Anemias of Childhood

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INDEX

PAGE

I. JOHN ADOLPH ANDERSON 106

II. ANEMIAS IN CHILDHOOD - CASE REPORTS . . . . . 106 - 108

III. ABSTRACT . . . . . 108 - 116

IV. MINNEAPOLIS SURGICAL SOCIETY 116

V. IT WOULD BE NICE 117

VI. MOVIES 117

I. JOHN ADOLPH ANDERSON

Born in Sioux Falls, South Dakota, graduate of Sioux Falls High School, pre-medic and medical course at University of South Dakota and University of Minnesota, Internship - University of Minnesota Hospitals; Research Assistant in Pediatrics, University of Minnesota since July 1st, 1934, prepared the program for staff meeting today.

II. ANEMIAS IN CHILDHOOD

Case I. Von Jaksch's Anemia.

., 4 months old, hospital , admitted November 2, 1934, expired November 21st (total stay 19 days).

Patient was born July 15, 1934, full term, difficult labor, vertex presentation. At 3 weeks of age, had hematemesis, approximately 1½ oz. of blood. Given intraperitoneal transfusion of citrated blood. At age of one month, had melena, 2d transfusion given. Subsequently, patient showed melena and hematemesis at times. At age of 2 months, weighed one pound less than birth weight.

Family History: Patient was the first child. Mother gives history of having been treated for syphilis for 2½ years, treatment terminating 4 years ago. Wassermann negative at present.

Physical examination on admission: slightly cyanotic, temperature 102°, has a feeble cry, quite listless. Eyes - convergent strabismus, sclerae blue, no petechiae. Abdomen - few petechiae; spleen slightly palpable below rib margin; liver not palpable. Extremities - marked hypoplasia of arms and forearms with radial deviation of hands.

Laboratory: Urine - negative. Blood - Hb. 62%, erythrocytes 3,370,000, leucocytes 33,700. Platelets - 75,000. Coagulation time - 6 minutes, 30 seconds; bleeding time - over 50 minutes. Wassermann test - negative; both parents - negative. Hemogram by Hematology Department - eosinophiles 3%, basophiles 1.5%, Myeloblasts 6.5%, leucoblasts .5%, monocytes 10%; impression - Von Jaksch's anemia. X-ray of pectoral girdle and feet - marked deformity of pectoral girdle with rudimentary scapula, only glenoid process being present. Deformed humerus on right, absence of radius. Left: scapula fairly well developed, ulna present. Several phalanges of feet missing. X-ray of long bones and skull - negative.

Progress:

11- 4-45 - 45 cc. intravenous blood.

11- 5-34 - 50 cc. whole blood (IV). Noticeable melena present first 5 days of hospitalization.

11- 7-34 - 100 cc. of blood given. No further melena. Afebrile for next 6 days. Temperature rose to 104. Loose watery stools developed.

11-19-34 - Otitis media diagnosed on right. Myringotomy performed. Pure culture - pneumococci. Antrotomy on right. Considerable pus obtained. 100 cc. citrated blood given. Fever continues, remaining elevated to 105 or 106°. Clinical evidence of pneumonia in both lungs. Expired.

Autopsy: Mal-developed, white male, 4 months of age, with congenital deformities of upper extremities and marked shortening of arms and forearms with radial deviation of hands. Operative incision of right antrum.

Peritoneal Cavity normal. Right Pleural Cavity contains about 300 cc. of thin purulent fluid. Heart normal.

Right Lung weighs 60 grams; shows marked consolidation of upper lobe. Left Lung weighs 90 grams; shows considerable consolidation throughout, most marked in lower lobe. On cut section, small abscesses found.

Spleen weighs 20 grams and appears normal. Liver weighs 200 grams and shows no abscesses or nodules. Gall-Bladder, Gastro-Intestinal Tract, Pancreas and Adrenals appear normal.

Diagnosis:

1. Visceral purpura (Henoch's)
2. Suppurative otitis media and [illegible] antritis, right.
3. Bronchopneumonia, bilateral.
4. Congenital anomalies (Micromelia).
5. Hematological diagnosis - Von Jaksch's syndrome.

