point will again be referred to in the next chapter.

Another form of treatment was with "valeriate of zinc", discovered by Prince L. Lucien Buonaparte (1844) and tried out successfully on a chlorotic girl by D. Odardo Torchetti, after iron and other drugs had failed to relieve the condition.

de Rici (1862), likewise, departs from the more usual remedies and recommends the use of "phlorydzine", a neutral principle "in the bark of the root of apple, plum and cherry tree---also, I believe, in some others." He states that it has the chemical formula $C_{21}H_{11}O_8$ plus 4 $\text{Ag}$, and differs from quinine in having no nitrogen, and is more akin to salicine which has the formula $C_{21}H_{12}O_9$ plus 2 $\text{Ag}$.

Other remedies which have been tried are bismuth, manganese and hydrochloric acid. Manganese was first used by Bréra in Italy (1822) as an antichlorotic. In 1830 Wurzer showed its presence in the body tissues and subsequently this was confirmed by Marchessaux (1844), Millon and Riché. Bartholow said of it "There is no doubt its combination with iron much increases the efficacy of the latter!"

This was not borne out by Stockmann (1893).

Zander (1881) stated that there is a deficiency of digestive juices in chlorosis, and as the result of which
iron in the normal diets could not be absorbed. He gave hydrochloric acid to remedy this defect. Stockmann repeated his treatment and found the results unconvincing.
Iron has played an important role in medicine. It was used in Ancient Egypt and Greece, but its therapeutic value remained hidden until almost recent times. That it should have been used by the ancients in debilitating conditions like chlorosis and cachexia is natural when we consider that Mars is said to have impregnated it with godly qualities and properties. That Mars was the keeper of the metal can be deduced from a number of facts. It was and still is the metal of machines of war, and then there is the positive proof that alchemists of the Middle Ages called it "mars"; and martian pills and draughts were common sales from their laboratories. Its early application was therefore symbolic. If the patient could by taking it become endowed with the strength of the metal then his complaint would be overcome.

The earliest authentic reference to the therapeutic use of iron is found in the writings of Apllodorus (2000 B.C.), where metal scrapings from a sword were dissolved in wine and administered as a draught. As a drug it is also mentioned in the Papyrus Ebers. Hippocrates believed in its therapeutic value, and Pliny, the Elder, regarded the rust it produced as a remedy for certain ills. In the Bible ninety-one references to iron are made.

Willis, in the early seventeenth century was probably one of the earliest authors to mention that it imparts colour to the blood and so to the cheeks. In 1720 Pierre Pomet wrote a treatise on the history and use of drugs. He hints at the value of certain iron preparations in chlorosis and various cachexias.

The real history of iron in medicine may be said to commence with Thomas Sydenham during the middle of the seventeenth century. He drew attention to its value in chlorosis and assigned to it the first place in his therapeutic list for this condition. He observes that it is best
given "in substance", since the chemists tend to destroy its properties by compounding it. The "crude" he says is better than the "refined"; "and next to the crude steel comes the syrup thereof". In 1681 he writes that after performing venesection "I comfort the blood and spirit belonging to it by giving a chalybeate thirty days running. This is sure to do good. To the worn-out or languid blood it gives a spur or fillip whereby the animal spirits which before lay prostrate and sunken under their own weight are raised and excited. Clear proof of this is found in the effects of steel on chlorosis. The pulse gains in strength, the face (no longer pale and death-like) a fresh ruddy colour. Here, however, I must remark that with weak and wornout patients the bleeding and purging may be omitted and the steel be begun at once."

Russel Haden mentions that after Sydenham iron was used for the next hundred-and-fifty years with indifferent and varying results. This is true to a certain extent, but there were physicians who tried and proved its value. For example Paxton (1711) says: "Steel is a true and real specifick in those diseases that arise from such a weak and debilitated state of the blood, because the blood only is in fault; wherefore that being better'd, all symptoms depending upon that, cease------But whatsoever symptoms appear, that are derived from the blood that is become low, degenerated, and sluggish, form its own nature, although the native beauty is changed, lost its colour, stomach depraved, separations encreased, as in urine and spittle, spirits weak, strength decayed, flesh consumed or wasted, and an universal languor over the whole body, yet these and many others, proceeding from the same cause, will undoubtedly be remedied by steel if it be duly and judiciously administered."

With regard to its action Dr. Freind (1675-1728) believes that it cures by "the attenuating power it furnishes with and from the gravity of its particles; which being (by computation) seven times heavier than any vegetable, acts in proportion with a stronger impulse and by that means is a
more powerful deobstruent." Dr. Keil tells us that other properties it possesses are those of heating the blood more than any other mineral by its elasticity, and of resisting the acidity in the circulation.

(692) Knight (1731) points out that iron can only get into the blood in a fluid form; and also that its weight has little to do with its therapeutic value, since many tinctures and chalybeate spring waters are light.

With regard to its uses during that early period, Slare mentions its application in the following conditions: vomitings, corrosive diarrhoeas, colics, scurvies, stranguries, cardialgiae or heart burnings, especially in cases where there is too much acid. In these last cases, he says, they act like weak alkalis.

What appeared to influence thought on the value of iron as a remedy, was the discovery that it was to be found in the ash of blood. This was done by Lemery and Geoffry (1713), who also found the rion of the blood could be increased by giving it therapeutically. The remedy these early workers preferred was "crocus martis" (i.e. iron exposed to dew or rain water).

(700) In 1799 Hufeland gives the following recipe for preparing muriate of iron and muriate of barytes—his favourite combination. It is made, he says, by dissolving pure iron-filings in muriatic acid, straining the solution and evaporating to dryness. One dram with one ounce of water is given along with muriate of barytes in equal parts.

Among the clinical indications he mentions, in addition to those given by Slare, scrofulous complaints, obstinate constipation, constipation with worms, glandular indurations, amenorrhoea and chlorosis.

Just about this time iron became widely used in cancer, puerperal fever, diphtheria, chorea, epilepsy, syphilis, and by 1840 was being used in neuralgia of the mammae, diarrhoea, tic douloureux, whooping cough, diabetes, gleet, furunculosis
and as an antidote for arsenic. The form preferred was the precipitated carbonate (Clarke (1808)), which was regarded as superior to the sulphate, reputed by some to cause intestinal colic. This action of the sulphate, even in large doses, was not accepted by all physicians. (Elliotson (1832)).

It is the common belief that Pierre B. Blaud, physician at the hospital at Beaucaire, Gard, France, first popularised the carbonate of iron. Although just credit must be given to Pierre, it is mostly to the advertising genius of his nephew, August Blaud, a chemist, that the immortal "veritable pills of doctor Blaud" commenced their roll down the years to therapeutie fame. In 1866 the formula was adopted by the French Codex. It is worthy of noting that a similar pill was already official in the "Pharmacopoeia Londonensis", 1809, the formula having been evolved by Dr. Griffith, Colchester (Eng.).

Dr. Blaud (1832) emphasised the specific action of iron in the treatment of chlorosis, for which he advocated large doses. He reports the successful treatment of thirty cases in from ten to thirty days. (He used the equivalent of 15–60 grains of ferrous sulphate daily). The value of his medicine he attributed to the finely divided state it is in.

An interesting case showing the beneficial effects of large doses of iron is recorded in the Dublin Medical Journal of 1834. It also shows the almost ludicrous extent to which bleeding was carried out:

The case was that of a man of twenty who commenced with pain in the side and palpitations. For this he was bled and from the effects of which he frequently fainted; his respiration became embarassed and he developed violent headaches; on making only two steps up a stair his pulse rose to at least 120 a minute. He was confined to the horizontal position for three months and during this period bled thirty two times, the greatest amount at each bleeding was two pounds and the least half a pound. During this same period 250 leeches
were applied. His diet, poor man, consisted of a few cherries or strawberries, and an ounce of sugar with a glass of water per day. At the end of the three months he was in the last stages of marasmus; the pulse was scarcely perceptible and the slightest alterations of temperature caused the greatest agitation. After he had been like this for five months, Dr. Pigeaux treated him with two grains of subcarbonate of iron eight times daily, and gradually the dose was increased to sixty grains during the day. Under this treatment the patient recovered. (Archives Generals, Oct. 1834).

During the third decade of the nineteenth century Gelis and Conté, internes at La Charité, introduced the lactate of iron which they regarded as a valuable addition to iron therapy. Its superiority they contended is due to its solubility. Another new compound was the outcome of M. Robiquet’s (1858) researches, the soluble pyro-phosphate of iron. Benoit (1859) offered yet another—a form of iron prepared by reducing it with charcoal. He claimed this to be highly efficient.

The principles laid down by Blaud and his contemporaries became general usage. Large doses were the order of the day. Felix von Niemeyer, the greatest german authority on medicine during his day, was a supporter of Blaud and popularised his pills in Germany, as well as in Britain, where his translated works were widely read. Immerman (1877) states that “large doses cure chlorosis far more certainly and quickly than small doses.”

By 1893 a change in iron therapy began to take place. Smaller doses were used and practitioners began to assume from the poor results obtained that iron was of little value in anaemia. For this change Bunge’s Theory was partly responsible. He believed that inorganic iron was converted into the sulphide and not absorbed from the intestine at all. He put forward the idea that organic iron would overcome this difficulty. Perhaps the strongest force that brought about this
change in ideas was Quincke and van Noorden's teaching. They advocated the use of no more than \( \frac{1}{2} \) grains of metallic iron daily in chlorosis. They based their teaching on the demonstration that only a few milligrams of iron were actually metabolised daily.

That such a teaching should have prevailed despite the contrary evidence produced by two schools of thought, is difficult to appreciate. To the first belonged Coppola, who supported the absorption theory of the action of iron. In 1890 he demonstrated that cocks deprived of iron in their diet increased their haemoglobin from 33 to 65 per cent in five days when this was added to their diet. Other experiments to show that iron is absorbed were also carried out by Cervello (1880), Kunkel (1891), Lewald, and Bistrow.

The second school, which advanced the 'stimulation theory' of the action of iron, held that the mucous membrane of the bowel is unable to absorb the iron in normal diets due to its anaemia, but that large doses of inorganic iron tone the membrane and so aid absorption. This view was supported chiefly by Buchheim, Kletzinsky (1854), who states "of all the hundredweights of iron given to anaemics and chlorotics, during centuries, not a single blood corpuscle has been formed"; Hamburger (1879), Schmiedeberg, Kober (1891) and Dujardin-Beaumetz (1876). Other physicians who adhered to this theory were Gottlieb, Müller, Jacobi and Socin.

It appears that the adherents of this last theory would have either stopped the use of iron altogether, in the belief that better, and more lasting tonic effects could be obtained with other drugs like arsenic and strychnine, or else it would have turned them to the use of massive doses of iron. This however did not occur, and those who preached 'small doses of iron for anaemics' were an increasing majority.

Even the work of Macallum failed to prevent this tendency. In 1890 he deduced from his study of blood formation in larval amphibia that haemoglobin is formed from nuclein...
(the chromatin of histologists).

By his micro-chemical means (1891) he arrived at the conclusion that "the most important of all elements in the life of every cell is an iron-holding compound."

He showed that absorption depends on the nature and the quality of the compound given. Large quantities, he says, first destroy the alkalinity of the intestinal fluids, and "the excess of salt unaffected and remaining in solution then undergoes absorption." He believed the blood plasma to be the chief vehicle in the transport of the iron from the villi to other parts of the body. He also mentions that the absorption of organic iron compounds (as found in egg yolk) of the "chromatin" class, occurs in the liver. The mode of absorption he believed to be in some way associated with the absorption of the fat, with which he took the iron compound to be closely related in the yolk.

As recently as 1925 we still find men like Williamson (722) disputing the therapeutic value of iron. They thought they had proved experimentally that iron was ineffective in artificial anaemia produced in cats and dogs. (by bleeding). They stated that "inorganic iron is absorbed and may be found in the liver and spleen but is not converted into haemoglobin", and concluded that in the light of the foregoing experiments the administration of inorganic iron has no therapeutic value in anaemia.

Further experiments showed their error. Heath, Strauss and Castle (723) showed that iron after it is absorbed is converted into haemoglobin in anaemic persons.

Recently the value of iron in large doses has again been emphasised. One of the first was Lichtenstein (724) who in 1918 showed that premature infants responded well to large doses of iron. Earlier Lindberg (725) had showed that the anaemia which followed influenza responded well to massive dosage.

With regard to the method of administration of iron,
hypodermic injection has long been tried and found affective in the treatment of the various forms of anaemia. Accounts (726) have been given by Da Costa (1878), and at an earlier date (727) by Rosenthal (1872) and later by Laton (1882), Neuss (1881), Glaevecke (1883), Chiara (1885), Mori (1885), Alvazzi (1891), Pao (1881), Gauthier (1884), Crainarelli (1880), Vachetta (728) (1884), Nasse (1885), Huguenin (1876) and Goudran (1883) (729) and later by Barlow and Cunningham (1911), Bullock and Peters (730) (1911). They found that the dose so given must be small on account of its toxic effects. This was particularly studied by Meyer and Williams (732) (1881).

Witts (1931) showed that chlorosis could be cured by the injection of 1-2 grains of iron and ammonium citrate in 5-10% solution daily. (This is equivalent to 10-20 mgm metallic iron daily).

Recently Maurice, Strauss and Castle have shown that "the amount of iron given parenterally corresponds closely to the amount of iron gained in the circulating haemoglobin, and is apparently utilised to a very large extent in the building of new haemoglobin."

The general conclusion, however, today is that, due to its toxicity, it is best given orally in most cases.

Of recent years it has been shown that the ferrous salts (733) (734) are better than the ferric (Witts ). Reimann and Fritsch (1930) obtained good results with as little as 22 to 100 mgm. of ferrous chloride given by mouth every day; whereas the necessary doses of reduced iron (Meulengracht (1923); (735) (736) Schulten (1932)) and of organic iron (Elvehjem (1920)) are large.

Organic iron in the form of haemoglobin and its derivatives were regarded until a short while ago as superior to the inorganic preparations, chiefly as a result of the work (738) of Hooper, Robscheit and Whipple (1920). The last two investigators at a later date showed that in certain types of severe anaemia haemoglobin injected intravenously into dogs
may be retained up to 90 per cent or more. Also that certain organic constituents (pyrrol substances) may be manufactured in the body from the haemoglobin molecule.

At present, however, there is a general tendency to revert to the inorganic iron compounds since the clinical and experimental work shows that it is better absorbed by anaemic patients.
Chapter 9

PERNICIOUS ANAEMIA (1800-1939)

A review of the early literature on pernicious anaemia as collected by Richhorst, Musser, and stockman (1874)

Lepine and Pye-Smith (1877) indicates that while the disease had been described by many earlier men, its true nature as a clinical entity was not recognised until Addison drew attention to its specific features in 1843, 1853 and 1855.

Of earlier reported cases those of Andrai (1821) in France, of Combe (1823) and Hall (1843) in England and Channing (1849) in America may possibly be examples of this condition. Other suggestive descriptions are those of Piercy, Tunderlich, Canstatt, Rokitansky, Schönlein and Lebert, who regarded their patients as suffering from chlorosis or anaemia following parturition.

(1845)

Combe's account deserves our particular attention. He says: "The case now recorded appears to me entitled to still further attention as exhibiting a well-marked instance of a very peculiar disease, which has excited little attention among medical men, and which has been altogether overlooked by any English author with whose writings I am acquainted. Unfortunately, however, such is the allowable diversity of opinion on most medical subjects that it is very possible the following case may be viewed in different lights, and receive different appellations; and while some may be disposed to regard the peculiar characteristics from which it derives its denomination of anaemia as constituting a morbid state sui generis, others may consider the defect of the red circulating mass as an accidental and occasional circumstance, denoting some peculiar change in the assimilative powers, the primary stages of which we have been unable to detect. Doubtful myself which of these opinions may be the most correct, I shall do little more than state correctly the phenomena of
the case, and minutely the appearances presented on dissection. One remark only I may at present offer; that any train of symptoms may be allowed to constitute anaemia a generic disease the following may be considered an example of it in its most idiopathic form.

"The case was a man, aged forty-seven, who had been born and had spent the greater part of his life in the country, where his duties were neither laborious nor unhealthy; who had led a regular and temperate life, and had enjoyed perfect health since childhood and had never lost any blood.

