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Erythroblastosis fetalis

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ERYTHROBLASTOSIS FETALIS

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INTRODUCTION

The term erythroblastosis fetalis embodies a disease process which manifests itself early in an infant's life. It may manifest itself while the fetus is still in utero or shortly thereafter when it is removed from the protective influence of the mother's body. It is differentiated from the disease entity known as erythroblastic anemia (59, 60) which has in common with erythroblastosis fetalis a disturbance of the hemopoietic system. The disturbance of the hemopoietic system is evidenced by a progressive anemia with large numbers of nucleated erythrocytes in the peripheral blood stream.

Erythroblastic anemia is characterized by a constant familial and racial, i.e., (people of the Mediterranean countries) incidence, enlargement of the spleen, distinctive changes in the bone and histologic lesions in the bone marrow and spleen. The average age of onset of the disease is about 16 months and the average age at which attention is called to them is about 34 months. These above features serve to set it apart as a separate disease entity as will be seen as this discussion of erythroblastosis fetalis develops.

Erythroblastosis fetalis has several manifestations and each manifestation has been known throughout literature by a number of terms. The first and most serious

manifestation has been called by different authors: 1. Universal edema of the newborn or fetus, 2. Hydrops fetalis, 3. Congenital hydrops and, 4. Congenital edema. The second most serious process has fortunately been termed by only one universally accepted name--Icterus gravis neonatorum. The least serious of the three manifestations has been variously termed: (1) Anemia of the newborn, (2) Congenital anemia, (3) Idiopathic anemia of the newborn and, (4) Hemolytic anemia of the newborn.

I shall endeavor to use just one term for each manifestation throughout this discussion. They will be (1) universal edema of the fetus, (2) icterus gravis neonatorum and, (3) anemia of the newborn of which aregenerative anemia is a type.

REVIEW OF LITERATURE

Universal edema of the fetus was discussed early in the literature. One of the most remarkable collections is that of Ballantyne (10). He collected in 1898 seventy cases which had occurred subsequent to 1614. Many of the cases were apparently due to a congenital abnormality. Others however, presented enlarged livers and spleen which were the only signs that might possibly point to an erythroblastosis. Jakesch and Klebs (42) (1878) and Sanger (78) (1888), as well as other authors reported cases of universal edema of the fetus associated with abnormalities of the blood cells. They were however, reported as cases representing a fetal type of leukemia. Swart (86) (1905) described a newborn infant with general edema, with an extra medullary hemapoiesis, but the etiologic signifcance was not realized. King (47) reported a somewhat similar pathological finding.

Schridde (80) in 1910 is considered the first author to describe certain types of universal edema of the fetus and attribute an underlying and causative disturbance of the hemopoietic organs. Since that year numerous verified reports have been made. Among them was Rautmann (74) (1912) who termed the underlying condition "erythroblastosis".

Cases of icterus gravis neonatorum were recorded

by Ashby (7) (1884) under familial jaundice, Blomfield (13) (1901), Auden (8) (1905) and still others in later years. They, however, did not give any data that might give a hint as to the underlying pathology. Buchan and Comrie (15) (1909) gave a thorough report of several newborn in two families that developed icterus gravis neonatorum and described the pathology with nucleated erythrocytes as it is recognized today.

Since their report many similar reports have appeared in the literature de Lange and Arntzenius (26) attention was called to the occurrence of dark yellow-colored amniotic fluid and a vernix caseosa of saffron yellow hue at the birth of patients suffering from the disease.

Ecklin (28) in 1919 is given credit for describing anemia in his report of "a case of severe anemia of the newborn". Finkelstein (30) (1911), Litchtenstein (60) (1917) and others suggested the occurrence of an unusual form of anemia in the newborn as did Buchan and Comrie (15) (1909). However the details of the features in these cases were not given and they cannot be credited with the first report. Since Ecklins (28) report, many cases have appeared in the literature.

RELATION OF UNIVERSAL EDEMA OF FETUS, ICTERUS GRAVIS NEONATORUM AND ANEMIA OF NEWBORN.

Diamond et al. (27) reported observations on 20 patients that conformed in every respect to the diagnostic criteria essential for the diagnosis of Universal edema of the fetus, Icterus gravis neonatorum and anemia of the newborn. The twenty cases may be classified as follows.

1. Universal edema of the fetus--two cases-----10%.
2. Icterus gravis neonatorum-----twelve cases--60%.
3. Anemia of the newborn---------six cases-----30%.

A summary of the facts in these 20 cases bearing out the relationship that exists between them will be given here.

As regards Universal edema of the fetus and Icterus gravis neonatorum: (1) A familial incidence is common to both. In one of the cases of universal edema of the fetus, the history of a previous pregnancy resulting in the birth of an infant with icterus gravis neonatorum was obtained. (2) Instances have occurred in each syndrome of enlargement of the placenta and the infant being covered at birth with golden yellow vernix caseosa. (3) Enlargement of the liver and of the spleen, and a relatively severe anemia with large numbers of circulating nucleated erythrocytes have been observed in each syndrome. (4) There was very little difference histologically between the tissues; equally large areas of

hematopoiesis occurred in the liver, spleen, kidney, adrenals, and other organs. (5) The microscopic changes in the placenta differed only in degree of involvement. There were large numbers of circulating erythroblasts in each condition, but areas of erythroblastic proliferation in the circulation were found only in placentas from cases of universal edema of the fetus.

A few, if not all, the above observations have been made by various other authors especially with reference to the familial tendency.

It would appear then that these symptom-complexes should be considered as clinical manifestations due to the same underlying disturbance, the only important distinction being that edema is the outstanding symptom in universal edema of the fetus, while in icterus gravis neonatorum, icterus is the most striking presenting sign.

As regards icterus gravis neonatorum and anemia of the newborn the following facts were noted which tend to bear out the relationship between them. Diamond et al. (27) presents the case of a last born of eight pregnancies in which the three preceding children had all shown an unusual pallor early in life. Two of these infants were seen and reported by the authors and presented the typical characteristics of anemia of the newborn. This last born child, nine and one half hours

after birth, showed pallor of mucous membranes, intense icterus, petechial hemorrhages, and an enlarged spleen and liver. The blood studies showed a marked anemia with a high number of nucleated red blood cells. These features suggested the diagnosis of icterus gravis neonatorum with erythroblastosis. After several transfusions the infants icterus disappeared, the liver and spleen diminished in size and at the age of eighteen days the patients showed a slight anemia with liver and spleen barely palpable. At this time, the patient presented clinical and hemologic characteristics identical with those of the two preceding children at the same age of life (seventeen days), in other words diagnostic criteria of anemia of newborn.

There is another type of anemia of the newborn which is now recognized as being a part of this picture (84). It is a nonregenerative form in which there is an extremely low red count with no accompanying erythroblastosis. The low red count is the only marked feature. Abbot and Abbot (1) and Pasahoff and Wilson (70) have presented cases showing its familial incidence along with anemia of newborn with erythroblastemia and universal edema of fetus.

Other cases have appeared in the literature which

show this same familial incidence and sequence of events in the individual patient--Buchan and Comrie (15) (1909).

Pasahoff and Wilson (71) reported on siblings, one of whom had anemia of the newborn and two of whom had hydrops. This further supports the familial relationship which is so evident in a large number of the cases reported.

Further evidence of the relationship is evidenced by a case reported by Shapiro and Cohen (81). They presented the case of identical twins, one of which had hydrops and the other anemia of the newborn. After five and one half weeks the twin with hydrops presented an anemia picture identical with that of his brother.

The accumulation of this evidence gives strong support to the association of anemia of the newborn with icterus gravis neonatorum and the dependency of anemia of the newborn upon the same underlying process.

