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Part I.—Original Articles.

THE Rh FACTOR: ITS ROLE IN HUMAN DISEASE, WITH PARTICULAR REFERENCE TO MENTAL DEFICIENCY.*

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MANY workers on both sides of the Atlantic have done intensive work on the Rh factor since its discovery was first published in 1940. The great majority of these workers have been concerned essentially with its influence on physical disease, the mental aspects being either ignored entirely or only lightly touched upon.

Recent work in America, however, has suggested that possibly the Rh factor may play an important part in the aetiology of some cases of mental deficiency, at present of unknown origin. The large number of cases of mental deficiency lends urgency to any research which will throw light on the cause of this distressing condition, as prophylaxis is even more essential in mental deficiency than in most other forms of disease. If a means of preventing even a small proportion of the present number of defectives from being born could be found, the results would be well worth while from an economic and social point of view, apart altogether from the avoidance of the distress caused to parents who have the misfortune to produce a mentally defective child.

EARLY THEORIES ON INCOMPATIBILITY OF FOETAL AND MATERNAL BLOOD.

The history of the development of the iso-immunization theory in relation to the Rh factor as the cause, in the vast majority of cases, of erythroblastosis foetalis and its sequelae is extremely interesting in that it shows how the truth was anticipated long before it was actually proved.

*Adapted from a Thesis for the M.D. Degree, accepted by the University of Edinburgh.

McQuarrie (1923) suggested there was a relationship between the incompatibility of maternal and foetal blood on the one hand and the development of eclampsia, or pre-eclamptic toxaemia, on the other. He proved that in 23·3 per cent. of the cases he studied the mother's serum agglutinated her own infant's red cells. The incompatibility referred, of course, to the ordinary blood groups.

Stimulated by this article Ottenburg (1923), also writing on eclampsia, referred to the work of Dienst in 1906. Dienst injected methylene blue solution into the umbilical artery or vein of the still attached placenta of women at the end of childbirth. In some of these women the dye appeared in the urine in considerable amount, and Ottenburg said that Dienst interpreted this as meaning there was a communication between the circulation of the mother and the child. Dienst also found that in a proportion of cases the mother's serum agglutinated the red cells of her own child. He propounded the theory, Ottenburg continued, that eclampsia was nothing but a transfusion of incompatible blood of the child into the mother's circulation as a result of a communication between the two. Ottenburg then said that later Dienst retracted his idea but that he, Ottenburg, was convinced it was correct. Ottenburg finally suggested the idea that several other unexplained diseases, especially jaundice of the newborn, might also be due to accidental placental transfusion of incompatible blood.

The same theory was also put forward by Darrow (1938). She showed how icterus gravis neonatorum could be linked up on the one hand with the severer condition of hydrops foetalis, and on the other with the milder one of congenital (idiopathic) anaemia, owing to the familial association of the three conditions. (Erythroblastosis foetalis, or, alternatively, haemolytic disease of the newborn, is the general term now used to denote these three diseases). Darrow tentatively suggested that the red cells of the infant are destroyed by the action of specific immune bodies, and she thought that foetal haemoglobin might be immunologically different from adult haemoglobin, and thus be the antigen involved.

Intra-group Agglutination.

Levine and Stetson (1939) reported an unusual case of intra-group agglutination, and put forward a theory to account for it. A woman having her second pregnancy developed signs of toxaemia, and was delivered of a macerated stillborn foetus. She was transfused with whole blood from her husband, both being group O, and ten minutes later she developed a chill and complained of pains in the legs and head. An irregular agglutinin was found in her blood, and out of 54 group O bloods, 13 only failed to react with her serum. The reactions were independent of the M, N, or P factors. The authors then expressed the view that since the patient had harboured a dead foetus for several months, it could be assumed that the products of the disintegrating foetus were responsible not only for the toxic symptoms of the patient, but also for her iso-immunization. They presumed that the immunizing property in the blood and/or the tissues of the foetus must have been inherited from the father, but they could not identify it.

Wiener and Peters (1940) described accidents following repeated intra-group transfusions, and then stated there were some reports of intra-group haemolytic reactions in patients who had never previously received a blood transfusion. They pointed out that these patients were women who had recently given birth to a child or had had a miscarriage. Thus was founded the suspicion that the two conditions might have a common aetiology.

Discovery of the Rhesus Factor.

In their epoch-making article, Landsteiner and Wiener (1940) first published their discovery of a new factor in human blood. This factor, because of its identity with a similar one already found by them to be present in the blood of Rhesus monkeys, they called the Rhesus Factor. It was found to be independent of the ABO group, the MN type, or the property P. In a second article (1941) these writers stated that this factor was found to be present in 85 per cent. of the cases they had examined, taken from the white population of America.

They then said that evidence of the clinical importance of this discovery was obtained when blood samples were got from patients who had shown haemolytic reactions after receiving repeated transfusions of blood of the proper group. The sera of these patients contained anti-Rh iso-agglutinins, while in the blood cells the factor was lacking. This proved that the antigen in question was able to induce the formation of immune iso-antibodies in certain human beings.

As a result of studies on heredity, these authors concluded that the property Rh was inherited as a dominant, not sex-linked, and they presumed it was transmitted by means of a pair of genes, Rh and rh, where the dominant gene Rh determines its presence. From this they concluded that three genotypes would exist, RhRh, Rhrh, and rhrh, the first two corresponding to the phenotype Rh-positive, and the third to the phenotype Rh-negative.

This work of Landsteiner and Wiener was quickly confirmed. In Britain, Boorman, Dodd and Mollison (1942) examined 1,610 people in the general population and found that 85·15 per cent. were Rh-positive and 14·85 per cent. were Rh-negative. Hoare (1943) tested 1,122 cases in South Wales and found 84·6 per cent. were Rh-positive. Cappell (1944), working in Dundee and district, found that in 3,000 cases 84·5 per cent. were Rh-positive. It was soon generally accepted that in the white population 85 per cent. are Rh-positive and 15 per cent. are Rh-negative to the original guinea-pig anti-serum used by Landsteiner and Wiener, and the corresponding standard human anti-serum.

Complexity of the Rh Factor.

It was soon found, however, that the Rh factor was indeed a complex structure. The whole subject has become extremely complicated, and it is not necessary for the present study to discuss in detail the intricacies of the Rh factor as it is now known. For this reason only a short outline, based mainly on Cappell (1946, 1948) will be given.

In the course of testing large numbers of people, four types of anti-serum, each containing a single agglutinin, were found comparatively soon, and by means of these sera seven types of Rh complex were distinguished, while an eighth very rare type was believed on theoretical grounds to exist. It was as a result of Fisher's interpretation of the situation (see below) that the existence of this rare eighth type, and also of two other anti-sera, was predicted. The Rh types were named Ro, R1, R2, Rz, R′, R″, Ry and rh. The first four were all Rh-positive and the latter four all Rh-negative according to their reactions with the original guinea-pig anti-Rhesus serum, and Cappell agrees with Wiener's suggestion that the four negative types should be designated by the small letters r′, r″, ry and rh. The ry type was the one believed to exist, and it has only recently been found, as described by van den Bosch (1948).

The genotype of each individual represents the sum of two Rh types, one derived from each parent. The Rh genes are carried on a chromosome pair different from those bearing the ABO, the MN, the P, and all the other blood group genes. The eight Rh types give rise to 36 possible genotypes. It was difficult to understand the various serological results that were being obtained in practice until Fisher interpreted the Rh phenotype as the sum of three closely linked pairs of allelomorphic genes, which he designated by the letters Cc, Dd, and Ee. Each of the six letters indicates a distinctive antigen in the red cell, and the triple-gene-complexes give rise to the eight theoretical Rh types.

The relationship between Wiener's nomenclature and Fisher's is shown as follows:

Rh positive types	Ro — cDe
	R1 — CDe
	R2 — cDE
	Rz — CDE
Rh negative types	r′ — Cde
	r″ — cdE
	ry — CdE
	rh — cde

Corresponding anti-sera to all the above antigens have now been discovered as it was predicted by Fisher that they would.

One point to which special attention should be drawn is the fact that the negative quality rh is not simply an absence of the positive factor Rh but is an entity in itself. Of the four subdivisions of rh, about 2 per cent. of people (Cappell, 1945) have the sub-types r′ (Cde) or r″ (cdE) in their blood, and are not completely negative rhrh (cde, cde). These sub-types, r′ and r″ do react with certain anti-sera (anti-C and anti-E respectively), and some workers for this reason have included these subgroups with the Rh positive series.

As Cappell pointed out, however, such individuals, since they do not have the D antigen, will be liable to develop anti-D as easily as a completely Rh-negative individual would. The D antigen is much the most potent and frequent cause of iso-immunization, either in intra-group transfusions or in pregnancy, and for these purposes, therefore, such women should be regarded

as Rh-negative. In the present investigation, it was therefore decided to include amongst the Rh-negative group any such cases found.

Relationship of Rh Iso-immunization to Erythroblastosis Foetalis.

Meantime, Levine and his colleagues were pursuing their investigations. Levine and Katzin (1940) and Levine, Katzin and Burnham (1940) gave further evidence in support of the theory that a mother may be immunized by her foetus, or the foetal parts of the placenta. They found a "warm" agglutinin which was similar to the anti-Rh of Landsteiner and Wiener (1940), and they believed that the foetus inherits certain dominant agglutinable substances from the father which, if lacking in the mother, may stimulate her to produce iso-antibodies.

Levine, Katzin and Burnham (1941) found atypical agglutinins in three patients who had given birth to infants suffering from erythroblastosis foetalis and who also had obstetric complications. They suggested that there was a connection between the occurrence of these complications and the presence of immune agglutinins in the mother. They stated that this relationship lent itself readily to form a theoretical basis for the aetiology of at least some cases of erythroblastosis foetalis. The hypothesis of iso-immunization, they said, could readily explain the familial incidence of this condition and also the blood picture characteristic of it. It was assumed by them that the agglutinins in the mother's circulation under certain conditions were able to penetrate the placental barrier. There was sufficient evidence to show that most of these sera contained an agglutinin similar to the anti-Rh agglutinin of Landsteiner and Wiener.

Levine (1941) suggested that anti-Rh agglutinins were responsible for about 90 per cent. of all intra-group transfusion accidents, either after repeated transfusion or in pregnancy at the first transfusion. He also suggested that erythroblastosis foetalis is the result of (1) iso-immunization of the Rh-negative mother by the Rh-positive blood of the foetus, and (2) the subsequent passage of the mother's agglutinins through the placenta to act on the susceptible blood of the foetus.