Case II: Nutritional Anemia.

[illegible], 18 months old, hospital [illegible], admitted December 21, 1931, discharged February 3, 1932.

Past History: History of frequent chest colds, possibly bronchitis, and occasionally nausea and vomiting. Showed marked pallor, apparently present since birth. Had considerable lack of appetite, failure to gain weight and develop normally since birth. Able to hold head up at 10 months, sit up, was in fairly good condition, and weighed 16 lbs. At age of 14 months, began to do poorly and refused most of feedings except milk. Given no cod liver oil but a slight amount of orange juice and the rest of the diet was apparently adequate. In view of the fact that he refused much food, it was questionable whether he had been getting the proper caloric intake.

Physical examination on admission: Weight - 8 kilograms. Poorly nourished with marked pallor and appearing quite ill. Temperature 103.8°. Poor muscular development. Muscles flabby. Axillary, cervical and inguinal nodes - palpable. Chest and heart - negative. Abdomen - spleen definitely palpable. Slight rachitic rosary and some grooving of ribs..

Laboratory: Urine - normal. Blood Wassermann - negative. Blood - hemoglobin 20%, erythrocytes 2,600,000, leucocytes 8,000, neutrophiles 46%, lymphocytes 30%, monocytes 24%, marked hypochromasia, anisocytosis, moderate poikilocytosis and slight polychromatophilia. No evidence of leukemia in blood studies. X-ray of chest - shows slight clubbing at ends of ribs and slight enlargement of heart.

Progress: Placed on 18 month's diet of high vitamin, high caloric value. Given subcutaneous fluid. Transfused with 50 cc. blood. In 5 days, temperature returned to normal. Given ferric ammonium citrate, copper sulphate solution, ultra violet radiation, and 2 subsequent transfusions. One month and a half following admission, hemoglobin was 81% and the blood picture apparently normal. Gain of 1,300 grams, or approximately 3 lbs. Appetite and general condition improved markedly.

3- 3-32 - Seen in O.P.D. Hemoglobin 84%. Still some evidence of bronchitis.

4-28-32 - O.P.D. Hemoglobin 75%, erythrocytes 4,300,000. Still evidence of bronchitis, but definite improvement. Weight - 11,685 grams.

Cases III & IV: Nutritional Anemia in Twins.

[illegible], 11 months, hospital [illegible]. Child was one of premature twins born at 7 months (weight 4 lbs.). Was in incubator 2½ months and fed breast milk and boiled cow's milk. After discharge, was fed whole cow's milk only until 11 months of age. Child had restlessness and head sweats for 2 months previous to admission. Past history consisted of chicken-pox at age of 5 months and frequent upper respiratory infections. Unable to sit alone. Developed no teeth.

Physical examination on admission: weight - 4,920 grams. Child is poorly developed, under-nourished and pale. There is some beading of the ribs and the fontanelles are open widely. No teeth present. There is a moderate nasal discharge. Cervical glands are palpable. Spleen not palpable.

Laboratory: Blood - hemoglobin 45%, erythrocytes 3,110,000, leucocytes 6,320, neutrophiles 29%, lymphocytes 68%, monocytes 2%, eosinophiles 1%; marked anisocytosis, moderate poikilocytosis, hypochromasia and slight polychromasia. Blood calcium - 10.2,

Phosphorus - 2.04 mg. %. Histamine gastric expression - shows free Hcl. X-ray shows rickets of moderate degree with beginning healing.

Progress: Given 2 blood transfusions, Haliver oil, viosterol, orange juice, and an adequate 11 months' diet. Hemoglobin rose to between 65 and 70%. Erythrocytes 4,150,000. Gained steadily. Blood calcium later - 10.00, blood phosphorus - 5.26 mg. %.

Case IV:

., 11 months of age, hospital admitted 2-25-32 and discharged 4-17-32.

Twin sister of above, A.P., premature at 7 months, birth weight 4½ lbs. Remained in incubator for 2½ months, took feedings of breast milk and complements (boiled milk formula). Discharged from hospital at age of 3 months, weighing 5½ lbs. Fed breast milk and complements until age of 6 months, then on whole cow's milk. No cod liver oil; only small amounts of orange juice given.

