THE HISTORY AND DEVELOPMENT OF OUR KNOWLEDGE RELATING TO ANAEMIA.

By Sarah H. McCarty, A.B.
Errata and Explanations:

Ehrlich's name is misspelled on Pages 8, 13, 12, 18, 19.

No reference can be found to Vierordt's publication. Boyd (11) spells his name Vierordt and says he was the first to make a R.B.C. giving the date as 1852. Da Costa (14) quotes Vierordt and gives the date of the first R.B.C. as 1854. Haden (personal communication) says the first R.B.C. on an anaemic subject was made by Welcker in 1853 and reported in 1854. Da Costa does not mention Welcker.

The statement that Witts has seen only 7 cases of chlorosis (Page 14) is made by Whitby and Britton (39) and refers evidently to the disease in young women, and not to that occurring in older women and in men, which Witts himself has lately differentiated.

There seems to be some confusion as to whether subacute combined sclerosis associated with P.A. was first noted by Lechtheim or by Lichtenstern. Both the references and the statement are taken from Cornell (2).

Page 1 of the References, line 36, should read "Buchan, A.H. and Comrie, J.D.," as Buchan was the senior author.

There is a good deal of variation in the spelling of some of the names (Rhindfleisch, Lechtheim, e.g.) and as I have no way of verifying the references, I've just had to use my own judgement. My own spelling is apt to get Transatlantic at times.
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Outline

INTRODUCTION PAGE 1-2

I. THE DESCRIPTIVE PERIOD (1554-1855) 2-5
   1. Lange 2
   2. Early Blood Transfusion 3
   3. Sydenham and Iron Therapy 3
   4. Combe 4
   5. Blaud 4
   6. Channing 4
   7. Andral 5
   8. Addison 5

II. THE CLINICAL PERIOD (1855-1913) 6-17
   1. The Development of Haematology 6-8
      A. Enumeration of Corpuscles 6
      B. Early Haemoglobin Estimations 7
      C. Staining Blood Films 8
   2. Physiology, Histology, Histogenesis 6-9
   3. Clinical Studies 10-17
      A. P.A. and New Anaemias (1855-1900) 10-13
      B. Chlorosis and Iron Therapy 14
      C. Early Textbooks 15
      D. P.A. and New Anaemias (1900-1913) 15
      E. Therapy for P.A. (Blood Transfusion, 1870-1913) 16-17

III. THE EXPERIMENTAL PERIOD (1913-1938) 17-27
   1. Advances in Diagnosis and Classification 17-19
   2. Haemoglobin and Bilirubin Metabolism 19-19A
   3. Fate of the Erythrocyte 19A-20
   4. Histogenesis of R.B.C. 20
   5. Development of Liver Therapy 20-21
   6. Aetiology of P.A.
      A. Castle and Collaborators 21A
      B. Gastric Factors in Other Anaemias 22
   7. Other Deficiency Anaemias 22-25
      A. Macrocytic 23
      B. Microcytic 24-25
         (1) Iron Deficiency
            (a) Idiopathic hypochromic 24
            (b) In Pregnancy 25
            (c) In Children 25
         (2) Vitamine C Deficiency 25
   8. Haemolytic Anaemias 25-26
      A. Achoruric jaundice 25
      B. Erythroblastaeemia, Type Cooley 26
      C. Icterus Gravis Neonatorum 26
      D. Acute haemolytic anaemia (Lederer) 26
      C. Sickle Cell Anaemia 26
   9. Miscellaneous Anaemias 27
      A. Toxic 27
      B. Hookworm 27
      C. Banti's 27
      D. Lipoid Histiocytoses 27
         (1) Gaucher's Disease 27
         (2) Niemann-Pick's Disease 27

CONCLUSION 27
Anaemia has had a curious and interesting history in medical annals. Our understanding of the essential nature of its varieties dates back, with few exceptions only about ten years. Yet long before this, and therefore before treatment could be rational, specific and efficient therapy was well developed and clinical and experimental data of enormous proportions had accumulated. Contributions to our knowledge have come from clinicians, from embryologists and histologists, from physiologists and from serologists and biochemists from all parts of the world. For many years there was a peculiar lack of co-ordination among these various observers, so that facts and principles established by original work and clinical observation were ignored or forgotten, only to be rediscovered and disinterred years later.

The big guns of the profession have been trained on the subject of anaemia for the past ninety years. But our knowledge has come at a humiliating snail's pace. This is understandable when we recall that in 1849 few doctors had a stethoscope, let alone access to a microscope. What microscopes existed were primitive by our standards. The first red blood count was not made until three years later. There was no haemocytometer and no haemoglobinometer. It was not even known that erythropoiesis takes place for the most part in the bone marrow and hence this tissue was not examined at necropsy on anaemic subjects. It was thirty-five years before the first "test meal" was done on an anaemic patient. Medical libraries were few and there was no Index Medicus. It took years for medical news to trickle from one part of the globe to another. Moreover, the clinical manifestations of anaemia are varied and puzzling, and its pathological anatomy is its result rather than its cause.
The latest monograph on anaemia (1) lists and describes over sixty varieties of the disease. Twelve years ago the Library of the Surgeon General at Washington contained over 2000 references to one variety alone. (2). The size of the literature and the amplitude of the subject make it obvious that a paper of this kind cannot be complete. I am limiting the discussion, therefore, to the history of the more common anaemias and to those with a spectacular or controversial background. References to the subject prior to 1554 have been omitted because they proved of indifferent value in advancing our knowledge.

The history of our knowledge of anaemia can be divided into three epochs. The first period extends from 1554, when Johannes Lange first published an account of chlorosis, till the publication of Addison's second paper in 1855. During this time the accounts of anaemia are descriptive in nature. The second, or clinical period, ended in 1913 when Whipple's researches began to appear in print. The approach to the problem during the past twenty-five years has been experimental.

THE DESCRIPTIVE PERIOD.
(1554 to 1855)

In 1554 there was published at Basle "Medicinalium epistolarum miscellaneous" by Johannes Lange. (3) In epistola xxi which is called "De morbo virgineo" there appears the first description of chlorosis, the strange "green sickness" which is now of historical interest only. Lange's letter is to a very dear friend whose daughter is afflicted with a weakness. "Cheeks and lips as if exsanguinated,—the heart trembles with every movement of the body." There was dyspnoea and oedema of the extremities. Various diagnoses had been made by home doctors. Lange explains that it is a disease of virgins at adolescence. He remarks on the amenorrhoea, and says "grave accidents appear in the viscera—edema of the liver, nausea of the stomach, cardalgia". He remarks that if menstruation can be restored, or if she marry and conceive, she will recover.

In the Seventeenth Century two of our most effective weapons against anaemia had their beginnings. The first crude attempts at blood transfusion were made and Sydenham introduced iron into clinical medicine as a haematinic.

The idea of curing disease by the transfusion of blood is said to have first occurred to Francis Potter about 1639 from his reflection upon Ovid's story of Eason and Medea. (4) He made an unsuccessful attempt to perform transfusion about 1650 using the hen as the experimental animal. In 1666 Sir Christopher Wren read his paper before the Royal Society on his results on "The Noble Anatomical Experiments of Injecting Liquors into the Veins of Animals." The actual transfusion was carried out by Richard Lower in the laboratory of Thomas Willis at Oxford.

Daniel, of Leipsic, had heard of Wren's researches and performed a transfusion in 1664, antedating Lower by two years. The first transfusion on a human being was performed in France by Jean Denys and his report published in the Philosophical Transactions for 22 July, 1667.

In October of the same year Gasper de Gurye reported Hæmoglobinuria following transfusion in "doggs". He also described a severe post-transfusion reaction in a man whose symptoms were "pain and heat in the arms, rapid pulse, pain in the back, nausea, vomiting and the passage of blood stained urine". For a time thereafter transfusion was carried out with increasing enthusiasm, but repeated disasters brought it into disrepute. Also there was the apprehension that in using the lower animals as donors, the recipients might develop horns and hoofs. So transfusion was almost entirely neglected in medical writings for the next hundred years.

Iron salts had been employed by physicians for various purposes since the time of Hippocrates. Their early application was symbolic, with the idea that iron was indicative of strength. To Sydenham in 1658 goes the credit for introducing iron into clinical medicine for the treatment of anaemia. (5) He included chlorosis under the general heading of "Hystera" which he says is the commonest disease next to fever. The aim of his treatment of chlorosis was the restoration of the blood. It included bleeding and purging, "after which I comfort the blood and the spirit belonging to it by giving a chalybiate thirty days running". The results - "the pulse gains strength, the face a ruddy colour. "We give Mars in the pale colours, the pallor disappears and once again the face is rosy and ruddy". With weak and worn out patients the bleeding and purging may be omitted. Two prescriptions used by him contain viss and xv gr of metallic iron, ample by the generous standards of to-day.

In 1712 was published "A Compleat History of Drugs" translated from the French of Pierre Forey by Lemery and Tournefort. This manual recommends a preparation of Crocus Martis in doses of 10 to 40 grains daily for dropy and green sickness. The Crocus Martis was prepared by exposing iron plates to dew, or sprinkling iron filings with honey. In 1713 Lemery and Geoffy demonstrated iron in the ash of the blood, and in 1746 Menghni showed that this ash could be increased by feeding iron-containing foods.

In 1739 Frederick Hoffmann gave a description of chlorosis but did not add much to the observations of Lange and Sydenham. (6).

In 1813 Dr. Blundell of St. Thomas' and Guy's Hospitals invented a special syringe for the transfusion of blood called his "impeilor" and began, after extensive animal experimentation, to transfuse patients with human blood.

Ewing (7) says that in 1821 Andral described a case of pernicious anaemia, but I can find no detailed reference to it.


(6) Garrison, F. H., An Introduction to the History of Medicine, Saunders, N.Y., 1914.

On 1st May, 1822, a paper entitled "History of a Case of Anaemia" was read before the Edinburgh Medical-Chirurgical Society by James Scarth Combe, M.D., F.R.C.S.E. (2), (3), (8). His description of this case leaves us in no doubt that Alexander Haynes suffered from the disease we now know as pernicious anaemia. He observed his patient carefully over a period of seven months, described the gastro-intestinal disturbances, the pallor, the oedema and a terminal hydrothorax. Alexander had one remission. His doctor searched his history and antecedents carefully for some cause of the anaemia and was forced to the conclusion that if any anaemia could be considered as constituting "a morbid state sui generis" this was such a case "a well marked instance of a very peculiar disease which has excited little interest among medical men." He concludes with a minute description of the appearances presented on dissection. He says "I am well aware that others may consider the defect of the red circulating mass as an accidental and occasional circumstance denoting some peculiar change in the assimilating powers". If Dr. Combe's successors had kept the same open mind that he calls the "allowable diversity of opinion on medical subjects", our knowledge of the disease he described for the first time would not have been thrown into the indescribable and acrimonious confusion of the 'Eighties and 'Nineties.