It should be noted here that not only is there a familial incidence of these three disease manifestations, but there is often a history of the mother having delivered premature still born infants or miscarried previous to the birth of an affected infant (56). A miscarriage is also frequently interspersed between the birth of two affected infants. It is felt that some of these complications of pregnancy have the same etiological basis as erythroblastosis fetalis.

The probable position of each of the clinical entities dependent on the common underlying etiology may be described as follows: In universal edema of the fetus, the disease reaches its greatest severity in utero. The early evidence of this severe fetal disease may be manifest in the development of an hydramnions and the delivery of a premature, edematous infant in the sixth, seventh, or eighth month of gestation, or in a few cases it is manifested by spontaneous abortions and miscarriages. In less extensive involvement, gestation may continue to term. At delivery the vernix caseosa and the amniotic fluid are often a deep yellow color. The infant is usually stillborn or dies shortly after birth. One case of universal edema of newborn has been reported as surviving (81). The pathology is, briefly, a universal edema of the infant and of the placenta in a few cases. There is microscopical evidence of erythroblastosis and of severe anemia in the peripheral blood stream and extensive extramedullary hemopoiesis which may be present also in the placenta. The body cavities contain large amounts of fluid which show an icteric tint as do the body tissues. The jaundice however is seldom visible on the body surface. Death usually precludes its development.

Icterus gravis neonatorum may be associated also

with the same changes in the placenta and a similar yellow colored vernix caseosa. At birth or shortly after icterus and pallor become visible. There is usually a marked increase in the icterus which masks the anemia. With the exception of edema, which however may develop to some extent, the pathology is that of universal edema of the fetus. Icterus is the noticeable development in this manifestation as is edema in universal edema of the fetus. A much higher percentage of these infants survive than do those affected with universal edema.

In anemia of the newborn, neither edema or jaundice are in evidence although they may develop to a slight extent over localized areas of the body. Pallor is frequently the only sign of the underlying process. Erythroblastosis, along with extramedullary hemopoiesis, may be evident from examination of the peripheral blood and internal organs. The liver and spleen may be enlarged as in icterus gravis neonatorum and universal edema. It is now recognized however that there is a non-regenerative type of anemia in which pallor and marked anemia are the only findings. It is believed to be the mildest manifestation of the underlying pathological process. A large percentage of these infants with anemia will recover spontaneously without treatment.

In the above description, each symptom-complex is

portrayed as a part of a sequence, dependent on the severity and duration of the disease process. Not only is such a sequence developed from an analysis of each entity but it is supported by the occurrence of numerous intermediate types of cases which develop symptoms pertaining to more than one entity.

INCIDENCE

The figures on the incidence of the disease vary greatly with the different workers. One reason for the great variation is the time factor involved; that is, some of the figures are reported before the three manifestations of erythroblastosis were recognized as belonging in one category. Another is the fact that very recently it has been discovered that certain abortions and miscarriages should be included--although no actual figures are available which include this group at least it is now recognized. Another is that the figures appear to depend to a great extent on the interest displayed by various clinics and workers.

Clifford and Hertig (20) in 1932 reported 7 cases of icterus gravis neonatorum associated with erythroblastosis in 2,400 newborn infants in nine months--an incidence of 1 in 340.

Pasahoff and Wilson (70) found three cases of congenital anemia in 6000 cases in 1935. They state, however, that perhaps several mild cases might have been discovered if blood counts had been performed routinely on all newborn infants.

Javert (43) reported in 1937 an incidence of 1 in 400 infants.

In 1940 Wolfe and Neigus (94) reported encountering 27 cases of erythroblastosis in 15,334 deliveries, an

incidence of 1 in 568 confinements. There were 4 cases of universal edema of the fetus, 1 in 3,833; 20 cases of icterus gravis neonatorum, 1 in 766; and 3 instances of anemia of the newborn, 1 in 5,111.

Macklin (62) reported two stillborn infants with normal external appearances in whom autopsy revealed erythroblastosis. Therefore it might be suspected that the incidence was even higher.

Burnham (16) found an incidence of less than 1 in 200 cases. He states that his series, 8 in 1,400 was small and felt that it probably represented selected cases but also calls attention to the fact that six of the eight cases would have been missed had they not been looking for them. He feels that this is a fair figure for the incidence since it is apparent that the erythroblastic group must be broadened to include some of the aborted and macerated fetuses and many, if not most of the anemias of the newborn.

The disease is not limited to any race of people and has been reported in many countries. Ku and Li (50) reported it in a child of Chinese parentage. Andrews and Miller (6) and Pasahoff and Wilson (70) reported its appearance in negro infants.

CLINICAL PICTURE AND PATHOLOGY OF UNIVERSAL EDEMA OF FETUS

Clinically, universal edema of fetus is the most severe form of erythroblastosis fetalis. A still born infant or death after feeble respiration is the rule.

The fetus presents a waxy skin with multiple zones of cutaneous hemorrhage. Edema is marked. Jaundice is occasionally noted. The face is enlarged and swollen and the neck is short. The abdomen is greatly distended by a combination of the subcutaneous edema, the peritoneal fluid and the greatly enlarged liver and spleen.

Pathologically, the skin presents marked subcutaneous edema. Petechial hemorrhages are noted in the external and internal organs. The pleural cavity often contains excess fluid. The lungs may be airless or only partially areated. The heart is enlarged and its weight definitely increased. There may be an abnormally large amount of fluid present in the pericardial cavity. The abdominal cavity holds a variable amount of serosanguineous fluid. The liver reaches from two to five or more times its normal dimensions and is reddish brown and glistening. Microscopically, zones of toxic necrosis and deposition of iron or bile pigments are encountered. Hemosiderosis may be noted in the body tissues throughout. Hemopoiesis is pronounced--so much so that the liver cords are crowded out of normal position. The sinusoids are distended and contain numerous premature

cells of the red cell series (megaloblasts, erythroblasts, and normoblasts). The white cell group is represented by the myeloblasts and myelocyte. The portal canals are filled with similar cells. The spleen is soft and reaches four to five times its normal size and weight. It is generally firm in consistency and red brown in color. Malphigian corpuscles are not reproduced. The pulp is filled with hordes of immature nucleated red cells and large progenitors of the white cell series. Pigment laden phagocytes are numerous. The pancreas, adrenals, kidneys, prostate, thymus and pituitary share in the extramedullary proliferation of immature blood cells. The bone marrow is hyperplastic and compactly filled with proliferating erythroblastic and myelocytic cells; the former largely predominating. The placenta is enlarged, soft, and friable. Its maternal aspect is deeply fissured. The yellow gray color is striking. The fetal placental weight ratio is altered from the normal 6:1 and can reach an extreme of 3:1. Edema of the organ is the accounting factor. Microscopically, the villi are large and even in premature placentas reach beyond the normal size. The syncytial cells are regularly spaced. Syncytial buds are frequent. The Langhans cells may focally persist. The stroma is edematous but hyperplasia may be pronounced. Hofbauer cells normally present

only in early placenta are encountered with moderate frequency. The capillaries are reduced in number and contain numerous red and white blood cells.

The blood picture of erythroblastosis fetalis is common to fetal hydrops, icterus gravis neonatorum and congenital anemia and for this reason and to save repetition, the hematologic changes will be given after the description of the two remaining entities: Icterus gravis neonatorum and congenital anemia.

