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THE PROBLEM OF HEMOLYTIC DISEASE OF THE NEWBORN AND ITS MANAGEMENT IN A GENERAL HOSPITAL[1]

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EDITOR'S NOTE: Since The Lenacre Quarterly *professes to be "a journal of the philosophy and ethics of medical practice," it is not our policy to publish articles whose content is exclusively medical. To do so, we feel, would be to compete needlessly and ineffectually in an area already adequately covered by the scores of excellent medical journals available to any doctor. The distinctive service which we hope to provide for our readers lies rather in the sphere of medico-morality.*

Dr. Sacks' article, because of its immediate and obvious implications, qualifies in an eminent degree for this latter category. The first duty of every physician is to provide his patients with optimum medical care. Specifically in the field of hemolytic disease of the newborn, where infant life and health hang so precariously in the balance, techniques which substantially improve the likelihood of a live and healthy baby are as morally imperative as they are medically superior.

As explained in the final section of this article, The Catholic Hospital Association has already undertaken a unique project in the form of a cooperative immunoserological laboratory program. To the extent that the interest and cooperation of hospital staff members may be necessary to implement this program, it is to be hoped that our doctors will not be found wanting.

IN any hospital where an obstetrical population exists, the problem of hemolytic disease of the newborn is present. This is especially true where a significant percentage of this population consists of multiparous women. The following data from this hospital help to emphasize the importance of this problem. The figures are approximate to the nearest round number.

In a two year period, slightly more than 10,000 infants were delivered. Of these, 13% had Rho negative mothers. The 1,300 mothers in this group had 900 Rho positive children: 100 of these children had hemolytic disease of the newborn as evinced by a positive Coombs test. About half of these affected children required replacement transfusion. In other words, *a case of hemolytic disease of the newborn may be expected about one in every 100 deliveries, and half of these will require replacement transfusion.*

1 In this summary discussion of hemolytic disease of the newborn, it has been necessary to leave out much significant detailed information which belongs more properly in a textbook. For the salient information to help put in practice the discussion enclosed herein, the author recommends the following excellent reference books:

1. *Erythroblastosis Fetalis Including Exchange Transfusion Technic*, by Fred H. Allen, Jr., M.D. and Louis K. Diamond, M.D., published by Little, Brown and Company.
2. *Blood Transfusion in Clinical Medicine*, by P. L. Mollison, published by Charles C. Thomas.

A survey[1] done elsewhere shows that by the [illegible]xth pregnancy at least one of [illegible]f every four Rh negative wo[illegible] will be sensitized to the Rh [illegible]or. This indicates that the greater the degree of multiparity in a given hospital population, the more cases of hemolytic disease of the newborn are to be expected.

If an adequate organization for the care of these patients is in existence in a hospital, and this organization can be set into motion with celerity, the mortality from this disease (or its terrible sequelae) can be reduced to 5% of cases. If the disease is not recognized early, or transportation to another hospital is necessary before treatment can be instituted, the mortality will rise sharply.

The fact that a mother has had an infant with severe hemolytic disease of the newborn does not prevent her from having subsequent children who may survive and be normal if adequate therapy is instituted in time. This is especially true if the husband is heterozygous for the offending antigen. We have in our records cases which fully substantiate this. One Rh negative mother was sensitized to the Rh factor by an intramuscular injection of blood given in childhood for measles prophylaxis. Her husband (we found subsequently) is heterozygous for this factor. Her first three infants were Rh negative. Her next three were all Rh positive; all had hemolytic disease of the newborn, and all three required replacement transfu[illegible]on, surviving normally. Her sev[illegible]ith child was Rh negative. Her [illegible]ext pregnancy resulted in ider[illegible]cal twins with hemolytic diseas[illegible] of the newborn. These were [illegible]ich premature but withstood the [illegible]ro-cedure of replacement transfu[illegible]ion well. Unfortunately both had p[illegible]im-ary pulmonary atelectasis, and ex-pired of this 14 hours after b[illegible]th.

Even if the husband is hom[illegible]zy-gous for the Rh factor, fam[illegible]ies may be large. One of our mot[illegible]ers who was sensitized to the Rh [illegible]ac-tor by transfusion in childhood [illegible]as had four children, all with se[illegible]ere hemolytic disease of the newb[illegible]rn; all surviving normally after e[illegible]ly replacement transfusion (wit[illegible]in the first hour of life).