"I was much struck by his peculiar appearance. He exactly resembled a person just recovering from an attack of syncope; his face, lips and the whole surface were of a deadly pale colour; the whites of the eyes bluish; his motions and speech languid; he complained much of weakness; his respiration, free when at rest, became hurried on the slightest exertion; pulse eighty and feeble; inner part of the lips and fauces nearly as colourless as the surface; bowels were irregular, generally lax, his stools very dark and foetid; urine reported to be copious and very pale; appetite unimpaired; of late his stomach has rejected almost any kind of food; constant thirst; he has no pain referable to any part and a minute examination could not detect a structural derangement of any organ.

"It was only about two months ago since he began to complain, but not until his friends had observed his altered complexion; he then lost strength and said his head troubled him. Of this last symptom, he has no distinct recollection. His feet became oedematous and his appetite failed him.

"My attention was drawn to the skin which was of waxen colour, soft and delicate, the cellular tissue about the eyes and breast slightly distended with watery effusion. The pulse was feeble and easily excited by any emotion. A very minute examination of the case, and a careful consideration of its history, scarcely solved the nature and the affection; and its
long continuance and inveteracy rendered our prognosis much more doubtful.

"He died six months after being first seen, from aggravation of all the symptoms, extent of the oedema to face and upper extremities; and evident marks of effusion into the chest. He died with all the symptoms usually attendant on hydrothorax. At first the treatment seemed to check the progress of the disease, but latterly the stomach and bowels became so irritable as scarcely to admit of any medicine and only the mildest diet.

"Post mortem------
The subcutaneous fat was scanty, of a pale yellow colour, and semi-fluid. Not a drop of blood escaped on dividing the scalp. The heart when cut into was of a pale colour and did not tinge linen when rubbed upon it; it appeared like flesh macerated many days in water. The right ventricle contained a pale coagulum. The left side was wholly empty. There was a considerable moisture bedewing the viscera of the abdomen. The liver was of its proper size and structure, but of a light-brown colour. The spleen was the only viscus of its usual colour; it was very soft, and its contents on pressure being applied, turned out like a sac. The kidneys were nearly bloodless; pancreas of a pale-reddish hue. The stomach and intestines were perfectly sound; thin, showing no vessels and transparent. The muscular substance throughout the body was, like that of the heart, very pale, and exuded no blood, but only a pale serum when cut into. The arteries were empty, and so were the jugular, femoral and humeral veins.

"The only morbid appearance detected may be considered the effusion into the thorax and the abdomen, the ossification of the dura mater, and the nearly bloodless state of every viscus and structure in the body, with the exception of the spleen. A state like that of our patient's, in which every organ was nearly deprived of its red blood, is one, I believe, of very rare occurrence, and of which we have very few cases
He concludes by saying that "Dr. Young considers it as a species of dyspepsia, and perhaps with propriety; for it is probably owing to some disorder of the digestive and assimilative organs, that its characteristic symptom has its origin, and to the correction of this derangement, we must look for a removal of the disease." He therefore anticipated Hunter's intestinal theory by nearly three-quarters of a century.

Several accounts of severe anaemias from then until 1855 are to be met with. These will be discussed later. Of importance here, however, is the fact that in 1851 Barclay first noted the presence of glossitis in a patient dying from severe anaemia.

Addison's description, beyond all doubt, "pigeon-holed" pernicious anaemia, at least in Britain. He writes:—"For a long period I had from time to time met with a very remarkable form of general anaemia, occurring without any discoverable cause whatever—cases in which there was no previous loss of blood, no exhausting diarrhoea, no chlorosis, no purpura, no renal, splenic, marasmic, glandular, strumous, or malignant disease. Accordingly, in speaking of this form in a clinical lecture, I, perhaps with little propriety, applied to it the term 'idiopathic', to distinguish it from cases in which there existed more or less evidence of some of the usual causes or concomitants of the anaemic state. The disease presented in every instance the same general character, pursued a similar course, and, with scarcely a single exception, was followed after a variable period by the same fatal result. It occurs in both sexes generally, but exclusively beyond the middle period of life, and, so far as I at present know, chiefly in persons of a somewhat large and bulky frame, and with a strongly marked tendency to the formation of fat. It makes its appearance in so slow and insidious a manner that the patient can hardly fix a date to his earliest feelings of that
languor which is slowly to become so extreme. The countenance becomes pale; the whites of the eyes get pearly, the general frame flabby rather than wasted; the pulse perhaps large, but remarkable soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement; there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless; the flabbiness of the solids increases, the appetite fails, extreme languor and faintness supervene, breathlessness and palpitation being produced by the most trifling exertion and emotion; some slight oedema is probably perceived about the ankles. The debility becomes extreme; the patient can no longer rise from his bed; his mind occasionally wanders; he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after sickness of perhaps several months duration the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect. On examining the bodies after death, I have failed to discover any organic lesion that could properly, or reasonably be assigned as an adequate cause of such serious consequences, etc."

Pernicious anaemia was more or less treated lightly in medical literature from this date until Bierman (1872) again drew specific attention to the condition under the title of progressive pernicious anaemia. Several fatal cases were however reported by Samuel Wilks in Guy's Hospital between the years 1847-9. He states that "nervous shock" may be an aetiological factor in the disease; quoting the case of a young lady, who was accidentally poisoned by her father, and was so overwhelmed with grief; that after a while she
took to her bed and died of anaemia. He mentions in the same report histories of moral shock in patients of Drs Babington and Hughes, and who died of extreme anaemia.

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

Cohnheim, Osler and Purser believed these marrow-changes cause increased destruction of red blood corpuscles and therefore are a direct contributory cause of pernicious anaemia. Finny cautioned against this by pointing out that such changes occur in other conditions like cancer and phthisis.

Dr. Addison was content to have described this disease. Its due recognition by the medical world he owes chiefly to the writings of his friend and colleague Dr. Wilks, who from 1847 repeatedly published articles in support of Addison's claim to priority in the description of this condition.

Although pernicious anaemia had become a diagnosible entity at Guy's Hospital by the middle of the century, matters were different on the Continent. In 1854 Lebert in Zurich, described a condition closely simulating it, but without reference to the work of Addison. With a similar atmosphere of uncertainty, and showing an ignorance on the literature of the subject, fragmentary reports were given in Germany from time to time by Zenker (1856), Wagner (1859) and Grohé (1861).
In 1868 Biermer described a condition which he called "progressive pernicious anaemia", which in spite of all therapeutic measures, progresses without abatement and ends in death without any organic disease being demonstrable.

In five years this observer met with fifteen cases of the affection in patients varying from 18 to 52 years of age, the majority being women. He states that it frequently follows chronic diarrhoea, and childbearing seems especially to predispose to it. Those affected became extremely pale, and the skin of their hands, feet and face acquired a swollen look. They became weak, and had fits of giddiness and palpitation of the heart; the appetite failed, and there was a feeling of pressure in the pit of the epigastrium. Transient diarrhoea often occurred, and there were attacks of feverishness without the fever assuming any particular type. Anaemic murmurs were sometimes present and of such intensity that organic disease of the heart was suspected, but none was ever found after death. With all these symptoms of failing health it is a very remarkable fact that no actual diminution of the fat covering the body could be made out. As the disease progressed, ecchymoses appeared in the retina, even though vision remained intact. Sometimes there were small petechiae under the skin, and less frequently haemorrhages took place from the nose and kidneys. Transient paralyses were probably due to small haemorrhages into the brain substance. Towards the end of life dropsy set in, and delirium also occurred. The course of the disease was always chronic, and the termination always fatal. The necropsy invariable showed a partial fatty degeneration of the papillary muscles of the heart and of the smaller blood vessels of various organs. No treatment proved of any avail. (Med. Times and Gaz. 21st Nov. 1874).

This conception changed later, particularly on the continent, where many authors divided the disease into two classes: (i) Primary or Idiopathic anaemia with the cause unknown, and (ii) Secondary Deuteropathic or Symptomatic
anaemia, due to intestinal parasites etc.

It is obvious that Addison's work had little effect on the continent, since Biermer writes: "We are not aware that any case has as yet been reported in Great Britain" This fallacy was pointed out by Wilks (1873) and Pye-Smith (1875). As a result of this some of the continental workers acknowledged Addison's priority. Dr. Eichhorst states "that this disease was first described in England both in the form of single cases and as a definite clinical disease". Notwithstanding such frank recognition, this condition became known on the continent as Biermer's anaemia—a title which it still holds today.

Since the time of Biermer's account numerous nineteenth century cases have been described here and abroad by Pye-Smith, Bradbury, Byrom Bramwell, Broadbent, Gardner, Osler of Montreal, Pepper, Lepine, Immerman, Rosenthal, Litten, Quincke, Eichhorst and many others.

Aetiology

Addison and the early workers were completely uncertain of its aetiology. Various suggestions had been offered, such as intestinal intoxication, but the general view held in this country was that its aetiology was in some manner wrapped up in the idiopathic tendencies of the patient. Although Biermer acknowledged this to some extent he states that the absence of clear aetiological factors is not the rule and that pernicious anaemia is associated also with poverty and its attendant evils, particularly chronic diarrhoea.

Biermer's definition therefore included a group of conditions among which Addison's anaemia held first place. As a result of this more comprehensive scheme much confusion resulted and report criticisms are found scattered throughout the literature on the subject. Biermer was supported by
Quincke, Immermann, Eichhorst. Pye-Smith at that time almost alone took the field in support of the purely idiopathic nature of the disease 

In 1863 Habershon adopted the view that pernicious anaemia must find its etiology in the "nervous supply of the stomach", for the first symptoms are those of "gastric irritation and an interference with digestion." In this he anticipated Fenwick, who in 1877 put forward the view that atrophy of the stomach was an important etiological factor of the disease. Hunter supported this. Fenwick describes four cases of idiopathic anaemia in which atrophy of the stomach was a definite pathological finding. In all the cases there was extensive disorganisation of the glandular structures of the stomach, attended with marked anaemia. To obviate the criticisms that the changes were produced post-mortem he states: "where the gastric juice has disorganised the mucous membrane, every trace of structure may be removed; but a solvent can never produce new tissues, such as we found by the microscope----viz., newly-formed cells and fibres, thickened membrane, enlarged and distended tubes and cysts."

To support the view that pernicious anaemia and atrophy of the stomach are related he gives the symptoms of the latter condition. Ther is, he says, insidious onset of ill-health, slight loss of strength, and "a failure of appetite as regards animal food, especially when the meat is underdone, are usually the earliest indications. At the same time flatulence is the only sign of indigestion, with the exception, perhaps, of slight constipation. At a later period the appearance of the patient is very striking. The face is of a pale yellow colour, the lips and throat are intensely white, and he looks as though he were suffering from chronic Bright's disease or some malignant tumour----. The strength is greatly reduced; and the loss of memory and incapability for mental exertion force themselves on the sufferer's attention. The least exertion induces palpitation and dyspnoea, which is often so
distressing that the patient is forced to keep in the recumbent position. The pulse is small and thready, but not necessarily quickened. The progress of the case is generally slow, and as time goes on the feebleness and anaemia increase from week to week. Some complain of severe pains of the limbs on the slightest exertion, and the pains are stated to be as if they had undergone an immoderate amount of muscular effort. As death approaches, dropsy of the limbs sometimes shows itself, or effusion may take place into one or both pleura. Some complain of tenderness over the epigastrium; others suffer from vomiting and uncontrollable diarrhoea; whilst others become delirious, and sink gradually into a state of coma."

Hunter endorsed the view that pernicious anaemia is an idiopathic condition and adds that it is due to the absorption of some haemolytic substance from the intestinal tract. He based this argument on the fact that in all cases he elucidated the presence of glossitis, gastro-intestinal sepsis and the remarkable siderosis in the liver. The hey-word of Hunter's thesis may be said to be infection, located in the alimentary tract, with haemolysis in the portal system. The blood, as a diagnostic criterion, he did not regard as important, as evidenced by his bare reference to it in a monograph of 1900. In 1909 he mentions in hi "Severest Anaemias" that his omission was intentional to show his disapproval of Ehrlich's views on the importance of the myeloblastic marrow.

Finny adds that it "does not appear quite clear as to whether the gastric atrophy stands in the position of cause or effect. If the former, its role is obvious. By arresting nutrition at its very portal the elements for healthy cyto genesis are wanting."

Despite Tye-Smith's firm views on the aetiology of pernicious anaemia those of Biermer had a greater following. The observation that 'diphyllobothrium latum' infestation
(Griesinger) produced a condition apparently indistinguishable from pernicious anaemia, and which recovered when the worms were expelled, supported the view that there is not always a cryptogenic factor in the aetiology of the disease. Likewise the changes in the marrow were for a time robbed of much of their pathognomic value by the report that almost identical changes are established in some cases of repeated haemorrhages (Neuman), tuberculosis (Litten) and gastric carcinoma (Eisenlohr). Further, the changes in the blood were reputed to be similar to those occurring in syphilis (Müller), malaria (Signami and Ewing), atrophy of the gastro-intestinal mucosa (Fenwick, Brabazon, Henry and Osler, Nothnagel and Stengel), typhoid fever (Quincke, Rosenstein, Grawitz), prolonged diarrhoea (Wilkes, Frankel, Stricker) and myeloid sarcoma (Litten). These observations cast much doubt on the idiopathic nature of pernicious anaemia, and tended more to the general belief that it had a multi-cause aetiology.

Pepper (1875) and Cohnheim (1876) first described the megaloblastic changes in bone marrow. They indicated that it was a reversal of the marrow cells to embryonic conditions. Ehrlich, however, went further and assumed that they were pathological changes and pathognomonic of pernicious anaemia. He adapted his theory to Biermer’s classification and hence there came into existence the so-called Biermer-Ehrlich anaemia.

Pepper, Müller and Ehrlich found that females were far more susceptible to this disease than males, and they attributed this to the predisposing influence of pregnancy. In Ehrich’s report of 240 cases he also finds that the greatest age incidence is between 20 and 40 years. Ahlfeld was unable to confirm the observation that pregnancy was a factor in precipitating the disease. In a wide experience he could not report a single case.
With regard to those who upheld the view that gastrointestinal disorders accounted for pernicious anaemia, there were three schools of thought. The first attributed the disease to lesions of the gastrointestinal tract, such as chronic gastritis and enteritis, followed by fatty degeneration of the secreting cells of the peptic and intestinal glands and resulting in atrophy and sclerosis of the mucosa. Ewing found this condition to be present in all the cases he examined post-mortem and termed it "anadenia". He believed it to be responsible for all idiopathic cases.

The second group of thinkers attributed pernicious anaemia to functional disturbances of the gastrointestinal tract.

The third view was that so firmly supported by Hunter. He attributed the condition to specific infection of the alimentary tract, the incriminating organism being the streptococcus and the toxin it produces, a haemolysin.

Other views were those of Klebs who claimed that he had observed flagellate bodies in the fresh blood; of Frankenhauser and Petrone, who reported the isolation of "leptothrices" in several cases; of Bernheim, who isolated a bacillus from the blood of one case after death; and of Perles, who observed highly refractive, very active amoeboïd bodies in several cases.

In 1898 Ehrlich and Lazarus published a monograph almost at the same time Hunter put forward his views. They treated the subject exactly opposite to him and laid greatest stress on the megaloblastic blood formation, while they dismissed the role of infection and haemolysis in a few words. Biermer's eminence as a scientist, however, gained for him many supporters, and this monograph along with that of Schauman and Tallquist on the anaemia following Bothriocephalus infestation, further strengthened his position.

During the present century Hunter's theory received fresh attention. Herter in 1906 pointed out that B. welchii
showed an increase in the bowel of pernicious anaemic patients, whereas Faber, Grassmann, Gorka, Bogendörfer, van der Reis, Seyderhelm and others indicated a decisive increase in B. coli. In 1928 Dr. Davidson made an intensive study of the whole problem and arrived at the general conclusions that:

"1). No evidence was found to indicate that any individual type of organism was specifically related to pernicious anaemia. 2). No evidence was found that bacterial haemolysis are of aetiological importance in the disease. 3). A great numerical increase of organisms, normal habitants of the bowel, e.g. B.Coli, Streptococci, and especially B. welchi, was found to occur in the gastro-intestinal contents of cases of pernicious anaemia. 4). No evidence was found that these organisms differed qualitatively from those in healthy persons. 5). The great quantitative increase of bacteria, especially at the levels of the small intestine, which in normal persons are relatively bacterial-free, may be a factor of great aetiological importance."