Burnham (1941) described cases linking up the common aetiology of erythroblastosis foetalis and transfusion accidents in pregnancy. In his own recent series of 1,400 deliveries there were eight cases, although previously the incidence of erythroblastosis was given as 1 : 2,000 births. He admitted, however, that six of these cases would have been missed if they had not been specially looked for.

Levine, Burnham, Katzin and Vogel (1941) reported that of 153 mothers who were delivered of one or more infants suffering from one of the three clinical forms of erythroblastosis foetalis, 93 per cent. were Rh-negative. Eighty-nine husbands and 76 affected infants in the series of Rh-negative mothers were tested, and they were 100 per cent. Rh-positive, the figure anticipated if the theory were correct. Anti-Rh agglutinins were present in 42 out of the 141 Rh-negative mothers, in 33 of whom the blood was examined within two months of labour.

Confirmation of the Iso-immunization Theory.

The relationship of Rh iso-immunization to erythroblastosis foetalis was soon confirmed. Boorman, Dodd and Mollison (1942) showed that out of 48 cases of the disease 96 per cent. of the mothers were Rh-negative, and all the infants were Rh-positive. Race, Taylor, Cappell and McFarlane (1943) found that in 50 cases 88 per cent. of the mothers were Rh-negative; Plaut *et al.* (1945) found 88·2 per cent. Rh-negative mothers in 136 cases; and Cappell (1946) reported 86 per cent. Rh-negative mothers in 114 cases of the disease. In all these series a high proportion of the Rh-negative mothers had Rh antibodies in their sera.

It has thus been proved that in about 90 per cent. of cases, erythroblastosis foetalis is due to Rh incompatibility between the mother and foetus, with the resultant iso-immunization of the mother's serum by the Rh antigen in the red cells of the foetus.

That iso-immunization can also occasionally occur due to a difference in the ordinary blood groups of mother and infant (hetero-specific pregnancy) has been shown by several workers: Boorman, Dodd and Mollison (1944); Polayes and Ohlbaum (1945); Aubert, Cochrane and Ellis (1945); Austin and Smith (1946).

Factors Influencing the Severity of Erythroblastosis Foetalis.

Levine, Burnham, Katzin and Vogel (1941) continued their article by stating that it was the continuous intra-uterine action of anti-Rh agglutinins on the Rh-positive foetal blood, over a period varying from weeks to months, which caused the progressive haemolysis of the foetal blood. The wide variety of clinical syndromes they suggested was probably the result of the varying degree and duration of iso-immunization during pregnancy. In this connection, Stratton (1943) and Cappell (1946) have shown that it is theoretically possible in some cases for an Rh-negative mother to be subject to the influence of the Rh antigen of her foetus over a period as long as six months.

Davidsohn (1945) considered that four factors may influence the severity of this condition:

(1) Age of foetus when Rh antobodies begin to act on it.
(2) Length of time during which foetus is exposed to such action.
(3) Strength of the Rh antibodies.
(4) Permeability of the placenta.

The "blocking" antibody of Wiener (1944), or, what is the same thing, the "incomplete" antibody of Race (1944), if present in the mother's serum, is now recognized to result in the most severe form of foetal disease—hydrops foetalis (Cappell, 1946).

Theories Regarding the Clinical Forms of Erythroblastosis Foetalis.

The clinically observed fact that some infants were born apparently free of the condition but in the course of a few days developed severe anaemia or jaundice was puzzling. Levine *et al.* suggested that the tissues of the foetus

stored the mother's agglutinins and the subsequent release of these could then induce haemolysis several days after birth. Levine (1943) commenting on this said it would involve the simultaneous presence of maternal anti-Rh agglutinin and its corresponding antigen in the blood stream of the affected infant, a rarely observed fact.

Wiener (1945*b*) thought that a third factor, X protein, might be responsible. He believed it to be important for *in vivo* haemolysis in cases where " blocking " antibodies were present, but Cappell (1946) criticized this theory on the grounds that in these cases the foetus often fails to reach full term and is commonly stillborn prematurely.

Wiener, Wexler and Grundfast (1947) suggested that a difference in the quality of antibody produced by the mother resulted in the different forms of the disease. They postulated two types of antibody, univalent and bivalent, the first passing the placental barrier during the last third of pregnancy, and the second mainly during parturition. In this case the infant at delivery often seems normal, and then may suddenly die without developing anaemia.

Cappell (1947) on the other hand said that the type of foetal disease could not be predicted with certainty from the nature and titre of maternal ante-natal Rh antibodies, beyond the general statement that a high concentration is likely to be associated with a fatal hydrops foetalis.

Skelton and Tovey (1945) believed that the absence of jaundice at birth was due to the fact that foetal bilirubin is excreted by the mother. The liver damage becomes manifest at birth, however, and jaundice develops shortly afterwards. Mollison and Cutbush (1949) showed that the haemoglobin value in the cord blood of an infant with haemolytic disease is well correlated with its severity.

Hereditary Nature of Erythroblastosis Foetalis.

Levine, Burnham, Katzin and Vogel (1941) concluded their article by stating the hereditary nature of this disease in terms of the iso-immunization theory. In some families every pregnancy is affected, except perhaps the first, while in others only some of the pregnancies are affected. Since the Rh factor is inherited as a simple mendelian dominant, the striking difference in the familial incidence of the disease is determined, genetically, by the homozygosity (RhRh) or heterozygosity (Rhrh) of the father's blood.

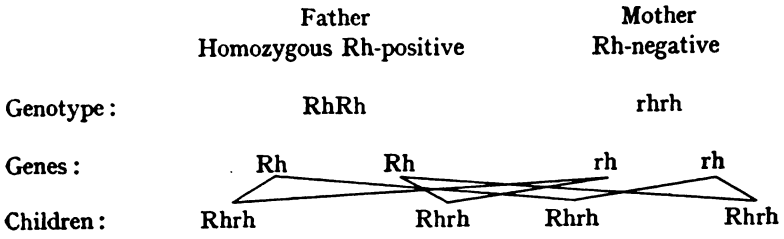
The diagram on p. 366 illustrates the above conception.

The homozygous father can produce only heterozygous Rh-positive children, whereas the heterozygous father may have 50 per cent. of his children Rh-negative, these escaping the disease.

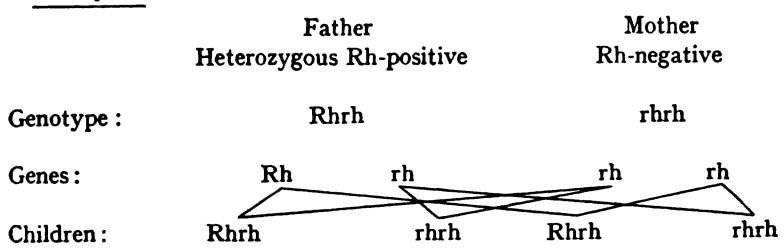
Factors Influencing the Incidence of Erythroblastosis Foetalis.

Snyder *et al.* (1945*a*) said that the effects of Rh incompatibility could be expected in 6 per cent. of pregnancies, but that it occurred only in 0·5 per cent. Similarly, Cappell (1946) said that Rh incompatibility occurred in 10 per cent of pregnancies, but that sensitization occurred only in 1 : 25 opportunities, giving an incidence of 1 : 250 for the occurrence of haemolytic disease.

Example 1.



Example 2.



This discrepancy has given rise to many theories to account for it. Taylor and Race (1944) and Cappell (1946) showed that the mating of a homozygous Rh-positive man with an Rh-negative woman has a much greater chance of producing an erythroblastotic baby than the mating of a heterozygous Rh-positive man with an Rh-negative woman, this chance being in addition to the points noted in the previous section of the present paper.

To explain the fact that some women are more sensitive than others to the Rh antigen, while some are not affected by it at all, Cappell (1946), quoting Race, said there was evidence that this aptitude to become immunized may also be an inherited character. Unger and Wiener (1945) also believed this and thought, in addition, that the wide spacing of a few pregnancies was more apt to give rise to sensitization than a larger number within a shorter period of time. This point was stressed by Young and Kariher (1945), while Mollison (1943) believed that the factors to be considered were (1) failure of the Rh antigen to cross the placenta in adequate amount, and (2) failure of the mother to respond to the stimulus of the Rh antigen.

Another factor of importance is the compatibility or otherwise of the ABO groups of the mother and foetus. Race, Taylor, Cappell and McFarlane (1943) thought that in their series of cases of haemolytic disease the proportion of homospecific pregnancies was higher than normal, although their records were incomplete. Cappell (1946) in an analysis of the table given by Plaut *et al.* (1945), showed that there was a significant deficiency of group O mothers, and an excess of group A; whereas it was the reverse amongst the husbands. Also the number of homospecific pregnancies was higher than normal. Cappell also found the same unduly high number of homospecific pregnancies in his own series of cases. Wiener (1945*a*) noticed the same thing and thought it was

due to the fact that the properties A and B were good antigens whereas the property Rh was not; hence when the ABO groups are compatible the Rh-negative mother is more likely to become sensitized to the Rh antigen than when they are not.

Clinical Manifestations of Erythroblastosis Foetalis.

According to Cappell (1946) this disease should be suspected when jaundice appears within a few hours of birth, although it may be delayed up to 48 hours. Rapidly deepening jaundice, accompanied by drowsiness and a failure to feed satisfactorily is highly suspicious. The haemoglobin and the red cells are both reduced, although reticulocytes are numerous and normoblasts, megaloblasts and primitive cells are all present, the latter being specially significant. Skelton and Tovey (1945) showed that biliary obstruction in children with icterus gravis may take one of two forms: a blockage of one of the larger bile ducts with inspissated bile, or conversion of the bile ducts into a fibrous cord. They believed that certain cases of so-called "congenital" obliteration of the bile ducts occur as a sequel of icterus gravis.

Drummond and Watkins (1946) thought that certain cases of hepatomegaly and splenomegaly in children and adolescents could result from haemolytic disease of the newborn, and they emphasized that Rh incompatibility must be excluded in the diagnosis.

Relationship of Erythroblastosis Foetalis to Kernicterus.

