

OBSERVATIONS ON THE RÔLE OF THE RH FACTOR IN HUMAN DISEASE,
WITH PARTICULAR REFERENCE TO MENTAL DEFICIENCY.

by

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INTRODUCTION.

The study of the Rh Factor in all its ramifications is an extraordinarily fascinating one, and the discovery of its presence in human blood has led to far-reaching consequences. Many workers on both sides of the Atlantic have done intensive research work on this subject since the discovery of the factor 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 aetiology. The number of cases of mental deficiency in our institutions, apart from the large number cared for at home, both in this country and in America, as well as in other countries, 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 owing to the fact that there is no possible cure. If a means of preventing even a small proportion of the present number of defectives from being born could be found, the result would be well worth while from an economic and social point of view, apart altogether from the avoidance of the distress/

distress caused to parents who have the misfortune to produce a mentally defective child.

The object of the present work is two-fold. In the first place, a review of the literature will be given, showing on the one hand how the Rh factor came to be associated with the condition known as Erythroblastosis Foetalis, and on the other how this condition was associated with Kernicterus and its consequences. An attempt will be made to correlate these two lines of research and to show how the idea developed that the Rh factor may cause certain cases of mental deficiency other than those obviously associated with Kernicterus. In the second place, my own investigations will be described, and my results compared with those already in the literature. Certain case histories will be described and commented on, and finally, attention will be drawn to any inference and conclusions that can be made.

REVIEW OF THE LITERATURE.

Early Theories on Incompatibility of Foetal and Maternal Blood.

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

Early in 1923 McQuarrie suggested, as a result of observations on 180 women, that there was a relationship between the incompatibility of maternal and foetal blood on the one hand and the development of Eclampsia, or pre-eclamptic toxæmia, on the other. He proved that in 23.3% of the cases 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 of McQuarrie's, Ottenburg, later in the same year and in an article also on Eclampsia, referred to the work of Dienst in 1906. He quoted how the latter worker injected Methylene Blue solution under low pressure into the umbilical artery or vein of the still attached placenta of women at the end of child-birth. In a proportion of these women, the dye appeared in the urine in considerable amount, and Ottenburg says that Dienst interpreted this as meaning there was a communication between the circulation of the mother and the child. Further, Dienst examined the blood of these mothers for agglutination when mixed with the blood of their own children, and/

and he found that in a proportion of cases the mother's serum did agglutinate the red cells of the child. Dienst, Ottenburg continued, propounded the theory 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 went on to say that a few years later Dienst retracted his idea, but that he, Ottenburg, was convinced it was correct. The matter was allowed to drop, however, until it was reopened in the article by McQuarrie. Ottenburg concluded his article by putting forward the idea that several other unexplained diseases, particularly the jaundice of the newborn, might be due to the same cause, namely, accidental placental transfusion of incompatible blood.

Again the subject was allowed to drop, and it was not until 1938 that the theory was once more put forward by Darrow. This writer gave an excellent and full description of the course and clinical manifestations of Icterus Gravis Neonatorum. (For reference purposes, an equally good description is given by Hawksley and Lightwood - 1934). Darrow then reviewed the literature on the subject and 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 condition of congenital (idiopathic) anaemia, owing to the familial association of the three conditions. (Erythroblastosis Foetalis is the general term now used to denote these three conditions. Another term, preferred by some writers, e.g. Parsons/

Parsons, Hawksley, and Gittins (1933) and McIntosh (1941), as being more accurate, is Haemolytic Disease of the Newborn).

After an exhaustive analysis of all the previous theories as to the aetiology of these conditions (with the exception curiously enough of Ottenburg's suggestion; I have carefully searched her paper and cannot find any reference to the earlier article mentioned), Darrow tentatively suggested that the red cells of the infant are destroyed by the action of specific immune bodies. She believed that the mother is actively immunised against the foetal red cells or some component of them, but she thought that foetal Haemoglobin might be immunologically different from adult Haemoglobin, and thus be the antigen involved.

Neither Ottenburg nor Darrow, however, produced any direct evidence in support of their theories. Ottenburg's was pure speculation, while Darrow's was more or less the result of a process of elimination.

Intra-group Agglutination.