In 1891 Klein observed the disease in three brothers. Shortly afterwards Byron Bramwell described a family with seven patients in two generations. There are numerous other records of the constitutional or hereditary factor in pernicious anaemia. The Watson family described by Ungley and Zusman is a good illustration of the relation between this disease and achlorhydria. This matter was further investigated by Barker (1926) and Zadek (1921), who found that 26 of 49 blood relatives of 20 pernicious anaemia cases had complete or nearly complete achlorhydria.

To explain why certain members of a family should develop pernicious anaemia and others escape Barker (1926) speaks of the "releasing factors", which come into play when stimulated (e.g. as by Diphyllobothrium infestation).

The modern views on the aetiology of pernicious anaemia have for their nucleus the observations of Ehrlich, who originally stated that megaloblasts and megalocytes are
present in the blood and also that in this disease blood-regeneration in the bone marrow proceeds on pathological and not physiological lines; and finally that this specific megaloblastic anaemia is a perverted type of haematopoiesis which is comparable to that of embryonic life... Pepper and Cohnheim formulated the view that the cause of this megaloblastic blood formation is some inborn error, or constitutional defect in the formative tissues. The other view, which we have already mentioned, is that toxins are absorbed into the blood-stream and so produce the blood changes so specific in this disease.

Concerning blood formation Davidson and Gulland say:

"We believe that there exists in the body, principally in the liver, but also in the kidneys and to a less extent in certain other structures, a substance whose presence in sufficient concentration is essential for normal blood formation. A deficiency of this unknown but specific factor causes a megaloblastic anaemia. The proof of this statement depends entirely upon the therapeutic effects achieved in the treatment of pernicious anaemia with liver or liver extracts."

How these ideas arose and how it came about that liver therapy was introduced, and what effects it had on the better understanding of the aetiology of pernicious anaemia is a volume in itself. The facts briefly are that in 1920 Whipple and Robbins began a series of experiments, in which dogs were first got into a state of severe anaemia and then fed on various diets to determine which possessed the highest value as a regenerator of haemoglobin and red blood corpuscles. They found liver and kidney possessed remarkable haemopoietic powers. In 1923 McCollum demonstrated that a liver liver diet greatly increased cell division and so growth. These experiments and others led Minot and Murphy to try this diet on anaemic patients—there followed the epoch-making discovery of the value of liver in pernicious anaemia.
To explain its action various views were put forward. McCollura suggested that Vitamin F. was the active principle; others advanced the view that it was the iron. There opinions were contested and proved wrong by Cohn, Minot etc. and West. The method of action of this unknown principle was demonstrated by Peabody (1927). As the result of tibial punctures in living patients he showed that during relapses there was a great increase of megaloblasts in the bone marrow, and that during remissions following liver therapy the conditions returned to normal.

A search for the active principle or principles was made. Extract of liver was prepared and Dakin and West (1935) showed that a preparation almost free of inorganic matter gave a maximum reticulocyte response in doses as small as 80 mgm.

With regard to the cause of the deficiency of the unknown specific factor in the liver, Davidson and Gulland suggest that the "liver functions may be normal but the elaboration of the specific factor in, or its absorption from, the gastrointestinal tract is deficient; or the liver may receive the raw material but be unable to use it." Castle (1928) found that beefsteak partly digested in a normal person's stomach caused a reticulocyte response in a case of pernicious anaemia when given in sufficient amounts. The next year (1929) he reported that eight out of ten cases had responded in the same way. He and his co-workers (Castle and Townsend, Castle and Heath, Castle, Heath and Strauss (1931)) deduced from their researches on the digestive powers of pernicious anaemia patients that there exist two principles necessary to elaborate the effective principle in the liver---an extrinsic factor present in meats and an intrinsic factor present in normal gastric juice.

The Extrinsic Factor---Wills (1931) found that marmite, an autolyzed yeast rich in vitamin B, was as effective as liver in the treatment of tropical megalocytic anaemia, which is similar to pernicious anaemia in many respects. The follow-
ing year Vaughan and Hunter (1932) found it as effective in the treatment of megalocytic hyperchromic anaemia associated with idiopathic streatorrhea; and Strauss and Castle (1932) obtained similar results in sprue. Such yeast preparations were, however, found of only little value in pernicious anaemia. (799) (800) (801) (802) (Goodall (1932), Davidson (1933), Ungley (1933) and James (803) (1934). Strauss and Castle (1932) found that yeast predigested with gastric juice was as potent as liver in the treatment of pernicious anaemia. Their researches tended to show that the extrinsic factor necessary for erythropoiesis was vitamin B_2 or some closely allied substance. A highly contradictory literature sprang up around this point, and the subsequent work of Wills and Naish (1933), Miller and Rhoads (1935), Lassen and Lassen (1934) tended to overthrow this view and show that the extrinsic factor was probably some protein breakdown product formed in the process of autolysis rather than vitamin B_2.

**Intrinsic factor**—Castle's intrinsic factor was shown to be probably of the nature of an enzyme. Meulengracht (1935) pointed out that this substance is secreted in the pyloric end of the stomach and by the Brunner glands of the duodenum, whilst the cardiac end of the stomach is almost devoid of such a function. According to Castle therefore the stomach is the organ primarily at fault in this disease. Sturgis and Isaacs (1929), also working on this problem, investigated the effects of extract of hogs-stomach on pernicious anaemia patients. They claimed that the results were as good as those in which only liver therapy was used.

We mentioned before that Fenwick (1870), Flint (1871), Pye-Smith (1883), Osler and Henry (1886), Hunter, and others observed that in pernicious anaemia there occurs extensive atrophy of the secreting tubules of the stomach, while some of them described degenerative changes in the intestines as well. These latter observations were overthrown by Faber and Bloch (1900) who indicated that the structural changes observed by
the earlier workers were post mortem for the most part. They, however, acknowledged that certain changes do occur during life, these being a chronic inflammatory gastritis with atrophy of the secreting tubules absent or present.

In order to explain the functions of blood formation in terms of these recently discovered principles I can do no better than to quote Whitby and Britton: "Briefly it may be stated that in a normal person the haemopoietic principle is produced as the result of the proper digestion and assimilation of an ordinary diet. The diet supplies a food that contains an 'extrinsic' factor which is particularly abundant in meat protein, especially beef. The normal gastric juice contains a substance, probably of ferment nature, known as the 'intrinsic' factor. The interaction of extrinsic and intrinsic factors produces the haemopoietic principle, which is then absorbed from the intestine and stored in the liver ready for use by the haemopoietic system. Experiments have proved that the haemopoietic principle can be extracted from the liver of normal adults and new-born infants and from the liver in pernicious anaemia when the disease is treated adequately. The principle is absent from the diseased liver, as in advanced cirrhosis, and is not present in the liver from a case of pernicious anaemia treated inadequately. The formation of the haemopoietic principle may be summarised by the equation:

Extrinsic factor + Intrinsic factor = Haemopoietic principle.
(Diet) (Gastric juice) (Absorbed from intestine)

The production of the haemopoietic principle therefore demands a co-ordination between food intake, digestion, absorption and storage.

The haemopoietic principle is essential for the proper maturation of megaloblasts. In the absence of this substance erythropoiesis becomes disordered so that the type of blood production becomes 'megaloblastic', characterized by the appearance of megaloblasts and macrocytes. The point of action
of the haemopoietic principle is invariably macrocytic and almost always markedly hyperchromic. Other features of such an anaemia are anisocytosis, poikilocytosis, and the appearance of haemoglobinized megaloblasts, as well as other nucleated and immature red cells. Under normal conditions an excess of haemopoietic principle is produced and stored in the liver. Liver is therefore curative in pernicious anaemia by virtue of the haemopoietic principle that it contains. The principle can be extracted in relatively pure form from liver and is highly potent for the cure of most macrocytic anaemias. A curative power is also possessed by dessicated hog's stomach, and to some extent by the autolysed yeast product known as marmite."

The relation of the gastric juice to the aetiology of pernicious anaemia was investigated by Mermod (1936) and Jacobson (1936).

The earliest observations to show that the acid in the stomach is hydrochloric acid dates from 1824. Before this time Bernard and his followers erroneously believed that the acidity of the gastric juice was due to lactic acid. In 1803 John R. Young, in America, published "An Experimental Inquiry into the Principles of Nutrition and the Digestive Process" and showed that the solvent principle of the gastric juice is an acid. This work was carried on by William Prout, an English chemist, who, in 1824 showed by careful titration and distillation, that the acid of the gastric juice is free hydrochloric acid. This was soon confirmed by other chemists, notably by Friederich Tiedemann and Leopold Gmelin. Further work in this field was magnificently carried out by William Beaumont, a surgeon in the United States army, who had the good fortune of studying the gastric juice, and the process of digestion in a Canadian half-breed, who had an accidental gastric fistula.

That hydrochloric acid is definitely present in the
gastric juice was conclusively proved by the laborious analyses of Bidder and Schmidt (1852). This work was carried further by Voit (1869) and Cahn (1886) who indicated that the hydrochloric acid is derived from the blood plasma.

Another factor which may be of importance in the aetiology of pernicious anaemia is the deficiency of iron and other metals in the blood. This is still the subject of much controversy. Numerous workers like Hart, Steenbock, Waddell, Elvehjem, Cunningham, Parson, Josephs, Mills, Young etc have shown that iron alone is insufficient for the proper formation of blood. Meyers and Beard (1931) pointed out that numerous other metals were effective supplements to small doses of iron—copper, nickel, manganese, arsenic, titanium, zinc, rubidium, chromium, vanadium, selenium and mercury. Beard, (815) Baker and Meyers (1931) conclude that these elements act as catalysts to the iron.

Clinical Features and Pathology

With regard to the general clinical description of severe and untreated cases of pernicious anaemia, we need add little to Combe's and Addison's accounts of this disease. (816) Isaacs (1936) gave an analysis of 580 cases of true pernicious anaemia: "From the data a patient with pernicious anaemia is defined statistically as a man or woman (equal possibility) between the ages of 35 and 55 years, of no specific nationality but generally of a race originating in northern European countries, who is underweight, who has light-coloured hair, generally blue eyes and pale skin, and long wide ears, and who shows no secretion of hydrochloric acid, at any time in the stomach; relative hypotension; a tendency to hyperchromic macrocytic anaemia, leukopenia and hyperbilirubinemia; atrophy of the lingual papillae, and
neurologic changes associated with lesions in the posterolateral columns of the spinal cord."

Modern diagnostic methods, however, have enabled physicians to make a diagnosis long before this complete picture has resulted. As a result many cases show no more than a slight anaemic pallor associated with vague symptoms of lassitude and breathlessness, or perhaps mild neural symptoms. (817)

In 1878 Mackenzie described an unusual case of pernicious anaemia in a schoolboy ten years old. There was headache, earache and waxy skin. There was a loud mitral systolic murmur and the pulse was small and soft. Optic neuritis was advanced. The red blood corpuscles were small and poorly coloured and some showed "tails" (poikilocytosis). Later retinal haemorrhages occurred with distressing vomiting. Occasional febrile attacks and frequent epistaxis and bleeding gums were evident. At autopsy the liver was mottled and there was extreme pallor of the viscera. The blood formed fawn-coloured coagula. The fat was well preserved; the retina showed haemorrhages with swelling of the discs. Lastly the marrow of the clavicles and ribs was of a red colour.

Other clinical features mentioned in this disease (818) were tenderness over the tibia (Finny), and diarrhoea, for which (819) Lepine created the term "anémie gastro-intestinale".

The clinical course of the disease has from its early recognition been shown progressive and downwards resulting in (820) death within six months to one year (Mackenzie, Wilks, Biermer, etc.), although recognised that temporary arrests of the condition may occur. Since the introduction of liver therapy this clinical course has been completely changed, and the expectancy of life under adequate treatment is now very much longer.

In 1854 Davies makes the statement that the "bruit de diable" so common in this condition is not due to the anaemia, since it "has been observed in a multitude of instances to coexist with the ruddiest complexion and the most
perfect health."

At this point it may prove interesting to indicate more fully the course the disease is likely to pursue. The passage by Davidson and Gullard (1930) cannot be bettered: "Let us trace the course of the disease in a case of pernicious anaemia starting with a blood count of five millions and reaching one million some six months later. In the earlier stage there occurs the normal removal of worn-out and effete red corpuscles by the cells of the reticulo-endothelial system. The iron-containing fraction of the haemoglobin ingested by these cells will be so quickly re-utilised by the bone marrow, that no siderosis of the liver will be found at autopsy.

This we know from our investigation of cases dying from intercurrent disease during the stage of remission. As the disease progresses, abnormal blood formation becomes a more or less prominent feature, resulting in a production of red cells which is defective, both quantitatively and qualitatively. The abnormal cells entering the circulation are unable to stand the stress and strain of intravascular life to the same degree as healthy corpuscles, and in consequence the amount of intracellular blood destruction rapidly increases. At this stage a delayed direct Van den Bergh reaction is given by the blood serum, and the icterus index starts to rise. Simultaneously the other fraction resulting from the breaking down of haemoglobin, namely the iron compounds, is found to be equally increased. In the terminal stages of a relapse when the red count reaches a million the bone marrow only requires about one-fifth of the iron used in health, but owing to the short intravascular existence of the abnormally formed circulating cells, which are more fully haemoglobiniferous than healthy cells, a plethora of iron compounds is available. A combination of lessened demand (due to deficient production of corpuscles) and excessive available quantity of iron exists, and in consequence it is not surprising that the liver, which is the natural storage reservoir of iron, should steadily accumulate that material."
The pathological investigation of pernicious anaemia commenced with Combe. He noted the extreme paleness of the blood and says "the heart did not tinge linen when rubbed upon it". The early workers, especially Wilks, had noted the marked oligaemia and feeble coagulation of the blood at autopsy, and by microscopic examination during life had demonstrated an excessive loss of red cells and a small proportion of leucocytes. For many years little advance was made beyond this point. In 1873 Ponfick found a relative increase of leucocytes in one case, associated with a greenish tinge of the blood serum.

In several cases Quicke (1876) described the appearance of microcytes and poikilocytes, while Eichhorst at the same time noted the increase of haemoglobin in some microcytes and the absence of rouleaux formation. These changes he regarded as pathognomonic of the condition.

Bizzozero and Neumann's demonstration of the function of the bone marrow as a haemopoietic centre caused Pepper and Tyson to investigate this tissue in pernicious anaemia. Pepper found uncertain evidence of a cellular hyperplasia in some portions of the marrow, that of the radius appearing paler than normal, while that of the sternum was quite red.

Cohnheim's communication on the bone marrow changes in pernicious anaemia attracted more attention to this tissue than hitherto. He states that there is unusual hyperplasia of the red marrow, with complete atrophy of the red cells; increase of myelocytes, large and small; absence of normal red cells, and the presence of megalocytes, microcytes, and large numbers of megaloblasts. Further study of this pathological manifestation was undertaken by Osler and Gardner, Neumann, Litten and Orth, and Grawitz.

The first enumeration of the red blood cells was reported by Sorensen, who found them in one case to be as low as 470,000; by Lepine, who gave readings of 909,000 and 378,750; and by Ferrard, who found 500,000 red cells and 10%
haemoglobin. Duncan first and then Lepine noted that the red cells were increased in size. The former called this state "achrocythaemia". Stricker saw them coloured brownish, and Sheby-Buch described them as possessing amoeboid processes. Heyem showed that the observations of Duncan, Lepine and Eichhorst, namely a pale red cell, were wrong and that in pernicious anaemia the characteristic feature was a small, highly coloured cell.

By 1880 only two cases had been reported showing nucleated red cells during life. Ehrlich, however, declared that all cases showed this feature. This was subsequently shown by Luzet to be only partially correct.

In 1876 Guincke noted that in three cases of pernicious anaemia the liver contained an excess of iron. This observation was lost sight of until Hunter and Ehrlich in 1900 published their books and showed it to be a constant feature in cases dying in the relapse stage.

An important fact not early realised is that the pathological features depend upon the stage in which the disease is at the time of death. This caused much early confusion of ideas.