CLINICAL PICTURE AND PATHOLOGY OF ICTERUS GRAVIS NEONATORUM

The most prominent symptom of icterus gravis neonatorum is jaundice which may be present at birth or be delayed for twenty-four to forty-eight hours after delivery. A saffron yellow vernix caseosa arouses suspicion. The amniotic fluid may be yellow. These latter two factors in combination should suggest to the attending obstetrician the diagnosis or at least arouse his suspicion as to the possible occurrence of the disease. Abt (3) suggests that the coloration of the vernix and amniotic fluid can be explained by the fetal excretion in utero of bile-containing urine, and such phenomena are therefore more to be expected in cases already jaundiced at birth. The jaundice often perceived first in the face, spreads rapidly over the trunk and limbs; the conjunctivae are usually affected. Drowsiness is perhaps the commonest accompanying symptom of jaundice. The feces are usually well colored with bile pigment. Exceptionally, they are pale or uncolored for the first few days after the meconium has been passed, and this may give rise to a strong suspicion of congenital obliteration of the bile ducts, but in icterus gravis the stools are never pale for long. In explanation of this temporary acholia three views may be quoted: first, that from excessive hemolysis the bile becomes too viscid to

pass freely along the bile-channels; secondly, that damaged liver cells being taxed with excessive excretory work during a period of great hemolysis fail in their function; and thirdly, that accumulation of excess bilirubin in the bile capillaries, perhaps mixed with a foreign substance, leads to coagulation of bile-pigments (bile casts and thrombi). Bile pigments are found in the urine and sometimes bile salts. Bilirubinuria diminishes with the lessening of jaundice and disappears before the urinary excretion of urobilin returns to normal. Albuminuria is exceptional and oliguria occurs only in the severest cases. In the results of the van den Bergh's test there is no uniformity. Grulee and Mebane (32) found it to be unreliable in differentiating between obstructive and nonobstructive type of jaundice in infants. Excessive hemolysis results in varying degree of the hyperchromic anemia. The liver and spleen are always enlarged particularly at the height of the hemolytic process. After recovery the spleen may be palpated for a time, but soon assumes a normal size. In cases that last a long time the organ becomes firm as it diminishes in size.

If the anemia is severe signs of dyspnea will be apparent, recognizable in the young infant by exaggerated movements of the epigastrium which result from the

resilience of the thorax and the increased excursions of the diaphram. Signs have been found also in connection with the circulatory system. There may be cardiac enlargement in which both dilatation and hypertrophy play a part, and murmurs are sometimes heard. Such symptoms occur in severe, and particularly in edematous cases and cyanosis may be present.

Sudden increases in the depth of jaundice and exacerbations after apparent recovery has set in may occur. During these set backs the drowsiness returns, the icterus index rises, and the anemia increases. Spontaneous hemorrhage is an important symptom of the more severe cases and may feature in a relapse. Purpura is frequent and visceral hemorrhages are a pathological finding at autopsy. Umbilical and intracranial hemorrhage are recognized causes of death.

Convulsions, increased deep reflexes, and spasticity are not infrequent, though they are seen in only a minority of cases. Kernicterus or nuclear jaundice is a pathological finding reported by Schmorl (79) and Orth (66). The following symptoms have been reported in cases of kernicterus which have been established pathologically: drowsiness and apathy, convulsions and spasticity, opisthotonos and signs of medullary failure.

In those cases which recover, the jaundice gradually

disappears, usually taking from 2 to 3 weeks to disappear completely, and rarely as long as 2 months. A marked pallor of anemia is observed as the icterus fades.

Spontaneous intracranial hemorrhage may occur and give the nervous manifestations peculiar to this development.

To complete the clinical picture it may be added that fever may be present, though it is not to be expected. Zimmerman and Yannet (96) reported a case with a varied temperature curve and explained it in the absence of infection upon the involvement of the temperature control center in the brain by kernicterus and its sequelae. The affected babies accept their feeds though usually with diminished appetite, and they gain weight slowly. The risk of contracting enteral and respiratory infections in hospitals is very great, and these infections probably rank with anemia and hemorrhage as chief causes of mortality.

Until recovery is well advanced, enlargement of the liver is the rule. In the earlier stages there is vascular congestion and an increasing infiltration with bile. The gall-bladder and bile ducts are always normal, though the bile may be thick and scanty.

From birth until the anemia improves, or a fatal issue previously ensues, histological examination

demonstrates capillary congestion and a widespread erythropoieses. Groups of developing red cells are seen in the sinusoids, separating the columns of liver cells or seeming to replace them, and a more diffuse erythropoiesis may be observed in some of the capillaries. The earlier and more severe the case the more immature are the developing blood cells, and often a striking resemblance to fetal histology is observed. In addition to erythropoiesis, granulopoiesis occurs and tends to center in the portal tracts and vessels, where myelocytes are usually to be seen. Degenerative changes in the polygonal cells have been a conspicuous feature observed by many workers. These changes consist in diminished staining affinity, cytoplasmic vacuolations, and loss of cell-outline. Sections obtained from cases dying during the first few weeks show an erythropoiesis, diminishing as the age of death increases. Meanwhile, deposits of bile pigment soon become one of the most conspicuous features. The pigment is deposited as fine granules in the polygonal cells, as coarser droplets in the bile capillaries, and as casts in the bile-ducts. Here and there a polygonal cell is seen with a large vacuole filled by a droplet of bile. As time goes on granules of iron pigment collect in the polygonal cells and in Küpffer's cells and a positive Prussian blue

reaction will be obtained. Some of the less-damaged polygonal cells begin to recover and others proceed to a stage of atrophy. In some cases which survived five weeks or longer there has been demonstrated the development of a fine fibrosis particularly among the polygonal cells of the atrophic areas and in the neighborhood of the portal tracts. With rare exception no infiltrating inflammatory cells are visible, though young proliferating fibroblasts may sometimes be seen. The liver of one case (34) was studied after complete clinical recovery. The patient died of pertussis at ten weeks. The bile-pigment had disappeared, a few normoblasts and some hemosiderosis were still present and no fibrosis was noted. In cases with incomplete recovery, fibrosis when present, assumed a lobular distribution and was seldom pronounced. Pseudo-bile canaliculi were not recognized and the bile ducts were always healthy.

The spleen, like the liver, is enlarged at all stages and congestion of the pulp is the rule. In the neonatal period the Malphigian bodies are normally not apparent to the naked eye and are minute in microscopical preparations. This is also found to be the case in icterus gravis. The accumulation of bilirubin, and later hemosiderin, follows the same course as in the

case of the liver, though bile staining is less. The earlier stages of the disease are marked by widespread erythropoiesis and granulopoiesis, which with recovery diminishes. Degenerative changes have not been reported. Evidences of fibrosis has been noted.

The kidney shows a lesser degree of erythropoiesis than other solid viscera. The chief histological changes are the result of an attempt to excrete the products of excessive hemolysis. The epithelial cells, particularly of the convoluted tubules, show granules of bile-pigment and hemosiderin. Naked-eye examination of fresh specimens shows icterus, chiefly of the cortex, and large amounts of uric acid deposited in the collecting tubules, apparent as yellow linear striations converging towards the apex of each pyramid. Microscopically, the tubules are often dilated behind these accumulations and occasionally local necrosis takes place in their vicinity, irregular cystic spaces resulting. It is held that the uric acid which is excreted in such quantity is derived from the nuclei of normoblasts after extrusion. Similar deposits may be seen in normal newborn infants during the first ten days, and in cases of severe hemolysis and anemia in other ages. The glomeruli are usually normal but their capsules may be slightly dilated. Interstitial hemorrhages may be seen.

Extramedullary hemopoiesis has been described in the pancreas, adrenals, gonads, intestinal tract, lymphatic glands, placenta, connective tissue, skin, and in other situations.

Investigators have agreed in finding the bone-marrow hyperplastic for all elements, though Diamond et al. (27) reported occasional reduction in the number of megakaryocytes. As regards erythropoiesis, there is a relative increase of the less-matured cells and a scarcity of fully developed erythrocytes. There has been observed an increase in megakaryocytes, after recovery from icterus and anemia, in the bone marrow in a case in which thrombocytes had been diminished at the height of the disease.