It was in the following year, 1939, that Levine and Stetson reported an unusual case of intra-group agglutination, and put forward a theory to account for it. The case was that of a woman having her second pregnancy and she developed signs of toxæmia. Labour started during the 33rd week and a macerated still-born foetus was delivered. Owing to considerable bleeding, the patient (group O) was transfused with 500 cc whole blood from her husband (also group O). Ten minutes later she developed/

developed a chill, and complained of pains in the legs and head. Her blood was examined, and an irregular agglutinin found. Out of 54 bloods of group O, thirteen only failed to react with the patient's serum. The reactions were as active at 37 degrees C. as at 20 degrees C., hence they differed from those due to so-called atypical agglutinins occasionally found in the sera of normal people. The reactions were independent of the M, N, or P factors. Levine and Stetson 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 the iso-immunisation of the patient. (The process is called iso-immunisation when the individual producing the agglutinins and the individual possessing the antigens which stimulate the production of the agglutinins belong to the same species). These workers presumed that the immunising property in the blood and/or the tissues of the foetus must have been inherited from the father. They were unable, however, to determine the nature of this iso-agglutinin or the antigen responsible for its production.

Wiener and Peters (1940) reviewed the literature dealing with haemolytic reactions following the transfusion of blood. After describing accidents following repeated intra-group transfusions (an intra-group transfusion is one where the ABO group of the donor is compatible with the ABO group of the recipient/

recipient), they stated that there were a number of reports of intra-group haemolytic reactions in patients who had never received a previous blood transfusion. They listed the reports, and then pointed out that in all the cases except one (which ultimately proved not to be a case of intra-group haemolytic reaction at all) the patients were women who had recently given birth to a child or had had a miscarriage. This article was the foundation of the suspicion that the two conditions might have a common aetiology although the cause was not yet known.

Discovery of the Rhesus Factor.

It was in this same year, 1940, that Landsteiner and Wiener published their epoch-making first article on a new factor they had discovered in human blood. In this article they described how they had previously discovered the capacity possessed by some rabbit immune sera, produced with blood of Rhesus monkeys, of reacting with human bloods that contain the agglutigen (antigen) M. Following up this work, they then found that another individual property of human blood, which they designated as Rh, could be detected by certain of these sera. On exhaustion of such a serum with selected bloods, e.g. OM, the absorbed serum still agglutinated the majority (39 out of 45) of other human bloods, independently of the ABO group, the MN type, or the property P.

This preliminary article was followed up the next year, 1941, with another article by the same authors. In this article/

article it was stated that it had been concluded, from observations made with immune sera, especially by tests with occasionally occurring normal and post-transfusional human sera containing irregular agglutinins, that there existed individual properties of human blood other than those demonstrable by readily available reagents such as A1, A2, B, M and N. The first attempts to find additional antigens were not successful till it was thought desirable to immunise with animal instead of human blood, considering that the blood of some animals contains antigens related to antigens present in individual human bloods. In this way, the factor they called Rh was discovered, as previously described. It was found to be present in 85% of the cases examined, taken from the white population of America.

These workers then stated 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.

In this paper, the authors also discussed the related fact of the appearance of immune iso-antibodies in pregnancy, following on the case reported by Levine and Stetson, and the review of cases by Wiener and Peters (1940).

By/

By using guinea-pigs instead of rabbits, Landsteiner and Wiener were able to obtain much more active immune sera, and, using these or human sera, or both, they tested 448 white individuals and found that 84.6% were Rh-positive and 15.4% were Rh-negative. Distribution in the sexes, and among the blood groups and M and N types did not reveal any definite correlation, nor was there any between Rh and P. Only 9 of 113 negro bloods were Rh-negative, this suggesting a racial distribution.