Mackern (1877) believed the abnormal shape of the red cells to their abnormally soft stroma (as the result of being "very young" or else "chemically altered"). He is the first to mention a "separation of the haemoglobin from the stroma --- i.e. the disintegration of those important oxidising elements of the blood", with consequent liberation of the haemoglobin from the stroma into the plasm.

Stockman (1895) drew attention to the frequency with which small haemorrhages occur in pernicious anaemia, and attributed the blood changes to this repeated intracellular loss of blood.

The lingual changes were first properly described by Hunter. Although they had been mentioned many years before the recognition of their importance as a diagnostic feature must go to this man.
The atrophic changes in the gastric mucosa have been mentioned elsewhere. Flint in 1860 was one of the first to make special note of this lesion as being almost invariably present in pernicious anaemia. This led to intensive investigation of gastric function and has today resulted in the almost universal adoption of the test meal as a diagnostic aid.

Free acid was found absent in gastric analyses of most cases of pernicious anaemia. This was reported by Faber and Gram (1924), Faber and Bloch (1900), Levine and Ladd (1921), Hurst (1923), Panton, Percy (1920) and others.

Achlorhydria may occur in persons who show no signs of anaemia, or if present is of the simple "secondary" type. This was shown to the the case by Bennett and Ryle (1921), who examined 100 medical students and found that in 4 per cent of them no free hydrochloric acid was secreted by the stomach.

Achlorhydria was found to arise in certain cases as the result of infective or toxic processes, in which cases it was referred to as acquired. Likewise gastro-enterostomy and gastrectomy has been shown to give rise to achlorhydria. Pernicious anaemia and such acquired achlorhydria are frequently associated as was shown by Hurst, who reported five cases of pernicious anaemia following gastrectomy.

When achlorhydria is congenital or present from early childhood, or when present without pathological lesions in the stomach wall it goes under the name of constitutional achlorhydria—a phrase created some years ago—and is then a true achyla gastrica. Numerous enquirers have shown that this type is associated with pernicious anaemia in the majority of cases (Hurst, Riley, Faber (1913), Hurst and Passey (1922)), and they assume that constitutional achlorhydria is of great importance in pernicious anaemia.

Many of the early observers mentioned symptoms referable to the central nervous system. In 1884 Leichtenstern reported two cases with posterior column degeneration, but
in both cases attributed it to tabes dorsalis. It was not
till 1887 that degeneration of the posterior columns was
associated with pernicious anaemia. Lichtheim in that year
described a case of severe anaemia with the classical signs
now taken to be diagnostic of subacute combined degeneration
of the cord. A special study of this condition was made by
Collier in 1920. He states that there is enlargement of the
cord due to oedema and a deficiency of new-formed neuroglial
tissue which would produce a condensation of the tissue.
This he mentions differentiates it from other posterior
column affections where shrinkage of the cord is the conspicu-
ous feature. He laid great stress on the fact that no
neuroglial increase occurred no matter how long-standing
the case may be.

The neural symptoms and lesions have recently received
the critical attention of Smithburi and Zerfas, Goldhamer,
Bethell et al., Baker and his confederates and Strauss
and his collaborators.

Gulland in 1902 noticed that certain areas, usually in
the middle zones of the liver lobules, appeared necrotic.
Between the necrotic cells were numerous capillaries filled
with nucleated red cells and phagocytes containing these
cells and pigment. Giant cells were usually present as well.
Some were possibly the same as Cooke's type II macropolycyte.

On the chemical and physical changes which occur in
the blood of patients suffering from pernicious anaemia a
great mass of literature has arisen. The older workers found
a reduction of the specific gravity of the blood (Grawitz,
Dieballa, Copeman, v. Jaksch, Grawitz, Stintzing)
and Gumprecht found a great reduction of the total albumen
of the blood, but an increased amount of albumen was observed
in the red cells (Grawitz).

Limbeck found a diminished resistence of the red cells.
During more recent years nitrogen metabolism has
received much attention. The majority of observers are agreed
that in the relapse stage a negative nitrogen balance occurs. Barker and Sprunt, and Gibson and Howard produced a normal nitrogen balance by high protein diets, which resulted in manifest clinical improvement. This opened up the experimental work of Whipple and Minot and Murphy.

The volume index, introduced into clinical medicine by Capps in 1903, has been found to be always above normal, while in secondary anaemia it has always been found below normal. Numerous investigators have demonstrated that the saturation index is but little altered and that the coagulation time is only slightly delayed. With regard to the haemoglobin Haden (1924) showed that the degree of saturation is unaltered. Sellars and Minot (1916) pointed out that a lowered kidney threshold to haemoglobin occurs in pernicious anaemia.

The van den Bergh Reaction, which is a modification of the Ehrlich-Pröscher reaction, and is due to the formation of azobilirubin from bilirubin, when the latter substance reacts with diazotised sulphanilic acid. Thaimhauser and Anderson (1921) improved on it. Rosenthal believed that the bile salts are responsible for the separation of the bilirubin from its absorption compound in the liver. In the case of pernicious anaemia these workers and many others found the serum to give an indirect positive. Early workers including van den Bergh (1918), Lepehne (1920), Mc. Nee (1923), and Andrews (1924), and more recently Cowen (1925), Fishberg (1926), Wiener (1926) and Schiff (1927) determined the content of normal sera, which varies from about 0.1 to 0.75 mg. per 100 cc of serum.

A recent investigation by Sheard showed that the bone marrow does not produce a uniform hyperplasia but that some areas may become actually aplastic. What the explanation for this phenomenon in pernicious anaemia is has as yet not been found.
The only pathognomonic finding in pernicious anaemia remains that originally described by Pepper and Cohnheim and later by Ehrlich, that of a megaloblastic degeneration. Carnegie Dickson in 1908 suggested that the haemolytic processes in the marrow, if the amount of myeloid tissue throughout the body be taken into account, form an extremely important aspect of the disease.

William Hunter et alia (1901) made analyses of the iron in the liver of pernicious anaemia cases and all are now agreed that the haemosiderin is greatly increased (from 5 to 10).

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Treatment.

The treatment of pernicious anaemia until recently was purely symptomatic. Up to the time of Minot and Murphy's (1926) investigations into the action of liver in this condition little need be said. Most of the treatment had been practically useless.

The majority of the early workers tried iron preparations without much effect although certain claims of cure are put forward. For example Hutchinson in 1881 reported a case which entered hospital with 10 per cent of haemoglobin and was discharged with 75 per cent haemoglobin, being treated with dialised iron and arsenic. Byrom Bramwell (1877) was the first to employ arsenic in pernicious anaemia. His records of successes, however, are few. With regard to dietetic treatment Habershon in 1863 indicated that a nutritious diet, combined with bracing air is beneficial, but he recognised that no known remedy was of any permanent value.

Pepper (1875) investigated the pathological changes occurring in the liver and gastric mucosa found post mortem and advised the necessity for a light and nutritious diet.

As a result of these remarks subsequent writers stressed
the dietetic aspect in the treatment of pernicious anaemia. (884)
Fraser (1894) quotes a case, which responded well to
treatment with bone marrow after iron and arsenic had failed.
In this case the red blood corpuscles rose from one to four
millions and the haemoglobin to 35 per cent in a short while.
Liver therapy as a specific remedy is now fully establish and the market is flooded with proprietary preparations of
liver extracts for injection parenterally as well as for
oral administration.

In 1928 Ordway and Gorham published the results of liver
therapy in a large number of countries; they unfortunately
did not include those cases which started treatment during
the period of remission. Other results were published by
Wilson and Evans (1924), and Panton and Valentin (1928).

Another form of treatment frequently used before the
introduction of liver is blood transfusion, which only became
practicable after the discovery of the group relationship
of the isoglutination phenomenon of Landsteiner and its
amplifications by Jansky, Moss and others. (887)

In 1928 Davidson showed that the administration of
hydrochloric acid in large quantities failed to sterilise the
upper alimentary tract even over long periods. He also
pointed out that successful treatment with liver in no case
restored the secretion of hydrochloric acid and the intestinal
infection remained as before. This was confirmed by Knott
(1923).
Chapter 10.

THE ANAEMIAS

(The Evolution of Our Ideas Concerning the Anaemias and Their Classification. 1800 - 1939).

General Discussion.

By the commencement of the nineteenth century the word "anaemia" was being used by certain authors, but its application to specific clinical conditions was vague. During the early part of the century, however, we find the word being more and more widely adopted, mainly due to Andrall's endeavours to popularise its use.

The early literature on the application of the word is confusing for it appears from some works that the term was used to indicate the general state of "poverty of red blood", and therefore included chlorosis, whereas others used it to indicate a definite clinical condition, which, however, appears to vary with the different authors. Thus Lieutaud uses it to indicate a condition which appears from his description to be either a primary or secondary anaemia, but which he says is almost invariably fatal; Halle's description could readily be that of infectious jaundice, whereas the condition described by Becker, Freytag, Janson, C.L. Hoffmann, Albert Moigling and other Continental authors during the latter end of the eighteenth century are just as confusing.

The nineteenth century brought about important changes in the use of the word. A better knowledge of the blood, from improved physical and chemical methods of examination, the intensive studies of cell morphology and the problems of haemopoiesis and the accumulating literature on the states of the blood in various clinical syndromes, gradually led to a classification of the anaemias into various groups according to the pathological changes produced in the blood. That "junk-heap" --the cachexias--was slowly diminishing
in size as technique and diagnostic skill improved and investigation aided investigation in a better understanding of normal and abnormal blood function.

Although anaemia was used in various senses during the early part of the nineteenth century one feature appears common to most of the writers, namely a deficiency of the red part of the blood. This state had been mentioned from the earliest times. Reiselius in his "Miscellanea Curiosa" mentions under the title "Exsangue fere corpus", a case who died on the 20th of October 1684, and who showed at autopsy a distinct absence of blood. He ends by stating that it is difficult to explain where this blood had gone to either before or after death. Schwenke at a later date mentions a case of chronic illness, in which at post mortem examination the body was found nearly deprived of its red blood. Halle's anaemia Combe thinks is more allied to the "chlorosis rachialgica" of Ramazzini and Sauvages.

Early in the nineteenth Halle wrote on a disease he called anaemia and which attacked all the workmen of a gallery in a coal mine, at Anzain, Frenes, and Vieux Conde near Valenciennes. The anaemia he describes is in many respects that of infective jaundice. He says: "It commences with violent colics, pains in the intestines and stomach, difficulty in respiration, palpitations, loss of strength, inflation of the belly, and black and green stools. This state continues for ten or twelve days, or more; then the abdominal pains cease; the pulse remains feeble, contracted and weak; the skin loses its colour and gets a yellow tinge; walking is difficult, and accompanied by extreme fatigue; frequent palpitations cause an extremely painful state of anxiety; the face is swollen; and there are frequent and even habitual sweats. This state continues for many months and even more than a year, and is always attended by wasting and emaciation. At last, the original symptoms recur, with violent headaches, frequent faintings, intollerence to light and sound,
inflation and pain of the belly, and purulent stools. These last torments are soon terminated by death."

The characteristic symptoms are: "universal loss of colour and yellow tinge of the skin, swelling, impossibility of walking without suffocation, palpitations, and habitual sweats."

He concludes by stating that it is best to call this condition anaemia, and to distinguish it from 'anaemia chlorosis' and 'anaemia consecutiva'. The latter being the result of haemorrhage.

The following case given by Elliotson in 1832 may possibly have been one of pernicious anaemia, and should have been included in the previous chapter. It is however inserted here to show what Elliotson took to be the same as the "anaemia" described by Lieutaud and Halle. He mentions the paucity of literature on this subject to commence with, thereafter he adds that the disease anaemia is one "in which the blood is not perfectly formed." He goes on to say "this is comparatively a rare disease and in this case it was made a little obscure by the circumstance of the individual having jaundice. The patient", he says, "was a man, aetat 44, who said that he had been ill five months with jaundice, for which he had been a patient in St. Bartholomew's Hospital. The jaundice just existed sufficiently for me to say that he was jaundiced and no more. He was pale and sallow throughout---not exactly yellow, but pale and just slightly yellow; the white of his eyes, however, had decidedly a yellow tinge. It appeared that he had pain, on pressure over the liver, and I certainly felt the liver full and hard. There was no obstruction to the bile at the time, for his motions were yellow.----

"I could discover nothing more in this case, than that the patient had got a slight degree of jaundice, which remained after a severe attack of that complaint, for which he had been treated at St. Bartholomew's Hospital and that he
had also anaemia.

Treatment——

The liver was larger and firmer than it ought to be and there was also a little tenderness, not, however, sufficient for me to think of bleeding him; for he complained of considerable weakness, and I therefore contented with exhibiting two grains of calomel every night, and rubbing iodine ointment over the liver. The jaundice entirely disappeared, the yellowness of his eyes went off but the man gained no ground. I then observed that the skin retained its former appearance and that he became paler, that his lips were pale, that his pulse was becoming weaker and sharp, and he complained of extreme debility. The sharpness of the pulse increased, the eyes now became very white, and he complained likewise of throbbing in the head, extreme fullness about the pit of the stomach, a sense of great exhaustion, and sometimes palpitation. I had a small quantity of blood, about an ounce, taken away for the purpose of examining it, and it was found to be far less firm than it should be. There was also a slight bellows sound in the region of the heart, just as is the case when a patient has lost a great deal of blood, or the blood has become watery.

"It struck me now, that although the jaundice had been got the better of he was in a state of anaemia, notwithstanding he had lost no blood before he came in, as far as I know and I had none taken away excepting about an ounce for the purpose of examining it. He was allowed meat and porter every day, and I ordered him full doses of carbonate of iron. His mind was a little disturbed; he had not full command of himself; he was not altogether reasonable at all times, at least there was a little weakness of mind shown, and he became weaker and weaker. Still I could discover no organic disease except the fullness and hardness of the liver, which was not very great. Through the imbecility of mind he made a number of complaints. One day he complained of intense pain in the
region of the liver, but on pressing his thigh, he made the same complaint with regard to that. His weakness, however, increased; his pulse was quick, and he gradually sank.

Before inspecting him, you will recollect I said I expected to find nothing but increased bulk and induration of the liver.

"On opening him, we met with the usual appearances in this disease. I found nothing more than what I expected. His liver was rather too large and indurated, but that would not explain the cause of his death. The blood in his veins was found exceedingly watery, almost like red ink, and on wounding the inguinal vein, a large quantity of blood came out quite thin, not like proper blood, very little better than red ink. The heart was flabby and intensely pale and the vessels of the pia mater nearly destitute of blood, and there was a great paleness of the whole body. No organic disease was found; the mesenteric glands were perhaps a little larger than usual, but that was all. It appeared, so far as the investigation went, to be mere bloodlessness."

The French, he adds, had found iron the method of treatment in such cases; at first they had given mercury "but as this was not an inflammatory disease, the mercury was found to do great harm: it was found to destroy the patients; but after giving iron in this free manner they improved in eight or ten days."

It is obvious that this case is not the same as those described as anaemia by the French writers, and points to the fact that a great deal of confusion existed concerning the anaemias.

From about 1836 the word anaemia is found much more frequently than hitherto in medical literature, and there is a greater tendency for it to be used in its generic sense. This was chiefly due to the writings of Andrall and Ancell. From the writings of the former author it is seen that he had a clearer insight into its true nature. He first clearly
signified anaemia as meaning a state where the red blood corpuscles are decreased. Before it had been used rather in the sense of diminished blood in the body.

The presence of the buffy coat in the chlorotic form of anaemia had long puzzled pathologists. They could not understand how it occurred in this condition and in almost opposite conditions like the inflammatory conditions. Andral cleared the point by showing that the buffy coat depended upon an absolute increase of the amount of fibrin and that this occurred in all the "phlegmatious" and inflammatory diseases. He also showed that it occurred in all those conditions where the red blood corpuscles diminished and the fibrin relatively increased.