Enlargement of the heart occurs in a few cases of icterus gravis. The enlargement is partly from dilatation and partly from hypertrophy.

The changes in the nervous system so far recognized, may be divided into spontaneous hemorrhage and icteric staining. Usually the hemorrhages are subdural and cortical. Petechial hemorrhage may also occur. Hawksley and Lightwood (34) found subdural and cortical hemorrhages in 6 of their 18 cases.

Icteric staining is sometimes seen in the meninges ependyma, and choroid plexus. Staining of the brain

substance is rare in icterus gravis and is said not to occur in other varieties of jaundice. Biemond and van Creveld (12) however, made it clear that septic jaundice may be a case. The incidence does not depend on the intensity of the general icterus, and a toxic factor may play a part. There are instances where the yellow coloring is circumscribed, being limited entirely to those areas of the brain where larger groups of ganglion cells are found, that is, the nuclear areas. This type was designated by Schmorl (79) as Kernikterus. The cortex of the cerebrum and cerebellum, the head of the striate body, the caudate nucleus and the optic thalamus are free from pigment, according to Schmorl. Zimmerman and Yannet (95) on the other hand, found that the structures most commonly affected are the caudate, lenticulate, subthalamic and dentate nuclei, the thalami, the mamillary bodies, the cornua ammonis, the nuclei of the cranial nerves, the olives and even parts of the cerebral cortex, as well as the anterior and posterior horns of the spinal cord. Many of the colored ganglion cells show necrotic changes, and the axis cylinders are especially intensely colored. Schmorl (79) felt that the sharp demarcation of the pigmentation shows that this yellow coloration is not related to simple imbibition of bile pigment but bound to definite structural elements.

Schmorl (79) found this condition in 6 of 120 necropsies in cases of jaundice of the newborn. Hawksley and Lightwood (34) found two in eighteen cases.

The sequela of icterus gravis neonatorum which has commanded the most attention is the central nervous system involvement which is, in the face of the present knowledge, very complex and not completely understood.

Zimmerman and Yannet (96) presented the case of a child who died at the age of 3 years. In early infancy the child had a severe icterus gravis neonatorum, following which developed extensive cerebral dysfunction. The neurologic phenomena consisted of bilateral athetosis, marked generalized extrapyramidal muscular spasticity, mental retardation and opisthotonos and convulsions. Necropsy revealed destruction of many cellular constituents of the caudate nuclei, putamina, cornua ammonis, substantia nigra and dentate, lateral thalamic and red nuclei. There was destruction of the cells and medullated nerve fibers of the pallida.

Fitz Gerald, Greenfield and Kounine (31) found in those cases with evidence of central nervous system involvement that the autopsy showed degeneration limited to those nuclei most deeply affected in kernicterus. They also reported the case of a 9 year old boy who presented the above neurologic phenomena in the most part

following icterus gravis neonatorum. They however, had no proof or disproof of the existing pathology as the child was still living.

Illingsworth (41) case is the oldest (11½ years of age) surviving case recorded with the supposed sequela of kernicterus. She displayed the nervous involvement thought characteristic. The only evidence given, however, that she had icterus gravis neonatorum was that it developed at 4 day of age and she was confined to the hospital for 1 month, during which time she was very ill. This seems to be poor proof. It is presented here however, to show that the upper limit of existence is not very high, even if this case is accepted.

The preceding presented cases seem to give a clear cut picture of the expected sequela of kernicterus. Then one finds the following report which throws the problem open to much speculation.

Zimmerman and Yannet (95) state that of those cases which present symptoms which may be interpreted as being the result of nuclear icterus, only a small per cent show kernicterus at post mortem. Conversely, a certain per cent of newborn in whom kernicterus is demonstrated at necropsy have revealed, during life, no definite signs that might suggest central nervous system involvement.

Sobel and Zucker (83) and Bushnell and Aldrich (17)

presented the cases of 3½ year old and 13 month old children respectively, who showed signs of kernicterus clinically but in which necropsy failed to prove that nuclear jaundice had existed.

Sobel (82) reported the cases of two infants who developed icterus gravis neonatorum and who recovered with transfusions. They showed no sequela at the ages of 6½ and 17 months of age that might be attributed to kernicterus.

Dr. Sidney Farbes (18) makes this statement concerning kernicterus which seems to summarize the present status; "The pigmentation may vary greatly in intensity. Its exact nature is not clearly proved; it is possible that we are dealing with a number of different pigments in this condition. We were under the impression until a year ago, that kernicterus was characteristic of erythroblastosis fetalis and that impression may be gained from literature. Dr.Trague Chisholm and I are studying a group of 26 patients with kernicterus. Only three of these gave evidence of erythroblastosis. Many of them were premature infants. The correct interpretation of kernicterus must await further study. It is safe to say that the icterus part of the name has been grossly overemphasized and may not be important."

CLINICAL PICTURE AND PATHOLOGY OF ANEMIA OF NEWBORN

The pallor of skin and mucous membranes usually becomes apparent about the fifth day of life, but in many may be masked by the existing jaundice. In mild forms the child may be otherwise well with a lusty cry, a good sucking reflex and normal response to stimuli. In more severe cases they are listless, weak and nurse poorly. A jaundice of varying intensity may be present but it is not a constant symptom. Either or both spleen and liver may be enlarged. Petechial hemorrhages of the skin may be noted.

As in the other forms, persisting hemopoiesis in the liver and spleen is classical. The degree, however, is not so advanced. Extramedullary blood formation in other organs may be present. The bone marrow is hyperplastic. The placenta is grossly normal. The hematologic findings are essentially those of icterus gravis and will be discussed later.

The prognosis is good, but the disease may run a prolonged course. Diamond et al. (27) indicates that the anemia may remain stationary or even become aggravated until the sixth week of life. At this time there is a return to the normal number of young erythrocytes. Finally, the hemoglobin and red cells increase to the normal, though a 4 month interval may be required for

complete restoration.

Stransky (84) expressed the belief that there are two types of primary anemia of the newborn. The first, and more frequent, is characterized by a non regenerative blood picture, with no true shift to the left and no embryonal cells, which he ascribed to a constitutional insufficiency of the bone marrow. The second type, which is more rare, shows an embryonal blood picture, with areas of extramedullary hemopoiesis.

That these two types represent differing individual responses to a similar etiologic factor is indicated by the appearance of both types in children of the same parents. Abbot and Abbot (1) reported a case in which the family history revealed such a relationship. The case presented, showed a definitely nonregenerative congenital anemia associated familially on the one hand, with a congenital anemia exhibiting erythroblastosis and, on the other, with one presenting the pathologic picture designated as "leucoblastosis" by Gierke (90). Pasahoff and Wilson (70) presented a report showing the extraordinary combination of congenital anemia of the newborn and universal edema in offspring of the same parents, and erythroblastosis was not present in either child.

The only marked feature in the nonregenerative type of congenital anemia is the extremely low red blood count

with no accompanying erythroblastosis. There is no accompanying jaundice, edema, petechial hemorrhages or the like. One may assume from these observations that there is no hepatic damage as is so common in the other forms of the disease.

NORMAL BLOOD PICTURE

The normal blood picture of the newborn infant should be briefly reviewed before the pathological blood picture of erythroblastosis fetalis is discussed. Holt (38) states that the average figures indicate that on the first day of life, most infants have a hemoglobin level of about 120 per cent (Sahli), an erythrocyte count of 5.5 millions, and a leucocyte count up to 20,000 per cu. mm., 60 per cent of which are polymorphonuclear.

In speaking of the normal number of erythroblasts found in infants, Hawksley and Lightwood (34), state that experience shows that between 1000 and 2000 cells per cu. mm. may be expected during the first few days of life in 40 per cent of the cases and that the total amount diminishes day by day. They accept, however, as the physiological maximum in full term infants at 5,000 cells per cu. mm. and of these the majority are pyknotic normoblasts. Wolf and Neigus (94) gave the upper and lower limits of normal as 1000 and 3750 respectively.