As a result of studies on heredity, these authors concluded that the property Rh was inherited as a dominant, not sex-linked, and by analogy to other individual human blood properties they presumed that the Rh factor 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, namely, 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 followed up, both in America and in Britain. In this country, Boorman, Dodd, and Mollison (1942) examined 1610 individuals in the general population, and they found that 85.15% were Rh-positive and 14.85% were Rh-negative. Similarly, Hoare (1943), who examined a series of 1122 people in South Wales, found that 84.6% were Rh-positive and 15.4% were Rh-negative. Cappell (1944) examined 3000 cases in Dundee and district, and found that/

that 84.5% were Rh-positive while 15.5% were Rh-negative. Plaut, Barrow and Abbott (1945) working in the London area examined 5,837 group O donors, this number being made up of two series. In the first, 84% were positive, and in the second 83.3% were Rh-positive. The figures of all these various workers agree very closely, and it is now accepted that in the white population 85% are Rh-positive, and 15% are Rh-negative, to guinea-pig anti-serum and the corresponding standard human anti-serum.

Complexity of the Rh Factor.

It was soon found however, as is very often the case, that the matter was not so simple as at first thought, and it became evident 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.

Only a short outline of the complexities of the subject, based mainly on Cappell (1946, 1948) will be given, followed, for the sake of completeness, by a very brief summary of the literature on this part of the subject.

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/

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 r. The ry type was the one believed to exist, but for some years it eluded detection. It has now been found, however, 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 allelomorphous genes, which he designated by the letters Cc, Dd, and Ee. Each of the six letters indicate 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:-

	Ro = cDe
Rh positive	R1 = CDe
Types	R2 = cDE
	Rz = CDE

Rh/

Rh negative	r'	=	Cde
Types	r''	=	odE
	ry	=	CdE
	r	=	ode

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

A very considerable literature is now available on the various anti-sera, on the Rh antigenic structure, and on technical methods etc., and the following articles are ones which I can recommend as being important contributions to the subject.

Anti-Rh sera which deviate from the standard (85%) serum (equivalent to the guinea-pig serum of Landsteiner and Wiener) have been described in articles by Race and Taylor (1943); Race, Taylor, Boorman and Dodd (1943); Race, Taylor, Cappell and McFarlane (1944); Race (1944); Mourant (1945); Callander and Race (1946); Haberman, Hill, Everist and Davenport (1948); Wiener (1941); Levine (1943); Wiener (1943a); Waller and Levine (1944); Wiener (1944a); and Wiener, Davidschn and Potter (1945). Several of these anti-sera were independently discovered by workers in America and in this country.

Contributions on the subject of Rh sub-types have been made by Wiener (1943b, 1944b, 1944c); Race, Taylor, Boorman and Dodd (1943); Race (1944) in which is first described Fisher's nomenclature; Wiener (1946) criticizes this terminology somewhat severely; Race, Taylor, Cappell and McFarlane (1944); McCall, Race and Taylor (1944); Taylor and Race (1944a); Race, McFarlane and Cappell (1945); Levine (1945) in/

in which he corrects a clerical error that had occurred in his article with Waller (1944) and which had misled some of the British workers; Cappell (1945); Murray, Race and Taylor (1945); Race, Mourant and Callender (1946); Callender and Race (1946); Stratton (1946); Cappell (1946).

Transfusion reactions in Rh-negative subjects have been dealt with by Wiener (1941); Unger and Wiener (1945); Maloney (1945); Drummond, Taylor and Rice Edwards (1945); Callender, Race, and Paykoc (1945); Gunz (1946); and Callender and Paykoc (1946).

On the technical side, i.e. the methods of detecting the presence of the Rh factor, iso-agglutinins, etc., there are articles by Wiener (1941); Taylor, Race, Prior and Ikin (1942); Taylor (1943); Wiener (1945b); Diamond and Abelson (1945); Baar (1945); Boorman, Dodd and Morgan (1945); and Coombs, Mourant and Race (1945; 1946).

Articles dealing with racial differences in the incidence of the Rh factor have been written by Levine (1943); Levine and Waller (1944); and Simmons, Graydon and Hamilton (1944).

A number of articles appear more than once in the above list of references as they deal with different aspects of the subject in the same article. I have referred to some of them also in greater detail elsewhere in this work. This list, while it does not pretend to be completely exhaustive, is comprehensive and covers the whole field of our present-day knowledge of the Rh factor, its various sub-divisions, and the methods/

methods whereby Rh antigen-antibody reactions may be detected.

The only point to which I need draw special attention at this juncture 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 already discussed, about 2% 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 sub groups with the Rh positive series.