All anaemias he divided into two stages—the commencing and the confirmed. (833)

After a severe haemorrhage he states the nervous system is particularly liable to disorder. Although there is weakness cerebral irritation seems to be a feature—delirium, convulsions, palpitation and dyspnoea. He proceeds to distinguish between the dyspnoea of pulmonary congestion, where there is "Too much blood in proportion to the air which enters the bronchial cells", and the dyspnoea of anaemia where the "proportion of air" is "too great for the quantity of blood to be vivified, and the phenomena produced resemble those arising when an animal is placed under a glass bell, filled with pure oxygen." (894)

In 1839 R. Christison made an interesting observation. Speaking of "granular degeneration of the kidneys", he says, "I am acquainted indeed with no natural disease, at least of a chronic nature which so closely approaches haemorrhage in its power of impoverishing the red particles of blood." This impoverishment he indicates as an increase in the serum and decrease of the clot. (895)

A good account of anaemia is given by Ancell in 1840 and to quote him will indicate what the state of knowledge was
at that time. He discusses the causes of anaemia which, he says, can be reduced to two series, firstly, "those by which part of the blood or its elements are lost" and secondly, "those which prevent the gradual renewal of its ordinary waste." Under the first heading he includes haemorrhages, both rapid and slow, and "fluxes" (profuse menstruation, lactation, leukorrhoea, diarrhoea, mucous discharges, albuminuria and granular nephritis, and long-continued suppuration). In his second series he mentions insufficient diet, dyspepsia, exclusion of the sun’s rays and nervous influences. To these Trousseau later added lead poisoning.

With regard to the blood he writes that "it is deficient in colouring matter, and contains a small proportion of iron, and is usually of a bright rose-red tine, but in worst cases it approaches in appearance the serum. It furnishes a small clot of slight consistency, with a large proportion of serum; and owing to slow and defective contractility, the clot often appears to be larger than it really is; the serum has little colour, and is very transparent, probably it has also a very small proportion of salt." He, however, adds that sometimes, when the mass of blood is diminished, the proportion of clot is really larger, and that of the serum small, as in cholera, which shows that the mass cannot be considered altogether apart from the qualities, and that these are different according to the causes producing the deficiency in quantity.

"In anaemia", he says, "the force, frequency, and sound of the hearts action is influenced directly, as it may be a recent or an old affection.

"The capillaries are remarkable for their discolouration, for their blueish pallor, the skin having a yellowish or rather cadaverous tint, resembling the tissue of the skin, containing no blood. If you compress the wrist in a case of anaemia, so as to retain the blood in the hand, the latter becomes coloured, which forms a strong contrast to its former tint." This according to Piorry distinguishes general anaemia
from "hydrohaemia", or a watery state of the blood, in which no amount of pressure on the wrist will change the anaemic colour of the hand.

"The lungs are extremely sonorous and elastic and the respiration greatly developed." The slightest exertion causes tachycardia. There is loss of mental vigour; sometimes there is excitability. There is inertia and muscular weakness; standing produces vertigo and superimposes syncope and occasionally epileptic fits. "The organs of sense are weakened, and the sclerotic coat a blueish tint; the liver is small, the secretions contain but little animalised materials; digestion fails. The abdomen is very frequently sonorous from distension with gas; morbid discharges are liable to dry up, the haemorrhoidal flux will subside, and there is commonly amenorrhoea. The symptoms become more and more severe, they are grouped in a thousand different ways, and terminate after a longer or shorter time, according to the intensity of the cause and the primitive vigour of the subject. If the anaemia has been rapid, and has proceeded from violent causes, the violent symptoms described precede the death of the patient; if it has been slow, and has proceeded from insidious causes, there is neither râle nor convulsions; but the patient dies, as it were, instantaneously, and most frequently at assuming the erect position."

After death, he concludes, there is pallor of the tissues and putrefaction is slow.

With regard to the analyses of the blood in cases of anaemia Becquerel and Rodier found the mean of thirty-one cases to be:

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density of defibrinated blood</td>
<td>1047.4</td>
</tr>
<tr>
<td>Density of defibrinated serum</td>
<td>1027.1</td>
</tr>
<tr>
<td>The following figures are per thousand parts of blood:</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>824.0</td>
</tr>
<tr>
<td>Globules</td>
<td>94.7</td>
</tr>
<tr>
<td>Albumen</td>
<td>68.0</td>
</tr>
<tr>
<td>Fibrin</td>
<td>3.5</td>
</tr>
<tr>
<td>Extractive matters and free salts</td>
<td>8.0</td>
</tr>
<tr>
<td>Fatty matter</td>
<td>1.806</td>
</tr>
<tr>
<td>Serolin</td>
<td>variable</td>
</tr>
<tr>
<td>Phosphorised fat</td>
<td>0.663</td>
</tr>
<tr>
<td>Cholesterin</td>
<td>0.110</td>
</tr>
<tr>
<td>Saponified fat</td>
<td>0.992</td>
</tr>
</tbody>
</table>
1000 parts of calcined blood contained:

- Chloride of sodium———3.5
- Soluble salts———2.4
- Phosphates———0.545
- Iron———0.32

The chief feature Ancell notes is the diminution of the density of the defibrinated blood, due to the decrease of 'red globules'; and also of the iron.

(897)

Andral gives an interesting table which shows the quantitative decrease of the red cells in a number of different diseases:

1000 parts of blood, he says, contain the following:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Parts of Globules</th>
</tr>
</thead>
<tbody>
<tr>
<td>In health</td>
<td>127</td>
</tr>
<tr>
<td>First five months of pregnancy</td>
<td>117</td>
</tr>
<tr>
<td>During last four months of pregnancy</td>
<td>111</td>
</tr>
<tr>
<td>During last three months of pregnancy</td>
<td>108</td>
</tr>
<tr>
<td>In phthisis</td>
<td>102</td>
</tr>
<tr>
<td>In diabetes</td>
<td>88</td>
</tr>
<tr>
<td>In chlorosis</td>
<td>77</td>
</tr>
<tr>
<td>Chlorosis (extreme case)</td>
<td>27</td>
</tr>
<tr>
<td>Cancer of the stomach</td>
<td>49</td>
</tr>
<tr>
<td>Extreme haemorrhage</td>
<td>21</td>
</tr>
</tbody>
</table>

Good tables of the relative proportions of the blood constituents in various conditions have also been given by Gavarret and Simon.

After Andral one of the earliest physicians to classify the anaemias was Bouilland. He divides them into "anaemia, hydraemia and chlorosis". In the first a diminution of the blood volume took place, in the second there was a decrease of the serum and therefore a relative increase in the size of the clot, and finally in chlorosis the serum was unaffected or increased whilst the red cells were diminished. Such a classification, based as it was on physical characters of the blood was the best at that early date.

(897)

About the middle of the century Wilks introduced a new disease he called 'Anaemia lymphatica' or 'Leucocythaemia splenica'. He mentions six cases who showed extreme pallor, enlargement of one or more of the various groups of lymphatic glands, either internal to the body or those situated in the
subcutaneous tissues; and a peculiar morbid condition, with occasional enlargement of the spleen; the last depending upon the deposition of of an opaque, white, lardaceous material, in isolated masses, or diffused throughout the substance of the organ, and resembling bacon-rind. All the cases he quotes proved fatal. Casually he mentions that an excess of white cells occurred. It is obvious that he was here dealing with cases of leukaemia, and it is possible that he was treating cases of Hodgkin's disease, though this seems strange for that physician had described the syndrome of lymphadenoma as early as 1823.

In 1863 Habershon offered the following classification of the anaemias, which was based more on cause than effect: Firstly anaemias due to causes "interfering with the proper formation or renewal of the blood, as diseased glands, mesenteric or lymphatic, etc. Secondly, those due to causes acting "directly upon the blood itself, as the effect of physical agents, mercury, water, alkalis; so also the actual loss of blood in the different forms of haemorrhage: here also we may mention albuminuria, and perhaps ague poison. Thirdly, anaemias arising from "excessive waste, the demand upon the nutritive power of the system being greater than the compensating supply; thus although the blood may be reformed properly that renewal is not sufficient to compensate for the constant loss which takes place from exhaustive discharges." Tuberculosis and Chlorosis he places in the first class. In addition to the above he assumed an idiopathic type of anaemia to exist the aetiology of which he attributed to some disorder of the "nervous supply of the stomach."

Although this is one of the earliest attempts at an 'aetiological' classification it must be recognised that Habershon himself must have found it rather unworkable since we find him still adhering to the older methods of grouping the anaemias and all blood diseases for that matter according to the physical and chemical characters of the blood, and only
uses the above classification as a subsidiary.

It may prove interesting to note what Habershon's list of blood diseases is:

1. Increase or diminution of blood as a whole—plethora, spanaemia.
2. Increase or diminution of red blood corpuscles—polypyranaemia, oligo-pyrenaemia.
3. Increase of colourless corpuscles—leucocythaemia.
4. Increase of fatty molecules—lipoaemia.
5. Increase of fibrin—as in inflammation
6. Decrease of fibrin as in fevers, purpura, scurvy, exanthemata
7. Increase of albumin—as in scrofula, cancer, and morbid growths.
8. Decrease of albumin—as in Bright's disease, cardiac dropy and puerperal fever.
9. Increase of uric acid—uraemia—as in rheumatism, gout and calculi composed of uthates.
10. Increase or diminution of earthy salts—as in rachitis, malacosteon, calculi composed of phosphates.
11. Increase of sugar—glycohaemia—as in diabetes, calculi composed of oxalates.
12. Increase of bile—cholaemia—as in jaundice.
13. Poisons of various kinds—toxihaemia—divided into:
   (a). Animal poisons—such as from putrid pus or ichorhaemia (commonly called pyhaemia); from syphilis, smallpox, scarlatina, measles, erysipelas, glanders, plague, etc.; from bites of venomous animals, etc.
   (b). Vegetable poisons—such as from opium, belladonna, aconite, strychnia, etc., etc.
   (c). Mineral poisons—as from carbonic acid gas, sulphur vapour, mercury, arsenic, etc., etc.

About the same time that Habershon published his paper Vogel and Walshe investigated in a large of anaemic patients the murmurs associated with this condition. These, they state, are of three kinds—cardiac, arterial and venous. The cardiac have a 'bellow sound', are systolic in time and
are heard more at the base than at the apex, where organic murmurs are more wont to occur (Walshe). They state that the diastolic murmurs are really venous in origin.

Vogel points out that the absence of murmurs does not indicate the absence of anaemia.

The arterial murmurs they write are seldom heard. They are "intermittent blowing", sometimes soft, sometimes sharp in sound, synchronous with the pulse, and heard in the larger arteries only. Most frequently after a severe haemorrhage or in chlorosis. Vogel has "heard them during the peroxysms of intermittent fever" and in typhus fever. Alone, they inform us, they mean little.

The venous murmurs are continuous, humming, buzzing and perhaps musical. They are most frequently heard on the right side of the neck at the junction of the external and internal jugular veins. "They may be heard also over the course of the superior longitudinal sinus, and at the maximum intensity over the torcular Herophili (Walshe)" When strong their thrill may be felt. These murmurs they tell us are seldom absent in severe anaemias.

Watson observes the presence of a murmur in chorea and he attributes it to the frequency with which this condition is associated with anaemia.

The whole outlook on the problem of anaemia became changed when Ehrlich introduced his tissue stains (1881). It afforded for the first time a suitable method for the proper study of the morphological characters of the blood cells. The modern conceptions of blood formation may be said to have originated from this discovery. The latter end of the nineteenth century was a period of intense activity in the field of haematology. In another chapter, dealing with the history of the development of the blood cells, we noted that by the end of the century most of the general conceptions had already been formulated. It is almost surprising that a classification of the anaemias was not advancing 'pari passu'
with these ideas.

From the early nineteenth century the anaemias had on various occasions been classified as idiopathic and secondary, but the usual method was to divide them into categories according to the features of the blood—chemical and physical. At the end of the century we find the clinical classification of primary or idiopathic and secondary anaemias assuming greater importance. This was supplemented by a morphological classification—the macrocytic, microcytic and normocytic anaemias. Although attempts have been made from time to time during this century to introduce a classification based on an aetiological basis, nothing really satisfactory has as yet been devised, although the one suggested by Castle and Minot (1936) shows its possibilities and is one of the best of a number of similar attempts. Among haematologists the primary and secondary anaemias, as a means of subdividing the group, no longer obtains, although it is still found among general practitioners of the older school. By improved diagnostic methods and accumulated experimental data and clinical facts the class of primary anaemias has steadily decreased and will probably continue to do so; whilst a few of the former secondary anaemias have now found a place among the primary. It is therefore obvious that such a mode of classification is of little value to the man of science although it may have its applications clinically.
Subdivision of the Anaemias

A. Anaemias due to Haemorrhage or Increased Blood Destruction

1). Haemorrhage:

From earlest times it has been shown that haemorrhage produces pallor, and from the time the word anaemia has been used, loss of blood has been regarded as the most potent cause of this condition.

Zuntz showed that following haemorrhage there is a rapid fall in the blood alkalinity. Bernard and Mering pointed out that the sugar increases correspondingly, being principally derived from the liver (Schenck), while the coagulability is much increased. Herz found the relative volume of the red cells tripled after ten hours and attributed this to the absorption of water.

The effects of haemorrhage on the red blood corpuscles have been demonstrated by Huhnerfauth, Lyon, Otto, Koepppe, Viola and Jona. The regeneration of the blood was investigated by Bierfreund.

The effects of acute blood loss have recently been studied by Neumann, Robertson, Meulengracht and Heath, while the anaemia of chronic haemorrhage has received the attention of Wintrobe, Murphy and Fitzhugh, Heath, Price-Jones and others.

The above workers have pointed out that if the blood loss is sufficiently rapid to produce syncope or even death, it will be found that about a third of the blood has left the body. On the other hand if the haemorrhage is slow and allows for the plasma proteins to be regenerated, little in the way of symptoms may result until the haemoglobin has fallen to 50 per cent of the normal. Castle and Minot describe the signs of deficient blood volume as follows:

"prostration, restlessness, thirst, sweating, rapid shallow breathing; a rapid thready pulse and a low blood and pulse pressure." They add that it is important to recognise that
the signs and symptoms are similar to those of shock and in some instances to those of peritonitis.

It has been shown by these workers that the blood picture is one of increased marrow activity. The blood platelets are numerous, a granular leucocytosis occurs, reaching its maximum in 2 to 5 hours. After 24 to 48 hours the reticulocytes increase to 5-15 per cent. In severe anaemia due to haemorrhage the white cells may reach 35,000 per cubic millimeter and the reticulocytes 50 per cent or more. Murphy and Heath have shown that the mean corpuscular volume is slightly increased due to the fact that the reticulocytes are for the most part larger than the red cells. There is a progressive lowering of the mean corpuscular haemoglobin concentration and of the mean corpuscular volume. In a normal person it has been shown that the red cells reach their full numbers in from 4 to six weeks and the haemoglobin in from 6 to 8 weeks.

Most of the investigators found that large doses of iron were necessary to procure a rapid recovery.

Those investigators who studied chronic haemorrhage found that the blood picture varies somewhat from the above. Castle and Minot state that the "blood picture of chronic blood loss may be summarised by saying that it is an exaggeration of the moderate hypochromic anaemia observed in anaemia due to acute blood loss after the marrow ceases to show evidences of relatively rapid blood regeneration. The haemoglobin is always proportionately more reduced than is the number of red blood cells, giving a lowered colour index. The mean corpuscular volume and haemoglobin concentration may be very markedly reduced. The Price-Jones distribution curve shows a peak indicating a smaller diameter and often a wide 'scatter' of cell diameter." They add that achromia is evident in smears and polychromasia is present "to some extent in relatively large round cells, which can be shown to contain reticulum." Poikilocytosis may be a very evident feature.
Increased Blood Destruction Due To Extrinsic Causes.

Infections

Hunter during the last century was a strong supporter of the view that infections produce anaemia, pernicious anaemia included; and in this last respect he formulated his "intestinal theory".

Much work has of recent years been done in the severe anaemia of puerperal infection with streptococci, staphylococci, Cl. welchii and other bacteria.

The association of malaria and anaemia dates back to early Greece if we can interpret the clinical descriptions of the ancients correctly. The introduction of cinchona in 1640 enabled Morton, Torti, Sydenham and others to separate this disease from other fevers. In their works we find reference to the associated pallor, enlarged spleen and periodic fever. The work of Meckel (1847), Virchow (1848), Laveron (1880), Manson (1894), Ross (1895) and others completely established the aetiology and diagnosis of malaria.