Strong and Marks (85) found that it was the opinion among hematologists that there may be as many as 5000 normoblasts per cu.mm., that these usually disappear by the second day, and that the presence of neucleated red cells younger than normoblasts should always be considered pathologic. Brenneman (14) also accepts the above expressed numbers.

BLOOD PICTURE IN ERYTHROBLASTOSIS FETALIS

The description of the blood picture common to universal edema, icterus gravis neonatorum and congenital anemia is taken in the most part from Hawksley and Lightwood (34). The different cell systems, for convenience, are discussed separately.

The erythron, in their conception, in the fetus differs from that of the post natal-period, which again is not the same as in adult life. In an early period of intra-uterine development erythropoiesis is widespread in the tissues, but later it becomes a function particularly of the liver and spleen until towards the end of pregnancy, when the bone-marrow gradually appropriates it. At birth, according to the degree of this change-over from erythropoiesis in the viscera to erythropoiesis in the bone-marrow, so, is the amount of extramedullary erythrogenesis to be measured. It is reasonable to argue that the change should be complete, or almost complete, at term, but a delay in the disappearance of extramedullary erythropoietic foci is a normal variation and certainly to be expected in prematurity. In erythroblastosis fetalis, as in prematurity, and perhaps in other disorders, this change is subject to considerable delay.

In icterus gravis neonatorum the changes in the erythron are indicative of two processes: severe destruction and compensatory regeneration. The former manifests

itself by rapid decrease of erythrocytes, an increased icteric index, and the excretion of urobilinogen and urobilin in excess. The latter, by the appearance in the circulation of immature erythrocytes in large numbers and a quick rise in the erythrocyte count as soon as the hemolytic process is checked. The number of immature red cells usually rises to a maximum after the improvement in the erythrocyte count has begun and then falls rapidly, the more immature cells disappearing first and the reticulocytes finally coming to rest at their normal level of under 1 per cent, shortly before recovery is complete. In a number of recovering cases the red cells do not rise above about 4,000,000 per cu. mm. for a considerable time, and in these a raised reticulocyte count of about 3 to 5 per cent suggests that hemolysis, slightly above physiological limits, is persisting. The confused nomenclature of nucleated red cells makes their classification unsatisfactory. The term erythroblast is here used to denote all the intermediate stages when the cytoplasmic basophilia of the megaloblast is giving place to hemoglobin formation, while the term normoblast denotes the later stage when nuclear pyknosis has occurred. The exact demarcation between erythroblast and normoblast is of necessity arbitrary. Of the abnormal cells the megaloblast and

erythroblast are the first to disappear, then the normoblast, and finally the number of reticulocytes returns to normal. Polychromasia occurs and parallels approximately the reticulocytosis. Punctate basophilia is usually seen: the stippled cells are not numerous and do not persist for long. Cases are recorded in which the erythrocyte count does not fall below four millions, and in these the outpouring of immature cells is proportionately less, but adequate serial counts on these cases are for the most part lacking. Although the anemia varies from case to case it is usually severe, and counts lower than half a million are recorded. The color index is at unity, or more frequently above one.

The individual characters of the red cells in icterus gravis are important; besides the changes already described, anisocytosis becomes apparent and is more apparent at the height of the erythropoietic response. At this time all varieties of nucleated red cells are usually to be observed and the phenomena of karyokinesis, karyorrhexis and nuclear extrusion are in evidence. The investigation into the cell volume has revealed certain changes, which may be peculiar to fetal erythroblastosis and indicates relationship of this form of hemolysis to that occurring in the premature infant. The mean erythrocyte diameter of normal

prematures was found by investigators (89) to be 8.084μ and 7.99 for full term babies in comparison with a normal adult mean diameter of 7.2μ. In both there is, after a slight initial rise, a drop in the mean diameter over the first eight weeks--an approach to normal. This drop was more rapid in premature than normal infants. The investigation of a case of icterus gravis revealed that the mean diameter was much greater, 9.215μ and showed a fall much more rapid than premature infants. It is of interest that a similar reduction of the mean diameter may be seen in a chronic hemolytic anemia. In this condition the erythrocyte is of smaller diameter than normal, but of greater thickness, and unduly fragile to hypotonic saline. Evidence from hematocrit readings in a case of icterus gravis showed that the average cell volume was not only above normal, but was still rising when the mean diameter was falling, a phenomenon indicating an increasing thickness of the cells. Further investigation may show that when a hemolytic process becomes chronic, the red cells become smaller and thicker in response.

The reaction of red blood cells to hypotonic saline is inconstant, some show a slight increase in fragility, while others show no abnormality.

The progress of the recovery, as seen in the

peripheral blood, is not infrequently interupted by exacerbations of the hemolytic process; these produce a fall, often of a million cells or more per cu. mm., occurring in a few hours, and the child may appear more clinically ill at these times. Such set-backs do not always evoke a further hemopoietic response because this may be maximal at the time in question. The effect of blood transfusions is seen most strikingly in the raising of the red cell count and hemoglobin content of the blood. Hemolysis may effect the transfused blood, the count falling in a day or so by a greater number of cells than can be accounted for by destruction of the infants blood. In other words, the hemolytic process, since it destroys also the normal cells of the donor, would appear to be a primary factor rather than an effect due to an abnormality of the infants cells (34). This view may have to be rectified according to the new concept as to the etiology of the disease. This increased hemolysis could be accounted for, by the introduction into the infants blood stream (Rh) of the donors anti Rh agglutinin, which is the underlying etiology. It is difficult to speculate as to this possiblility, however, because very few workers have given the source of their transfusions because not until recently was this considered important.

An increase in immature cells of the blood may be

seen after transfusion.

Trought (88) has shown that in the first month of life the dissociation of hemoglobin into acid hematin, when hydrochloric acid is added takes from thirty to sixty minutes as opposed to forty to sixty seconds in the adult. Likewise it was found that complete carboxylation could not be accomplished and it is felt that there is probably some specific difference in the hemoglobin molecule.

Different observers have recorded cases in which the platelets were increased, decreased and normal. The diverse methods of counting, the normal variation from method to method and from observer to observer, the lack of information on the thrombocytes in infancy, and the numerous factors that influence them, make it probable that variations through a wide range may normally occur. The discrepancy in the results of different observers may be due to different phases of the disease being studied. Diamond et al. (27) reported a low thrombocyte count in the first few days, followed by a rise to normal. They gave this as one reason for the hemorrhagic tendency.

The leukocytes in infancy form such a labile system that it is difficult to estimate the significance of all departures from the normal. When seen at an early

stage in the disease, there is a leucocytosis which varies in degree but is frequently above 35,000 per cu. mm. As the disease is checked this figure falls, to rise again from any further stimulus--a bout of hemolysis or a complicating infection. The rise in white cell count is due chiefly to an increase in the granulocytes. Here again, the swift changes in the normal infant's count over the first weeks of life, together with the variation encountered from case to case must be remembered. The appearance of immature cells of the granulocyte series is the rule, principally metamyelocytes and unsegmented neutrophils, but at the height of the regenerative process myelocytes and myeloblasts are commonly seen in the blood, though they rarely form more than 5 per cent of the total white count.

Hawksley and Lightwood (34) found no immaturity of the lymphocytes but Diamond et al. (27) stated that immature cells of every type, granulocytes, monocytes, and lymphocytes, are present. This latter observation was not made by others, that is, the increase in young forms of lymphocytes and monocytes. At the onset of the disease there is no characteristic change in the eosinophil or basophil cells, but as recovery occurs the number of eosinophils very frequently rises both absolutely and relatively. A similar, less constant, rise in monocyte

count occurs in some cases over the same period.