In summary, it may be sta[illegible]ed that hemolytic disease of the n[illegible]w-born is a serious problem in a h[illegible]os-pital, but if an adequate warn[illegible]ng system exists, and if adequate th[illegible]er-apy is readily available, the pr[illegible]ob-lem is by no means insuperable.

THE MANAGEMENT OF HEMOLYTIC DISEASE OF THE NEWBORN

Much has been written on the treatment of hemolytic disease of the newborn and its serological complexities. The very number of these publications tends to repel anyone desiring to set up a system for managing this disease, in the absence of a specialized blood bank, obstetrical or pediatric staff.

Our hospital has a very active obstetrical service and consequently employs a large staff. After some years of trial and error, an approximation of the system described below has become routine.

[1] Clemens, K. and Walsh, R. J.: The Frequency of Immunization of Rh-Negative Women by Rh Antigens. Med. J. Australia, Oct. 30, 1954, p 707.

I. Responsibility of the obstet[illegible] staff (i.e., all those who deliver bab[illegible]

Any prenatal patient is to be typ[illegible] to $Rh_o(D)$ factor. This is by f[illegible] most likely factor (90%) in whic[illegible] compatibility between mother and [illegible] will result in hemolytic disease [illegible] newborn. It is the *one* essential s[illegible] be done before the patient is admi[illegible] the hospital. If any obstetrical pa[illegible] admitted to the hospital without [illegible] ing ascertained and available on [illegible] the patient should be typed on [illegible] sion. In primigravidas, presence [illegible] sence of atypical isoantibody sho[illegible] determined at the seventh month. [illegible] tiparas, a test for this should be [illegible] at the third month, and again at the [illegible] enth month for purpose of comparison of the levels, if present. The absence of antibody in the seventh month is no guarantee there will be no difficulty, but the presence of antibodies is a warning of probable difficulty. In the presence of antibody levels, more frequent samples for titration may be drawn subsequently to appraise changes, but these are not essential.

On admission to the hospital a red sticker or some similar attention-drawing mark is attached to the mother's chart. After delivery a similar sticker is attached to the infant's chart.

II. Responsibility of the pediatric staff (i.e., those who take care of the newborn).

When the baby is born, cord blood is taken directly to the blood bank where it is typed for $Rh_o(D)$ factor and a Direct Coombs test is done. If the Direct Coombs test is negative, it is not likely that the baby has hemolytic disease of the newborn, and nothing further is done unless signs of this disease appear. If the Direct Coombs test is positive, other tests are done, since the baby has hemolytic disease. In Rh hemolytic disease of the newborn due to $Rh_o(D)$ sensitization, a word of warning is necessary. Occasionally the red blood cells of a severely affected infant appear to be $Rh_o(D)$ negative, while the Direct Coombs test is positive. This apparent inconsistency is due to a very heavy coating of the infant's red blood cells by anti $Rh_o(D)$ maternal antibody, which prevents the usually observed clumping of $Rh_o(D)$ cells by anti $Rh_o(D)$ test serum. In such cases the Direct Coombs test is more important. It is also pos[illegible]le for the Direct Coombs test to be pos[illegible]e in cases where the mother is $Rh_o(D$ [illegible]ositive; in such case the blood fact[illegible] involved is one other than $Rh_o(D)$.

If the Direct Coom[illegible]est is positive, replacement transfusion should be performed wherever any one of the following conditions is also encountered:

(a) Prematurity — The premature infant is far more susceptible to kernicterus than the full-term infant.

(b) A history of a previous sibling with severe hemolytic disease of the newborn.

(c) Clinical icterus within the first six hours of life (and most with clinical icterus within the first twelve hours). These infants almost always develop a high serum bilirubin level.

(d) Hemoglobin less than 14 gm./100 ml. at birth.

(e) Reticulocytosis over 10%, or marked erythroblastosis.

(f) Cord bilirubin over 5 mg./100 ml. serum.

(g) If spectrophotometric studies are to be had, elevated levels of heme pigments other than bilirubin will give an indication of severity of illness. These are not generally available.

(h) High maternal antibody titer (level).

