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Erythroblastic anemia (Cooley)

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(Cooley)

by

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ERYTHROBLASTIC ANEMIA

Introduction

Erythroblastic anemia is a somewhat obscure but none the less important anemia that is found in infants and children particularly those of ancestery arising in countries bordering upon the Mediterranean sea. There have been many names applied to this condition, prominent among which are "erythroblastic anemia" (Cooley, 1927), "familial hemolytic anemia" (Wollstein & Kreidel, 1930), "Cooley's anemia" (Baty, Blackfan, & Diamond, 1932), "Mediterranean disease" (Atkinson, 1932), "Thalassemia" (Whipple and Bradford, 1936), and "target-cell anemia" (Dameshek, 1940). These names are apparently given with reference to the outstanding feature of this disease in the estimation of that particular authority. Although the hematological findings in this disease are by no means limited to this condition, the name of erythroblastic anemia is applied here out of deference to Cooley (1927) who set forth this disease as a distinct clinical entity.

Attention was first called to this clinical condition in 1925 when Cooley and Lee presented five cases which at that time they considered to be a peculiar manifestation of "Von Jaksch's disease" or "pseudoleukemia infantum." At this time any disease appearing

in infancy or early childhood with anemia, a large hard spleen, some hepatic swelling, a high leukocyte count, and pronounced changes in the size and shape of the erythrocytes associated with varying degrees of anemia of a chlorotic type passed as von Jaksch's anemia. (Cooley, 1927) Indeed, this name is even today given on far less evidence to infants and children showing any form of secondary anemia associated with faulty nutrition and prolonged infections. (Koch & Shapiro, 1932). Further study of these and additional cases, however, convinced Cooley (1927) that he was dealing with a separate and distinct clinical entity which he set up as a sub-group of von Jaksch's anemia, calling it erythroblastic anemia because of the blood findings.

The cases reported originally by von Jaksch differ in many respects from erythroblastic anemia. In his cases, large numbers of circulating nucleated erythrocytes were not a prominent or constant feature. The ultimate prognosis was good, the patients usually making a complete recovery, whereas in erythroblastic anemia, the prognosis is poor. The patients seen by von Jaksch and his associates, contemporaries and followers were most probably not of Mediterranean ancestry. Certainly no mention is made of any such possibility. The char-

acteristic facial and skeletal changes so striking in patients with erythroblastic anemia should not have escaped recognition, and yet no mention of this finding was made either in the original descriptions of von Jaksch's anemia or in subsequent accounts. (Baty et al, 1932).

Cooley (1927) also calls attention to the following: "The patients are usually of a sallow complexion, and may have a 'sub-icteric' color, or even a definite jaundice. Often they have a Mongolian appearance due partly to the color of the skin, and partly to prominence of the bones of the cheek as a result of hyperplasia of the marrow. They are likely to be undersized and to have prominent abdomens because of the splenic and hepatic enlargements. The great size of the spleen with hard, smooth surface, is a marked characteristic. The liver is relatively not so large nor firm. Moderate hyperplasia of the lymph glands may or may not be present. Secondary phenomena of anemia, cardiac dilatation and murmurs, serous effusions, etc., may be present in proportion to the stage and severity of the disease. Hemorrhages are not uncommon."

Despite the rather definite and clear cut clinical picture set forth by Cooley, this disease has been one that has proved difficult to recognize and far more dif-

ficult to treat. Certain changes have occurred with the passage of time in the regarded importance of some of the signs, symptoms, and laboratory findings, and new diagnostic evidence has been presented which must also be given its due consideration. It is important therefore, to consider these changes and evaluate them in the light of present day knowledge.

Clinical findings

The following discussion is based upon a compilation of facts from the accompanying chart. Often the records were incomplete, however, this evaluation was made upon the information given.

Chief among the signs and symptoms noticed in those children and infants unfortunate enough to have this disease are a peculiar discoloration of the skin, cardiac pathology, enlargement of the abdomen, a mongoloid facies, and weakness and failure to grow and develop properly.

The discoloration of the skin is due to a pallor and an icteric or sub-icteric tinge to the skin. Pallor is one of the most consistant findings recorded, being seen as early as the cases first reported by Cooley and Lee (1925) and even in the cases reported by Stillman (1917) which have since been thought to

be cases of erythroblastic anemia instead of von Jaksch's anemia as originally reported. (Hitzrot, 1928; Allen, 1936) The pallor is due to an anemia which is seen in all of these cases.

The sub-icteric tinge is not as consistant a finding as is the pallor as it seems to vary with the authority reporting the case. Some authorities the presence of this tinge routinely and others seem to completely overlook it. Possibly this is due to confusion of this yellowish tinge with the naturally dark coloration of the skin of these persons as most of them are of Greek or Italian descent. There are several explanations for this sub-icteric tint, one as has already been mentioned being that it is the natural coloration of the skin in these persons. Another explanation attributes it to an accelerated breakdown of the erythrocytes and a resulting deposition of pigment in the skin. This interpretation seems to be opposed by the failure to find these pigments in excessive amounts in the body excreta although such cases have been reported, (Barker, 1938) however, these cases have been interpreted as cases of obstructive jaundice and probably not erythroblastic anemia (Barrett, 1938). Still another explanation and one which probably best explains the situation is that this peculiar coloration is due

to an abnormal metabolism of the body pigments causing a condition resembling hemachromatosis. (Whipple & Bradford, 1936) This last explanation is upheld by the autopsy findings which show the deposition of an abundance of iron containing pigment in the liver, pancreas, lymph glands, gastric mucosa, thyroid and adrenals, and the pigments which are normally present in the body tissues such as the reticular zone of the adrenal, the epidermis, the choroid plexus, and the interstitial cells of the testis, are as a rule increased in amount. (Whipple & Bradford, 1936)

Another symptom that is most frequently observed in infants is a failure to grow properly. This usually starts at about the third month of life in those very rapidly fulminating cases, and becoming apparent at about one year in other cases. Also associated with this is a feeling of weakness that is found in these patients no matter what their age. This finding is also rather recorded being consistantly present in about one-half of the cases. It is most probably caused by the anemia present that decreases the body metabolism and lowers tissue efficiency.

A progressive enlargement of the abdomen is reported in almost every case and may be the presenting symptom. It is to be found to a varying degree in

every case and although it is not in itself diagnostic it would serve to rule out erythroblastic anemia by its absence. This enlargement results chiefly from an increase in size of the spleen and to a lesser extent the liver; the spleen often extends below the crest of the left ilium and the liver extends down to and beyond the level of the umbilicus. This enlargement often causes the patient considerable discomfort because of its size and shape alone.