In 1934 Fairley gave a detailed account of the blood changes in the various clinical forms and emphasised that a reticulo-eryte crisis follows the proper control of the clinical course with quinine and allied drugs. The severe blood destruction in Blackwater fever was investigated by Chiron (1932); and other workers have shown that increased platelets and reticulocytes are to be found during attacks.

An anaemia occurring in Oroya fever due to the organism 'Bartonella bacilliformis' was first placed on a firm aetiological basis by the self-sacrifice of Carrion, a medical student who in 1885 fatally inoculated himself. It is believed that this was the disease which almost wiped out Pizarro's army in the sixteenth century. The haemolytic anaemia and leucocytosis it produces were fully investigated by H. Fox, Landa, and Rhoads and Miller.

Chemicals.

Numerous chemicals have been shown to produce a
haemolytic anaemia. The best-known investigators of this phenomenon are Dudley, Bomford, Meyer, Panton, Minot and Hamilton. An unusual form of haemolytic anaemia occurs in Italy from ingesting "fava" beans or even smelling the blossoms (Preti).

3. Anaemias due to Intrinsic Causes of Increased Blood Destruction

Lederer's Anaemia.

This anaemia was first described by Mac Intosh and Cleland (1902) but Lederer popularised it some few years ago. The original investigators showed that it is a haemolytic anaemia of unknown origin and associated with leucocytosis and pyrexia. Recently O'Donoghue and Wits have studied the problem more fully.

Paroxysmal Haemoglobinuria.

In this condition an extravascular haemolysis occurs and is usually associated with syphilis. As long ago as 1794 Stewart recognised this condition. A review of the literature up to 1894 may be found in Chvostek's monograph.

In 1904 Donáth and Landsteiner showed that the haemolysis was due to a haemolysin in the patients' blood.

An excellent review of the subject was given by Mackenzie in 1929.

Chronic Haemolytic Jaundice.

This condition was originally described by Chauffard and Minkowski. They showed that a familial condition exists in which crises of excessive blood destruction occur. Hayem and Widal described an acquired form of the disease. The last assertion has been doubted by Dawson (1931) and others.

Synonyms for this disease are 'chronic acholuric jaundice' and 'haemolytic splenomegaly'. Gänsslen originally put forward the suggestion that the increased fragility of the red cells was due to their sphericity. This peculiarity of the red cells has been examined by many
(941-3) workers

Cases in which the fragility of the red cells were normal have been recorded by Dawson and Günsslen, who therefore pointed out that there is little correlation between the degree of anaemia and the degree of osmotic resistance of the red cells.

Sickle Cell Anaemia.

This condition was originally described by Herrich in 1910 in negroes, and characterised by sporadic attacks of anaemia associated with joint pains, abdominal pain and a predisposition to leg ulceration. The cells are sickle-shaped. Huck (1923) indicated that the condition is transmitted as a dominant Mendelian character and females are more susceptible to it than males. The crescentic shape of the cells was shown by Cooley and Lee to be not necessarily associated with the anaemia, since they found 7.5 per cent of healthy negroes had this condition of their erythrocytes. It has also been reported to be present in the blood of a few Caucasians. Leivy and Schnabel found frequent rarefaction of the bones as evidenced by X-ray examination.

Rich considers this anaemia to be due to a lesion of the spleen. It has however been shown not to be cured by splenectomy.

B. Anaemias due to Decreased Blood Production.

This group of anaemias is characterised by a comparative absence of signs in the peripheral blood of bone marrow response consistent with the state of the anaemia.

(1) Nutritional Deficiency of the Blood Forming Organs.

It was chiefly due to Minot and Murphy's investigation of the action of liver on haemopoietic function that a number of widely different anaemias were placed under this heading.

(a). Macrocytic Anaemias due to deficiency of the Anti-Pernicious Anaemia Principle.
Pernicious Anaemia.

The history of this condition has been discussed in a previous chapter.

Macrocytic Anaemias of the Tropics.

i) Sprue

Vincent Ketelaer first described this condition in 1669 but his account is not as well known as that of William Hillary. Manson and van der Burg, during modern times drew fresh attention to this condition. Its clinical features have been well described by Fairley, Baumgartner and Smith, Manson-Bahr and Ashford, who regard it as a chronic wasting disease peculiar to certain regions of the tropics and subtropics. In many respects it has been found to resemble pernicious anaemia with regard to the gastro-intestinal abnormalities, neural lesions and anaemia found in that condition.

The blood was shown to vary considerably in its haemoglobin content. Few cases show less than 50 per cent of the normal haemoglobin (Ashford), but most of them tend to become progressively worse as was pointed out by Baumgartner and Smith, Krjukoff and others.

A number of workers demonstrated that in this condition the bone marrow changes resemble closely the megaloblastic proliferation of pernicious anaemia. Ashford found achlorhydria present in 39 out of 41 cases.

ii). Tropical Macrocytic Anaemia of Pregnancy.

Balfour and McSwiney both in 1927 and Wills described a macrocytic anaemia common to the lowlands of India and more often found in pregnant women. Wills and Mehta attribute it to a deficiency of animal protein and vitamins A, B and C in their diet.

The effects of treatment with yeast and liver extracts is fully discussed by Wills.
Macrocytic Anaemia of Pellagra.

This condition was first described by Casal (1763) in Spain, under the name of "mal de la rosa". In Italy, Odoardi (1776) called it "Alpine scurvy". According to Stannus the first authentic case in Great Britain was reported by Howden in 1866.

The early descriptions make little mention of the anaemia with which this condition is associated; this is natural to understand for ordinarily it is not marked. The fact that it responds readily to liver extracts led to the opinion that it was closely related to pernicious anaemia. The effects of liver therapy have been investigated by Ruffin and Smith, Spies, Ramsdell and Magnus and others.

More recently pellagra has been shown to occur in areas where the solar rays are intense. Goldberger and his colleagues believe the condition to be due to a deficiency of vitamin B.

Wilson showed that the complete picture of combined sclerosis of the spinal cord, so common in pernicious anaemia, may be demonstrated post-mortem in cases dying from pellagra.

On occasions a "secondary" or microcytic anaemia has been mentioned.

Pernicious Anaemia of Pregnancy.

As early as 1842 Channing mentioned a severe form of anaemia in pregnancy. Brady (1924) indicated the rareness with which the condition occurred, since on reviewing the literature of America and Europe over a period of 38 years he was able to find records of only 68 cases. Esch (1921) obtained reports of 23 cases in Germany during the 20 years previous to his investigation; Beckmann (1921) found only six cases in 80,000 labours; Evans (1929) investigated 4,083 labours at Queen Charlotte's Hospital and brought not a single case to light; in 1925 Larrabee mentions 17 cases in America, while Smith in the same year discusses 8 cases.
From the haematological aspect the condition has been found to be almost indistinguishable from true pernicious anaemia and its aetiology has followed the same rough road. The "haemo-toxigenic" theory, formerly adhered to, has now been discarded. Whitby and Britton point out that haemolysis is not a feature of the disease and advocate the discontinuance of the term "haemolytic anaemia of pregnancy".

A point that has received much attention is the question of recurrence in future pregnancies. Larrabee, Allan, Peterson, Field and Morgan hold that future pregnancies do not cause a recurrence of the condition, whereas in the other camp are the majority of observers. Whitby, Vermelin and (981) Vigneul, Gallupe and O'Hara, Reist and others contend that recurrences do occur and become progressively more severe with each succeeding pregnancy.

**Macrocytic Anaemias due to Pathological Conditions of the Gastrointestinal Tract.**

It has been observed at various times that an anaemia of the pernicious type may arise following a variety of lesions of the alimentary tract. They have been classified under the heading of anaemias due to hypofunction of the bone marrow, and respond to liver therapy.

1). **Diphyllobothrium latum Infestation.**

Hoffman, in 1885, was the first to draw special attention to the association between infestation with this parasite and an anaemia of the pernicious type. His observations were confirmed by Bodkin, Reyher and Runeberg. These workers showed that on expulsion of the worms the anaemia disappeared. The last two workers and Müller claimed that the morphology of the blood elements in severe cases is identical with that of pernicious anaemia.

Active work on this disease was also carried out by (988) (989) (990) Schaumann, Wiltschur and Askanazy.
Shapiro and Dehio finding some dead parasites in their cases concluded that only decomposing worms produce the specific haemolytic toxin responsible for the anaemia.

Wiltschur thought that alterations of a chemical nature in the eggs of the worms was the cause of the blood poisoning. Birkeland has recently published a survey of the literature and pointed out that although the disease is widely associated with man around the Baltic area it is but rarely associated with anaemia. Early observations of this fact were taken by Israel, Ehrlich and Renvers.

ii). Gastrectomy. (997)

In 1929 Finney and Rienhoff showed that of 9 complete gastrectomies two later developed pernicious anaemia. Since then this observation has been confirmed by numerous men. Similar records of a macrocytic anaemia have been recorded after partial gastrectomy.

iii). Other Gastrointestinal Lesions. (1004)

Strauss, Meyer and Bloom observed that polyps; and Du Bois that chronic pyloric stenosis may cause a typical macrocytic anaemia. Similar observations have been made in cases of extensive carcinoma of the stomach.

Other pathological conditions of the stomach and intestinal tract which have been shown to produce pernicious anaemia are gastroenterostomy, gastro-colic and other short-circuiting fistulae. Faber, Hurst, Meulengracht, Seyderhelm and others observed that intestinal stricture may result in a blood picture typical of pernicious anaemia. Keefer and his associates have observed in China the occurrence of this condition in cases of amoebiasis.

iv). Idiopathic Steatorrhoea. (1015)

In 1888 Samuel Gee described a condition he termed
"the coeliac affection", in which there occurred pale, bulky and offensive stools associated with digestive disorders and which was frequently associated with anaemia.

Bennett, Hunter and Vaughan reviewed the literature up to 1832 and found mention of 19 cases.

The blood picture has been shown to vary. The last-mentioned observers saw a macrocytic anaemia in two of their own series of 15 cases, whereas, two were erythroblastic and five hypochromic. Theyesen records hypochromic anaemia in 20 of 29 cases.

(b). Hypochromic Anaemias due to Deficiency of Iron and other Substances producing Haemoglobin.

Under this heading are included all the so-called "secondary anaemias", a term rapidly dying out.

1). Hypochromic Anaemia of Infancy and Childhood.

Various theories to explain this anaemia have been put forward: 1) Functional inadequacy or weakness of the blood-forming organs, especially in premature infants.

2) Certain pathological factors e.g. infections and dietetic errors.

3) Constitutional anomalies or hereditary predisposition.

4) Iron deficiency at this age.

Most investigators agree that it is due rather to a combination of factors than to any single cause.

The historical survery at present is on the so-called "simple anaemia" the primary or idiopathic anaemia of infants will be dealt with later.

Simple anaemia, variously called under different heads by different authors e.g. "nutritional anaemia", "alimentary anaemia of infective origin", "alimentary anaemia", "cows' milk anaemia", "chlorotic anaemia of infants", "simple anaemia of infancy", "oligosideremia", "anaemia of premature infants", etc., all show a similar blood picture (Baar and
stransky (1928)), and may be described as chlorotic in type, namely a reduced haemoglobin percentage with often no other change.

Some believe that this disease and the anaemia pseudo-
leukaemia infantum, with its profound blood changes, to be
grades of the same condition. (lichtenstein (1917), evans
(1039) and haff (1922)).

interest in infantile anaemia dates chiefly from the time
of Bunge's experiments. Between 1889 and 1892 he published
three papers on the subject and so drew the attention of the
medical profession.

He showed that the proportion of iron in dogs' milk
was very small as compared with that in the blood and tissues
of the pup. The experiment was repeated on rabbits by Abder-
halden (1898). Bunge (1892) also showed that iron pro-
gressively decreases from birth (in young animals) till the
animal takes mixed food.

He compared this with infant feeding and stated that
infants fed too long on milk might become anaemic when the
liver store became exhausted.

He showed that the liver of a newborn animal contains
five or six times more iron than the adult liver weight
for weight. (1043)

Hugounenq (1899) pointed out that in human foetuses
two-thirds of the iron present in the body at full term
was laid down during the last three months of intra-uterine
life. Thus a premature child has relatively much less iron
per kilo body weight than a full term child.

This whole problem was investigated experimentally
in the laboratory, by a large number of workers. Haussermann
(1897) produced anaemia in young laboratory animals by
feeding them on milk alone or milk and rice after the lactation
period was over. Others like Schmidt (1912), Haff (1922),
scott (1923), Mitchell and Schmidt (1926) and Mitchell and
Vaughan (1927) found that in order to produce anaemia in
this way in rats and mice, it was necessary to deprive the animals of iron for two or three generations.

Most of these workers investigated the effects of treatment in such animals, and found iron and green food beneficial. Mitchell and Schmidt, and Mitchell and Vaughan found a good response to certain iron salts as ferric chloride and ferric ammonium citrate, and a poor response to others such as ferric oxide, ferric carbonate, ferrous lactate, and reduced iron, and they considered that the degree of solubility had a definite bearing on the curative value of the individual salts. Elvehjem and Hart (1927) discovered that insoluble salts might not be assimilated at all by young chicks, and certain workers assumed that inorganic iron was not taken into the blood stream at all (Williamson and Ets (1925).

Whitehead and Barlow (1929)) by laboratory animals. Their results have been disputed on the grounds that their experiments were fallacious and not properly controlled.

**Chlorotic Anaemia of Infancy and the French School**

In 1771 Sauvage reported a case of 'chlorosis' in an infant and in 1864 three cases were quoted by Nonat.

At the beginning of the century after the work of Bunge the French studied this type of anaemia. They called it "chlorotic anaemia of infancy". According to Rist and Guillemet (1906) at a meeting of the Société Médicale des Hôpitaux de Paris, Hallé and Jolly were the first to describe the condition (1903) as a clinical entity.

For this condition Marfan (1906), Leemhardt (1906) and Texier (1911) advocated iron treatment, although they believed that there was a more fundamental cause of the low haemoglobin content of the blood than the lack of iron e.g. sudden change in diet, intoxications and disturbances of the digestive functions.
With regard to iron retention in the infant Blauberg in 1900 demonstrated that this varied with the diet and was highest when human milk was given, and with cows' milk only one-fifth of this. Krasnogarski (1906) comparing human and goat's milk confirmed this.

Cantley (1910) considered the cause of "simple infantile anaemia" to be due to primary deficiency of iron in the foetal tissues, and he dismissed the toxaemia theory as a cause of the anaemia.

In 1912 Czerny read his paper before the Association Internationale de Pédiatre, in Paris. He gave a new twist to the subject, for he said that before his so-called "alimentary anaemia" could develop one must presuppose a "constitutional anomaly". He could not believe in the iron-deficiency theory as the cause for the anaemia, but stated that the cows'-milk fat was the cause, which by producing fatty stools depleted the body of bases and that the resultant acidosis produced the anaemia. This view was supported by many, but has now been generally abandoned.

Kleinschmidt (1916), who gave an excellent review of the literature up to his time, agreed with Czerny but with certain modifications. He considered that for the anaemia to develop the children should come from defective stock, and he attributed the anaemia to a toxic principle in the milk, associated with the congenital abnormalities of such weakly infants and particularly the premature. Like with Czerny, iron deficiency played no part in his aetiology.

Bass, Denzer and Herman (1924) were unable to confirm his views.

The study of anaemia in premature infants really dates from the observations of Gundobin in 1893, who reported the condition in a number of cases which came under his observation. Others who did important work in this field were Kunckel (1916) and later Lichtenstein (1917) and Landé (1918). Lichtenstein examined 90 cases and found that during the
first three months of life the red blood corpuscles dropped to three millions and the haemoglobin to 40 per cent, and at 4-5 months the red cells increased without the haemoglobin rising. The anaemia during the first three months he attributed to insufficiency of the haemopoietic system, and the later 'oligochromia' to deficiency of iron.

With regard to treatment and prophylaxis of this condition iron in some form has usually been recommended. J.H. Hess (1922) advises the use of arsenic as well as iron. Another strong supporter of iron in the treatment is Webb Hill (1924). Of the opposite opinion is Lehndorff (1923) who definitely states that iron serves no useful purpose and that treatment should be directed against the primary cause of the disease. Baar and Stransky (1928) steer a middle course.

ii) Chlorosis.

