Sturge-Weber Syndrome.—N. F. ELLIOTT BURROWS, B.M. (for W. G. WYLLIE, M.D.).

A. McK., aged 1 year. Born with capillary angioma over entire left side of face and scalp. History of frequent twitchings, and turning of the eyes generally to the right. Pneumo-encephalography revealed a gross defect inside the skull on the side corresponding to the angioma.

Dr. F. Parkes Weber considered the diagnosis completely proved. The typical calcification would probably develop later. In regard to the relative parts played by Dr. W. Allen Sturge (1879), the pathologist, Dr. S. Kalischer (1901), and others, in the discovery of the syndrome, *see* F. P.Weber, *Rare Diseases and Some Debatable Subjects*, second edition, London, 1947, p. 9.

Dr. Parkes Weber continued: The condition is obviously a result of dysplastic development (partly definitely "hamartomatous") of the vascular elements of the affected portions of the skin and lepto-meninges (with underlying surface of the cerebral cortex). Sometimes there is congenital glaucoma (buphthalmus) on the same side as the cerebral lesion—evidently of analogous dysplastic origin. Apart from a possible inborn tendency in some families to dysplastic and hamartomatous development of various kinds, the condition seems not to be hereditary, but seems more likely due to some local accident of unknown causation, affecting the embryo during early intra-uterine life. Cases of the syndrome are by no means so rare as was formerly supposed.

Exophthalmic Goitre.—J. M. ALEXANDER, M.R.A.C.P. (for W. G. WYLLIE, M.D.).

J. L., aged 9 years, the second child of nervous parents, started having night terrors about 6 months before admission, when eyes became protuberant and pulse very fast. Also had profuse sweats.

On admission: Enlargement of thyroid gland, and fibrillary tremor of outstretched hands.

POSTSCRIPT (22.7.47).—Thyroidectomy has been performed. Symptoms have disappeared and eyes now appear normal.

Neurofibromatosis.—J. M. ALEXANDER, M.R.A.C.P. (for W. G. WYLLIE, M.D.).

M. B., aged 10 years, only child of healthy parents, born with two café-au-lait spots on buttocks and one on chest.

In 1941 had a fall; left shoulder became swollen two weeks later; glandular swelling in this region. Biopsy: Neurofibromatotic tissue. Given deep X-ray treatment, but three months later egg-shaped swelling underneath outer part of left clavicle re-appeared. Café-au-lait spots increasing in number.

Pseudo-hypertrophic Muscular Dystrophy.—J. M. ALEXANDER, M.R.A.C.P. (for W. G. WYLLIE, M.D.).

G. Y., aged 5 years, has had difficulty in walking, particularly upstairs, for three years. "Climbs up himself".

Weakness of proximal muscles of legs and hypertrophy of calves.

[*May* 23, 1947]

Erythroblastosis Fœtalis or Hæmolytic Disease of the Newborn

(Abstract of Illustrated Talk)

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RECENT and more widespread interest in erythroblastosis fœtalis or hæmolytic disease of the newborn has led to the erroneous impression that this is a new condition of recent origin. Actually it was well described, in the English literature, before 1900, being then recognized in the form of fœtal hydrops. Between 1900 and 1910, there were numerous articles, published in this country, dealing with familial icterus gravis, another manifestation of the same disease, and even the severe anæmia and

erythroblastæmia were recorded as important features. Next, interest shifted to the pathology, studied and fully described by German investigators, between 1910 and 1920. Finally, the anæmia developing unexplainably in newborn infants was considered a new entity, shortly after 1920.

Our own interest in and experience with erythroblastosis fœtalis dates back twenty years, and in 1932 we collected and published records of 20 infants, suffering from œdema at birth, or jaundice and anæmia shortly after birth, splenomegaly and erythroblastæmia—all being manifestations of a single underlying morbid process.