This relationship was clearly brought out by Zimmerman and Yannet (1933). They stated that "kernicterus" was a term coined by Schmorl in 1903 to designate jaundice of various nuclear masses of the brain, but that it was Orth who, in 1875, first described the condition. The structures most commonly affected in this disease are the caudate, lentiform, subthalamic and dentate nuclei; the thalami, mammillary bodies, cornu ammonis, and the nuclei of the cranial nerves; the olives, and even parts of the cerebellar cortex, as well as the anterior and posterior horns of the spinal cord. The writers said that jaundice of these structures was not a disease *sui generis*, but occurred as one of the lesions that could be found in newborn infants with severe jaundice, and only in a small number of these. In other words, kernicterus is most frequently, if not exclusively, associated with icterus gravis neonatorum. In support of their statement, they described four cases of their own, and compared kernicterus with Wilson's disease (progressive lenticular degeneration). They believed septic infection to be the most likely cause of icterus gravis, although they admitted this did not explain, for example, the familial incidence of the disease.

Hawksley and Lightwood (1934) described the symptoms of kernicterus, the presence of which has been proved pathologically. They are: drowsiness and apathy, convulsions, spasticity and signs of medullary failure. Paralysis of the vital medullary centres is the usual mode of death, but they said that the condition occurs comparatively rarely in icterus gravis, and quoted Schmorl who found six cases in 120 autopsies on cases of icterus gravis. McIntosh

(1941) gave the incidence as not over 10 per cent., and Cappell (1947) also thought the incidence to be from 10 per cent. to 12 per cent. He believed that the damage to nerve cells must occur after birth, or certainly not long before birth, for in infants dying in the first few days the damaged tissue shows no sign of disintegration or removal. Hawksley *et al.* said that mental deficiency was the most important of the nervous sequelae of icterus gravis neonatorum.

Pasachoff (1935) described a case that was clinically erythroblastosis foetalis at the beginning of the illness, and then obstructive jaundice. The autopsy findings showed the presence of icterus gravis, kernicterus and complete atresia of the cystic, hepatic and common bile ducts. There was also cerebral aplasia. He stated that kernicterus did not occur in obstructive jaundice, but had been found almost exclusively as a rare accompaniment of icterus gravis neonatorum.

Zimmerman and Yannet (1935) discussed the possible pathogenic factors that might cause kernicterus to follow icterus gravis, and they reported in full the case of a child who had severe icterus during the first four weeks of life and who died aged three. The post-mortems were so strikingly similar to those seen in cases ending fatally from kernicterus during the first two weeks of life that the relationship could hardly be accidental.

The evidence produced by these workers is so conclusive that it seems well established that an infant surviving icterus gravis, even without developing definite signs of kernicterus during the period of generalized jaundice, may yet become a mental defective with signs and symptoms of involvement of the basal ganglia.

Fitzgerald, Greenfield and Kounine (1939) said they disagreed with Zimmerman *et al.* that kernicterus is solely associated with icterus gravis, and they cited Pasachoff (1935) as reporting a case of congenital atresia of the bile ducts with erythroblastosis and kernicterus. To the present writer this criticism is unwarranted, because, firstly, Zimmerman *et al.* (1933) stated that kernicterus was most frequently, if not exclusively, associated with icterus gravis, and in 1935 they reiterated that it occurred "almost" exclusively in association with that condition. Secondly, Pasachoff (1935) did not say that his case had congenital atresia of the bile ducts, but that it had complete atresia of the cystic, hepatic, and common bile ducts. Also, he stated categorically that kernicterus does not occur in obstructive jaundice. In addition, as has already been pointed out, Skelton and Tovey (1945) showed that certain cases of so-called "congenital" obliteration of the bile ducts were really sequelae of icterus gravis.

After severe jaundice has developed, Fitzgerald *et al.* said that symptoms referrable to involvement of the central nervous system manifest themselves within 24 hours. In this connection it has now been established as a result of the modern treatment of erythroblastosis foetalis with the early transfusion, repeated if necessary, of Rh-negative blood, that even this treatment, although it has a reasonable chance of saving the infant, does not prevent the onset of kernicterus. Clinically, according to Fitzgerald *et al.*, the children who survive kernicterus present a varied symptomatology, but in all the cases they described there was evidence of involvement of the extra-pyramidal system, such as

choreo-athetoid movements and rigidity. Invariably, also, there was a marked degree of mental retardation, in many cases approaching the idiot class.

Rh Incompatibility as a Cause of Mental Deficiency Associated with Kernicterus.

It was thus definitely established, by the time the Rh factor was discovered in 1940, that mental deficiency was one of the sequels of kernicterus, which, in turn, occurred almost exclusively as a sequel of icterus gravis neonatorum, one of the forms that erythroblastosis foetalis might take. Hence, when it became established that the Rh factor was responsible for about 90 per cent. of all cases of that disease, it followed naturally that at least nine cases out of ten of mental deficiency associated with kernicterus were the ultimate result of Rh incompatibility. That the Rh factor can be responsible for mental deficiency in this way has now been generally accepted.

Theory that Rh Incompatibility may Cause Undifferentiated Mental Defect.

Yannet and Lieberman (1944) were the first to wonder if a more direct relationship between the Rh factor and mental deficiency could be established. They said that since the cerebral changes in kernicterus were most frequently described in cases of erythroblastosis foetalis, it appeared as a reasonable corollary that the pathogenesis of the cerebral pathology was in some way related to the mechanism of iso-immunization.

On the basis of present knowledge, they continued, the aetiological importance of iso-immunization in Rh-positive individuals with severe mental retardation, clinical evidence of basal ganglia involvement, a neonatal history suggesting erythroblastosis foetalis and an Rh-negative mother, would appear reasonably well established. However, if this specific syndrome were the only manifestation of iso-immunization, its importance in the overall picture of mental deficiency would be slight.

They stated, however, that there was some evidence which suggested the possibility that iso-immunization, as an aetiological factor, might possibly be involved in instances where central nervous system injury is not confined to the basal ganglia and where a characteristic history of erythroblastosis foetalis is not obtained. Two series of observations led to this idea. Firstly, in certain families where proved cases of kernicterus had occurred, as well as repeated pregnancies ending in erythroblastotic children, certain of the surviving infants presented clinical pictures in which evidence of basal ganglia involvement was not present. Instead, severe mental retardation either alone or associated with gross motor weakness, inco-ordination and convulsions, was present. Secondly, autopsies in some cases of neonatal deaths showed the presence of kernicterus, but the blood picture was not considered to be abnormal, and the jaundice was thought probably to be physiological.

The authors therefore came to the conclusion that it was reasonable to suggest the possibility that a certain proportion of the idiot and imbecile population, without an aetiologically significant clinical history or abnormality

on physical examination, and now classified as "undifferentiated," might conceivably also represent the end result of iso-immunization during pregnancy.

Results of Investigation of the New Theory.

They thereupon set out to investigate the incidence of Rh incompatibility in a series of low-grade institutionalized mental defectives. They examined altogether 109 defectives and their mothers. Of the defectives, 53 came into the category of recognized diagnostic groups (mongols, spastic diplegias, post-natal infective cases, birth traumas, cranial anomalies, etc.), and 56 were regarded as undifferentiated, cases where the cause of the deficiency could not be found. The former group were used as a control, and the findings were as follows: Control group, 6 mothers Rh-negative (11·3 per cent.). Of these mothers, 4 had an Rh-positive defective child, giving 7·5 per cent. as the incidence of Rh-incompatibility in the control group. In the undifferentiated group, however, 14 mothers were Rh-negative (25 per cent.), and of these, 11 had an Rh-positive defective child, giving 19·6 per cent. as the incidence of Rh incompatibility.

These figures show a striking difference, but Yannet *et al.* rightly admitted in their discussion that the simple demonstration of an Rh-negative mother of an Rh-positive child does not establish iso-immunization as the aetiological mechanism, but they pointed out that it does greatly limit the cases in which this possibility must be considered. They suggested that by concentrating on these children in the undiagnosed group, it might be possible eventually to establish the clinical syndrome in which the blood analysis would serve as a confirmatory finding.

In analyzing their results they pointed out that five cases of the incompatibility would be the result of random distribution, and that the remaining cases would represent 10 per cent. of the undifferentiated group studied. This would give an incidence of 3 to 4 per cent. for iso-immunization as an aetiological factor in institutionalized mental defectives, and this is about half the incidence of mongolism.

Commenting on these results, Cook (1944) agreed that they were striking, but rightly added the note of warning that the series was too small for definite conclusions to be drawn.

The work of Yannet *et al.* was soon checked by Snyder, Schonfield and Offerman (1945*a*). They examined 66 mothers, and their 68 mentally defective children. Of the 66 mothers, 17 were Rh-negative, nearly twice the expected frequency. Of the 68 defective children, 11 were Rh-positive from Rh-negative mothers, and this is more than double the expected frequency.

Snyder *et al.* (1945*b*) added some further figures to their previous total. They examined another 47 cases, but they found that the very high incidence of Rh-negative mothers and of Rh-positive children from these mothers was not maintained, and was only slightly higher than expectation. Their combined results, however, from 113 mothers and 115 mentally defective children, were still in excess of those expected, although only significantly so instead of highly significantly so.

Yannet and Lieberman (1946), however, followed up their original series with another larger one. They examined 277 defectives all with an I.Q. of less than 30. Of these, 158 fell into the well-defined categories, and the remaining 119 were regarded as being undifferentiated. In the control group, 22 (14 per cent.) of the mothers were Rh-negative and 12 of these had an Rh-positive child, giving a 7·6 per cent. incidence of Rh incompatibility. Among the undifferentiated cases, however, 26 (22 per cent.) of the mothers were Rh-negative and 19 of these had an Rh-positive child, giving an incidence of 16 per cent. for Rh incompatibility in this group. The difference between the two ratios (7·6 per cent. and 16 per cent.) was stated to be statistically significant.

In this article, Yannet *et al.* discussed possible theories as to the mechanism whereby mental deficiency could result from iso-immunization of the mother by the foetus. The suggested theories were (1) the possibility of irreversible cellular injury due to an antibody-antigen reaction ; (2) cerebral injury entirely secondary to the destruction of red blood cells during foetal life, this being really an anoxaemia ; and (3) the possibility that the products of extensive red cell destruction *per se* may be injurious to the developing neurone.

Criticisms of the New Theory.

Yannet *et al.'s* theory has been criticized by Scholl, Wheeler and Snyder (1947) and by Cappell (1947). The former writers stated that the final acceptance of the theory of a positive relationship between Rh immunization and feeble-mindedness would require immunological confirmation and a systematic experiment on a larger scale than hitherto carried out. For such an experiment to be conclusive they maintained it should include the following factors :

(1) Case material should include a much larger number of patients, preferably more than 25 Rh-positive children from Rh-negative mothers.