As Cappell points 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-immunisation, either in intra-group transfusions or in pregnancy, and for these purposes, therefore, such women should be regarded as Rh-negative. In my own investigations, therefore, I decided to include amongst the Rh-negative group any such cases found, and, as will be shown later, I actually did find two mothers of the sub-type r'.

Relationship of Rh Iso-immunisation to Erythroblastosis Foetalis.

Meantime, Levine and his collaborators 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 immunised by her foetus, or the foetal/

foetal parts of the placenta. What they called "warm" agglutinins, i.e. those that reacted better at 37 degrees C. than 20 degrees C., were found in four out of seven cases, and the specificity of one serum containing a warm agglutinin corresponded to the anti-Rh of Landsteiner and Wiener (1940). The assumption was made that these warm agglutinins were one of several varieties of anti-bodies resulting from iso-immunisation of the mother by the products of conception. 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) discussed five patients in whom atypical agglutinins were observed, three of these patients having given birth to infants suffering from Erythroblastosis Foetalis. Obstetric complications were described in each case, and it was 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-immunisation, 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 capable of penetrating the placental barrier. They stated that there was sufficient evidence/

evidence to indicate that most of these sera contained an agglutinin which paralleled the anti-Rh agglutinin of Landsteiner and Wiener.

Levine (1941) suggested that anti-Rh agglutinins were responsible for about 90% of all intra-group transfusion accidents, either after repeated transfusions or in pregnancy at the first transfusion. In other words, according to Levine, a certain proportion of Rh-negative individuals can produce anti-Rh agglutinins either by immunisation with the Rh factor of the foetus or by repeated transfusions with Rh-positive donors. He stated that the findings on investigation of several cases suggested that Erythroblastosis Foetalis is the result of (1) iso-immunisation 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. He stated that previously the incidence of Erythroblastosis Foetalis was given as 1:2000 births, this figure including the three accepted clinical forms of the condition (Hydrops Foetalis, Icterus Gravis Neonatorum, and Anaemia of the newborn). In his own recent series of 1400 deliveries, there were actually eight cases, a proportion of less than 1:200. He admitted that six of these cases would have been missed if they had not been specially looked for and/

and without blood investigations. Of the six, two would have been considered foetal deaths in utero of unknown cause, and the remaining four idiopathic anaemias of the newborn. Comparative figures given by other workers for the incidence of Erythroblastosis Foetalis are 1:200 (Snyder et al, 1945) and 1:250 (Cappell, 1946).

Levine, Burnham, Katzin and Vogel (1941) carried on the investigation. They examined 153 mothers who were delivered of one or more infants suffering from one of the three clinical forms of Erythroblastosis Foetalis. The blood of each of these women was tested by one or more three known human potent anti-Rh sera. Each serum did not give exactly parallel results, but the combined figures were that out of the 153 women, 93% were Rh-negative. 89 husbands and 76 affected infants in the series of Rh-negative mothers were tested, and they were found to be 100% Rh-positive, the figure anticipated if their theory was correct. Anti-Rh agglutinins in the 141 Rh-negative mothers were present in 42 cases, in 33 of which the blood was examined within two months of parturition. This, they stated was in conformity with the accepted fact that the course of antibody production in general is characterized by a gradual rise, a period of maximum activity and a gradual disappearance. (It is now known that the titre rises during pregnancy in such cases). In a few cases the anti-Rh agglutinin was demonstrated as long as two years after parturition.

Reference is made in this article to the previous theory that/

that a difference in the blood groups of mother and infant was the cause of familial Icterus Gravis (Ottenburg, 1923). The concept was known as "heterospecific" pregnancy. The authors then stated that it is now known that a mother's normal iso-agglutinin anti-A (or anti-B) is increased in titre as a result of iso-immunisation with the A (or B) blood of the foetus. However, they continued, the maternal agglutinins are specifically inhibited from acting on the foetal blood because of the wide distribution of the A and B factors in the tissues and body fluids. This wide distribution of these factors occurs in only 80% of individuals, however, such individuals being known as "secretors", and Levine et al, put forward the theory that if a foetus say of group A is a "non-secretor", i.e. does not have the factor in other tissues and fluids besides the blood, it is conceivable that the maternal iso-agglutinin anti-A may serve as the source of the intra-uterine haemolytic process.

