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The Criteria for the differential diagnosis of Rh incompatibility (erythroblastosis fetalis)

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THE CRITERIA FOR THE DIFFERENTIAL DIAGNOSIS OF RH INCOMPATIBILITY (ERYTHROBLASTOSIS FETALIS)

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INTRODUCTION.

The progress in the field of blood groups has rapidly expanded since Landsteiner first discovered the four basic blood groups. The new Rh factor has explained many previous problems in medicine. It has explained the intragroup transfusion reactions and erythroblastosis fetalis. Besides these two conditions it has found importance in legal medicine and in the study of genetics.

Erythroblastosis fetalis has long been known as a clinical entity but not until 1941 was there any specific etiology given for this condition. This problem has been publicized very much and has received much attention in the last few years. It has intrigued many as well as myself. Through some study of this disease the condition of jaundice in the newborn has stimulated interest in it as to other possible causes besides erythroblastosis fetalis.

This interest, therefore, leads to the problem of the differential diagnosis of jaundice in the newborn. The diagnosis, and thus the differential diagnosis, is important in the prognosis for future childbearing and in the treatment.

This paper will attempt briefly to present the clinical picture of erythroblastosis fetalis and most of the conditions that simulate this disease. A short discussion will also be given on the normal blood picture in infants

and some of the criteria for the diagnosis of the disease in the living infant as well as in the post mortem examination.

HISTORICAL REVIEW.

Since the discovery in 1900 of different blood groups within the species by Landsteiner (38) other subgroups have been identified. It was not until January of 1940 that Landsteiner (39) following along his experiments with animal sera found that rabbits injected with rhesus monkey blood would agglutinate the cells of 39 of 45 random human bloods. He stated at this time in his article:

> "The capacity possessed by some rabbit immune sera produced with blood of Rhesus monkeys, of reacting with human bloods that contain the agglutinogen M has been reported previously. Subsequently it has been found that another individual property of human blood (which may be designated as Rh) can be detected by certain of these sera."

The character thus made demonstrable in human cells by the new agglutinin was called Rh since the rhesus monkey had been involved in its production. Cells which contained the Rh antigen and were agglutinated by the serum were designated Rh-positive; those which did not contain the antigen and were not agglutinated by the serum were designated Rh-negative.

This new knowledge was first applied clinically by Wiener and Peters (72) in June 1940 in a study of blood trans-

fusion reactions which were shown to be due to iso-immunization to the Rh factor as a result of transfusing Rh-positive blood into an Rh-negative patient.

Later in 1941 Levine, Katzin and Burnham (42) in their studies of transfusion reactions in mothers with clinically and pathologically proven erythroblastosis in their infants found these "atypical agglutinins" that paralleled those described as Rh factor by Landsteiner. He thus helped to establish the clinical relationship of the Rh factor to the disease of erythroblastosis fetalis. However, this concept of an antigen-antibody reaction as a basis for the etiology of erythroblastosis fetalis had been previously mentioned as a possible theoretical cause by Ottenberg (50) in 1923 and Darrow (12) in 1938.

Thus, at the end of 1941 the clinical importance of the Rh factor had become well recognized. Through further studies Wiener and his co-workers stimulated the production in rabbits of antibodies which they had named anti-Rh agglutinins. They also had demonstrated that agglutinins of identical specificity could be formed in human beings as a result of the introduction of Rh-positive blood by transfusion. They had solved the mystery of the cause of erythroblastosis and had demonstrated that an Rh-negative woman might become immunized by the Rh antigen contained in the blood cells of her off-

spring, and that maternal anti-bodies might pass through the placenta to the fetus and cause erythroblastosis.

In 1932 a review of the literature by Diamond (15) showed that Ballantyne in 1898 had collected 70 cases after 1614 of jaundice of the newborn but that all of these were not erythroblastosis. Universal edema of the newborn with abnormalities of the blood was reported as a fetal type of leukemia by Jakesch and Klebs in 1878, Sanger in 1888, and Pollmann in 1898. Swart in 1905 (69) reported an infant with generalized edema with foci of blood formation in the liver, spleen, and kidneys. After an article by Schriddle in 1910 (66) many other reports followed with like information, i.e., universal edema associated with hematopoietic organs, enlarged liver and spleen, evidences in tissues of anemia, icterus, and enlargement of the placenta. Many authors reported on icterus gravis neonatorum in the period between 1901 to 1929 but they only mentioned the familial incidence and no mention as to possible etiology. Diamond continued the review stating that seventeen authors from 1912 to 1931 gave descriptions of familial icterus gravis neonatorum with associated changes in the blood and extramedullary blood-forming organs. Dark yellow-colored amniotic fluid and vernix caseosa of saffron-yellow was noted by Lange and Arntzenius in 1929 (40). It was Rautmann (61) in 1912 that termed the under-

lying condition "erythroblastosis." Evidence by Oberndorfer (49) showed that the incidence of the disease in only one of twins and the other infant normal was against the previous etiological ideas as maternal toxemia or metabolic disturbance of pregnancy. Report of 24 cases of erythroblastosis fetalis from 1922 to 1931 had in common the following signs: extraordinary erythrocyte formation in the liver, spleen and kidneys, enlarged liver and spleen -- usually with general edema and occasionally with jaundice, pallor of body tissues, increased nucleated red cells, enlargement and edema of the placenta.

In their extensive article in 1932 Diamond, Blackfan and Baty (15) organized all the previous information and made sense out of the maze of confusion appearing in the literature. They suggested that universal edema of the fetus, icterus gravis neonatorum and anemia of the newborn were all manifestations of the same disease and could conveniently be grouped together and known as "erythroblasosis fetalis." They did not at this time have any thoughts of a possible serologic origin of the disease.

Since the year 1940 the literature on this subject has been very extensive covering many phases. Much is known now but further studies are necessary to explain the whole complicated subject and how to specifically treat the condition.

THE CLINICAL ENTITY --- ERYTHROBLASTOSIS FETALIS.

Before attempting to differentiate between the conditions that can cause hemolytic jaundice in the newborn it would be well to establish the clinical entity of congenital hemolytic anemia of the newborn. This should include not only the clinical picture of the three degrees of this disease, namely, fetal hydrops, icterus gravis, and congenital anemia of the newborn, but include a good definition, its place in the anemias, incidence and mortality.

Fetal erythroblastosis or congenital hemolytic disease is a familial disease manifesting itself in a trial of clinical entities, namely: 1) congenital edema of the fetus (fetal hydrops), which is the most severe form; 2) icterus gravis; and 3) hemolytic anemia of the newborn. The last of this group is the mildest manifestation.

It is a condition in which the blood of the fetus exhibits immature cells of the erythroblastic series which are not normal as to the type or quantity for the developmental stage of the fetus. This condition may be elicited by numerous factors and may or may not be accompanied by hemolysis and extramedullary hematopoiesis. When the disease is due to an antigen-antibody reaction (the Rh antigen in this case), there will be hemolysis, accumulation of iron in the fetal liver and usually persistent extramedullary hemopoiesis.