Many of these patients also show a change in facial appearance called "mongoloid facies". This finding is reported in about one-half of the cases, being consistantly noted by some writers and by others being ignored who may at the same time list the enlargement of the head, the yellowish coloration, and the x-ray findings that would indicate changes in the cheek bone that would be consistant with mongoloid facies. These changes that occur have been reported to be so striking and so constant that a presumptive diagnosis can often be made by inspection, indeed the patients are said to bear a greater resemblance to each other than to the normal members of their own families. (Baty et al, 1932) The mongoloid facies arise from a combination of many factors; the yellow hue, a widening of the malar bones, prominence of the eyes and in

some cases the presence of an epicanthal fold. The intelligence of these individuals is unimpaired by the disease.

Changes in the size of the heart occur only after the disease has been in progress for some time as it is a condition secondary to the anemia that is present. The cardiac enlargement is accompanied by and often preceeded by a soft systolic murmur often spoken of as a hemic murmur. This finding is of little importance in itself for by the time they have become manifest they are preceeded by other signs and symptoms of greater diagnostic importance.

As has been stated erythroblastic anemia is found most commonly in infants and children of mediterranean ancestery especially of Greek and Italian parents. In the earliest reported cases the first symptoms appear at or before one month. (Baty, 1930; Caffey, 1937) The symptoms are rather commonly seen as early as the third month of life. Cooley, Witwer, and Lee (1927) state that this disease begins in infancy and this idea is further amplified by the statement of Baty, Blackfan, and Diamond (1932) indicating that the symptoms may occur at any time during the first decade, most commonly during the first two years. The symptoms usually become visable at about

the age of sixteen months. At first it was thought that few if any cases ever lived to become adults, how-ever, six such cases have been reported up to 1939. (Thalheimer, 1939) The opinion is now held that this disease may exist in different degrees of severity; the rapidly fulminating cases appearing in infancy followed by the sudden death of the infant; those cases in which the symptoms appear slightly later in life, the symptoms not being as acute as in fulminating cases, and which live to or beyond the age of puberty; and those cases in which the disease is so mild that the symptoms may never be severe enough to be recog-nized as such and allowing reproduction thus perpetu-ating the disease. (Cooley, 1941)

The view that erythroblastic anemia was heredit-ary was not at first recognized by Cooley (1927) al-though he did appreciate that the disease was more often seen in the members of certain families and that it was a congenital condition. In the list of cases upon which he based his assumption that this was a separ-ate disease entity (Cooley & Lee, 1925; Cooley, Witwer, & Lee, 1927) he reported the presence of this disease in an English girl and a mulatto. Later, however, he stated that these cases had not shown a typical course and that they were probably not examples of erythro-

blastic anemia, the mulatto being a definite case of hemolytic icterus (Cooley & Lee, 1932). He also agreed with Blackfan and his co-workers (1932) that this dis-ease was probably hereditary and limited to persons of mediterranean ancestery especially the Greeks a.nd Italians. This conception has been rather generally accepted although Downey (1938) expresses the opinion that it is not limited to this particular distribution but that it could be more widely found if only this condition were kept in mind when patients of other nationalities were examined.

There are a number of other symptoms that occur infrequently and when they do occur are of minor importance. There is generally a slight degree of largement of the peripheral lymph nodes. Constipation of varying degree may be present and may at times be a troublesome factor. Unexplained attacks of fever-ishness may occur and these attacks may be consta nt,intermittant or undulant. More rarely loss of appetite and vomiting may be prominent symptoms. Such complaints as precordial pain, abdominal pain, dyspnea on exertion and ulcers on the legs are present in some instances. Pathologic fractures of the bones of the extremities are very rare, but do occur.

Laboratory findings

For the most part there has with a few notable exceptions been little if any change in the hematologic findings and the x-ray findings. The autopsy findings too are remarkably consistant, the chief differences being those that would be associated with the degree of sererity and the stage of progress of the disease at the time of the patients death.

Hematological data--The blood picture reveals an anemia of varying degree which is directly proportional to the duration and the severity of the clinical symptoms. This anemia is of the hypochromic, macrocytic type, (Baty et al, 1932; Atkinson, 1939) although Bradford and Dye (1936) report that they found an anemia of a hypochromic, microcytic type. The erythrocyte count may be between 1,000,000 and 4,000,000 per cubic millimeter, most commonly being between 2,000,000 and 3,000,000. The hemoglobin percentage is relatively low, usually from 25 to 45 and averaging about 36 per cent. The color index is therefore, low. The blood platelets are normal or moderately increased in numbers, rarely being at a low normal level, and number-ing as a rule, from 200,000 to 400,000 per cubic millimeter by the more commonly used methods of counting. A leukocytosis is almost constantly present, the white

blood cell count is usually between 10,000 and 25,000 per cubic millimeter, but may be as high as 50,000. Here the presence of large numbers of nucleated erythrocytes have been noted to confuse the counting of the white cells because of their resemblance in the count-ing chamber to the white cells, especially the lympho-cytes. This difficulty may be overcome by the use of a 3% solution of acetic acid as the diluting fluid in preference to the 1% solution commonly used. (Bohrod, 1941) Another method of obtaining a correct count is to determine the percentage of normoblasts present in a differential smear as compared to the number of white cells counted and from this calculate the percentage of white cells from the total cells counted in the counting chamber.

The differential leukocyte count shows a preponderance of cells of the myeloid series. These cells form from 60 to 90 per cent of the white blood cells. The majority are polymorphonuclear leukocytes, many of which are young forms, so-called metamyelocytes. There are a few myelocytes and more rarely myeloblasts. Eosinophils and basophils are constantly present in small numbers and may be moderately increased above the normal. The percentage of lymphocytes is relatively decreased, being usually from 10 to 30. The majority are small,

adult forms, although large, young lymphocytes may be present. The percentage of monocytes is also relatively low, being from one to five. (Baty et al, 1932)

These findings in short indicate a marrow hyper-plasia which floods the blood stream with immature and atypical cells, chiefly of the red series. (Cooley, 1927)

Several investigators have noticed oddly shaped erythrocytes in the circulating blood of these persons with erythroblastic anemia. (Cooley, 1932; Smith, 1940; Dameshek, 1940) One is a large, pale erythro-cyte pointed out by Cooley (1932) which contains ir-regularly distributed hemoglobin which is clumped and whose intervening areas seem to possess staining defects. This cell is extremely thin and leaf-like; the edges are observed to fold over in wet preparations and the several layers thus formed possess a remarkable transparency. Ridges are sometimes produced by wrinkling within the cell and this together with the scattered hemoglobin causes the cell to assume a peculiar appearance which typifies the disease. This cell is probably the most specific type of cell to be found in this condition. (Smith, 1940)