Part of this theory has subsequently been proved by other workers who have described cases of Erythroblastosis Foetalis resulting undoubtedly from a heterospecific pregnancy, and where the mother was Rh-positive, or both parents were Rh-negative. (Boorman, Dodd and Mollison, 1944; Polayes and Ohlbaum, 1945; Aubert, Cochrane and Ellis, 1945; Austin and Smith, 1946).

The idea, however, that Erythroblastosis Foetalis may occur when the foetus is a non-secretor and not when it is a secretor/

secretor is rather contradicted by the work of Smith (1945) who found exactly the opposite when investigating the effect on the anti-A and anti-B agglutinin in heterospecific pregnancies. Also, in the case described by Austin and Smith (1946), the child was proved to be a secretor. From their considerations, however, it was assumed by Levine et al. that the Rh factor was not present in the tissue cells or body fluids, but was limited to the red blood cells only. That there is a relative absence of soluble Rh substance in the plasma appears to be fairly generally accepted as correct.

Factors influencing the severity of Erythroblastosis Foetalis.

Levine et al. (1941) went on to state 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, from the invariably fatal Hydrops Foetalis to the mild, frequently unrecognisable, Anaemia of the newborn, they suggested was probably the result of the varying degrees and duration of iso-immunisation during the course of pregnancy.

In this connection, it is interesting that Stratton (1943) demonstrated that the blood of a 48 mm embryo, approximately eleven weeks old, could readily be typed for the Rh factor, and that Cappell (1946) has shown that the red blood cells of several foetuses of ten to twelve weeks gestation were strongly Rh-positive. This means that it is at least theoretically possible/

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, so that the theory of Levine and his colleagues may well have some truth in it.

This is not the whole story however. Davidsohn (1945) considers that four factors may influence the severity of Foetal Erythroblastosis and its manifestations:

- (1) age of foetus when Rh antibodies begin to act on it.
- (2) length of time during which foetus is exposed to such action.
- (3) strength of Rh anti-bodies of which the titre of anti Rh agglutinins in the blood of the mother may or may not be a measure.
- (4) permeability of the placenta. It is possible there are quantitative differences in different women and at different times even in the same women.

An unusual type of antibody was discovered by Wiener (1944a) which he termed a "blocking" antibody, and independently by Race (1944) which he called an "incomplete" antibody. I need not elaborate on this except to say that, according to Cappell (1946), it is now recognised that the development of such an antibody in the mother's serum is usually followed by the most severe form of foetal disease, Hydrops Foetalis.

Theories regarding the Clinical Forms of
Erythroblastosis Foetalis.

One difficulty that Levine et al. encountered in connection with their iso-immunisation theory was the clinically observed/

observed fact that some infants were born apparently free of the condition, but in the course of a few days severe anaemia or jaundice appeared. One explanation they gave was the storage of the mother's agglutinins by the tissue of the foetus and their subsequent release could then induce haemolysis several days after birth. Levine (1943) commenting on this theory said it would involve the simultaneous presence of maternal anti-Rh agglutinin and its corresponding antigen in the blood stream of the affected infant, while in practice the survival of maternal anti-Rh agglutinin in the infant had been rarely demonstrated.

Another theory was that of Wiener (1945b). In his description of what he calls the "conglutination" test, devised to overcome the difficulty produced by the presence of "blocking" antibodies, Wiener stated that a third factor, X protein, is necessary for in vitro conglutination. (X protein is a large molecular complex of albumin, globulin and phospholipid). He believed it is therefore probably important for in vivo haemolysis. In the cases where symptoms do not arise till some hours after the baby is born, he suggested that X protein does not form till after birth at which time the profound physiological changes occurring bring about aggregation of serum protein into more complex molecules. Cappell (1946) criticised this theory on the grounds that when a mother's serum is rich in blocking antibodies, the foetus often fails to reach full term and is commonly still-born prematurely; or there is even/

even a miscarriage as early as the fifth month.