Abt (2) described a case of anemia of the newborn in which he observed erythrophagocytosis by circulating mononuclear cells but stated that he felt that it had no bearing on the etiology. The erythrophagocytosis he felt was not sufficient to give such a marked anemia.

There is recognized now a nonregenerative form of anemia of the newborn which may have below the arbitrarily set 5000 erythroblasts and still be diagnosed anemia of the newborn. The only striking feature in the blood stream is the extremely low red blood cell count and the lack of any marked erythroblastic response.

The treatment consists almost wholly of blood transfusions (20, 26, 27, 34, 65, 66, 67, 68, 69, 112) and is agreed upon by most men. This treatment, however, has run the gamut of intramuscular injections of whole blood (65), serum (33) and concentrated liver extract (40), vitamin K therapy (63), and antenatal controlled feeding of the mother (76, 1, 2, 8) and others (48).

Repeated transfusions of 10-15 cc of blood per pound of body weight (34) are timed (77) by the observed fall in erythrocyte and hemoglobin levels. The selection of a donor will be discussed later under the etiology.

Edema and dropsy (27) may be due to several possible causes acting either singly or in combination. The severe anemia may cause so high a degree of anoxemia as to damage the cells of the capillaries and result in loss of fluid from the circulation. The same damage from anoxemia may result in part from the lowered oxygen-carrying power, as has been shown, of the immature nucleated cells which abound in the blood of these patients. Associated with the anemia there may be a protein discrepancy from the altered liver function, or a change from the normal albumin-globulin ratio, such as has been shown to account for edema in other forms of severe anemia, Keefer, (46). Another possible cause for the edema may be related to decompensation of the hypertrophied heart which is so frequently present in such cases.

The anemia is the result of the extensive hemolysis of red blood cells brought about while the fetus is still in utero or shortly after its birth. The extramedullary hemopoiesis is a compensating mechanism in an attempt to keep the red blood cells at their normal level. Previous to the discovery of the true etiology, some workers (27) felt that the hemopoiesis was the primary condition due to a metabolic disturbance. The anemia, they felt, was due to a combination of the failure of development and

delivery of mature erythrocytes.

The hemosiderosis (34), so extensive in the liver, and present in other organs, may best be explained by the increase in amount of circulating "break down" products of the erythrocytes, or by disturbance in the metabolism of iron pigments.

The bleeding tendency (34), as evidenced by petechiae, ecchymosis and gross hemorrhages, is more difficult to explain. One theoretical possibility is that an increase in phagocytosis of erythrocytes by the reticuloendothelial cells also causes increased destruction of the blood platelets, which, when they are sufficiently decreased, allow free bleeding. Another is that hypertrophy and hyperplasia of erythroblastic tissue in the bone-marrow may crowd out the megakaryocytes , which produce blood platelets, just in leukemia, overgrowth of leucocytic cells is said to produce megakaryocyte destruction and lowered blood platelets. The combination of lowered platelet level with destruction of liver substance and severe jaundice increases the tendency to hemorrhage.

The icterus is first of a hemolytic type. The continuation of this process may so overburden the liver cells of the young organism, that functional insufficiency may occur and a greater degree of icterus result.

Or, another possibility, which may operate independently or in conjunction with the increased hemolysis and possible hepatic insufficiency is that the overcrowding of the liver with hemopoietic foci causes pressure atrophy of the liver cells, and general interference with liver function sufficient to cause an obstructive as well as hemolytic jaundice. It has been suggested that the staining of the brain nuclei occurs only in the presence of severe icterus as well as liver damage. Fitz Gerald, Greenfield and Kounine (31) state quite definitely that the development and location of the kernicterus is dependent upon two factors: (1) A preceeding damage to brain cells probably secondary to liver damage and (2) partial anoxemia to the brain areas.

REVIEW OF THEORIES OF ETIOLOGY AND RECENTLY PROVED ETIOLOGY

The theories as to the etiology of the disease may be grouped into two groups: (1) Those implicating the mother primarily and (2) those finding the cause solely with the child.

Under theories involving the mother one finds ascribed the following possible factors:

Nutritional disturbances in the mother attributed to a number of causes. Parsons (68) held that maternal anemia resulting from a long deficient diet was the most probable cause of congenital anemia in the offspring and other authors (5) recommended the administration of liver or iron or both to the mother before the birth of the child. Careful supervision of the diet of a number of cases (1), (81) has proved that antepartum therapy administered to the mother does not affect the offspring and hence one can consider that nutritional disturbances are not the cause of the anemia in the child. Some of the earlier writers failed to differentiate between icterus gravis neonatorum and the disease picture caused by syphilis and ascribed the cause to syphilis. It has been shown again and again, however, that the parents of the diseased children have negative serological tests as do the children and in a number of cases the complete absence of spirochetes in pathological specimens has been demonstrated. This definitely rules out syphilis as a

causative factor. Tuberculin tests and pathologic evidence of tuberculosis has likewise been negative. Acute infection in the mother could be a factor in a sporadic case, but it does not account for the familial tendency. A number of cases of the disease have been reported in which there was an associated toxemia in the mother. On the other hand a majority of the cases reported have described the mother's pregnancy as normal and uneventful. These facts discredit the toxemia of pregnancy theory. It is felt now, however, that some cases of toxemia may be related in effect to the underlying etiology of erythroblastosis fetalis and not as its cause. Theories that locate the cause in the child are in predominance. The fact that there have been a number of cases reported in which one twin was affected with erythroblastosis fetalis and the other one apparently normal shifted the search for the cause from the mother to the offspring. It was felt that such occurences spoke against the maternal influence in the causation of erythroblastosis.

Some of the earlier theories of jaundice in the newborn were based on the conception set forth by Eppinger that the bile pigment was elaborated by the liver cells and that the jaundice was the result of obstruction either in the extrahepatic ducts or within the liver, where blocking of the canaliculi was thought to be caused

by formation of bile thrombi by inspissated bile. It is now known that the pigment bilirubin is formed outside of the hepatic epithelial cells, by the reticuloendothelial cells, especially those in the liver, spleen and bone-marrow, from hemoglobin, and that jaundice may result from an abnormally rapid breakdown. From the pathological evidence found at autopsy and from the recognized increased destruction of red blood cells, it has been concluded that the jaundice of icterus gravis neonatorum is not due to obstruction only.

Hawksley and Lightwood (34) suggested the possibility of a mendelian recessive characteristic as responsible for the primary defect in the hemopoietic system. The assumption of a defect in the germ plasm provides an explanation for the appearance of these three related diseases in the subsequent children of the same family. The incidence, however, of the disease conditions in a large family or in a series of families is too large to be explained on a mendelian recessive characteristic.

Macklin (62) after making a statistical study of the disease came to the conclusion that they are inherited rather as a dominant mutation. Mallory (18) in discussing a case in 1941 fell in with this same idea. The manner in which Macklin arrived at her figures, the fact that if the diseases were dependent on a dominant mutation they

would be distributed at random among the offspring, has discredited the dominant mutation theory.

Gierke (90) considered as the cause of both fetal hydrops and icterus gravis neonatorum a "primary constistutional anlage defect of the hemopoietic system". Clifford and Hertig (20) felt that such a defect was the most likely cause. A. F. Abt (3) likewise based his theory of "embryonal hemopoietic persistence" in the familial type of case on a defective anlage as a defect in the germ plasm. An argument against this theory as de Lange (25) pointed out is the fact that in those cases that recover there is no further evidence of a defective anlage of the hemopoietic system.

Diamond et al. (27) were also impressed by the pronounced extramedullary erythropoiesis and set forth the view that a metabolic disturbance of the hemopoietic system was the underlying cause of the disease conditions. They attributed the erythroblastosis to a primary over activity of the hemopoietic system rather than to a secdary response caused by the excessive destruction of blood cells. They did not, however, offer any explanation of the nature or cause of the metabolic disturbance and several phases of the three disease process are not explained by this theory.