Past History: Had chicken-pox at 5 months and since this time had a series of upper respiratory infections but no gastro-intestinal upsets.

Physical examination on admission: shows a poorly developed, poorly nourished, very pale, female infant, 11 months of age, weighing 5,225 grams. Marked beading of ribs. Anterior fontanelles widely open. No teeth. Quite marked nasal discharge. Palpable cervical adenopathy. Child is pot-bellied but the liver and spleen are not palpable.

Laboratory: Urine - negative. Blood - Hemoglobin 45%, erythrocytes 2,700,000, leucocytes 9,250, neutrophiles 41%, lymphocytes 54%, eosinophiles 2%, monocytes 1%; moderate poikilocytosis, slight hypochromacia, marked anisocytosis, slight polychromatophilia. Blood Wassermann - negative. Phosphorus - 2.6 mg. %, calcium - 9.8 mg. %. Gastric expression - 7.5° of free Hcl in fasting specimen, 55° free Hcl following histamine. X-ray of long bones and ribs - shows rickets of extreme grade with healing and multiple pathological fractures.

Progress: Placed on 11 months' diet, including Haliver oil, yeast, ferric ammonium citrate, subsequently given 2 transfusions of 100 cc. citrated blood. During course of 53 days in hospital, gained 800 grams. Hemoglobin - 70% on discharge.

III. ABSTRACT

I. Nutritional Anemia

A. Historical

1889: Bung (1889) found amount of iron present in liver and spleen, and total amount of iron in body expressed as percentage of body weight was highest at birth, and thereafter fell progressively until it reached a minimum at end of lactation period.

1899: Abderhalden produced nutritional anemia in animals by limiting their diet to milk for a considerable period after end of lactation period, and found that the addition of inorganic iron to diet of these animals did not bring about an increase in hemoglobin.

1920: Whipple and Robscheit-Robbins studied rate of hemoglobin formation in dogs rendered anemic by repeated bleedings and which were given diet low in iron.

1925: Hart, Steenbach, Waddell found that impure salts of iron cured nutritional anemia but that pure salts were quite ineffective, further that to obtain a cure the addition of copper to the iron salts was essential. Results were challenged along two main lines: one stated that certain amino-acids which they claimed to be copper free will cure nutritional anemia; others agree that copper is most effective curative supplement to iron and state that other metals, nickel, germanium, manganese,

arsenic, vanadium, titanium, zinc, rubidium, chromium, selenium, mercury can also act as curative supplements, and that the addition of pure iron alone to a milk diet will effect a cure. However, Elvehjem and Sherman show that in absence of copper, inorganic iron is readily assimulated by rats suffering from nutritional anemia and stored in the liver and spleen, but that it cannot be used until copper is supplied, when the greater part of the iron in the liver is removed and built into hemoglobin.

(1). Blood Changes in Normals Following Birth.

After birth, there is a fairly rapid destruction of red cells, the more fragile immature cells which are present in greater proportion in the blood of immature infants, being early destroyed. Hence, there is a rapid fall in hemoglobin in the first week of life, greatest in infants of low birth weight, and less in infants of higher birth weight. This destruction causes a further increase in blood bilirubin, and may give rise to an icteric tinge to the skin, namely "physiological" jaundice. During this stage of physiological blood destruction, red cell formation is presumably decreased as shown by the small number of reticulocytes in the blood of normal infants between 1 and 4 weeks old. The drop in red cells continues until about the third month of life. The meager evidence available seems to point to red cell formation again increasing between 5 and 8 weeks old, though it does not usually exceed destruction until the 3d or 4th month. Red cell hemolysis of pathological grade in the first weeks of life may call out a counteracting increase in red cell production.

B. Etiology.

As far as essential minerals are concerned, and taking iron as the example, the shortage causing anemia may therefore occur as follows:

(1) Deficient Ante-natal Storage
(a) Iron deficiency in the mother.
(b) Deficient transference of iron to fetus.
(c) Prematurity of fetus resulting in insufficient storage.
(d) Twins, the iron storage obtainable from the mother being insufficient for both children.