The preceding rules appear to involve a great deal of laboratory work, time consuming and fatiguing to both doctor and patient. However, the entire tabulation may be condensed to the following statement:

In the presence of a positive Direct Coombs test and any other of the factors listed, replacement transfusion is the treatment of choice. It is the unusual case which will require more than one or two tests to classify it. Indeed, the milder the case, the more laboratory work and observation will be required.

If the infant has a positive Direct Coombs test with no other positive findings, the serum bilirubin level must be determined at four to eight hour intervals in order to determine the speed of rise. *A rise of serum bilirubin approaching one mg./hr. is an absolute in-*

dication for replacement transfusion. Under these circumstances, do not wait until the bilirubin rises to a given critical level. A serum bilirubin of 10 mg./100 ml. at twelve hours or 15 mg./100 ml. at twenty-four hours is also an absolute indication. A level of 20 mg./100 ml. at any time is an indication for replacement transfusion.

The hemoglobin level should not be used as a test for the progression of this disease after birth. The bone marrow may produce (for the first day or two) enough red blood cells to maintain a constant hemoglobin level in the face of increasing red cell destruction, so that a maintained hemoglobin level leads to a false sense of security.

Hemolytic disease of the newborn due to antibodies other than $Rh_o(D)$ is more difficult to discover. To obtain compatible blood for replacement transfusion where the causative antigen of the hemolytic disease is unknown, it is necessary only to give blood compatible with the mother's serum. Compatibility determinations should be made using mother's serum and low titered Group O blood. Three methods of compatibility testing must be used together—the saline tube test, the high protein slide method, and the Indirect Anti-Human Globulin (Indirect Coombs) test.

In a recent study performed by one of the blood grouping laboratories[2], the following incidence of

molytic disease of the new m
nfants of Rh positive mo rs
gorized according to the f-
ding antigens are listed:

Antibody Specificity	*Number Cases*
hr'(c)	1
rh"(E)	
$rh^w(C^w)$	
hr, and rh"	
rh'(C)	
Fy^a	
hr"(e)	
$Rh_o(D)$*	
A or B	
Total	3-

* The mother in this instance was a Du variant.

The significant fact is that most of the above mothers had previously been transfused or were highly multiparous (i.e., 6 to 13 pregnancies). The maternal charts and the charts of infants born to mothers with such a history should also have an attention-drawing mark affixed to them and the same testing and observation exercised to protect these infants.

The first warning of disease usually noted in the nursery is manifested as an early icterus. For this reason nursery personnel should be indoctrinated with the need for the *immediate* reporting of observed jaundice and to watch for its occurrence. Then, a Direct Coombs test, a complete blood count, and a serum bilirubin are done. Maternal serum should be tested for evidence of antibody. It may not be possible to demonstrate maternal antibody with the limited facilities of the average laboratory.

[2] Schlutz, C.: Hemolytic Disease of the Newborn in Rh-Positive Mothers. Bulletin American Association of Blood Banks, 2: 194-195, May 1958.

For example, if the ABO system is involved (and this diagnosis frequently made with inadequate testing to eliminate the rarer antigen systems as culprits), the direct Coombs test will usually be negative and the maternal serum will have antibody in every case since it is present normally. In such case, *if no clear-cut serological evidence of hemolytic disease of the newborn is found, the serum bilirubin level and its speed of rise is the sole criterion for performance of a replacement transfusion, and the critical levels are the same as those aforementioned.* In borderline cases, it is safer (if the operator is experienced) to do the replacement transfusion than to withhold therapy. In this way, practical, immediate therapy may proceed without definitive serologic diagnosis.

All sera in every case of hemolytic disease of the newborn (samples from mother and baby) should be sent to a blood center for detailed testing, confirmation of diagnosis, and definition of antigen system. This will check results of the hospital laboratory, add knowledge and experience in the disease, and occasionally supply a rare antiserum from the mother which may be used for research purposes. (It will also protect the mother from incompatible transfusions in the future, should she need any.)

Certain elements of the actual performance of the replacement transfusion remain to be discussed. It is safer not to warm the blood but rather to keep the patient warm. It is essential that the operator have an alternative technique available in the rare case where the umbilical vein cannot be catheterized. If the patient has hepatosplenomegaly, cardiac failure is probably present in some degree, and blood should be withdrawn until the venous pressure is about 7 cm. water; then the exchange of blood should be begun. Enough calcium (as 10% calcium gluconate) should be given at intervals (1 to 2 ml. for every 100 ml. blood used) to prevent hypocalcemia, which is manifested by irritability before tetany appears.