The discovery of the Rhesus blood factor in humans in 1940 and in 1941, its important relation to erythroblastosis fœtalis, once more focused attention on this disease. In the succeeding five years, so much has been written on the Rh factor, and the disturbances which result from it, that it is worth while reviewing the subject and considering what is established fact and what is hypothesis.

The Rh blood factor is present in the red cells of 85% of the white population and absent in 15%. Since it is foreign to the system of the latter group, the Rh factor can act antigenically to start isoimmunization, when introduced into the body, either by transfusion or, in women—and even then only in a small percentage of them—by pregnancy. The antibodies produced by the Rh-negative individual, after sensitization, are agglutinins, capable of clumping and eventually destroying Rh-positive red cells. It usually requires one or more transfusions of Rh-positive blood into an Rh-negative patient, and an interval of two weeks or more, before a hæmolytic reaction is produced.

In women, subject to sensitization via pregnancy, even a first transfusion of Rh-positive blood may cause a serious untoward reaction. The factors which govern this are, first, the combination of an Rh-negative mother and an Rh-positive father, to whom are born Rh-positive children. These may serve to sensitize the woman when fœtal erythrocytes or tissues enter her circulation during gestation. Thereafter, the transfusion of this Rh-negative woman with Rh-positive blood will lead to a hæmolytic crisis.

Actually the danger of isoimmunization of the Rh-negative woman by pregnancies involving an Rh-positive fœtus is relatively small, since about 13% of all marriages are between an Rh-negative woman and an Rh-positive man, but only 1 in 150 deliveries produces an infant with erythroblastosis fœtalis, and even so the first Rh-positive infant almost always escapes. This means that less than one such woman in twenty need be concerned about becoming sensitized through pregnancy alone. However, a single transfusion of Rh-positive blood, followed by pregnancies, will increase the chances of trouble from 5% to over 50%.

Another hazard of isoimmunization following transfusion affects the fœtus. If an Rh-negative woman is given Rh-positive blood, the antibodies which develop may produce hæmolytic disease in any subsequent Rh-positive fœtus, even if it is a firstborn.

The modes of Rh sensitization of the Rh-negative woman then are, first, through transfusion of Rh-positive blood, second, through repeated pregnancies with Rh-positive babies, and third—a little appreciated menace—through the injection intramuscularly of even small amounts of Rh-positive blood, a mode of therapy fortunately now discarded for the treatment of hæmorrhagic diseases, pernicious vomiting of pregnancy and stubborn dermatitis. Although such intramuscular blood probably does little or no harm alone, if followed by Rh-positive pregnancies, even years later, it may be important in initiating isoimmunization.

The woman who, through any of the above mechanisms, has become sensitized against the Rh factor, may face several serious problems in subsequent child-bearing. If she is fortunate enough to marry an Rh-negative man—about one chance in seven—she need have no fears, since Rh-negative children will not be affected. If the sensi-

tized woman has an Rh-positive husband who is homozygous, i.e. carries two Rh-positive genes, every infant will be Rh-positive and will be affected, usually with increase in severity of the disease. If the husband is heterozygous, Rh-negative children are possible and only the Rh-positive infants may have erythroblastosis fœtalis.

It is important, therefore, not only to determine the Rh type of every recipient of blood and every woman during child-bearing, but if Rh sensitization is detected in the woman, to test the husband's blood for homozygosity or heterozygosity and so be able to prognosticate the chances of successful pregnancy. For such special tests, the ordinary simple Rh-typing serum must be supplemented with special specific anti-Rh serums which can only be found in certain diagnostic laboratories.

