streptomycin only than in those on combined therapy; among the latter it was higher in those patients for whom the daily dose of P.A.S. was 5 or 10 g. than in those receiving 20 g. daily. The clinical significance of streptomycin resistance is discussed. In patients with a similar initial condition the results were worst in those who developed high degrees of drug resistance. Moderate drug resistance seems to be of less clinical significance.

This report is based on the work of clinical investigations directed first by the Medical Research Council Streptomycin in Tuberculosis Trials Committee, and then by a Joint Subcommittee composed of members from the parent committee and from the Research Committee of the British Tuberculosis Association. In these trials a large number of clinicians and pathologists have taken part. Their names appear in the report of each trial. To them the gratitude of the medical profession is due; only by their constant adherence to a centrally devised scheme and by a most remarkable team spirit on a large scale have these investigations been possible.

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KERNICTERUS WITHOUT PREMATURITY OR BLOOD-GROUP INCOMPATIBILITY

BY

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Blood-group incompatibility was formerly believed to be a necessary precursor of kernicterus (Wiener and Brody, 1946; Claireaux, 1950). However, Aidin, Corner, and Tovey (1950), and also Zuelzer and Mudgett (1950) established the occurrence of kernicterus in premature infants without blood-group incompatibility. Zuelzer and Mudgett (1950) described a number of cases in which serologically compatible premature babies died of kernicterus, and also eight cases in which babies with birth weights of over 5½ lb. (2.5 kg.) showed presumptive evidence that no blood-group incompatibility existed, although none were first pregnancies. In only one of these eight instances does evidence for serological normality seem conclusive, in that direct Coombs tests were negative on the infants' cells, ABO groups were compatible, and no abnormal antibody was present in the maternal serum, either before or after delivery. Aidin, Corner, and Tovey (1950), although they included one baby whose birth weight was over 5½ lb. (2.5 kg.) in their group of kernicteric infants without blood incompatibility, gave no serological data for this case.

Thus, although the occurrence of kernicterus in the absence of blood-group incompatibility seems established in premature babies; only one unequivocal instance of this lesion occurring without either blood

incompatibility or prematurity has yet been published. For this reason the following case is presented in which kernicterus occurred in a first-born infant, weighing 6 lb. 6 oz. (2.9 kg.) at birth, in whom blood-group incompatibility is believed to have been excluded, so far as is possible at the present day, by serological testing.

Case History

The patient was a first baby, born in the Obstetric Hospital at University College Hospital on July 2, 1951. The mother was a primipara aged 21. Her Wassermann reaction was negative, and there were no previous abortions or stillbirths, blood transfusions or other injections of blood or serum. The antenatal period was normal. Spontaneous labour occurred at 39 weeks and 1 day, followed by a normal vertex delivery. The first stage occupied three hours and the second stage 15 minutes. There was no foetal distress. The infant was a girl whose birth weight was 6 lb. 6 oz. (2.9 kg.). She was cyanosed at birth and remained so for several hours, but cried lustily at once and breathed normally within one minute. At the age of 3 hours the infant became restless, with an anxious facies and a high-pitched irritable cry. There was also pronounced inspiratory recession of the lower ribs with poor air entry at both bases. A diagnosis of intracranial irritation and atelectasis was made, due probably to a precipitate second stage of labour. The baby was transferred immediately to the resuscitation unit, where she was nursed in 50% oxygen and treated prophylactically with intramuscular penicillin, 100,000 units twice daily.

She remained irritable for the first 24 hours, but then her general condition improved, the cyanosis disappeared, and she began to suck. Oral feeding was started at 24 hours with expressed breast milk given three-hourly. At 36 hours jaundice first became apparent and deepened progressively for the next eight days, the spleen being just palpable from the third day onwards, when a peripheral blood count at 72 hours showed: red cells, 5,480,000; Hb, 110%; white cells, 12,800 (P. 63%, L. 27%, M. 7.5%, E. 2.5%). There were 1.5 normoblasts per 100 white cells. In view of the early onset of a deepening jaundice, with a negative direct Coombs test on the infant's cells (see Serology), a careful search was made for infection, but this revealed only a transient seropurulent umbilical discharge on the sixth day which disappeared 24 hours later but grew on culture *Bact. coli* and a penicillin-resistant *Streptococcus faecalis*. A course of oral sulphadimidine (total 4.5 g.) and chloramphenicol (total 1.7 g.) was therefore given for the next few days. The urine contained on one occasion 0.5 g. of albumin per litre, with occasional pus cells and three red blood cells per 1/6 microscopical field, with numerous epithelial and some granular casts. A transient apical systolic murmur was heard on the fifth and sixth days.

