SB

41

Alaska State Legislature

Senate

Judiciary Committee

Official Business

Pouch V
State Capitol
Juneau, Alaska 99811

M E M O R A N D U M

TO: File

FROM: Oleta Simmons

DATE: April 5, 1981

SUBJECT: SB 41

The following individual would like to be informed of the next committee hearing or SB 41:

Susan Miller
Alaska Court System
303 K Street
Anchorage, Alaska 99501

(264-0553)

Alaska State Legislature

Senate

Judiciary Committee

Official Business

Pouch V
State Capitol
Juneau, Alaska 99811

March 30, 1981

David Cates, Ph.D.
Alaska Native Health Board
1689 C Street, Suite 230
Anchorage, Alaska 99501

Dear Dr. Cates:

Thank you for your interest in SB 41.

Several members of the Committee feel that, although comparatively few cases have been uncovered by this statute, it acts as a screening device for individuals planning to marry, and may induce someone to seek medical attention.

Additionally, the Committee feels that the fiscal considerations are minor when balanced against the agony some persons may be spared by the test.

Again, I appreciate your expressing your views on this matter.

Sincerely,

Pat

Patrick M. Rodey
Chairman

PMR/ods

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FROM: ROBERTA TO: JUNO INFO
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TO: SENATOR PAT RODEY, CH. JUDICIARY COMMITTEE

FROM: DAVID E. CATES, PHD., AK NATIVE HEALTH BOARD 1689 C STREET, SUITE 230: 276-8989

THE ALASKA NATIVE HEALTH BOARD HAS RESOLVED ITS SUPPORT FOR PASSAGE OF SB 41 AND URGES YOUR COMMITTEE'S APPROVAL. IF THERE ARE REASONS THAT ARE CAUSING ITS HOLD UP MAY WE PLEASE BE ADVISED SO THAT WE MAY SPECIFICALLY ADDRESS THEM?

Alaska State Legislature

Senate

Judiciary Committee

Official Business

Pouch V
State Capitol
Juneau, Alaska 99811

April 23, 1981

Ms. Barbara Hoffmann
Executive Director
Alaska Council on Prevention
of Alcohol and Drug Abuse
7521 Old Seward Highway
Suite A
Anchorage, Alaska 99502

Dear Ms. Hoffmann:

Thank you for your comments in support of HB 41, an act providing mandatory coverage of drug and alcohol treatment for State employees.

This piece of legislation is scheduled to come before the House for vote on Friday, April 24, and its supporters are confident of its passage.

I will make every effort to ensure the passage of HB 41 when it reaches the Senate floor for vote.

Again, I appreciate your sharing your views.

Sincerely,

Pat

Senator Patrick M. Rodey
Chairman

PMR/ods

Alaska Council

ON PREVENTION OF ALCOHOL AND DRUG ABUSE

7521 Old Seward Hwy., Suite A
Anchorage, Alaska 99502
(907) 349-6602

April 7, 1981

Dear Senator:

The Alaska Council would like to go on record as being in support of HB-41, which would provide mandatory coverage of drug and alcohol treatment for State employees. It would also provide a sliding fee schedule for moderate income employees.

We believe that early intervention is the best way to combat these problems and, therefore, heartily endorse HB-41.

Sincerely,

Barbara Hoffmann

Barbara Hoffmann
Executive Director

BH/SH/vab

Steven Rose MD
Family Practice
SUBMITTED BY STEVEN ROSE MD.

OBSTETRICS and GYNECOLOGY Journal of

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Volume 52 July 1978 Number 1

The Management of Rh-Isoimmunization

JOHN M. BOWMAN, MD

The Rh-isoimmunized woman can only be identified through routine blood grouping and antibody screening of all pregnant women at their first prenatal visits in all pregnancies. Rh antibody titrations at regular intervals must then be carried out. If there is a preceding history of stillbirth or a baby requiring exchange transfusion, or failing that, an Rh antibody titer placing the fetus at risk (1:16 in albumin or higher in the Winnipeg Rh Laboratory), amniocentesis and spectrophotometric examination of the amniotic fluid are indicated as early as 20½ weeks' gestation. Serial amniotic fluid optical density (ΔOD_{450}) measurements by the Liley method are 95% accurate in predicting severity of fetal erythroblastosis and only 2 to 3% life threateningly inaccurate. If a single ΔOD_{450} reading reaches or exceeds 0.400 or serial readings rise into the upper 75 to 80% of Zone 2, prompt fetal transfusion is indicated. Waiting until the ΔOD_{450} measurement rises into Zone 3 is frequently associated with the presence of hydrops. Survival rates when fetal transfusions are required are 70% overall if the initial transfusion can be delayed until 26 weeks' gestation, 59% if the initial transfusion is necessary before 26 weeks' gestation, and 42% if initial transfusion is required between 21½ and 23 weeks' gestation. Fetal transfusion should be undertaken if the fetus has gross ascites (hydrops). Survival rates are 21% if ascites is encountered at the first transfusion, 76% if ascites is not encountered until the second transfusion, and 78% if no ascites is found at any time. Optimal management of the fetus doomed to become hydropic unless delivered early or subjected to fetal transfusion can only be carried out in a tertiary level perinatal center with a fully developed intensive care neonatology program. With such management, perinatal mortality from Rh erythroblastosis has been reduced from 14.3 to 1.5%.

TREMENDOUS STRIDES have been made in the management of Rh-isoimmunization in the past 2 decades. With the advent of an effective means of prevention of Rh-isoimmunization the obstetrician will see very few Rh-isoimmunized pregnant women and his expertise in the management of the problem in all of its aspects will diminish. The present review concerns itself with advances in the management of Rh-isoimmunization, particularly the prediction of severity of disease and its modification by early delivery or early delivery combined with intrauterine transfusion. The material discussed comes predominantly from the Rh Laboratory of the University of Manitoba and the Winnipeg Health Sciences Centre. The laboratory, founded in 1944, has been the sole provider of laboratory and clinical management services for Rh-negative pregnant women derived from a population base in excess of 1 million.

HISTORY

Following the discovery of the Rh blood group system by Landsteiner and Wiener[1] in 1940 and the demonstration of its relationship to transfusion reactions in the mother and erythroblastosis in the fetus by Levine, Katzin, and Burnham[2] in 1941, the pathogenesis of isoimmunization and of erythroblastosis fetalis was placed on a firm footing. However, the perinatal mortality from erythroblastosis fetalis remained about 40 to 50% until Wallerstein introduced the technique of exchange transfusion in 1945.[3] The use of exchange transfusion halved the perinatal mortality rate, theoretically preventing all deaths and brain damage from kernicterus but doing nothing for the 20 to 25% of erythroblastotic infants doomed to die of hydrops fetalis before term.

RESIDUAL PROBLEMS IN MANAGEMENT OF Rh-ISOIMMUNIZATION

The problems remaining since 1945 have been 1) Identifying the erythroblastotic infant destined to become hydropic *in utero* before he becomes hydropic; 2) Determining when hydrops is going to occur, 3) Taking steps to prevent hydrops from developing; and 4) Delaying delivery until there is a reasonable chance of infant

From the Department of Pediatrics and the Rh Laboratory at the University of Manitoba and the Health Sciences Centre, Winnipeg, Manitoba, Canada.

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survival. In this context it should be noted that half the fetuses doomed to become hydropic will become hydropic before 34 weeks' gestation (some as early as 22 weeks' gestation), the remaining half will become hydropic between 34 and 40 weeks' gestation.

The division of isoimmunized pregnancies in which fetuses will become hydropic into the two groups (hydrops before and after 34 weeks' gestation) is related to differences in management between the two. In the prefetal transfusion era, (1952 to 1963) approximate survival rates of severely erythroblastotic nonhydropic infants delivered prematurely in Winnipeg were as follows: 65% at 32, 80% at 33, 88% at 34, 94% at 35, and 96% at 36 weeks' gestation. Although the development of highly sophisticated perinatal treatment units in the past 10 to 12 years may have improved survival rates, the above figures have been useful in deciding, in the face of impending hydrops, what treatment measures should be taken—fetal transfusion or immediate early delivery. Although a 35% risk of death following delivery at 32 weeks' gestation was entirely acceptable when the alternative was death from hydrops *in utero*, it is no longer acceptable since fetal transfusion at 32 weeks' gestation carries with it a lower risk. Conversely, since initial fetal transfusion carries with it about a 10% risk, the 12% risk of delivery at 34 weeks' gestation may be acceptable.

DETERMINATION OF THE MOTHER AT RISK OF ISOIMMUNIZATION

It is self evident that unless the obstetrician knows the Rh and isoimmunization status of his pregnant patients he will not be aware of which patients are at risk and therefore what management steps must be taken. The simple step of sending a blood sample for blood grouping and antibody screening at the first prenatal visit in every pregnancy must never be neglected. Knowledge that the patient is Rh-positive is not sufficient, the occasional Rh-positive woman may develop atypical blood group antibodies which may be just as lethal as Rh antibodies. Kanti-e and Kell are the commonest) and require the same type of management.

TRANSPLACENTAL HEMORRHAGE

The obstetrician should also be aware of the risks of Rh-immunization in certain situations. The mode of exposure of the Rh-negative woman to Rh-positive red cells is by fetal transplacental hemorrhage.[4] With the development of the acid elution technique for differentiating fetal from adult red cells by Kleihauer et al[5] in 1957 a very sensitive method became available for determining the incidence and size of fetal maternal hemorrhage and relating transplacental hemorrhage to risk of immunization.

About 50% of women show evidence of transplacental hemorrhage at some time during pregnancy or immediately after delivery.[6] In half of these the amount of the hemorrhage is less than 0.1 ml of fetal blood. Less than 1% of women will have more than 5 ml and only 0.2% will have more than 30 ml of fetal blood in their circulation. Cesarean section and manual removal of the placenta increase the frequency of transplacental hemorrhage.

Incidence and amount of transplacental hemorrhage are less in early pregnancy, increasing as gestation progresses. Very small hemorrhages may be found by the eighth week in 5 to 15% of pregnancies. During the third trimester, hemorrhages may be found in up to 20% of pregnancies and occasionally volumes may be considerable. Toxemia is associated with more and larger hemorrhage. External version and abruptio placentae have also been implicated.

Amniocentesis carries a risk. Prior to placental localization, 11.2% of 410 amniocenteses in Winnipeg were associated with transplacental hemorrhage,[7] many in excess of 1 ml of fetal blood. Ultrasound placental localization reduces the risk of transplacental hemorrhage but does not remove it entirely.

Abortion is associated with a significant incidence of transplacental hemorrhage. Volumes following spontaneous abortion are usually less than 0.1 ml. Transplacental hemorrhage following therapeutic abortion occurs in up to 20% of cases and in 4% the volume will be greater than 0.2 ml.

THE INCIDENCE OF RH-ISOIMMUNIZATION

As might be expected, the volume of transplacental hemorrhage influences the risk of Rh-isoimmunization of the pregnant woman. If the observed volume of transplacental hemorrhage is always less than 0.1 ml of fetal blood, the incidence of overt Rh-immunization appearing within 6 months of delivery is about 3%.[8] If volumes greater than 0.1 ml are found, the observed incidence in the same period is 34%.[8]

The risk of demonstrable Rh-immunization within 6 months after delivery of the first Rh-positive ABO compatible infant is about 8%.[9] Development of a secondary immune response in the next Rh-positive pregnancy due to "sensibilization" as a result of the first is also 8%.[9] Therefore, the overall risk of Rh-immunization as a result of the first Rh-positive ABO compatible pregnancy is about 16%. If sensitive manual enzyme and/or Auto Analyzer antibody screening methods are used more instances of overt Rh-immunization will be detected and less "sensibilized" women will be identified due to a secondary immune response in the next pregnancy. However, the overall 16% incidence of Rh-immunization will remain the same.[9]

The risk of Rh-immunization with subsequent Rh-

positive ABO compatible pregnancies has been stated to be the same but this is not altogether true. As parity increases, the number of good "responders" will diminish through prior sensitization and the number refractory to Rh antigen will be increased relatively. By the end of the fifth Rh-positive ABO compatible pregnancy there is at least a 50% chance that Rh-immunization will have developed.

ABO incompatibility of the Rh-positive fetus with his Rh-negative mother confers some protection against Rh-immunization. The protection may be due to the destruction of the ABO incompatible fetal red cells in the material circulation and removal of red cell debris by phagocytes in the liver, an organ with a relatively small number of potential immunocytes. The protection conferred by ABO incompatibility is only partial, the risk of Rh-immunization following an ABO incompatible Rh-positive pregnancy being about 1.5 to 2%.[10]

A significant number of Rh-negative women are Rh-immunized during pregnancy or within 3 days after delivery (1.5 to 2.0%).[11] This important problem will be considered in detail in the discussion of problems of Rh prophylaxis.

Since transplacental hemorrhage occurs after abortion, one would expect abortion to carry with it some risk of Rh-isoimmunization. This risk has been reported to be as high as 4.3%,[12] although 2 to 3% is probably a truer estimate of the risk. Therapeutic abortion appears to carry a somewhat higher risk than spontaneous abortion. Although the risk would appear to be very low in the first 6 to 8 weeks, it becomes significant by 12 weeks' gestation.

PATHOGENESIS OF ERYTHROBLASTOSIS FETALIS

The underlying pathogenesis of erythroblastosis fetalis is hemolysis of fetal Rh-positive red cells by maternal IgG Rh antibody (anti-D). The result is fetal anemia and increased production of erythropoietin. Initially, all marrow resources are called into play. If these are insufficient, extramedullary sites, primarily liver and spleen, are called into play with the release of immature nucleated red cells (erythroblasts) into the circulation (Figure 1). Enlargement of the liver and spleen is one of the diagnostic hallmarks of erythroblastosis fetalis.

PATHOGENESIS OF HYDROPS FETALIS

Twenty to twenty-five percent of fetuses with Rh erythroblastosis have such severe hemolysis that they

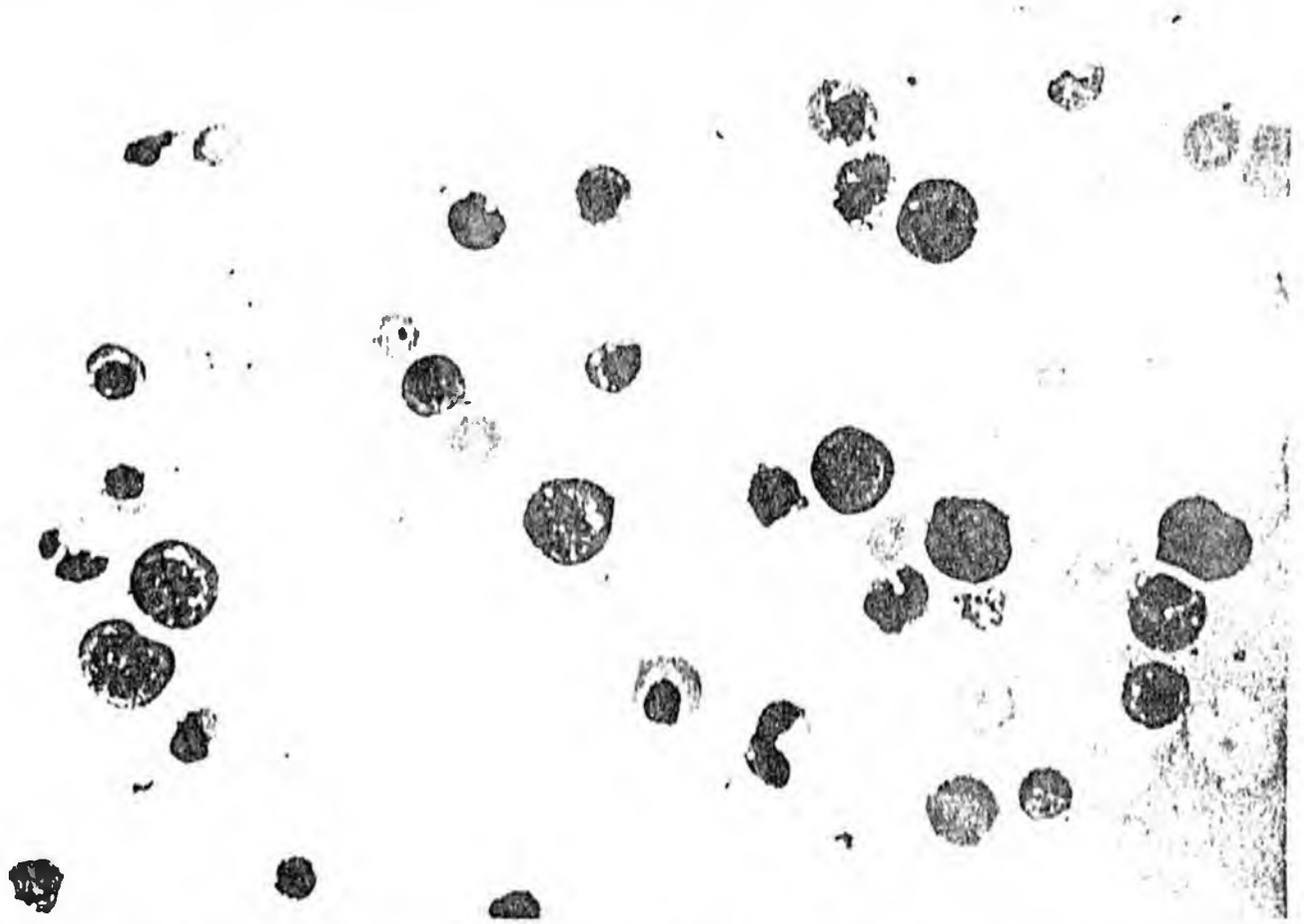

Fig 1. Cord blood smear from infant with severe erythroblastosis; nucleated cells are in the erythroid series from normoblasts to early erythroblasts

ultimately develop universal edema with extreme ascites (hydrops fetalis). It was originally thought that hydrops fetalis was due to fetal heart failure caused by progressive anemia and resultant hypervolemia. Although heart failure will develop in the hydropic neonate if he lives long enough, it is rarely present at birth and is rarely, if ever, the primary cause of hydrops fetalis.

With severe hemolysis and extensive hepatic erythropoiesis, there is a marked distortion and enlargement of hepatic parenchyma by islets of erythropoiesis. Portal and umbilical venous hypertension develop. Placental edema and trophoblastic hypertrophy occur. There is diminution in placental transfer of nutrients to the fetus. Ascites appears as a result of portal hypertension. Distortion of hepatic cell cords and reduction of blood flow due to obstruction reduces the synthesizing capacity of the liver. Hypoalbuminemia develops. As hypoproteinemia increases, ascites becomes more severe and then generalized edema appears. Finally, because of hypoproteinemia and portal hypertension, the edema and ascites become extreme (anasarca). In the final stage of hydrops, hydrothorax with compression hypoplasia of the lungs and pulmonary edema make adequate respiratory exchange impossible after delivery.

Although the above explanation is partially hypothetical,[13] experimental studies have shown that hypervolemia is not usually present at birth[14] and therefore the heart failure theory as the primary cause of hydrops is not tenable. The portal hypertension liver failure hypothesis explains the variable relation of hydrops to hemoglobin concentrations in the fetus. Because the condition of hydrops is due to hepatic dysfunction and not anemia, some fetuses become hydropic with hemoglobin levels of 7 g/100 ml or higher, others are not hydropic with hemoglobin levels below 3 g/100 ml.

IDENTIFICATION OF THE FETUS AT RISK OF BECOMING HYDROPIC

When a physician discovers that his Rh-negative pregnant patient is Rh-immunized, he must be able to predict accurately whether the fetus is severely affected and if so, at what gestation hydrops will develop. It is imperative that only fetuses who will not survive past 34 to 35 weeks' gestation are subjected to fetal transfusion and that only these babies and those who will become hydropic between 34 to 40 weeks' gestation are delivered early. It is also essential to select the latest period for initial fetal transfusion and early delivery compatible with intact survival. The risk of death from fetal transfusion is at least 15% at 22 weeks' gestation and remains at about 10% throughout gestation if the placenta is anterior. The risk is around 3% for second, third, and fourth transfusions after 28 weeks' gestation if the placenta is not anterior.

In order to assess the risks of hydrops developing when the pregnant patient is Rh-isoimmunized, the obstetrician has three considerations—history, Rh antibody titer, and amniotic fluid spectrophotometric readings, each of which will be considered in some detail.

HISTORY OF PREVIOUSLY AFFECTED SIBLINGS

Erythroblastosis may remain of the same degree of severity in subsequent pregnancies or become progressively more severe. A sensitized woman who has had mildly affected fetuses in two or more pregnancies is likely, but by no means certain, to have a mildly affected baby in a subsequent pregnancy. The other pattern is one of increasing severity from mild to hydropic with or without an intervening moderately affected infant. Following one hydropic fetal death, the risk of hydropic fetal death of a subsequent Rh-positive fetus is at least 90%. Infrequently, but not rarely, subsequent disease may be less severe and a moderately severely affected easily treated infant may be born near term after an earlier hydropic fetal death.