Dr. Combe deserves a special niche in any literary effort on this subject by a student of this University. He received his degree at the age of 20. When the Castle guns announced the victory at Waterloo he was undergoing one of his examinations. He was 26 when he wrote the above paper, and it was 55 years before any other member of the Edinburgh School wrote on the subject of pernicious anaemia. But he was still living when Dr. Bramwell's papers were published, a busy and active Edinburgh practitioner, an examiner of the College of Surgeons and an assessor of examiners. His "erect, gentlemanly figure and handsome, genial countenance" were well known.

An article entitled "On the Chlorotic Maladies and on a Method of Specific Treatment of these Affections" by Pierre Bleud was published in 1831. He emphasized the specific action of iron in chlorosis and suggested a method for its administration that has never been improved on. He reported on the treatment of thirty cases who received a daily ration of his famous pills equivalent to 15 to 60 gr of ferrous sulphate. His treatment lasted 10 to 30 days. His original prescription is still the official preparation of the French Codex Medicamentarius to-day. He remarks that this treatment "has never foundered in our hands". He even recognised the essential nature of chlorosis and said "it arises from a faulty formation of blood as a result of which the blood is an imperfect fluid or the colouring matter defective, so that it is no longer suitable."

In 1835 Bischoff partially overcame some of the technical difficulties of transfusing blood by defibrinating the blood of the donor.

In 1838 Majendie pointed out the serious effects of reactions following transfusions and as a result they were discontinued for many years.

In 1842 Channing reported and described several cases of severe anaemia "principally in its connections with the puerperal state". Even as late as 1928 Channing's cases were confused with pernicious anaemia but they depended on the presence of sepsis in the endometrium. Channing's report represents the first contribution on the subject from the New world and it aroused considerable interest amongst the American Profession. (9)


In 1843 there appeared "Essai d'hematologic pathologique" by Gabriel Andral, translated the next year in Philadelphia by J. F. Mieg and Alfred Stille. It occurred to Andral to examine the large quantities of blood made available by the fashionable therapeutic bleedings of the day by such crude chemical methods as were then available. He determined the proportions of the globules, the fibrine and the solids of the serum which he said were mostly albumen. He pointed out that the globules were diminished by bleeding and the deprivation of aliment and increased by the force of the constitution. One section is entitled "Of the Blood in Anaemia".

Anaemia occurs when "the amount of globules falls much below the physiological mean." He noted the progressive diminution of the corpuscles until in one case they occupied only one fifth of their normal volume. The anemias he studied were both post-haemorrhagic and spontaneous. The first effect of any haemorrhage, he says, is to diminish the red globules. He noted that pregnant women lost blood globules and found that they always showed a slight anaemia. Men also are attacked by spontaneous anaemia with all the symptoms of chlorosis — "I have noted it in men still young, and in others 40 to 60." In cases of chronic lead poisoning he found there is a "profound diminution of corpuscle substance".

Andral was the first to undertake the microscopic study of the blood. He announced his results in lectures at the Faculte during 1840-1841. In two cases of chlorosis "it seems to me that the globules were become smaller than we usually see them, and they no longer had their accustomed form but appear broken and disseminated." (10)

Elliotson in the second edition of his "Practice of Medicine" (London, 1846) describes certain cases of grave anaemia which were probably Addisonian. He referred to Combe's case, and noted that no aetiology had been discovered. He recommended iron as treatment but admitted that "relapses are very common".

In 1849, Dr. Thomas Addison of Guy's Hospital read a paper before the South London Medical Society entitled "Anaemia, Disease of the Suprarenal Capsules." He later expanded this into a full length monograph "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules." (2) (11) (12) This monograph described two diseases, the one "Addison's disease", the other what he termed "Idiopathic anaemia". His clinical description of pernicious anaemia is the best that has ever been written. He says it is an anaemia "without any discoverable cause whatever.—no previous loss of blood, no exhausting diarrhoea, no chlorosis, no purpura, no renal, splenic, ischaemic, glandular, stromous or malignant disease". He noted the slow onset, the weak pulse, the weakness and languor, the weak skin and that it was most apt to attack those of bulgy frame who did not waste. He was aware of "Professor Bennett's interesting essay on leucocyaemias" but as his cases had occurred prior to that publication he had made no microscopic study of the blood. He said the disease, though noted incidentally by various writers, had not attracted the attention it deserved and that the subject had been with him for years the "subject of earnest inquiry".

During the interval between Addison's two papers some important contributions to our knowledge of anaemia were made. In 1851 A. W. Berkeley in a paper entitled "Death from Anaemia" described a case of pernicious anaemia and noted glossitis. In 1852 Griessinger described a severe and progressive anaemia which occurs in hookworm infestation. Dressler in 1854 described peroxysmal haemoglobinurias as "intermittent albuminuria and chromaturia", the first haemolytic anaemia to appear in print.


In 1852 Vierordt made the first erythrocyte counts (11) and on April 25, 1853 Dr. Hermann Welcker bled Margaret Mueller and counted her red cells. He says Margaret Appeared "full-blooded" but her R.B.C. numbered only 1,909,966 per cu. mm. so she was full-blooded by clinical observation only. She complained of lassitude and headache and was bled because her illness remained puzzling. Her symptoms were probably caused by too little, rather than too much, blood. This experience emphasized the need for quantitative study of the blood. (13)

Addison was the last of the descriptive school. He enjoys the somewhat unique distinction of having propounded no aetiological hypothesis for the anaemia that is sometimes called by his name.

THE CLINICAL PERIOD.  
(1855-1913).

During this 58 years most of the types of anaemia were defined or described, haematological technique was developed, vascular surgery was perfected, blood groups recognized, so that the transfusion of blood became a safe procedure, and studies on the histology and origins of the blood cells were begun.

The Development of Haematology.

Vierordt's and Welcher's method for the determination of the globular richness of the blood was to allow a stated amount of a definite dilution to dry upon a glass slide and then by the aid of the micrometer eyepiece, to count the number of globules. (14) Imperfect as was this method, they both determined normal standards which hold good to-day, Vierordt stating that the normal number of red blood corpuscles for a healthy adult male is between 5 and 6 millions and Welcker determining that 5 million s were normal for men and 4,500,000 for women. These standards are said to have based on two counts alone. (11)

In 1867 Potain invented his blood diluting pipette. The illustration looks like the white "counter" of to-day except for the graduations and the absence of the glass bead.

In 1872 Malassez described a method for counting the corpuscles and the following year published the first monograph on the red cells. He used Potain's pipette and diluted the blood with an "artificial serum" composed of 5 to 6 % sodium sulphate (sp. gr. 1.020 to 1.024). The diluted blood was then introduced into a flattened capillary tube of known capacity and the globules in a given length of tube counted, using the micrometer eyepiece.


In 1877 Gowers introduced his haemocytometer, which is the ancestor of the modern counting chamber. In 1880 and 1882 Malassez modified his tube into a cell, a thick glass slide with a ruled plateau surrounded by a moat filled with fluid to prevent evaporation. The ruling on the plateau was in twentieths of a sq. mm. oblongs. Thoma made a more convenient ruling and the instrument was manufactured by Zeiss. He recommended $3\%$ NaCl as a diluent.

In 1880 we hear from Dr. J. Norman Henry of Philadelphia that Gower's instrument had been in use for at least 6 months in the Episcopal Hospital in that city and that "when used by a competent person the haemocytometer is very satisfactory in diagnosing and noting the progress of these (i.e., anaemic) cases". (15)

But there were many complaints that such procedures took too much "time, trouble and eyestrain". To obviate this, Hedin in 1885 invented his "haematokrit" which was modified by Daland in 1894. Such tubes give the packed volume of cells in a given amount of blood but contribute no information as to their actual numbers because of the variations in their size in anaemias. In 1903 Capps suggested using this haematocrit reading plus the red count to determine the "volume index", a very valuable haematological procedure.

Oliver about 1890 described a haemocytometer which did not involve actual counting. And in 1897 Durham devised a self-filling blood pipette. Both these instruments enjoyed some popularity but haematologists soon realized they were unreliable and gladly suffered a little headache and eyestrain for the sake of accurate counts.

Early Haemoglobin Estimations.

The development of a reliable haemoglobinometer took a longer time, and indeed it is only in the last five years that a really satisfactory clinical instrument has been devised. (14) (7) (16) The multiplicity of the early haemoglobinometers is indicative of their inadequacies. Gowers devised an early instrument, the standard consisting of laked "normal" blood. He later made a more satisfactory standard of indigo carmine. Haldane modified Gowers' idea using CO-haemoglobin as the standard. von Fleischl's haemoglobinometer was invented in 1895 and was the standard on the Continent for many years. Oliver's instrument was the choice in Great Britain. There is still one extent in Ward 25 R.I.E. Talqvist first described his much maligned instrument in 1900. Admittedly it was inaccurate, but it was cheap and convenient, and it served its purpose in making American doctors "haemoglobin-minded".

In France Hayem recommended Henocques' haematoscope, and in Italy Bizzozero's chromatometer was used.

The biggest stumbling block in devising a satisfactory haemoglobinometer was in deciding how many grams of haemoglobin = "100%". Häfner in 1894 undertook the first chemical studies of haemoglobin, made a determination of its molecular weight, and discovered that 1 gram of haemoglobin combines with 1.34 cc of CO. This figure 1.34 is called Häfner's factor and is used to-day in the calculation of haemoglobin. In 1898 Haldane and (Lorraine) Smith writing on "The Mass and Oxygen Capacity of Blood in Man" suggested that the oxygen capacity be adopted as the measure of haemoglobin. This method has had increasing favour and all the accurate colorimetric methods are based on standard prepared thus. Haldane and Smith used only twelve subjects in their investigations and their resulting standard was too low. Standards, i.e. "100%" of haemoglobin have ranged in the instruments in use from 12 to 17 grams per 100 cc of blood.

Recent work has, however, remedied this confusion and modern instruments are reliable, cheap and easy to read. (Vide infra). (17)
Staining Blood Films.