On the morning of the fifth day her general condition deteriorated rapidly with onset of head retraction and drowsiness, punctuated at intervals by athetoid movements of the limbs and occasional myoclonic twitchings. The anterior fontanelle was not full, but tone appeared to be increased in the limbs. A lumbar puncture produced only a small quantity of xanthochromic fluid, insufficient for chemical estimation, but with no excess of white blood cells or organisms in the Gram-stained centrifuged deposit. The baby became increasingly lethargic and refused to suck; intravenous fluids were given on the fifth day for 24 hours in the form of half-strength Hartmann's solution with 5% glucose. In view of the deepening jaundice, amino-acid supplements in the form of "pronutrin," 10 g., and choline chloride, 250 mg., were given daily by stomach tube, together with "becosym," 0.5 ml., and "synkavit," 10 mg. intramuscularly. By the sixth day the infant became febrile—101° F. (38.3° C.)—and was in a stage of opisthotonos and had two small generalized convulsions. All feeds had to be given by tube and were followed frequently by respiratory distress and cyanotic attacks, while large quantities of

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blood-stained mucus were aspirated from the pharynx. From the sixth day to the tenth day the infant became progressively weaker and more jaundiced and the temperature fluctuated from 100 to 103° F. (37.8 to 39.4° C.). The central nervous signs remained unchanged, but on the tenth day breathing became irregular and gasping, and death supervened from respiratory failure on the morning of the eleventh day. Terminally the jaundice had subsided slightly, but was still deep in the skin and conjunctivae.

Serology

Infant.—Blood group O. Rh-positive (D+). Direct Coombs test negative at 72 hours of life and negative on infant's cells taken one hour after death. No abnormal blood-group antibodies discovered in infant's serum taken one hour after death, using cells from a panel of known Rh-positive and Rh-negative donors and other mixed genotypes.

Mother.—Blood group O. Rh-positive (D+). Indirect Coombs test negative, using mother's serum taken 11 days post partum and baby's cells taken one hour after death. Indirect Coombs test negative, using mother's serum taken 11 days post partum and cells from a known panel of Rh-positive and Rh-negative donors and other mixed genotypes. Indirect Coombs test negative, using mother's serum taken 14 days post partum (neutralizing with A-substance) and father's cells.

Father.—Blood group A. Rh-positive (D+).

Post-mortem Findings

External examination revealed the body of a full-term female infant weighing 2,530 g. Crown-heel length was 500 mm. and crown-rump length 335 mm. The skin showed definite jaundice, as did the conjunctivae. No maceration or oedema was present, the cord site was healthy, and the pupils were equal.

Respiratory System.—The pharynx, larynx, trachea, and main bronchi appeared normal and the airway was clear. The pleural spaces were free of fluid, but the pleural surface of both lungs showed scattered fresh petechiae. The lungs themselves were pale in colour and exhibited some surface emphysema. Their cut surfaces showed no evidence of consolidation, and portions from all lobes floated in formal-saline. The thymus was normal in appearance and free of haemorrhages.

Cardiovascular System.—The heart and great vessels were normal, apart from a few petechiae on the pericardial surface of the ventricles. The ductus arteriosus was barely patent and the foramen ovale widely patent.

Gastro-intestinal System.—Normal apart from congestion of the gastric mucosa.

The liver was of normal size, but was a deep olive green in colour. The surface was smooth and the lobular pattern normal for a neonate. The consistence appeared to be slightly firmer than is usual. The spleen weighed 10 g., which is within normal limits. The Malpighian follicles were not prominent but the appearances were otherwise normal, as was the consistence. The pancreas and adrenals were normal.

Biliary System.—The gall-bladder contained very viscous dark-green bile and the bile ducts were patent. No other abnormality was present. The kidneys showed "bilirubin infarcts"—that is, heavy deposits of bright-orange material arranged in linear streaks in the pyramids and as masses around the renal papillae.