In addition, in these families a history is frequently given of repeated miscarriages, intrauterine fetal deaths and premature still-births.

The classification of the anemias differs very much with the various authors (15, 17, 37, 46, 51, 63). Parson's and Hawksley's classification as reviewed by Fallon (17) is:

I. Anhematopoietic anemias
(deficiency diseases of the erythron)

A. Nutritional anemia
B. Anemias of prematurity
C. Scurvy
D. Celiac disease
E. Hyperchromic megalocytic deficiency anemia

II. Hemolytic (erythronclastic) anemia of neonatal period

A. Hemolytic anemia of the newborn

1. With hydrops fetalis
2. With icterus gravis
3. Without edema or icterus gravis

. Hemolytic anemia in the late neonatal period

Without edema or icterus gravis.

III. Hemolytic (erythronclastic) anemia of later infancy and childhood.

A. Acute hemolytic anemia (Lederer type)
B. Subacute hemolytic anemia
C. Von Jaksch's Syndrome (subchronic hemolytic)
D. Acholuric jaundice

The exact incidence of hemolytic disease is extremely difficult to determine. Since 1941 the number of cases has increased and the diagnosis has been made on many surviving infants. The range of incidence is from one in twenty children

born of Rh-negative women to one in forty or fifty given in more conservative estimates (60, 36). Later figures by Diamond (16) in 1945 reported an incidence of one in a hundred and fifty births. The mortality rate is about seventy per cent for the whole group (35, 60).

HYDROPS FETALIS.

Fetal hydrops is found in fetuses or in infants living for not more than 36 hours. There is no change which is constant. Consequently, the definition is based upon the presence of some or all of certain clinical and pathological features and the exclusion of other diseases which may also produce them. This condition is the most severe manifestation of erythroblastosis fetalis.

As already stated, erythroblastosis can be divided into three groups, one more sever than the previous one. Potter (60) and others divide these groups further. She divides hydrops into 1) stillborn fetuses without generalized edema, and 2) infants with generalized edema. The former is the severest form and the same as the fourth type of the disease according to Henderson (31).

In this severest form or the fourth type, Henderson states that hydramnios is common, intrauterine death occurs some time before delivery, there is no edema, a severely macerated fetus is common, the liver shows diffuse hepatic

cirrhosis, splenomegaly is found, and the placenta is greatly enlarged and is pale pink in color. Macklin (47), however, did not find cirrhosis in any of the macerated fetuses examined nor in those where iron was demonstrated in the liver. If these fetuses live long enough a characteristic picture of the hemolytic disease is seen. The face is usually somewhat edematous, the tongue frequently protrudes. The fetus is usually macerated.

In the infants with generalized edema (the other subdivision of hydrops) the degree of edema is found to vary greatly. There can be mild and easily overlooked edema or very extreme edema with large amounts of fluid in the body cavities. The skin is never jaundiced. If the baby is born alive there is difficulty with respirations. The blood shows about one million red cells per cu. mm. with a high number of nucleated red cells. All of these infants die during delivery or very soon after. The post mortem shows marked splenomegaly and extramedullary erythropoiesis. A more complete description of erythroblastosis will be given under the discussion on icterus gravis.

ICTERUS GRAVIS.

Definition: Icterus gravis is the commonest type of erythroblastosis that is seen in infants at birth or in the first weeks of life, with jaundice as the predominant feature (30). The jaundice is associated with one or more other

characteristics. Among these features is nuclear jaundice. Along with the other signs and symptoms as enlargement of the liver and spleen, abnormality of hemopoiesis, a familial incidence, a tendency to hemorrhage, one finds nerve involvement as evident by convulsions (20).

Signs and Symptoms: The three principal symptoms of which any one may predominate are: 1) jaundice, 2) edema, and 3) anemia (8, 12, 14, 16, 20, 28, 38, 67). Jaundice is the most frequently seen clinical manifestation. It may occur within two hours of birth in the severest cases, but generally appears within 48 hours. Gilmour (20) in 1944 reports 54 cases of jaundice at birth and 97 cases within the first three days. Snelling (67) reports that out of 81 cases of jaundice 65 occurred from birth and only 16 cases had their onset later. The degree of jaundice is variable as well as the duration. Campbell (8) puts the duration in the mild cases from one week to three weeks. The jaundice usually becomes intense, the color deepening often to a deep bronze.

Edema or hydrops may sometimes replace the jaundice but it is of little importance clinically since it is incompatible with life (15, 29, 37). Snelling (67) reported six cases of edema with jaundice in a total of 102 cases and Javert (35) reports three cases.

A profound anemia is constantly found. This usually reaches a peak about the third week but this can vary. The red

red counts often are reduced below one million per cu. mm. and may even go as low as 400,000 red cells per cu. mm. of blood (15, 20, 30, 37). Further information about the blood will be taken up later.

Other clinical findings include: 1) pallor, 2) hemorrhage, 3) convulsions, 4) purpuric spots with jaundice or pallor, 5) drowsiness, 6) enlarged liver and spleen, 7) yellow vernix, 8) respiratory embarrassment, and 9) tachycardia.

In the severest form the baby is desperately ill, has an intense jaundice with yellow sclera and heavily bile-stained urine, fever, some degree of edema and ecchymosis, head retraction frequently occurs with rigidity of limbs and usually dies within the first two or three days. However, in the milder case the baby may be only drowsy, have some pyrexia and slight edema, appetite may be poor with vomiting and digestive difficulty, stools are ill digested, green and curdy, and the spleen and liver enlarged. Some cases may show striking pallor due to anemia without jaundice, because hemolysis has occurred slowly liberating bilirubin in amounts which the liver can excrete readily. Snelling (67) reports 16 cases with pallor alone in a total of 102 cases and four presented by Javert (35).

Convulsions, rigidity and opisthotonus is due to the damage of the brain that seems to be a frequent occurrence in this disease. This condition is called kernicterus or nuclear

icterus because the degenerated basal nuclei as well as other parts of the brain are icteric on gross examination. The spleen is enlarged in eighty-four per cent of the cases and the liver is enlarged in one hundred per cent of the cases (67). Blackfan and Diamond (4) say there is respiratory embarrassment and the tachycardia may dominate the clinical picture and focus attention on the cardio-respiratory system.

Hematologic and Other Laboratory Data: The erythrocytes are macrocytic, well filled with hemoglobin, and the color index is greater than one. Only in severe forms is there more than a slight degree of anemia in the first twelve hours of life. As the disease progresses the erythrocytes decrease very rapidly, sometimes by as much as a million cells per cu. mm. per day, and a profound anemia may ensue by the third or fourth day. Javert (36) states that the average red count is 3,400,000 red blood cells per cu. mm. and the lowest is about one million per cu. mm.