Prior to 1944, tests for sensitization of Rh-negative individuals were often quite unsatisfactory since, even in instances of proven hæmolytic transfusion reaction or definite erythroblastosis fœtalis, the serum of the affected individual often failed to disclose Rh agglutinins. In 1944, new tests were developed which detected antibodies coating Rh-positive red cells or blocking their further agglutination in saline suspension, or clumping them only in protein media. These new and more complex antibodies were named "incomplete antibodies", "blocking antibodies" or "hyperimmune antibodies". The latter name arose from the finding that if human experimental subjects were injected repeatedly with Rh-positive blood cells, their serum first contained ordinary agglutinins acting against Rh-positive red cells suspended in saline. These were named "early antibodies". With continued injections, such Rh-negative persons gradually lost their simple Rh agglutinins, but developed the "incomplete" or "blocking" form which no longer agglutinated Rh-positive cells in saline but did become attached to such cells and could clump them in plasma, serum, or albuminous suspension media, and, of course, did produce agglutination within the body. These were named "hyperimmune antibodies". They are more complex, much more stable and long-lasting and probably can produce more damage, especially to Rh-positive infants developing erythroblastosis fœtalis.

Just as in these experimental subjects stimulated by blood injections, Rh-negative women bearing Rh-positive infants, tend first to develop early saline-acting agglutinins but with succeeding pregnancies, form more of the hyperimmune antibodies and, later, only this form. However, the form of Rh antibody and its concentration or titre bear no direct relation to the severity or the type of erythroblastosis fœtalis which develops in the child of the sensitized woman.

Certainly only the roughest parallelism is to be found between the type of Rh antibody and its amount during and after pregnancy, and the form of the disease or its severity in any given infant. In general, the hyperimmune and high titred Rh antibodies are found in association with the more serious or more often fatal types of hæmolytic disease in the newborn. But a prognosis based on antibody tests and titres, in any given case, must be offered with reservations.

With regard to the clinical problems faced by the pædiatrician or practitioner, our own experience began about twenty years ago, when we first treated newborn infants with jaundice and anæmia, using compatible blood from the father (therefore Rh-positive) for transfusion. Many transfusions were often necessary since the red cells did not seem to survive long, but eventually a majority of such children recovered, especially if they had no complications such as severe jaundice, œdema, diffuse hæmorrhage or cardiac failure with secondary pneumonia. Over a period of fifteen years, including the infants who were born dead and diagnosed by the pathologist, we found a gross mortality of about 40%. Several features were intriguing then, just as they are now. Often, newborn infants displayed very little anæmia, but developed early and severe jaundice. Transfusion did not materially benefit these and sometimes they developed signs of brain damage, about the fourth or fifth day of life,

and fortunately did not recover. If they did improve, marked developmental retardation and muscle unbalance might result. Pathologically, kernicterus was usually found in such patients. This is a diffuse and symmetrical staining of nerve cells. It is unrelated to simple mechanisms such as intravascular thrombi or agglutination of red cells.

The tendency for the recurrence of infants with erythroblastosis fœtalis was always disturbing, especially since the disease became progressively more severe in succeeding siblings. Often, this resulted in the birth of hydropic stillborns, with severe anæmia, tremendous splenomegaly, hepatomegaly, and dilated hearts. Then again, a single child might escape serious damage and exhibit only moderate and easily repaired anæmia.

Not all of these clinical observations have been explained by the discovery of the Rh factor and the knowledge of the action of anti-Rh agglutinin on the Rh-positive infant's red cells. The serologists have tended to oversimplify the pathogenesis of the disease and draw too many analogies between what happens in the baby and what can be demonstrated in the test-tube.

With the disclosure of the role of maternal Rh antibodies in damaging the infant's Rh-positive red cells, it seemed logical to use only compatible Rh-negative blood for transfusion of the anæmic infant with erythroblastosis fœtalis. Such transfusions were given as frequently as needed, always into an easily accessible superficial vein, in amounts of about 10 c.c. per pound of body-weight, using a pressure system. More may be given, but if the infant has cardiac dilatation or a tendency to develop petechial hæmorrhage, sudden collapse may occur during large transfusions from cardiac decompensation or diffuse hæmorrhage.

During a period of about three years when our treatment consisted only of repeated small transfusions of Rh-negative blood, the gross mortality from erythroblastosis fœtalis seen in our clinic was about 30%. This improvement may have been due to earlier recognition and treatment of such infants as well as the use of Rh-negative blood transfusion.