(2) Deficient Post-natal Supply.
(a) Insufficient supply of iron in the breast milk, possibly due to iron deficiency in the mother's milk.
(b) Artificial feeding with ocw's milk which contains less iron than human milk, and gives an iron retention only 1/5 that of breast milk.
(c) Prolongation of milk feeding beyond the normal lactation period.

It is probable that both physical immaturity and anemia in the mother predispose to anemia in the child. The babies of primiparae and multiparae had about the same hemoglobin level. No evidence was obtained connecting anemia in the infant with dietetic deficiencies in the mother, though, no doubt by analogy with laboratory experiments, a deficiency of iron in the diet of the pregnant mother, should it exist, would predispose to anemia in the infant.

C. Age Incidence.

(1) McKay, H., demonstrated that iron administration raised the average hemoglobin level at 3 to 4 months in artificially fed infants, and concluded that iron want, and the consequent anemia are becoming apparent in artificially fed infants by this age. In breast fed, it occurred a little later. There is evidence that anemia occurs before 3 months but there is no knowledge

of this being due to an iron want. Premature infants are frequently anemic by 2 months of age.

D. Pathology.

(1) There is a reduction in the hemoglobin content of the blood as severe as 30 to 40%. The red blood cells fall slightly. The color index is .5 to .6. Blood smears in mild cases show a variation in size, shape and in staining. In uncomplicated cases, the white blood count is normal. Splenic enlargement and lymphadenopathy are not characteristic.

E. Symptoms and Course.

(1) The anemia is insidious in onset, and pallor is present. There is usually no icteric tinge in uncomplicated cases. The general health is usually good. The most important feature, according to McKay, is the susceptibility to infections, as demonstrated by anemic infants shown to have a morbidity rate twice as great as those given prophylactic treatment. This lowered resistance shows itself in liability to colds, otorrhoea, bronchitis, enteritis, and in a tendency for these infections to become chronic.

F. Treatment.

(1) Ferric Ammonium Citrate.

(a) Since anemia in the mother tends to predispose to anemia in the infant, treatment of the anemic expectant mothers is indicated in the interests of both. The treatment of the anemia of the adult is a separate question. Infants, both breast and artificially fed should be given prophylactic treatment. 4½ grains for a 10 lb. infant is probably adequate of ferric ammonium citrate. The diet should also be adjusted. Iron so given will raise the hemoglobin in a 5 months old child to 80%. Infants should be started before 2 months and prematures when 4 weeks old. The curative treatment follows the same line, and is begun gradually. There seems to be a depletion of iron storage during infections, and the hemoglobin response may be slight or not at all until the infection subsides. Many investigators state that iron administration is ineffectual. This is probably due to first, too short a period of treatment, second, the presence of pyogenic infections, and third, disturbances in the alimentary tract, or to too low solubility or chemically pure iron salts.

(2) Liver causes a rise in the hemoglobin because of the high content both of iron and copper. Liver extract alone shows little or no response, because it contains very little iron.

(3) Yeast therapy has a curative effect on nutritional anemia of the rat, and animals so cured are capable of reproduction, and the progeny show nutritional anemia shortly after birth. Evidence is brought forward showing that the beneficial effects are due in part to iron, organic and inorganic, copper, vitamin B complex, and possibly amino-acids. It has also been shown that iron is effective only if absorbed in the divalent condition, i.e. as the ferrous salt. Ferrous sulphate has been used and shown to produce a greater and more rapid response than ferric. Do not produce dyspeptic symptoms (Lathrop).

(4) Iron-copper and Iron-sodium Glutamate.

(a) Drabkin has shown that iron therapy stimulated the bone marrow to increased cell formation, but did not cure the anemia. Both iron-copper and iron-sodium glutamate were effective therapeutic agents, the latter being somewhat superior. None of the forms of therapy employed, however, was completely adequate from the standpoint of continued maintenance of effect.