In 1879 Erlich first used aniline dyes to stain blood cells. This was an enormous advance and made careful microscopical studies of the blood possible. To our eyes a coloured plate of blood stained by Erlich's method looks unfamiliar and ugly. The staining method itself was exceedingly tedious. The preparations were made on coverglasses and fixed by heat. The red cells took a dirty yellow stain (Orange G). Their nuclei when present were green or black. (13) (16)

In 1891 D. L. Romanovsky in the Imperial Medical Military Academy, Dissertation No. 38, described in Russian a stain of eosin and methylene blue for demonstrating malarial parasites. He recognized that a new compound was set up in this stain which he called azure. (18) Nocht in 1895 prepared a better stain along the same lines by "polychroming" the methylene blue artificially with potassium carbonate. Jenner in 1898 collected the precipitate from this stain and re-dissolved it in methyl alcohol. This stained the cytoplasm beautifully but did not give a good nuclear stain. In 1901 Reuter and Lieshman improved Jenner's stain and Giemsa introduced his modification in 1902. Wright's stain was described shortly thereafter. More recently MacNeal (1906, 1922, 1925) has made a chemical approach to the problem of the Romanovsky stains, and devised an almost "fool-proof" stain.

All these improvements greatly facilitated haematological studies.

Up until 1880 only five people had made blood counts on patients with pernicious anaemia. In the following years haematology developed so rapidly that by the middle Nineties the physiological ranges of red counts had been ascertained and their pathological significance studied by Helling, Fredericksen, Zaslein, Neubert, Graber, Stierlin, Rienecke, Hayem and many others.

Physiology, Histogenesis and Histology of the Erythrocytes.

Elliotson in his textbook had mentioned the idea that the "grave anaemia" which he described was the result of a "degeneration to a white-blooded condition". The misapprehension that the white globules were converted by transformation into red ones was probably the result of not being able to see the cells well and it has survived into the Twentieth Century and left its mark on the literature in such terms as "leukanaemia" and "pseudoleukaemia". Köllicker in 1852 claimed to have found cells in the blood of Batrachians which represented these transition forms (19) Klein (20) differentiated 3 kinds of white corpuscles in the blood of the newt but stated that the human ones were less varied and active in movement. Indeed, these unstained leucocytes must have been very difficult to see for even Virchow, the discoverer of leucocytosis thought that this cellular increase was lymphocytic rather than polymorphonuclear.

In 1864 Preyer had observed that certain of the white corpuscles are phagocytic, and will engulf carbon particles or even red cells.

In Dalton's "Treatise on Human Physiology" (1867) he confesses that he is unable to find any of the transition cells in the blood of a frog. He says that in ordinary analysis the corpuscles represent only about one-fifteenth of the weight of the blood (Andral had got about one-thirteenth), but this is because the dried residue is used, whereas in the fresh state they represent "fully half the entire mass of the blood." He thought it unlikely that the blood cells are produced or destroyed anywhere in the body, "they are as permanent as muscle fibres or nerve cells."

In 1868 Bizzozero and Neumann almost simultaneously published papers on researches which pointed to the bone marrow as the tissue to be studied in anaemia since they both concluded that the red marrow is probably the exclusive depot for the formation and possibly the destruction of the red cells in man.

In Carpenter's Physiology (1876) he states that both the red and white cells have a definite term of life, though it is unknown. This book also describes the action of acids, alkalis and water on red cells and tells something of their chemical composition.

Schäfer, Renvier and Hayem also studied the histology and embryology of the red cells and all came to the conclusion that both the vessel wall and the primitive erythrocyte are derived from the same group of cells. Bizzozero and Torre showed in 1882 that the formation of red corpuscles in the marrow of birds is confined within the vessel walls. Ziegler in 1889 recognized that the parent leucocytes lie originally outside the vessels and enter them later by their own amoeboid motion.

Later on (about 1898) the histologists got into a spirited controversy as to whether or not the leucocytes and red cells arise from a common ancestor. The participants in the argument were Pappenheim and Naegeli who supported the monophyletic view, and Bizzozero, Ferrata, Denys and many others. Since the bone marrow is confusing tissue to study, and since embryonic blood cells are extremely difficult to differentiate, their conclusions were statements of opinion rather than of fact, and the argument was not finally settled until Doan, Cunningham and Sabin published the results of their work in 1925.

Measurements on the diameters of the red cells were made by a number of early observers and in 1896 von Limbeck collected their results in the table given below. The measurements were made with the micrometer eyepiece mostly on fresh cells.

<table>
<thead>
<tr>
<th>Observer</th>
<th>Normal Limits:</th>
<th>Average Diameter:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcker</td>
<td>Diameter = 4.5(\mu) - 9.5(\mu)</td>
<td>7 (\mu)</td>
</tr>
<tr>
<td>Valentin</td>
<td>Diameter = 6(\mu) - 8.8(\mu)</td>
<td>7.5 (\mu)</td>
</tr>
<tr>
<td>Malinin</td>
<td>Diameter = 6(\mu) - 9(\mu)</td>
<td>7.075 (\mu)</td>
</tr>
<tr>
<td>Hayem</td>
<td></td>
<td>7.85 (\mu)</td>
</tr>
<tr>
<td>Malassez</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lasche</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bizzozero</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average Diameter: 7.5 \(\mu\)

The description of Hodgkin's disease in 1832, with its profound anaemia and the splenic lesions had aroused speculation as to the function of the spleen and the part it plays in the manufacture and destruction of the blood cells. Mosler (1882) and Malassez (1878) were among the first to study the effects of splenectomy on the experimental animal. Cerny was the first to perform splenectomy in man successfully, and he studied its effects on the blood picture as did Regnier and Hartley and McBurney shortly afterwards. As soon as the operation could be performed with reasonable safety it was advocated and tried in diseases of the blood.
Addison's papers occasioned remarkably little comment. But his colleagues at Guy's Hospital kept a weather eye cocked for cases of pernicious anaemia and Wilks in 1857 reported seven cases. Guy's Hospital Reports contain records of 23 cases from the years 1864-1878. Zenker (1856), Bristow (1859) and Wagner (1859) each reported a case of severe anaemia, probably pernicious. Lebert in 1858 described under the name "essential anaemia" a group of cases, some of true Addisonian type. Howard Palmer in Montreal and Trouseau both taught pernicious anaemia to students in the 'Sixties. The former is said to have been the first to note the familial incidence of the disease. Cases were reported also by Casenave (1860), Grohe (1861), Habershohn, Barclay and Dickinson each reported cases in 1863. Gaichard in his "Clinical Medicine" in 1862 speaks of a mysterious form of anaemia showing deficiency of red and certainly no increase of white corpuscles. "It has no relation to the chlorosis of young women". Bennett in his "Practice" (1867) totally ignores the subject of pernicious anaemia, a remarkable omission because his studies on leucocytæmia had directed his attention to the blood. Perroud (1869) is said to have been the first of the French School to write on pernicious anaemia. Lugui Corrazzo of Bologna reported an undoubted case of pernicious anaemia in 1869.

In 1871 Austin Flint and later Fenwick (1870-1877) raised the question of the function of the gastric mucosa in pernicious anaemia, both pointing out the extensive atrophy of the secretory tubules and the latter demonstrating that such a stomach had lost its digesting power. Gusserow in 1871 described some cases of severe anaemia in pregnant women and Horatio C. Wood in America (21) published an article on "The Relations of Leucocytæmia and Pseudoleukaæmia" in which he mentions Neumann's work and reports his own studies on the marrow and spleen in one mysterious case with fatal outcome. He studied the blood of his patient post mortem.

In 1872 Biermer published a paper which was a result of work carried on in Zurich for the previous five years. It was a report of 15 cases of fatal anaemias of which he gave a systematic description of the clinical symptoms. He paid little attention to the pathology and none to the haematology. His cases included some of Addisonian type, as well as anaemias resulting from cancer, diarrhoea, malaria, and bothroœphaly infestation and from puerperal infection. He called this group "progressive pernicious anaemia" and if idiopathic, he added the qualification "primary". He added little to Addison's description except for noting the tendency to petechial haemorrhages. Biermer's publication created the greatest immediate interest in Britain, America and on the Continent. It is unfortunate that Biermer confused the terminology to such an extent. It took almost thirty years to disentangle the various types of anaemia described by him.

In 1874 Sorensen reported the first blood counts on patients with pernicious anaemia. One of his cases had only 470,000 R.B.C. per cu. mm. ! Immersmann also took an interest in the microscopic studies of the blood in pernicious anaemia, but his examinations were limited to comparing the proportions of the leucocytes, which he found to be absolutely and relatively diminished.

In the Medical Times and Gazette, November, 1874, p. 581, there appeared an editorial on "Pernicious Anaæmia; A New Disease". One sentence read, "We are not aware that any case has as yet been reported in Great Britain." This editorial excited more medical attention than had Addison's original studies. Pye-Smith, a pupil of Addison's, in an article in Virchow's Archiv drew the attention of Germany to his master's work in 1875. Later he differentiated Addisonian anaemia from the others described by Biermer, and established Addison's priority. (1883).

Pepper in 1875 published a paper entitled "Progressive Pernicious Anaemia or Anaematoisis" which drew the attention of his colleagues in America to the disease. It is a remarkably full report on three cases, two with autopsies. He was aware of Addison's papers, and of the work of Biermer, which he calls an "able memoir", and remarks on the editorial mentioned above, saying, "Is it not a little melancholy that in the native land of that great clinical master (Addison), one of the leading journals is unaware of his work?" The recent "brilliant" studies of Neumann and Bizzarro were familiar to him and directed his studies toward the bone marrow which he was able to study at post mortem in his last case. He examined the blood antemortem and noted that the red cells were not biconcave as normally, and that the red globules were much diminished but "I do not know of any careful analysis to show how far their proportion is reduced". He observed nucleated red cells in the marrow and noted their variation in size but this was before staining was devised and he was unable to identify them. He remarked on the jaundice and said it was due to rapid destruction of the red globules. He tried iron, arsenic, quinine and even blood transfusion for treatment, the last with fatal result. He concludes with a discussion of aetiological factors and of the terminology, which he finds very unsatisfactory. He says the term chlorosis should be reserved for the complex long recognized, and that the word anaemia should be used only where "without lesions of the blood-making tissues the mass of blood or its solid ingredients are diminished". He also objects to the term "pseudoleukaemia" which he considers responsible for many missed diagnoses.