Central Nervous System.—On opening the cranial cavity extensive haemorrhage was found localized to the temporal and parietal regions of both sides. This blood was for the most part still fluid, but its viscosity revealed that a good deal of its water content had been resorbed. The haemorrhage was both subarachnoid and subdural, and much of it remained adherent to the dura of the overlying cranial bones when these were reflected, the remaining blood

covering the lateral aspect of the temporo-parietal lobes. Apart from one or two small areas of fraying in the tentorium, this membrane, together with the falx, dural sinuses, and vein of Galen showed no sign of damage, but some blood was present beneath the tentorium around the anterior and lateral margins of the cerebellar hemispheres. No bleeding into the ventricles of the brain had occurred. Section of the brain revealed numerous areas of bright-yellow pigmentation in its substance. This staining was visible in the basal ganglia in the thalamus, caudate, and lentiform nuclei, in the flocculus and dentate nucleus of the cerebellum, in the uncus and hippocampus, in the quadrigeminal nuclei, in the olives of the medulla, and in the floor of the fourth ventricle.

The diagnosis was traumatic intracranial haemorrhage, kernicterus, and jaundice.

Histological Examination

The lungs showed good aeration, with patchy emphysema and exudate in the lumen of some bronchioles, and small bronchi consisting of necrotic material, polymorphs, and mononuclear cells, without evidence of inflammation in the bronchial walls or lung substance. No evidence of erythropoiesis was present. The liver showed extensive "bile thrombi" in the biliary canaliculae and a mild degree of fatty infiltration. Haemopoiesis was practically absent and there was no evidence of hepatic necrosis or fibrosis. The spleen showed a good deal of broken-down blood pigment, but no more than is often found in the neonatal period. Scattered haemopoiesis of both red and white cells was present and lymphoid follicles were few in number, while the pulp was congested.

The kidney was congested and pigment granules were present, both lying free and within the epithelium of the collecting tubules. The pancreas, adrenals, and heart muscle showed no abnormality. Sections of the stomach wall revealed no evidence of inflammation. Paraffin sections of the affected portions of the brain, prepared in the standard way and stained with haematoxylin and eosin, showed no abnormality.

Discussion

The most widely accepted view of the pathogenesis of kernicterus is a dual-factor hypothesis in which the brain cells of the basal ganglia and other regions are rendered susceptible by some form of focal damage and then take up bile pigment from a coexistent hyperbilirubinaemia. In cases associated with blood-group incompatibility it has been suggested that this damage to brain cells occurs as a result of antigen-antibody reaction within the cells, or else is due to cellular anoxia caused by the presence of agglutination thrombi in the local capillaries (Wiener and Brody, 1946). Abnormally increased permeability of vascular endothelium in the brain due to capillary damage has also been postulated as a cause of kernicterus (Richards, 1951).

It now seems, however, that blood incompatibility is not an essential precursor of kernicterus (Aidin, Corner, and Tovey, 1950; Zuelzer and Mudgett, 1950), and that brain damage capable of making nerve cells permeable to bile pigment may also possibly occur as a result of hypoglycaemia, or even secondary to liver disease (Pärsons, 1947), assuming that some relationship exists between liver damage and the central nervous system as in Kinnier Wilson's disease. Liver immaturity may certainly be a factor in the kernicterus of premature infants, many of whom have hyperbilirubinaemia and sometimes also hypoglycaemia (Norval, 1950) in the early neonatal period.

In the case reported here the major disorder, apart from kernicterus and jaundice, was subdural and subarachnoid haemorrhage. Assuming that prior damage to nerve cells, as discussed above, is necessary for kernicterus to develop, it may be that the brain cells of the infant were injured either as a result of compression caused by the haemorrhage within the cranial cavity, or by direct trauma or indirect damage following vascular injury incurred at the time of

birth. The severe jaundice appears, for want of evidence to the contrary, to have been of the "physiological" type, which is widely held to be a result of inadequate liver function. The presence of neonatal hepatitis was ruled out histologically and no significant infection was found anywhere.

Whatever the factors that led to kernicterus in the present case, it seems that a great deal of evidence now exists for the occurrence of symptomatic kernicterus as distinguished from a similar condition arising in conjunction with blood-group incompatibility. Thus a tentative aetiological classification of kernicterus may be put forward as (1) blood-group incompatibility; (2) a mixed group, comprising principally prematurity, and also severe infection, congenital anomalies, and maternal diabetes; and (3) cerebral damage following birth trauma.

Summary

A case of kernicterus is described in a full-term first-born infant in whom blood-group incompatibility was absent. The possible aetiology of the lesions is discussed, with particular reference to a coexistent intracranial haemorrhage.