In the early stages there is a great increase in the number of immature and nucleated red cells in the peripheral blood. As has been stated before over 5,000 nucleated red cells per cu. mm. is considered abnormal (16, 43, 60, 640 68). The usual number found in this disease runs from 50,000 to 100,000 nucleated erythrocytes per cu. mm. These red cells are mainly of the early erythropoietic series that are normally not

found in the peripheral blood, that is, except in small numbers in premature babies and in normal infants during the first day or so of life. These immature cells are usually erythroblasts, proerythroblasts and normoblasts. The nucleated erythrocytes tend to diminish and may even disappear entirely at the end of three or four days. Their absence should not confuse the diagnosis. The macrocytosis persists throughout the active stages of the disease and is one of the diagnostic criteria not to be overlooked according to Blackfan and Diamond (4). Hawksley and Lightwood (27) report that the anemia is always macrocytic and the average cell diameter in the early stages is 9.5 microns. Potter (60), however, states that the most characteristic change in the non-nucleated red cells is the excessive variation in the size. These cells may vary from 5 to 10 microns in diameter. The reticulocytes are present in numbers above those usually found at the same age, but are not commonly increased above 10 or 15 per cent.

The average leukocyte count of a normal infant within the first 24 hours as already stated is about 10,000 cells per cu. mm. In this disease the number of leukocytes is usually increased slightly and not to infrequently above 50,000 per cu. mm. Leukopenia has rarely been reported. A few myelocytes and an occasional myeloblast are commonly present (4, 27, 37, 60).

In the severe forms the platelets are generally greatly reduced in number in the first few days. The average is about 80,000 per cu. mm. In the severest form the bleeding time tends to be greatly prolonged thus there is a hemorrhagic tendency in this group. A prothrobin deficiency may be present to augment this bleeding tendency. After the first week the platelets return to normal levels and then the bleeding tendency subsides (1, 4, 37).

The icterus index generally is high immediately after birth and tends to increase to 100 or more within the first week. The index may rise to a height of 200-300 units by the third or fourth day (60). If the symptoms subside promptly, the icterus index may return to normal within a couple of weeks. At times, however, jaundice may persist for a long period, and six weeks or more after birth the icterus index may still be in excess of 50 units. The van den Bergh is both direct as well as indirect (15, 47, 60).

Fragility of the erythrocyte in hypotonic saline solution shows a slight increase in the concentration at which hemolysis begins and a decrease at its termination, a stage usually described as an increased resistance by Abt (1), Blackfan and Diamond (4), Haymond and Giordano (28), and Josephs (37).

It is not unusual for the feces to become clay colored and the urine bile tinged about the sixth and twelfth

days. This acholic state lasts for a few days or weeks. Blackfan and Diamond (4) further state that during the active hemolysis, both the urine and feces show an increase in the amount of urobilinogen excreted. Damashek, Greenwalt and Tat (11) determined the fecal urobilinogen to be in a range of 0.25 to 11 mg. per day with the normal found to be from a trace to 0.7 mg. per day. These same investigators found that that the fecal bilirubin was greatly increased in the first two weeks of life. In the icterus gravis infant the range was from 19.4 to 109 mg. per cent with 16 mg. per cent in the normal infant.

The serologic tests in this disease are of great importance but at the present time some are somewhat confusing. Of course, the tests for syphilis are all negative (this is important in the differential diagnosis). Since the discovery of the Rh factor in 1940 many other blood groups have been added to this Rh series. This has added to the confusion of the situation but has helped to clear up many unexplained cases. These finer serologic agglutination determinations are only done in a few special laboratories in the country so the peditrician will ordinarily run the sera only to determine whether the parents and the infant are Rh-positive or Rh-negative. The red cells of the infants with icterus gravis as well as the other two forms of the disease triad are found

to be Rh-positive, as are the father's, whereas the mother's are Rh-negative. As stated before, there are many subgroups and thus many reactions possible. These subgroups are used to explain the disease syndrome in infants where the Rh setup is apparently normal and compatable.

It might be interesting to include here a summary of the laboratory data from the mothers of such erythroblastotic infants as well as from the infants suffering from the disease. This date is from Javert (36).

Infants Hematologic Data

	Hydrops (5 cases) per cu.mm.	Icterus gravis (3 cases) per cu.mm.	Icterus gravis (11 cases) per cu.mm.
Red cells	1.51	3.56	3.10
Hemoglobin	5.50	14.70	13.60
Cell volume	25.00	52.00	. . .
Luekocytes	54,300	21,200	18,500
Nucleated reds	37.60	21.20	18.50
Index-vol.	1.50	1.30	. . .
Index-color	1.30	1.40	1.40
	(9 cases)	(6 cases)	
Normoblasts	304. /cu.mm.	71. /cu.mm.	
Erythroblasts	98. " "	14. " "	
Reticulocytes	7.1 %	...	
Immature polys	34. /cu.mm.	10. " "	
Immature lymphs	16. " "	0. " "	
Red cell diameter	9.5 micra	8. micra	

Infants Blood Chemistry Data

			Control
NPN	41.7 mg.	60.0 mg.	35.0 mg.
Uric acid	7.8 "	3.8 "	3.1 "
Chlorides	563.0 "	395.0 "	500.0 "
Serum protins	3.8 Gm.	5.3 Gm.	5.9 Gm.
Fibrinogen	0.05 "	0.1 "	0.3 "
Prothrobin	5. %	7. %	23.0 %
Icterus index	91. units	36. units	18.0 units

Maternal Blood Chemistry Data

	Mothers with erythroblastosis	Control at Term (Stander)
NPN	31.2 mg.	28.0 mg.
Urea nitrogen	13.7 "	12.5 "
Uric acid	5.1 "	3.0 "
Chlorides	515.0 "	494.0 "
Sugar	83.0 "	80.0 "
CO_2 combining power	38.1 vol. %	48.0 Vol. %
Icterus index	5-9 units	2-3 units

The Gross and Microscopical Findings: The fetus is likely to be overweight for the stage of development. Javert (35) found that in ten cases the average weight of the fetus was 3,457 gm., a weight which was excessive when the average duration of the pregnancies in these cases is only 37 weeks. He further stated that in 110 infants whose weight exceeded 1,500 gm., five per cent had erythroblastosis.

Jaundice is seldom present at birth and yellow vernix and amniotic fluid may be present or not (47). One usually finds hydrops, petechiae, possible maceration, and many show no external change except extreme pallor (60).