Unfortunately, history is not helpful in a first sensitized pregnancy where the risk of hydrops, contrary to general belief, is about 8%,[15] nor is it helpful when there is a past history of severe disease and the husband is heterozygous for the Rh factor (D). A history of previous hydropic stillbirth does not indicate at what stage of gestation a subsequently affected fetus will become hydropic. Treatment of impending hydrops at 23 to 24 weeks' gestation is vastly different than treatment of impending hydrops at 36 to 37 weeks' gestation.

MATERNAL Rh ANTIBODY TITER

Contrary to beliefs held by many, Rh antibody titers, if carried out by the same individuals using the same techniques and the same Rh-positive test cells, are of some prognostic significance. However, since other factors such as the binding constant of the Rh antibody, the Rh antigen content of the fetal red cell membrane, and the ability of the fetus to replace destroyed red cells without compromising hepatic function are also important, one would not expect the antibody titer to reflect severity of erythroblastosis with great accuracy.

Before discussing the significance of Rh antibody titers in predicting the fetus at risk of becoming hydropic, a brief description of methods and titers is necessary.

Saline Titers

Serial dilutions of maternal serum containing Rh antibody are mixed with Rh-positive red cells suspended in isotonic saline. Only IgM antibody will produce agglutination of red cells suspended in saline. The highest dilution at which agglutination occurs is the saline titer (1:1, 1:2, etc). The titer indicates the presence and, very crudely, the amount of IgM antibody. Usually the saline titer is low since most isoimmunized women produce little, if any, IgM Rh antibody.

Albumin Titers

Serial dilutions of maternal serum containing Rh antibody are mixed with Rh-positive red cells suspended in a thicker more viscous medium (usually bovine serum albumin). Both IgM and IgG Rh antibody will agglutinate Rh-positive red cells suspended in albumin. The highest dilution at which agglutination occurs is the albumin titer, (1:1, 1:8, 1:64, etc). If the saline titer is low, indicating little or no IgM antibody, the albumin titer is a crude but reasonable measurement of IgG Rh antibody (the antibody that crosses the placenta and causes fetal red cell destruction). If there is a significant saline Rh antibody titer present, the albumin titer represents a mixture of IgM and IgG Rh antibody and therefore is less helpful. IgM Rh antibody can be destroyed by mercapto-ethanol. Subsequent retitration by the albumin technique will then allow a more accurate determination of the IgG Rh antibody level.

Indirect antiglobulin Titers

Serial dilutions of maternal serum containing the Rh antibody are incubated with Rh-positive red cells (usually for 1 hour). Red cells are then washed with isotonic saline and mixed with antihuman globulin (Coombs test serum, made by injecting human serum into another animal species (rabbits, guinea pigs, goats, etc). The greatest dilution at which the antihuman globulin produces agglutination is the indirect antiglobulin Rh antibody titer (1:1, 1:16, 1:128, etc). Antiglobulin Rh antibody titrations are more sensitive than the albumin method (a titer of 1:64 by the antiglobulin method corresponds approximately to a titer of 1:16 by the albumin method).

It cannot be emphasized too strongly that techniques of antibody titration vary greatly in sensitivity from one laboratory to another. It is imperative therefore that the obstetrician become familiar with the methods and the significance of the titers reported by the laboratory which he uses. The titers which indicate that a fetus is at risk of developing hydrops vary from laboratory to laboratory and the figures quoted in this review pertain only to titers carried out by the Rh Laboratory in Winnipeg, using an albumin titration method.[15]

In a first sensitized pregnancy or in a subsequent pregnancy where preceding affected infants did not require exchange transfusion, an albumin Rh antibody titer of 1:8 or less is not associated with stillbirth before term. A titer of 1:16 prior to 32 weeks' gestation carries a 10% risk, 1:32 a 25% risk, 1:64 a 50% risk of hydrops developing before term if the fetus is Rh-positive.[15] If there has been a preceding history of hydrops or severe Rh erythroblastosis requiring fetal transfusion and/or early delivery, subsequent affected fetuses may become hydropic with titers as low as 1:4 or 1:8.

To determine whether there is an Rh antibody level which places the fetus at risk, it is essential that the isoimmunized women have Rh antibody titer estimations at regular intervals. We suggest every 4 weeks prior to 26 weeks' gestation, every 2 weeks thereafter. Unfortunately, antibody titers are rarely helpful in differentiating an Rh-positive from an Rh-negative fetus when the husband is heterozygous. Rarely does the titer rise during such a pregnancy.

Assessment of material history and Rh antibody titer is not sufficiently accurate to be the basis for institution of correct management of the Rh-immunized mother and her fetus. In one series of 426 isoimmunized pregnancies (from 1954 to 1961), in which there were 67 stillbirths and neonatal deaths, and 54 babies salvaged only by early delivery, the degree of severity of erythroblastosis, using history and titer in the 121 most severely affected fetuses, could only be predicted accurately in 62% of cases.[15]

AMNIOTIC FLUID SPECTROPHOTOMETRY

The introduction of amniotic fluid spectrophotometry by Bevis in 1956[16] and its subsequent refinement by Liley[17] and others has completely revolutionized the prediction of severity of Rh erythroblastosis fetalis. Most methods in use depend on the spectrophotometric measurement of bilirubin in amniotic fluid, the amount of bilirubin present being related to severity of erythroblastosis.

It is beyond the scope of this report to describe all the various methods used and to weigh the pros and cons of each. However, a careful comparison by Bartsch of the various methods in use in 1970[18] revealed no particular advantage of one over another. Of far greater importance than the actual method of measurement is the familiarity and experience of the obstetrician with the significance of the readings reported to him by the laboratory to which he sends amniotic fluids for testing.

THE LILEY METHOD (AS USED BY THE Rh LABORATORY)

Liley's method reports optical density rises at 450 mμ (ΔOD_{450}) in specific figures, allowing accurate comparison of measurements from one laboratory to another. Amniotic fluid, once obtained, is protected from light which oxidizes bilirubin to colorless compounds *in vitro* as it does *in vivo*. It is then centrifuged and filtered. Optical density readings are made over the wavelength range 700 to 350 mμ, using a good quality spectrophotometer. The readings are plotted either automatically or manually on semilogarithmic graph paper (Figure 2), using wavelength as the horizontal linear coordinant and optical density as the vertical logarithmic coordinant. The readings are joined. A characteristic rise in optical density at 450 mμ is found. This rise is proportional to the degree of severity of Rh disease in the fetus.

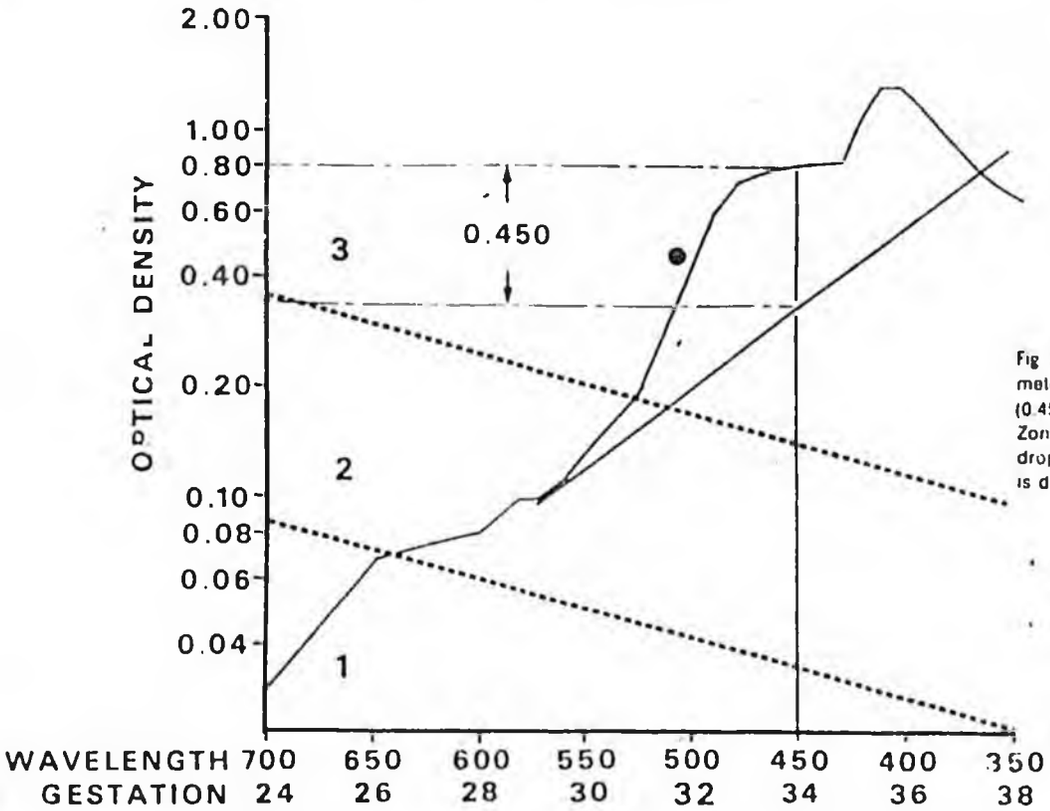

Fig 2. Amniotic fluid spectrophotometric reading, Liley method. ΔOD_{450} (0.450 in this example) falls into Zone 3, indicating impending hydropic death; further rise at 405 mμ is due to heme pigment

A further rise at 405 mμ unaccompanied by 540 and 580 peaks is due to heme pigment. Since other factors contribute to optical absorption across the entire spectrum, the rise in optical density, ie, the deviation from linearity, at 450 mμ is the figure of prognostic importance. This figure is obtained by drawing a tangent joining the curve at 550 mμ to that at 365 mμ and measuring from the point at which this line intersects 450 mμ to the actual optical density reading at 450 mμ (Figure 2).

The 450 mμ optical density rise, once obtained, must then be replotted using gestation as the arithmetic horizontal coordinant. Such replotting is necessary because the normal fetus produces bilirubin in early gestation which reaches peak levels at 23 to 25 weeks' gestation. The spectrophotometric graph is divided into three zones (Figures 2 and 3). Fluids falling into the upper zone (Zone 3) indicate severe disease, usually impending fetal death; fluids falling into the lower zone (Zone 1) an Rh-negative infant or an Rh-positive baby with minimal anemia but the possibility of requiring exchange transfusion. Fluids in the middle zone (Zone 2) indicate intermediate disease, becoming more severe as the optical density rise approaches the Zone 3 boundary.

The slope of the boundaries demarcating the three zones indicates that, as gestation progresses and the amniotic fluid bilirubin normally present diminishes, the same optical density rise is indicative of more severe erythroblastosis. Although single amniotic fluid examinations after 29 weeks are reasonably accurate in predicting severity of disease, serial fluid examinations, plotting consecutive 450 mμ optical density rises and determining the slope of the serial rises in relation to the zone boundaries, give a more accurate index of severity of erythroblastosis (Figure 3).

The following statements are made on the basis of 2823 amniotic fluid examinations carried out on 997 isoimmunized women from December 15, 1961, to February 28, 1978 (Table 1).[19]

1) A single amniotic fluid optical density rise of 0.400 or higher at any stage of gestation indicates hydrops fetalis at the time of the amniocentesis in 65% of cases.

2) Hydrops fetalis may be present with amniotic fluid 450 mμ optical density rises as low as 0.250 at 28 weeks' gestation (0.180 on one occasion).

3) If serial amniotic fluid 450 mμ optical density rises show an ascending slope and the final fluid reaches into the upper 75 to 80% of Zone 2 by 28 weeks' gestation, delay of fetal transfusion until a further examination shows a rise into Zone 3 frequently results in hydrops fetalis.

4) If an optical density rise is in mid Zone 2, a delay in repeating the amniocentesis for 2 weeks may result in a Zone 3 fluid and hydrops at the time of the second examination.

5) On rare occasions a single reading of 0.200 to 0.250 at 22 to 24 weeks' gestation may be associated with an Rh-negative fetus.

Serial amniotic fluid spectrophotometry has increased

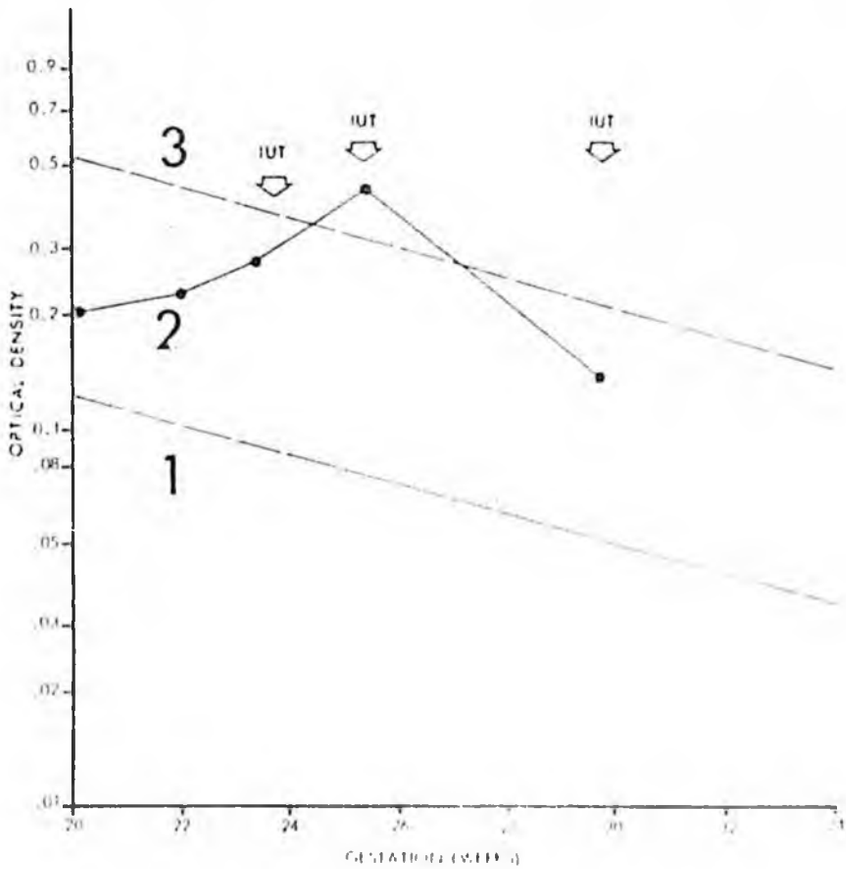

Fig 3. Serial Δ OD_{450} readings; first IUT when Δ OD_{450} at 75% level Zone 2, Δ OD_{450} in Zone 3 at second IUT; fetus not hydropic; Δ OD_{450} at 65% level in Zone 2 at third IUT; fetus survived.

the accuracy of prediction of severity of erythroblastosis to 90 to 95% (Table 1).[20] However, life-threatening spectrophotometric inaccuracies resulting in too early or too late intervention occur in 2 to 3% of isoimmunized pregnancies.

OTHER METHODS OF ASSESSMENT

The reader is referred to the papers of Freda, Robertson, Knox et al, Wintfield, Queenan[21–25] and others for description of the spectrophotometric methods of assessing severity of erythroblastosis which they use.

Methods other than simple spectrophotometry such as the chloroform extraction method of Brazie et al,[26] the bilirubin protein ratio of Cherry et al,[27] and biochemical methods of measuring bilirubin in amniotic fluid[28] have been extolled by their proponents. There is no convincing evidence that there is any great improvement in predictive accuracy with their use.

Similarly, urinary and amniotic fluid estriol levels have been examined[29] and have not been found of value in predicting impending hydrops early enough for preventive management measures to be undertaken.

TECHNIQUE OF AMNIOCENTESIS

Because the hazards of transplacental hemorrhage with an increase in maternal antibody titer and increased severity of erythroblastosis are present if the placenta is penetrated at amniocentesis, initial amniocentesis should be preceded by placental localization, preferably by an ultrasound method or by a radioisotope technique if ultrasound is not available. If the placenta is situated on the anterior wall of the uterus, amniocentesis should be carried out in the ultrasound department under direct ultrasound guidance. With its use, the placenta can usually be avoided and a blood free amniotic fluid sample obtained. Direct ultrasound guid-

TABLE 1. RESULTS OF AMNIOTIC FLUID SPECTROPHOTOMETRY (LILEY METHOD)

Zone of last fluid examination	*Number of women*	*Prediction inaccurate (%)*	*Predictive inaccuracy that was life threatening* (%)*
1	231	2.6	1.3
2	434	9.3	4.0
3	292	8.2	2.7
TOTAL	997	5.5	2.4

* On the basis of the inaccurate amniotic fluid the treatment embarked on (early delivery or fetal transfusion) or withheld placed the life of the fetus in jeopardy.

ance also allows insertion of the needle to the proper depth to obtain amniotic fluid with the least trauma possible.

The procedure is carried out under aseptic technique. A preamniocentesis clotted blood sample should be taken—about 10 ml of amniotic fluid is aspirated and a postamniocentesis clotted blood sample is obtained. The amniotic fluid is sent for spectrophotometry and after 32 weeks' gestation for L/S ratio as well. The two blood samples are sent for Kleihauer fetal cell screening and Rh antibody titers.

MATERNAL AND FETAL HAZARDS WITH AMNIOCENTESIS

Maternal hazards following amniocentesis are negligible. Infection can be avoided with careful attention to aseptic technique. Precipitation of labor has been reported as a rare complication as has abruptio placentae also.

The main hazards of the procedure are fetal. On rare occasions, direct trauma to the fetus has occurred[10] but the most important hazards which have already been alluded to are placental trauma, transplacental hemorrhage, and increased severity of erythroblastosis. Although exsanguination from massive transplacental hemorrhage is a real risk with placental trauma at fetal transfusion, it should rarely, if ever, occur at amniocentesis.

SOURCES OF ERROR IN AMNIOTIC FLUID SPECTROPHOTOMETRY

Blood, either maternal or fetal, if present in amniotic fluid, produces optical density peaks at 580, 540, and 415 mμ which destroy the validity of the 450 mμ bilirubin reading. Methemalbumin which produces a characteristic 405 mμ peak decreases the 450 mμ optical density rise. Meconium very markedly increases the 450 mμ optical density peak. Exposure to light destroys bilirubin by photooxidation. Unless the sample is protected from light it will give a false low reading.

Occasionally, aspiration of fluid at amniocentesis other than amniotic fluid will be a source of error. Maternal urine produces no 450 mμ peak. In the presence of a hydropic fetus, ascitic fluid may inadvertently be obtained. Ascitic fluid is a clear yellow and is more viscous because of its high protein level. Bilirubin levels are higher in ascitic fluid which usually has to be diluted two or three times for optical density readings to be possible. The fluid has its highest absorption peak at 460 mμ. The 450 mμ optical density rise is usually greater than 1.500.

Congenital anomalies such as anencephaly and obstructive anomalies of the upper gastrointestinal tract such as tracheoesophageal fistula and duodenal or jejunal atresia will produce marked 450 mμ optical density rises which may be misleading if the mother coincidentally is Rh-isoimmunized.

INDICATIONS FOR AND TIMING OF AMNIOCENTESIS

If an isoimmunized woman has had a previous stillborn infant or an infant requiring exchange transfusion, amniocentesis is indicated no matter what the titer. Initial amniocentesis in this case should be undertaken at 20½ to 21 weeks' gestation. In the absence of such a history, a decision to carry out amniocentesis is made on the basis of antibody titer alone. Using Winnipeg Rh Laboratory titers, if the albumin titer never exceeds 1:8, amniocentesis is not carried out. If the albumin titer is steady at 1:10 or higher, initial amniocentesis is undertaken at 20½ to 21 weeks' gestation. If the titer is initially below 1:16 but reaches or exceeds 1:16 at any time between 20 and 36 weeks' gestation, immediate amniocentesis is carried out. Repeated amniocenteses are carried out at 5- to 21-day intervals depending on the optical density of the preceding test. In many instances, weekly amniocenteses may be necessary for 5 to 6 weeks or even longer before the frequency of the procedure may be reduced or definitive treatment undertaken.

MANAGEMENT OF THE ISOIMMUNIZED PREGNANCY WHERE HYDROPS IS NOT A FACTOR

If history and antibody titer have precluded the need for amniocentesis or if serial spectrophotometric readings have remained consistently parallel to the zone boundaries in the lower half of Zone 2 or have dropped into Zone 1 or the lower half of Zone 2, the mother may be allowed to deliver at or near term. We would suggest induction, if feasible, at 38 to 39 weeks' gestation. In the presence of a history of severe erythroblastosis and/or an albumin titer of 1:16 or higher and a heterozygous husband, spectrophotometric readings remaining in or falling into Zone 1 or low Zone 2 indicate that the fetus is almost certainly Rh-negative and the mother should be allowed to go into spontaneous labor. If the husband appears to be homozygous for Rh and the last optical density reading falls into the 30 to 60% area of Zone 2, induction should be carried out at 37 to 38 weeks' gestation if the mother is obstetrically suitable and her dates are accurate. On no account should she be allowed to go past term. If there is any uncertainty regarding the gestation of the fetus, pulmonary maturity should be determined by an amniotic fluid L/S ratio prior to delivery.