Another type of cell is a macrocyte that is usually round or sometimes slightly oval with a narrow rim of

hemoglobin or varying thickness with a large area of central achromia in which a faintly stained island of hemoglobin may occasionally be discerned. This type of cell has been frequently observed in early cases as well as in the blood of chronic cases which may not have undergone splenectomy. (Smith, 1940)

More recently another type of cell has been noted in both the stained smears and wet preparations of blood from patients with erythroblastic anemia. (Smith, 1940; Dameshek, 1940) This type of cell was first recognized by Haden and Evans (1937) who described what they termed dimpled" cells in a stained smear. They were described more fully the following year by Barrett (1938) who claimed that in the circulating blood some of the red cells were bowl-shaped; that in the process of drying they formed a hump in the center, giving rise to what he appropriately named "target-cells" and that these cells were very resistant to hypotonic solutions of sodium chloride in vitro. The target-cell has been seen in other types of diseases namely obstructive jaundice, severe hepatitis, some cases of hypochromic anemia, following splenectomy, and in sickle-cell anemia among others. (Barrett, 1938; Smith, 1940; Dameshek, 1940; Bohrod, 1941)

Target-cells are usually of normal diameter. In

the stained smear they too are made up of a rim of hemoglobin-containing material and a central zone which is clear, unstained, and which Barrett (1938) conjectured was due to a central knob-like projection in a cup or bowl-shaped cell. That this is actually the shape of the cell can be seen by oblique illumin-ation of dry smears or in bas-relief photographs.
(Bohrod, 1941) Variations from the typical target form are seen in every smear which exhibits the char-acteri stic appearance.

There are no target cells seen in wet preparations, but instead a number of cells equivalent to the pro-portion which appear as target cells in the stained smear appear as shallow or, more commonly, deep bowls or cups. (Bohrod, 1941)

When the blood is diluted with hypotonic salt solutions of varying concentrations the proportion of bowl-shaped cells (or of target-cells in the dry smears) increases as the salt concentration decreases. This is due to the hemolysis of the normal appearing cells and the preservation of the target-cells. Even in dis-tilled water a few target-cells may resist hemolysis, and most of them resist hemolysis in 0.3% saline. The target cells are resistant to acetic acid in concentra-tions which destroy normal cells. This consequently

provides a rather adequate test that has assumed some degree of importance. (Smith, 1940)

Hematological data following splenectomy--Rather striking changes occur in the peripheral blood following the therapeutic removal of the spleen. The erythrocyte counts and hemoglobin percentages remain essentially unaltered, although in some cases there seems to have been a slight but persistent increase. The total number of leukocytes and the percentage of immature forms increase rapidly for from ten days to two weeks after the operation, and then decrease slowly to a level slightly above the preoperative level. There is, however, a sharp rise in the number of nucleated red blood cells following splenectomy which remains above the previous level. These cells constitute from fifty to ninty per cent of the total nucleated cell count. There is a coincident rise in the number of other immature erythrocytes and a marked increase in the anisocytosis and poikilocytosis, so that it is often impossible to find a normal-appearing mature erythrocyte in the stained blood film. The blood platelets increase in number and remain very slightly altered for an indefinite period of time after splenectomy, whereas the changes in the blood after removal of the spleen in other types of anemia are very trans-

itory.

The icteric index of the blood is normal or only slightly increased. The bleeding time and the coagula-tion time are normal. In hypotonic saline solutions following removal of the spleen the erythrocytes exhibit a definite prolongation of the "resistance span," the resistance span of the red blood cells of the normal person being from about 0.46 to 0.34; that is, hemolysis begins in 0.46 per cent saline and is complete in 0.34 per cent solution. The resistance span of the erythrocytes of the patients with erythroblastic anemia on the other hand, usually ranges from 0.54 to 0.28, or even greater; hemolysis beginning in 0.3 to 0.2 per cent solution. It may not be complete even in distilled water. (Baty et al, 1932)

Roentgen findings--Examination of the skeleton by the x-ray reveals certain changes that are constant and characteristic, although varying in degree, tend-ing to become more marked as the disease progresses.

The bones show the following typical changes roentgenologically: In the cranium there is thickening of the vault due to widening of the diploic space, while the tables, particularly the outer, are unusually thin. Early the skull shows only slight thickening with diffuse osteoporosis. Older and more severe

cases show a wider dilatation of the diploci space--2 to 2.5 cm., with coarse vertical striations at right angles to the inner table. In such cases the outer table is frequently completely absent. The non-striated portion of the skull shows a spongy osteoporosis. The profile view of the skull gives the appearance of a surface studded with small radiating spicules per-pendicular to the tables of the skull. This fuzzy

outline is described best by the phrase "hair standing on end." The rest of the skull plate has a fine spongy appearance. (Mandeville, 1930; Strong, 1935; Allen, 1936; Caffey, 1937; Atkinson, 1939)

The long and short tubular bones are uniformly involved. Widening of the medullary canals gives a swollen appearance, with rectangular external contours. The cortices are thinned and usually spread apart. These bones are generally osteoporotic due chiefly to loss oc compact bone in the reduced cortices. Heavy trabeculations, particularly near the ends of the shafts, cross irregularly through the medullary spaces; this last being most marked in the small bones, the metacarpals and metatarsals, because of the better detail obtained in roentgen-ray films. (Mandeville, 1930; Strong, 1935; Allen, 1936; Caffey, 1937; Atkinson, 1939)

The flat bones are also osteoporotic, but with increased reticulation. In the ilia and scapulae the increased reticulation has a radial "fan-like" pattern.

Changes have now been demonstrated throughout the skeleton, with the same findings in the epiphyses as in the shafts. Growth and development of the skeleton have been significiantly retarded in the severe cases. Sub-periosteal changes and joint involvement have not been described though multiple fractures have been seen in several cases.