In 1876 Cohnheim made further studies of the bone marrow in pernicious anaemia. He noted the megaloblasts, microcytes and myelocytes in the post mortem specimens of blood and says the marrow was unusually hyperplastic, the marrow fat atrophic, and its appearance led him to the conclusion that the essential element of the disease is primary in a morbid process of the marrow which has undergone reversion to the embryonal type of blood formation. In the same year, Quincke described the appearance of polikocytes and microcytes in the blood in cases of pernicious anaemia and reported the lowest blood count on record (143,000). He noted the increase of cells following transfusion and stated that a case of sarcoma of the bone had a similar blood picture to that of P.A. Bradbury called attention to the oval shape of the red cells in P.A. and Ferrand did some red counts and haemoglobin estimations, getting in one case a colour index of 2 ! Lepine also reported some red counts and noted that the average diameter of the red cells is large in P.A. and that the cells increase in size during the relapses.

The following year Osler and Gardner reported a case of P.A., describing the post mortem appearances of bone marrow and the atrophy of the gastric mucosa. Osler with his usual energy continued his interest in the study of anaemia and inspired many of his pupils with his enthusiasm. Bramwell in a series of clinical lectures recommended arsenic as specific therapy in pernicious anaemia. He seems to have secured a strikingly good remission in one case treated with Fowler's solution in gradually increasing doses. Arsenic had previously used by Pepper and its use was continued by physicians during the next fifteen years with varying results.

In 1876 Hayem published the first edition of his "Recherches sur L'anatomie Normale et Pathologique du Sang". He remarked on the progressive and extreme leucopenia in P.A. and first called attention to the high colour index. This book described his method of blood examinations and went through numerous editions and revisions. It was translated in America in 1886. He studied the effects of many diseases on the blood picture and by the 1889 edition the book numbered 1053 pages. It contained descriptions of all the recognized kinds of anaemia. A large part of the book is concerned with haematological technique and the reports of his own work and it is a valuable contribution to our knowledge for Hayem concerned himself largely with practical problems and left hypothetical red herrings for others to follow. Eisenlohr in 1878 wrote "On the Bone Marrow Changes in Pernicious Anaemia and Carcinoma of the Stomach", calling attention to the similarity of changes in the two diseases and mentioning that some of the leucocytes in P.A. show phagocytic activity.
Neumann continued his studies on the bone marrow and reported changes similar to those in P.A. in animals subjected to repeated bleedings. (1878) Orth and Litten confirmed this. Eichhorst in this year wrote the first monograph on pernicious anaemia. He studied about seventy cases and a large percentage followed pregnancy. He noted the heavily stained macrocytes and said that size, pallor and scarcity of the red cells was the most striking characteristic of the blood picture but because he had noted all these in a case of carcinoma of the stomach he concluded it was impossible to make a diagnosis of pernicious anaemia on the blood picture alone.

In 1879 Glaister was the first to publish an account of icterus gravis neonatorum. He noted its strong familial character. The physiological jaundice of the newborn had been recognized for centuries and it is said that all the fifteen children of Morgagni were jaundiced shortly after birth.

Erlich made his first publication on pernicious anaemia in 1880. He continued his interest in the subject for many years finally publishing with Lazarus a monograph on anaemia. (1898) His interest was principally in the bone marrow and the blood, and his technique of staining and his enthusiasm for Cohnheim's views confirmed the bent of his studies. Erlich's theory of the essential nature is too involved to give here but he regarded the megaloblast (a term with a wider connotation than it has to-day) as the sign manual of the disease and thought that any bone marrow showing "megaloblastic degeneration" represented a reversion to the foetal type of blood formation, and any anaemia showing megaloblasts was of pernicious type.

The anaemias of children began to excite investigation about this time. Cardarelli said he had observed severe anaemia with splenomegaly in children in 1880 but did not publish till 1892. Mosler and Senator in 1882 described severe anaemia in children associated with marked enlargement of the spleen.

Gaucher in 1882 described the disease which bears his name and noted the extreme chronic anaemia which accompanies it.

In 1883 Laache of Christians published a monograph on anaemia. It drew the attention of his colleagues to pernicious anaemia, which is a disease with a strong predilection for the Scandinavian races, and initiated enquiries which have added substantially to our knowledge. In his book Laache showed that the high colour index in P.A. is referable to the many megalocytes with their increased load of haemoglobin.

In 1884 Lichtenstern described two cases of severe anaemia which were almost certainly P.A. and were associated with degeneration of the posterior columns of the cord, and three years later Lechtheim described "subacute combined sclerosis" of the cord in association with pernicious anaemia. He noted the spasticity, ataxia, Rombergism and paraplegia.

In 1885 Osler included pernicious anaemia in the section of anaemias in his "System of Practical Medicine" and Musser read a paper on pernicious anaemia before the Philadelphia County Medical Society in which he gave a full report of the early literature. In this year Murchison first described acholuric jaundice.

In 1886 Hoffman reported thirty cases of anaemia caused by Bothrioccephalus latus and showed that it was a grave form of anaemia indistinguishable from idiopathic P.A. This same year Cohn and von Mehring first examined the gastric contents in a case of pernicious anaemia and noted the achlorhydria. This observation was confirmed on other cases in the next few years by von Noorden, (1890) Einhorn, (1892) Stewart, (1894) and Martius, (1897). By 1900 Faber and Bloch were able to collect 33 cases in which the gastric contents had been examined and a deficiency of HCl noted, and shortly thereafter with the introduction of the Einhorn, Rehfuss and Ryle tubes, the fractional test meal as a routine diagnostic measure was made possible.
In 1886 the first of the many articles on pernicious anaemia by William Hunter appeared. It was a gold medal thesis for the M.D. degree, University of Edinburgh. Hunter continued to study the disease throughout the next twenty years and his sustained enthusiasm gave a powerful impulse to the studies of the clinical, rather than the histological features of P.A. He described the hepatic siderosis in two monographs (1901 and 1909) and this was confirmed by Muir. He insisted on the presence of glossitis as a point in diagnosis and he thought that the haematological changes were secondary to the gastro-intestinal disturbances. Hepatic siderosis was the result, he thought, of excessive blood destruction in the portal area, where some toxin absorbed from stomach or intestine, must be at work. It is to Hunter that we owe the conception of "focal infection" for to him the fundamental cause of the disease was due to toxic products absorbed from lesions caused by a long-chained streptococcus which he cultivated from the tongues, teeth and gums of some of his patients. He was a strong exponent of the disease as a clinical entity and pointed that Addison in his paper had insisted on the cryptogenic nature of the disease. He said that cases described by Biermer and others could not all be pernicious anaemia since some of them had demonstrable cause.

There were thus defined two schools as to the aetiology of pernicious anaemia. The Continental school, led by Erlich and Cohnheim believed that any severe anaemia showing "megaloblastic degeneration" was pernicious, the British school, led by Hunter and Muir, regarded the abnormal blood destruction in the portal area as the essential feature of the disease. When English or American authors found any pathology in the organs at post mortem, such as atrophy of the gastric mucosa, they assumed this to be the cause of the disease and so did not regard it as idiopathic. There was further the uncertainty which the remissions imposed on the interpretation of treatment, and so as Cornell remarks, "it became a sort of international medical pastime to exclude cases from the published reports on the basis of purity of type", each critic using his own standards.

In 1889 von Jaksch published an article on "Anaemia Infantum Psuedoleukaemica" described by him as a relatively commonly anaemia in children associated with splenic and hepatic enlargement, lymphadenopathy and a high leucocytosis. The prognosis was not considered as bad as in leukaemia, since one of his cases, a girl of nine months with associated rickets, recovered on administration of iron. Furthermore, there were not the typical leukaemic infiltrations found in the organs at autopsy. Hayem's paper on the same subject appeared almost simultaneously with von Jaksch's. Some of Hayem's cases at least were leukaeamic. Hayem called attention to the large numbers of nucleated red cells. The following year Di Lorenzo amplified the conception of von Jaksch's anaemia and limited the disease to the age period 6 months to 4 years. In 1891 Fede reported some cases which he called " Infective splenic infantile anaemia" and Luzet called attention to the myelocytes and made pathological studies of the viscera. By 1892 Monti and Beggrun were able to collect 16 cases from the literature and add 4 of their own.

In 1890 Rindfleisch made some excellent histological studies on the bone marrow in pernicious anaemia and reported some megaloblasts which had reached the extreme size of 50 μ. (These were probably either the macrocytes described later by Cooke, or megakaryocytes) He noted the myelocytes in P.A. and said that these cells and the extreme leucopenia were due to the proliferation of the other marrow cells. Needless to say, he lent his support to Erlich's side of the controversy with Hunter.

In 1892 and 1893 Konried reported blood studies on 200 cases of syphilis, saying that the anaemia in this disease is often very severe and almost like P.A., that it is affected unfavourably by treatment with mercury, and that the red counts and haemoglobin values never reached their original levels.
In 1892 Bunge demonstrated that the liver of young animals contains, weight for weight, five times more iron than that of adult animals, and Hugumeng in 1899 discovered that in humans two thirds of this iron is laid down in the last three months of pregnancy. This pointed the way to rational treatment for the more common form of anaemia in pregnancy, in the anaemias of premature infants and twins, and in the rare congenital anaemia of infants, but it was some years before these anaemias were studied carefully.

In 1893 Askanaé made some studies on the megaloblast and watched such a cell divide on the warm stage under dark ground illumination.

In 1894 Schau mann studied Botaricophilus anaemia and showed that it was of the severest type and differed from P.A. only in its curability by explosion of the worm. He reported 38 cases. In the same year Banti described Banti's syndrome and differentiated it from cirrhosis of the liver. In his second paper in 1910 he described the three stages of the disease.

Le Breton in 1895 reported anaemia of macrocytic, hyperchromic type in myxoedematous patients and noted the improvement following thyroid feeding. In 1879 Koplick described the anaemia of cretins.

In 1898 Hayem established acholuric jaundice as a clinical entity. Widal in the same year emphasized the exacerbations which take place in this disease. Its familial occurrence was first noted by Minkowski, in 1900, and Chauffard in 1907 did the first "fragility test" on such a patient, and published his results in 1909.

Chlorosis.