A. F. Abt (3) presented a theory based on the

presence of erythroblastosis. He stated that the cause was an "embryonal hemopoietic persistence" and that further considerations "must commence with the cause for the persistence of the embryonal type of blood formation". He accounts for the liver damage by attributing it to the anoxemia which is in turn due to the reduced oxygen-carrying power of the overwhelming number of immature cells. The jaundice, he attributes to the plugged biliary capillaries with resulting diffusion of bile into the blood. They are plugged because of the increased production of bilirubin which cannot be handled by the capillaries and bile thrombi result. The increased production of bilirubin and anemia he explains as being due to the increased fragility of immature cells. This latter premise is not universally agreed upon and is one criticism of the theory. Based upon statements of Rich (75) the distention of biliary capillaries with bile may be construed as an effect due to the same process which causes injury to the parenchymatous cells. Dilated bile capillaries are furthermore, not invariably observed in the histologic section of the liver in erythroblastosis.

Pasahoff and Wilson (70) and Parsons, Hawksley, and Gittens (69) have reported cases of universal edema of fetus and anemia of the newborn in which erythroblastic foci were very limited in extent or entirely absent.

This is another argument against the theory that the cause of the three disease entities lies primarily in the erythroblastosis.

Knöpfelmacher (49), Thorling (87), Beneke (11), Esch (29), and others because of the frequent occurrence of terminal infections in association with the severe forms of jaundice concluded that icterus gravis neonatorum always was due to an infectious or septic process. This theory, however, has been discredited by the bacteriologic work done which yielded negative results in the hands of several observers (4), (27).

Parsons, Hawksley and Gittens (69) among others, felt that some toxic factor must be the responsible agent in this disease. They reasoned that the toxic factor was at work some time before birth but that the placenta offered an avenue of escape so that the fetus may not have shown its effects except in universal edema of fetus where it was believed that such a large amount of substance was produced that all of it could not be adequately excreted. The difficulty in such a theory arises when an attempt at the explanation of the nature and source of the toxin is made and the familial tendency has to be accounted for.

Wooley (95) suggested that there was something of an analogy between erythroblastosis fetalis and leukemia.

Leukemia, he stated, is often considered a form of neoplastic overgrowth, in which the tissue concerned in the production of white blood cells, is affected. He reasoned that if the above conception had any force that erythroblastosis might be looked upon as also belonging to the group of tumors and in this case it was the erythroblastic tissue which was involved. This theory can not be accepted in the face of numerous reported recoveries and it does not explain the familial tendency or the aregenerative type of anemia.

Capon (19) came to the conclusion that the sequence of events was as follows: An overgrowth of intravillous connective tissue, which is out of proportion to the increase in the epithelial surfaces of the villi, damages the nutrition of the fetus in two. It causes a compression of the intervillous vessels, and it makes for less absorptive surface in comparison with the bulk of the tissue. The fetus tries to compensate by raising the blood pressure and increasing the production of blood. Cardiac hypertrophy results. The nutrition remains impaired, and the result is an exudation of fluid into the tissue spaces and serous cavities. This, however, does not explain the aregenerative anemia, familial tendency and other known conditions.

Darrow (25) concluded that the etiology could be

explained in an antigen-antibody reaction and reconstructed the etiologic events as follows: The mother is actively immunized against fetal red cells or some component of them. This seemed to be plausible because of the work of Trought (88), which suggested that fetal hemoglobin may differ in molecular structure from adult hemoglobin of the same species, and was capable of acting as specific precipitinogens as confirmed by Hektoen and Schulhof (35). The immunization may conceivably occur as the result of an accident within the placenta whereby the fetal cells or their hemoglobin gain entrance to the maternal blood sinuses. The antibodies formed in the maternal organism may then pass to the child through the placenta or possibly to an even greater extent through the colostrum and milk, since the diminution of red cells in congenital anemia appears to be most acute following birth. The time elapsing before such antibodies are present in the infant in sufficient concentration to produce a marked affect may correspond to the delay in the appearance of symptoms noted in most cases of congenital anemia. Such a transfer of immune bodies from an actively immunized mother to the fetus or newborn child sets up in the offspring a state of passive immunity. Such an immunity is relatively short lived and would eventually disappear completely, leaving

no trace to be passed on to succeeding generations. Furthermore, each child born and suckled subsequent to this active immunization in the mother would possess to a greator or less degree a passive immunity to the specific antigen, while any children born before the immunization of the mother would be entirely unaffected. This explains the familial tendency and its distribution among the children of an affected family. This mechanism, she states, bears no relation to a difference in blood groups in mother and child. Diamond et al. also stated that a difference in blood groups was not a factor in this group of diseases.

She attributes the symptoms of (1) edema, (2) hemorrhagic diathesis, (3) increased bleeding and coagulation time, (4) gastro-intestinal irritability, (5) somnolence and flaccidity, (6) twitchings and occasional convulsions, (7) respiratory distress; and signs of (1) marked increase in nucleated red cells, (2) extravascular migration of polymorphonuclear leukocytes and others to an anaphylactic type of reaction. Anaphylaxis may occur when there are marked changes in the liver and has been demonstrated in dogs by R. Weil (91) and by Dean and Webb (24).

She then concludes that in these diseases in which symptoms indicate injury of the liver, passive sensitization

to the hemoglobin of his own red cells has been transmitted to the fetus from the mother, primarily through the placenta while the infant was in utero and through her milk after birth. In the aregenerative form of congenital anemia, on the other hand, it is likely that immunization rather than sensitization has taken place in the mother and has been transmitted as such to the child, or that, in some cases, desensitization or possibly mitigation of the sensitization reaction has in some way been accomplished.

The difference in blood groups of mother and fetus was the basis for the theory of etiology of icterus gravis neonatorum of Hirszfeld (45) and Ottenberg (44). The concept was referred to as "heterospecific pregnancy". According to the concept of heterospecific pregnancy, given a mother of Group O and an infant of Group A (or Group B), the maternal anti-A (or anti-B) is increased in titer as a result of iso-immunization with the A (or B) blood of the fetus. Nevertheless, the maternal agglutinins are specifically inhibited from acting on the fetal blood because of the wide distribution of the A and B factors in tissues and body fluids.

However, this applies to about 80 per cent of all individuals (secretors) and if a fetus of Group A belongs to the class of non-secretors (20 per cent), it

is conceivable that the maternal iso-agglutinin anti-A may serve as the source of the intra uterine hemolytic process.

The accepted concept of the etiology of erythroblastosis has been worked out during the past few years and there is good statistical evidence to support it. The etiology was finally hit upon while studying transfusion accidents in obstetrical cases. Levine and Stetson (58) and Weiner and Peters (93) found atypical agglutinin present within apparently matched blood groups. Their case was that of a transfusion accident following the delivery of a macerated fetus, and the origin of atypical agglutinins was for the first time suggested to be the immunization of the mother by the baby.

Landsteiner and Weiner (51) reported on an agglutinin which was developed in rabbits by the injection of blood from the Macacus rhesus monkey. When tested with human bloods this agglutinin demonstrated the presence of a new substance in human red blood cells which they called the Rh factor (Rh from rhesus). The agglutinin is called the anti-Rh agglutinin.

Levine, Katzin, and Burnham (55) reported this agglutinin to be the destructive antibody responsible for several manifestations of erythroblastosis fetalis.