(2) The immunological studies should be performed as soon as the child is found to be mentally deficient, preferably within a year following delivery.

(3) Subsequent children in the families should be studied for evidence of erythroblastosis at birth, thus causing a postponement of the publication of the study for a number of years.

(4) Criteria for the classification of the defect should be stated.

(5) Data on the occurrence of other neurological disorders such as athetosis, convulsions and spasticity, which are known to accompany kernicterus, should be stated.

These authors then gave the results of a careful restudy of the cases reported by Snyder *et al.* (1945*a* and *b*). They concluded that this restudy offered no support to the theory of Yannet *et al.*, but they admitted that it did not disprove it. They also admitted that the data on which the relationship was originally postulated were statistically significant.

Cappell (1947) was much more severe in his criticism. He agreed it was known that icteric staining of the brain may sometimes take the form of a diffuse colouration of the cortex in greater or less degree, either alone or along with basal nuclear staining, and he admitted that it may be accepted without

hesitation that mental deficiency may follow consequently upon icterus gravis, even in the absence of clinical signs of kernicterus. He said that Yannet *et al.*'s figures were unsound, however, for they included in the undifferentiated group six cases of undoubted icterus gravis and kernicterus. If these were placed in the specific group, then the difference in the incidence of Rh-negative mothers between the two groups disappears. In a series of 200 cases of defective children, examined from his department, Cappell found no significant increase in the incidence of Rh incompatibility, and he concluded that it seemed improbable that Rh incompatibility could cause mental deficiency in the absence of overt haemolytic disease in the neonatal period.

Object and Method of Present Investigation.

The aim of the present study has been to test Yannet *et al.*'s theory under as stringent conditions as possible, and to see whether any definite conclusions can be drawn as to its truth or otherwise. The investigation, however, has been widened to include feeble-minded cases and those living at home under guardianship or supervision, because it was felt, as suggested in a *British Medical Journal* editorial comment (August 10, 1946), that if there were any truth in the theory, the figures in feeble-minded cases should be even more striking than they were in the low-grade defectives.

The method adopted was the simplest that could be devised in the circumstances. The case records of all the defectives on the books of the local authorities concerned were examined, and those whose mothers were still alive were picked out. These mothers were invited to co-operate, and although by no means all of them did so, I was able to examine 427 cases altogether. They were quite a random selection, and there was no picking or choosing of cases. In fact, at this early stage of the investigation I deliberately kept myself in ignorance of the degree and type of defect present in the offspring of the mother from whom I was taking the blood.

As complete histories as possible were obtained in every case, irrespective of whether the mother proved to be Rh-negative or not, and no assumptions, for example, were made as to the effect of a bad fall in early childhood without special enquiries regarding all the circumstances at the time. This was all the more necessary as it was found that parents were prone to blame the slightest extraneous factor as being the cause of their child's mental defect.

A special history form was prepared setting forth all the points on which information was wanted, as it was found that the case records, quite understandably, were incomplete from the point of view of this investigation. When all the facts available in each case were obtained, it was finally decided into which category each defective was to be placed. At this stage, the records of the Rh investigation were kept separate, so that when each defective was classified it was not known whether Rh incompatibility was present or not. The aim was to be left with a residue of cases quite undifferentiated in type (including some epileptics where there was no other factor operating which might be the cause of both the defect and the epilepsy, e.g. meningitis, or birth injuries) and where it was impossible to obtain evidence of any adequate cause

of the defect. It should be noted that in the type of case where another possible cause was present, but reasonable doubt existed as to its actual responsibility in producing the defect, such a case was included in the undifferentiated group.

Further, a fair proportion of the defectives examined had reached adult life, so that in a few instances the mother was unable to remember details of the birth and first few weeks of life of the defective in question. In all such cases where the history was incomplete and the defective was not a mongol or one of the other recognized types, he or she was placed in the undifferentiated group. As a rule, however, there was little difficulty in classifying the defective, and it was not considered that this factor would influence the results to any significant degree.

Requiring special mention were those cases of otherwise undifferentiated mental defect where the family history was such that the factor of heredity had to be taken into account as a possible cause of the deficiency. At first I was definitely of the opinion that these cases should be classed along with the specific group, as a factor at least in the causation of the deficiency was reasonably well established. On thinking the matter over further, however, I was compelled to admit that these cases did not belong to any specific type of mental defect, and I felt then that they should be classed with the undifferentiated group. I was still not satisfied, however, because now the undifferentiated group would not fulfil all the conditions laid down for it.

In order to obtain comparable figures with those of the American workers, I had decided to use the specific group of defectives as a control against the undifferentiated group, so now, in order to get over the difficulty noted above, I decided to do two complete series of calculations, the first with the " heredity " cases in the control group, and the second with these cases in the undifferentiated group, and to compare the results to see if any significant difference was made to the test (undifferentiated) group. The idea was conceived that, since the Rh factor is inherited on Mendelian lines, and since it has been suggested that the tendency for an Rh-negative woman to become immunized against the Rh antigen is also inherited, possibly Rh incompatibility might be a factor in the inheritance of otherwise undifferentiated mental defect. I realized that a comparison between the two series of results might at least show whether this theory was worth pursuing or not.

The specific, or control, group, excluding the " heredity " cases, consisted of 152 cases divided as follows : mongols 56, organic nervous disease (excluding spastics) 29, spastics 26, microcephalics 11, birth and early childhood injuries 8, hydrocephalics 7, endocrine disorders (excluding cretins) 5, cretins 4, congenital G.P.I. 2, kernicterus and icterus gravis 4.

I have put the kernicterus and icterus gravis cases into the control group, and not the undifferentiated group as did the Americans, for in my opinion Cappell's criticism is justified that this is an investigation into the possibility of Rh incompatibility being a cause of undifferentiated mental defect without associated evidence of kernicterus or a history of erythroblastosis foetalis. These were the conditions laid down by Yannet and Lieberman themselves in their original article and therefore they ought to be adhered to strictly.

Results of Investigation.

The total number of cases investigated was 427 inclusive of control and test cases, and the results for the whole series are shown in Table I.

Table I.

Total number of cases investigated . .	427
,, ,, of Rh-negative mothers .	84 = 19·7%
Number of Rh-negative mothers with Rh-positive children	52 = 12·2%

Tables II and III show the results for the control group.

Table II.—*Control Group (including "Heredity" Cases).*

Number of cases investigated . . .	177
,, Rh-negative mothers . .	42 = 23·7% (S)
,, Rh-negative mothers with Rh-positive children . . .	23 = 13·0%

S = significant.

Table III.—*Control Group (excluding "Heredity" Cases).*

Number of cases investigated . . .	152
,, Rh-negative mothers . .	35 = 23·0% (S)
,, Rh-negative mothers with Rh-positive children . . .	20 = 13·2%

S = significant.

Tables IV to IX show the results for the test group. I divided this group into two classes, (1) the feeble-minded, or high-grade cases of mental defect, and (2) the imbeciles and idiots, or low-grade cases of mental defect. The results are given for the whole group and then for the two classes within the group.

Table IV.—*Whole Test Group (excluding "Heredity" Cases).*

Number of cases investigated . . .	250
,, Rh-negative mothers . .	42 = 16·8%
,, Rh-negative mothers with Rh-positive children . . .	29 = 11·6%

Table V.—*Whole Test Group (including "Heredity" Cases).*

Number of cases investigated . . .	275
,, Rh-negative mothers . .	49 = 17·8%
,, Rh-negative mothers with Rh-positive children . . .	32 = 11·6%

TABLE VI.—*Feeble-minded Cases (excluding "Heredity" Cases).*

Number of cases investigated	113
,, Rh-negative mothers	21 = 18·6%
,, Rh-negative mothers with Rh-positive children	16 = 13·3%

TABLE VII —*Feeble-minded Cases (including "Heredity" Cases).*

Number of cases investigated	122
Number of Rh-negative mothers	24 = 19·7%
,, Rh-negative mothers with Rh-positive children	17 = 13·9%

TABLE VIII.—*Imbecile and Idiot Cases (excluding "Heredity" Cases).*

Number of cases investigated	137
Number of Rh-negative mothers	21 = 15·3%
,, Rh-negative mothers with Rh-positive children	14 = 10·2%

TABLE IX.—*Imbecile and Idiot Cases (including "Heredity" Cases).*

Number of cases investigated	153
,, Rh-negative mothers	25 = 16·3%
,, Rh-negative mothers with Rh-positive children	15 = 9·8%

For the purposes of comparison, all the above results have been summarized in Table X (percentages only).

TABLE X.

	Percentage Rh-negative mothers.		Percentage Rh-negative mothers with Rh-positive children.	
	Excluding "heredity" cases.	Including "heredity" cases.	Excluding "heredity" cases.	Including "heredity" cases.
Control group	23·0% (S)	23·7% (S)	13·2%	13·0%
Whole test group	16·8%	17·8%	11·6%	11·6%
Feeble-minded cases	18·6%	19·7%	13·3%	13·9%
Imbecile and idiot cases	15·3%	16·3%	10·2%	9·8%

ANALYSIS OF RESULTS AND CASE MATERIAL.

Owing to the limited time at my disposal it has not been possible to examine a series of normal children and their mothers to get normal control figures, and it is therefore necessary to define exactly the basis which has been taken for comparing the above results with the normal average figures for the general population.

Race, Mourant, Lawler and Sanger (1948) gave the observed and the expected genotype frequencies in 2,000 cases. The expected frequencies

(based on the chromosome frequencies calculated by Professor Fisher) and the observed frequencies agreed closely, and I have therefore taken as the normal standard the expected frequencies as given by Race *et al.*

The frequency of the genotype rr (cde/cde) is expected to be 15·10 per cent. If to this figure are added the expected frequencies of the genotypes made up from combinations of r′, r″, and r, the expected frequency of all genotypes lacking the antigen D is 16·84 per cent. This figure agrees closely with the observed figure of 17·07 per cent. for all subtypes of Rh-negative cases, as given by Race *et al.*, and it is therefore being taken as the normal standard in the present investigation. The expected frequency of Rh-positive children from Rh-negative mothers can be calculated from the gene frequencies given by Race *et al.*, and it is 9·92 per cent. This figure agrees very closely with the one of 10 per cent. mentioned by Cappell (1946), and it has been adopted as the normal standard in this study.