In a later article, Wiener, in conjunction with Waxler and Grundfast (1947) developed yet another theory to explain the different clinical manifestations of the disease in infants. These writers suggested that a difference in the quality of antibody produced by the mother is responsible for the difference. They based this theory on the study of two cases described in detail, and they said that univalent antibodies pass the placental barrier during the last third of pregnancy. These may give rise to still births, live births with minimal jaundice if hepatic function is good, or, if it is poor, severe jaundice with its accompanying toxicity, and the dangers of ultimate kernicterus if intra-vascular conglutination with capillary damage to the brain occur. Bivalent antibodies on the other hand gain access to the circulation principally during parturition, and the infant at delivery often seems normal. Intra-vascular agglutination, if it occurs, does so suddenly, so that an apparently healthy infant may die suddenly without developing anaemia.

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

A much more likely theory, it seems to me, is that of Skelton and Tovey (1945). These workers believe that the absence/

absence of jaundice at the time of delivery is probably accounted for by the fact that while the child is in the uterus it is not called upon to excrete its own bilirubin, but this is excreted for it by its mother. Once the child has to lead a separate existence, however, the liver damage, which they believe occurs in utero in cases of Icterus Gravis, becomes manifest, and jaundice develops shortly after birth.

The most comprehensive contribution to this aspect of the problem is the recent publication by Mollison and Cutbush (1949). These writers show that the haemoglobin value in the cord blood of an infant with Haemolytic Disease is well correlated with the severity of the disease. They believe also that the form of Rh antibody in the mother's serum and the antibody titre show some correlation with the severity of the haemolytic process in the infant, but exceptions are frequent, and hence antibody tests can be used only to forecast probabilities.

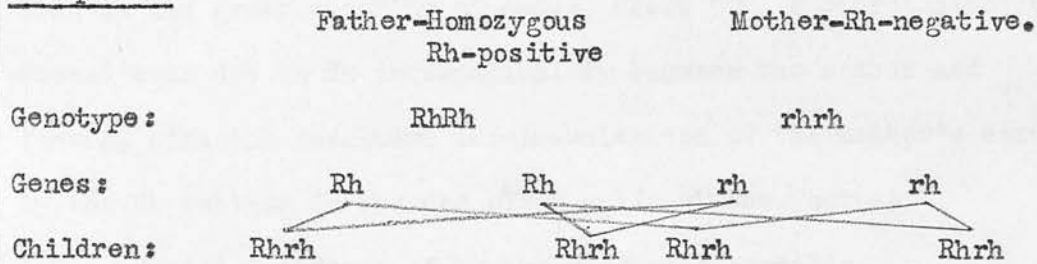
Hereditary Nature of Erythroblastosis Foetalis.

Levine et al. (1941) concluded this article by stating the hereditary nature of Erythroblastosis Foetalis in terms of the iso-immunisation theory. In some families every pregnancy is affected, except perhaps the first, while in other families only one of several pregnancies results in an affected infant. Since the Rh factor is inherited as a simple mendelian dominant, they continued, it is obvious from a genetic standpoint that this striking difference in the familial incidence of the disease is determined by the homozygosity (RhRh) or heterozygosity/

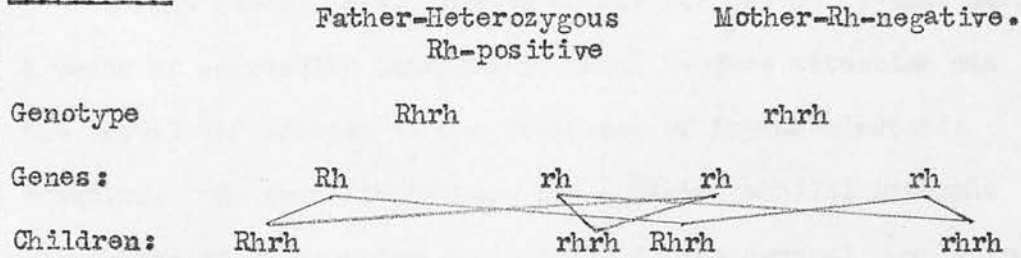
heterozygosity (Rhrh) of the father's blood. They said that the first pregnancy is frequently, but not always, spared, as more than one pregnancy with an Rh-positive foetus may be required before a sufficient degree of iso-immunisation is attained.