Bone changes have been recorded as early as four and one-half months (Caffey, 1937) and were present in both the skull and long bones. Early in the disease there is a thickening in the skull of the lower portion of the frontal squamosa and of the horizontal plates of the frontal bone. This early lesion is due to widening of the diploic space and to an external displacement of the outer table. This thickening tapers off gradually above, disappearing completely before the frontal eminence is reached. The remainder of the skull may be normal at this time. Typically the early thickening of the frontal gradually increases, extending backward toward the coronal suture. While the frontal lesion is increasing in extent and degree the mid-portion of the parietals develop a thickening with gradual spread

toward the coronal and lambdoidal sutures. The thickening of the occipital bone develops last and usually is first seen in the bone near the lambdoidal suture. The sequence of striation of the skull does not follow the sequence of thickening, striations never develop-ing in the lower portions of the frontal, the site of earliest thickening nor in the nasal process. These changes in the skull may differ greatly in patients of the same age. Late in the skull there may be a disap-pearance of vertical striations and trabeculation with a tendency toward osteosclerosis; however, as a rule the changes are not too marked. (Caffey, 1937)

In the tubular bones, changes are also seen early throughout the skeleton, but they are most conspicuous in the distal ends of the femora. Widening of the medullary canals with cortical thinning is the significant early finding. Fullness of the shaft and rectangular contours are also clearly made out even as early as the fourth month. At the eighth month there may be an increase in the trabecular pattern and at about the eleventh month, heavy, irregular trabeculations may be present. The heavyness and coarseness of the trabeculations increase with advancing age. Late in the course of this disease there is usually a definite increase in

bone density and a disappearance of the coarse reticulation previously present. This is apparently due to an increase in the trabecular bone which more completely fills the marrow cavities, tightening the mesh of the trabecular pattern, and causing a moderate osteosclerosis. The cortical bones, however, remain atrophic and the rectangular outline of the bones persists unchanged. In patients of the same age changes in the long bones do not differ greatly. (Caffey, 1937)

Although expansion of the shafts of the long bones is usually a diffuse uniform process, occasionally expansion occurs more rapidly at the ends of the shafts than at the central portions. This terminal swelling transforms the shape of the shaft into that of an hour-glass rather than the rectangular outline seen after the usually diffuse lateral expansion through all levels. The changes are most conspicuous at the lower end of the femur where the bilateral flaring looks not unlike the outline of an Erlenmeyer flask. (Caffey, 1937)

The cardiac hypertrophy demonstrated roentgenologically in young patients early in the disease is strikingly consistand and surprising in that the cardiac change has been thought to depend on severe anemia over a long period of time. (Caffey, 1937)

Other laboratory data--The urine and stools usually show an increased urobilinogen content at one time or another, indicating abnormal hemolysis. (Barker, 1938) Analysis of the gastric contents may reveal hypochlorhydria, but not a complete achlorhydria, a normal secretion of hydrochloric acid occurring after the subcutaneous injection of histamine. (Nussbaum, 1931; Baty et al, 1932) Other laboratory tests yield normal results.

Autopsy findings--The autospsy findings of the bones and bone marrow are entirely consistant with the x-ray findings. In the long bones there was a thinning of the cortex and a partial replacement of the cellular marrow by cellular connective tissue of the osteoid type probably due to an aplasia of the erythroblastic marrow and hyperplasia of the leukoblastic marrow. (Mandeville, 1930) Earlier in the disease there will be an extreme hyperplasia that shows a great pre-dominance of the erythrocytic elements. Similar changes occur in the bones of the skull. (Baty et al, 1932)

The spleen is always greatly enlarged usually from three to seven times the normal. Grossly it suggests a chronic process with much connective tissue being present. There is considerable evidence of metaplasia and marrow activities in some areas of the spleen.

The liver shows a similar picture. (Baty et al, 1932)

The other organs of the body are essentially normal except for an excessive deposition of pigment intheir structures.

Treatment

The treatment for erythroblastic anemia is still extremely confused and is entirely symptomatic. The patient should be given an adequate well balanced diet, and attention should be paid to general hygienic measures. As the course of the disease when untreated tends to be chronic and the severity of the symptoms varies widely in the different patients, it is difficult to evaluate accurately the efficacy of the diverse therapeutic measures that have been attempted.

The addition to the diet of iron and liver in large amounts may produce a slight improvement in the anemia and thereby improve the general condition of the patient, however, this effect is not striking and in many instances no definite benefit is derived from either iron or liver or both, even when given in large amounts over a long period of time. Transfusions of whole blood and plasma have also been tried with only little success.

Removal of the spleen of patients with erythro-

blastic anemia has failed to alleviate the symptoms or to cause improvement to any extent except in a few doubtful cases. In cases where enlargement of the spleen is so great as to be annoying, removal may relieve symptoms produced by the mechanical effects of the enormously enlarged organ.

Therapeutic exposures to a "spray of x-rays" has not been used sufficiently to permit accurate judgement of its effectiveness, however, in the few patients treated in this manner over a short period of time, there has been no appreciable benefit. (Hunter, 1936)

Quinine was tried on a series of eight cases with apparently good results by Nittis and Spilopulos (1937) and they associate this condition with malaria.

Correlation of physical findings and laboratory data with special referrence to etiology.

Most of the symptoms seen here can be explained on the basis of the severe degree of anemia present. The pallor, weakness, fatigue, failure to grow and dev-elop in the normal manner, and the cardiac findings of enlargement and a soft systolic murmur are all directly attributed to the anemia present. This anemia is in itself a peculiar finding in view of the marked de-gree of hyperplasia of the bone marrow as is to be

seen by x-ray and autopsy, and the rather rapid rate at which the red cells are being turned out. It would seem to be explained on the basis of an increased breakdown of the red cells which despite the increased resistance they show in vitro due to their flat shape, may be broken down in some unknown manner in the body. This would apparently, be substantiated by the pigmentation of the skin and other tissues and the spleen would at first thought be considered to be the member causing hemolysis due to its tremendous size.

At the same time it should be remembered that erythroblastic anemia is an hereditary disease implying that there is some inheretid defect present. Cooley (1932) was disinclined to believe that this was an hereditary disease for it was his opinion that that this condition was so severe no children ever passed the age of puberty and so were unable to transmit the disease to their off-spring. He explained the boneand other changes on the basis of a secondary marrow hyperplasia to the increased hemolysis. Whipple and Bradford (1936) believe that it is an inherited defect involving the hematopoietic and osseous systems. Dameshek (1941; 1942) expressed the opinion that the inherited factor may be the target-cell which is inherited as a dominent characteristic. This view was

opposed by Bohrod (1941) on the basis that the target-cell was by no means limited to the disease. In 1941 Cooley stated that as yet he thought that the evidence is not sufficient to classify the trait, but that it is probably a simple dominent and that clinical evidence would seem to indicate a disturbance of metabolic func-tion with a secondary effect on the marrow and reticulo-endothelial system. He is also of the opinion that as this trait is a mutation it may be found in other parts of the world in a different group of people due to the tendency of mutations to recur. He explains that the probable reason for its being established in the peoples of the mediterranean region is in inbreeding and inter-marrage.

Differential diagnosis

If these patients are thoroughly studied there are only a few conditions that will cause difficulty in the diagnosis. These conditions are congenital hemolytic icterus and sickle-cell anemia. Here the x-ray findings are similar in all three cases although the changes are most marked in erythroblastic anemia. (Vogt & Diamond, 1930; Snelling & Brown, 1936) Con-genital hemolytic icterus can usually be eliminated by examination of the blood smear for the spherocytic

erythrocyte which has a decreased resistance span to hypotonic saline solutions as opposed to the flat, thin cell and normal or increased resistance span of erythro-blastic anemia.