(a) *Whole Group of Mental Defectives.*

It will be seen from Table I that out of a total of 427 mothers of mental defectives of all types and grades, 84, or 19·7 per cent. were Rh-negative, while 52, or 12·2 per cent. of these mothers had an Rh-positive defective child. Neither of these figures is statistically significant, so that the mental defective population as a whole does not appear to differ materially from the normal population.

(b) *"Control" Group of Mental Defectives.*

Tables II and III, giving figures for the control group, should be taken together as they show the difference in the figures when the "heredity" cases are included and excluded respectively. Out of 177 cases there were 42, or 23·7 per cent. Rh-negative mothers, and of these 23, or 13·0 per cent., had an Rh-positive defective child; whereas out of 152 cases there were 35, or 23·0 per cent., Rh-negative mothers, and of these 20, or 13·2 per cent., had an Rh-positive defective child. It will be seen that the inclusion or exclusion of the "heredity" cases gives almost identical percentages in the control group. The figures of 23·7 per cent. Rh-negative mothers in 177 cases, and 23·0 per cent. Rh-negative mothers in 152 cases are both statistically significant.

In Table XI the control group (excluding "heredity" cases) is further analysed. It will be observed that in the first two main groups, the mongols and cases of organic nervous disease, the figures in columns 2 and 3 are quite within normal limits, but in the third group, the spastics, there is a high proportion of cases both in columns 2 and 3.

In Appendix A (Cases 1–20) are described the clinical histories of the control cases in which Rh incompatibility has occurred, and of these the six cases amongst the spastics are Nos. 7–12. The very high incidence of incompatibility, even in this small series of 26 cases, could lead to the supposition that possibly it has something to do with the condition, but in Cases 7–11 there was no history suggestive of erythroblastosis, and no atypical agglutinins were found in the mothers' sera. Case 9 had meningitis at the age of 6 months, and this may have caused the paralysis. Case 11 showed tremor and inco-

ordination of all movements, but no true athetosis was present. Case 12 did have a history of neonatal jaundice which lasted intermittently for three months and paralysis involving the right side subsequently developed. There was no athetosis, and the family history did not definitely suggest that iso-immunization had occurred, so I did not class this case as one of icterus gravis, although it may possibly have been.

TABLE XI.

	1 Total cases.	2 Total Rh—ve mothers.	3 Rh—ve mothers with Rh+ve children.
Mongols	56	7	3
Organic nervous disease	29	4	3
Spastics	26	8	6
Microcephalics	11	4	2
Birth and early childhood injuries	8	2	-
Hydrocephalics	7	3	-
Endocrine disorders	5	2	2
Cretins	4	1	-
Congenital G.P.I.	2	-	-
Kernicterus and icterus gravis	4	4	4
Total	152	35	20

The histories of both the microcephalics in which Rh incompatibility occurred (Nos. 13 and 14) in each case suggested that the mother was in fact immunized, although not necessarily by the defective in question. In neither case were atypical agglutinins found in the mother's serum, nor was there any history of jaundice. In both cases the family history was rather typical of iso-immunization, and in Case 14 the child was very anaemic when born. I did not feel justified, however, in classifying either of these cases as erythroblastosis foetalis.

There were four definite cases of erythroblastosis foetalis (Nos. 17–20), and in three of these (Nos. 18, 19, 20) there was no doubt whatever of the presence of kernicterus. In all four cases there was a history of neonatal jaundice and the family histories were typical of iso-immunization having occurred. Case 20 is particularly interesting: the defective, aged 15, was the youngest in the family and there were no subsequent pregnancies, yet strong antibodies were found in the mother's serum, and these agglutinated Rh-positive cells. For such strong antibodies to persist for 15 years must be comparatively rare.

Erythroblastosis foetalis is expected to occur in the general population in 1 : 200 to 1 : 250 births. Further, of the cases surviving erythroblastosis, not more than 10 per cent. may be expected to show the clinical signs of kernicterus. This means that in the general population kernicterus occurs in

not more than 1 : 2,000 cases. In my total number of 427 cases, therefore, it would not have been surprising if no cases of kernicterus had been found, were it not for the fact that this disease is a definitely recognized cause of mental deficiency. It is reasonable to assume, therefore, that on testing a sample of mental defectives one would expect to find a slightly higher incidence of Rh incompatibility than in the general population, due to this concentration of kernicterus cases.

As has been shown, the percentage of negative mothers and of negative mothers with positive children in the total sample is not significantly high; but in the control group, which has concentrated still more the cases of kernicterus, the incidence, both of negative mothers and of those with positive children, is higher than in the total sample, although only in the first case is the figure significant.

The control group was therefore recalculated, the three cases of kernicterus being omitted. It would then read as in Table XII.

TABLE XII.—*Control Group (excluding Kernicterus Cases).*

	Including "heredity" cases.	Excluding "heredity" cases.
Number of cases investigated .	174	149
,, Rh-negative mothers .	39 = 22·4%	32 = 21·5%
Rh-negative mothers with Rh-positive children . . .	20 = 11·5%	17 = 11·4%

The figures for the incidence of Rh-negative mothers are now brought below the level of statistical significance, and the figures for the incidence of Rh incompatibility are proportionately reduced practically to the normal average for the general population.

(c) *Test Group of Undifferentiated Mental Defectives.*

Table IV shows that there were 250 cases of all grades of defect, excluding the "heredity" cases. Of these, 42 mothers (16·8 per cent.) were Rh-negative, while 29 of these mothers (11·6 per cent.) had an Rh-positive defective child. Neither of these figures differs materially from the normal standards. When the "heredity" cases are added (Table V), it will be seen that out of 275 cases, 49 (17·8 per cent.) mothers were Rh-negative, and of these, 32 (11·6 per cent.) had Rh-positive defective children. Again neither figure is significant.

Table XIII shows how the "heredity" cases were divided.

TABLE XIII.—"*Heredity*" *Cases.*

	Total cases.	Total Rh-negative mothers.	Rh-negative mothers with Rh-positive children.
Feeble-minded . .	9	3	2
Imbeciles and idiots .	16	4	1
Total . .	25	7	3

When the test group is divided into feeble-minded cases (high-grade defect) and imbecile and idiot cases (low-grade defect), the results are equally interesting if only for their normality.

Table VI shows the feeble-minded cases, excluding the feeble-minded "heredity" cases. Out of 113 cases, 21 (18·6 per cent.) mothers were Rh-negative, and of these, 15 (13·3 per cent.) had Rh-positive defective children. These figures are not significant. Even when the "heredity" cases are added (Table VII), out of a total of 122 cases, 24 (19·7 per cent.) mothers were Rh-negative, while of these, 17 (13·9 per cent.) had Rh-positive defective children. Although these figures are slightly higher than those in Table VI, they are still not statistically significant.

The figures for the low-grade group are even more striking. From Table VIII, "heredity" cases excluded, it is seen that out of 137 cases, 21 (15·3 per cent.) mothers were Rh-negative, and of these, 14 (10·2 per cent.) had Rh-positive defective children. Addition of the "heredity" cases (Table IX) shows that out of 153 cases, 25 (16·3 per cent.) mothers were Rh-negative, and of these, 15 (9·8 per cent.) had Rh-positive defective children. These figures could scarcely be more normal.

The clinical histories of the cases ot undifferentiated defect in which Rh incompatibility occurred are described in Appendix B (Cases 21 to 52).

Case 24 showed slight jaundice immediately after birth and its duration was unknown, but there was nothing else in the history to suggest erythroblastosis, and the jaundice was regarded as physiological and nothing more.

Case 25 was thought to have had a head injury when she fell downstairs at the age of four, but there was no evidence that this had any bearing on the mental defect, and there was nothing else in the history to suggest this was not an undifferentiated case.

Case 26 did have slight jaundice just after birth, but, in view of his position in the family (8th out of ten pregnancies), and the family history of the second and third pregnancies having ended in stillbirths, followed by four siblings alive and well, then the defective, and finally two more siblings alive and well, it is reasonable to suppose that if the stillbirths had been due to iso-immunization the effect on the defective would have been much more serious. The jaundice was therefore regarded as physiological.

In Case 30 the mother had a bad fall during the early stages of the pregnancy, but she carried on successfully to term with no threat of a miscarriage at the time of the fall, so that it is very unlikely it had anything to do with the defect in the child.

The family history in Case 32 rather suggested that iso-immunization had occurred, although no atypical agglutinins were found in the mother's serum. In the defective's history, however, there was no evidence of erythroblastosis, and so he was classed as undifferentiated.

Case 35 is especially interesting. There were ten pregnancies of which he was the first, so that it would not be expected that iso-immunization would occur in his case. Atypical agglutinins were found in the mother's serum, however, proving that she was sensitive and had been immunized, but there was no evidence that the defective had been affected.

Case 45: The early history of this defective and the family history suggested that syphilis was the cause of the stillbirths and miscarriages. In view of the fact, however, that no confirmation could be obtained from the hospital where the defective was supposed to have been treated, and that she now shows no stigmata of syphilis, she has been classified as undifferentiated.

Case 46: The family history in this case strongly suggested that iso-immunization had occurred in the mother, although no confirmation could be obtained. As there was no history of erythroblastosis in the defective (2nd pregnancy), however, he has been classed as undifferentiated.

The rest of the cases described in Appendix B are all quite straightforward and require no further comment.

(d) *Homospecific and Heterospecific Pregnancies.*

It was noted earlier in this study that some evidence had been produced showing that iso-immunization to the Rh factor was favoured by a homospecific pregnancy rather than a heterospecific one. In a series of pregnancies where iso-immunization had been proved to have occurred the proportion of homospecific pregnancies was unduly high, and there was also an undue number of Group A bloods amongst the Rh-negative mothers. In Table XIV is listed the distribution of the ABO groups amongst the mothers and defectives in the 52 cases where Rh incompatibility occurred. It will be seen that this distribution is quite within normal limits, both amongst the mothers and the defectives.

Normally, a heterospecific pregnancy may be expected to occur in about 20 per cent. of cases. Table XV shows the proportion in the present series of cases of Rh incompatibility. In the whole group, the control group, and the test group (all cases) the frequency of the homospecific pregnancies as compared with the heterospecific ones could scarcely be more normal, and in the subdivisions of the test group the numbers are so small that the slight variation is not significant.

TABLE XIV.

	Mothers.	Defectives.
Group O	24	27
Group A	23	21
Group B	2	1
Group AB	3	3
Total	52	52

TABLE XV.

	Total pregnancies.	Homospecific pregnancies.	Heterospecific pregnancies.
Whole group	52	41	11
Control group	20	16	4
Test group (all cases)	32	25	7
Feeble-minded cases	17	15	2
Imbecile and idiot cases	15	10	5

Discussion.