This condition has been considered in a former chapter.

iii). "Idiopathic" Hypochromic Anaemia.

(Simple achlorhydric anaemia, cryptogenic achylic chloranaemia, Witt's anaemia, chronic microcytic anaemia, idiopathic hypochromaemia, chronic chlorosis, erythronemoblastic anaemia).

This condition was originally described by Faber who pointed out that it is probably due to a deficiency of the normal gastric acidity—an almost constant feature of the disease. (1071-2)

Wintrobe and Beebe have recently reviewed the voluminous literature on the subject and point out what work has been done by Davies, Kaznelson, Heath, Witts, Meulengracht and others.

A hereditary predisposition to this disease has been suggested by Heath and other workers.
Most of the writers have pointed out the high incidence with which this disease occurs in females. Certain cases occurring in males have been recorded by Meulengracht and Witts.


The anaemia occurring during pregnancy has been observed since earliest times. Hippocrates notes the condition as a pale and greenish colour of the skin in women who are pregnant. Among Channing's descriptions, 1842, of the anaemias of the puerperal state may also be found clinical pictures which appear to be this condition, and so too in most of the medical works of the nineteenth century.

Recently the matter has been brought up to date in the light of modern knowledge, by Strauss and Castle.


The history of this disease may well have been included in the list of the microcytic anaemias due to the same pathological conditions.

vi). Hookworm Anaemia.

From earliest times this condition has probably been recognised. It has been assumed by Joachim that the $\text{XXX}$ and the UNA disease mentioned in the Ebers' Papyrus indicates the condition of hookworm infestation or 'chlorosis Aegyptiaca'.

The real history of the disease commences with Dubini (1838), who discovered the worm. It was, however, not until 1854 that Griesinger showed it to be the specific agent in the so-called 'Egyptian chlorosis'. Wucherer in Brazil and Perroncito in Italy later identified it as the cause of many forms of tropical anaemia. The St. Gotthard epidemic among tunnel workers finally called general attention to the condition, chiefly through the writings of Sonderegger. The work
of Grassi and Cinisella is also worthy of mentioning. Ancylostomiasis was first mentioned in Germany by Feisse, who observed the condition among brickmakers working with wet, and clayey soil, and by Menche in an epidemic at Cologne.

The pathological action of the worm and the changes it produces in the blood were first investigated, with any degree of accuracy, by Leichtenstern, Bohland, Sandwith, Zappert, Ashford, Müller, Rieder and Bucklers.

The blood picture found is that of hypochromic anaemia, and the condition readily responds to treatment with iron.

(c) Anaemia due to Deficiency of Vitamin C.

Scurvy would make the subject of an interesting essay. The number of references to this disease in medical literature are legend. It was noted in Ancient Greece, Egypt, China and India, and there is no writer of medicine of any repute during the Dark and Middle Ages who does not mention the condition. Since Britain became a maritime power the history of its sailors is the history of scurvy.

Various causes for this disease have been put forward. From a very early date it has been associated with poverty and a deficiency of the diet. During the last century Garrod, Liebig and Hirsch attributed it essentially to a deficiency of potassium in the blood. Ralfe and Cantani held that a deficiency of salts of vegetable organic acids and a corresponding diminution in the alkalinity of the blood is the important factor. Wright maintained that it was a form of acid intoxication due to a diet containing excess of mineral acids. This he concluded from a study of seven cases that occurred in the beleaguered garrison of Ladysmith. The experiments of Murri, Petrone and Rosenell suggested a bacterial aetiology. This was disproved by Babes, Wierschky and others.
Most of the early workers like Uskow, Hayem, Albertoni and Becquerel demonstrated a reduction of the number of red cells in scurvy, and Litten saw many megalocytes and shrunken microcytes in severe cases. (1103) (1104)

Within recent times Mettier, Minot and Townsend have reviewed the literature and reported nine cases.

There is a distinct paucity of accounts on the bone marrow pathology in this condition. Schmorl, Maxwell, and Vedder may be mentioned among the few men who have written on this subject.

The blood picture is frequently of the hypochromic type, though normocytic and macrocytic anaemia have been mentioned.

The observations of Mettier, Minot and Townsend have made it reasonably clear that a deficiency of vitamin C is the causative factor of this disease with its associated anaemia.

In 1919 Aschoff and Kock first put forward the view that scurvy has a primary deficiency due to lack of cement substance, and later Wolbach demonstrated that deposition of collagen in the organisation of the blood clots in the state of absolute scorbutus was referable to the administration of vitamin C.

(d). Anaemia due to Deficiency of Thyroid Secretion.

Myxoedema has long been associated with anaemia. (1110)

Kunde, Grew and Burns showed in 1931 that the operation of thyroidectomy on experimental animals produced a macrocytic anaemia with a colour index greater than one, and associated with a degree of bone marrow hyperplasia. (1111-2)

Lehrman and Means showed that in some 60 per cent of patients suffering from myxoedema the red blood corpuscles were less than 4,000,000. An important finding was that 50 per cent of cases gave gastric anacidity. Associated (1113) (1114) (1115) with this fact is that Lissen, Davis and Means et al. have reported the development of pernicious anaemia in some
patients with hypothyroidism.

A low colour index anaemia in myxoedema was described (1116) by Lehrmaan and Means, and Mc Cullach and Dunlap.

II Anaemias due to Toxins and Poisons.

A number of chemical poisons and toxins have been shown to interfere with normal haemopoiesis. It has further been shown that this may be brought about either by absorption from outside the body or produced through perversions of its metabolism.

Of the external poisons benzol (Hamilton), gold (1118), compounds (Dameshek), arsphenamine (Mac Carthy and Wilson, (1120) Madison and Squier, Kracke and Parker), lead, mercury, phosphorus, carbon monoxide, methane and mustard gas have all been reported as causative agents in anaemia. Generally it has been found that there is a leucopenia and thrombopenia in addition to the alterations in the red cells.

The anaemias due to chronic infections are perhaps the commonest type of "secondary anaemia" associated with microcytic and sometimes hypochromic blood changes. For other references on this subject the excellent monograph of (1123) Blackfan, Baty and Diamond and the articles by Douglas, (1125) Kugelmass and Lutembacher should be consulted.

That chronic nephritis is associated with anaemia was observed by Bright as early as 1836. During the last century and early twentieth century Leichtenstern, Sorensen, (1129) Grawitz, Sadler and Cabot found that the so-called "chronic exudative or parenchymatous nephritis" is associated with a moderate "chlorotic anaemia". The general opinion held was that the continual draining of the body of albumen produced (1131) the blood changes. Peiper, Bostock, Stintzing and a number of other workers (1134, 1135, 1136, etc) examined the blood chemically but could arrive at no definite conclusions with regard to aetiology. The problem of uraemia and the changes produced in
the blood cells was investigated particularly by Spiegelberg, Hoppe-Seyler, Bartels, Landois, Schottin, Feltz and Ritter, Limbeck, Bouchard and Pumpf; they, however, failed to demonstrate the true nature of this intoxication. Recently Parson and Ekola Strolberg have given an excellent discussion of the problem and they conclude that anaemia is almost a constant feature of chronic nitrogen retention regardless of the kidney lesions.

III. Anaemia from Physical Injury of the Blood.

(1145) Heinke has shown that degeneration of the lymphoid tissue and a fall of the lymphocyte count occurs after exposure to large doses of radiation. Warthin and others observed that this change is later followed by bone marrow changes affecting the myeloid cells.

Recently Rolleston has reviewed the subject and he pointed out that many of the early workers with the roentgen-ray died of anaemia, probably aplastic in nature.

The effects of absorbed radio-active material introduced orally and parenterally is a problem only of recent years. Hartland, Flinn and Castle and his co-workers have shown the serious and fatal effects of radium poisoning in industry. They state that the blood picture corresponds with that of inactive bone marrow, where a severe degree of megalocytic anaemia and elevated colour index occurs.

IV. Mechanical Interference with the Blood-Forming Organs.

(Myelophthisis anaemias)

Leukaemias.

The earliest records of probable cases of leukaemia are those of Bichat (1801), Andral (1823), Hodgkin (1832), Donne (1830). At that time the general view was that it
was a suppurative "haematitis" (Diorry). Donne appears to be the first to attribute it to a failure of transformation (1151) of the leucocytes into red cells. In 1841 Craigie showed that suppurative lesions were by no means essential to the production of the disease and concluded that the purulent matter arose from the spleen where the histological structure "does not favour the gathering of pus in abscesses". In the same year Bennett described a case and demonstrated the appearance of the leucocytes as identical with pus cells and therefore due to some zymotic principle in the blood. A few weeks later Virchow described another case complicated with furunculosis and termed the condition "weisses blut" (white blood) or leukaemia. He held the view that it is due to lesions of the haemopoietic organs, and distinguished it from pyaemia.

An illuminating monograph on this disease was published (1154) by Bennett in 1851, wherein he describes the clinical and pathological features of 37 cases, both macroscopical and microscopical. He alters the term leukaemia to leucocythaemia.

Virchow (1853) divided the condition into two classes, the lymphatic and the splenic. This he based on the observation that a case which came under his care in 1847 presented a small spleen and greatly enlarged lymph glands, whereas subsequent cases showed the reverse state of affairs.

Leucocytosis occurring during life was first demonstrated (1155) by Fuller (1846); this was confirmed by Vogel five years later. (1156) Neumann's work in 1869 led him to recognise the "myelocytic" variety of the disease. His description of the bone marrow (1159) changes is the first worthy of mentioning. Waldeyer (1871) followed up this work. Ponfick made the important observation that in certain cases the bone marrow was yellow and fatty whereas in others it was pink or red. (1160)

Bottger (1858) attributed the enlargement of the liver to collections of cells derived from the blood. In the previous year Friedrich had described cases showing metastatic
tumours of the pleura, and hyperplasia of the gastrointestinal lymphatic patches.

(1162)

Schultz and Erb (1865) were the first to classify the leucocytes according to their morphology, and showed that the new cells of leukaemic blood are not all of the same varieties found in normal blood. Much doubt, however, existed on this point. Mosler settled this doubt by puncturing the sternum and securing from the marrow large numbers of identical cells to those seen in the circulation. It was therefore concluded that these cells must be characteristic of the myelogenous type of the disease.

(1163)

Neumann (1878) suggested that some cases are purely myelogenous in origin and that the marrow is always involved, whereas splenic or lymphal disease could not alone cause the condition. These views were later supported by Walz,

(1166) (1167) (1168)
Pappenheim, Hirschlaff and Kormezi.

Ehrlich's staining methods (1879-1880) greatly advanced the study of this condition and aided in a better diagnosis of early cases. Litten described the first pure case of myelocytic leukaemia.

(1169) (1170)

Jaderholm and Schwarze had noted an eosinophilia and this observation Ehrlich took to be pathognomonic of the condition. He later discarded this view due to the work of Müller, Cornil, Rieder, Troje, Limbeck and others, and returned to the myelocyte of Mosler. Cornil described a large myelocyte with a pale eccentric nucleus, and later this became a diagnostic feature of the disease mainly due to the support of Eberth, Eisenlohr, Hayem and particularly Müller.

Absence of amoeboid movement of the myelocytes, or their reduced activity in leukaemia was noted by Biesiadecki, Löwit and others. Mayet stated that this loss of amoeboid movement is associated with a loss of reproductive capacity.

Erb, Bottger and Klebs demonstrated the nucleated red cells in the blood of leukaemic cadavers shortly after this cell had been described for the first time in adult human blood.
The Megaloblasts were first observed in leukaemia by Utheman (1175) and Troje, whereas Arnold (1884), Hayem (1889) and Müller (1889) first demonstrated mitotic figures in the blood of leukaemics.

In 1857 Friedrich recorded the first description of acute leukaemia. The case lasted six weeks. By 1889 Ebstein had managed to collect sixteen records of cases with histories varying from 5 to 20 weeks.

The chemistry of leukaemic blood was originally investigated by Robertson and Parkes in 1850 and shortly afterwards by Strecker. The work was extended by Becquerel, Robin and Scherer and subsequently by numerous other workers.

By 1904 the leukaemias had become subdivided into myelocythaemia, in which there was excess of leucocytes (150,000 - 1,000,000) with an eosinophilia of 3,000 - 100,000; chronic lymphocythaemia—-excess of leucocytes (150,000 - 1,000,000) with 35 - 95 per cent lymphocytes; pseudoleukaemia (Hodgkin's disease), Chronic splenic anaemia with a red cell count of 3,000,000 to 4,000,000, moderate poikilocytosis, low colour index, diminished leucocytes with a relative lymphocytosis and scanty mast cells. The spleen is enlarged but not the lymph glands. This disease excluded v. Jaksch's anaemia, chronic splenitis of the type of Gaucher (epitheliome primitive), cirrhosis of the liver and all infective splenomegalies, but was taken to represent a condition somewhere between the splenomegaly of the marasmic infant and Banti's disease.

The so-called pseudoleukaemia was first recognised by Craigie in 1828 when he called attention to the difference between certain firm tumours of lymph nodes and the scrofulous and cancerous enlargements. In 1832 Hodgkin described several cases in Guy's Hospital, two of which we now recognise belong to the syndrome bearing his name.

The frequent affection of the spleen was noted by Wilks, Woillez, Griesinger, Müller, and Strümpell. Griesinger
termed the condition "splenic anaemia".

Bonfils in France in 1865 described the condition under "cachexie sans leukemia", whereas Trousseau designated it "adenia". French writers from Trousseau to Gilbert are found to employ the term "lymphadenie aleukenique".

The first full description of the disease from all aspects was given by Murchison and Sanderson in 1870.

The so-called dermal type of Hodgkin's disease has been described by many writers including Kaposi, Hochsinger, Biesiadecki and Joseph, but the first description appears to be by Gillot, of France.

The condition has of recent years been investigated by Bunting, Medlar, Steiger, Krumbaar and others.

Metastatic carcinoma of the bone marrow may produce anaemia and unless the source of the malignant growth is known it goes under the name of carcinomatosis.

Other conditions which may produce anaemia are *myeloma* and *plasmoma* where any of the leucocytes may assume malignancy and remain as single or multiple tumours (lymphoma), invade the tissues (lymphosarcoma), or appear in the circulating blood (lymphatic leukaemia).

Further reference to this subject may be found in the works of Vaughan and Turnbull, Jackson, Muller and McNaughton, etc.

**Gaucher's Disease**

Gaucher first described this condition in 1882 and considered it a primary endothelioma. Its aetiology at present is unknown. It has been shown to be almost peculiar to Jews and Anderson recently recorded the history of a family where seven sisters were affected as well as the maternal grandmother and two sisters, which suggests that a hereditary form of
the disease may exist.

Gaucher originally described certain cellular changes in the spleen, liver, lymph glands and bone marrow; these changes have since become known as "Gaucher cells". He in this condition he observed an early leucopenia and a diminution of the myeloid cells. The red cells he found were normal.

**Niemann-Pick's Disease.**

The condition was first recognised by Niemann in 1914, but it was not until Pick added his contribution that it became recognised as a distinct entity. He describes the blood changes as follows: "The red blood cells are moderately increased. Occasionally there is a leucocytosis in the late stages and sometimes a leucopenia. The presence of large vacuoles in many lymphocytes and polymorphonuclear leucocytes is remarkable. The number of blood platelets is normal. The blood cholesterol may be normal or greatly elevated."

**Osteosclerosis.** (Marble-Bone Disease)

Albers-Schonberg (1904) described a condition in which the marrow cavity is obliterated by hyperplasia of cancellous tissue.

Various synonyms for this condition have been used such as osteopetrosis, osteofibrosis and diffuse osteosclerosis. Stephens and Bredek in 1932 reported 24 cases of this disease and found one-third of them had blood changes resembling myeloid leukaemia.

Ellis (1934) suggested that the aetiology was in some way associated with the parathyroid.

**Myelosclerosis.**

(Osteosclerotic anaemia, osteopathia condensans disseminata)

This is a rare condition recently brought to the notice of the medical profession. It has been shown that in this
condition there is an increase of fibrous or bony tissue, and that the disease occurs in adults.

Both the conditions, osteosclerosis and myelosclerosis, produce an anaemia which is leuco-erythroblastic in type and similar to that found with carcinomatous metastatic deposits.