B. Anemia of the Premature.

(1) Possibly due to: (1) Deficient ante-natal storage of iron, and perhaps of copper in the liver and spleen. (2) Josephs maintains that as in the normal child, the fall in red cells and hemoglobin is due to the adjustment of blood formations, and destruction at a

lower level than at birth, but that this failure of the hemopoietic tissue is more profound and prolonged in the premature child. (3) Others stress importance of blood destruction rather than failure of formation and regard many of these anemias as being of the hemolytic type, and due to an increased severity and prolongation of the hemolysis which normally occurs at birth. The bilirubin in the blood of the normal infant returns to normal.

From a study of reticulocytes, it is shown that there is no basis for the idea that the fall in red cells and hemoglobin was dependent on hypoplasia in any strict anatomic sense. There was a period failure to react to the administration of iron that lasted for from six to ten weeks after birth, the duration of the period depending largely on the degree of prematurity. After this early period of non-reactivity there followed a short transition period with delayed response, after which administration of iron was followed by prompt response of the reticulocytes and a rise in red cells and hemoglobin. Apparently, lack of iron plays no important part in the development of anemia before the third month. Later, although iron may raise the hemoglobin content, transfusion is still the method of choice. Copper had no demonstrable effect.

Clinically, the appearance of babies suffering from nutritional anemia and anemia of prematurity is the same with the exceptions: (a) Splenomegaly and lymphatic hyperplasia are perhaps more common when anemia is fully developed. (b) In the earlier stages, the anemia is of a hyperchromatic type, but later changes to that of nutritional anemia.

(2) Treatment and Prophylaxis:

Merritt and Davidson, Abt and Nagel show that majority of premature infants develop a more or less severe anemia. It cannot be entirely prevented but can be ameliorated by the early administration of iron in large doses. Ferric ammonium citrate (50% aqueous or .3 grams per kilogram) appears to be adequate. Liver and vitamin D or iron and vitamin D also prevented severe grades of anemia. Blackfan, Baty and Diamond state that the development of anemia has been prevented by repeated blood transfusions. Hampson proposed that normal serum supplies an anti-hemolytic factor which is lacking in icterus gravis, and it is possible that the premature infant also is deficient in this factor or in something which stimulates its formation.

C. Anemia of Scurvy

The existence of anemia due to absence of vitamin C but occurring before frank symptoms of scurvy become manifest (pre-scorbutic anemia) has been shown, and this anemia resisted treatment by iron but was cured by lemon juice. Rohmer and Bindschelder investigated 22 anemic infants. Six of these cases failed to respond to iron, but when vitamin C was added, prompt cure resulted. This demonstrated that more than one factor may be lacking in some cases of deficiency anemia.

D. Anemia of Celiac Disease.

The anemia of celiac disease is manifested as a hypochromic anemia similar to those already discussed, but also in some cases as a hyperchromic megalocytic anemia.

The hematological picture differs in no way from that found in the nutritional anemia of infants and like theirs it is usually an iron, or iron and copper, deficiency anemia. There is nothing characteristic about it except that sometimes scurvy may be an element in its production.

Recently Straus, Castle, Bennet, Hunter and Vaughan have drawn attention to the existence of a hyperchromic megalocytic anemia in celiac disease, indistinguishable from that of sprue, tropical megalocytic anemia, and in association with gastrocolic fistula, but differing from Addisonian pernicious anemia. This anemia has been shown to respond to marmite. In order that the maturation of the megaloblast to the

normoblast may occur it is essential to supply the bone marrow with the hematinic factor which is produced by interaction of an intrinsic factor present in normal gastric juice with an extrinsic factor. Strauss and Castle hold that the extrinsic factor is closely related to vitamin B2, if not the vitamin itself. Marmite is rich in B2 and its efficiency in preventing or curing the megalocytic anemia of celiac disease is due to the fact that this form of anemia will occur when lack of extrinsic factor has prevented the specific action taking place.

Parsons and Hawksley reviewed 19 cases of celiac disease: 14 were in initial stage of treatment; ages varied from 18 months to 10 years. Nine were free from anemia of the hypochromic type, 3 a mild degree of hypochromic anemia, and in 1 anemia approximating a hyperchromic megalocytic anemia.