Since Rh incompatibility occurs in practically 10 per cent. of pregnancies, the theory that such an incompatibility might be a factor in the genesis of otherwise undifferentiated mental defect of unknown origin is a very important and attractive one, because of the profound and far-reaching implications involved. Yannet and Lieberman's figures, although on small numbers of cases, particularly in their first series, appeared to support this theory, but it was obvious that further confirmatory evidence would be necessary before such a theory could be accepted and acted upon. In the present work the conditions laid down by these writers have been adhered to as strictly as possible, so that my results would bear an exact comparison, and any conclusions drawn could not be criticized on the grounds of a difference in these conditions. One difference, a fundamental one, has emerged, however, and it is the conception of what is the normal incidence of Rh-negative individuals and of Rh incompatibility. This point will be discussed more fully presently.

The principles laid down by Scholl, Wheeler and Snyder (1947) that should be observed in the conduct of an investigation such as this have already been quoted, and it must be admitted that it has not been possible to fulfil them all in the present study. The number of cases of undifferentiated defect showing Rh incompatibility is 32, thus exceeding the 25 stipulated by Scholl *et al.* as a minimum. It has not been possible to examine any case within a year of birth, but an appreciable number were quite young children although many of the cases had reached adult life. The family histories were studied in each case, and any suggestion of erythroblastosis in other siblings was noted. All the cases examined had been certified under the M.D. Acts of this country, and earlier on in this work I have stated how it was finally decided which cases were truly undifferentiated. Finally, in the clinical histories given in the Appendices, any neurological abnormalities found to be present have been noted.

A comparison between Yannet *et al.*'s figures and those in the present work is both interesting and instructive. If their two series of cases are added together, they examined a total of 386 cases, 41 fewer than in this series. Table XVI shows the results of the two total series.

Table XVI.

	Total cases.	1 Total Rh-negative mothers.	2 Rh-negative mothers with Rh-positive children.
Yannet and Lieberman	386	68 (17·6%)	46 (11·9%)
Gilmour . . .	427	84 (19·7%)	52 (12·2%)

Table XVII compares the results when the two groups are divided into "control" and "undifferentiated." For this purpose I have included the "heredity" cases of my series in the undifferentiated group.

TABLE XVII.

	Total cases.	Total Rh-negative mothers.	Rh-negative mothers with Rh-positive children.
Yannet and Lieberman control cases	211	28 (13·2%)	16 (7·6%)
Gilmour control cases	152	35 (23·0%)	20 (13·2%)
Yannet and Lieberman undifferentiated cases	175	40 (22·9%)	30 (17·1%)
Gilmour undifferentiated cases	275	49 (17·8%)	32 (11·6%)

It is seen from Table XVI that my percentages are very slightly higher in both columns 1 and 2 than those of the Americans, and it is also seen that there is no statistical significance in the American figures for their total series of cases. From Table XVII the difference in the two sets of figures, both as regards total cases and the percentages, is at once apparent.

One reason for at least part of the difference in proportion between the control numbers and the undifferentiated numbers in the American series and mine is that I widened the scope of the investigation to include feeble-minded cases. Amongst my controls the big majority were low-grade (3·34 : 1), whereas amongst the undifferentiated the numbers were more nearly equal (1·25 : 1). The main reason for the marked difference in the percentages is undoubtedly that mentioned by Cappell (1947) and which has already been discussed, namely, the inclusion of the kernicterus and erythroblastosis cases by Yannet *et al.* in the test group and by me in the control group.

Another point, already hinted at, to be discussed in this comparison between the two sets of figures is the question of what are the normal figures with which to compare those in the test groups of cases. On this point there appears to be some difference of opinion between workers in America and in this country. Snyder *et al.* (1945*a*) stated unequivocally that in the general population 87 per cent. are Rh-positive and 13 per cent. Rh-negative; while Rh incompatibility occurs in about 8 per cent. of pregnancies. They obtained this figure of 13 per cent. for the incidence of Rh-negative people by regarding as negative only those who are completely so (cde/cde). Cook (1944), in the *Journal of Heredity*, said that conceptions in Rh-negative women will average 60 per cent. incompatible. If this figure is applied to the 13 per cent., the percentage of Rh-positive children from Rh-negative mothers certainly works out at about 8 per cent. (actually 7·8 per cent.).

It has already been discussed, however, why this conception of what should be regarded as Rh-negative is not correct when applied to incompatible pregnancies. If the figure of 15 per cent. for the incidence of Rh-negative individuals is taken as the normal, the expected percentage of incompatible pregnancies then becomes exactly 9 per cent. on Cook's formula. Race *et al.* (1948), however, have clearly shown that the percentage of completely negative individuals, rhrh (cde/cde), is in fact 15 per cent., and that when to these are added the other Rh-negative groups r′ and r″ the figure for all Rh-negative

individuals is then 16·84 per cent. Cook's formula applied to this gives the expected proportion of incompatible pregnancies as 10·1 per cent. The figure on which the present results have been statistically assessed is actually a shade lower, however, (9·92 per cent.), as this figure was calculated from the gene frequencies of the elementary antigens as given in the paper by Race *et al.*

Some trouble has been taken to emphasize this point, because if the present figures had been assessed on the American percentages, some of them, apart from the total number of Rh-negative mothers in the control group (see Tables II and III) would have been just statistically significant.

Finally, it should be observed that the percentages for my test group of imbeciles and idiots, the group comparable to Yannet and Lieberman's test group, could scarcely be more normal. In my series there were 153 cases (including the " heredity " ones) against the Americans' 175, and the respective percentages were 16·3 per cent. against 22·9 per cent., and 9·8 per cent. against 17·1 per cent.

Homospecific and Heterospecific Pregnancies.

The distribution of the ABO groups and the proportion of homospecific to heterospecific pregnancies were calculated because of observations made about their effect on iso-immunization, in relation to the Rh antigen. It was felt that although the total numbers were small, an observation on these points might at least produce confirmatory evidence one way or the other. This has, in fact, been the case, since both the distribution of the ABO groups and the ratio of homospecific to heretospecific pregnancies are within normal limits. They therefore suggest that iso-immunization in the cases of proved Rh incompatibility would not occur more often than normal. This is consistent with the actual findings in the present study, when allowance is made for the rather high incidence of cases of kernicterus. This increased incidence was to be expected, as has already been shown, and in all three cases of kernicterus the pregnancies were homospecific.

Effect of " Heredity " Cases.

Although throughout this work the 25 cases in which mental defect was found in the family history, apart from the defectives under consideration, have been referred to as " heredity " cases, it has not been meant to imply thereby that these cases were thought to be due solely to a bad heredity. What has been felt is that in these cases the hereditary factor must at least be taken into account. It will be seen from a study of Table X, where all the percentages have been summarized, that the inclusion or exclusion of these " heredity " cases makes virtually no difference to the figures, and there is no evidence to suggest that the Rh factor plays any part in the hereditary transmission of mental deficiency.

Conclusion.

The following points have been established as a result of the present work :

Compared with the percentage for the general population of this country, there was no significant difference in the percentage number of cases of Rh

incompatibility either in the whole group of defectives, in the control group, or in the test group, either in its entirety or when subdivided into high grade and low-grade cases.

Similarly, there was no significant difference between the figures for the control group and the test group.

Further, in the cases in which Rh incompatibility occurred, the ordinary blood group distribution and the proportion of homospecific and heterospecific pregnancies were quite normal.

From a careful consideration of the above points and of all the factors detailed in this work, I have come definitely to the conclusion that, so far as my results are concerned, the sample of cases from which they were obtained could equally well have been taken from the general population instead of a mental defective one. For this reason it is my opinion that Rh incompatibility, apart from when it causes erythroblastosis foetalis and kernicterus, plays no part in the aetiology of mental deficiency.

Summary.

The literature on the Rh factor and its relationship to human disease, physical and mental, has been reviewed.

My own investigation into the incidence of Rh incompatibility in 427 cases of mental deficiency has been described.

The conclusion has been drawn that Rh incompatibility, *per se*, is not a factor in the causation of mental deficiency.

Appendix A.

Control Group of Cases showing Rh Incompatibility.

Note.—Unless otherwise stated, there was no history in the defective of erythroblastosis foetalis, nor were atypical agglutinins found in the mother's serum.

1. *Mongols.*

Case 1.—R. C—, aet. 12. Third of three pregnancies. Homospecific. Mother's group, A Rh−ve; Defective's group, A Rh+ve.

Pregnancy and confinement were normal. Defective was always delicate, and is a typical mongol.

Family history: Eldest sibling is alive and well. Second pregnancy ended in a stillbirth, but details not known. Father's sister had a mental breakdown.

Case 2.—D. J. O—, aet. 4. First of two pregnancies. Heterospecific. Mother's group, A Rh−ve; defective's group, AB Rh+ve.

Pregnancy was normal, but child was premature, although otherwise normal. Defective is a typical mongol.

Family history: Younger sib. is a. and w. Otherwise *nil.*

Case 3.—M. W—, aet. 11. Sixth of six pregnancies. Homospecific Mother's group, B Rh−ve; defective's, O Rh+ve.

Pregnancy and confinement normal. Defective a typical mongol.

Family history: The three eldest sibs. are a. and w. They were followed by two miscarriages and then the defective. Cause of miscarriages not known. Otherwise *nil.*

2. Organic nervous disease.

CASE 4.—D. T. C—, aet. 4. Second of three pregnancies. Heterospecific. Mother's group, O Rh—ve; defective's, A Rh+ve. Defective is a twin.

Pregnancy normal, but defective and twin were three weeks premature. An instrumental delivery. Defective a very small child who has never developed properly. Has optic atrophy and is practically blind. There is rigidity of all muscles which go into spasm. Mentally he is very backward, being an imbecile.

Family history: First pregnancy, twins, premature. Both died 36 hours after birth. Defective's twin is a. and w., and youngest child is a. and w. Otherwise *nil.*

CASE 5.—J. N. S—, aet. 24. Third of six pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, O Rh+ve.

Pregnancy normal, prolonged labour, and child had convulsions at birth. Meningitis at two weeks, resulting in paralysis of the left side. Operation to eye at three months. Pneumonia at one year and three months. He is a feeble-minded epileptic.

Family history: First pregnancy ended in miscarriage, second in stillbirth. Fourth child died of pneumonia at three months; the fifth child died of T.B. Sixth is a. and w. No history of jaundice in the other children. Mother said to have had " brain fever " when she was born.