MANAGEMENT WHEN THE FETUS IS AT RISK OF DEVELOPING HYDROPS FETALIS

Early Delivery

When the 450 mμ optical density rise reaches the upper 75 to 80% level in Zone 2 or an initial reading falls into Zone 3 after 34 weeks' gestation, prompt induction

and delivery should be carried out if an amniotic fluid L/S ratio indicates pulmonary maturity. If the L/S ratio is less than 2.0:1 and the placenta is not anterior, we have, in recent years, elected to carry out an initial fetal transfusion at 34 weeks' gestation, a second at 35½ weeks, and delivery at 37 to 37½ weeks. In the presence of an anterior placenta we will elect early delivery at 34 weeks' gestation even if the L/S ratio is below 2.0:1, preferring to accept the hazards of respiratory distress rather than the increased risk of fetal death at intrauterine transfusion when there is an anterior placenta.

Intrauterine Fetal Transfusion

Prior to the introduction of fetal transfusion, induced delivery as early as 32 to 33 weeks' gestation was acceptable because no other treatment was available. Since about 8% of all affected fetuses will become hydropic before 32 to 33 weeks' gestation, 8% had to be accepted as the irreducible perinatal mortality from Rh-immunization before 1963.[15] The introduction of fetal transfusion by Liley in that year[30] completely transformed the outlook for these most severely affected of all erythroblastotic fetuses.

Physiology of Intrauterine Fetal Transfusion

Red cells infused into the peritoneal cavity are absorbed intact via the subdiaphragmatic lymphatics into the right lymphatic duct and thence into the circulation. If whole blood is injected, plasma is absorbed more rapidly than red cells and there may be a further drop in hemoglobin levels of 1.0 to 1.5 g/100 ml in the first 48 hours, a drop likely to be detrimental to the already anemic erythroblastotic fetus. Tightly packed red cells, negative for the antigen to which the mother is isoimmunized (Rh-negative if she has a Rh antibody), with the least amount of residual plasma are used for fetal transfusion. Since there is no way of determining the ABO status of the fetus, Group O blood is recommended no matter what the ABO constitution of the father and mother. The blood should be drawn not more than 24 hours prior to the transfusion and should be crossmatched against the mother's serum.

In the absence of ascites about 12% of the red cells infused into the peritoneal cavity are absorbed daily. Absorption is therefore complete in 8 to 9 days. The volume infused is limited by the capacity of the fetal peritoneal cavity. If excessive volumes are infused, intraperitoneal pressure rises above umbilical venous pressure, placental circulation is obstructed and the fetus dies.[32] In the early fetal transfusion era, infusion of excessive volumes of blood was a not infrequent cause of unexplained fetal death.

Intraperitoneal pressure may be monitored during fetal transfusion, discontinuing the transfusion when the pressure reaches 10 mmHg. However, the introduction of a pressure transducer with the catheter may increase the risk of significant loss of transfused blood back into the amniotic fluid when the catheter is withdrawn. If the following transfusion volume formula is followed, intraperitoneal pressures will not be excessive and placental umbilical blood flow will not be interfered with: gestation in weeks, minus 20, times 10 ml (at 24 weeks, 40 ml, at 30 weeks, 100 ml).[21]

Ability to estimate residual donor hemoglobin concentration in the fetal circulation at intervals following fetal transfusion is important in determining the intervals between fetal transfusion and the appropriate time after 34 weeks for induction and delivery. At birth the transfused baby will have about 55% of all the theoretically available residual red cell donor hemoglobin in his circulation. The remainder will be in the adnexa or will have been lost in the transfusion process.

If one uses 55% as the constant, fetal weight charts at various gestations, and 85 ml/kg fetal body weight as fetal blood volume, the increase in hemoglobin concentration expected from a fetal transfusion of a known amount of red cell hemoglobin can be calculated. By allowing for an attrition rate of 1/120 of donor red cells per day and calculating the increase of blood volume as fetal weight increases, the donor hemoglobin level at any time in the future may be calculated within an accuracy range of plus or minus 1 g/100 ml.[33]

The aim of fetal transfusion is to maintain a donor hemoglobin level in the fetus of 10 to 11 g/100 ml. The interval between the first and second fetal transfusion is 10 days; subsequent intervals are approximately 4 weeks, the last transfusion being usually no later than 33½ to 34 weeks' gestation with delivery again being approximately 4 weeks after the last transfusion.

FETAL TRANSFUSION OF THE HYDROPIC INFANT

The purpose of fetal transfusion is that it be carried out early enough to prevent development of hydrops fetalis. However, in 25 to 30% of cases the fetus will be hydropic (as evidenced by the presence of gross ascites) at either the first or second transfusion. The hydropic fetus does absorb erythrocytes from the peritoneal cavity adequately, almost if not as efficiently as does the nonhydropic fetus.[34] The likelihood of survival following fetal transfusion is reduced to 21% if the fetus has ascites at the first transfusion. Since 21% survival is better than no survival, a fetus with ascites should be given the benefit of fetal transfusions.

A considerable percentage of surviving hydropic fetuses, particularly those with gross ascites only at second fetal transfusion, are no longer hydropic at delivery.

Reversal of hydrops with relief of ascites and anasarca may depend on the ability of the liver to regenerate and produce adequate amounts of albumin. It is possible that as donor hemoglobin levels are raised by transfusion, erythropoietin levels drop; if the fetus continues to survive, extramedullary erythropoiesis will be reduced, portal and umbilical venous pressures will fall, hepatic circulation and hepatocellular function will improve, serum albumin levels will rise, and ascites and anasarca will disappear. Whereas ascites lowers the survival rate to 21% at the first fetal transfusion, the salvage rate when ascites is first noted at the second fetal transfusion is 76% (Table 2).

Indications For Fetal Transfusion

Since intrauterine fetal transfusion carries with it very definite risks, the procedure should be reserved exclusively for those fetuses who are at risk of becoming hydropic prior to 34 to 35 weeks' gestation. Selection is made by amniotic fluid spectrophotometry, patients subjected to amniocentesis being selected on the basis of history and antibody titer criteria which have already been discussed.

Initial amniocentesis, when indicated, is carried out at 20½ weeks' gestation. Fetal transfusion is indicated when serial amniotic fluid spectrophotometric readings rise into the upper 75 to 80% of Zone 2 prior to 30 weeks' gestation (Figure 3) and into Zone 3 between 31 and 34 weeks' gestation. If the initial reading falls high into Zone 3 (≥0.400 at or before 24 weeks, ≥0.350 at or after 25 weeks, ≥0.300 at or after 27 weeks, ≥0.250 at or after 29 weeks, and ≥0.200 at or after 31 weeks' gestation), fetal transfusion is carried out on the basis of the single reading.

The Fetal Transfusion Team

A word must be said about the personnel, experience, and facilities required before fetal transfusions are undertaken. As the incidence of Rh-immunization declines, the number of candidates for fetal transfusion will become fewer and the necessary expertise to maintain adequate proficiency in the procedure with satisfactory survival rates will be more difficult to achieve. Whereas, in 1964 there were 20 to 25 fetuses requiring fetal transfusion from each million total population, in 1978 there are only 3 to 4. In 1969 the Rh Laboratory Fetal Transfusion Team carried out 78 fetal transfusions on 37 fetuses; in 1977 it carried out 17 transfusions on 7 fetuses.

Although the technique itself is well within the grasp of any capable obstetrician, total management of the woman and her fetus requires not only a highly competent obstetrician but expert neonatal and laboratory input with all the resources of a sophisticated high-risk antenatal and neonatal facility. Each fetal transfusion facility, as a minimum, should deal with at least 4 to 5 fetuses yearly on whom 12 to 16 fetal transfusions are carried out. To accomplish this, each team must draw from a population base of at least 1 to 2 million and have referred to it all fetal transfusion candidates within that population base. It is only in this manner that expertise will be maintained in the carrying out of fetal transfusions and the overall management of the severely

TABLE 2. DATA ON FETAL TRANSFUSIONS PERFORMED BETWEEN JANUARY 2, 1964, AND JANUARY 3, 1978

	First 2 years		*Next 4 years*		*Final 8 years*		*Total*	
	No.	*Percent*	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*
All fetal transfusions	86		232		293		611	
All fetuses transfused	40		104		113		257	
Liveborn infants	16		68		87		171	
Surviving neonatal period	12	80	61	89	79	70	152	89
Hydrops transfused	14	35	24	23	34	30	72	28
Hydrops surviving neonatal period	1	7	8	33	17	50	26	36
Nonhydrops transfused	26		80		79		185	
Nonhydrops surviving neonatal period	11	42	53	66	62	78	126	68
Neonatal deaths	4	25	7	10	5	9	19	11
Traumatic deaths	15	38	20	29	16	14	51	20
Traumatic death rate/ transfusion		17.5		8.6		5.5		8.4

Neonatal deaths: 5 hydrops, 6 respiratory distress syndrome, 4 previable (delivery precipitated by fetal transfusion), 1 incidental (congenital heart disease), 1 Pseudomonas pneumonia (membranes ruptured from 20 weeks' gestation), 1 exchange transfusion complication (necrotising enterocolitis), and 1 Down syndrome (untreated after delivery).

Postneonatal deaths: 1 died at 8 weeks in septic shock, disseminated intravascular coagulation unrecognized gram-negative sepsis, 1 died at 12 weeks of sudden infant death syndrome ("cot" death).

affected erythroblastotic fetus and infant who will never disappear entirely from the perinatal scene.

Technique of Intrauterine Fetal Transfusion

Many modifications of Liley's original method have been devised in an attempt to improve the ease and safety of fetal transfusion. The fetus has been immobilized by a limb impaling technique;[35] image intensification fluoroscopy has been used;[36] blood has been injected down the needle rather than through a catheter[37] or through a Teflon sheath left *in situ* after the needle inside the sheath, which punctured the peritoneal cavity, has been withdrawn.[38] Although these modifications are undoubtedly helpful to some, the Fetal Transfusion Team in the Rh Laboratory has had excellent results using Liley's original technique.[31-33] One very promising modification in certain difficult situations is the insertion of the needle and catheter under direct ultrasound guidance using real time span ultrasonography.

Once fetal transfusion is decided on, 12 to 16 ml of a radioopaque medium is injected into the amniotic cavity and lateral and anteroposterior x-rays are taken (amniogram). The amniograms show placental site, fetal position, and the presence or absence of fetal edema. Fetal edema is not a contraindication to fetal transfusion.

Two to twelve hours later, under sedation, with careful asepsis and local anesthesia, the fetal transfusion is carried out in the x-ray department. Suitable coned anteroposterior and cross table lateral x-rays of the maternal abdomen are taken after the placing of 4 radioopaque markers on the maternal abdomen in a grid over the likely position of the fetal peritoneal cavity. The x-rays determine the site of the fetal peritoneal cavity in relation to the markers and the depth of the fetal peritoneal cavity from the maternal skin surface.

The best position for the fetus is lateral, less ideally in an abdominal anterior position, for then the insertion of the umbilical vessels into the fetal abdomen is the center of the target area. Fetal transfusions should not be undertaken if the fetal back is in an anterior position but every effort should be made to change it to a back lateral position. If this proves to be impossible, fetal transfusion may be undertaken only if real time span ultrasonography is available to allow an oblique insertion of the needle and catheter into the fetal peritoneal cavity under direct guidance.

The presence of an anterior placenta is always a serious complication, tripling the risk of fetal transfusion. Every effort should be made to avoid the placenta or if necessary to traverse it as near its periphery as possible. This may involve carrying out external version.

The usual technique carried out by the obstetrician member of the Rh Laboratory Team, after adequate aseptic and local anesthetic preparation, is to insert the needle (an 18-cm 16-guage Tuohy needle) directly and vertically in one movement to the required depth as determined from the lateral x-ray exposure. The stylette is withdrawn from the needle and an epidural catheter (Portex) of a diameter that just fits the lumen of the needle is threaded down the needle. If the catheter can be threaded, the tip of the needle lies within a cavity, hopefully the fetal peritoneal cavity. About 25 to 30 cm of catheter is threaded down the needle and the needle is then withdrawn to lie on the maternal abdominal wall. Two milliliters of radioopaque medium is injected down the catheter and a repeat x-ray is taken. If the catheter lies free in the fetal peritoneal cavity, characteristic semilunes of dye outline the fetal small bowel.

In about 50% of cases the fetal peritoneal cavity is catheterized at the first attempt. However, problems may arise particularly if the fetus is small and active. If the catheter threads down the needle but no dye is apparent in the fetal peritoneal cavity, the catheter is probably in the amniotic cavity. This is confirmed by the dye outlining the catheter in the amniotic cavity and may be doubly confirmed by aspiration of amniotic fluid. If the catheter cannot be threaded past the tip of the needle, the needle is not free in a cavity but is embedded in fetal thigh, buttocks, back etc. or in the maternal uterine wall. In this situation, no attempt should be made to force the catheter down the needle. The needle should be withdrawn and redirected. If reinsertion of the needle is unsuccessful, a repeat anteroposterior x-ray is taken to redetermine fetal position.

If on insertion of the needle to the required position and depth, fluid spurts up the needle, the tip of the needle lies in either fetal bladder (fetal urine is almost colorless), or in the peritoneal cavity of a fetus with ascites (the fluid is clear and bright yellow at first fetal transfusion or heavily blood stained if the procedure is a second fetal transfusion). Dye may be injected down the needle to confirm its position in the fetal bladder, although this is unnecessary since the fluid is so characteristic. The bladder is emptied, and the needle withdrawn and reinserted in the same site to the same depth.

A variation of the needle insertion technique which may be used is as follows: the needle is advanced to a depth where the tip is calculated to lie in the amniotic cavity. The stylette is withdrawn, a sterile 5- or 10-ml syringe is attached, and amniotic fluid is aspirated. The needle is then advanced toward the fetal abdomen, aspirating at every centimeter of further insertion. When resistance is encountered with failure of aspiration of fluid, the needle is probably just entering the fetal skin. It is thrust quickly an additional 1 or 2 cm. If aspiration of fluid is still impossible, the catheter is threaded. This

technique should be carried out quickly. There should be no hesitation or delay in the final advance of the needle. Otherwise, the fetus will move away from the sharp needle point. The fluid aspiration method just described should not be used in the presence of an anterior placenta.

Once the catheter has been shown to be in the fetal peritoneal cavity, the fetal transfusion is carried out. Fresh, Group 0, Rh-negative blood which has been crossmatched with maternal serum, centrifuged, and has had all of its supernatant plasma and buffy coat removed is now readied for use. The hematocrit of the unit (95) is such that without dilution its viscosity is so great that it cannot be injected down the catheter. Just prior to connection to the transfusion tubing, 12 to 15 ml of sterile 0.9% saline are injected through one of the entry ports of the unit into the blood. This entry port is then attached to the blood infusion set and the side arm of a sterile three-way stopcock is attached to the other end of the set. The unit of blood and saline is then shaken. The fetal peritoneal transfusion catheter is cut off approximately 10 cm from the maternal abdomen and a 22-gauge blunt needle or cannula is inserted into the cut end of the catheter. The hub of the needle or cannula is attached to the stopcock. A 10-ml syringe is then attached to the remaining arm of the stopcock and the transfusion is begun.

The transfusion is carried out in 10 ml aliquots. The fetal heart is monitored by ultrasound at the beginning and end of each 10-ml infusion. It is monitored continuously throughout the final 10 ml of the amount of blood planned to be administered, according to the gestation, -20×10 ml formula. If the fetus is in good condition, the transfusion produces a tachycardia of 160 to 180 beats/min (occasionally 200). Fetal tachycardia during the procedure is reassuring. Fetal brachycardia early in the procedure is very ominous and usually portends fetal demise. Sudden bradycardia as one approaches the end of the transfusion is an indication for immediate termination of the transfusion.

Following completion of the infusion, the fetal catheter is slowly withdrawn from the fetal peritoneum with careful fetal heart monitoring. Profound fetal bradycardia, probably vagal in origin, may occur. If bradycardia appears, further catheter removal is delayed until the bradycardia disappears. The mother is usually discharged 36 to 48 hours after the procedure.

When ascitic fluid is encountered, an attempt should be made to aspirate fluid before the catheter is threaded. A volume of ascitic fluid equal to the volume of blood to be transfused is aspirated, if possible and the catheter is then threaded. When fetal ascites is present, the dye injected is shown diffusing through the ascitic fluid and no semilunes can be seen (Figure 4). Depending on the amount of residual ascites apparent on x-ray, a further volume may be aspirated. However, no attempt should be made to empty the peritoneal cavity completely. An empiric rule is not to remove more than a volume double that of the proposed transfusion with a maximum removal of 120 to 150 ml.

When more than the proposed transfusion volume of ascitic fluid is aspirated, the total volume of the blood infused is increased by 20 to 30%, (50 ml at 24 weeks, 120 ml at 30 weeks, etc). Although digitalization of the fetus logically would appear to be valueless, our empiric experience with 44% hydropic fetal survival (26 of 59)

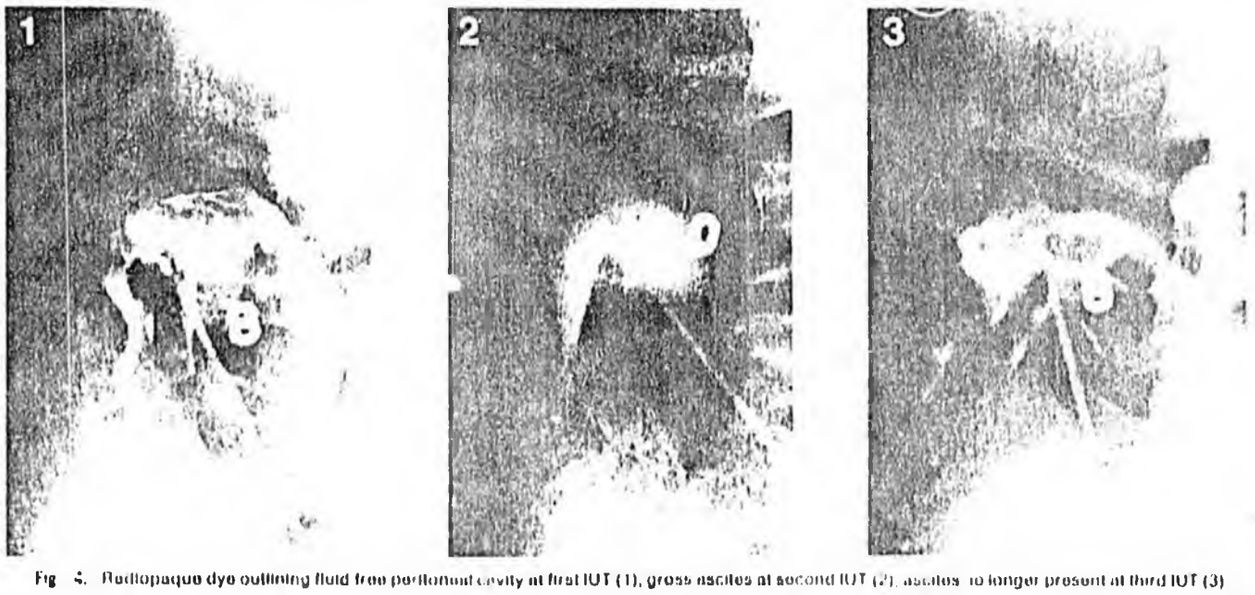

Fig 4. Radiopaque dye outlining fluid free peritoneal cavity at first IUT (1), gross ascites at second IUT (2), ascites no longer present at third IUT (3)

following its introduction[33] causes us to advise its use (0.035 mg/kg estimated fetal weight of digoxin is infused intraperitoneally). The mother is placed on maintenance digoxin and furosemide orally. The diuretic may be a more important factor than the digoxin in improving the hydropic fetus's chance of survival.

Since the hydropic fetus absorbs blood from his peritoneal cavity adequately,[34] but possibly more slowly, the interval between the first and second transfusions should be lengthened to 12 days. Ascitic fluid, if encountered again, should be aspirated and again digoxin should be instilled. Third and fourth transfusions are carried out at 20- to 22-day intervals if ascites is still present.

HAZARDS OF FETAL TRANSFUSION

Maternal Risks

Fetal transfusions should carry very little if any risk to the mother. Maternal infection can be avoided by very careful attention to aseptic technique. Nevertheless, some fetal transfusion teams, including ours, prescribe oral broad spectrum antibiotic therapy for 12 hours before and 48 hours after the procedure. No complications have been noted following such short term antibiotic use.