Two other forms of hyperchromic megalocytic anemia, dibothriocephalus and pernicious anemia are extremely rare in childhood.

E. Hemolytic Anemia of the New-born.

(1) With congenital hydrops fetalis.

Frequently stillborn although the infant may live a few hours or a few days. Ascites is usually present and enlargement of the liver and the spleen; jaundice may be slight, and there may be marked pallor. Blood shows severe anemia and a striking erythroblastemia.

(2) Hemolytic anemia with icterus gravis.

Is usually severe-fatal jaundice with marked anemia and often familial. Jaundice deepens at birth and by the 3d day has mahogany brown color. Death occurs on 4th or 5th day. If child recovers, jaundice disappears in 4 weeks and severe anemia is present.

A high degree of erythroblastemia directly after birth has been reported. During recovery there is a profound anemia of the hypochromic type with high color index.

Hampson reported in 1929 the recovery of 22 of 23 patients with familial icterus gravis of the newly born, following the use of intra-muscular injections of the maternal blood serum. Kramer of Brooklyn reports similar results. Josephs has prepared an alcoholic extract of plasma, and injected the redissolved dried extract into cases of sickle cell anemia, and produced an immediate reduction in the daily excretion of urobilin in the stools, and suggests its use in other hemolytic anemias. This demonstrates the possibility of a substance in normal plasma which prevents excessive hemolysis.

F. The hemolytic or the erythronoclastic anemia of later infancy and childhood.

(1) These are grouped into 4 types:

(a) The acute hemolytic anemia (Lederer type).

(b) The subacute hemolytic anemia.

(c) Von Jaksch's syndrome or subchronic hemolytic anemia.

(d) Acholuric jaundice.

The acute hemolytic anemia manifests itself usually by symptoms of acute intestinal infection with diarrhea, pyrexia and vomiting. This is followed by a severe degree of pallor which may reach its maximum in one or two days, or longer. It has a curious yellow waxy appearance suggestive of acute leukemia. There may be severe respiratory distress, air hunger and a severe degree of anemia at the onset. The spleen is palpable in 6 of 9 cases reported by Parsons. The anemia is severe, secondary hyperchromic type with evidence of intense marrow reaction as shown by high reticulocyte count and erythrocytes' immaturity.

There is usually a positive indirect Van den Bergh reaction, and a presence of excess urobilinogen and urobilin in the urine which is undoubted evidence that hemolysis has occurred.

Treatment: Immediate and repeated transfusions are indicated in all cases of acute hemolytic anemia. Although, occasionally some cases will recover without transfusion. There is a possibility that if transfusion is delayed permanent damage may have occurred to the marrow and no response be obtained.

Etiology: There is no certain knowledge as to the cause. The picture suggests that the illness is the result of some infection. The age incidence is from 7 months to 5 to 10 years.

Third group - Von Jaksch's syndrome or subchronic hemolytic anemia.

There has been much controversy centered around the syndrome known as Von Jaksch's anemia (subchronic hemolytic anemia of infants, anemia pseudo-leukemica infantum), the condition is insidious in onset, and is confined to the first 3 years of life, and the majority of the patients are under 2 years of age. Many agree that it is a special form of a biological response to any injury, infectious process, or alimentary disturbance, etc. and such a response can only occur during the first few years of life. The child is well nourished with a marked pallor, rather waxy in type. Edema of the ankles may be present and not infrequently petechiae on the limbs and trunk. The liver and spleen are enlarged.

The lymph glands are not as a rule palpable. In many instances, clinical signs of rickets are obvious. Both rickets and syphilis have without any evidence been regarded as factors. The prognosis is good and recovery when it occurs is complete.

Cooley has made a special study of this anemia. He thinks that one of the best descriptions of it is given by Eppinger who emphasizes its gravity and chronicity. The remarkable degree of splenomegaly, the moderate degree of enlargement of the liver, the appearance in the blood of numerous normoblasts and megaloblasts, the occurrence of moderate leucocytosis, and the frequent occurrence of cells of the marrow series. Eppinger regarded the disease as chronic, progressive, and often fatal, and made no mention of any tendency of recovery. He apparently held the view that it was secondary hemolytic anemia. One striking point in the various descriptions of the disease relates to prognosis. Some regard the prognosis as good and others as bad. Some state that anemia is a hyperchromic, others a hypochromic type.