Insofar as aftercare is concerned, the child should be kept in a heated bed, and routine nursery feedings may be started after twenty-four hours. Serum bilirubin levels at four to eight hour intervals are done to ascertain whether a repeat replacement transfusion is needed; 20 mg./100 ml. serum is the critical level. As soon as this danger is passed, and the child is otherwise in satisfactory condition, it may be discharged. Thereafter, weekly hemoglobin and microhematocrit levels should be done. This is necessary to follow the progressive anemia which usually occurs in these infants. The faster the weight gain, the more precipitous the drop in hemoglobin. This is due to several factors: the bone marrow is temporarily exhausted and does not begin to form erythrocytes for several weeks after birth; the life of transferred cells is shorter than the infant's own; so that a gradually decreasing number of erythrocytes in an increasing body mass and circulating volume manifests itself as anemia. Any antibodies remain-

ing after repla ment therapy may also add to anemia by the destruction any cells newly formed.

If the in remains healthy, the drop in hemoglobin, even to 6 or 7 gm./100 ml. blood, does not constitute an emergency, but care should be taken to prevent infection. If the child shows evidence of illness in the presence of anemia, transfusion is necessary. If not, the anemia will usually begin to correct itself by six to eight weeks of life. If transfusion is necessary, it does not matter now whether Rh positive or Rh negative blood is used.

A COOPERATIVE IMMUNOSEROLOGICAL LABORATORY PROGRAM FOR THE CATHOLIC HOSPITAL ASSOCIATION[3]

The Catholic hospital has a moral obligation to seek out the most modern and scientific methods and to apply them to the proper care of its patients. Since there is no substitute for experience in this field of immunoserology, experience can be gained only by properly testing large numbers of blood samples. Small facilities rarely have enough well trained people or equipment to perform certain special tests, and only by cooperating with larger facilities can these tests be done accurately for them.

A cooperative program now exists which will permit such smaller

[3] Schlutz, C. Institute for Applied Immunology, Cibcago, Ill.: Personal communication (A summary of an official program of the Medical Technology Committee of the Catholic Hospital Association of the United States and Canada).

holic hospitals to send lab ca- specimens (if they are n at nt equipped to exa ne to specially trained nd ed institutions which ve set up to perform these pe- rocedures.

s program is in its rst ph An immunoserolog al tra g program to instruct m- bers of religious communities a ve high degree of skill thro gh "workshop" type meetings has en held. The religious, technic ns and pathologists attended d ly sessions of six hours each. C ly fourteen laboratory persons, e ch from a different facility, v re trained because it was felt at such a limitation permitted ry close supervision of workers nd resulted in higher levels of ill in the performance and un erstanding of the procedures n- volved.

A coordinating laboratory ill now send unknown test sample to each facility. Successful identif a- tion and testing of these sam les by the trainees working in t ir own laboratories will start ano er phase of the program; namely, n- vitation of "satellite" hospitals to send blood samples to these "q al- ified" laboratories for testing.

The laboratory procedures t be initiated are:

1. Maternal Rh sensiti ity tests and titers.
2. Phenotyping or deter in- ation of heredity trans it- ting characteristics of he father.
3. Detection and identifica- tion of atypical antibod es.
4. Other special serodiag tic and consultation ices.
5. A serum exchange gram.

Cooperation between the " fied" laboratories and the ho expected to cooperate wit will be solicited by the M Technology Committee Catholic Hospital Associa a request to the admini each hospital asking for operation in sending blood ples to the "qualified" labora for testing. The "qualified" la atories will eventually instruct "satellite" hospitals i recommend- ed procedures for Rh blood grouping, and compatibility tests so that the physician c be assured that his hospital will be set up to provide the maximum scientific training and experience for the needs of his p ents, and that only experienced d informed personnel will be forming vital immunoserological tests.

NOTE: Because most hospitals will have fewer than twenty cases of hemolytic disease of the newborn in a year, it would be better if a few members of the medical staff agreed in advance to care for these patients when the need arose. Thus, one man would always be available, and the experience needed for the acquisition of technical skill would not be spread too thinly among too many people.

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