It is more difficult to rule out sickle-cell anemia for this disease has been reported in members of the white race. (Haden & Evans, 1937) Indeed these two conditions are so closely related that transitional forms between them have been recorded. (Dameshek, 1943) Diagnosis is made, however, on the presence or absence of the sickling phenomenon and to a lesser extent upon the race of the individual.

Conclusion

Erythroblastic anemia is then, a disturbance of the hematopoietic system, probably on an hereditary basis. It is characterized by its consistant racial and familial incidence, a typical facial appearance and skin discoloration, a progressive anemia with large numbers of nucleated erythrocytes in the peripheral blood, enlargement of the spleen and to a lesser ex-tent the liver, pigment abnormalities, distinctive changes in the bones and, finally, histologic lesions in the bone marrow and spleen.

As has been shown, no one feature is diagnostic

in itself. The condition should at all times be considered as a possibility when examining patients of mediterranean ancestry especially Italians or Greeks. The presence of an enlarged spleen in an infant or child of this descent should immediately cause a further examination of the blood picture to be made and x-rays to be taken. Positive blood findings consisting of an anemia with a large, thin type of erythrocyte, the presence of nucleated red cells, marked variation in size and shape of the cells, and an increase in resis-tance of the cells to hypotonic saline solutions along with the positive x-ray findings of widening of the diploic space with radial striations in the skull and thinning of the cortex, and trabeculation of the long bones should serve to establish a diagnosis of erythro-blastic anemia.

The mongoloid facies and muddy-yellow complexion when present are helpful, but are by no means as important in the diagnosis as the radiologic and hematologic findings.

That there is sufficient evidence to consider this a disease entity has been shown and it is pro-bable that it need only be more often considered as a possibility to make the diagnosis of erythroblastic anemia a more frequent one.

Author & case	Age of Hospital Record	Age of first Symptom	Sex	Race	Skin Color Pallor	Skin Color Icterus	Abdominal Enlargement Spleen	Abdominal Enlargement Liver	Mongoloid Facies	Blood Hgb.	Blood RBC's	Blood WBC's	Blood Nucleated Red Cells	Blood Fragility	X-ray	Misc.
Stillman 1917 #1	9yrs.	2yrs.	♀	Italian			+			25%	2.30	8,100	+	N-I		Heart enlarged & systolic murmur marked anisocytosis + poikilocytosis Splenectomy -- showers of nucleated reds
#2	8 mo.		♂		+		+			30%	1.4	37,000	+			Splenectomy -- showers of nucleated reds Died 2½ mo. later
#3	18 mo.	10 mo.	♀				+	+		45%	2.7	12,000	+			Splenectomy; anisocytosis + poikilocytosis Patient apparently recovered
Cooley, Witwer, + Lee #1		10 mo.	♀		+	+	+	+	+	30-40%	2.225	30,000				Heart enlarged & systolic murmur Died
1927 #2		8 mo	♂				+	+		48%	2.5	12,500	+	D		Died
#3		8 mo	♂	Greek			+			35%	2.62	18,000	+			Died: calvarium thickened at autopsy
* #4		3yrs.	♀	English		+	+	+	±	36%	2.9	26,000	+	D		Recovered
#5		8 mo	♂	Greek	+	+	+		+	56%	4.17	13,900	+	D		
#6		2⅓yr	♂	Greek	+	+			+	30%	2.072	34,330	+		positive	Heart showed systolic murmur
* #7		12 mo	♂	Mulatto	+		+			35%	3.2	12,000			positive	
Friedman 1928 #1		18 mo.	♀	Italian		+	+		+	28%	2.56	25,000	+	I	moderate	Heart enlarged & systolic murmur
#2		4 yr.	♀	Italian				0		40%	2.5	20,000	+	I	"	Systolic murmur Splenectomy
#3		7 yrs.	♂	Italian		+	+	+		40%	3.58	7,200		I	"	
#4		1 yr	♀	Italian	+	+	+	+		66%	3.66	11,000		I		Heart enlarged & systolic murmur
Hitzrot 1928 #1	9 yr		♀	A report on case #1 of Stillman												Patient living & well
#2	4 yrs.		♂		+	+	+			22%	2.64	8,850	+		moderate typical	Heart enlarged Splenectomy & shower of nucleated red. Alive for several yrs at report
#3	2⅔ yr.		♂		+	+	+	0		18%	2.992	34,594	+	D		Heart negative. Anisocytosis + poikilocytosis. Splenectomy & showers of nucleated reds. Died.
#4	14 yr.		♀	Italian	+	+	+	+	normal	35%	3.20	9,400	+		negative	Heart neg. Anisocytosis + poikilocytosis. Splenectomy & showers of nucleated reds.
Whipple, Reeves + Cobb 1928 #1	7yr	3-5yrs	♀	Italian		+	+	+	+	25%	1.67	5,100	+	N	questionable	Systolic + diastolic murmur. Splenectomy. transfusions, Fe, quinine + strychnine Improved.
#2	3yr		♀	Italian	+	+	+	+	+	35%	3.5	29,100	+	I	"	Anisocytosis + poikilocytosis. Transfused -- Fragility became normal
Baty 1930 twins #1 #2	8 mo	birth		Greek	+		+		+	anemia			+		typical	Transfusions + large doses of iron + liver. Died at 18 + 19 mo.
#3	8yrs	3yrs.	♂	Greek			+		+						"	Splenectomy: Alive at 11 yrs.