Potential serious morbidity may occur if the needle and catheter penetrate maternal tissues and dye is injected into them (maternal muscle, peritoneal cavity, and particularly uterine wall behind the placenta). If the transfusion needle perforates a retroperitoneal maternal sinus, there is a serious risk of introduction of amniotic fluid into the maternal circulation with abruptio and coagulation difficulties.[35]

Administration of hydrochlorothiazide to the pregnant woman with a hydropic fetus has been associated with fatal pancreatitis. When a diuretic is used in such a situation, furosemide should be selected.

Fetal Hazards

Early hazards. Fetal risks are considerable. The hazards of overtransfusion and how they may be prevented have been described. The early major hazard is the puncture of a fetal arterial or major venous vessel or heart by the needle with fetal death either from exsanguination or cardiac tamponade. Since fetal transfusion is basically a blind procedure, the risk of fetal exsanguination cannot be prevented completely. However, avoidance of the placenta as far as possible and taking care not to insert the needle too deeply will reduce the risk.

Provided that a major fetal vessel is not damaged, inadvertent placement of the needle and transfusion catheter in other fetal organs and tissues appears to be harmless provided that the improper site is recognized, blood is not infused, the catheter is removed, and the needle reinserted properly.

Precipitation of delivery by fetal transfusion represents a real hazard to the fetus. Unexpected early delivery occurred in 46 instances in our fetal transfusion series. There were two very fresh stillbirths and 12 neonatal deaths. The neonatal deaths were evenly divided between hydrops fetalis and prematurity. Indeed 4 of the 12 who died were considered to be previable (less than 28 weeks' gestation).

Of the 32 who survived after unexpected early delivery, 3 were grossly hydropic, being born at 31 $^{5}/_{7}$, 31 $^{6}/_{7}$, and 31 $^{6}/_{7}$ weeks' gestation. Of the remaining 29, 2 were born between 29 and 31 weeks' gestation, 10 between 31 and 33 weeks, 16 between 33 and 35 weeks, and 1 at 35 $^{2}/_{7}$ weeks' gestation.

Late Fetal Hazards

Donor lymphocyte grafting, with the development of fatal graft versus host disease following fetal transfusion has been reported.[39] It is for this reason that some advise the use of x-radiated blood for fetal transfusions. Animal experiments would lead one to expect that by 21 to 22 weeks' gestation the human fetus should be immunologically mature enough to reject living donor leukocytes. The rare lymphocyte graft and the even rarer graft versus host response probably occurs in the occasional abnormally immunologic immature fetus or one with a specific immunologic defect.

The amount of radiation the fetus receives is significant—up to 3,5 to 4.0 rads in some fetuses in our series.[40] Exposure of the fetus to radiation is unavoidable but should be kept to the absolute minimum compatible with the successful carrying out of fetal transfusion. Expert radiologic assistance with proper coning of the x-ray beam will reduce radiation. The use of fluoroscopy should be kept to a minimum. Our series (some children are now 13 years of age) has none with evidence of radiation injury. However, the period of observation is too short and future generations must be awaited before the true radiation risks of fetal transfusion may be assessed. One instance of acute leukemia in a fetal transfusion survivor has been reported,[41] but this probably does not exceed the expected incidence of acute leukemia in a pediatric population. The use of ultrasound real time span guidance should materially reduce x-radiation exposure.

Transient susceptibility to viral infections in the first year of life with acute recurrent bronchiolitis and bronchopneumonia of adenoviral or respiratory syncytial viral origin appears to be a very real hazard for some fetal transfusion survivors. The hazard is temporary.

disappearing by 12 to 18 months of age. It may be related more to prematurity than the fetal transfusions themselves.

SURVIVAL RATES AFTER FETAL TRANSFUSION

Contrary to recent reports from England,[42,43] there is no question that fetal transfusion represents a major advance in the management of severe Rh-isoimmunization.

The recent report by Hamilton[36] notes excellent survival rates (84.6% in the past 5 years), but apparently he does not transfuse fetuses in whom the diagnosis of hydrops fetalis is made.

Our own results are outlined in Tables 2 and 3. As can be seen survival rates (Table 2) have increased over the years. We can now offer a fetal transfusion candidate an overall 70% chance of having a surviving infant; 50% if the fetus is or becomes hydropic (21% if hydropic at first, 76% if not hydropic at first transfusion); 78% if the fetus is not hydropic at any time.

Although many centers report poor survival rates if fetal transfusions must be started before 26 weeks' gestation, this has not been our experience (Table 3). Although it is true that survival rates are 11% lower if transfusions must be started before 26 weeks' gestation, an overall survival rate of 59% in this most severely affected group of fetuses is nevertheless very encouraging. Indeed, salvage rates are acceptable if there is need to carry out the first procedure as early as 21½ to 23 weeks' gestation (11 of 26 (42%) fetuses in our series).

DEVELOPMENT OF FETAL TRANSFUSION SURVIVORS

The majority of fetal transfusion survivors develop normally. In our series 74 of 89 tested at 18 months of age or later are completely normal. Because many survivors are born prematurely and have varying degrees of severity of residual erythroblastosis with the management problems (thrombocytopenia, anemia, hyperbilirubinemia, heart failure, and hepatocellular damage) that this entails, there is some evidence of minor neuromuscular problems and mild developmental delay with probably a normal IQ ultimately in 11 of the 89 cases. The remaining 4 are abnormal. One infant who was very premature has a normal IQ, but a moderate spastic hemiparesis, a second who was hydropic and premature has an IQ of 75, and a third, hydropic and very premature, developed hydrocephalus as a result of subarachnoid hemorrage and has an IQ of 80. One infant who may now be dead, has cerebral agenesis which may or may not be related to the fact that he was hydropic *in utero* but not hydropic at birth.

DELIVERY OF THE SEVERELY AFFECTED ERYTHROBLASTOTIC INFANT AND MANAGEMENT AFTER BIRTH

The severely affected erythroblastotic infant who must be delivered early and often has undergone fetal transfusions requires neonatal care and facilities of the highest order. For this reason, delivery should be carried out in a fully developed tertiary perinatal care center where personnel and facilities are available to monitor fetal conditions prior to labor and during labor and delivery, and the skilled neonatal personnel and nursery resources are available to manage a sick premature hemolyzing and occasionally hydropic neonate.

If the placenta is not on the anterior uterine wall and if serial amniotic fluids indicate the need for interference at 34 weeks' gestation, a decision regarding prompt induction of fetal transfusion repeated in 10 days with delivery at 37 weeks' gestation should be made on the basis of an L/S ratio or the presence or absence of stable foam. If the placenta is anterior, delivery should be carried out at 34 to 34½ weeks even if the L/S ratio and/or foam test indicate the risk of respiratory distress. As a

TABLE 3. DATA ON INITIAL FETAL TRANSFUSIONS DONE BEFORE AND AT OR AFTER 26 WEEKS' GESTATION

	Fetuses														
		Alive		*Dead*			*Traumatic deaths*		*Hydrops*[†]				*Nonhydrops*		
											Alive			*Alive*	
Time of transfusion	*Total No.*	*No.*	*Percent of total*	*Total No.*	*Neonatal deaths*	*Stillbirths*	*No.*	*Percent of total*	*Total No.*	*Percent of total*	*No.*	*%*	*Total*	*No.*	*%*
< 26 weeks' gestation	108	62	59	44	6*	37	27	25	24	23	8	33	84	54	67
≥ 26 weeks' gestation	113	79	70	44	9	25	12	11	35	30	18	51	78	61	78

* One infant with Down syndrome died of kernicterus because postdelivery treatment was withheld.
† Hydrops at first transfusion, survival 21% (7 of 33); hydrops at second transfusion, survival 76% (19 of 25).

general rule one should not allow a fetus who has been tranfused to remain undelivered after 37 to 37½ weeks' gestation no matter what the L/S ratio and foam tests show, provided that the duration of gestation is known to be accurate.

Once induction is decided on, every effort consistent with maternal and fetal welfare should be made to deliver the infant via the vaginal route. We achieve this aim in 80% of cases. Resorting to cesarean section should be considered if good labor has not ensued within 16 to 20 hours of rupture of the membranes.

Fetal monitoring by external tocodynamometry and subsequently by scalp clip electronically with concomitant monitoring of uterine contractions is an essential component of management. Scalp vein fetal blood pH measurements, if available, should be carried out if fetal heart monitoring indicates fetal distress. If there is evidence of fetal distress and immediate vaginal delivery is not possible, immediate cesarean section under epidural or some other form of regional anesthesia should be undertaken.

During the course of the mother's labor and delivery, all measures possible to insure adequate oxygenation and optimum condition of the fetus should be carried out. At delivery the cord should be clamped promptly, 10 to 15 ml of heparinized cord blood should be obtained, immediate gentle but thorough resuscitative measures should be undertaken, and the baby given into the care of an expert neonatologist.

The management of the sick premature erythroblastotic newborn is outside of the purview of this review. Suffice it to say that successful management of the primary disease and the complications that may develop in such a sick infant will tax the skills and resources of the most highly developed neonatal intensive care unit and its personnel, and should only be undertaken where such resources are available.

OTHER FETAL TRANSFUSION METHODS

Fetal exchange transfusion carried out by open hysterotomy, exteriorization of a leg, and catheterization of the femoral vein has been carried out in the past.[44] The procedure, a major surgical one, has been associated with only 2 surviving infants and was carried out in them at 28 to 32 weeks' gestation, at a time when intraperitoneal fetal transfusion, technically, would have been relatively easy. Most attempts at fetal exchange transfusion have been followed by prompt labor, the need for further hysterotomy, and neonatal death.

Similarly, incision of the uterus with dissection through the membranes at the placental margin with isolation and catheterization of a major fetal vessel on the placemental surface carries with it the same hazards.[45] When fetal transfusions are indicated, neither of these very dangerous techniques should be resorted to; the method used should be that of Liley or a modification thereof.

CONCLUSIONS

The importance of amniotic fluid spectrophotometry, early delivery, and intrauterine fetal transfusion in the management of Rh-isoimmunization have been outlined in some detail. In Manitoba, in the 3-year period ending October 31, 1977, there were only two perinatal deaths from erythroblastosis fetalis, a perinatal mortality rate of 1.5%. Both were losses early in gestation at fetal transfusion: one from trauma, the other from hydrops fetalis. This rate of 1.5% compares favorably with the 14.3% perinatal mortality rate (82 fetuses and infants) for the 3-year period ending October 31, 1964.

However, the rate of 1.5% was only possible with a closely integrated centralized management program utilizing a highly skilled transfusion team and a tertiary neonatal care center of good quality. The generally accepted perinatal mortality rates from erythroblastosis fetalis in other parts of Canada at the present time are on the order of 5 to 10%.

Although an experienced Rh-isoimmunization management team will reduce stillbirths and neonatal deaths from erythroblastosis to a very low level, it will not reduce the perinatal mortality rate to zero. Hydrops fetalis on occasion occurs as early as 22 weeks' gestation; traumatic deaths will occur at fetal transfusion; amniotic fluid spectrophotometry will be life threateningly inaccurate in 2 to 3% of cases. The only means of reducing perinatal deaths from Rh-isoimmunization to zero is to prevent Rh-isoimmunization altogether through a well coordinated comprehensive Rh prophylaxis program.

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delivery. It is best treated by a combination of oral hygiene and a well-balanced diet. An *epulis*, a focal, highly vascular swelling of the gingiva, is an occasional complication (see Fig. 9-15, p. 247).

Porphyria. Acute idiopathic porphyria is a rare metabolic dysfunction caused by an inborn error of porphyrin metabolism. It may present a wide range of symptoms often suggestive of diseases involving the gastrointestinal tract, pelvic organs, and nervous system. Brodie and co-workers (1977) have reviewed the pregnancy experiences of 39 women with this autosomally dominant disease. One woman died; total wastage was 13 percent. The diagnosis must be kept in mind whenever a pregnant woman describes bizarre acute abdominal pain.

OTHER VIRAL INFECTIONS

Various viruses have been recovered from the fetus, but only rubella virus, cytomegalovirus, herpesvirus hominis, and varicella-zoster virus are at all likely to be teratogenic. Others that may reach the fetus include the viruses causing measles (rubeola), smallpox (variola), vaccinia, poliomyelitis, hepatitis, Western equine encephalitis, mumps, and the Coxsackie B group.

About 5 percent of pregnancies are complicated by clinically apparent viral infections, according to the Collaborative Perinatal Research Study. When the common cold is excluded, the most frequent viral infections are influenza, flulike disease, herpesvirus infections, viral gastroenteritis, and viral infection of larynx, pharynx, and tonsils.

Rubella (German Measles). Rubella, a disease of minor importance in the absence of pregnancy, has been directly responsible for inestimable perinatal loss and serious malformations in the liveborn infant. The relation between maternal rubella and grave congenital malformations was first recognized by Gregg (1942), an Australian ophthalmologist.

DIAGNOSIS. The diagnosis of rubella is at times quite difficult. Not only are the clinical features of other illnesses quite similar, but subclinical cases with viremia and the capability of infecting the embryo and fetus do occur. Diagnosis of rubella, therefore, can be made with certainty only by isolation of the virus or by the more practical demonstration of a rising rubella antibody titer in the serum. Absence of rubella antibody indicates lack of immunity. The presence of antibody denotes an immune response to rubella viremia that may have been acquired anywhere from a very few weeks to many years earlier. If maternal rubella antibody is demonstrated at the time of exposure to rubella or sometime before, the mother can be assured that it is exceedingly unlikely that her fetus will be affected.

The nonimmune person who acquires rubella viremia demonstrates peak antibody titers 1 to 2 weeks after the onset of the rash, or 2 to 3 weeks after the onset of viremia, since the viremia precedes clinically evident disease by about 1 week (Cooper and Krugman, 1967). The promptness of the antibody response, therefore, may complicate serodiagnosis unless serum is collected initially within a very few days after the onset of the rash. If, for example, the first specimen was obtained 10 days after the rash, detection of antibodies would fail to differentiate between two possibilities: one, that the very recent disease was actually rubella and, two, that it was not rubella, but the person was already immune to rubella. The demonstration of specific IgM globulin in the pregnant woman indicates a primary infection within the previous month or so. Therefore, specific IgM estimations, if available, are useful for diagnosing recent rubella infection (Field and Murphy, 1972).

IMMUNIZATION. There is no known chemotherapeutic or antibiotic agent that will prevent viremia in nonimmune subjects exposed to rubella. The use of gamma globulin for this purpose is not recommended. Brody and co-workers (1965), during a rubella outbreak in an isolated community, gave rela-

tively large doses of gamma globulin to boys but not to girls at the time of, or even before, exposure. The attack rate, measured by seroconversion, among the boys was 44 percent and among the girls 85 percent. The group that received gamma globulin therefore, was only partially protected. The data of Brody and associates also suggest that large doses of gamma globulin given at or before exposure to rubella may only minimize the clinical features of the disease. Viremia without clinically apparent disease can, of course, lead to fetal infection with disastrous consequences.

Even though women who are pregnant or who may conceive within the next 6 weeks or so should not be vaccinated, some states attempted to require women seeking marriage licenses either to have demonstrable immunity or to be immunized. In Colorado during 1971 and 1972, of those without immunity and about to enter wedlock, 21 percent were already pregnant! (Judson et al., 1974). Although the risk appears low (Hayden et al., 1980), rubella vaccine is contraindicated just before and during pregnancy.

The following program for immunizing women of childbearing age susceptible to rubella has proved satisfactory: (1) Identify susceptible women by means of the hemagglutination-inhibition antibody test. The majority of women will be immune to the rubella virus and can be so assured. (2) Nonimmune women are eligible for vaccination only if pregnancy can be avoided for at least 2 months after vaccination. Women least likely to become pregnant are those who have been delivered within the week before vaccination and those who take oral contraceptives in the approved way. Although there is laboratory evidence of prolonged fetal infection and tissue reaction, according to Brandling-Bennett (1974) and Modlin and associates (1976), no infant born alive to a woman vaccinated shortly before or after conception has provided clinical or laboratory evidence of rubella infection. Vaccinelike rubella virus has been recovered, however, from a fetus with histologic evidence of a cataract. The seronegative mother had been immunized 7 weeks before conception. These observations suggest that attenuated rubella virus might be teratogenic when given to a woman early in pregnancy or up to at least 2 months before conception.

Mass vaccination programs in children have been undertaken. A very important question concerning the value of such immunization programs has yet to be answered: Will the antibody titers persist at levels sufficient to maintain immunity or will they fail to leave the woman vaccinated as a child susceptible to rubella?

EFFECTS OF NATURAL VIRUS. The numerous reports concerned with the frequency of major fetal developmental defects that are thought to be caused by rubella are difficult to interpret because of the lack of precision inherent previously in the diganosis of rubella. Forbes (1969) believed that the diagnosis of rubella may have been erroneous in as many as 50 percent of the cases. The frequency of congenital malformations, therefore, is probably higher than some reports have indicated. Rubella during the first month of pregnancy probably causes serious defects in up to 50 percent of the embryos and perhaps even more if those that abort spontaneously are considered. During the second month, the rate appears to be halved to about 25 percent, and during the third month, approximately halved again to about 15 percent.

It is now evident that many infants who are born alive suffer stigmata of continuing intrauterine and neonatal rubella infection. The syndrome of congenital rubella includes one or more of the following abnormalities:

1. Eye lesions, including cataracts, glaucoma, microphthalmia, and various other abnormalities.
2. Heart disease, including patent ductus arteriosus, septal defects, and pulmonary artery stenosis.
3. Auditory defects.
4. Central nervous system defects, including meningoencephalitis.

5. Retarded fetal growth.
6. Hematologic changes, including thrombocytopenia and anemia.
7. Hepatosplenomegaly and jaundice.
8. Chronic diffuse interstitial pneumonitis.
9. Osseous changes.
10. Chromosomal abnormalities.

Infants born with congenital rubella may shed the virus for many months and thus be a threat to other infants, as well as to susceptible adults who come in contact with the affected infants.

Although the likelihood of major malformations at birth from rubella is relatively slight if it is acquired after the first trimester, the infants whose mothers contracted the disease after the first trimester will not necessarily be healthy as demonstrated by the investigations of Hardy and associates (1969). Their long-term prospective epidemiologic inquiry to assess the impact of the extensive 1964 rubella epidemic in this country revealed 24 instances of serologic evidence of infection by rubella virus after the first trimester. Of the 22 liveborn infants, only 7 could be considered completely normal when followed for periods of up to 4 years. Townsend (1975) and Weil (1975) and their associates have reported progressive panencephalitis beginning in the second decade in children with congenital rubella infection. Even more recently, an unusually high incidence of juvenile diabetes has been identified among individuals who had congenital rubella (Rayfield and Seto, 1978).

An estimated 14 million children in the United States have not been vaccinated against rubella. Moreover, there is cause for concern regarding the duration of immunity following immunization. The possibility exists for a major rubella epidemic and its disastrous consequences for the affected fetus. Further consideration of the problems for the obstetrician posed by rubella are provided by Horstmann (1979).

Cytomegalovirus Disease. The virus responsible for cytomegalic inclusion disease may be harbored in the genital or urinary tract or both by a healthy mother and transmitted to the fetus across the placenta or during passage through the cervix and lower reproductive tract, or it may be harbored by the infant who ingests the virus in breast milk. Cytomegalovirus disease in the infant may cause hydrocephaly, microcephaly, microphthalmia, seizures, encephalitis, blindness, hepatosplenomegaly, and hematologic changes including thrombocytopenia and hemolytic anemia. At autopsy, cytomegalic inclusion bodies may be found in many organs of the body. The virus usually can be isolated in tissue culture of human cells. There are different antigenic types of the virus.

Although about 12 percent of women excrete the virus in urine or from the cervix during pregnancy and are likely to excrete the virus in their milk, few have offspring that are afflicted. Most often, a primary maternal infection seems necessary for the virus to be transmitted to and replicate in the fetus. Since primary infection is usually asymptomatic in the mother or, rarely, causes a mononucleosis-like syndrome, the disease is seldom suspected. Alford and co-workers (1974) emphasized that mental and auditory dysfunction occurs frequently enough to place this entity among the leaders of prenatal insults that induce developmental disability. No effective therapy for mother or infant is available. Cytomegalovirus disease seldom recurs in subsequent fetuses of the mother of one so afflicted.

Varicella. Varicella infections seem to be made worse by pregnancy. Varicella pneumonia, while very uncommon, is a grave illness during pregnancy, with high maternal mortality (Mendelow and Lewis, 1969; Pickard, 1968). Varicella may infect the embryo and fetus by transplacental passage of the virus. It may prove to be teratogenic when the embryo or fetus is infected (De Nicola and Hanshaw 1979). The virus may be acquired by the fetus in utero or during the course of delivery. Exposure to the virus just before delivery poses the greatest risk. If the baby is delivered before receiving varicella antibody from the mother, he may develop dis-

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acid elution principle described by Kleihauer, Brown, and Betke, or any of several modifications. Very small volumes of red cells commonly escape from the intravascular compartment of the fetus across the generally intact placental "barrier" into the maternal intervillous space. Although the bleed is usually small, it may incite maternal isoimmunization, as discussed below. Interestingly, evidence of maternal to fetal bleeding is very much less common (Bernard et al., 1977). Presumably a pressure gradient which is higher on the fetal than on the maternal side persists across the placenta.