It seems that the hyperchromic anemia, the presence of a high reticulocytosis, of megaloblasts, of anisocytosis, polychromasia, poikilocytosis and punctate basophilia, of megalocytosis and finally the occurrence of an increased amount of urobilinogen in the urine, are changes which, although quite different from those found in the deficiency nutritional diseases of infancy, are typical of a hemolytic anemia with a marrow response. (Parson and Hawksley).

G. The Erythroblastemia of Childhood (Cooley's Anemia).

This is an anemia with familial and racial tendencies, and limited almost entirely to children of Syrian, Italian and Greek stock which in infancy begins and runs a chronic and progressive course to a fatal termination. Splenomegaly is very marked. There is some degree of icteric discoloration of the skin. There may be progressive enlargement of the cranial and malar bones due to marrow hyperplasia which gives characteristic radiograph pictures, and also a somewhat Mongolian facial appearance. The red cells show marked variation in size, but less in shape. Nucleated red cells are seen in unusual numbers and megaloblasts are common. The anemia varies from a moderate to a severe degree. The color index is usually low. Polychromasia and reticulosis are very common. Leucocytosis is usually present. Lymphocytes usually predominate, and myelocytes and other elements of the bone marrow are usually

present. Cooley originally regarded this disease as hemolytic in nature, and that it displays a congenital diathesis allied to that seen in congenital hemolytic jaundice, and sickle cell anemia. Later, however, he states that although hemolysis is a constant and important feature, he no longer records the disease as primarily hemolytic in origin, in the same sense as congenital hemolytic icterus.

Pigmentary abnormalities were found in one case by Whipple and Bradford. Pigment deposits were found in the liver, pancreas, stomach, salivary and mucous glands, parathyroids, suprarenals, and pituitary that were similar to hemochromatosis, but the accompanying fibrosis was much less.

H. Other Forms of Hemolytic Anemia.

There are 2 other forms of hemolytic anemia that may be encountered in infancy, in childhood. First, the sickle cell anemia, and that disease described under various titles as congenital hemolytic jaundice, acholuric jaundice. Both of these forms of anemia are regarded as congenital malformations of the red blood cell.

Probably the reason why jaundice is so much more conspicuous in acholuric jaundice than in other forms of hemolytic anemia, is because in it there is not only a more constant but also a greater destruction of red cells. This is due to the fact that here the marrow is always active and turning out more cells than normal; whereas in, for instance, the acute hemolytic anemias, the marrow may be completely paralyzed during the period of hemolysis.

Note: The aplastic forms have been discussed. (See Aplastic Anemia)

SUMMARY

I. The iron content of the liver and spleen expressed in percentage of body weight is highest at birth and falls progressively to a minimum at the end of lactation period. Hart, Steenbach, and Waddell demonstrated that impure iron salts cured nutritional anemia. Copper was also essential. Its effect is to release the iron stored in the liver to form hemoglobin.

II. The blood changes in the normal following birth are: a rapid destruction of the more fragile immature cells, and a subsequent fall in hemoglobin during the first week, being greater in infants of low birth weight. Following this "physiological" jaundice the red blood cells continue to decrease until the third month of life, as shown by the small number of reticulocytes. There is some evidence that red cell building increases between five and eight weeks of age, though it does not exceed the destruction until the third or fourth month.

III. The cause of nutritional anemia when iron deficiency is considered may be due to (1) Deficient ante-natal storage. (Iron deficiency in the mother, deficient transference of iron to fetus, prematurity and twins.) (2) Deficient post-natal supply. (Inadequate iron in breast milk, and prolonged breast feeding or artificial feeding of cow's milk.)

IV. Infants demonstrate nutritional anemia as early as three to five months. Prematures are frequently anemic at two months.

V. Nutritional anemia is demonstrated by the insidious onset of pallor. The morbidity rate of acute and chronic infections is double that of the normal.