The excitement about pernicious anaemia had been so great, and the definition of new forms of anaemia was so much more fun, that the subject of chlorosis was somewhat neglected during this second period and was treated with the familiarity of contempt. But the new haematological methods had been used for careful studies of the blood pictures in this disease. In 1878, Lichtenstern made microscopic studies of the blood in 191 cases and noted the low colour index and the diminution of the average diameters of the cells. Bramwell had written extensively on the subject, reporting in one case a colour index of 0.2. Von Noorden wrote a monograph on chlorosis in 1897 and first noted the "normoblastic crisis" which he recognized as a favourable sign in any form of anaemia. Von Gravitz wrote a monograph on the blood in 1906 which described his observations on chlorosis and his studies on pernicious and other forms of anaemia. He was the first to observe "stippling" in cases of lead poisoning, and the first to note the low volume of the cell mass in chlorosis. Von Limbeck, Hoffmann, Hayem, Cabot (179 cases) Pepper, and many others wrote on chlorosis. Romberg reported full blood studies on 100 cases in 1897.

Von Neimeyer in his textbook had stressed the importance of using large doses of iron in the treatment of chlorosis and said that his success in the treatment of the disease was the foundation of his large practice. Osler and Immermann had also recommended Blaud's pills given by Blaud's original method. But toward the Nineties, big doses of iron went out of fashion. Von Noorden recommended only gr i to iss daily and Bunge in 1895 stated that all inorganic preparations of iron were useless, since such iron salts were converted into iron sulphide. Stockman (1892) had previously shown that iron sulphide was a potent haematinic. Romberg (1897) made the scientific suggestion that the dosage of iron should be controlled by observing the blood picture and that if treatment was adequate, there was a gain of 10% haemoglobin and 500,000 red cells every ten days. The new interest in endocrinology also led to attempts to treat the anaemorrhoea of chlorosis with ovarian extract, which was found effective against the anaemia as well.

About 1903 chlorosis, which had been a very common complaint suddenly began to disappear all over the world. Witts, who has had an enormous experience with modern anaemias, has seen only seven cases.
About the turn of the Century two textbooks on the blood appeared in America which are interesting in that they show how far our knowledge had advanced and how much "duck pond" a young doctor in Boston or New York was supposed to know at this time. Cabot's book was based on "a single group of blood examinations superior in bulk and in detail to any elsewhere recorded". He gives no bibliography as this alone "is now large enough to form a volume by itself." He reports full studies on the blood is 121 cases of pernicious anaemia and 179 cases of chlorosis and 6 cases of "splenic anaemia." He devotes a chapter to blood pictures in children and states that "splenic anaemia" and von Jaksch's anaemia are not specific anaemias. He reports blood counts on every case that had been admitted to the Massachusetts General Hospital during the last five years and gives full details of technique of blood examinations.

In Ewing's "Clinical Pathology of the Blood" he gives a good description of post-haemorrhagic anaemia. He remarks on two cases of pyloric stenosis without cancer who showed a blood picture like P.A. He describes the pathological features in one case of von Jaksch's anaemia very fully calling attention to the extramedullary islands of erythropoiesis in the liver. He gives early methods on blood chemistry as well as microscopic technique and describes Jenner's "new" stain. (1903)

At this time it seems appropriate to mention a few anaemias which like Topsy, just "grew" and about which our knowledge has been acquired so gradually that they have no history. These anaemias include those produced by chemical and metabolic poisons, especially phosphorus, bensol, amidopyrine, potassium chlorate, C0, arsenic, and lead, and the anaemia of rickets and malaria, the post-haemorrhagic anaemias including those following the "bleeder's diseases" and the anaemia in nephritis, infection and sepsis. These were all well known to Hayem, Cabot and Ewing, and to others before. Pepper in 1875 says that "splenic anaemia" had long been differentiated, a more optimistic statement than we can make to-day.

The first thirteen years of the new century added little to our knowledge about any kind of anaemia, although there was "much making of books".

In 1900 Osler described twelve cases of splenic anaemia and Ashford wrote an excellent report on hookworm anaemia in Porto Rica, reviewing the literature from British Guiana, Italy, France, Germany and Peru.

In 1904 Donath and Landsteiner demonstrated the autohemolysin in the serum in peroxysmal haemoglobinuria.

In 1905 Pianese first described "infantile splenic anaemia" due to Leishmania infantum and demonstrated the parasites in punctures taken from spleen, liver and tibial marrow.

Attempts were being made at this time to produce P.A.-like blood pictures in animals by various experimental agents such as ricin, saponin, pyrogallie acid and B. Welchi poison. One of the best of these reports was by Bunting on "The Etiology and Pathogenesis of Pernicious Anemia". (1905)

In 1909 Faber gave the first description of idiopathic hypochromic anaemia and the same year Buchan and Comrie first described the extramedullary islands of erythropoiesis in icterus gravis neonatorum.

In 1910 Herrick of Chicago first described Sickle Cell Anaemia. His paper is a case report in which he describes the peculiar poikilocytosis, the ulcers on the legs and the severe anaemia and concludes "The question of diagnosis must remain an open one unless reports of other similar cases with the same peculiar blood picture shall clear up this feature." Similar reports were not long in coming into print. (23)

Theory for Pernicious Anaemia.

Pernicious anaemia resisted every drug in the pharmacopoeia. Iron was, of course, the first to be tried and arsenic as introduced by Bramwell was widely used. Stockman studied the action of arsenic and showed that it was a narrow stimulant and irritant. (1894). Other recommended remedies were cod liver oil, phosphates (Pepper), milk and "whiskey in abundance". Fraser in 1894 reported good results with feeding bone marrow. He used one iij of fresh marrow daily. Galen is said to have been the first to recommend marrow in the treatment of anaemia. (12)

As the disease became more widely recognized and its invariably fatal outcome was known, and as more and more patients presented themselves for treatment, physicians were faced with the awful situation of passing a death sentence every time they made a diagnosis. It is small wonder, then, that they resorted to blood transfusion as a desperate remedy even though they realized its dangers as did Pepper, whose patient died eight hours after the second transfusion with symptoms which "were such as are frequently observed before death after transfusion."

The first "successful" transfusion for pernicious anaemia is credited to Dr. Louis Starr of Philadelphia in October 1880. The patient was an Irish labourer, 30 years old, with all the clinical manifestations of P.A. His red cells numbered 745,000, his white cells 5000 per cu. mm. Quinine, iron, punch by mouth and opium were unsuccessful in securing any improvement. After a haematemesis, it was decided to transfuse and 20 ozs of blood were injected into the left median basilic vein. The patient felt much better immediately after transfusion and his red count rose to 1,245,000. But in the afternoon, his pulse became very feeble and in spite of stimulation, he died about 23 hours after transfusion. At autopsy the bone marrow was examined and studied histologically and the pathologist noted "cells which possess are the appearances of foetal blood". (15)

A really successful transfusion for anaemia was performed by Joseph W. Howe, M.D., sometime in 1879, who had the good fortune to secure a compatible donor without knowing it. His patient had a post-haemorrhagic anaemia following abortion and was cold and pulseless when he arrived. He made up his mind "to waste no time in defibrinating the blood" but opened at once the veins of the patient and donor and using a Colin's cannula, allowed one iij to viii to flow directly into the cylinder. Within half an hour the pulse returned at the wrist and when the attending doctor (who had gone away earlier without hope for her recovery) returned, she was so much better that he said it was "a veritable transformation scene". Her convalescence was uneventful. (24)

Another early transfusion for anaemia was performed by Dr. Charles Cary of Buffalo in 1881. He made a diagnosis of pernicious anaemia but this was certainly not correct. His patient was a young woman with a very severe anaemia, who in spite of quinine and iron for some weeks grew steadily worse and appeared to be in extremis. The iron was administered in small doses (Tr. iron, M X t.i.d., Dialyzed Iron M xx t.i.d., Ferrum Redact gr. iij.). Only one iij of blood were transfused but the immediate effects were remarkable and the patient made a good recovery. Three weeks and four days after both patient and donor developed the prodromal symptoms of typhoid fever and the disease ran its course in both of about equal severity and duration! In spite of this there was no return of the anaemia in the patient and she recovered. (25)


The two biggest difficulties in the way of transfusion, were the technical operative difficulty and the occurrence of the unexplained reactions which frequently followed them. Landois in 1866 and 1875 had shown that the blood of one species, when introduced into the circulation of another species results in haemolysis of the donor's red cells. Shattuck in 1899 discovered agglutinins and Landsteiner in 1901 found that on the basis of agglutinins the blood of 22 individuals examined by him could be divided into three groups. The fourth group was described by Descatello and Sturli the following year. In 1907 Jansky made his classification and in 1910 Moss described his, together with the method for determining the blood group. The basis of the reactions was thus made plain.

Meanwhile, Eck (1879), Murphy (1897), Carrell (1902), Horsley and others had developed vascular surgery and Crile in 1909 reported more than 200 experimental, and 32 clinical transfusions. Kippton and Brown introduced their blood transfusion tube in 1913 and the same year Lindemen described his multiple syringe method for direct transfusion. Even so, the transfusion of blood, though safe, required a highly skilled surgeon to carry it through, and an editorial in the Journal of the A.M.A. for August 17, 1912, runs:

"In secondary anemia, such as results from traumatic hemorrhage, from "post-partum hemorrhage, and from other conditions, it would often be desirable to transfuse after bleeding is controlled, if the technic were as "simple as, for instance, the injection of salt solution."

THE EXPERIMENTAL PERIOD.
(1913 - 1938)

So we come to the end of the second era. Hard work and rather unsatisfactory progress had marked it. During the next twenty-five years, specific treatment for pernicious anaemia was discovered, the etiology of it, and of all the deficiency anaemias was established, the problem of the histogenesis of the blood was finally settled, haemoglobin and bilirubin metabolism was worked out and the mechanism of haemolytic jaundice was explained. Normal red counts and haemoglobin levels were ascertained, several new varieties of anaemia were defined and blood transfusion became so simple that any resident can do it single-handed, when in 1914 almost simultaneously Hustin of Brussels, Lewensohn and Weil of New York, and Agote of Buenos Aires introduced sodium citrate as an anticoagulant.

Diagnosis and Classification.

I must here interpolate a few remarks on the development of haematological diagnosis and classification which will not be in chronological order but which will give a more symmetrical arrangement to the account of the subsequent growth of our knowledge on anaemia.