Rarely, fetal to maternal hemorrhage may be so severe as to kill the fetus. The hypovolemic or severely anemic fetus-infant may be salvaged if the condition is recognized and treatment with blood, red cells, or both is promptly initiated. The fetus who is severely anemic is more likely to demonstrate one or more ominous heart rate patterns (see Chap. 14, p. 357). On occasion, the hemorrhage may have been chronic and so severe as to produce evidence of iron deficiency in the fetus (Pritchard and Cunningham, unpublished data). Maternal iron deficiency, however, even when severe, is not accompanied by anemia in the fetus; the same holds true for megaloblastic anemia due to folate deficiency (see Chap. 28, p. 720).

With large fetal to maternal hemorrhage there is most likely a placental lesion which fostered the leak. Chorioangiomas have been identified. Moreover, we know of two instances of severe fetal to maternal hemorrhage in which the mothers were later found to have choriocarcinoma. While neither placenta was studied, the subsequent recognition of choriocarcinoma in the mothers is suggestive that there was a placental lesion which was the site of transfer of blood from the fetus to the mother. Abruptio placentae, in our experience, does not appear to lead commonly to severe fetal to maternal hemorrhage.

At Parkland Memorial Hospital, for some time, maternal blood has been investigated for fetal red cells in each instance of stillbirth whenever a cause was not readily apparent. Massive fetal-maternal bleeds have been identified in a very small minority of stillbirths.

Large fetal to maternal hemorrhages may also prove dangerous to the mother. It is possible for up to 400 ml of fetal blood to be transferred from the fetal-placental circulation into the maternal circulation. A transfusion reaction may then develop in the mother whenever A or B antigen is present in fetal red cells but not the red cells of the mother. Bergin and associates (1978), for example, have described many of the characteristic features of a transfusion reaction developing in a mother who was blood type O immediately after delivery of an infant who was blood type B. The subject of fetal-maternal hemorrhage has been reviewed by Renaer and associates (1976).

HEMOLYSIS FROM MATERNAL Rho (D) ISOIMMUNIZATION

Ranking as major contributions to medicine are the delineation of the pathogenesis of most cases of hemolytic disease in the fetus and newborn infant by the observations especially of Levine and associates (1941), the related discovery of the Rh factor by Landsteiner and Wiener (1940), and the development of effective maternal prophylaxis by Freda, Gorman, and Pollack (1963) in the United States and Finn, Clarke, and associates in Great Britain (1961).

Blood Group Factors. Originally, the Rh concept was extremely simple, defined by one antiserum and two blood group factors, namely Rh positive and Rh negative. The Rh factors, however, have become increasingly complex, and a host of other red cell antigens have been identified. Although some of them are immunologically and genetically important, fortunately, many are so rare as to be of little clinical significance in the genesis of erythroblastosis fetalis.

Any person who lacks a specific red cell

antigen r st likely will create an antibody when exposed to that antigen. The antibody may prove harmful to the individual in case of a blood transfusion or to her fetus when she conceives. The vast majority of human beings have at least one such factor inherited from their father and lacking in their mother. In these cases, the mother could be sensitized if enough erythrocytes from the fetus were to reach her circulation and an immune response were to be stimulated by the foreign antigen. In these terms, hemolytic disease is a possibility in nearly every pregnancy. That the disease occurs in very few pregnancies is a result of several circumstances. These include (1) the varying rates of occurrence of the offending red cell antigens, (2) their variable antigenicity, (3) insufficient transplacental crossing of antigen from fetus to mother, (4) the variability of maternal response to the antigen, and (5) lack of transfer of antibody across the placenta from mother to fetus in amounts sufficient to affect the fetus.

The Rh antigens are inherited independent of all other blood group antigens. There is apparently no difference in the distribution of the various Rh antigens with regard to sex. There are, however, important racial differences. American Indians and Chinese and other Asiatic peoples are almost all Rho (D) positive (99 percent). Among black Americans there is a lesser incidence of Rho negative individuals (7 to 8 percent) than among white Americans (15 percent). Of all racial and ethnic groups studied thus far, the Basques show the highest incidence of Rho negativity (34 percent).

At times, hemolysis in the fetus involves other antigen–antibody interactions, especially the ABO system. These are considered subsequently. *All pregnant women should be routinely tested for the presence or absence of Rho (D) antigen in their erythrocytes and for irregular antibodies in their serum, including anti-Rho.*

Mortality. The number of perinatal deaths from Rho hemolytic disease has dropped dramatically for the following reasons:

1. Pregnant women who are Rho negative and possess antibody to the Rho antigen can be readily identified.
2. Hemolysis in the fetus of the sensitized Rho negative woman can be predicted with considerable accuracy by the identification of abnormally high levels of bilirubin in the amniotic fluid.
3. The fetus who is most likely to be seriously affected can be treated by intraperitoneal transfusions of Rho negative red cells, or be delivered preterm before he expires in utero, or both.
4. Of greatest importance, the appropriate administration to the mother who is Rho negative of Rho immune globulin during or immediately after pregnancy has eradicated most, but not all, Rho isoimmunization among Rho negative women!

The favorable impact on reducing perinatal mortality as the consequence of these procedures is exemplified by the experiences in Manitoba. In that Canadian province, the number of perinatal deaths from hemolytic disease decreased from 29 in 1964 to zero in 1974 and one in 1975 (Bowman et al., 1977).

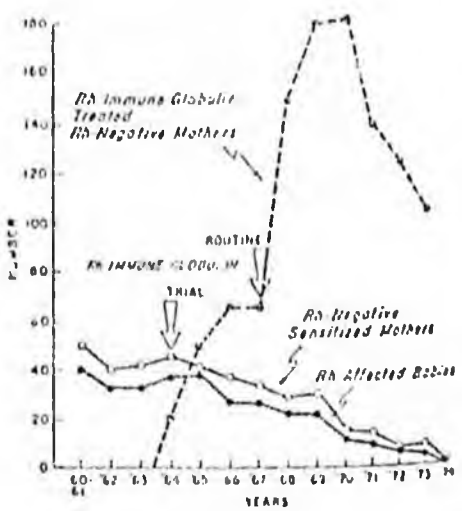

FIG. 38-1. Incidence of Rh disease correlated with Rh immune globulin treatment. (From Freda et al. *N Engl J Med* 292:1014, 1975)

Immune Globulin Prophylaxis for the Rho (D) Negative, Nonsensitized Mother. Hemolytic disease of the fetus and newborn from Rho (D) isoimmunization has become a problem almost totally limited to Rho negative women who were sensitized before Rho (D) immune globulin* was available. Freda and co-workers (1975) summarized their 10 years of clinical experience with Rho immune globulin, confirming their original observations that such immune globulin given to the previously unsensitized Rho negative woman within 72 hours of delivery is highly protective, although not absolutely so (Figs. 38-1 and 38-2). There is good evidence to support the practice of giving the immune globulin promptly to previously unsensitized Rho negative women who have aborted including ectopic pregnancies and possibly hydatidiform moles, to women who undergo amniocentesis, and to those who bleed vaginally during pregnancy. The observation of Blajchman and co-workers (1974) of detectable fetal–maternal hemorrhage after at least 6 percent of amniocenteses has provided support for a policy that all unsensitized Rho negative women suspected of having an Rho positive fetus should receive Rho immune globulin following such a procedure. Freda (1973) has emphasized that when in doubt whether or not to give Rho immune globulin, the rule of thumb should be to give it.

While adherence to the above guidelines, including the administration of Rho immune globulin to the apparently nonsensitized mother within the first 72 hours after delivery of a Rho positive infant, has dramatically decreased the risk of maternal isoimmunization, the problem has not been eliminated. For example, Bowman and Pollock (1978) identified 1.8 percent of women to become isoimmunized in spite of adherence to the above recommendations for administering Rho immunoglobulin. He and his colleagues deduced that most often the failures were the consequence of spontaneous silent fetal–maternal bleeds that occurred some time before delivery and therefore some time before the administration postpartum of Rho immune globulin. Therefore, to try to avoid isoimmunization from fetal–maternal bleeds that occurred remote from term, he administered routinely 300 μg intramuscularly to all nonsensitized Rho negative women at 28 weeks, and again at 34 weeks gestation, as well as at the time of amniocentesis or uterine bleeding. If the infant was Rho positive, a third dose of the immunoglobulin was administered to the mother after delivery. This program was followed by a reduction in the incidence of development of Rho isoimmunization during pregnancy from 1.8 percent to 0.07 percent. A single dose at about 28 weeks proved to be almost as effective as did the two doses antepartum; only 2 of 1799 Rho negative women showed evidence of Rho immunization, despite antenatal prophylaxis (Bowman and Pollock, 1978).

The small amount of antibody that crossed the placenta resulted at times in a weakly positive direct Coombs' test on cord and infant

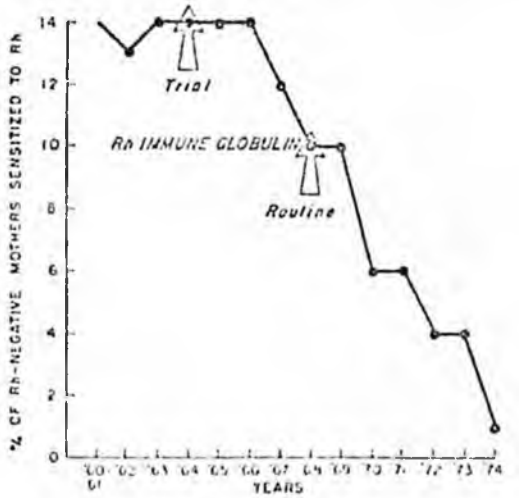

FIG. 38-2. Incidence of sensitization as a percentage of the total number of Rh-negative mothers seen per year. (From Freda et al. *N Engl J Med* 292:1014, 1975)

* Rho (D) immune globulin is a 7S immune globulin (IgG) extracted by cold alcohol fractionation from plasma containing high titered Rho antibody. Each dose provides not less than 300 μg of Rho antibody as determined by radioimmunoassay.

blood. None of the infants, however, showed evidence of anemia or exaggerated hyperbilirubinemia.

RECOMMENDATIONS. A single intramuscular dose of 300 μg of Rho immunoglobulin is administered routinely to all Rho negative, *nonimmunized* women at 28 to 32 weeks of gestation and again within 72 hours of the birth of a Rho (D) positive infant. A similar dose is also given at the time of amniocentesis and whenever there is uterine bleeding, unless the routine dose at 28 to 32 weeks had been given very recently. If a massive fetal–maternal hemorrhage is recognized, more immune globulin should be given, as described below. One dose of 300 μg will protect the mother against a bleed of up to 15 ml of Rho positive red cells. Adoption of these dosage schedules should reduce the incidence of maternal isoimmunization to essentially zero.

ADVERSE MATERNAL REACTIONS. Only rarely do reactions occur after the intramuscular injection of commercially available Rho immunoglobulin. Usually the individual is IgA deficient and has previously developed an antibody to IgA. The Rho immune globulin that is currently available is likely to contain a small amount of IgA (Bowman, 1978). Rho immune globulin suitable for intravenous use very likely will become available.

MATERNAL–FETAL BLEED. Rarely, the Rho negative woman will have been exposed in utero to Rho antigen from her mother and become sensitized as the consequence. For this to occur, the woman's mother must have been Rho positive and a maternal-fetal bleed must have occurred sometime before the cord was severed. As with fetal–maternal bleeds, a major blood group (ABO) incompatibility most often appears to offer appreciable protection against Rho sensitization. Jen-

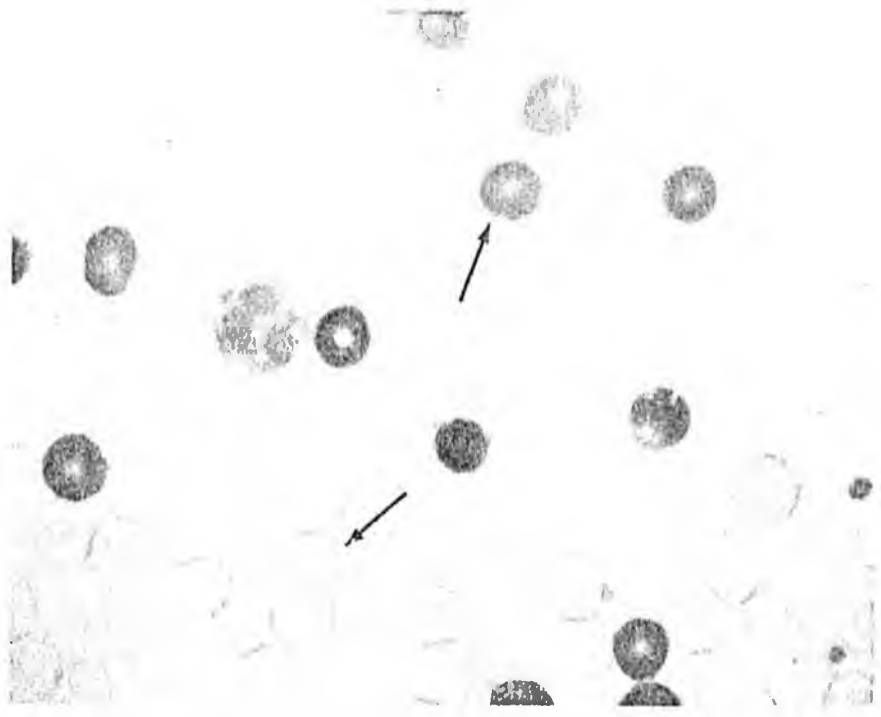

FIG. 38-3. Massive fetal to maternal hemorrhage. After acid elution treatment, fetal red cells rich in hemoglobin F stain darkly (upper arrow) whereas maternal red cells with only very small amounts of hemoglobin F (lower arrow) stain lightly.

nings and Clauss (1978) in a study of 105 Rho negative infants born to Rho positive mothers identified a maternal–fetal bleed in only two instances, or 1.9 percent, a value in very close agreement with that found by Cohen and Zuelzer (1965). Jennings and Clauss (1978) and Bowman (1978), on the basis of their extensive studies, do not believe that Rho immune globulin prophylaxis is warranted for Rho negative babies born to Rho positive mothers.

In case of larger fetal–maternal hemorrhage, the Rho positive erythrocytes may by careful examination be identified, at times, as clumps in the cross-match of the erythrocytes from maternal blood and the Rho immune globulin. The acid-elution technic, however, for identifying erythrocytes that contain appreciable alkaline-resistant (fetal) hemoglobin is best used to identify a major bleed and to approximate its magnitude.

When the acid-elution test is performed appropriately, red cells rich in fetal hemoglobin are easy to identify (Fig. 38-3). A careful differential count will serve to approximate closely the percentage of fetal cells in the maternal blood. From this value, coupled with the maternal hematocrit and an approximation of the maternal blood volume, an estimate of the volume of fetal red cells in the maternal circulation can be made. (Maternal blood volume will average about 5 liters before delivery and 4 liters shortly afterwards.) The volume of fetal red cells so calculated, then divided by 15 and multiplied by 300, provides a reasonable estimate for Rho immune globulin dosage in μg. If the estimate is doubled, almost certainly more than adequate protection would be afforded the mother.

Moreover, in cases of recognized major fetal–maternal hemorrhage, sensitization of the mother may be prevented by injecting sufficient immune globulin intramuscularly to maintain a demonstrable excess of antibody in the maternal serum.

In a case of massive fetal-maternal hemorrhage successfully treated at Parkland Memorial Hospital, 14 units of Rho immune globulin (4200 μg at least) were injected intramuscularly over 48 hours to maintain a clearly demonstrable excess of antibody after delivery of a recently exsanguinated, very large infant. From the differential count of erythrocytes of maternal and fetal origin identified by acid-elution treatment of maternal blood and measurements of maternal hematocrit and blood volume, at least 150 ml of type O, Rho positive fetal erythrocytes were demonstrated to have entered the maternal circulation (Fig. 38-3). The mother did not become sensitized and subsequently gave birth to three unaffected type O, Rho positive infants, including twins. She remains free from evidence of Rho sensitization.

The Rho (D) Negative Sensitized Mother. The mother who is sufficiently immunized to produce enough antibody to cause overt hemolytic disease in the fetus and newborn infant will have demonstrable Rho antibody in her serum by the 36th week of gestation. Most often, if appropriate technics are used, the antibody will be demonstrable much earlier.

According to Freda (1973), if nothing is done in the way of interference in the pregnancy of a sensitized Rho negative woman with a Rho positive fetus, the perinatal mortality rate can be anticipated to be about 30 percent. With aggressive management, including diagnostic amniocenteses, intrauterine transfusions in selected cases, and early delivery in most cases, the perinatal mortality rate can be lowered to about 10 percent.

For optimal outcome, individualization of management should be practiced, aided by the following information:

1. Past obstetric history with emphasis on fetal outcome and how that outcome was achieved.
2. Accurate knowledge of fetal age.
3. The Rho zygosity of the father to identify those pregnancies in which the fetus has about a 50 percent chance of being Rho negative.
4. Maternal antibody measurements repeated throughout pregnancy.
5. Spectrophotometric analyses of amniotic fluid.

6. Identification of other maternal complications such as pregnancy-induced or -aggravated hypertension.

An antibody titer (indirect Coombs' test) that goes no higher than 1:16 almost always means that the fetus will not die in utero from hemolytic disease and that with appropriate care after birth he will survive. A titer higher than this indicates the *possibility* of severe hemolytic disease. It is emphasized that the titer in the previously sensitized woman may, during a subsequent pregnancy, rise infrequently to high levels even though her fetus is Rho negative.

A suspicious titer, i.e., 1:16 or higher, in most cases warrants appropriately timed amniocenteses and measurements of bilirubin pigment in amniotic fluid. The technic for amniocentesis is described in Chapter 14 (p. 330). If use of intrauterine transfusion is being considered, amniocentesis may be initiated at about 22 weeks' gestation.

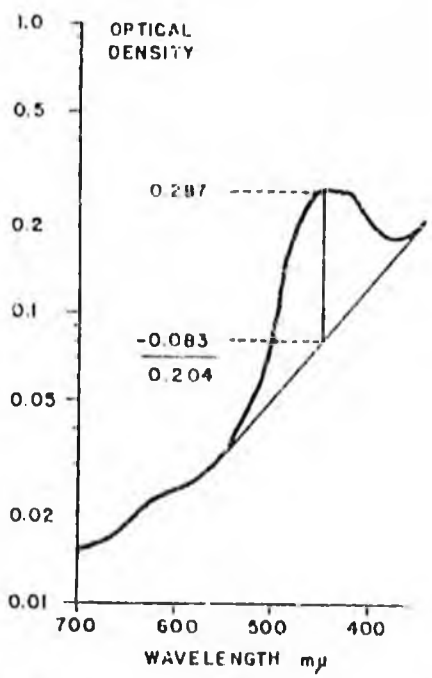

FIG. 38-4. Spectral absorption curve of amniotic fluid in hemolytic disease. (From Liley. In Greenhill I. (ed.). *Yearbook of Obstetrics and Gynecology, 1964–1965* series, p 256. (Year Book)

The absorbence of the breakdown pigment, mostly bilirubin, in the supernatant of amniotic fluid, when measured in a continuously recording spectrophotometer, is demonstrable as a hump with maximum absorbence at 450 nm wavelength (ΔOD_{450}) as shown in Figure 38-4. The magnitude of the increase in optical density above baseline at 450 nm most often, but not always, correlates well, for any gestational age, with the intensity of the hemolytic disease.

Liley (1964) constructed a graph which provides for reasonably precise prediction of the severity of the hemolytic disease, a modification of which is demonstrated in Figure 38-5. His recommendations are as follows:

If the increase in optical density falls in Zone I at 28 to 31 weeks, the fetus will be unaffected or will have mild hemolytic disease. Repeat the amniocentesis in 2 or 3 weeks.

For Zone II, the prognosis is less accurate and may require repeated amniocenteses to indicate a trend. In lower Zone II, the infant's expected hemoglobin at birth will be between 11.0 and 13.9 g, whereas in upper Zone II, the infant's anticipated hemoglobin will range from 8.0 to 10.9 g. Trends and time of gestation will obviously indicate the necessity for early delivery or intrauterine transfusions.

Values in Zone III indicate a severely affected infant, and fetal death within 1 week to 10 days may be expected. The treatment—early delivery or intrauterine transfusion—will depend on the stage of gestation.