Fragility
N--normal
D--decreased
I--increased

Author + Case	Age		Sex	Race	Skin Color		Abdominal Enlargement		Mongoloid Facies	Blood					X-ray	Misc.
	of Hospital Record	of First Symptom			Pallor	Icterus	Spleen	Liver		Hgb	RBC's	WBC's	Nucleated Red Cells	Fragility		
bro. of #3 & 4	7yrs		♂	Greek			+		+						typical	Splenectomy: Died of mesenteric thrombosis. Increase in nucleated reds
Whitcher 1930 #1	9mo	birth	♂		+	+	+	+	+	43%	2.34	19,800	+			Anisocytosis + poikilocytosis. Fowlers solu. tomngs juice. Died
#2	5½mo		♂		+	+	+	+		22%	2.08	50,000	+			Fowlers + citrate of iron Died
#3	6mo		♂		+		+	+		28%	1.808	23,000	+			Transfused Died
Wollstein + Kreidel #1	3½yr.		♂	Italian	+	0	+	+		38%	1.5	9,000	+			Splenectomy & showers nucleated reds Transfused -- Died
1930 bro. of #1 #2	7mo		♂		+		+	+		30%	2.0	35,000	+			Died in one month.
#3	4½yr		♂	Italian	+	+	+		+	35%	3.5	19,600	+	N		Splenectomy & increase in nucleated reds Died in 4 yrs.
#4	25mo		♀	Greek	+		+	+		43%	2.704	18,069	+		Rarefaction of shafts of long bones.	Anisocytosis + poikilocytosis Splenectomy -- increase in nucleated reds
bro. of #4 #5			♂	Greek	+		+	+		30%	1.829	50,190	+			Splenectomy & increase in nucleated reds Died in 4 days & bronchopneumonia
#6	3½yrs		♀	Italian	+		+	+		25%	1.5	14,000	+			4 + wassermann · Splenectomy & increase nucleated reds & Died
#7	11mo		♀	Italian	+		+	+		20%	2.08	14,200	+			Hemic murmur · Anisocytosis + poikilocytosis. Splenectomy & decrease in normoblasts.
#8	7½mo		♀	Italian	+		+	+		45%	3.0	1700	+			Died at 3yrs
#9	7½mo		♀	Italian	+		+	+		18%	1.032	31,100	+	D		Hemic murmur Died at 21 mo.
Capper 1931 #1	2½yr		♂	Italian	+		+	+	+				+		positive	Systolic murmur. Splenectomy & Nucleated reds.
#2	9mo		♀	Italian	+	+	+	+					+	D	slightly positive	
Baty, Blackson & Diamond #1	33mo	28mo	♂	Greek	+	+	+	+	+	30%	2,072	34,300	+	N	typical + progressive changes	Systolic murmur
1932 #2	8½yr	3yr	♂	Greek	+	+	+	+	+	45%	3.86	12,200	+	D	moderate chg.	Heart enlarged & systolic murmur.
#3	4⅔yr	4yr	♂	Greek	+	+	+	+	+	45%	3,256	13,450	+	D	positive	Heart enlarged & systolic murmur Splenectomy; Purpuric spots & showers of normoblasts. Died
#4	11mo	3mo	♀	Greek		+	+	+	+	24%	2.4	17,600	+		positive	Heart enlarged & systolic murmur Died at 18 mo
twin of #5			♀	Greek	+	+	+	+	+	28%	2.6	11,000	+	D	"	Heart enlarged & systolic murmur. Died at 18 mo.
#6	3½yr	2yrs	♀	Italian	+	+	+	+	+	38%	3.9	6,400	+			systolic murmur only Fe + liver extract -- Progressing O.K.
bro. of #7	16mo	11mo	♂	Italian	+	0	+	?+	+	47%	4.5	13,800	+			Systolic murmur only Symptoms progressing.

Author + Case	Age		Sex	Race	Skin Color		Abdominal Enlargement		Mongoloid Facies	Blood					X-ray	Misc.
	At Hospital Record	At First Symptom			Pallor	Icterus	Spleen	Liver		Hgb	RBCs	WBCs	Nucleated Reds	Fragility		
#8	10 mo	2 mo	♀	Italian	+	+	+	+	+	36%	2.70	15,000	+	D		Systolic murmur only. Transfusions + diet. Splenectomy & showers of normoblasts. Died in 3 mo
#9	7 mo	5 mo	♀	Italian	+	0	+	?	+	40%	2.30	10,000	+	D	Positive	Heart enlarged & systolic murmur. Given liver extract; died
#10	3 yr	3 mo	♂	Sicilian	+	+	+	+	+	49%	3.48	49,000	+	D	moderate	Heart enlarged only. Given Fe & X-ray & improvement
#11	26 mo	1 yr	♀	Greek	+	+	+	+	+	28%	2.36	23,500	+		"	Heart enlarged & systolic murmur. Fe + NH_4 citrate & improvement
#12	20 mo	12 days	♀	Italian	+	+	+	+	+	30%	1.75	16,800	+	D		Heart enlarged & systolic murmur. Splenectomy -- Died at 6½ mo.
#13	18 mo	1 yr.	♀	Greek	+	+	+	+	+	37%	2.73	43,200	+		moderate	Heart enlarged only. Given liver + one dose of X-ray. Died at 28 mo
#14	4 yr	8 mo	♂	Greek	+	+	+	+	+	24%	1.80	32,000	+		advanced	Heart enlarged & systolic murmur. Died in 2 wks
#15	2 6/12 yr	1 yr	♀	Italian		+			+	43%	3.40	19,000	+	D	marked chg.	Heart enlarged. Diet high in liver + meat
#16	3 11/12 yr	2 yr	♀	Armenian	+	+	+	+	+	40%	3.0	10,000	+	D	moderate	Systolic mur mur only. Splenectomy & shower of nucleated reds
#17	2 yr	3 mo	♀	Greek	+	+	+	+		25%	1.65	42,000	+			
#18	17 mo	infancy	♀	Greek	+		+	+		anemia			+		severe	
Sister of #19	12 mo	infancy	♀	Greek	+		+	+	+?	anemia			+		severe	
#20	4 yr		♂	Italian												
Koch + Shapiro #1	3 yrs		♀	Italian	+	+	+	+	+	anemia				N		
1932 #2	2 yrs		♂	Italian	+	+	+	+	+	anemia				N		
LeWald 1932 #1	1 4 yr		♂	Italian	+		+	+		anemia						Given X-ray to reduce size of spleen & some improvement.
Cousin of #2	11 yrs		♀	Italian	+		+	+		anemia						
Whipple + Bradford #1	2 yrs		♀	Italian	+	+	+			24%	2.4	11,000		N		Transfused. Died at 5 yrs
1932 Bro of #1 #2	2¼ yrs		♂	Italian	+	0	+	+	+	40%	3.224	45,700	+	I	typical	Systolic murmur. Give Liver, Fe, Ventriculin, t thyroid -- Alive
#3	8 mo	7 mo	♂	Italian	+	+	+	+		40%	3.67		+	D	positive	Systolic murmur. Anisocytosis + Poikilocytosis. Splenectomy & shower of nucleated reds
Fries 1933 #1	7 yrs	2 yrs	♂	Greek	+	+	+		+	43%	2.55	8,900			typical	Systolic murmur. Splenectomy & showers of nucleated reds. Died in 8 mo
Bro. of #1 #2	3 yrs		♂		+	+	+	+	+	35%	2.8	14,000	N		typical	Systolic murmur. Anisocytosis & Poikilocytosis.