V. Idiopathic Disturbances of the Blood-Forming Organs.

Congenital Anaemias of Infants.

i) Anaemia of the premature infant

This condition was referred to in a previous section. (1190, 1191, 1192).

ii) Erythroblastosis fetalis

Recently a number of workers have drawn attention to a group of conditions in which severe anaemia is observed in infants and characterised by the production of extra-medullary red cells, which are nucleated and found in large numbers in the circulating blood. Because gross damage is frequently done to the erythron in these anaemias Parsons, Hawkesley (1190) and Gittins named them "Erythronoclastic". (1193)

The subject has been fully reviewed by Brannan (1927).

The aetiology has not been settled. In the British School Parsons, Hawkesley, Gittins and Lightwood hold that a primary haemolytic agent is the cause and that the blood changes are secondary and compensatory. The American School led by Clifford and Herig, Diamond, Blackfan and Batty, believe that the primary fault lies with the red cells. (1190) Parsons, Hawkesley and Gittins have classified "haemolytic" or "erythronoclastic" anaemias of infancy and childhood as follows:

1. Erythroblastic Anaemias in the Foetus.
   a. With oedemas----hydrops foetalis.
   b. Without oedema.
2. Erythroblastic Anaemia in the New-Born.
   a. With anaemia and jaundice---Icterus gravis neonatorum.
   b. With anaemia but no jaundice---Anaemia haemolytica neonatorum.

3. Haemolytic Anaemias of Infancy and Childhood.
   a. Acute haemolytic anaemia---type: Lederer.
   b. Subacute and chronic haemolytic anaemia---type: von Jaksch.
   c. Acholuric jaundice.
   d. Sickle cell anaemia.

4. Erythroblastaemia of Childhood.
   Type: Cooley.

With the exception of von Jaksch's and Cooley's anaemias the other types have been mentioned under II (b).

Cooley's Anaemia.

Cooley (1927) and his confederates described a condition during early life which has certain features in common with von Jaksch syndrome. In America there is a tendency to use the term Cooley's anaemia synonymously with that of the von Jaksch's syndrome; in this country, however, the latter term is reserved for that condition which is characterised by a chronic haemolytic anaemia of infancy and childhood.

Cooley's anaemia is found almost exclusively in the Mediterranean peoples but occurs in them wherever they may travel. Cases have been recorded by Carran and Etcheverry, Capper, Koch and Shapiro, Whipple and Bradford, Moncrieff and Whitby and others.

The blood changes show a moderately severe anaemia. The red cells are reduced to 4,000,000 or 2,000,000 and the haemoglobin is 30-60 per cent (Haldane) of the normal. Large numbers of normoblasts are found, true megaloblasts are absent, but erythroblasts may number more than 10 per 100 leucocytes (Kato and Downey). The majority of workers...
have also demonstrated a well-marked anisocytosis and poikilocytosis.

von Jaksch's Anaemia.

**Anaemia infantum pseudoleukaemia**

In 1889-90 v. Jaksch described a form of infantile anaemia which clinically resembles leukaemia, but failing at autopsy to show the visceral lesions of that disease.

Shortly after v. Jaksch's first reference to this condition Hayem described a case in whose blood he found a number of nucleated red cells showing many mitotic figures, and an eosinophilia. Luzet's case did not show many such red cells but the number of eosinophils were increased.

By 1892 Monti and Berggrun were able to collect 16 cases, not including those of Hausse and Loos, and added four of their own.

As early as 1880 Cardarelli believed such cases to have an infectious origin, a view which was supported by Somma and Fede.

Monti and Berggrun found rickets in 16 of their 20 cases. Fischl, on the other hand associated the condition with syphilis, chronic intestinal catarrh and chronic tuberculosis. Löwit reported a case in which he was able to demonstrate the "hemamoeba leukaemiae magna", whatever that may have represented.

In 1904 Hutchinson gave an excellent description of the blood picture.

Much confusion arose concerning this condition due to the fact that various workers used the term to include a number of conditions that bore little relation to the one v. Jaksch originally described. At present this term is not used in a collective sense. Although v. Jaksch originally described what he took to be a clinical entity, his description might readily include the anaemias resulting from rickets,
congenital syphilis, infection, malnutrition, deficiency of iron or even the initial stages of leukaemia. To indicate the modern usage of the term Whitby and Britton say: "To the British pediatrician the term conveys the clinical picture of a well-nourished, pale, waxy-looking child between the ages of six months and three years exhibiting splenic and hepatic enlargement, severe hypochromic anaemia and often oedema and petichial haemorrhages. Large abdominal veins may be present on a prominent abdomen. The lymph glands are not usually enlarged. There is reticulocytosis, often erythroblastaemia, anisocytosis, polychromasia, poikilocytosis, and, usually leucocytosis with a fair proportion of primitive cells."

Aplastic Anaemia.

The conception of the pathology of the aplastic anaemias has in part been emphasised by by Lescher and Hubble. On the basis of their descriptions Whitby and Britton have drawn up the following classification for the aplastic anaemias:

A. Aplasia of Erythroblastic Tissue:

(1) Pure red cell anaemia-----

This represents a true aplasia of erythroblastic tissue only; the leucoblastic and megakaryocytic divisions are unaffected, but no red cell precursors are produced. As a separate entity it is rare enough to be a curiosity. Four cases are recorded in medical literature. (Kaznelson (1922), Baar (1928), Lupu and Nicolau (1931), and Mills (1931)).

(2) Aplastic anaemias from maturation defects.

The dyshaemopoiesis of pernicious anaemia and other deficiency anaemias may terminate as an aplastic condition if the maturation factor is never supplied.

B. Aplasia of Leucoblastic Tissue.

(1) Aganulocytic angina (aplastic type)-----
The most fatal types of this disease are characterised by a bone marrow showing no evidence of leucoblastic activity. Such cases appear not to respond to nucleotide therapy. Nucleotide is more a chemiotactic stimulus than a maturation factor, but some evidence of maturation action is provided by Doan's investigations on rabbits, in which animals the substance produced definite myeloid hyperplasia.

(2) Agranulocytic angina (maturation type)-----

In one type of the disease, despite the lack of granulocytes in the blood, there has been found a marked myeloblastic reaction of the marrow, the tissue containing also a few myelocytes. Such cases have responded to nucleotide therapy more readily than the true aplastic type and probably represent a disease due to defect of leucocytic maturation factors.

C. Aplasia of Thrombocytoblasts.

(1) Essential thrombocytopenia (aplastic type)------

In severe cases of this disease the bone marrow shows no megakaryocytes and the peripheral blood contains no platelets. This type is usually acute and is probably the form in which there is no rise in platelets after splenectomy;

(2) Essential thrombocytopenia (maturation type)-----

The bone marrow contains numerous megakaryocytes yet the peripheral circulation has very few platelets. Minot (1917) and Askanazy (1930) have recorded examples. In this type splenectomy is probably beneficial by removing a factor which inhibits platelet maturation.

D. Combinations.

In the complete form of aplastic anaemia there is aplasia or hypoplasia of all three elements of the marrow. The condition may be produced by exhaustion of a congenitally weak marrow, marked sepsis, by toxins, or by irradiation. It may also be the terminal phase of an anaemia due to maturation deficiencies. Combinations where but
two essential tissues are aplastic come readily to mind, such as the platelet deficiency in pernicious anaemia or the minor grades of benzol poisoning.

Aplastic anaemia was first mentioned specifically by Frank as "aleukia haemorrhagica" and characterised by a severe anaemia, leucopenia and thrombocytopenia; due to aplasia or hypoplasia of the bone marrow. The original vague description by Ehrlich in 1888 of idiopathic aplastic anaemia indicated a condition of unknown origin, rapidly fatal, occurring mostly in young adults and characterised by high fever, bleeding gums, ulceration of the mucous membrane, and later purpuric haemorrhages into various organs.

(1216)

For aiding diagnosis Benda in 1930 devised an adrenalin test, which indicates the reaction of bone marrow function to the drug. After injection of the substance he found that in aplastic conditions only the monocytes increased and no young granular cells were found.

The aleukia haemorrhagica of Frank has now been subdivided into 1) Idiopathic aplastic anaemia (the same as Ehrlich's) 2) Symptomatic aplastic anaemia produced by certain poisons like benzol, arsenic, gold, etc. 3) Pure red cell aplastic anaemia. 4) Agranulocytic angina, originally described by Schultz (1922) as a necrotising throat infection with fever, mostly occurring in elderly females and producing slight jaundice and rapid exhaustion and soon followed by death. 5) Secondary agranulocytic angina due to certain poisons, severe intoxications and infections. A review of this subject has been given by Kastin and Roberts and Kracke.

Macrocytic Anaemia of Liver Disease.

(1226)

Babonniex and Tixier in 1913 drew attention to a case of severe macrocytic anaemia in a patient with cirrhosis of
of the liver and which was at first taken to be a pernicious anaemia. From that time several cases have been described, but no real advance was made in the understanding of the condition until recently when Wintrobe and Schumacher, Van Duyn, Goldhamer and Wright studied the problem in its relation to pernicious anaemia. They arrived at the conclusion that the anaemia was in some way due to a slowing down of red cell production without the haemoglobin formation being affected.

Banti's Syndrome. (Splenic anaemia)

Although Gressinger had used the term "splenic anaemia" in 1866 there was much confusion in the correct usage of the word until Banti in 1886 made a detailed study of this condition. In 1898 in a paper titled "Splenomegalie mit Lebercirrhose" he describes this disease in three stages: first there is splenomegaly with anaemia of the microcytic type, leucopenia and slight thrombopenia, haematemesis and occasionally cirrhosis of the liver with jaundice and ascites. The spleen he says shows a characteristic "fibro-adenie" and the liver an "interlobular cirrhosis like the alcoholic". The latter change he regarded as secondary. The occurrence of old phlebitis of the portal system Banti regarded as the main feature of the disease. His views on aetiology were vague. In 1900 and 1902 Osler published valuable papers on the subject. He regarded the disease to be "an intoxication of unknown nature characterised by great chronicity, primary progressive enlargement of the spleen, which cannot be corrected with any known cause, anaemia of secondary type with leucopenia, a marked tendency to haemorrhage, particularly from the stomach and in many cases, a terminal state with cirrhosis of the liver and jaundice." Castle and Minot suggest, in the light of present knowledge, that this description is suggestive of no clinical entity unless it be portal cirrhosis. They make a further statement that the
problem of Banti's disease is as real today as it was in 1898, since it has not been shown that the spleen is concerned in the primary aetiological rôle of this disease nor has any structure been detected in the spleen which is not found elsewhere in the body.

With regard to aetiology Boyd (1226) suggests some toxic agent which produces the hepato-splenic fibrosis. McNee considers it to be some unusual type of portal cirrhosis in which high blood pressure and changes in the spleen precede the onset of hepatic cirrhosis. Gibson suggests a fungus in the spleen.

Generally speaking it may be said that the aetiology is still unknown.
CONCLUSION

When we review the history of so vast a subject as anaemia it becomes evident that we cannot do justice to it within the bounds of an essay. Each of the numerous anaemias which has evolved from the observations of Leeuwenhoek, from the experiments of Lavoisier and Hunter, from the insight of Fewson, Andral, Addison and Ehrlich could well fill these pages. All that can be hoped for here is to give a few facts which may show that what knowledge we today possess has not come as a gift, but has accumulated from the laborious endeavors of the giants of genius and the little men who lie buried in the dust of the archives of medicine.

I offer no apologies for giving a brief outline of the history of medicine at the commencement of this essay. Incomplete as it is I hope that it has been of some use to the reader by showing him those landmarks in the history of our science, which are so important if we are to see in true perspective only one branch of it.

The early history of anaemia is confusing. It is lost in the description of other conditions. This is hardly surprising for we have seen that the causes of anaemia are legend. From Hippocrates to Galen there is a description of chlorosis and of the various cachexias. This probably represented the total classification during that time. We saw that the early conceptions of aetiology and pathology were founded upon various fallacies regarding the physiological functions of the blood, the circulation and the respiration. The doctrine of the humours dominated the medical views of all the ancient writers.

Hippocrates was concise and practical. His reason was built on observation. Speculation and philosophy were hardly to be reckoned as part of his mental make-up. Galen had a clearer knowledge regarding the circulation but he slipped into the very error Hippocrates so keenly avoided.
Yet in Galen we observed the germ of Harvey's discovery of the circulation.

The Dark and Middle Ages contributed next to nothing to the knowledge of anaemia. With the coming of Harvey came a beam of light. His discoveries, the advent of experimental medicine and the birth of chemistry may be said to be the chief factors that brought a flood of knowledge to the better understanding of the functions of the blood. The invention of the microscope and its applications to the study of the blood by Borelli and van Leeuwenhoek, and the intense interest in the chemical and physical examination of the blood, were the outstanding forces that created the science of haematology.

The seventeenth and eighteenth centuries mark a period of untiring research into the physical properties of the blood, particularly coagulation, and the chemical analyses of its inorganic constituents. The earliest attempts at correlating the functions of the respiration and the circulation were highly speculative, and it was not until Black, Priestly, Lavoisier, Scheele and others had solved the meaning of the air we breathe that there developed a clearer understanding of the true nature of the blood.

During the eighteenth century we still found men adhering to the somewhat ludicrous superstitions of the previous ages, but we saw that slowly experimental evidence of truth and the unbiased conclusions of true scientific workers were making their indelible impression on the medical profession. The great investigators were, however, for the most part isolated and lived in worlds of their own.

The change came in the nineteenth century. Closer collaboration between men and men opened up new fields of thought. Scientific periodicals sprang into existence like mushrooms overnight; organic chemistry, the discovery of the analine dyes and the introduction of animal experiments on a large scale paved the way for the discovery of the multitude of facts which mark the second half of the century.
The advances in the history of anaemia were so rapid during the final decades of last century that it leaves one astonished at the drag of the preceding ages, and yet who knows what future generations may think of that time and these years of ours. Year by year our knowledge of the anaemias and the blood diseases increases. We profess to know so much more than did Hippocrates and Harvey and Lieutaud and Addison on the problems of the blood and its pathological features; and yet we know very little—wherever we use the term 'idiopathic' we profess ignorance; the words hyperplasia, hypoplasia and aplasia convey to our minds certain states, what the true nature of the changes underlying these states are, we only surmise; what the intricate mechanism is which alters an inorganic iron substance into the highly complex organic haemoglobin, we fail to answer; how a simple blood cell is created we do not know, it is true we speak of parent cells, of haemopoietic tissue, of mitosis, of chromosomes and genes, but still we do not know what active principle lies behind the division of the chromosomes and how the theoretical genes are juggled about in these limited bodies; why a single fertilised ovum should develop and form our brains and hair and marrow and reticulo-endothelial system is another little problem. To continue thus would make us despair, since we see how much we are still groping on the surface whilst below lie the real problems of physiology. Let us however be content with the knowledge that what is being done today may some day help those neo-physiologists of a Utopian world to understand the real meaning of the human economy and its multitude of diseases—anaemia included.
CHAPTER I.


3. Herodotus: ii, 34.


5. " " : Cap. 6.


10. Leviticus: XIII:XV.


15. Diodorus Siculus: Bibl. hist., Lib. 1;


17. Plato: lib. 6, de republica.

18. Porphy: de abstin. ab esu animalium.


27. Diogenes Laertius: Life of Democritus.
24. " : Ibid. p. 32, etc.
29. Mackenzie: The Hist. of Mth. and the Art of Preserving it, Edinb. 1730: 122, etc.
36. Galen: De Anima et corporis sanitate ad Hieronium Verallum Cardinalem, 1552.
37. de Hamusco, J.V.: De anima et corporis sanitate ad Hieronium Verallum Cardinalem, 1552.
41. See Paul Triaire: Bretonneau et des Correspondants, Paris, 1832; i:303; ii:593.
42. Andral: Essai d'hématologie pathologique, Paris, 1843.
47. Semmelwies: Die Aetioologie der Begriff und die Prophylaxis der Kindbettsfiebers, Budapest and Vienna, 1851.

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CHAPTER II ETC.

2. Galen: de aem., I. 2. de Melanch. II.
4. Galen: Com. in iii; epidem. I:5.
11. Hippocrates: de Nat. hum., I.
12. See Hippocrates (11)
The rest of the bibliography is in the process of being typed and will be handed in to form part of the body of this essay as soon as it is ready.


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