Pathologic Changes in Hemolytic Disease of the Fetus and Newborn. Maternal antibodies gain access to the fetal circulation. In Rh positive infants, such antibodies are both adsorbed upon the Rho positive erythrocytes and exist in a free form in the infant's serum. The adsorbed antibodies act as hemolysins, leading to an accelerated rate of destruction of the red cells. The earlier this process begins in utero and the greater its intensity, the more severe will be the effect upon the fetus.

Maternal antibodies detectable at birth

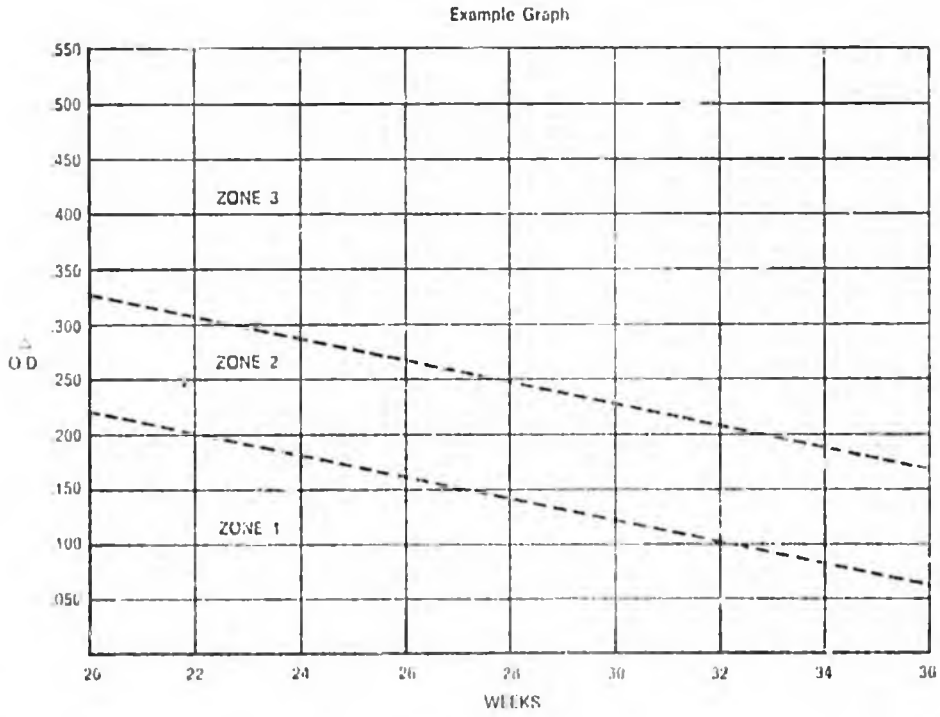

FIG. 38-5. The ΔO.D. value is plotted for the appropriate week of gestation. Zone 1 implies minimal hemolytic disease in the fetus, Zone 2 moderate to severe hemolytic disease, and Zone 3 impending fetal death. (From ... College of Obstetricians and Gynecologists *Technical Bulletin No. 17*, July 1972)

gradually disappear from the infant's circulation over a period of 1 to 4 months. Their rate of disappearance is influenced to some extent by exchange transfusion. Detection of adsorbed antibodies is best accomplished by the direct Coombs' test. If Rho red cells coated with Rho antibody are typed with an anti-Rho saline agglutinin serum, they may be reported incorrectly as Rho negative because of the blocking effect produced by the adsorbed antibody. Therefore, erythrocytes reported to be Rho negative from an infant whose mother may be isoimmunized must always be checked by the direct Coombs' test.

The pathologic changes in the organs of the fetus and newborn infant vary with the severity of the process. The severely affected fetus or infant may show considerable subcutaneous edema as well as effusion into the serous cavities (*hydrops fetalis*). At times, the edema is so severe that the diagnosis can be identified in the fetus by roentgenography (Fig. 38-6), or sonography (Fig. 38-7). In these cases, the *placenta* also is markedly edematous, appreciably enlarged and boggy, with large, prominent cotyledons and edematous villi. Excessive and prolonged hemolysis serves to stimulate marked erythroid hyperplasia of the bone marrow as well as large areas of *extramedullary hematopoiesis*, particularly in the spleen and liver. Histologic examination of the liver may serve to demonstrate, in addition, fatty degenerative parenchymal changes as well as deposition of hemosiderin and engorgement of the hepatic canaliculi with bile. There may be cardiac enlargement and pulmonary hemorrhages. Heart failure, however, at least at the outset, does not appear to play a prominent role in the development of ascites. Rather, portal hypertension and severe hypoalbuminemia are more likely the major factors in its develop-

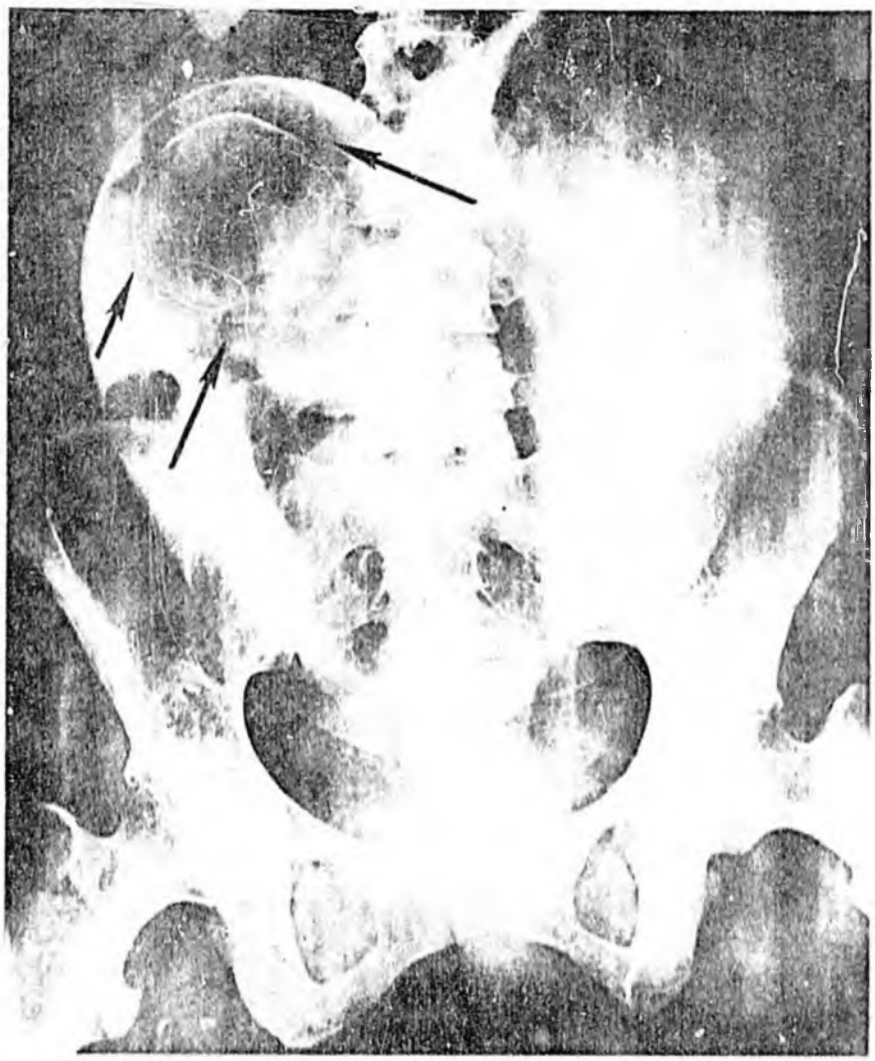

FIG. 38-6. Amniogram of a fetus with hydrops fetalis. *Arrows* point to severe edema of the scalp. (Courtesy of Dr. John T. Queenan)

ment. The ascites, and to a lesser degree hepatomegaly and splenomegaly, may be so massive as to lead to severe dystocia as the consequence of the greatly enlarged abdomen. Hydrothorax may be so severe as to compromise respirations after birth.

Fetuses with hydrops fetalis may die in utero from profound anemia and circulatory failure (Fig. 38-8). The liveborn hydropic infant appears pale, edematous, and limp at birth, often requiring resuscitation. The spleen and liver are enlarged, and there may be widespread ecchymoses or scattered petechiae. Dyspnea and circulatory collapse are common. Death may occur within a few hours in spite of transfusions.

Less severely affected infants may appear well at birth, only to become jaundiced within a few hours. Marked hyperbilirubinemia, if untreated, may lead to central nervous system damage, especially to the basal ganglia, which is characterized clinically by lethargy, stiffness of the extremities, retraction of the head, squinting, a high-pitched cry,

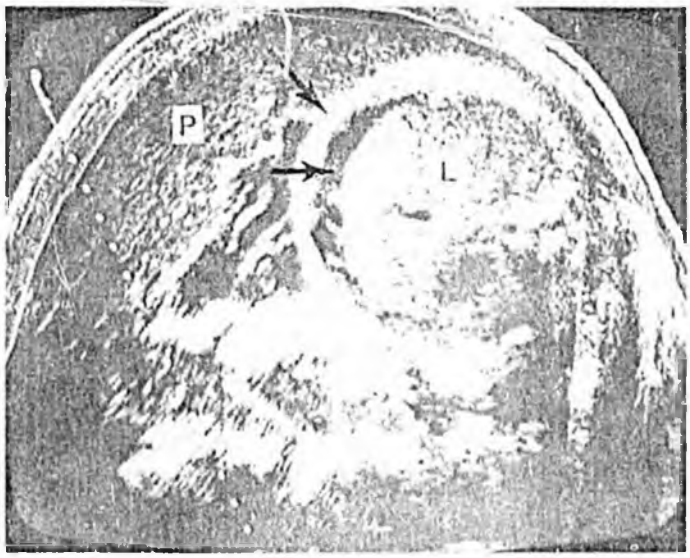

FIG. 38-7. Transverse sonogram of a hydropic fetus. Illustrated are fetal ascites (lower arrow), edema of fetal abdominal wall (upper arrow), liver (L), and large placenta (P). (Courtesy of Dr. R. Santos)

FIG. 38-8. Fatal erythroblastosis fetalis. Severely hydropic macerated stillborn infant and characteristically large placenta.

poor feeding, and convulsions. These signs are indicative of *kernicterus*. In such cases, death usually occurs within the first week of life. Surviving infants may be physically helpless, unable to support their heads or sit. Ability to walk is delayed or never acquired. In less severe forms, there may be varying degrees of motor incoordination, whereas some infants demonstrate residual nerve deafness as the only manifestation of neurologic injury.

Anemia, in part resulting from impaired erythropoiesis, may persist for many weeks to months in the infant who has demonstrated hemolytic disease at birth. In the absence of hypoxia, erythrocyte production normally falls after birth, especially in the premature infant. The observations of McIntosh (1975) serve to implicate low production of erythropoietin in this phenomenon.

Fetal Transfusions. The refinement in prognostic precision furnished by the analysis of amniotic fluid led Liley (1963) to try in apparently hopeless cases intrauterine transfusion of blood into the fetal peritoneal cavity. The procedure, in general, should be limited to cases in which, between 23 and 32 weeks, the spectrophotometric tracings and history forecast, in all likelihood, death of the fetus. Thirty-two weeks represents about the earliest gestational age at which the nontransfused affected fetus, if delivered, has a reasonable likelihood of surviving the adverse effects of prematurity, hemolytic disease, and exchange transfusion. For reasons that are not clear, the preterm infant with hemolytic disease from maternal Rh isoimmunization, unfortunately, is at increased risk of developing severe respiratory distress-hyaline membrane disease. Bowman (1978) has emphasized that, in his hands, mortality following fetal transperitoneal transfusions at 32 weeks' gestation and delayed delivery is appreciably lower than with delivery at 32 weeks.

With intrauterine transfusion the overall survival rate in more recent years probably has been about 50 percent. Bowman reported a survival rate of 70 percent if the initial transfusion was postponed to 26 weeks compared to 42 percent if the initial transfusion was required at 21½ to 23 weeks. Hamilton (1978) reported the survival of 76 percent of nonhydropic transfused fetuses. The results reported by some others have not been this good (Palmer and Gordon, 1976; Robertson et al., 1976).

Not only does fetal age and size at the time of the first transfusion affect the survival rate, the presence or absence of hydrops is of great importance. In Bowman's experience, the survival rate was only 21 percent if fetal ascites was encountered at the first transfusion, but 78 percent if no ascites was found at any time. In the presence of hydrops, absorption of the red cells from the peritoneal cavity appears to be markedly impaired. In the absence of hydrops, practically all of the erythrocytes are absorbed into the fetal circulation and survive there in normal fashion (Taylor et al., 1966).

The technic that has been used for fetal intraperitoneal transfusion at Parkland Memorial Hospital is very similar to that described in detail by Bowman (1978).

SUBSEQUENT CHILD DEVELOPMENT. Of 44 survivors of intrauterine transfusion followed by Holt and co-workers (1973), 43 were judged to be developing normally. Also, in Bowman's experience the great majority of fetal transfusion survivors developed normally; 74 of 89 tested when 18 months of age or older were completely normal and 4 were abnormal, while development in 11 appeared to be delayed somewhat perhaps because of preterm birth.

Delivery Before Term. In many circumstances, delivery before term is advantageous. Obviously, when it was considered necessary to utilize intrauterine transfusions, delivery, rather than further attempts at intrauterine transfusion, is desirable at the earliest date compatible with sufficient maturity to provide a good chance of survival. The exact timing of delivery in these cases de-

pends on both clinical judgment and the results of the various laboratory tests. Delivery before the 32nd week in most instances is contraindicated by the extreme prematurity. Delivery may best be carried out at 34 weeks. At that time, the risk from prematurity probably is less than the risk of another intrauterine transfusion, at least at some institutions.

When intrauterine transfusion has not been performed, delivery before term may be considered for the following reasons: (1) previous history of an infant with unmistakable evidence of erythroblastosis, (2) a high titer of antibodies, (3) reasonable evidence of homozygosity of the father, and (4) evidence of potentially severe fetal disease from analysis of the amniotic fluid. The last is the most compelling reason for intervention, either delivery or an intrauterine transfusion.

Whenever a decision is reached to terminate pregnancy before term, adequate facilities for care of premature infants must be available, as well as the necessary equipment for carrying out exchange transfusion. The neonatologist should be advised of the situation well in advance of delivery, so that skilled personnel, blood, and equipment can be immediately available in or adjacent to the delivery room. The need for immediate transfusion is determined by the hemglobin concentration. Subsequently, the plasma bilirubin concentration is the important determinant.

METHOD OF DELIVERY. The fetus who is to be delivered remote from term because of evidence of hemolytic disease will sometimes benefit from cesarean section. By so doing, the time of birth is set and the "first team" of neonatologists and laboratory personnel can be assembled to provide for precise evaluation of the infant at birth and optimal treatment at that critical time, as well as subsequently. Moreover, the likelihood of a difficult, prolonged, or unsatisfactory induction of labor is avoided.

Exchange Transfusion for Hemolytic Disease of the Newborn. Examination of cord blood should be carried out immediately for any pregnancy in which the Rho negative mother is known to be sensitized. The cord blood hemoglobin concentration and the direct Coombs' test are of considerable importance when the infant is Rho positive. When the infant is overtly anemic, it is often best to carry out the initial exchange promptly to correct the anemia using recently collected packed type O, Rho negative red cells.

For infants who are not overtly anemic, exchange transfusion is determined by the rate of increase in bilirubin concentration, the maturity of the infant, and the presence or absence of other complications. While exchange transfusion is not an innocuous procedure, if moribund, hydropic, and kernicteric infants are excluded, the mortality rate is 1 percent or less.

Sensitization to Other Blood Group Factors. A variety of other fetal red cell antigens which are lacking in the mother may be involved in the genesis of hemolytic disease in the fetus and infant.

ABO INCOMPATIBILITY. The "major" blood group factors A and B are important causes of hemolytic disease. For example, group O women may from early life have anti-A and anti-B agglutinins, which may be augmented by pregnancy, particularly if the fetus is a secretor. Although about 20 percent of all infants have a "ma[illegible] maternal blood group incompatibility, only 5 percent of them (1 percent of all babies) show overt signs of hemolytic disease. Moreover, when they do, the disease is usually much milder than that concerned with the Rho factor. Black infants are more likely to develop ABO disease than are white infants, according to Kirkman (1977). The disease does not appear to be any more severe, however, in black than in white infants (Peevy and Wiseman, 1978).

Desjardins and co-workers (1979) have intensively studied a large number of infants of blood group O mothers to try to identify a relationship between the degree of red cell

sensitization by antibody and the cord blood hemoglobin and bilirubin concentrations. They found that when the infant blood type was A or B, the bilirubin was higher and hemoglobin was lower than in cord blood from blood group O infants even when no antibody was identified on the type A or B red cells. They concluded that ABO incompatibility represents a spectrum of hemolytic disease which ranges from those in which there is little laboratory evidence of red cell sensitization, but some evidence of hemolysis, to those with severe hemolytic disease in which red cell sensitization is readily demonstrable.

The usual criteria for diagnosis of hemolysis due to ABO incompatibility include the following: (1) The mother is group O, with anti-A and anti-B in her serum, while the fetus is A, B, or AB. (2) There is onset of jaundice within the first 24 hours. (3) There are varying degrees of anemia, reticulocytosis, and erythroblastosis. (4) There has been careful exclusion of other blood group sensitization. Unlike the result in Rh hemolytic disease, the Coombs' antiglobulin test in ABO incompatibility may be negative.

The principles of management of the newborn infant with Rh disease may be applied to ABO hemolytic disease, particularly with reference to the behavior of hemoglobin and bilirubin. For simple transfusion or exchange transfusion, group O blood is used. Quite dissimilar to Rh hemolytic disease, the incidence of stillbirths among ABO-incompatible pregnancies is not elevated (Freda, 1973). There is seldom justification for early induction of labor on this basis or for performing an amniocentesis.

Since there is no adequate method of antenatal diagnosis, careful observation is essential in the neonatal period if cases are to be detected. Although the infants with ABO hemolytic disease most often are less severely affected than are those with Rh hemolytic disease, they are equally incompetent in coping with excess bilirubin and its toxic effects on the central nervous system. Unlike Rh hemolytic disease, ABO disease frequently occurs in infants of primigravidas. It is likely but not certain to recur in subsequent pregnancies.

OTHER FETAL–MATERNAL BLOOD GROUP INCOMPATIBILITIES. Rho incompatibility and ABO heterospecificity account for approximately 98 percent of all cases of hemolytic disease. Instances of hemolytic disease resulting from rarer blood factors have been reported, but the detection of such cases requires extensive serologic study. The potential for hemolytic disease with rare blood groups may be suspected from the results of the screening test for abnormal antibodies in maternal serum. Summarized in Table 58-2 are various red cell antigens and their capacity for causing hemolytic disease when the fetus possesses the red cell antigen, and the mother is isoimmunized.

HYPERBILIRUBINEMIA

Bilirubin is formed from heme and transported in the circulation bound to albumin. In the sinusoidal circulation of the liver, a small fraction of bilirubin which dissociates from albumin enters hepatocytes where it attaches to receptor carrier proteins, the so-called Y and Z anion-binding proteins. Within hepatocytes, the bilirubin is conjugated with glucuronic acid.

Disposal of Bilirubin. Before birth, unconjugated, or free, bilirubin is readily transferred across the placenta from the fetal-maternal circulation (and vice versa, if the maternal plasma level is high). Unconjugated bilirubin is not excreted in the urine or to any extent in the bile, whereas the glucuronide of bilirubin is water-soluble and is normally excreted into the bile by the liver and when the plasma level is elevated by the kidney. Glucuronic acid is made available for this reaction by transfer from uridine diphosphoglucuronic acid catalyzed by the microsomal enzyme uridine diphosphoglucuronosyl transferase. The conjugated bilirubin is secreted from the hepatocytes through the can

FAITH HOSPITAL
Central Alaskan Missions, Inc.
GLENNALLEN, ALASKA
99588

JAMES S. PINNEO, M.D.

February 10, 1981

State of Alaska
Senate HESS Committee
Pouch V
Juneau, Alaska 99801

RE: SB 41 Pre-marital Blood Testing

Dear Sirs,

Please register our opinion concerning this proposed legislation.

Although the general public has the belief, which is fostered by public officials, that the only requirement for the pre-marital certification is a blood test for syphilis, it becomes apparent when it is properly considered, that again the best interest of the patient would be for an evaluation of the presence of the communicable disease. At the present time, when a doctor signs a pre-marital certificate, he is thereby certifying that the patient has no communicable disease. In addition to syphilis, therefore, other veneral diseases must be ruled out. If the patient is a virgin, has never been married, the initial pre-marital examination is the ideal time when the patient comes under the care of the doctor and the proper doctor-patient relationship is established. Therefore, the many concerns of the girl about sexual relations, marriage, ability to have a child, etc. can be considered. Even if the patient is already pregnant, a doctor-patient relationship must be, not only should be, established, so that there is proper care of the unborn child. Therefore pre-marital examination is much more than a simple taking of a blood sample. As to the extent of the examination, again, that should be the prerogative of the doctor and his relationship with the patient.