VI. Ferric ammonium citrate was demonstrated to be effective in the prevention and the cure of nutritional anemias by McKay. Liver is effective probably because of the high content of both iron and copper. The value of yeast probably lies in the combination of iron, copper, vitamin B complex, and possibly amino acids. Ferrous sulphate and iron-copper, and iron-sodium glutamate have been shown to be somewhat superior to the ferric ammonium citrate.

VII. The premature infant develops anemia more readily than the mature probably because of deficient ante-natal storage of copper and iron, delayed development of the hemopoietic tissue, or an increased severity and prolongation of the normal red blood cell hemolysis. The administration of iron and vitamin D, and blood transfusions will not entirely prevent, but will lessen the severity of the anemia.

VIII. The presence of an anemia associated with scurvy in infants that does not respond to iron, demonstrates the fact that more than one factor may be lacking in some cases of deficiency anemia.

IX. The anemia of celiac disease may be either a hypochromic or a hyperchromic megalocytic anemia. The first differs in no way from that of nutritional anemia of infants, and is probably a deficiency of iron or iron and copper. The latter is similar to the anemia of sprue and tropical megalocytic anemia, and has been shown to respond to yeast compounds which supply an extrinsic factor to unite with the intrinsic factor of normal gastric juice.

X. The hemolytic anemia of the new-born with icterus gravis is characterized by a severe jaundice with marked anemia, and a familial tendency. There is a high degree of erythroblastemia directly after birth, and a subsequent profound hypochromic anemia. The use of normal maternal blood serum intra-muscularly will apparently prevent further hemolysis. This demonstrates the possibility of a substance in normal plasma which prevents excessive hemolysis. Immediate and repeated transfusions are helpful.

XI. The acute hemolytic anemia of later childhood manifests itself usually by symptoms of an acute intestinal infection. The subsequent anemia is a severe secondary hyperchromic type, with evidence of intense marrow reaction. The cause is not known. Immediate and repeated transfusions are indicated in all cases.

XII. The syndrome known as Von Jaksch's anemia is confined to the first three years of life, and many agree that it is a special form of a biological response to any injury, infectious process, or alimentary disorder. Rickets and syphilis have been regarded as factors. There is splenomegaly and marked immaturity in both the myeloid and red cell series. Eppinger believes that it is a secondary hemolytic anemia.

XIII. Cooley's anemia has familial and racial tendencies, limited almost entirely to Syrian, Italian and Greek stock, and begins in infancy and runs a chronic and progressive course to a fatal termination. Splenomegaly and icteric discoloration of the skin is present. The Mongolian facial appearance is due to marrow hyperplasia of the cranial and malar bones. Cooley regards the disease as hemolytic in nature, but not in the same sense as congenital hemolytic icterus. The blood morphology has been described by Downey. Pigment deposits similar to hemochromatosis, but with much less fibrosis have been found. in the liver, pancreas, stomach, etc.

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IV. MINNEAPOLIS SURGICAL SOCIETY

Program to be given January 10, 1935 at 8:00 P.M.,
Todd Amphitheater.

Dr. N. Logan Leven -
Visualization of the biliary tract by injection of opaque media post-operatively.

Dr. Vernon L. Hart -
Subastragaloid and triple arthrodesis.

Dr. William T. Peyton -
The treatment of some types of arterio-venous aneurysms and cavernous hemangiomas.

Dr. Ralph T. Knight -
Current events in anesthesia.

Dr. Herbert A. Carlson -
Variation in the technique of thoracoplasty.

Dr. C. Donald Creevy -
Litholapaxy.

Dr. Melville H. Manson -
Biological phenomena in Hodgkin's disease.

Dr. Owen H. Wangensteen -
The surgery of hyperinsulinism.

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Anyone interested is cordially invited to attend.

V. IT WOULD BE NICE

If the first persons who meet incoming patients in the Admission Department or Wards would find out if the referring physician has suggested that they see a particular member of our staff. The referring physicians frequently ask later if we have seen these patients, which makes everybody's face red.

VI. MOVIES

Title: Born to Die -

Produced by the Fox Film Corporation. One Reel.