As Macklin (47) points out that many infants-fetuses are not accompanied by placenta at the autopsy examination a valuable aid is lost. The placental weight is greater than normal and in a series of cases by Javert (35) ten cases were one-sixth heavier than normal. The average weight was 7,756 Gm. It is unusually thick, the cotyledons are prominent and the color is light pink instead of the usual deep red. Histological study shows the cells covering the villi are often more immature than the stage of gestation warrants and both Langhans and syncytial layers may be visible in some areas. This persistence of the cellular layer of Langhans around the chorionic villi is said to be a characteristic of this condition (29, 30, 60). The villi are edematous and hyperplastic

and the blood vessels are at the periphery of the villus. Potter and Adair (56) state that a diagnosis can be made alone from the placenta by finding nucleated red blood cells in the villur vessels.

The spleen is enlarged (10, 15, 35) but not more than 25-35 gm. Extremes of from 15-50 Gm. have been encountered (60). On microscopic examination the spleen shows excessive numbers of immature red cells in the pulp, reduced lymphoid tissue, malpighian corpuscles are very small or absent, and the sinusoids are dilated.

The liver is also enlarged but not increased proportionately as much as the spleen. They are increased two or three times normal size (15), are firm, smooth, show many hematopoietic foci and cellular degeneration (10). Iron or hemosiderine was found in the liver in the Kupffer cells by several authors (10, 15, 47). Macklin (47) puts much emphasis on this particular finding.

The pancreas, heart, adrenals, intestine, thyroid gland and the sex glands rarely show specific changes associated with hemolytic disease (35, 47, 60). Macklin (47) raised a question about hypertrophy of the islets of Langerhans in this disease as differing from that found in diabetes. The heart is usually slightly enlarged but there are no structural changes. The kidneys show local formation of red cells next in degree to that found in the liver and spleen.

Cloudy swelling and some tubular degeneration is found but the glomeruli are usually normal. The lungs are usually normal in size, shape and color unless secondary changes are present. Potter (60) says that areas of local erythropoiesis are rare but it is common to find immature red cells in the pulmonary capillaries when there is extensive extramedullary erythropoiesis in the body. She (59) puts stress on the finding of these immature red blood cells in the lung in a macerated fetus. She says this is often important in establishing a diagnosis in such cases. The brain is a common site of pathologic changes especially in icterus gravis. This change, however, is found only in those infants that survive a few days after birth. There is evidence of icterus in the basal ganglia as well as other areas of degeneration. Hyperplastic bone marrow with many immature red cells and normal epiphyseal line was found by Clark (10).

The Diagnosis of Icterus Gravis: The diagnosis of this disease, as made in many other diseases, is made upon the summation of many facts rather than just one or two facts. In some cases the diagnosis is made with relative ease and in others the diagnosis is hard or many not even be made (60). As in every field of endeavor there are many disputed points. Some of these disputed points as well as the generally accepted findings will be summarized.

The disease is a familial disease that occurs in eight out of 1,000 deliveries (15) to one in 400 by present day figures (60, 13, 36). If you can show a familial incidence, the first step of the diagnosis is fulfilled. Sometimes the diagnosis can be made in an uncertain case if the mother later gives birth to a subsequent infant suffering from the disease. The disease is suggested when the jaundice, typically "mahogany-brown", is present at birth or appears in 48 hours. Apparently the race has no influence in this disease. The condition is further suggested when one finds amber-colored amniotic fluid or a golden-yellow vernix.

Macklin (47) stated that in the diagnostic criteria of this disease you must show either that the fetus possessed anti-bodies in its circulation against its own Rh-positive cells or that the blood of the fetus and mother were of different Rh groups and that the fetal tissues showed changes from the normal which were characteristic of the Rh antigen-antibody reaction. You must also show that there was opportunity for an antigen-antibody reaction to occur, because of the difference in the Rh blood groups of the mother and child, and that it is possible that the reaction took place by the evidence of the alterations in the tissues of the fetus or child.

The serologic agglutination tests are usually characteristic. That is, the infant and father are Rh-positive and the mother is Rh-negative (4, 13, 28, 47). This may, on the other hand, be difficult to demonstate in a few cases because of the different and many new subgroups of the antigen-antibody reaction. Many other groups await discovery and others a further explanation. These conditions are so rare that, for general purposes, can be ruled out.

To prove that anti-bodies are present in the fetal blood that is positive, is dependent upon several factors. The mere presence of Rh-positive blood in the fetus and Rh-negative in the mother is not sufficient for a diagnosis, because in ten percent of the cases diagnosed as this disease, the mother is Rh-positive (47). Also many Rh-negative mothers have Rh-positive children who are normal.

After it has been proved that the fetus possesses an antigen that the mothers blood lacks one must show that the reaction took place by the destruction of blood and other tissue reactions. These tissue reactions and blood changes have been discussed to some extent previously. Some of the differences in opinions will be given regarding these changes and some of the points in a diagnosis given by other obsersers.

As has been stated before, the weight of the infant at birth is about 3,457 Gm. Javert (35) stated that, although the incidence of this condition was one in 400 deliveries in

his clinic, of 110 infants whose weight exceeded 1,500 gm., five, or four and one-half per cent, had erythroblastosis. This is an incidence eighteen times normal. This led Javert to suspect Rh incompatibility in overweight fetuses. Overweight in the fetus may be found in other conditions. It may exist when a diabetic or when a prediabetic state exists in the mother (48), or when either one or both of the parents is very large, or when fluid exists in the tissues or body cavities of the infant. Potter also showed that hydrops could occur in other conditions than in erythroblastosis (57). In early history many other authors along with Ballantyne (as cited by Diamond 15) in 1892 found that hydrops was not a specific disease, but only a symptom common to several different morbid conditions.

Prior to 1941 most pathologists were unwilling to make a post-mortem diagnosis of erythroblastosis unless there was evidence that red blood cells were being formed in abnormal locations within the body. This finding coupled with clinical evidence of anemia was the most common basis on which a diagnosis was made. It is now evident that in infants with the milder forms of the disease, as well as in some infants who die, abnormal foci of erythropoiesis may be rare and, few if any, immature red cells may be present in the circulating blood (60). This does not include those infants that live a

few days thus giving a chance for the extramedullary erythropoiesis to disappear. Macklin (47) says that this persistance of extensive hemopoiesis in the liver and spleen past the time such hemopoiesis is normally found in these tissues is wrong. The diagnosis, based upon such a criterion, would cause many cases not due to Rh incompatibility to be included in the category of erythroblastosis according to him. He further states that even when the mother is Rh-negative and the fetus Rh-positive, and when the fetus had excess hemopoiesis in the liver it might be suffering from one of the numerous causes indicative of extramedullary hemopoiesis other than Rh incompatibility.

Macklin (47) places great weight on the presence of iron in the liver of these infants as evidence of hemolysis of the red cells which in turn is indicative of Rh incompatibility. He divides the cases of erythroblastosis into two groups:-

1. Those which at autopsy show the evidence of hemolysis, namely, the presence of iron in the liver. This corresponds to hemolytic disease of the newborn due to Rh incompatibility.
2. Those without hemolysis, and hence without iron in the liver.