Even though pre-marital blood testing may be considered not cost effective, it seems evident that such prompting for a pre-marital couple to seek medical evaluation, would be in the best interests of the couple involved and the entire state of Alaska. Thus the responsibility of marriage is involved, and if there is adequate deterent for hasty marriages, there would be less divorce. Although this can not be documented, it seems evident that tragic, social problems are existing because of hasty marriages and quick divorces. Not only is birth control advisable, but also control of veneral disease.

Overall then, it seems apparent to us that whever indoctrinates the people of Alaska for considering the responsibilities of marriage, procreation, and disease, would be beneficial to the establishment of marriage, the family, the home, and a stable society. Whatever not detracts from realization of responsibility, adds to social problems. Therefore, eliminating pre-marital blood tests although not cost effective to many people, and irrelevant, and

a nasty interference into private lives, it seems evident from all of the points expressed above that it would be wise for the best interest of the Alaskan citizen to maintain the requirement.

Sincerely,

James S. Pinneo, M.D.

JSP:ms
cc

STATE OF ALASKA

DEPT. OF HEALTH AND SOCIAL SERVICES
OFFICE OF THE COMMISSIONER

JAY S. HAMMOND, GOVERNOR

POUCH H 01
JUNEAU, ALASKA 99811
PHONE:

FEB 10 1981

23-81

Honorable Tim Kelly
Alaska State Senate
Alaska State Legislature
Pouch V
Juneau, Alaska 99811

Dear Senator Kelly:

We would like to respond to your request for information about the projected impact of the natural gas pipeline on venereal disease in Alaska.

In addressing your concerns, I would first like to talk about our experience from the oil pipeline and its impact on the venereal diseases.

Syphilis

During the 1970's and at the peak of the oil pipeline construction, we observed no significant increases in the rate of syphilis in Alaska. The rate (number of cases per 100,000 population) in Alaska remained relatively constant and was always below the rate of syphilis in the United States population.

Civilian Syphilis Cases and Rates
(All Stages) per 100,000

	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
Alaska rate*	27.6	28.9	31.0	33.9	34.7	15.0	25.4	27.4	14.2	15.6	11.4
U. S rate**	45.5	47.0	44.2	42.0	39.9	38.0	33.7	30.1	30.0	30.7	30.0***

*Based on population estimates from the Alaska Department of Labor
**Based on population estimates from the U.S. Bureau of Census
***Projected

During the oil pipeline, pre-employment blood testing for syphilis was required by the industry as a condition of employment. Pre-employment syphilis blood testing is anticipated to continue to be required during gas pipeline construction and will allow detection and treatment of syphilis before the disease is spread to others.

Furthermore, the epidemiology of syphilis has shifted dramatically in the past decade. Syphilis is now primarily occurring in the male homosexual population. Reflecting this nationwide trend, 65% (15 of 23) of the cases of early syphilis diagnosed in males in Alaska in 1950 occurred in homosexuals while only 12% (3 of 26) of all our early cases occurred in females. From this, we would consider female pipeline employees and dependents to be an extremely low risk group of being infected with syphilis. In general, we do not expect the construction of the natural gas pipeline to increase the rate of syphilis in Alaska.

Alaska's population is projected to increase by approximately 34,000 people due to the natural gas pipeline construction. Based upon our present rate of syphilis in all stages, we would expect four additional cases of syphilis to occur each year as a consequence of the pipeline activities.

The main objective of our syphilis control program is the prevention of congenital syphilis. We plan to increase our efforts to ensure that all pregnant women receive prenatal syphilis blood testing as required by Alaska's prenatal laws (A.S. 18.15.150-.180).

Gonorrhea

While Alaska's rate of syphilis has consistently been lower than the U. S. rates during the 1970's, such is not the case with gonorrhea. The rate of gonorrhea in Alaska has averaged about three times the national rate, as illustrated in the following table, giving Alaska the dubious distinction of having the highest gonorrhea rate in the nation.

Civilian Gonorrhea Cases and Rates per 100,000

	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980
Alaska cases	2225	2540	2098	2766	2903	3,14	4342	5103	5133	4986	4076
Alaska rate*	821.7	897.5	714.9	911.9	916.0	979.0	1116.5	1341.9	1303.1	1303.5	1081.1
U.S. rate**	298.5	328.1	371.6	404.9	432.1	472.9	470.5	465.8	468.3	459.4	460.0***

*Based on population estimates from the Alaska Department of Labor
**Based on population estimates from the U. S. Bureau of Census
***Projected

In reviewing this data, it should be understood that gonorrhea did not become a priority of the VD Control Programs either in the "lower 48" or in Alaska until 1972. With the introduction of control measures, some of the increases occurring both in the "lower 48" and in Alaska during the mid-1970's can be attributed to our screening and case finding activities which resulted in previously undetected cases being diagnosed and reported. At the same time, Alaska experienced tremendous population increases as a result of the construction of the oil pipeline. The dramatic increase in the number of gonorrhea cases and rates reported during this period undoubtedly were due to a combination of these factors.

During the oil pipeline construction period, the VD Control Program worked very closely with the Alyeska Medical Program to assure that physician assistants (P.A.'s) in the pipeline camps were equipped to diagnose, treat, and report all cases of gonorrhea, as well as to provide the VD Program with the necessary epidemiologic information to conduct investigative follow-up on contracts. Extensive efforts were made to improve medical services through education and on-site visits to pipeline camps. We intend to implement and follow these same procedures during the construction of the natural gas pipeline.

The population increase anticipated by the gas pipeline at its peak is estimated to be 34,000, less than one half of the increase of 85,000 caused by the oil pipeline. Based on our current rate of gonorrhea (1081.1 per 100,000 population) we project that there will be an increase of at least 465 cases per year at the peak of construction in 1984.

This increase is based on the assumption that the rate of gonorrhea will not increase. The increase in population will require additional VD control activities to establish screening, diagnostic testing and treatment capability, reporting, and epidemiologic follow-up in the pipeline camps. In addition, increased efforts will be needed to educate and inform dependents of pipeline workers of the nearest available health resources which will need expansion to handle not only the anticipated increased number of gonorrhea cases, but also other venereal diseases such as herpes, non-gonococcal urethritis, scabies, pubic lice (crabs), trichomoniasis, and monilia which are now more commonly referred to as "sexually transmitted diseases."

None of these sexually transmitted diseases can be diagnosed by a blood test. Therefore, their detection and treatment would not be affected by the repeal of the premarital blood test which the Venereal Disease Control Program strongly supports.

Summary

There will be two major areas requiring increased Venereal Disease Control Program activities as a result of the gas pipeline:

Honorable Tim Kelly

(1) Special increased program activities will be needed to establish adequate procedures for venereal disease education, prevention, detection, and treatment directly related to pipeline construction. These activities will require the VD Program to work closely with the gas pipeline medical staff, physician assistants, and remote pipeline camps. There will also be requirements to coordinate VD control efforts with Canadian health authorities because of the international component to the gas pipeline construction, not an issue with the oil pipeline.

(2) Generalized increased VD control efforts will be needed to effectively provide continuation of the same level of comprehensive services to the increased population of Alaskans which will accompany gas pipeline construction.

In closing, let me thank you for your concern and interest, and suggest that should you have additional concerns, our staff is available to respond in detail.

Sincerely,

Helen D. Beirne

Helen D. Beirne
Commissioner

MEMORANDUM State of Alaska

TO: The Honorable Helen D. Beirne
Commissioner
Department of Health & Social Services

DATE: July 22, 1980

FILE NO:

TELEPHONE NO:

FROM: Wilson L. Condon
Attorney General

By:
Bruce M. Botelho
Assistant Attorney General
Department of Law

SUBJECT: Authority to repeal blood test statutes
Our File: J-66-633-80

You have asked whether your department can suspend the requirement for premarital testing for infectious or heritable diseases by regulation.

AS 25.05.101(a)(2) and (3) require an applicant for a marriage licen to present a premarital certificate from a licensed physician or osteopathic physician stating that the applicant has been tested for the presence of infectious or heritable disease and that the physician or osteopathic physician has examined the report or reports and has advised the applicant of any medical implications of any abnormal tests. AS 25.05.105 directs the department to adopt regulations prescribing the approved test required for the premarital certificate.

Your opinion request suggests that the premarital blood testing has been limited to serologic testing for syphilis. Your memorandum implies that the department considers this testing to be unduly burdensome, given the cost involved to individuals relative to the low number of positive tests (i.e., tests showing the presence of syphilis).

Since AS 25.05.105 directs the department to adopt regulations describing the approved tests, it would be inconsistent for the department to adopt a regulation indicating that in its judgment no tests should be required. This obtains because no regulation adopted can be valid or effective unless it is consistent with the statute and reasonably necessary to carry out the purpose of the statute. AS 44.62.030. AS 25.05.101 and AS 25.05.105, when read together, evince a legislative decision that premarital tests for the presence of infectious or heritable diseases be conducted. Accordingly, discontinuation of the requirement for premarital testing would require repeal of AS 25.05.101 and AS 25.05.105.

BMB:md

ALASKA SYPHILIS SURVEILLANCE

Year	Number Premarital Tests[1]	Total Number Tests	Positive Tests	Early <1 yr.[2]	Late Latent[3]	Cases Found Con-Genital	Other	Total
1975	9,504	136,013	1,199	22	41	1	0	54
1976	9,828	134,028	1,618	56	47	2	3	114
1977	10,376	110,159	1,643	64	50	0	0	114
1978	10,234	95,644	1,232	20	42	1	0	63
1979	10,034	91,642	995	45	21	0	1	66
1980	10,000	N/A	N/A	26	25	0	0	51
Total	59,976	567,486	6,687	233	222	4	4	472

1. Determined from total number of Alaskan marriages. The actual number may be 20% greater because the number of health certificates issued is greater.

2. Two cases found from premarital testing effort.

3. Three cases found from premarital testing effort.

ALASKA GONORRHEA SCREENING

Year	Number Females Tested	Positive Tests	Percent
1973	27,370	1,135	4.15
1974	36,620	1,335	3.66
1975	40,340	1,550	3.84
1976	40,386	1,787	4.42
1977	48,500	1,953	4.03
1978	54,518	2,410	4.42
1979	55,388	2,237	4.03
1980	61,303	2.029	3.30

SB 41

MEMORANDUM State of Alaska

TO: Dean F. Tirador
Deputy Commissioner
Department of Health
and Social Services

DATE: February 10, 1981

FILE NO: J-66-535-81

TELEPHONE NO: 465-3603

FROM: WILSON L. CONDON
ATTORNEY GENERAL

SUBJECT: Request of Senate Committee on Health, Education, and Social Services

By:
Thomas H. Robertson
Assistant Attorney General

You have asked two questions on behalf of the Senate Committee on Health, Education, and Social Services. You have asked (1) whether prenatal serologies are statutorily required, and (2) whether a person or group of persons can be required to undergo blood or other laboratory tests in the event of an epidemic or other public health emergency.

Prenatal blood tests are addressed by AS 18.15.150-180. These statutes require that medical professionals obtain serological tests of most pregnant women. 1/ They are largely self-explanatory.

Your second question is not so easily resolved. Emergency diagnostic tests are not specifically addressed by statute. The Alaska Supreme Court has not had an opportunity to examine state authority in this area.

It has generally been held that a state may, for the purpose of protecting the public health, resort to reasonable, compulsory physical examination of persons suspected of being infected with a contagious or communicable disease. Reynolds v. McNichols, 488 F.2d 1378 (10th Cir. 1973); Irwin v. Arrendale, 159 S.E.2d 719 (Ga. 1967); Huffman v. District of Columbia, 39 A.2d 558 (D.C. 1944); 164 A.L.R. 967; 25 A.L.R.2d 1407; 39A C.J.S. Health and Environment § 19. However, at least with respect to venereal diseases, some courts have concluded that this power can be exercized only by state officials whose authority is clearly established by statute or regulation. Rock v. Carney 185 N.W. 798 (Mich. 1921). Wragg v. Griffin, 170 N.W. 400 (Iowa 1919).

1/ A physician or nurse who fails to administer the test is subject to criminal prosecution under AS 18.15.180. A pregnant women who refuses to cooperate is not.

Pursuant to AS 18.05.040(a)(1), the Department of Health and Social Services is under an obligation to adopt regulations for "the definition, reporting and control of diseases of public health significance." 2/ Contagious diseases are the subject of 7 AAC 27.010:

> 7 AAC 27.010. CONTROL OF COMMUNICABLE DISEASES IN MAN. (a) The provision on methods of control of communicable diseases outlined in the Control of Communicable Diseases in Man, American Public Health Association, Eleventh Edition, 1970, are adopted by reference as the regulations governing "Preventive Measures," "Control of Patients, Contacts and the Immediate Environment," and "Epidemic Measures."
>
> (b) The provisions of (a) of this section are not applicable to the control of rabies in animals or on the reporting of diseases of public health significance.

It is not immediately clear what this regulation purports to accomplish. 3/ While it addresses both the prevention and control of diseases of public health significance, it neither vests authority in particular public officials nor establishes procedures to govern its exercise. 4/

2/ Statutes providing, among other things, for the confinement of persons infected with contagious diseases were repealed upon enactment of AS 18.05.040(a)(1). Chapter 63, SLA 1972.

3/ One purpose of the text cited in this regulation is, as described in its preface, to "serve public health administrators as a guide and as a source of materials in preparing regulations and legal requirements for the control of the communicable diseases. . ." BENENSON, CONTROL OF COMMUNICABLE DISEASES IN MAN, (11th ed.), p. x, American Public Health Assoc., 1970. This has apparently been taken quite literally.

4/ The text, for example, cites "[c]orrection of such social conditions as overcrowding and poverty" as a means of preventing tuberculosis. It is unlikely that 7 AAC 27.010, in conjunction with AS 18.05.060, is intended to impose criminal sanctions upon all those who live under, or tolerate, these conditions.

It appears, in light of the foregoing, that the authority of state officials to require blood or other laboratory tests is not well established. As a result, a public health emergency could necessitate adoption of emergency regulations, institution of legal proceedings, or both. We suggest that the Department of Health and Social Services take steps to clarify 7 AAC 27.010 in this regard.

THR/jal

SB 41 – Repealed Sections

Article 3. Procedure to Obtain a License.

Section	Section
91. Application for license	111. Issuance of license
101. Premarital certificate	121. Marriage license
105. Prescribed tests	

Sec. 25.05.091. Application for license. One of the contracting parties to a prospective marriage shall, at least three days before the time of issuance, file with the licensing officer written, verbal, or telegraphic application for a license. Before issuance of the license, each contracting party shall file with the same licensing officer a premarital certificate; and shall make a statement under oath that the contemplated marriage meets the requirements of law, giving the names, relationship if any, residence, occupation, and age of each party; naming guardians of any party under the legal age for marriage; and describing any prior marriage or marriages of either party, and the manner of dissolution of them. This statement may be made and executed before a notary public or postmaster who shall certify it to the licensing officer. (§ 21-1-42 ACLA 1949; § 1 ch 58 SLA 1963)

Repealed

Sec. 25.05.101. **Premarital certificate.** (a) Before a licensing officer issues a marriage license, each party shall file with him a premarital certificate from a licensed physician or osteopathic physician stating

(1) the name and age of the applicant;

(2) that the applicant has been tested, as prescribed in the regulations of the department, for the presence of infectious or heritable disease; and

(3) that the physician or osteopathic physician has received and examined the report or reports of testing and that he has advised the applicant of the medical implications of each abnormal test.

(b) A license may not be issued more than 30 days after laboratory testing. (§ 1 ch 64 SLA 1949; am § 1 ch 63 SLA 1953; § 1 ch 58 SLA 1963; am § 1 ch 103 SLA 1971)

Repealed

Sec. 25.05.105. **Prescribed tests.** The department shall by regulation under the Administrative Procedure Act (AS 44.62) prescribe the approved tests required for the purposes of this chapter. (§ 2 ch 105 SLA 1971)

Sec. 25.05.111. Issuance of license. No marriage license shall be issued unless both of the contracting parties are identified to the satisfaction of the licensing officer. If all requirements have been met, and there is no legal objection to the contemplated marriage, and neither party is under the influence of intoxicating liquor or otherwise incapable of understanding the seriousness of the proceeding, the licensing officer

shall issue a license. (§ 21-1-11 ACLA 1949; am § 1 ch 93 SLA 1955; § 1 ch 58 SLA 1963)

Sec. 25.05.121. Marriage license. The marriage license issued by a licensing officer in this state authorizes the marriage ceremony to be performed anywhere in the state. The license shall be directed "to any person authorized by the laws of this state to solemnize marriage," and shall authorize him to solemnize marriage between the parties identified by the license within three months of the date of the license. If either party is not of legal age for marriage, his or her age and the fact of the consent of his or her parents or guardian shall be stated. If either party has previously been married, the number of previous marriages shall be stated. The registrar may require other matter necessary to identify the parties to be included in the license. The issuance of a license does not remove or dispense with any legal disability, impediment, or prohibition rendering marriage between the parties illegal, and a statement to that effect shall be included in the license. (§ 21-1-15 ACLA 1949; § 1 ch 58 SLA 1963)

Article 4. Medical Reports.

Section	Section
131. Laboratory reports of tests of infectious or heritable disease	141. Laboratory results confidential
	151. Tests and laboratories

Repealed **Sec. 25.05.131. Laboratory reports of tests of infectious or heritable disease.** The person in charge of the laboratory making the test or tests or some other person authorized to make the reports shall make the required report on the premarital certificate setting out the name of the test or tests, dates made, the name and address of the physician or osteopathic physician to whom the report was sent and the name and address of the person whose blood was tested, but not stating the result of the test. (§ 2 ch 64 SLA 1949; am § 2 ch 63 SLA 1953; § 1 ch 58 SLA 1963; am § 3 ch 103 SLA 1971)

Repealed **Sec. 25.05.141. Laboratory results confidential.** A detailed report of the test or tests for infectious or heritable disease on a separate laboratory report form to be furnished by the department, together with the premarital certificate, shall be sent from the laboratory to the physician or osteopathic physician requesting the report. The physician or osteopathic physician shall retain this report as a part of his confidential files. A duplicate shall be sent by the laboratory to the department where it shall be held in absolute confidence and shall not be open for public inspection. The report shall not be produced for evidence in any court. The reports may be used in the epidemiological investigations of infectious or heritable disease by the department. The reports may be used in the compilation of aggregate statistics and

reports but the identities of the persons involved shall never be disclosed. (§ 5 ch 64 SLA 1949; am § 5 ch 63 SLA 1953; § 1 ch 58 SLA 1963; am § 4 ch 103 SLA 1971)

Repealed

Sec. 25.05.151. Tests and laboratories. For the purposes of this chapter, tests for infectious or heritable disease is a test or series of tests for the presence of infectious or heritable disease approved by the department, made at a laboratory or clinic approved by the department. The department may make regulations under the Administrative Procedure Act (AS 44.62) governing the approval of laboratories or clinics for tests for infectious or heritable diseases. The laboratories of the department may make required premarital laboratory tests without charge on the request of any licensed physician or osteopathic physician. In submitting the sample to the laboratory the physician or osteopathic physician shall identify it as a premarital test sample. (§ 4 ch 64 SLA 1949; am § 4 ch 63 SLA 1953; § 1 ch 58 SLA 1963; am § 1 ch 124 SLA 1967; am § 5 ch 103 SLA 1971)

Article 5. Special Circumstances.

Section
161. Waiver of waiting period
171. Persons capable of consenting to marriage: Minimum ages, and consent of parents or guardian
181. Waiver order

Sec. 25.05.161. Waiver of waiting period. If a three-day waiting period would result in undue hardship or delay in an individual case, the licensing officer may waive the three-day requirement. (§ 21-1-11 ACLA 1949; am § 1 ch 93 SLA 1955; § 1 ch 58 SLA 1963)

Sec. 25.05.171. Persons capable of consenting to marriage: Minimum ages, and consent of parents or guardian. (a) A person who has reached the age of 16 but under the age of 18 years shall be issued a marriage license if the written consent of the parents of each person who is underage, or of the parent having actual care, custody and control, or of his or her guardian is filed with the licensing officer issuing the marriage license as provided in § 111 of this chapter.