CASE 6.—L. L. E—, aet. 28. Fifth of seven pregnancies. Homospecific. Mother's group, O Rh—ve; defective's, O Rh+ve.

Pregnancy and confinement normal. Defective developed encephalitis lethargica when a few years old, since when she has never been right. She is feeble-minded.

Family history: Eldest three sibs. a. and w. Fourth died at three years of measles. Sixth and seventh sibs. a. and w. Otherwise *nil.*

3. *Spastics.*

CASE 7.—N. D. F—, aet. 20. Fourth of four pregnancies. Homospecific. Mother's group, B Rh—ve; defective's, O Rh+ve.

Pregnancy and confinement normal, although he was one month premature. Spasticity noticed when he did not begin to walk. Now walks with difficulty, and cannot go far from home.

Family history: Eldest sib. a. and w., second died at 16 months of measles. Third a. and w. Otherwise *nil.*

CASE 8.—R. F—, aet. 31. Seventh of eight pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Pregnancy and confinement normal as far as known. Defective paralyzed from birth, and is bedridden and helpless.

Family history: Eldest five sibs. a. and w. Sixth died at one year, cause unknown. Eighth a. and w. Otherwise *nil.*

CASE 9.—R. E. A—, aet. 23. Third of seven pregnancies. Heterospecific. Mother's group, O Rh—ve; defective's, A Rh+ve.

Pregnancy and confinement normal. Defective had meningitis at six months, and suffers from spastic paralysis.

Family history: Eldest sib. a. and w. Second died at 18 months, thought to be due to food poisoning. Fourth died at two days, cause unknown. Fifth and sixth a. and w. Seventh a miscarriage at three months. Otherwise *nil.*

CASE 10.—J. W., aet. 10. Second of two pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Pregnancy and confinement normal. Spasticity first observed when defective due to start walking. Shows inco-ordination of hands, but no true athetosis.

Family history: Elder sib. died at 14 months of bronchitis. Mother and maternal aunt are epileptics.

CASE 11.—J. A. W—, aet. 11. Only pregnancy. Homospecific. Mother's group, A Rh−ve; defective's, O Rh+ve.

Pregnancy normal. Breech birth, six weeks overdue it is stated by mother. Defective a spastic, and all movements show tremor and inco-ordination.

Family history: *Nil.*

CASE 12.—B. J. R—, aet. 17. Fourth of four pregnancies. Homospecific. Mother's group, AB Rh−ve; defective's, A Rh+ve.

Pregnancy and confinement normal. Child apparently normal at birth, but at three days developed jaundice which lasted intermittently for about three months. A few months later, paralysis of right side developed, and defective can walk only a little with support. Defective is also an epileptic, fits having occurred since the age of ten.

Family history: Eldest two sibs. a. and w. Third pregnancy ended in miscarriage at three months. Otherwise *nil.*

4. *Microcephalics.*

CASE 13.—J. H. W—, aet. 35. Second of 14 pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy normal, but birth premature, 6½ months. Defective very delicate and blind for six months.

Family history: Eldest sib. died aet. 24, of nephritis. Third a. and w.; fourth died at 14 months, paralysed. Pregnancies 5 to 9 all ended in stillbirths. Tenth sib. died within a few hours. Pregnancy eleven ended in stillbirth. Pregnancies 12 and 13 ended in miscarriages. Fourteenth sib. a. and w. Both grandmothers are believed to have been epileptics.

CASE 14.—M. M. S—, aet. 17. Fourth of five pregnancies. Homospecific. Mother's group, A Rh−ve; defective's, O Rh+ve.

Pregnancy normal. Extended breech birth. Child very anaemic when born and had no finger- or toenails. No jaundice.

Family history: Eldest two sibs. a. and w. Third pregnancy ended in miscarriage. Fifth sib. a. and w. Otherwise *nil.*

5. *Endocrine disorders.*

CASE 15.—F. B—, aet. 20. Third of seven pregnancies. Heterospecific. Mother's group, A Rh−ve; defective's, AB Rh+ve.

Pregnancy and confinement normal. Defective did not develop normally physically owing to endocrine imbalance for which he was treated in hospital.

Family history: First sib. died at nine months of meningitis. Second and fourth a. and w. Fifth died at ten months of mastoid trouble. Sixth and seventh (illegitimate) a. and w. Mother not very bright intellectually.

CASE 16.—J. W. J—, aet. 24. First of two pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy and birth normal. This individual is a moral rather than an intellectual defective. He is a dwarf, and has been in trouble many times for slitting girls' mackintoshes.

Family history: Younger sib. a. and w. Otherwise *nil.*

6. *Erythroblastosis foetalis and kernicterus.*

CASE 17.—P. S—, aet. 20. Third of six pregnancies. Homospecific. Mother's group, A Rh−ve; defective's, A Rh+ve.

Pregnancy and birth normal. Defective developed jaundice on day of birth and this persisted for about 14 days. He had fits just after birth, and again between ages of two and three. There is now no evidence suggestive of kernicterus. Defective is feeble-minded.

Family history: Eldest sib. died aged 21 of tubercle. Second a. and w. Fourth a. and w. Fifth and sixth pregnancies ended in stillbirths. Otherwise *nil.*

CASE 18.—R. B—, aet. 18. Third of five pregnancies. Homospecific. Mother's group, AB Rh—ve; defective's, B Rh+ve.

Pregnancy and birth normal. Jaundice said to have developed about the third day, but its duration is uncertain. The child was said to have a doubtful positive W.R. when young, and she and her mother attended hospital for injections. Defective's W.R. is now negative. She did not walk or talk till age of seven, and her articulation even now is very defective. She shows definite athetosis and is physically poor in health. She is an imbecile.

Family history: Eldest sib. (by first husband) a. and w. Second (by second husband) a. and w. Fourth pregnancy ended in stillbirth. Fifth sib. a. and w. The mother in this case is herself not very bright, but is not classed as a defective.

CASE 19.—J. C. H—, aet. 12. Fourth of four pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, O Rh+ve.

Pregnancy and birth normal. Defective was jaundiced at birth, but this cleared apparently satisfactorily. Owing to the development of spasticity and athetoid movements of all limbs, defective was unable to attend any school. His speech is poor.

Family history: First two sibs. a. and w. Third died at two days of jaundice. Otherwise *nil*.

CASE 20.—J. T—, aet. 15. Seventh of seven pregnancies. Homospecific. Mother's group, O Rh—ve; defective's O Rh+ve.

Pregnancy and birth normal. Severe jaundice developed on the third day, and lasted about three months. Child not expected to live, and she later developed athetosis. In this case the mother's serum agglutinated saline suspended Rh-positive cells, and the reaction was greatly enhanced when the cells were suspended in albumin, a titre of 1 : 8 being obtained. The indirect Coombs test was strongly positive when Rh-positive cells were used, and negative with Rh-negative cells.

Family history: Eldest and third sibs. died at nine months of meningitis. Second is a. and w. The fourth pregnancy ended in a miscarriage. Fifth and sixth sibs. a. and w. All the children were slightly jaundiced at birth. Otherwise *nil*.

APPENDIX B.

Test Group of Cases of Undifferentiated Mental Deficiency showing Rh Incompatibility.

Note.—Unless otherwise stated, there was no history in the defective of erythroblastosis foetalis, nor were atypical agglutinins found in the mother's serum.

1. *Feeble-minded cases.*

CASE 21.—R. H—, aet. 20. First of two pregnancies. Homospecific. Mother's group, O Rh—ve; defective's, O Rh+ve.

Pregnancy normal. No qualified help available at birth. Defective first attended an ordinary school, then special school.

Family history: Second pregnancy ended in a miscarriage during seventh month. Uncle of defective was an epileptic and died in a mental hospital.

CASE 22.—I. M. B—, aet. 18. First of three pregnancies. Heterospecific. Mother's group, O Rh—ve; defective's, A Rh+ve.

Pregnancy and birth normal. Nothing of note in later development, apart from fairly mild mental defect.

Family history: Second and third sibs. a. and w. No history of jaundice. Otherwise *nil*.

CASE 23.—J. S—, aet. 48. Fifth of nine pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Early details vague, but nothing of note then or in later development apart from mental defect.

Family history: First two sibs. died in infancy; third, fourth and sixth a. and w. Seventh, eighth and ninth (by second husband) a. and w. Otherwise *nil*.

CASE 24.—C. A—, aet. 36. First of two pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy normal. Breech birth. Slight jaundice just after birth, duration unknown. Nothing of note in later development apart from mental defect, and nothing to suggest that the early jaundice was of the icterus gravis type.

Family history: Second sib. a. and w. A cousin of the defective, on the father's side, is also a defective.

CASE 25.—A. M. W—, aet. 38. Sixth of ten pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy and birth normal. Backward development generally from early age. Fell downstairs and broke leg at four years, with doubtful head injury. Defective always delicate, but on examination no evidence of icterus gravis or kernicterus.

Family history: Eldest sib. died at 10 weeks, cause unknown. Second and third a. and w. Fourth died at 1½ years, and fifth at three years, both of meningitis. Seventh a. and w. Eighth pregnancy ended in stillbirth, mother being unwell due to worry and lack of food. Ninth and tenth sibs. a. and w. Otherwise *nil*.

CASE 26.—W. H. H—, aet. 41. Eighth of ten pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy and birth normal. Some jaundice noticed just after birth, but no history of defective having been seriously ill at the time. Backward in general development, and did not walk till aged 3. Thought at that time to be due to paralysis, but now no evidence of this. Was certified under the M.D. Acts in 1924, and under the Lunacy Acts in 1945.

Family history: Eldest sib. a. and w. Second and third pregnancies ended in stillbirths. Fourth to seventh and ninth and tenth sibs. a. and w. Otherwise *nil*.

CASE 27.—A. L. W—, aet. 54. Only pregnancy. Homospecific. Mother's group, A Rh−ve; defective's, O Rh+ve.

Pregnancy normal. Confinement very difficult, and it was feared child would be lost. Nothing of note in later history apart from mental defect apparent from an early age and the later development of mental illness.

Family history: Parents were second cousins. Father was intemperate. A cousin of the defective died in a mental hospital.

CASE 28.—P. T—, aet. 29. Fourth of four pregnancies. Homospecific. Mother's group, AB Rh−ve, the genotype being r'r (Cde/cde); defective's AB Rh+ve.

Pregnancy and birth normal. Nothing of note in history till he was aged 23, when he developed epilepsy. Life-long defective.