He summarizes this, thus:

Erythroblastosis - -

With Iron in Fetal Tissues.

Due to hemolysis
of megaloblasts
of normoblasts
of mature red cells

by
Rh factor
other factors
aplastic phase

Hemolysis, excessive, causes death of the fetus before blood can regenerate; iron present, indicating destruction of blood, but no increase in hemopoiesis.

Without Iron in Fetal Tissues.

Due to factors other than hemolysis.
operating early - - with the site of hemopoiesis extra-medullary and in bone marrow.

operating late - - with the site of hemopoiesis in bone marrow.

Idiopathic erythroblastosis due to developmental arrest in hemopiesis, permitting early embyonic type of formation of blood to persist; no destruction, hence no iron.

Potter agrees that iron is found in fetal livers (60). She says that the iron present parallels the pigment visible in the skin. When the skin is intensely icteric large amounts of hemosiderin can be demonstrated in the hepatic parenchyma. This iron is greatly concentrated in and about the portal areas and at the periphery of the lobules. Macklin (47) finds that, for the most part, that the iron is in the Kupffer cells, but is sometimes present even in the liver cells and in the peri-portel connective tissues. He uses the Prussian Blue technique

on these tissues to detect the iron and indicates that this technique has great value in the diagnosis. This same author disagrees with others in their statement that iron is normally stored in the fetal livers. Chemical examinations of iron in two fetal livers indicated that there was a large amount of iron stored in the liver before birth, which rapidly decreased after birth (7). This finding according to Macklin may have been caused by examination of livers of fetuses dying of hemolytic disease. The author (47) examined 139 fetal livers and found 60 per cent without iron, 33 per cent showed presence of appreciable quantities of iron and seven per cent showed extremely small traces of iron. This indicates that the fetal liver does not store iron. Thus, when iron is found in livers of jaundiced infants the author concluded that excessive blood destruction has taken place and that the most frequent cause excessive blood destruction is probably the Rh incompatibility between mother and fetus.

The enlargement of the spleen is one of the most significant diagnostic criteria according to Potter (58,60). She makes a statement that if the spleen extends two cm. or more below the costal margin or weighs 25 gm. or more, either erythroblastosis or syphilis is almost certain to be the causative factor. Syphilis gives large spleens and, therefore, must rule out syphilis on all cases of enlarged spleens. She further states that in several thousand autopsies on fetuses and newborn infants she has never seen this degree

of enlargement of the spleen other than in the two causes given. She goes on to make the statement that if it were necessary to make a diagnosis of erythroblastosis on observation of a single organ or on a single laboratory finding, a study of the spleen would yield the highest percentage of correct results. She adds that this criterion can be applied only to fetuses at term or to the newborn. Potter goes on to say that before a definite diagnosis is made, however, the general symptom complex, anemia, immature red cells, extramedullary erythropoiesis and the characteristic agglutinins must be present.

Anemia is more constantly present than any other symptom. This is generally agreed by most observers (8, 15, 41, 47, 58). Macklin (47) points out that anemia will be found in fetuses and children with Rh incompatibility, as well as in children suffering from hemorrhage, from increased fragility of the red cells and many other causes. The other causes will be taken up under the discussion on the differential diagnosis.

Potter (60) goes on to say that it is almost impossible to make a diagnosis of anemia from histologic examination of the tissues, but that anemia is the one characteristic abnormality that is found in practically all of infants with this disease. Therefore, she concludes, that if anemia

exists in an infant whose mother is immunized to an Rh or Rh antigen present in its red blood cells, a diagnosis of hemolytic disease seems warranted even though specific pathologic changes are absent.

The study of the gross and microscopical appearance of the placenta is another valuable aid in the diagnosis of icterus gravis. Potter and Adair (56) stated that a diagnosis of erythroblastosis can be made from the placenta alone. They say that the presence of nucleated red blood cells in the villus vessels is found in no other condition.

In the diagnosis of late premature or term fétuses with marked maceration, Potter (59) places the diagnosis on the pathology in the lungs. Here she states that the tissues are better preserved than the rest of the tissues and that finding immature erythrocytes (basophilic erythroblastos megaloblasts and hemocytoblastos) in the pulmonary capillaries makes the diagnosis more certain. The other findings with such a macerated fetus are: edema, especially of the face; mild macroglossia; hypertrophy of the spleen and liver;normal zone of growth at the ends of long bones; enlargement of the placenta and erythroblastemia in the placental vessels and the absence of Rh in the mother's erythrocytes and the presence of Rh in the father's erythrocytes. In such a macerated fetus syphilis must be ruled out because this disease is one of the most common causes.

CONGENITAL ANEMIA OF THE NEWBORN.

Congenital anemia of the newborn is the third and least severe of the three groups in erythroblastosis fetalis. The diagnosis is harder to make in this phase of the disease because the dividing line between the milder cases and physiologic anemia on the one hand, and the severer forms with icterus gravis on the other, is not clear-cut in many cases. The milder cases according to Potter (60) probably occur with greater frequency but they are not recognized because the infants recover before the cell destruction has progressed very far and because of the absence of the usual easily detectable characteristic symptoms. She says that these cases will only be recognized if Rh studies are done in all pregnancies and on the infants after birth.

This disease is found in infants that survive the first three days of life. It is characterized by extreme pallor, anemia, slight jaundice, listlessness, weakness, no edema, slight enlargement of the liver and spleen, and a generally good prognosis. These findings are only the general findings and many are not agreed upon by several authors.

Pallor is accepted by most writers and Gilmour (20) reports pallor in eleven cases at birth with 28 cases within the first 17 days in a total of 39 cases. Pallor of the skin and mucous membranes is one of the chief characteristics according to Litchfield (44) but that this is usually obscured

by the icterus that is present. When the icterus leaves, the pallor becomes more pronounced. Some times the diagnosis is not made until the second or third week and then is only made on the presence of extreme pallor (60).

The anemia present is another prominant feature but this may be varied in its presence. The number of red cells may drop to two million and the hemoglobin to ten grams by the time the diagnosis is made according to Potter(60), and the infant may die of the anemia unless treated. Diamond, Blackfan and Baty (15) have stated that the anemia may remain stationary or may even become aggravated until the sixth week of life and then return to normal. Potter (60) states that the anemia is present with jaundice because she found only one case of anemia without jaundice in 206 infants with hemolytic disease delivered by 122 Rh-negative mothers.

Immature erythrocytes may be absent from the circulation or may be present in very small numbers. The hemolytic anemia is characterized by a hyperchromia, erythroblastemia and a variable degree of reticulotytosis (30). Sanford (65) states that not over eight per cent nucleated red blood cells are present with only an occasional erythroblast.

A diagnosis should not be made unless one or more of the following is present, namely: a family history, excessive hemopoiesis, erythroblastemia and leukocytosis, the death of

infant from three to fourteen days, a defective development of the latter stages of the erythron and the absence of erythroblastemia, splenomegaly and hemosiderosis in the liver (20).