The methods used in haematological diagnosis were for the most part those described on pp 6 to 8 but four new tests became exceedingly useful and the older tests, especially that for ascertaining haemoglobin content, were greatly improved.
The new tests were:

1. The "fragility test". The resistance of the R.B.C. to hypotonic solutions of salt was a problem which had interested physiologists for years but the origins of the "fragility test" itself are shrouded in mystery. Carpenter in his Physiology in 1876 makes no mention of it, but Cabot gives full details of it, states the normal range and quotes Hayem and von Limbeck (1896) on their figures in various diseases including jaundice. About 1890 Viola had devised a rough quantitative fragility test. With the demonstration by Chauffard in 1907 that in haemolytic jaundice the red cells show an abnormally decreased resistance to hypotonic NaCl solutions, the test was recognized as having definite clinical value. Ponder in 1922 in a monograph on "The Erythrocyte and the Action of Simple Hemolysins" reviewed the subject well and an exact quantitative test was devised in 1935 by Whitby and Hynes.

2. The estimation of the amount of bilirubin in the serum. It had been known since 1909 that normal blood serum contains minute amounts of bilirubin and this had been determined quantitatively in jaundice by ascertaining the "icteric index" that is, comparing the colour of the serum with that of a standard solution of potassium bichromate (Naustengracht). In 1915 to 1918, Van den Bergh (26) revived the old Erlich's diazo reaction, described by Erlich in 1886, for the quantitative estimation of bilirubin in the serum and used it for the first time to differentiate between bile pigment due to obstructive jaundice, and that derived from haemolysis.

3. The supravital staining of reticulocytes. The dye used is brilliant cresyl blue. Up until 1909, polychromasia was considered as a degenerative process taking place in old red cells, but in that year Hawes (27) showed that the number of polychromatophilic cells is always parallel to the reticulocytes which were known to be young red cells. This initiated subsequent investigations by Pappenheim (1919), Key (1921) Krumbhaar (1922), Cappell (1929) Whitby and Hynes (1935) and others as to the nature of the reticular substance, and now the "reticulocyte response" has become of increasing importance in judging the results of liver and iron therapy. A good description of "Reticulocyte Reactions" is given by Castle and Minot (1935).

4. The determination of the size of the red cells. This may be done either by the "volume index" method of Capps (1903) or the Price-Jones curve (1910) (28). The volume index gives the volume of the packed cell mass and is simpler and less time-consuming than plotting a Price-Jones curve. It is, moreover a more valuable determination, since the curve gives information as to the cell size in one dimension only, and in cases where the diameter-thickness ratio of the cells are disturbed, it gives an entirely erroneous impression of the cell size. The Price-Jones method is highly statistical and takes a very substantial amount of time and skill, so that it is not, as yet, applicable for routine clinical use.

The determinations of the normal haemoglobin levels were carried out by Williamson (1916) Peters and Stadie (1921), Haden (1923) (1925) (1932), Krumbhaar (for infants, 1932), Osgood (1926, 1934), Wintrobe and Miller, 1926, 1934, 1935.

References:
(27) Van den Bergh, A.A.H., Presse Medicale, 22, pp 441-443, 1921.
(1929) Mackay (for infants, 1932), Whithy and Hynes (1935) Linneburg and Sebartum-Hansen (1935) and many others. Their results indicate that the haemoglobin content of young males is 15.6 gms per 100 ccs of blood. The values for women and children are somewhat lower. All the modern instruments are standardized to this level, and some, like the new Sahli, and the Haden, permit readings directly instead of in per cent. No doubt it will take some years for doctors to become accustomed to this change, but it is certainly a less confusing and more exact way of speaking. Chemical studies on haemoglobin are still going forward and the exact iron content "of human haemoglobin is a problem that still awaits solution" (17).

The classification of anaemias had up to this time been into two great groups the "primary", for which no cause could be discovered, and the "secondary" or symptomatic. This was admittedly unsatisfactory but since no aetiological basis for classification was then possible, it was suggested that a morphological division of the anaemias on the basis of their volume and colour indices would prove a useful working hypothesis. Haden (29) worked this out very fully and pointed that another index, the "saturation" index, was necessary to make the classification complete. Later Wintrobe and others (30), suggested a method for making these indices absolute, that is, reporting the mean corpuscular volume in cu. and the mean corpuscular haemoglobin in micromicrograms ('). It is always a good idea to reduce measurements to exact terms but it is much easier to remember indices in variations of one, than to remember eighty-eights and twenty-sevens and I do not believe that to clinicians this elaboration will prove acceptable.

The Relations of Haemoglobin and Bilirubin.

The earlier students of anaemia had all felt the need for a knowledge of erythropoiesis. Pepper said in 1875 "the idiopathic disease (i.e. P.A.) must await explanation till we know where and how the red globules are developed." The opening sentence of Saltzer's report on Starr's transfusion reads: "As long as the origin of the blood corpuscles remain mystified, in ill-defined theories and facts, so long will our knowledge of disease of the blood remain incomplete and our treatment unsatisfactory or of no avail." But the first step in the study of haemoglobin metabolism did not come till 1913. In that year, Whipple and Hooper (1913), ligated the liver of dogs and injected haemoglobin intravenously. The dogs speedily developed jaundice. This work was reported under the title "Icterus. A Rapid Change of Hemoglobin to Bile Pigment in the Circulation outside the Liver" (31).
Previously it had been thought that bilirubin was manufactured only in the liver. Virchow in 1847 had shown that when iron is split off from haemoglobin, the resulting pigment which he called "haematoeldin" gave reactions similar to that of bilirubin. But in 1886 Minkowski and Naunyn removed the livers from geese and injected various agents like $H\text{}_2\text{As}$ which normally cause intense jaundice, and the geese produced absolutely no bile. This led to the conclusion that the liver manufactured the bile. McNeel in 1913 repeated the work of Minkowski and Naunyn and confirmed it but demonstrated that the bile was produced, not by the parenchymatous cells of the liver, but by the Kupffer cells. These cells are part of the reticulo-endothelial system and in birds this tissue is largely confined to the liver. But in man it has a very different distribution, being present in the spleen, bone marrow, lymph nodes and other tissues as well.

The work of Whipple and McNeel received confirmation from Mann (1925) who removed the entire liver from a dog, succeeded in keeping the animal alive and produced bilirubin formation to the point of jaundice. He studied the bilirubin content of the various organs and found most of it in the bone marrow. Haldeman also studied the site of haemoglobin formation by injecting laked blood and examining the organs for iron. Within an hour heavy deposits of iron appeared in the bone marrow and later smaller amounts in spleen, lymph nodes, liver and kidneys. (11)

This work formed a new basis for investigation and gave a new point of view for starting to work. How were the red cells formed, where did they get their haemoglobin, what happened to them in the circulation and how long did they live? What sort of cells were the reticulo-endothelial cells (hereafter referred to as the R-E cells) and where were they situated? For the first time the study of anaemia began with first principles.

The Fate of the Erythrocytes.

In 1917 Rous and Robertson (32) published the "Normal Fate of the Erythrocytes". They injected 10 ccs of blood daily into rabbits' veins running the haemoglobin up from 80 or 90% (Sahli) to about 150%. They also made rabbits anaemic by daily bleedings, reducing the haemoglobin to 20 to 30%. The blood and the washings from the spleen of both the plethoric and anaemic animals contained large numbers of poikilocytes and microcytes which Rous and Robertson recognised as being fragmentation forms or schizocytes. These deformed cells are in the process of being "threshed to bits". They are present in normal blood but in small numbers so they pass unnoticed. They concluded that they were probably finally disposed of by the spleen. Erlich in 1886 had suggested that poikilocytes are fragmented red cells, but of course, could offer no experimental evidence to prove it, and Andral, who first noted microcytes and poikilocytes had said they appear "broken or disintegrated.

Ashby in 1919 studied the life span of the erythrocyte by transfusing blood from a donor in another group and titrating the recipient's serum daily for the presence of foreign agglutinins. He found that some of the cells survive as long as 26 days. Wearn, Warren and Ames in 1922 confirmed this.

Sabin (1923) (33) undertook studies on the embryology and histology of the red cells. By the use of a supravital stain, neutral red, she confirmed the work of Rous and Robertson, actually watching a poikilocyte in the process of formation. The poikilocytes and microcytes were then en-

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gulfed by the action of the phagocytic R-E cells, which could be definitely identified by their reactions to neutral red. She also watched the formation of primitive red cells in a three-day-old chick embryo and observed that these cells came from the angioblasts (R-E cells) in the vessel walls.

The Histogenesis of the Erythrocytes.

In 1925 Doan, Cunningham and Sabin published their results of their work done on the histology and histogenesis of the blood cells and the connections of these cells with the R-E system. They simplified the red marrow of pigeons by starving them, and then watched erythropoiesis. They were able for the first time to trace out the vascular pattern in the bone marrow. The capillaries lead into sinusoids which are lined by endothelial cells and are invisible in fatty marrow when the walls lie in opposition to each other. The young red cells take origin from the R-E cells lining the sinusoids, multiply, distend the sinusoid, receive their complement of haemoglobin, become smaller, lose their nuclei and reticular structure and are finally inducted into the active circulation outside the sinusoid. The leucocytes arise from the R-E cells outside the sinusoids. A modified polyphyletic theory of the origin of the blood cells is thus proved to be the correct one. This view was the same as that originally advanced by Peppenheim in 1896. All the blood cells come from a parent R-E cell, but their first division determines whether or not they will be leucocytes or erythrocytes. Controversy is at present confined to the stage at which the cells become finally committed to their developmental potentialities, and the original ideas of Maximow and Naegeli should here be mentioned, but their consideration is more a matter of academic than of practical interest. (34).

Peabody in 1926 was able to trace erythropoiesis in man by the study of serial sections from the marrow in a man dead of typhus. In this disease the marrow undergoes practically pure erythropoiesis. (35) He confirmed the results of Doan, Cunningham and Sabin and later Sabin studied the process in rabbits. Turnbull (1926) is practically the only modern observer who denies the intravascular origin of the red cells (1).

The Development of Liver Therapy.

Meanwhile from 1920 to 1925 Whipple continued his researches and reported with Robscheit-Robbins the effects of various foods in restoring the blood in post-haemorrhagic anemias in dogs, to its former levels. These reports (36) included results from I. Mixed Diets, II Fasting and Sugar Feeding, and III, Meat and Liver. The latter was found to be exceedingly efficient as a haematinic, large numbers of reticulocytes and young red cells appearing in the circulation. By 1922 Whipple's researches had led him to make the first suggestion that pernicious anaemia might be a deficiency anaemia. "The decreased numbers of red cells is due to insufficient avail-


Whipple, G.H., Robscheit-Robbins, F.S., Am. J. Physiology, 72, 1925.