Author + Case	Age		Sex	Race	Skin Color		Abdominal Enlargement		Mongol-oid Facies	Blood					X-ray	Misc.
	of Hospital Record	of First Symptom			Pallor	Icterus	Spleen	Liver		Hgb	RBCs	WBCs	Nucleated Reds	Fragility		
Monerieff + Whitby #1 1934	1½yr		♀	Greek	+	+	+	+		38%	3.16	18,800	+		typical	Systolic murmur. Anisocytosis + poikilocytosis Died
Yaqude 1935 #1	7 mo		♀	Italian	+	+	+	+		30%	1.7	30,000	+	N	typical	Died shortly
#2		5 mo	♀	Greek	+		+	+	+	anemia			+		typical	Condition progressively worse
Allen 1936 #1	24yr	boyhood	♂	Italian		+	+	+		blood picture			typical	D	typical	Systolic murmur. Splenectomy & showers of nucleated reds.
Whipple + Bradford #1 1936	5yrs		♂	Italian			+			30%	2.6	33,600	+		typical	Systolic murmur. Given parathormone, spleen extract, liver, thymus. Died
#2	5⅚yr	infancy	♂	Italian		+	+	+	+	33%	2.6		+	D		Heart enlarged & systolic murmur Died of terminal pneumonia
#3	2½yr		♂	Italian			+	+	+	48%	2.96	19,840	+	D	typical	Heart enlarged & systolic murmur.
#4	4yrs		♀	Italian			+	+	+	27%	2.3					Heart enlarged & systolic murmur Given 11 transfusions also Cu + Fe
Cassey 1937 #1	4½ mo	3½ mo	♂	Italian	+	+	+	?+	o	40%	3.0	17,000	+	N	positive	
#2	6 mo		♀	Italian	+		+		o	45%	3.6	7,700	+		"	
#3	6 mo	3 mo	♂	Italian	+	+	+	+		28%	1.9	29,000	+	N	"	Systolic murmur
#4	7 mo		♂	Greek	+	+	+		o	50%	3.4	8,500	+		"	
#5	8 mo	4 mo	♀	Italian	+	+	+			30%	2.3	18,500	+		"	
#6	8 mo		♂	Italian	+	+	+		+	43%	3.3	7,900	+		"	Systolic murmur
#7	15 mo	4 mo	♂	Italian	+	+	+	+	+	anemia			+		"	Systolic murmur
#8	23 mo	9 mo	♀	Italian	+		+	+	+	47%	3.7	11,300	+		" slight	systolic murmur
#9	25 mo	19 mo	♀	Greek	+	+	+	+	+	93%	2.7	18,400	+	N	"	
#10	2½yr	3 mo	♂	Italian	+		+			45%	2.2	7,250	+	N	"	
#11	2½yr		♀	Italian	+		+			37%	2.3	11,800	+		"	
#12	3yr		♂	Italian	+	+	+	+	o	25%	1.8	12,000	■ o		"	Systolic murmur
#13	3yr		♂	Italian	+	+	+	+		15%	1.1	3,650	+		"	systolic murmur

Author + Case	Age of Hospital Record	Age of First Symptom	Sex	Race	Skin Color Pallor	Skin Color Icterus	Abdominal Enlargement Spleen	Abdominal Enlargement Liver	Mongoloid Facies	Blood Hgb	Blood RBCs	Blood WBC's	Blood Nucleated Reds	Blood Fragility	X-ray	Misc.
#14	3 yrs		♀	Italian	+	+	+	+	?	50%	3.1	18,000	+	N	positive	Systolic murmur + Enlargement
#15	3½ yrs		♂	Greek	+	+	+	+	+	48%	3.1	6,700	+	N	"	Cardiac systolic murmur
#16	4 yrs	3 yrs	♂	Greek	+	+	+		+	18%	1.5	35,000	+	N	"	Heart enlarged c̄ systolic murmur
#17	3¾ yr	1 yrs	♂	Italian	+	0	+	+	0	28%	2.2	4,100	+	N	"	" " " " "
#18	5 yrs	1½ yrs	♂	Italian	+	+	+		+	23%	2.1	14,100	+	N	"	
#19	5 yrs	6 mo	♂	Italian	+	+	+	+	+	30%	1.0	11,000	+	?	"	Heart enlarged c̄ systolic murmur
#20	7 yr	4 yrs	♀	Italian	+	+	+		+	38%	2.6	4,600	+	I	"	Systolic murmur. No microcytosis
#21	8 yrs		♀		0	+	+		+	60%	3.8	9,900	+		"	Heart negative
Nittis + Spilopulos #1	5 yrs		♂				+		0	37%	2.23		+			Anisocytosis + poikilocytosis become normal c̄ treatment. Quinine + Atebrine
1937 #2	14 mo	2 mo	♂				+	+	+	24%	1.91	22,000	+		positive	Had also malignant tertian malaria. Given quinine. Removed prematurely from treatment. Died
#3	12 mo		♀		+		+	+	+	50%	3.1	19,000	+		"	Given quinine + recovered in 2 mo c̄ regression of Spleen + Liver
#4	18 mo		♂		+		+	+	+	40%	3.5	16,400	+		"	Quinine c̄ recovery!
#5	5 yrs.		♀		+		+	+	+	23%	1.46	16,400	+		"	Quinine + Atebrine c̄ recovery!
#6	16 mo		♂		+		+		+	50%	2.89	14,600	+		"	Had tertian malaria also. Quinine given c̄ recovery
#7	12 mos		♂		+		+	+	+	58%	3.32	18,200	+		"	Quinine gave recovery
#8	2 yrs		♀		+	+	+	+	+		2.76		+		"	Quinine given c̄ recovery!
* Barker 1938 #1	6 yrs		♂	Greek		+							0	D	negative	Probably obstructive jaundice
Akinson 1939 #1	20 yrs	8 yrs	♀			+	+	+		45%	3.9	9,820	→	D	moderate	Dist + vitamins
bro. of #1 #2	17 yrs	4 yrs	♂			+	+	+	+	20%	1.992	10,000	+	D	marked	Systolic murmur. Anisocytosis + poikilocytosis. Dist. Splenectomy
Thalhermer 1939 #1			♀	Italian												was alive at age of 14
Goldhamer 1942 #1	30 yrs		♀	Italian			+	+					+	N		Splenectomy c̄ clinical course same
child of #1 #2	16 yrs		♂				0			many target cells				D		
child of #1 #5	3½ yrs		♀				+			"	"	"	+	D		

Author + Case	Age		Sex	Race	Skin Color		Abdominal Enlargement		Mongoloid Facies	Blood					X-ray	Misc.
	of Hospital Entry	of First Symptoms			Pallor	Icterus	Spleen	Liver		Hgb	RBCs	WBCs	Nucleated Reds	Fragility		
Schmitz + Anday #1 1942	12 yrs	birth	♀	Italian	+		+	+	+					D	typical	
Smith 1942 #1	4 yrs		♀	Sicilian	+		+	+	+				+			A benign course & Systolic murmur

Bibliography

1. Allen, E.G., & Childs, D.S., 1936, Erythroblastic Anemia; New York State Jour. Med., 36: 641.

2. Atkinson, D.W., 1939, Erythroblastic Anemia; Amer. Jour. Med. Sci., 198: 376.

3. Barker, W.H., 1938, Excretion of Bile Pigment and Hepatic Function in Diseases of the Blood; Arch. Int. Med., 62: 222.