Family history: Eldest three sibs. a. and w. Otherwise *nil*.

CASE 29.—J. B—, aet. 12. First of two pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy and birth normal. Nothing in history of note apart from mental defect.

Family history: Younger sib. a. and w. Otherwise *nil*.

CASE 30.—D. E. M—, aet. 23. Third of six pregnancies. Heterospecific. Mother's group, O Rh−ve; defective's, A Rh+ve.

Mother had a bad fall during early stages of the pregnancy, but she carried on to term. Birth normal. Epilepsy began at one year and has continued since.

Family history: Other five sibs. a. and w. Otherwise *nil*.

CASE 31.—F. B—, aet. 29. Sixth of 15 pregnancies. Homospecific. Mother's group, O Rh−ve; defective's, O Rh+ve.

Pregnancy and birth normal. Defect present from early age.

Family history: First, fourth, fifth, seventh, ninth and thirteenth sibs. died at an early age of physical illness. The rest, eight in all, a. and w. No defectives among them. One grandparent on each side of the family said to be backward. The defective's father was a heavy drinker.

CASE 32.—J. G. P—, aet. 31. Second of eight pregnancies. Homospecific. Mother's group, A Rh—ve; defective's group, A Rh+ve.

Pregnancy and birth normal. Nothing of note in later history apart from mental defect.

Family history: Eldest sib. died at two years, cause not known. Third died at two years of meningitis. Fourth and fifth a. and w. Sixth, seventh and eighth died at one week, two and three days respectively, cause unknown. An uncle of the defective's mother was ill mentally for some years.

CASE 33.—R. L. S—, aet. 18. Third of three pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Pregnancy and birth normal. Nothing of note in later history apart from mental defect.

Family history: Eldest sib. died at 13 of cerebral tumour. Second a. and w. The mother is a patient in a mental hospital, and her father died of mental trouble (senility or comparable trouble almost certainly.)

CASE 34.—J. H. W—, aet. 34. Third of three pregnancies. Homospecific. Mother's group, O Rh—ve; defective's, O Rh+ve.

Pregnancy and birth normal. Defective has been an epileptic since age of three and a half.

Family history: Eldest two sibs. a. and w. Otherwise *nil.*

CASE 35.—K. J. W. D—, aet. 21. First of ten pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, O Rh+ve.

Pregnancy normal: Forceps delivery, but child apparently normal, and nothing in later history apart from mental defect. Atypical agglutinins were found in the mother's serum, which did not agglutinate saline suspended cells, but agglutinated strongly all the albumin suspended Rh-positive test cells. The indirect Coombs test was also strongly positive. This finding occurred five years after the birth of the youngest sib., but it was impossible to obtain specimens from the rest of the children owing to lack of further co-operation.

Family history: Second, fourth, fifth, seventh, ninth and tenth sibs. a. and w. Third died at $2\frac{3}{4}$ years of pneumonia. The sixth and eighth pregnancies ended in stillbirths. Otherwise *nil.*

2. *Imbecile and Idiot Cases.*

CASE 36.—J. G. D—, aet. 20. First of two pregnancies. Homospecific. Mother's group, O Rh—ve; the genotype being either r'r (Cde/cde) or r'r' (Cde/Cde); defective's group, O Rh+ve.

Pregnancy and birth normal. History of fits from six months to $2\frac{1}{2}$ years. Otherwise nothing of note apart from mental defect.

Family history: Second sib. a. and w. Otherwise *nil.*

CASE 37.—E. A. S—, aet. 42. First of four pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Pregnancy and birth normal. Epilepsy present since age of 13, but mental defect was evident from an early age.

Family history: Difficult labours and instrumental deliveries at all confinements after the first. Second and third sibs. a. and w. Fourth pregnancy resulted in twins, one being a. and w., the other dying aged 6 of diphtheria. No jaundice in any of these sibs. at birth. Otherwise *nil.*

CASE 38.—S. H—, aet. 15. Only pregnancy. Homospecific. Mother's group, O Rh—ve; defective's, O Rh+ve.

Pregnancy normal. Umbilical haemorrhage at birth, after prolonged instrumental labour. Epilepsy present since age of two.

Family history: *Nil.*

CASE 39.—M. B—, aet. 34. First of three pregnancies. Heterospecific. Mother's group, O Rh—ve; defective's A Rh+ve.

Pregnancy and birth normal (seven months). No jaundice developed, but defective was anaemic and delicate. Fell out of bed when a few weeks old, but no

evidence this had any bearing on the mental defect, although the forehead was injured.

Family history: Second sib. died at ten weeks, said to be due to T.B. of bowel. Third sib. a. and w. No history of jaundice in either case. Otherwise *nil.*

CASE 40.—E. M. G—, aet. 36. Second of six pregnancies. Heterospecific. Mother's group, O Rh−ve; defective's, A Rh+ve.

Pregnancy, birth, and later history normal, apart from mental defect.

Family history: All the other five sibs. a. and w. with no history suggestive of erythroblastosis. Otherwise *nil.*

CASE 41.—B. M. B—, aet 7. First of four pregnancies. Heterospecific. Mother's group, O Rh−ve; defective's, A Rh+ve.

Mother had chronic nephritis and pregnancy was terminated four weeks early. Birth normal. Defective had blood transfusions from mother at two months because of attack of gastro-enteritis. Subsequent history normal apart from defect.

Family history: Induced labours for all the sibs. owing to the nephritis. Three younger sibs. a. and w., but last child was slightly jaundiced at birth. Otherwise *nil.*

CASE 42.—P. E. B—, aet. 9. First of two pregnancies. Heterospecific. Mother's group, O Rh−ve; defective's, A Rh+ve.

Normal pregnancy. Breech delivery, one week overdue. Baby "slate-coloured" at birth and he had two transfusions from father on same day. No actual jaundice developed. Defective said to have had meningitis at three years, but there is no evidence that defect was due to this.

Family history: Younger sib. aet. 5, a. and w. He also is Rh+ve, with no history suggestive of erythroblastosis, so that defective's condition at birth could in no way be related to iso-immunization. Otherwise *nil.*

CASE 43.—A. F—, aet. 12. Second of three pregnancies. Heterospecific. Mother's group, O Rh−ve; defective's, A Rh+ve.

Pregnancy, birth, and later history normal apart from defect.

Family history: First and third sibs. a. and w. Mother has suffered from thyrotoxicosis.

CASE 44.—C. R. H—, aet. 16. Seventh of eight pregnancies. Homospecific. Mother's group, A Rh−ve; defective's, A Rh+ve.

Mother had a fall while pregnant and this caused a large "lump on the privates." This was removed and baby was born a few days later, a fortnight prematurely. Birth normal. Epileptic fits occurred between aged of 4½ and 12 years.

Family history: First pregnancy ended in stillbirth at 7½ months. Second, third and fourth sibs. a. and w. Fifth died aged 11, said to be due to diabetes. Sixth pregnancy ended in miscarriage at 4½ months. Eighth sib. a. and w. Otherwise *nil.*

CASE 45.—B. D. J—, aet. 26. Fourth of six pregnancies. Homospecific. Mother's group, A Rh−ve; defective's, O Rh+ve.

Normal pregnancy: Caesarean birth at 8 months. Defective always delicate and for first 12 months was stated to be in hospital receiving blood tests and injections, but the hospital in question could find no trace of this individual in their records. She now shows no stigmata of syphilis, and there was nothing else of note in her history apart from mental defect.

Family history: First pregnancy ended in stillbirth, and second sib. died at ten weeks, cause unknown. Third pregnancy ended in stillbirth (eight months), and fifth in miscarriage (four months). Sixth sib. a. and w. Otherwise *nil.*

CASE 46.—W. J. R—, aet. 21. Second of five pregnancies. Homospecific. Mother's group, A Rh−ve; defective's, O Rh+ve.

Pregnancy and birth normal. Defective fell downstairs at eight months, but no evidence that this had anything to do with the mental defect. Nothing else of note in later history.

Family history: First sib. a. and w. Third, fourth and fifth pregnancies ended in miscarriage. Otherwise *nil.*

CASE 47.—L. M. S—, aet. 11. Only pregnancy (twin). Homospecific. Mother's group, O Rh—ve; defective's, O Rh+ve.

Pregnancy and birth normal (eight months). Defective had severe diarrhoea at ten weeks, but later history normal apart from the mental defect.

Family history: Other twin a. and w. Otherwise *nil*.

CASE 48.—G. J. P—, aet. 17. First of two pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, O Rh+ve.

Pregnancy, birth and later history normal apart from defect.

Family history: Second sib. a. and w. Great-aunt was mentally ill, and grand-uncle was said to have committed suicide. Both were on father's side.

CASE 49.—J. C. A—, aet. 32. First of two pregnancies. Homospecific. Mother's group, O Rh—ve; defective's, O Rh+ve.

Pregnancy normal; instrumental delivery at eight months caused bruising on head. Defect first noticed at about two years. Nothing else of note in subsequent history.

Family history: Second sib. a. and w. Otherwise *nil*.

3. "*Heredity*" *Cases*.

CASE 50.—B. G. C—, aet. 11. Sixth of seven pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Mother had kidney trouble during last six weeks of pregnancy. Defective a twin, dissimilar. Birth and subsequent history normal apart from mental defect. Defective is an imbecile.

Family history: Other seven sibs. a. and w. An aunt and uncle of defective on father's side are imbeciles. Another aunt on father's side is in a mental hospital.

CASE 51.—H. R—, aet. 19. Eighth of 15 pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, A Rh+ve.

Mother had pneumonia during late pregnancy and was very ill during and after birth of child. Later history normal apart from mental defect. Defective is feeble-minded.

Family history: First sib. a. Is a discharged defective. Details of rest of family not clear. Three died in infancy of physical illness; there was a stillbirth about the tenth pregnancy, and also a miscarriage; position in family sequence not known. The mother herself seemed of poor intelligence. Eldest sister of defective is feeble-minded. Two cousins, brothers, are both feeble-minded with superadded schizophrenia.

CASE 52.—C. Y—, aet. 30. First of two pregnancies. Homospecific. Mother's group, A Rh—ve; defective's, O Rh+ve.

Pregnancy and birth normal. Defective and mother were knocked down by a motor cycle when he was aged two years, since when he has not spoken. There is no evidence that this was the cause of the defect, and there is nothing of note in the later history. Defective is feeble-minded.

Family history: Younger sib. a. and w. The mother is feeble-minded. The father was in a mental hospital for many years. A half-sister of the defective (same father) is an imbecile.

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