Part I, p 151.

Part II, p 167.

Part III, p 236.
able stroma material and the resulting disturbed pigment metabolism is due to more pigment being formed than can be used."

Minot and Murphy (37) decided to try Whipple's meat and liver diet on patients with pernicious anaemia in 1924. On May 4, 1926, they read before the Association of American Physicians their "Observations of Patients with Pernicious Anaemia Partaking of a Special Diet". They had tried the diet containing from 120 to 240 gms of fresh liver daily on forty-five patients and in each case had secured an excellent remission. In this first paper, they noted the reticulocyte response, the drop in the icteric index, the rise in haemoglobin and red cell levels and the steady increase in corpuscule volume. However, they cautiously conclude that the average duration of treatment was so far, only seven months, and they feared that these remissions might not be more permanent than those appearing spontaneously.

Immediately the Minot and Murphy diet was announced, attempts were begun to extract the active principle from liver and isolate it, some under Minot's direction and some independently. These researches had a very practical basis as patients living at a distance from markets found it impossible to secure a supply of liver, moreover, the diet was very unpalatable to some people and to make it acceptable required considerable culinary skill, and the price of liver jumped from fifteen to sixty cents a pound, making the new treatment prohibitive for the poor. The number of liver extracts and preparations now available is quite bewildering, but they are all effective if standardized as in the U.S. by the "double reticulocyte response" of Minot and Castle (1925) or as in Britain by the method recommended by the Association of Clinical Pathologists of Great Britain. The investigators who have worked on this problem include: Cohn (1927), Cohn, Minot and Allen (1926), Gunzlin "Campolon" (1931), Helmer, Fouls and Zerfas (1925, 1924), Reimann (1931), Cohn, McMeekin and Minot (1930), Weldon and Clowes - "Extralin" (1932), Strauss and Castle (1932), Wills and Stewart (1935), Dakin, West and Ungle "Anaheamin" (1935, 1936). Some of these extracts are of such concentration that they will maintain the patient in remission for long periods.

Sturgis and Isaacs showed in 1929 (38) that desiccated hog's stomach will produce remission in pernicious anaemia. Some of the other macrocytic anaemias will respond to Marmite and to Vitamin B1. The potency of liver extracts may be increased by incubating them with normal gastric juice, or intrinsic factor, and some of the preparations mentioned above are thus prepared. Some contain Marmite and Vitamin B1.

Another fraction of liver, not present in the extracts used for treating P.A., is effective in post-haemorrhagic anaemia. This fraction was studied thoroughly by Murphy and Powell (1929) and Sturgis and Farrar (1936).

The Aetiology of Pernicious Anaemia.

Meanwhile, Castle and his collaborators, set to work to find out by just what mechanism liver feeding secures remission in pernicious anaemia. These researches were successful, and the results of them are included in the following chart, from Whitby and Britton, pp-126-127. : (39)

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### Experiments Proving the Nature and Distribution of Haemopoietic Principle

<table>
<thead>
<tr>
<th>Investigator and Date</th>
<th>Experiment</th>
<th>Activity of the Resulting Product in Recovery from P.A.</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bock, 1921</td>
<td>Administration by stomach of beef juice or of beef protein by stomach</td>
<td>+</td>
<td>The haemopoietic principle is produced by and is mediated by the juice of the stomach.</td>
</tr>
<tr>
<td>1923</td>
<td>Administration by stomach of beef juice or of beef protein by stomach</td>
<td>-</td>
<td>The haemopoietic principle is mediated by and is produced by the juice of the stomach.</td>
</tr>
<tr>
<td>Bock, 1921</td>
<td>Administration by stomach of beef juice with an independent protein and an independent juice from a patient</td>
<td>-</td>
<td>The haemopoietic principle is not produced by the juice of a patient.</td>
</tr>
<tr>
<td>Bock, 1921</td>
<td>Administration by stomach of beef and juice from a patient</td>
<td>-</td>
<td>The haemopoietic principle is not produced by the juice of a patient.</td>
</tr>
</tbody>
</table>

The interaction of a normal gastric juice with beef protein produces the haemopoietic principle, whereas the absence of the juice or of the protein does not. It is concluded that two factors are necessary, (a) the intrinsic factor in gastric juice, and (b) the extrinsic factor present in certain foods which act upon (a).
Although it is to Castle that the laurels go for demonstrating the mechanism of pernicious anemia, a number of others have made valuable contributions to our knowledge of the gastric factors and their relationship to pernicious and other anemias. Hurst in 1923 had recommended HCl in the treatment of P.A., and has continued to investigate the achlorhydria in pernicious anemia and in the Plummer-Winson syndrome. He has recently reported five cases of pernicious anemia following gastrectomy. Studies on the incidence of achlorhydria in pernicious families have been carried out also by Cornell, who in 1927 wrote an excellent monograph on "Pernicious Anemia" and reviewed the literature to that date very fully. Davidson and Gulland in "Pernicious Anaemia" 1920, gave very full clinical reports of their studies and included the summary of extensive bacteriological studies made previously by Davidson. MacLachlan and Klein in 1926 reported four generations of pernicious anemia and achlorhydria in one family, and Wilkinson and Brockbank in 1931 found that 24% of the blood relatives of subjects with pernicious anemia had achlorhydria, and half of these had achylia also.

Moreover, the gastric acidity has been shown recently to be lowered or absent in the iron deficiency anemias, particularly in that of the idiopathic hypochromic variety. Mettler and Minot in 1931 described this in the "The Effect of Iron on Blood Formation as Influenced by Changing Activity of the Gastro-duodenal Contents in Certain Cases of Anemia". Davies (40) in the same year described the progressive failure of gastric secretion in its relation to anemia. Davies' results are summarized below:

<table>
<thead>
<tr>
<th>Before Histamine</th>
<th>After Histamine</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl + Pepsin</td>
<td>Volume HCl Pepsin</td>
<td>Usually no Anemia.</td>
</tr>
<tr>
<td>Nil + Pepsin</td>
<td>Usually nil</td>
<td>Simple, Achlohydric Anemia</td>
</tr>
<tr>
<td>Nil</td>
<td>Nil</td>
<td>Hypochromic Anemia+ Tendency toward Microcytosis.</td>
</tr>
<tr>
<td>Nil + Nil</td>
<td>Nil</td>
<td>Pernicious Anemia.</td>
</tr>
</tbody>
</table>

Studies on Other Deficiency Anemias.

The realization that pernicious anemia was in fact a deficiency disease, caused by lack of haemopoietic principle called for a revision on the ideas as to the aetiology of all the anemias, particularly those which might be due to absence of some of the other substances known to be necessary for the maturation of the erythrocyte. The following diagram modified from Boycott (1929) gives an indication of the line that subsequent investigations of deficiency anemias took.
Macrocytic Anaemias.

Macrocytic anaemias are now considered to be due to lack of extrinsic factor, lack of intrinsic factor, or inability to manufacture, absorb, store or utilize haemopoietic principle. The purest example of macrocytic anaemia due to lack of extrinsic factor is tropical macrocytic anaemia which has been studied particularly by Wills (41) who found that the cheapest way to supply extrinsic factor is to give 30 gms of Marmite (autolyzed yeast) daily. This anaemia is frequently found in association with pregnancy and this feature has been investigated by Wills as well as by De (1930) and by Balfour (1927)

The mechanism of the macrocytic anaemia of pregnancy occurring in temperate climates was demonstrated by Castle and Strauss (1932) to be due to lack of haemopoietic principle consequent upon altered gastric secretion, that is, it is a sort of temporary P.A., which responds well to liver extract by injection. Stewart and Hardie advocate delivery by Caesarian section and the use of transfusion in intractable cases. (1931)

From an historical point of view, Bothriocephalus anaemia is the most interesting of the macrocytic anaemias because it was so early confused with true P.A. This anaemia can be cured by large doses of liver extract, even before the worms are expelled, so it is assumed that the worms simply eat the haemopoietic principle and that big doses of liver extract give ample supply to both parasite and host. The most interesting recent discoveries about Bothriocephalus anaemia have been made by Birkeland (42) in 1932, who found that of 508 reported cases, 391 came from Finland and that in 32 cases occurring in the U.S., 21 were in Finnish immigrants. In Japan, Italy and Roumania the population is heavily infested with Bothriocephalus, but only four cases of Bothriocephalus anaemia have ever been reported from these countries. This anaemia has also a strong familial incidence, and is frequently observed in families other members of which have P.A. (Schaumann, 1930, Talqvist, 1907).

Sprue, idiopathic steatorrhoea, celiac disease and cases where large segments of the gut have been resected, may all show hyperchromic macrocytic anaemias due to failure to absorb haemopoietic principle. The similarity of the blood picture in sprue, and the gastro-intestinal symptoms, had led Wood (43) and others to the conclusion that sprue and P.A. were the same disease. (1925) Recent studies of the blood pictures in sprue have been made by Castle, Rhoades and Lawson (1935) and the blood in sixteen cases of celiac disease has been studied by Neale, Smallwood and Shippen (1935).

Inability to store haemopoietic principle occurs in disease of the liver especially cirrhosis. This has been reported recently by Wintrobe and the cause of the macrocytic anaemia was demonstrated by Goldhammer, Isaacs and Sturgis in 1934. Cabot in 1901 had reported two cases of hyperchromic anaemia associated with cirrhosis, and he says that Hayem also reported a high colour index, anaemia and jaundice in a case of hypertrophic cirrhosis.

A fortunately rare form of anaemia is achreptic anaemia described by Wilkinson and Klein in 1936. These patients are unable to utilize haemopoietic principle even when it is supplied in large doses.

Although the usual anaemia resulting from thyroid deficiency is microcytic, it may be macrocytic, and in this case the clinical picture has a striking resemblance to P.A. MacKenzie in 1926 reported 4 cases mistakenly diagnosed as P.A. cured by the administration of thyroid extract. Indeed, thyroid extract in small doses, improves the effect of liver extract especially when the basal metabolic rate is lowered.

The macrocytic anaemias of children have studied particularly by Parsons, Haksley and Gittens (1932).
Microcytic Deficiency Anaemias.