Halbrecht (26) and Sanford (65) have a different terminology for the condition because they say that it is characteristic of both erythroblastosis fetalis and physiologic icterus of the newborn. They call it icterus neonatorum precox. The typical signs and symptoms are like those found in erythroblastosis but there is no weight loss, the blood is normal and the child nurses well. In this group 95 per cent were found to have incompatibility of blood groups of the mother and child. This is three times as often as with physiologic icterus and four times as often as in newborns without interus. The mortality is reported as 60 per cent. Litchfield (44) says that the prognosis is good while Henderson (30) says that there usually is a spontaneous recovery and Diamond, Blackfan, and Baty (15) say that there is 100 per cent recovery.

THE NORMAL BLOOD PICTURE IN THE NEWBORN.

THE RED CELL

The Number of Red Cells At Birth: The infant at birth may have from four to nine million cells per cu. mm. of blood with an average between four and one-half to five million per cu. mm. (19, 34, 37, 51, 68, 75). Isaacs (34) in his paper reviewed some elevan authors and their averages for the number of red cells was from 4.51 to 7.63 cells in millions per cu. mm.

Observer	No. cases	Average
Mayers	41	7.63 (5.06-9.61)
Heath	13	5.77 (4.58-7.17)
Lippman	71	5.20
Fehrsen	40	5.89
Lilvette	30	4.51
Engelsen	40	6.24
Light		5.74
Lucas, et all.		5.50
Sanford		5.80
Mitchell		5.70
Rosenbloom		6.48

Isaacs (34)

Also, the blood findings varied with the age in days and from the sourse as shows in another table by Haden and Neff (25).

Age in days	Sinus blood	Blood from heel
5	3.52 - 3.86	5.94 - 6.23
9	3.81 - 3.87	4.34 - 5.09
13	3.68	3.68
24	3.40	4.08

Thus it will be seen that the red blood cells decrease in total number until about the fourth day with a slight rise at the end of the first week, and then another decrease again on the tenth day.

The Size of the Erythrocyte: The mean diameter of the erythrocyte according to Holt (33) and others (68) is eight microns on the first day of life. Griffith and Mitchell (22) state that the erythrocyte is large at birth, having a size of 110 cu. microns by six months the average size is 88 cu. microns. The adult normal is 92 cu. microns.

The Nucleated Erythrocyte: In reviewing the literature on this subject one finds a wide variation in the numbers normally found in the normal infant. The literature is also confusing in that many of the authors have reported their findings according to the number of nucleated red cells per 100 white cells without stating the number of leukocytes found for that same count. In this way the total number of the nucleated red cells cannot be determined.

It is generally conceded today that the physiological maximum is 5,000 immature red cells per cu. mm. of blood or estimated from a slide is from five to ten immature red cells per 100 leukocytes (60). Strong and Marks (68), Hawksley and Lightwood (27), Sanford (64), Lippman (43) all agree that the upper limit is 5,000 immature red cells. Diamond, et al (15, 16) state that normally 200 to 2,000 nucleated red cells

per cu. mm. or 5 to 10 per 1000 leukocytes are found at birth. Other authors report the nucleated reds number 54 to 1,686 per 100 white cells (62), 500 cells is upper limit (37), up to 2,500 is normal and 1,000 to 3,750 per cu. mm. (74). Casey in 1943 (9) defines another method of counting these cells so that he considers more than two immature red cells per 10,000 erythrocytes counted is abnormal. The older authors reported their findings per 100 leukocytes counted. Lucas, Dearing and Hooble (45) in 1921 found that one immature red cell per 100 white cells occurred on the first day in 52 per cent of all their cases and one-half immature red cells per 100 leukocytes on the second day in five per cent of the cases. Lippman's normal was four per 100 white cells or 37 per cent of the leukocytes (43). Aitken (2) back in 1902 found the lowest count to be one immature red cell in two cover glasses observed and the highest was 116 immature reds to 500 leukocytes. Bungler and Schwartz said the average was from one to one and one-half per 100 leukocytes and the highest being 24 per 100 white cells. The erythroblasts usually disappear by the second day and are rarely present at the end of the first week. (6).

The Reticulocyte: The reticulated erythrocytes are present in the blood in the proportion from four to ten per cent of the total number of erythrocytes. By the second week they

are about 0.2 to 1 per cent and by two months they are between 1.5 and 5 per cent (22, 37). Strong (68) and Forkner (19) state at birth the average count is from 1.4 to 1.9 per cent.

Hemoglobin: The hemoglobin in the infant again is high as is the number of erythrocytes. Dehydration is said to account for both these conditions in the newborn. The values given for the hemoglobin range from 18 to 25 Gm. hemoglobin per 100 cc. of blood, or above 120 per cent. Wollstein (75) reports values from 22.4 - 23.9 Gm. or 130 to 142 per cent with the Sahlie 17 Gm. as standard. Holt (33) and Griffith and Mitchell (22) state that the hemoglobin initially is around 18 Gm. per 100 cc but Strong and Marks (68) say that the value is 143 per cent or about 24 Gm. at birth.

Forkner (19) showed that the hemoglobin values increase about the fourth day from 148 per cent to 152 per cent, drop rather rapidly to the seventh day value of 141 per cent, and then subside more gradually to the eleventh day to 138 per cent. This drop in hemoglobin is in contrast to the drop in the number of erythrocytes which decrease until the fourth day, then with a slight rise at the end of a week to drop again on the tenth day.

Color Index: The color index is generally over one at birth. This is easily accounted for by the erythrocyte counts and the high hemoglobin.

The Leukocyte: The leukocyte count in the first few days of life vary from 15,000 to 25,000 per cu. mm. (2, 19, 22, 33, 68, 75).

The proportions of the different forms of leukocytes is also variable and fluctuate in the same child throughout the day. At birth the polymorphonuclear granulocytes constitute nearly 75 per cent, with a predominance of the younger forms. Within the first 48 hours the lymphocytes begin to increase in number.

SUMMARY.

The following chart will help to summarize the normal blood findings in the newborn infant. The chart is made from all the observers reviewed. The average number of erythrocytes at birth is 5.5 million per cu. mm. of blood. The hemoglobin value is around 21 Gm. per 100 cc of blood. The number of immature red cells is 5,000 cells per cu. mm. The average reticulocyte count is 3.0 per cent of the red cells. The mean diameter of the cell is 8.0 microns. The leukocytes are mainly polymorphonuclear, later with a rise in the lymphocytes. The total count at birth averages around 20,000 per cu. mm. The platelets are about 350,000 per cu. mm. and the color index is above one.

NORMAL BLOOD FINDINGS IN THE NEWBORN.