Our thanks are due to Dr. B. E. Schlesinger and Dr. R. E. Bonham Carter, under whose care the baby was treated, and to Professor G. R. Cameron, for their advice. We are also grateful to Dr. Plaut, of the North London Blood Transfusion Service, for carrying out the serological testing.

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A STUDY ON THE A FACTOR AS A CAUSE OF HAEMOLYTIC DISEASE IN PREMATURE BABIES

BY

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The view that anti-A and anti-B, as well as anti-Rh, can cause haemolytic disease of the newborn has been the subject of much controversy. The most common arguments against this view are based on the presumption that the abnormally increased titre of anti-A or anti-B antibody is the result of non-specific stimulation rather than a true iso-immunization such as occurs in the Rh system. Wiener (1951) thought that all the alpha and beta antibodies were of heterogenetic origin.

In recent years such arguments have lost some of their force because of accumulating evidence that there exist at least two varieties of A and B antibodies—namely, the complete (bivalent) and incomplete (blocking, immune, or univalent) ones. The behaviour of incomplete A and B antibodies is comparable to that of Rh

blocking antibodies (Boorman and Dodd, 1946; Polayes and McNally, 1948; Witebsky, 1948, 1949; Hubinont, 1949; Wiener *et al.*, 1949).

This report is designed to furnish additional evidence of sensitization to the A factor as a cause of foetal erythroblastosis resulting in premature birth and neonatal death.

Materials and Methods

Cord blood from the affected babies was examined for the A, B, M, N, C, D, E, c, and e antigens; red- and white-cell counts, and differential and haemoglobin estimations were also performed. The serum was titrated for the A, B, and Rh antibodies, and the icterus index was determined. Gross post-mortem examinations were also made on the infants, followed by histological studies.

The blood of the parents was examined for the same blood-group antigens; the mother's serum was tested for anti-A, B, Rh, Kell, S, Le^a, and Fy^a agglutinins, and, in addition, titrations were carried out upon it for complete and incomplete A and B antibodies.

Four methods were employed to detect and titrate the antibodies: (1) the conglutination method of Wiener *et al.* (1947), (2) the trypsinized red-cell method (Morton and Pickles, 1947), (3) the anti-human-globulin test of Coombs *et al.* (1945), and (4) the neutralized serum method of Witebsky and Engasser (1949). Methods 2 and 3 were modified so that they could be applied to the ABO system.

Case 1

A white woman aged 19, a primigravida, was admitted to the department of obstetrics and gynaecology, Quincy City Hospital, because of irregular labour pains in about the 33rd week of gestation. Menstruation had begun at the age of 11, the cycle being 26 to 30 days, with periods lasting from four to six days. She was married in September, 1949, and strongly denied abortion prior to this pregnancy. To the best of her knowledge she had never felt menstrual moulimina except at the onset of the present gestation, and had never received any injection of or had been transfused with whole blood or with blood products. In childhood she had been vaccinated against whooping-cough and diphtheria.

Physical examination showed a pregnant woman weighing 179 lb. (81.2 kg.), without oedema, anaemia, or jaundice. Temperature, respiration, and pulse were within normal limits. Her blood pressure was 130/78, 120/80, and 120/80 mm. Hg on three consecutive days. A serological test for syphilis (Hinton) gave a negative result. The erythrocyte count was 4,800,000 per c.mm., haemoglobin 14.2 g.% and white blood cells 8,500 per c.mm.; the differential count was non-contributory.

Spontaneous delivery took place under anaesthesia and was uneventful. Five days after parturition the fasting blood sugar was estimated at 110 mg. per 100 ml. of blood. Urinary examination for casts, albumin, blood, and sugar gave negative results.

The baby, a boy, was born on June 13, 1950, and weighed 4 lb. 4 oz. (1,920 g.); he had no deformity. The umbilical cord and sclerae were reported to be moderately icteric. Cutaneous petechial haemorrhages were observed at the extremities. The heart sounds were normal, but there were diminished breath sounds in the left chest. The liver and spleen were not palpable. He was kept in an incubator at 90° F. (32.2° C.), the treatment consisting of injections of "crysticillin," 30 ml. of whole compatible blood, calcium gluconate, vitamin K, and nikethamide. He died after three days and seven hours.

His red-cell count was 3,800,000 per c.mm., haemoglobin 13 g.%, and white-cell count 18,000 per c.mm.; the differential count gave 1% promyelocytes, 2% myelocytes, 4% band forms, 37% segmented cells, 1% basophils, 9% eosinophils, 6% monocytes, and 40% lymphocytes. The stained