(b) A superior court judge may grant permission for a person who has reached the age of 14 but under 18 years of age to marry and order the licensing officer to issue the license if he finds, following a hearing at which the parents and children are given the opportunity to appear and be heard,

(1) that the parents have given their consent; or

(2) that the parents are

(A) arbitrarily and capriciously withholding consent; or

(B) absent or otherwise unaccountable; or

(C) in disagreement amongst themselves on the question; or

(D) unfit to decide the matter; and

(3) that the marriage is in the best interest of the minor. (§ 21-1-12 ACLA 1949; am § 1 ch 65 SLA 1951; am § 1 ch 37 SLA 1953; § 1 ch 58 SLA 1963; am § 93 ch 127 SLA 1974; am § 2 ch 28 SLA 1975)

Effect of amendments. — The 1974 amendment deleted "for males and 16 year of age for females" following "18 years of age" in subsection (a).

The 1975 amendment rewrote this section.

Cited in RLR v. State, Sup. Ct. Op. No. 706 (File No. 1156), 487 P.2d 27 (1971).

Repealed **Sec. 25.05.181. Waiver order.** (a) A licensing officer may, on joint application by both applicants for a marriage license, waive the requirements as to laboratory tests and premarital certificates if he believes that the public health and welfare will not be adversely affected and if

(1) there is no licensed physician or osteopathic physician in the area in which the applicants and the licensing officer reside; or

(2) a delay has been certified by the physician or osteopathic physician taking the blood specimen in a community where no laboratory is located, the certificate stating that the blood specimen was sent to the laboratory at least three days before the certification and that no return has as yet been received from the laboratory; or

(3) the test or tests are contrary to the tenets or practices of the religious creed of which the applicant is an adherent.

(b) The waiver order shall be filed with the marriage license docket in lieu of the premarital certificate. No fee or court costs for the waiver order may be charged. (§ 7 ch 64 SLA 1949; am § 7 ch 63 SLA 1953; § 1 ch 58 SLA 1963; am § 6 ch 103 SLA 1971)

Article 6. Forms, Records and Reports.

Section	Section
191. Marriage license docket	231. Reports of licenses issued
201. Notes on docket	241. Fees
211. Reports by marriage commissioner	251. Vital Statistics Act
221. Forms	

Sec. 25.05.191. Marriage license docket. Each licensing officer shall keep in his office, in a book to be provided to him by the bureau, a marriage license docket, and shall enter a complete record of the applications for and the issuance of all marriage licenses and of all other information he is required by law to obtain. Marriage commissioners shall keep the marriage license docket in duplicate. The marriage license docket shall be open for public inspection or examination during office hours. (§ 1 ch 58 SLA 1963; am § 3 ch 28 SLA 1975)

Effect of amendment. — The 1975 amendment deleted the former fourth sentence.

Repealed **Sec. 25.05.201. Notes on docket.** When the licensing officer issues a marriage license, he shall indicate on the corresponding marriage license docket sheet that he has on file the premarital certificates of each applicant or a waiver order. He shall enter the dates of the laboratory tests or the waiver order. The licensing officer shall attach the premarital certificates or waiver order to the docket sheet. (§ 1 ch 58 SLA 1963)

Sec. 25.05.211. Reports by marriage commissioner. Before the first of each month, each marriage commissioner shall forward to the magistrate acting as recorder for the recording district in which the marriage commissioner has jurisdiction the duplicate copies of all marriage license docket sheets executed during the preceding month, the completed original marriage certificates and duplicate copies for any marriage ceremonies performed by him during the preceding month, and any fees and reports required by rule of the supreme court. (§ 21-1-34 ACLA 1949; am § 3 ch 28 SLA 1960; § 1 ch 58 SLA 1963)

Sec. 25.05.221. Forms. (a) Forms for application, statements, consent of parents, affidavits, licenses, and other forms necessary to comply with this chapter shall be prescribed by the registrar and provided at the expense of the state. The registrar shall furnish all necessary forms to each licensing officer. He shall provide him with a suitable book in which to keep the marriage license docket. The forms for the premarital certificate shall be provided and distributed by the department to approved laboratories or clinics inside the state and to proper authorities in an official state or Canadian province public health laboratory. A premarital certificate which has been approved by the proper authority in a state or Canadian province requiring premarital examinations for infectious or heritable disease shall be accepted in Alaska.

(b) The registrar shall supervise the record work and required reporting of the licensing officers. In other respects the licensing officers are under the supervision of the supreme court. (§ 1 ch 58 SLA 1963; am § 7 ch 103 SLA 1971)

Sec. 25.05.231. Reports of licenses issued. The registrar may require reports of licenses issued upon forms to be furnished by him. (§ 1 ch 58 SLA 1963)

Sec. 25.05.241. Fees. The supreme court shall establish marriage license fees and provide for accounting for and disposing of the fees. (§ 21-1-35 ACLA 1949; am § 4 ch 28 SLA 1960; § 1 ch 58 SLA 1963)

Sec. 25.05.251. Vital Statistics Act. Nothing in this chapter repeals or abrogates any part of AS 18.50, the Vital Statistics Act. The records and requirements leading up to and including the issuance of the marriage license are not included in the definition of "vital statistics" under that Act. However, the registrar shall supply the necessary forms and instructions for the record work of the licensing officers. (§ 1 ch 58 SLA 1963)

(4) obtain, by purchase or donation from surplus federal property or otherwise, medical supplies and equipment useful in carrying out this program and to allot or resell these supplies and equipment to private institutions engaged by the department to carry out this program;

(5) contract with hospitals, associations, or sanatoria qualified and equipped to give adequate care inside or outside the state;

(6) employ necessary and trained personnel to carry out the purposes of §§ 120—140 of this chapter;

(7) pay the costs of care and incidental expense for residents of the state, in whole or in part, depending on the ability of each patient to pay, and the temporary costs of care and transportation for nonresidents on the same basis until they can be transferred to their residence;

(8) enlist the cooperation of state and federal agencies operating in the state for the furtherance of this program;

(9) establish standards in accordance with department procedure for the care of tuberculars receiving treatment under §§ 120—140 of this chapter. (§ 40-2-11 ACLA 1949)

Am. Jur. reference. — 25 Am. Jur., Health, § 24 et seq.

Sec. 18.15.130. Department to cooperate with other agencies. The department, in conducting a study and case finding survey of the tuberculosis problem, shall cooperate with state and federal agencies operating in the state, and obtain as much information and data as possible from them. (§ 40-2-12 ACLA 1949)

Sec. 18.15.140. Title to and inventory of equipment allotted to private institutions. Equipment purchased for the purposes of carrying out §§ 120—140 of this chapter which is allotted to private institutions remains the property of the state. Before February 2 in each year, each allottee shall file a complete inventory of the equipment with the department. (§ 40-2-13 ACLA 1949)

Article 4. Prenatal Blood Tests.

Section	Section
150. Taking of blood sample	170. Report of birth
160. Test for syphilis	180. Penalty.

Sec. 18.15.150. Taking of blood sample. Each licensed physician and in absence of a licensed physician each licensed graduate nurse who attends a pregnant woman for conditions relating to her pregnancy during the period of gestation or at delivery shall take, or have taken, a sample of the blood of the woman at the time of her first professional visit or within 10 days after the visit, unless the serological test is contrary to the tenets or practice of the religious creed of which she is an adherent. The blood specimen shall be submitted to an approved laboratory or clinic for a standard serological test of syphilis. Any other person permitted by law to attend pregnant

women but not permitted by law to take blood samples shall have a sample of blood taken by a licensed physician, or on order of a licensed physician and shall submit the sample to an approved laboratory or clinic for a standard serological test for syphilis. (§ 1 ch 39 SLA 1949)

Sec. 18.15.160. Test for syphilis. For the purposes of §§ 150 — 180 of this chapter a standard serological test is a test for syphilis approved by the department and shall be performed in a laboratory or clinic approved by the department. On request the laboratory test required by §§ 150 — 180 of this chapter shall be performed without charge at the laboratories of the department. (§ 2 ch 39 SLA 1949)

Sec. 18.15.170. Report of birth. In reporting a birth and stillbirth, the physician and other person required to make the report shall state on the certificate whether a serological test for syphilis has been made upon a specimen of blood taken from the woman who bore the child and the approximate date when the specimen was taken. A birth certificate may not state the result of the test. (§ 3 ch 39 SLA 1949)

Sec. 18.15.180. Penalty. A licensed physician or licensed nurse attending a pregnant woman during the period of gestation or at delivery, or a representative of a laboratory or clinic who violates §§ 150 — 180 of this chapter is guilty of a misdemeanor, and upon conviction is punishable by a fine of not more than $500. However, a person attending a pregnant woman during the period of gestation or at delivery, who requests the specimen in accordance with § 150 of this chapter, and whose request is refused, is not guilty of a misdemeanor. (§ 4 ch 39 SLA 1949)

Article 5. General Provisions.

Section
190. Definitions

Sec. 18.15.190. Definitions. As used in this chapter, "department" means the Department of Health and Social Services. (am § 6 ch 104 SLA 1971)

Effect of amendment. — The 1971 amendment substituted "Department of Health and Social Services" for "Department of Health and Welfare."

Article 6. Phenylketonuria (PKU).

Section
200. Screening infants for phenylketonuria

Sec. 18.15.200. Screening infants for phenylketonuria. (a) A physician who attends a newborn child shall cause this child to be tested for phenylketonuria (PKU). If the mother is delivered in the absence of a physician, the nurse who first visits the child shall cause this test to be performed.

(b) The Department of Health and Social Services shall prescribe

regulations regarding the method used and the time or times of testing as accepted medical practice indicates.

(c) The necessary laboratory tests and the test materials, reporting forms and mailing cartons shall be provided by the department.

(d) All tests considered positive by the screening method shall be reported by the screening laboratory to the physician and to the department. The department shall provide services for the performance of a quantitative blood phenylalanine test or its equivalent for diagnostic purposes. A confirmed diagnosis of phenylketonuria shall be reported to the physician and to the department. The department shall provide services for treatment and clinical follow-up of any diagnosed case.

(e) When presumptive positive screening tests have been reported to the department, it shall provide, on request, either the true blood phenylalanine test or subsidize the performance of this test at an approved laboratory.

(f) A licensed physician or licensed nurse attending a newborn or infant who violates this section is guilty of a misdemeanor, and upon conviction is punishable by a fine of not more than $500. However, a person attending a newborn or infant whose request for appropriate specimens from the newborn or infant is denied by the parent or guardian is not guilty of a misdemeanor. The fact that a child has not been subjected to the test because a request for appropriate specimens has been denied by the parents or guardian shall be reported to the department. The department shall administer and provide services for testing for other heritable diseases which lead to mental retardation and physical handicaps as screening programs accepted by current medical practice and as developed.

(g) In this section, "physician" means a doctor of medicine licensed to practice medicine in this state, or an officer in the regular medical service of the armed forces of the United States or the United States Public Health Service assigned to duty in this state. (§ 1 ch 90 SLA 1965; am § 1 ch 39 SLA 1967; am § 6 ch 104 SLA 1971)

Effect of amendments. — The 1967 amendment rewrote this section.

The 1971 amendment substituted "Department of Health and Social Services" for "Department of Health and Welfare" in subsection (b).

POSITION PAPER

SENATE BILL NO. 41

"An Act relating to marriage and domestic relations".

The bill repeals AS 25.05.101 and AS 25.05.105 requiring premarital medical certificate for marriage license.

The Act repeals AS 25.05.131 requiring that the report of results of test shall not be made a part of the premarital certificate.

The Act repeals AS 25.05.141 requiring that results of tests be sent only to physicians or osteopathic physicians requesting the report and that duplicate reports of test be held in absolute confidence by the Department. The Act repeals AS 25.05.151 governing the approval of laboratories and clinics for tests for infectious or heritable diseases.

Definition

Premarital blood testing has been limited to serological testing for syphilis by the Department of Health under authority granted by AS 25.05.105.

Need for Premarital Blood Testing

A decision to employ syphilis screening should be based upon; local epidemiologic circumstances that indicate geographic clustering of syphilis in a community, the distribution of syphilis cases by sexual preference (nationally it has been estimated that one half of all cases of syphilis are occurring in homosexual men), the distribution of syphilis cases by ethnic and occupational groups and of particular importance in Alaska, the availability of such groups for testing. Comparative costs and benefits of maintaining surveillance in screening groups must also be considered. The Department, after considering all factors, has determined that results from premarital syphilis screening are of little consequence in the national or State VD control effort. Nationally in 1976 four million premarital syphilis screening examinations were performed resulting in the discovery of only 456 cases. Mass screening of low-risk groups such as premarital applicants, however is still required in 44 states as of 1976, although many states are in the process of repealing such legislation. In Alaska it has been estimated that 25,000 serologies have been performed during the past 5 years with the discovery of only 2 cases of primary syphilis. Although the law in effect requires couples to have physician contact before marriage and is an apparent opportunity to counsel on matters pertaining to parenthood, hereditary diseases, sex and contraception and to possibly detect and corect illnesses and disabilities, it does not as currently written and administered carry out the intent of the law that is to contribute significantly to the control of infectious and heritable disease in the general population.

Experience in Alaska

For several months the Section of Communicable Disease Control of the Division of Public Health, Department of Health and Social Services, State

of Alaska, has been reviewing the need to continue to require premarital serologic blood tests for syphilis. In 1979, the State of Alaska reported 67 cases of syphilis: 45 cases of early syphilis (primary or early latent), and 22 cases of late latent syphilis. None of the 67 cases of syphilis were discovered through the use of premarital syphilis serological blood tests. In order to obtain more data on our experience in Alaska, the results of premarital serological testing for syphilis dating back to 1973 were reviewed. Since 1973, only five cases of syphilis in all stages were diagnosed through premarital blood tests. No cases of syphilis have been diagnosed since August 1978 from premarital syphilis serologies. Although Alaska has the highest rate of gonorrhea in the nation, the rate of syphilis has remained relatively constant and is lower (5.9 per 100,000) than the national average (30 per 100,000). In addition, the majority of syphilis cases now occur in the homosexual population not subject to premarital screening.

We have reviewed this data with the Venereal Disease Unit of the Section of Communicable Disease Control and with the Center for Disease Control, Atlanta, Georgia. Based upon our experience in Alaska in uncovering cases of syphilis through use of premarital serologic testing, the Center for Disease Control, the Venereal Disease Unit of the Section of Communicable Disease Control, and the Division of Public Health have concluded that the requirement for premarital syphilis serologic testing should be repealed.

Effect of Repeal on Venereal Disease Control Programs

Passage of this act would not alter or significantly affect syphilis serology testing programs in high-risk groups or prenatal groups to prevent congenital syphilis. Quality control and proficiency testing programs in laboratories that are currently performing syphilis serology testing would not be effected by passage of this act. Passage of this bill will reduce syphilis serology workload in the state public health laboratories by 18%.

We wish to emphasize that our commitment to discover, diagnose, and bring to treatment all persons with syphilis remains undiminished. We will vigorously pursue the continued requirement for prenatal serologic blood testing and continue to test for syphilis all blood specimens from public health clinics and from private physicians suspecting the diagnosis of syphilis.

Cost Savings

The FY 81 budget already reflects a cost savings to the Division as it was initially believed that repeal of premarital legislation would not be necessary. Premarital syphilis serological tests can be eliminated without impairing the cost effectiveness of Venereal Disease Control efforts in the State of Alaska.

POSITION PAPER/Department of Health & Social Services

Department Position

The Department of Health and Social Services recommends passage of this bill.

Recommended by: David Bruce
David Bruce, Deputy Director
Division of Public Health

Date: January 20, 1981

Approved by: Helen D. Beirne
Helen D. Beirne
Commissioner

Date: 1-21-81

ALASKA STATE HOSPITAL ASSOCIATION INC.
319 Seward Street
Juneau, Alaska 99801
Phone: (907) 586-1790

October 10, 1980

Dr. John Middaugh, M. D.
Room 301 MacKay Bldg.
338 Denali Street
Anchorage, AK 99501

Dear Dr. Middaugh:

The Alaska State Hospital Association wishes to inform you that on October 6, 1980 our Board of Directors voted to endorse your request to repeal the premarital syphilis serology requirement.

If we can be of help in the future, please let me know.

Sincerely,

Dennis L. DeWitt
Executive Director

DLD/sam

Alaska Native Health Board

1689 C STREET, SUITE 230, ANCHORAGE, ALASKA 99501 PHONE (907) 276-8989

Reference #A80-0960

September 24, 1980

The Honorable Jay S. Hammond
Governor
State of Alaska
Pouch A
Juneau, Alaska 99811

Dear Governor Hammond:

The Alaska Native Health Board endorses the repeal of the statute requiring premarital syphilis serological blood testing.

By doing so, the Board recognizes the continuing need to actively seek to discover and treat all cases of syphilis but it is believed that premarital testing is not the most effective means. The nearly $81,000 required for the 9,000 tests given in 1979 could better be used in a more promising, productive manner. This change should not impair the effectiveness of the Venereal Disease Control efforts of the State.

As always, the Board is concerned with the well-being of all Alaskans. It seeks the epitome of service delivery and to eliminate waste. It believes to continue the "routine testing" to be such a waste.

Sincerely,

for Bonnie Galaida

David E. Cates, Ph.D.
Executive Director

DEC:blg

cc: John Middaugh, M.D.

4107 Laurel Street, Suite #1, Anchorage, AK 99504

October 17, 1980

Honorable Jay Hammond
Pouch A
Juneau, Alaska 99801

Dear Governor Hammond,

At our regular meeting on October 4, 1980, in Anchorage the Alaska State Medical Association council passed a resolution supporting deletion of the requirement for a premarital serologic test for syphilis. We do not believe that this is warranted on a screening basis, but that it should be done on a case by case basis as decided by the individual person and his or her physician.

We wish to make it clear that in no way do we believe that the requirements for prenatal serologic testing should be disturbed.

We will support legislation to delete maldatory premarital serologic testing.

Yours truly,

David E. Johnson, M.D.

DEJ/cjj

WHEREAS, the control of Public Health in a cost-effective manner is of the highest priority, and

WHEREAS, a review of the effectiveness of current statutes requiring premarital syphilis serologies has revealed this requirement to be ineffective in controlling syphilis, and

WHEREAS, a substantial saving can be realized through the suspension of premarital blood testing without decreasing the effectiveness of venereal disease control efforts,

BE IT SO RESOLVED::

That the Alaska Public Health Association endorse the position of the Department of Health and Social Services in presenting legislation to repeal the current requirement for premarital blood testing.

THE LEGISLATURE OF THE STATE OF ALASKA
ELEVENTH LEGISLATURE

FISCAL NOTE

I. REQUEST

Bill/Resolution No. Senate Bill No. 41

Title "An Act relating to marriage and domestic relations"

Requested by Commissioner's Office Date January 21, 1981

II. FISCAL DETAIL

Agency Affected

Program Category Affected Division of Public Health

BRU, Program, or Subprogram(s) Affected

(Note: If more than one budget component is affected, separate line-item amounts and funding for each component in the analysis section.)

EXPENDITURES (Thousands of Dollars)

	FY 80	FY 81	FY 82	FY 83	FY 84	FY 85
100 PERSONAL SERVICES	0	0	0	0	0	0
200 TRAVEL	0	0	0	0	0	0
300 CONTRACTUAL	0	0	0	0	0	0
400 COMMODITIES	0	0	0	0	0	0
500 EQUIPMENT	0	0	0	0	0	0
600 LAND & STRUCTURES	0	0	0	0	0	0
700 GRANTS, CLAIMS, ETC.	0	0	0	0	0	0
TOTAL	0	0	0	0	0	0

FUNDING (Thousands of Dollars)

GENERAL FUND	0	0	0	0	0	0
FEDERAL FUNDS	0	0	0	0	0	0
OTHER (Specify Fund Source)	0	0	0	0	0	0

POSITIONS

FULL TIME	0	0	0	0	0	0
PART TIME	0	0	0	0	0	0
TEMPORARY	0	0	0	0	0	0

III. ANALYSIS (See Fiscal Note Preparation Instructions, Section III)

IV. DATE 1/21/81 PREPARED BY Harry Colvin

AGENCY Public Health

Original: Legislative Finance PHONE 465-3140

cc: Budget and Management

Prime Sponsor (First Legislator Named) M&B Approved [signature] Date 1/21/81

33-001 (Rev. 12/79)

SB41

4 for ✓ DEAN F. TIRHOOK ~~3603~~ 3030
Dep. Com. HSS

Colvin — ✓ John Brook — ✓ 3393

opp. 822-3205 2/24 sent letter a day ago;
822-3203

— NO ✓ JAMES S. PINNEO MD.
FAITH HOSPITAL, GLENNALLEN

4 for ✓ DENNIS D. WITT (Barbara 586-1790 WILL BE THERE
AK STATE HOSPITAL ASSOCIATION

— for ✓ DAVID CATES M.D.
AK NATIVE HEALTH BOARD 276-8989

— for ✓ DAVID JOHNSON MD. (Ketchikan)
AK STATE MEDICAL ASSOCIATION touch. 277-6891

4 NO. TERRY MARTIN'S OFFICE
BILL MOFFITT 3783-4 ✓

✓ materials re: rescheduling of Committee Hearing for Fri., 3/6