	Days.				Weeks.	
	1st	4th	6th	11th	2nd	4th
RBC million per cu.mm.	5.5	5.49	5.58	5.25	5.0	4.7
Hb. Gm. per cu.mm.	21		21		18	16
Nucleated reds/cu.mm.	5,000	0	0			
Retics. in % of RBC.	3.0	1.2	0.7	0.53	0.2	0.2
Mean diameter of reds	8.0 microns					7.7
Leukocytes per cu.mm.	20,000	10,636	15,000	12,000	12,000	.....
Polymorphs. per. cu.mm.	70		62		31	
Lymphocytes per cu.mm.	20		31		63	
Monocytes per cu.mm.	10		7		6	
Platelets per cu.mm.	350,000		325,000		300,000	
Color index	Above one					

DIFFERENTIAL DIAGNOSIS OF HEMOLYTIC DISEASE.

In an infant that shows early appearance of icterus, possible edema, numerous erythroblastos and normoblasts in the peripheral blood, as well as a general macrocytosis and anemia, occasionally a bleeding phenomena, enlargement of the liver and spleen, a familial incidence, and an enlarged placenta and yellow vernix, the diagnosis of erythroblastosis fetalis is suggested. However, there are many other conditions in the newborn that can have this similar picture and must be ruled out. Conditions to be ruled out are: 1) physiological jaundice, 2) spesis, 3) congenital syphilis, 4) atresia of the bile ducts, 5) nuclear icterus, 6) intracranial hemorrhage, 7) Winckel's disease, 8) congenital heart disease, and 9) other primary blood diseases.

THE HEMOLYTIC GROUP.

Physiologic Jaundice (Simple Icterus Neonatorum): Before po out the differences between this condition and hemolytic disease it might be well to summarize briefly what normally takes place at birth as far as the erythrocyte is concerned.

In a recent paper on the genesis of physiologic hyperbilirubinemia Weech (71) points out that physiologic hyperbilirubinemia (an increase in the bilirubin in the blood shortly after birth) may be viewed as an explosion which marks the infant's entry into the world. The sudden change from life in the amniotic fluid to life in an atmosphere of air con-

stitutes the trigger which fires the charge in all infants. Jaundice, the external manifestation of hyperbilirubinemia, may be lacking entirely and, when present, it rarely persists through more than one-tenth of one per cent of the expected span of life.

He continues to say that an accelerated destruction of hemoglobin begins within a few hours after birth, the destruction apparently being initiated by the onset of pulmonary respiration. There is more destruction during the first two or three days of life than after the infant is older. This increased destruction of hemoglobin gives rise in bilirubin concentration in the serum. When the hepatic function is relatively mature most of the bilirubin will be excreted rapidly into the bile and the post-natal increase in bilirubinemia will be slight. When the hepatic function is relatively immature the excretion will be delayed and the serum concentration will thus rise to high levels and will show up as jaundice. This condition, however, subsides rapidly in the normal infant.

Physiologic jaundice differs from the jaundice of hemolytic disease in the time of its appearance, in its severity and in the lack of associated symptoms. The age of onset is not at birth but is some place between the second and tenth day of life. There are none of the characteristic symptoms of hemolytic disease. The icterus index is increased with

sixteen units as an average. The skin does not become discolored but may have a golden-yellow tint. All the infants show these signs of blood destruction but anemia is not present. The hemoglobin rarely drops below 16 Gm. and the immature red blood cells are rarely present during the period of jaundice (8, 13, 27, 60, 65, 68).

THE NON-HEMOLYTIC GROUP.

Antenatal and Prenatal Infection: Antenatal infection is rare and usually comes from the mother. Josephs (37) presents one instance of an erythroblastotic-like disease which occurred as a result of intrauterine infection with the spirillae of recurrent fever. Nonspecific infections in the prenatal life may cause a jaundice, mild anemia and an increase in the number of immature red blood cells. Usually such infections are located in the umbilical stump. These symptoms and findings differ from those in hemolytic disease in their late appearance. The spleen does not enlarge unless systemic infection occurs, and then a rise in temperature may be accompanied by a positive blood culture. Infection was given as the cause of icterus gravis by many early investigators (16). Diamond presents a more drastic picture in infection acquired at birth than do other writers (8, 14, 27, 37, 64, 68). Severe anemia, intense hematolytic icterus, immature cells in the blood, fever, diarrhea, vomiting, localization of the process in the body structure, positive blood cultures are

the findings presented. Henderson (32) summarizes the problem of infections to say that they usually occur in the first month of life. They rarely bring on death in the first three days or in the latter part of the first week. It is after the first week of life that most deaths are caused by infections. He reports 71 fatalities from infections that occurred from the second to the wourth week.

Congenital Syphilis: This disease at times may bear close resemblance to icterus gravis more than does any other pathologic condition. These two conditions are usually easily distinguished. Syphilis tends to decrease in each infant with each pregnancy while erythroblastosis tends to increase in severity with each pregnancy. There also is more of a tendency toward prematurity than those affected with the hydropic and macerated types of erythroblastosis. The disease usually occurs after the third day of life but may occur at any time. Both syphilis and erythroblastosis may cause edema of the fetus, enlargement of the placenta, hypertrophy of the spleen and liver, immature red cells in the circulation and extramedullary erythropoiesis (8, 15, 27, 37, 65, 69).

Osteochondritis involving the ends of long bones has been generally accepted as a specific indication of syphilis (60). Henderson (30) says osteochondritis is a common finding in 50 per cent of syphilitic cases at birth. At autopsy a thick irregular yellowish epiphyseal line in the long bone is

usually found while in erythroblastosis osseous manifestations are absent.

Placental findings are of importance in both these conditions. Both may show grossly a pale pink color, increased weight and greatly increased thickness. The syphilitic placenta in addition has infarction. Multiple small infarcts are more common than large ones (20, 30, 61). Histologic study of the placenta shows an increased amount of connective tissue within the villi. The blood vessels rarely contain an increased number of nucleated red blood cells as is found in erythroblastosis. Other findings in the syphilitic placenta include varying degrees of endarteritis up to complete occlusion, abnormal epithelium, and more conspicuous villus capillaries than in erythroblastosis. Enlargement and pallor of the placenta, persistence of the Langhans' layer of cells is the most characteristic feature in erythroblastosis.

Both of the conditions have extramedullary erythropoiesis with heptosplenomegaly. The liver is heavily infiltrated with erythropoietic cells but the distribution is usually focal in hemolytic disease and more diffuse in syphilis. Fibrosis of the liver, pancreas, lungs, thymus or kidneys can almost always be found in syphilis, and is rare in hemolytic disease (20, 30).

The identification of the spirochaeta pallida in the fetal tissues as well as finding a positive serological

reaction in the mothers blood will make the diagnosis of congenital syphilis. The serologic test is unreliable in the infants until after ten days but after this time the diagnosis could be made in the living infant (31, 60).