4. Barrett, A.M., 1938, A Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline; Jour. Path. & Bact., 46: 603.

5. Baty, J.M., 1930, Anemia in Infants and Children; New Eng. Jour. Med., 203: 319.

6. Baty, J.M., Blackfan, K.D., & Diamond, L.K., 1932, Blood Studies in Infants and Children; Amer. Jour. Dis. Child., 43.1: 667.

7. Bohrod, M.G., 1941, Decreased fragility of Erythrocytes Interferring with Leukocyte Counts; Jour. Lab. & Clinical Med., 26: 1953.

8. Bohrod, M.G., 1941, The Significance of Target-Cell Anemia; Amer. Jour. Med. Sci., 202: 869.

9. Bradford, W.L., & Dye, J., 1936, Observations on the Morphology of erythrocytes in Mediterranean Disease; Jour. Ped., 9: 312.

10. Caffey, J., 1937, The Skeletal Changes in the Chronic Hemolytic Anemias; Amer. Jour. Roent., 37: 293.

11. Capper, A., 1931, The Nature of von Jaksch's Anemia and the Effect of Splenectomy; Amer. Jour. Med. Sci., 181: 620.

12. Cooley, T.B., 1927, Von Jaksch's Anemia; Amer. Jour. Dis. Child; 33: 786.

13. Cooley, T.B., 1941, Hereditary Factors in the Blood Dyscrasias; Am. J. Dis. Child., 62: 1.

14. Cooley, T.B., & Lee, P., 1925, A Series of Cases of Splenomegaly in Children, with Anemia and Bone Changes; Trans. Amer. Ped. Soc., 37: 29.

15. Cooley, T.B., & Lee, P., 1932, Erythroblastic Anemia; Amer. Jour. Dis. Child., 43: 705.

16. Cooley, T.B., Witwer, E.R., & Lee, P., 1927, Anemia in Children; Amer. Jour. Dis. Child., 34: 347.

17. Dameshek, W., 1940, Target-cell Anemia; Amer. Jour. Med. Sci., 200: 445.

18. Dameshek, W., 1941, Hematology: New Eng. Jour. Med., 224: 729.

19. Dameshek, W., 1942, Hematology: New Eng Jour. Med., 226: 339.

20. Dameshek, W., 1943, Hematology; New Eng. Jour. Med., 228: 157.

21. Downey, H., 1938, Handbook of Hematology; Vol. 3, 2191.

22. Friedman, L.G., 1928, Osseous Changes in Hemolytic Icterus; Amer. Jour. Roent., 20: 440.

23. Fries, J.H., Duhan, E., & Shair, H.M., 1933, Erythroblastic Anemia; Jour. Ped., 2: 487.

24. Goldhamer, M.L., 1942, Mediterranean Anemia in Adult; Ohio State Med. Jour., 38: 321.

25. Haden, R.L., & Evans, F.D., 1937, Sickle cell Anemia in the White Race; Arch. Int. Med., 60: 133.

26. Hitzrot, J.M., 1928, Unclassified Type of Splenomegaly in Children; Ann. Surg., 88: 361.

27. Hunter, F.T., 1936, Spray X-ray Therapy; New Eng. Jour. Med., 214: 1123.

28. Koch, L.A., & Shapiro, B., 1932, Erythroblastic Anemia; Amer. Jour. Dis. Child., 44: 318.

29. LeWald, L.T., 1932, Roentgen Evidence of Osseous Manifestations in Sickle-cell Anemia and in Mediterranean Anemia: Radiology, 18:792.

30. Mandeville, F.B., 1930, Roentgen-ray Findings in Erythroblastic Anemia; Radiology, 15: 72.

31. Moncrieff, A., & Whitby, L.E.H., 1934, Cooley's Anemia; Lancet, 2: 648.

32. Nittis, S., & Spilopulos, G.G., 1937, Similarity of Erythroblastic Anemia and Chronic or Congenital Malaria; Amer. Jour. Dis. Child., 54: 60.

33. Nussbaum, S., 1931, Anemias of Infancy and Childhood; Arch. Ped., 48: 578.

34. Schmitz, H.L., & Anday, G.L., 1942, Congenital Hemolytic Anemias; Med. Clinic North Amer., 26: 219.

35. Smith C.H., 1940, The Anemias of Early Infancy; Jour. Ped., 16: 375.

36. Smith, C.H., 1942, Mediterranean Anemia in a Youth of 19; Jour. Ped., 20:370.

37. Snelling, C.E., & Brown, A., 1936, A Case of Hemolytic Jaundice with Bone Changes; Jour. Pediat., 8: 330.

38. Stillman, R.G., 1917, A Study of von Jaksch's Anemia; Amer. Jour. Med. Sci., 153: 218.

39. Strong, R.G., 1935, Erythroblastic Anemia; Jour. Ind. Med. Assoc., 28: 57.

40. Thalheimer, E.J., Mezetti, A., & Gershon-Cohen, J., 1939, Cooley's Anemia; Jour. Ped., 14: 349.

41. Vogt, E.C., & Diamond, L,K., 1930, Congenital Anemias Roentgenologically Considered: Amer. Jour. Roent., 23: 625.

42. Whipple, G.H., & Bradford, W.L., 1932, Racial or Familial Anemia of Children; Am. J. Dis. Child., 44: 336.

43. Whipple, G.H., & Bradford, W.L., 1936, Mediterranean Disease; Jour. Ped., 9: 279.

44. Whipple, A.O., Reeves, R.J., & Cobb, C.C., 1928, Atypical Hemolytic Anemia; Ann. Surg., 88: 380.

45. Whitcher, B.R., 1930, Erythroblastemia of Infants; Amer. Jour. Med. Sci., 179: 236.

46. Wollstein, M., & Kreidel, K.V., 1930, Familial Hemolytic Anemia of Childhood--von Jaksch; Amer. Jour. Dis. Child., 39: 115.

47. Yaguda, A., 1935, Erythroblastosis in the Newborn and in Early Childhood; Am. J. Clin. Path., 5: 266.