Iron Deficiency Anaemia:

The idiopathic hypochromic anaemia first described by Faber in 1909 has recently been recognized to be very prevalent among the middle aged women of the working classes. Investigations have been carried out by Wintrobe and Beebe in Baltimore (44) in 1933 who give a full bibliography and by Davidson and his associates in Aberdeen (45). Witts (46) has had the widest experience with this anaemia (46). Heath, Strauss and Castle in 1932 showed that iron absorbed by a person with iron deficiency anaemia is converted quantitatively into haemoglobin (47). Witts' results with iron therapy are so excellent, and the differences in the utilization of various iron preparations are so conclusively demonstrated by him, that his results are summarized below:

(From the Lancet, I, p 1, 1936)

<table>
<thead>
<tr>
<th>Preparation:</th>
<th>Daily Dose in Gms or ccs</th>
<th>Iron Content in mgms</th>
<th>Utilization per cent:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferra :</td>
<td>Daily - 6.4</td>
<td>100 - 300</td>
<td>0.5 - 2.0</td>
</tr>
<tr>
<td>Ferrous :</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>0.25 - 0.5</td>
<td>100 - 200</td>
<td>12.5 - 25</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.6</td>
<td>150</td>
<td>14</td>
</tr>
<tr>
<td>Photo lactate</td>
<td>1.5</td>
<td>100</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Folic acid</td>
<td>3.4</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Ferrous :</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate :</td>
<td>40 - 10</td>
<td>1500 - 2150</td>
<td></td>
</tr>
<tr>
<td>Ferrous :</td>
<td>100</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Lactate :</td>
<td></td>
<td>1500 - 2150</td>
<td>6.0</td>
</tr>
<tr>
<td>Photo lactate</td>
<td></td>
<td>100</td>
<td>11 - 17</td>
</tr>
</tbody>
</table>
| But other factors besides the iron salt used and its dosage and method of administration enter into the conversion of iron into haemoglobin. Some of them are Chlorophyll, whose action was described by Minot in 1924, bilirubin, whose action was studied by Robacheit-Robbins and Whipple in 1934 and certain vitamins, described by Nyfeldt in 1936. The gastric factors have already been discussed.

A recent very effective iron preparation, ferrous adenylate, was announced by Ruskin and Katz in 1936.

A "reticulocyte response" is obtained in idiopathic hypochromic anaemia if iron therapy is adequate and optimum, as was first demonstrated by Heath in 1932.

One occasional but interesting association with idiopathic hypochromic anaemia is what is known as the Plummer-Vinson syndrome. According to Vinson (1922) this syndrome was first noted by Plummer in 1914. It consists of Dysphagia, an atrophic glossitis, spoon-shaped nails and a microcytic anaemia with achlorhydria. Hurst says the dysphagia is a result of achalasia.

96% of cases of idiopathic, hypochromic anaemia occur in women between 40 and 50. (44).
Recent studies have been made on iron metabolism in pregnancy by Coons (1932), Baer and Fowler (1934) and Dieckmann and Fowler. Coons demonstrated that the normal pregnant woman suffers from iron starvation. Women of the childbearing age require to metabolize about 15 mgms of iron daily and men require about half this amount. During pregnancy the requirement is tripled. Boycott in 1936 found that 22% of all women entering London maternities have iron deficiency anaemias. Strauss and Castle made good studies of all the anaemias of pregnancy and showed that gastric acidity was lowered in over 80% of pregnant women. This hypochlorhydria prevents, of course the utilization of the available iron.

The iron deficiency anaemias of infants and children have been most extensively studied by Mackay (49) who made full clinical and haematological investigations on all the anaemias of childhood. She gives the results of iron treatment in anaemias in breast- and bottle-fed infants, in twins, in premature infants and in the congenital (non-haemolytic) anaemia.

The anaemia produced by deficiency of Vitamin C has been most recently studied by Parsons and Smallwood.

The Haemolytic Anaemias

Haemolytic anaemia is defined as an anaemia in which there is an increased icteric index, an indirect Van den Bergh reaction and a hyperplastic marrow as evidenced by the large numbers of reticulocytes and other young red cells in the circulating blood. These anaemias are due to excessive haemolysis occurring within the vessels.

Some of these anaemias are not "anaemias" at all, the characteristic abnormality of the red cells may, and usually does, exist without causing any depression of the red cell and haemoglobin levels because the marrow is fully able to compensate for the excessive haemolysis. Such individuals however, always show large numbers of reticulocytes in the blood films. As Chauffard said, patients with haemolytic jaundice are not so much "sick as jaundiced" and Graham paraphrased this to apply to sickle cell anaemia, saying these subjects were not so much "sick as sickling."

The most interesting pathological feature of this group of anaemias is the changes occurring in the long bones in the chronic cases. In radiographs these bones and the small bones of the hand and foot are porous looking with sharp trabeculations and thinning of the cortex. The skull in profile shows a surface studded with radiating spicules, the tables are unusually thin, and there is medullary thickening.

1. Acholuric Jaundice:

The fundamental pathology of this anaemia lies in the fact that the erythrocytes are deformed so that they are shorter, thicker and broader than normal. They have a very large volume index, but appear in films as small, round and heavily stained. Haden in 1934 and 1935 (49) showed that normal erythrocytes, when subjected to hypotonic solutions, undergo an alteration in shape so that they approximate the shape of the cells in acholuric jaundice. This explains the decreased resistance of such cells to hypotonic NaCl, since they have already, so to speak, undergone the first step in haemolysis. He suggests the name "spherocytosis" for this deformity of the cells.

The bone changes have been well studied by Friedman in 1928. Hawksley and Bailey (1934) and Hawksley (1936) have studied the way in which splenectomy affects the exacerbations of haemolytic jaundice, and their investigations indicate that the favourable results are due to the removal of a large block of R-E tissue, so cutting out the phagocytic activity of large numbers of these cells and preventing their contact with the fragile red cells.

Erythroblastaemia, Type Cooley.

It is generally agreed that von Jaksch originally described a syndrome and not a specific anaemia. In America the term von Jaksch's anaemia is now discarded and the term erythroblastaemia, as suggested by Cooley, is used to designate a haemolytic anaemia with large numbers of erythroblasts in the circulation, a high leucocytosis with myelocytes and splenomegaly. Most of the cases occur in young children of Mediterranean extraction. British haematologists and paediatricians still retain the term von Jaksch's anaemia to designate the more chronic form of erythroblastaemia. Cooley in 1927 and 1928 (50) defined erythroblastaemia and later with colleagues made extensive studies on all the haemolytic anaemias of children. Parsons, Hawksley and Gittens have also made full studies of these haemolytic anaemias of children and call them the "erythronoclastic anaemias". (1933) Others who have contributed to our knowledge in this field include Evans (1922), Bass and Denzer (1924, 1926) and Brannan, (1927).

Icterus Gravis Neonatorum.

Despite the researches of numerous investigators, the exact cause of this anaemia still remains obscure, some contending that it is due to an haemolysin in the serum, some that the fault is in the erythron. In its pure form this anaemia is congenital and usually does not affect the first-born child. Small transfusions are curative if given early enough, but the ultimate prognosis is poor.

Acute Haemolytic Anaemia of Lederer.

An acute haemolytic anaemia was described by Lederer in 1925 and 1926. Still also contributed to early studies of this anaemia (1926). The haemolytic agent is unknown. Most of the cases occur in children, and of those seen in adults, the vast majority have been in pregnant women (Witts).

Transfusion is curative.

Sickle Cell Anaemia.

After Herrick's original report (23) many papers appeared on this remarkable anaemia. Sydenstricker in 1923 (51) recognised that the peculiar polikilocytosis does not always cause anaemia and used the terms "latent" and "active" sicklers. About 10% of the negro admissions to American Hospitals show the sickling trait. Graham (52) in 1924 gave one of the best descriptions of the morbid anatomy. Hahn and Gillespie in 1927 showed that when these cells are suspended in a moist chamber and subjected to a stream of CO₂, "sickling" occurs and that this process may be reversed and the cells will again "round up" when O₂ is passed in. They concluded that the exacerbations are due to anaemia, but this has not been substantiated. Rich in 1928 demonstrated a malformation of the splenic sinusoids. The bone changes have been studied by Moore in 1929, Vegh and Diamond in 1928 and Cooley and Lee and more recently by Biggs (1932). (53)


Miscellaneous Anaemias.

Toxic Anaemias.

Industrial poisoning has assumed great economic significance in recent years. The two chemical poisons which are most important from the point of view of producing anaemia are lead and radium. Aub, Fairhall, Minot and Reznikoff demonstrated the effects of lead on the red cells and Lane in 1931 has made recent studies on lead poisoning. Radium and its effects on the blood picture has been studied fully by Martland, Conlon and Knef (1925, 1929). Radium produces an aplastic pernicious anaemia which does not respond to liver. Madame Curie died of it.

Hookworm Anaemia.

This had always been considered to be a pure post-haemorrhagic anaemia, until Wells in 1931 studied its mechanism. In dogs infested with ankylostoma caninum he found that each worm removed 0.84 ccs of blood per day, but the anaemia was not always proportional to the number of worms present. De Langen showed that the anaemia depends also on dietary factors and that the worms interfere with protein digestion.

Banti's Disease.

McMichael (1934) has made the most recent studies on Banti's disease but its etiology is still unexplained. Davidson in 1934 compared the results of medical treatment of Banti's disease (iron therapy) with splenectomy and his report will make the physician still more reluctant to advise splenectomy.

The Lipoid Histiocytoses.

It is generally agreed that the anaemia occurring in these diseases is due to imperfect functioning of the diseased R-E tissue. The chemistry of the abnormal lipoids has been pretty thoroughly worked out but there have been few recent blood studies in Gaucher's disease.

Pick in 1933 separated into a clinical entity Niemann-Pick's disease, first described by Niemann in 1914. The disease is accompanied by a severe anaemia and is invariably fatal. It occurs in Jewish children under two years of age and is due to the abnormal deposition of lipoid in the R-E cells.

This is the state of our knowledge of anaemias at the present time. The advances during the last few years have been very rapid and only a few odds and ends are left to be tidied up in the future.

Such a good foundation of the pathological physiology of anaemia has now been laid, and such efficient therapy devised that the average modern doctor enters the practice of his profession much better equipped to diagnose and treat it than even the most brilliant of his predecessors.

Let us hope that he will not forget his debt to the past, that he will remember the patient work and clever minds that have built up this knowledge, that he will use the haemoglobinometer and haemocytometer even on his busiest days, and that he will prescribe his haematinics not promiscuously, but rationally.
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