By 1944, most of the obstetricians were well aware of the dangers of Rh antibodies in Rh-negative women, and were testing such patients more regularly. We had organized several prenatal clinics for the care of these problems and were following the titres in sensitized women throughout pregnancy. It was always distressing to detect a rising or a high titre, to wait for the delivery of the infant at term, and to have the infant succumb *in utero* only a few weeks from term, or even shortly after birth. In such cases, it seemed reasonable therefore to try to deliver the sensitized woman two or three weeks before term. During the years that this has been practised in conjunction with frequent transfusions of Rh-negative blood, as needed, the gross mortality has been lowered to 20%.

Finally, another improvement in therapy was attempted. We had shown for some time that the erythroblastotic infants who were most seriously ill or suddenly collapsed after being quite normal in appearance at birth, usually showed free maternal antibody in their cord blood. It seemed likely that this continued acting in the child's system and caused the sudden change for the worse in succeeding days. In addition, many of the babies' red cells were proved to be coated with maternal antibody. The removal of as much as possible of the affected infant's circulating blood, shortly after birth, in proper cases, seemed desirable.

The first attempts to do an early exsanguination-transfusion were complicated by mechanical difficulties. The longitudinal sinus is a dangerous vessel to puncture blindly, particularly in a newborn infant, whose head is moulded out of shape with normal anatomic relations distorted. Peripheral veins are small and fragile. Even arteries may be too small for ready cannulization and the exposure of a sick newborn infant for an hour or two while vessels are exposed and used may be a cooling and

shock-producing procedure. Needles and tubing tend to clog as the blood thickens or the flow slows. The injection of heparin to prevent clotting is a decided risk in an infant who usually has hypoprothrombinæmia and a well-marked bleeding tendency.

Only through the development of special plastic catheters and their use in the umbilical vein were all these difficulties resolved and the techniques of exsanguination-transfusion made easier.

The indications for this operation have been fixed as follows until such time as sufficient data have been accumulated to evaluate the results. If the mother has been known, or is quickly demonstrated, to have Rh antibodies in her serum, and the infant shows definite clinical signs of erythroblastosis fœtalis, at or shortly after birth, treatment is begun at once. If the infant born to a sensitized mother exhibits no symptoms at birth, but is found, by immediate testing of the cord blood, to be Rh-positive and to have detectable Rh antibody still present in its serum, treatment is also indicated. If the infant not only looks well, but though Rh-positive has no free maternal antibody by suitable tests, no treatment is given at present. To date, about ten such infants have had no serious anæmia later, although a few of them have required single transfusion.

The results of exsanguination-transfusion have been quite satisfactory in many cases. Infants, very sick and anæmic at birth, have survived. Most of them have been ready for discharge with the mother in seven or eight days. Only a few have developed moderate anæmia by the third week and required another small transfusion.

Statistically, our mortality in about fifty sick infants has been near 10%. Several babies who succumbed had atelectasis, intracranial hæmorrhage and other signs of immaturity, rather than erythroblastosis fœtalis.

Much more study and data are needed before the problems of the management of blood incompatibility—antibody action between mother and child—and the best care of the newborn infant with hæmolytic disease are all solved. Notable advances have been made. But there is no justification for complacency or surety. Neither is there reason for undue anxiety when faced with the problems of Rh incompatibility.

[*June* 14, 1947]

MEETING HELD AT ROYAL VICTORIA INFIRMARY, NEWCASTLE-UPON-TYNE

The following papers were read:

Problems in the Organization of a Professorial Unit.—Professor J. C. SPENCE, M.C., M.D.

A Method of Recording Neonatal Infections in a Maternity Hospital.—MARY TAYLOR, M.D.

Prematurity in an Industrial Town.—F. J. W. MILLER, M.D.

Treatment and Prognosis of Bronchiectasis.—ALAN OGILVIE, M.D., F.R.C.P.

A Consideration of Acute Intussusception in relation to Medical Teaching.— DONALD COURT, M.R.C.P.