Congenital Atresia of the Bile Ducts: This disease, according to Potter (60) is rarely diagnosed as hemolytic disease, although hemolytic disease may occasionally be erroneously mistaken for bile duct atresia. The jaundice appears in the second or third week of life and steadily increases. This differs from hemolytic disease in which the jaundice is seen from birth on, and it may remain the same or increase later. The stools are pale from birth or turn pale later, but once pale they remain so. These stool changes are not seen in erythroblastosis. There is usually no change in the blood and the spleen is only slightly enlarged while the liver may be greatly enlarged (65). The van den Bergh, however, is direct and the icterus index is high with an average of about 100 plus units (65). Other symptoms and signs are: malnutrition, no fever, poor appetite, vomiting, and hemorrhages from the mucous membranes (8, 14, 15, 27, 65, 68).

Nuclear Icterus: Nuclear icterus or Kernicterus (a term used by pathologists to describe nuclear jaundice) is a disease of the newborn period that develops early giving signs and symptoms of brain damage. The condition is observ-

ed particularly in icterus gravis. The clinical signs are dyspnea, difficult swallowing, lack of appetite, general apathy, somnolence and coma (52, 70). There are also signs of brain damage, especially of the basal ganglia. Extrapyramidal spasticity, athetoid and choreiform movements, and emotional instability plus more or less marked mental retardation are the neurological findings (63). The number of red cells is usually low but it may be above three million (70). The spleen weight is from six to 47 gm. varying from one to three fingerbreadths below the costal margin. Extramedullary erythropoiesis is minimal and the onset of the jaundice seems to no significance as to the prognosis.

Anatomically, nuclear icterus is characterized by intense yellow coloration of the basal ganglia and by cellular lesions destructive in type scattered amont the nuclear groups (52). The icterus index is stated by Sanford (65) as being 75 units. Vaughan (70) concludes from the fact that kernicterus is very common in infants who develop icterus only after birth and the fact that certain of the infants dying with kernicterus have little or no sign of longstanding injury due to maternal anti-body suggest further that these factors associated with delivery may be of such significance as to account for kernicterus

in some babies.

Intracranial Hemorrhage: Birth trauma may be associated with early jaundice, and at times with a marked increase in immature cells in the circulating blood. These infants, however, rarely are anemic and the spleen and liver are not enlarged (60). This disease manifests itself during the period of the greatest intensity of simple icterus. Grulee and Sanford (23) list the symptoms as somnolence, cephalic cry, convulsions, rise in temperature, an early rise in the pulse rate that later drops, rigidity, bulging fontanel and a change in the Moro reflex. They say that the somnolence, cephalic cry and the rise in temperature are suggestive only and are not reliable. The convulsions may be general or local there being no special pattern reaction. They may be clonic, tonic or both over a varied period of time. The bulging fontanel is not seen in many cases with marked hemorrhage but that a tense and bulging fontanel is diagnostic. Then to, the spinal puncture may show blood, increase in the cells and yellow fluid aiding the diagnosis (23, 60, 68).

Winckel's Disease: This disease was given the name of Winckel's disease after the man who in 1879 described 23 cases and gave the name of "Cyanosis afebrilis icterica perniciosa cum hemoglobinuria" to this condition (73). This disease was first reported not by Winckel but by Pollack in 1871 and described

later by many other authors as Laroyenne in 1874, Charren in 1873, and Bigelow in 1875. This fact was cited by Polayse and Kramer (54) in their article on this subject. Since then many other names have been given on this condition including hemoglobinuria neonatorum, acute epidemic hemoglobinuria, and acute infectious hemoglobinemia of the newborn.

The disease is a symptom complex of the newborn with cyanosis, jaundice, and hemoglobinuria the prominent findings (22).

The icterus usually develops suddenly on the fourth day to the twelfth day then deepens and becomes bronze color (25). Polyuria develops and the urine is dark brown, containing numerous erythrocytes, and an increased amount of hemoglobin but bile pigment is usually absent. The constitutional symptoms are suggestive of a septic condition. These include marked restlessness, cyanosis, rapid pulse and a rapid respiration (21, 54). The temperature is, however, normal.

In the pathological study one finds icterus and multiple punctate hemorrhages in all organs. The kidneys show swelling, punctate hemorrhages in the cortex and the renal tubules contain hemoglobin crystals. The heart and liver show fat replacement (54). The blood changes to a syrupy character that is chocolate brown in color (21). The hemoglobin is markedly reduced as well as the number of erythrocytes. The urine

shows the characteristic finding of an increased amount of hemoglobin (24, 54).

Thus Winckel's disease differs from hemolytic disease in that it begins some days after birth and not from birth on, cyanosis is prominent, as well as the presence of large amounts of hemoglobin in the urine (21, 24, 37, 54, 65, 73).

Other Conditions: Several other conditions have been mentioned in the literature that give similar findings as those found in erythroblastosis but these offer little difficulty in diagnosis. Congenital heart disease may occur from birth to the fourteenth day with some jaundice but more cyanosis. The spleen may be slightly enlarged and there may be a slight rise in the icterus index. The condition is usually associated with convulsive siezures. These symptoms are due to cerebral anoxia. There is not a family history or evidences of hemolysis with anemia. This helps to distinguish it from hemolytic disease (23, 65).

Familial acholuric jaundice rarely causes symptoms in the newborn period since the disease usually starts after five years of age. It can be distinguished by the presence of a family history and the presence of microspherocytosis. Also, it can be excluded on the basis of the fragility test. This test reveals decreased resistance to hypotonic saline solutions (8, 27, 60, 68).

Hemorrhagic disease is not often confused with hemolytic disease. It usually occurs on the third to sixth day of life, the jaundice is mild and fleeting, splenomegaly and hepatomegaly are not present, the anemia is proportional to the blood loss and there is no positive family history to support erythroblastosis (15, 60).

Hemorrhage from the umbilical cord or placenta during the delivery, a severe anemia of unknown origin, leukemia, severe asphyxia, prematurity are given as further conditions for differential diagnosis by many observers but these again offer little difficulty in diagnosis (15, 27, 60).

SUMMARY.

A brief clinical and pathological picture of erythroblastosis fetalis has been presented as well as the normal blood picture in the newborn and a differential diagnosis of hemolytic disease.

If any expectant mother reveals in his history of a former reaction to a transfusion or has an unexplained abortion, miscarriage, or a stillborn infant the factors of isoimmunization should be suspected.

If an infant presents the symptoms and signs of anemia, increasing early jaundice, edema, enlarged liver and spleen, with a blood smear showing evidence of erythroblastemia, lethargy, dark amber urine, diffuse or localized petechiae and a Rh-positive blood in the father and the infant and Rh-negative maternal blood, the possibility of isoimmunization is highly suggested until other conditions are ruled out. Such conditions as syphilis, physiological jaundice, infection, atresia of the bile dusts, various hemorrhagic diseases, birth injuries and Winckel's disease must be ruled out.

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