The etiology of erythroblastosis fetalis resides

in an immunologic incompatability between the fetus and the mother. In other words, there is present in the fetal red blood cells an antigen inherited from the father which is lacking in the mother. This antigen is the Rh factor which induces in the Rh- mother an agglutinin which passes back through the placenta into the fetal blood stream and there brings about a hemolysis of the fetal blood cells and a consequent compensatory hemopoiesis and its manifestations. This process is known as iso-immunization, that is, immunization within the same species and the source of the antigen belongs to the same species.

The striking difference in the incidence of the Rh factor in the selected population of mothers with erythroblastic babies and in the random population strongly supports the concept of iso-immunization. Since the incidence of Rh- bloods is very high in these mothers (54) it could be anticipated on the basis of the iso-immunization theory that the affected infants and the fathers in the series of Rh- mothers are exclusively Rh+. This was statistically proven as shown in the following table.

TABLE I (53)

All tests were made with Human anti-Rh sera.

	Rh+ %	Rh-%
Random Population 1,035 individuals	86	14
153 mothers of infants with erythroblastosis	8	92
89 husbands of Rh- mothers	100	0
76 infants with erythroblastosis	99	1

It will be noted in this above table that a few of the mothers of erythroblastic infants were Rh+. It was assumed that blood factors other than the Rh could also produce an iso-immunization. Levine and Polayes (57) described an atypical agglutinin in an Rh+ woman who suffered from a post partum transfusion accident. This case makes the preceding assumption seem acceptable. Levine, Javert and Katzin (in preparation 53) described another atypical agglutinin in an Rh+ mother of an erythroblastic infant. This agglutinin had the unusual specificity of reacting mainly with bloods which are Rh- with a particular variety of anti Rh agglutinins. It is probable that the blood factor described by this new agglutinin is genetically related to the Rh factor and for this reason it is designated as Hr. (53).

It will be recalled in discussing the etiologic theory of Hirszfeld and Ottenberg that it was stated that the anti A or anti B agglutinins of the mothers

blood was specifically inhibited from acting on the fetal blood by the wide distribution of the A and B factors in the tissues and body fluids. If, however, the fetus belongs to the 20 per cent which are non-secretors it is possible that the fetal blood would be hemolyzed by the anti A or anti B iso-agglutinin in the mothers blood. Therefore this older theory of heterospecific pregnancy may have to be revived for a few selected cases of erythroblastosis fetalis in which the Rh or other blood factors fail to indicate iso-immunization by the fetus.

In acquiring the data for table I a complicating factor was the failure of the human anti Rh sera to give entirely parallel results. A small number of cases were observed in which the mother was Rh+ with one serum but Rh- with another. These cases could be included as instances of iso-immunization because the father and / or the affected infants were Rh+ with the latter serum. The figures in table I suggest that these agglutination reactions provide a diagnostic test for erythroblastosis fetalis which has an accuracy of more than 90 per cent.

The final proof for iso-immunization can be made demonstrating the presence of the anti Rh agglutinin in the affected mothers serum. From table II (54) it will be noted that this can be accomplished much better if the test is performed soon after the birth of an infant with erythroblastosis fetalis.

TABLE II

Interval after last delivery of an affected infant.	Agglutinins present	Agglutinins not found
2 months post partum	33	37
2 months to 1 year post partum	5	15
1 year or longer post partum	2	39
During next pregnancy	2	5
No data	0	3
Total	42	99

The fact that the anti Rh agglutinin was not demonstrated shortly after delivery of an affected infant does not exclude their presence during some part of the pregnancy. The agglutinin may have exerted its affect upon the infants blood and disappeared at the time of delivery. It is also possible that the agglutinins capable of reacting in vivo cannot be demonstrated because of the limitations in the sensitivity of the technique employed.

The hemolysis of fetal blood by the agglutinins anti A and anti B, as previously discussed, are specifically inhibited by the widely distributed A and B substances in body fluids and tissue cells. This suggested that the Rh factor is probably limited to the red blood cells. Tests by Levine and Katzin, unpublished data, (53) with numerous specimens of saliva and a small number of specimens of sperm cells and seminal fluid showed that the Rh factor is not present in the material tested, Weiner and Forer, (92).

A peculiarity of this anti Rh sera which must be remembered if any matchings are attempted is that it is a so termed "warm agglutinin". It was discovered that many of the anti Rh sera react more intensely at 37°c than at lower temperatures (56), hence the name "warm agglutinin". It has been recommended that the mixture of the patients serum and donors cells or the suspected anti Rh serum and the Rh+ cells be incubated in a small tube at 37°c for about 30 minutes (54). Then centrifuge the cells at 500 R. P. M. for one minute for sedimentation; then resuspension of the red cells is attempted. Reactions negative to the naked eye should be confirmed by microscopical examination.

The figures quoted in the tables give some hint as to the transmission of the Rh factor. Studies by Landsteiner and Weiner (52) have shown that the Rh factor is inherited as a mendelian dominant property and that its absence is recessive. It is not a sex linked character nor does it bear any relationship to any of the blood groups or factors recognized. Should the father be heterozygous Rh rh, half of the offspring will be Rh- and therefore incapable of immunizing the mother. If the father is homozygous Rh Rh, all the offspring must be Rh+ and each pregnancy offers an opportunity for immunization of the mother. The first Rh+ infant may be spared, and this accounts for those cases in

which the first born is spared, because one or, in certain instances, more than one pregnancy with an Rh+ offspring may be necessary to induce a sufficient degree of iso-immunization.

Some infants are born apparently free from any disease condition, but in the course of a few days, severe anemia or jaundice may make its appearance. It is difficult to correlate this fact with the iso-immunization theory since the baby is free from further action by the anti Rh factor. Colostrum has been suspected as the source of the anti Rh factor but several of the cases were not breast fed. An alternative explanation is the storage of mothers agglutinins by the tissues of the fetus so that their subsequent release may then induce hemolysis several days after birth.

There are indications from a small number of cases that the affected infant maintains higher levels of hemoglobin and red cell counts if he is transfused with Rh- blood (53) instead of Rh+ blood. The rationale for this suggestion is drawn from the fact that the infants own Rh+ blood is undergoing destruction by the anti Rh factor. The Rh- blood, however, should come from a male who has never received a transfusion or a female who has never been pregnant or received a transfusion. This, however, is an ideal hard to attain since such a small percentage of the population is Rh-.

The blood of the infant and donor should always be cross matched since 11 per cent of the infants (64) show definite blood groups.

Since 12 per cent (53) of all matings offer an opportunity for iso-immunization of the mother (Rh+ father and Rh- mother), one could expect a high incidence of erythroblastosis. However, Javert (46) found an incidence of 1 in 400 and Burnham (16) felt that 1 in 200 might be a closer figure. Obviously there must be a number of factors that tend to reduce its incidence, such as the inability of many Rh- mothers to respond to iso-immunization and the current tendency to small families.

CONCLUSION

Erythroblastosis fetalis is a disease of the fetus or newborn infant which can be divided into three entities. They are universal edema of the fetus, icterus gravis neonatorum, and anemia of the newborn.

There are many pathological features common to all three entities. The most common of these features is a persistence of an embryonal blood picture after birth and a marked anemia.

The etiology of the disease seems to have been definitely proven to be an antigen antibody reaction with a resultant destruction of red blood cells and a hemopoietic compensation with the appearance of embryonal forms. The antibody is designated as anti Rh, the production of which is stimulated in an Rh- mother by a Rh+ child in utero. Many of the finer points of this theory remain to be worked out but it answers most of the questions of etiology. Since the main body of this thesis was completed there has appeared an article by Witebsky et al. (98), which has answered the question of the secretion of the anti Rh factor in mothers milk. They presented the case of an erythroblastic infant in which they demonstrated the Rh antibody in the milk of the mother. They obtained the first milk specimen about a week following delivery of the infant.

The treatment of the disease consists almost wholly of frequent transfusions of matched Rh- blood from adults who have never had a transfusion or a pregnancy.

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