I append the following diagram to illustrate the importance of the father's genotype and to show how a homozygous father can produce nothing but Rh-positive children, all heterozygous, whereas a heterozygous father may have 50% of his children Rh-negative (these children escaping the disease), the other 50% being heterozygous Rh-positive.

Example 1.



Example 2.



Confirmation of Iso-immunisation Theory.

The work of Levine and his colleagues was soon confirmed. Boorman, Dodd and Mollison (1942) showed that out of 48 mothers whose babies had definite Erythroblastosis Foetalis, 46 were Rh-negative (96%), and in 44 of these cases Rh antibodies were present/

present. In all 48 cases the infant was Rh-positive. Then Race, Taylor, Cappell and McFarlane (1943) found that out of 50 mothers with erythroblastotic babies 44 (88%) were Rh-negative, and in the sera of 38 of these anti-Rh agglutinins were found. Plaut et al. (1945) found that out of 136 mothers who had babies with haemolytic disease, 88.2% were Rh-negative, and 79.6% of these had anti-Rh agglutinin in their sera. Similarly Cappell (1946) reported that out of 114 cases of Haemolytic Disease of the Newborn, 98 (86%) of the mothers were Rh-negative, and 86 of these had antibodies in their sera.

It has thus been established beyond all question of doubt that in the great majority of cases, about 90%, Erythroblastosis Foetalis is due to Rh incompatibility between the mother and foetus, with the resultant iso-immunisation of the mother's serum by the Rh antigen in the red blood cells of the foetus.

Racial Incidence of Erythroblastosis Foetalis.

Levine (1943) gave a review of the subject up to that date. A point of particular interest to which he drew attention was the racial differences in the incidence of Erythroblastosis Foetalis. He found that there was a close parallel with the proportion of Rh-negative individuals in the general population. For example, in the Chinese race, where the incidence of Rh-negative people is only .7% as compared with 15% in the white races, Erythroblastosis is very rare indeed, whereas in the American Negro population the incidence of both conditions is in between.

The/

Factors Influencing the Incidence of Erythroblastosis Foetalis.

The next question that arose was the discrepancy between the incidence of Erythroblastosis Foetalis as found in actual practice, and its theoretically possible incidence from the matings of the Rh-negative women with Rh-positive men. Figures have already been quoted (page 16) and the incidence at the present time appears to be from 1:200 to 1:250 births. Snyder et al. (1945a) giving figures for its occurrence in America, state that in random mating Rh-negative women will marry Rh-positive men in 11.31% of all marriages. The proportion of Rh-positive children from Rh-negative mothers works out at about 8%. According to the size of the average American families (3.24 children), excluding the first-born, the proportion expected to show the effects of iso-immunisation of the mother by the Rh factor is reduced to 6%. The actual incidence is found to be 0.5%. Hence only one in twelve pregnancies which could result in Erythroblastosis Foetalis actually do so.

Comparable figures for this country are given by Cappell (1946). He states that approximately one marriage in eight involves an Rh-positive man and an Rh-negative woman, and that in about one pregnancy in ten the foetus is Rh-positive and the mother Rh-negative. He says that sensitization occurs only in about 1:25 opportunities, however, and hence he obtains his figure of 1:250 for the actual occurrence of haemolytic disease.

It is thus evident that, very fortunately, Erythroblastosis Foetalis occurs with only a small fraction of the frequency with/

with which it theoretically could do. The real reason why this should be so is not yet clear, although several facts have been noted and suggestions made in an attempt to explain this discrepancy.

Taylor and Race (1944b) gave results of investigations on 46 fathers in whose families Erythroblastosis Foetalis had occurred. For this purpose they used a serum which they called St and which they had previously described (Race and Taylor, 1943) as having the power to distinguish heterozygotes from homozygotes. In a random sample of Rh-positive males, they stated that 3 in 7 are homozygous and 4 in 7 are heterozygous. From these figures they calculated that out of 46 random Rh-positive men, 20 should be homozygous. In the case of the 46 fathers concerned, however, they found that no fewer than 36 were homozygous, and they expressed the opinion that these findings show that there is a marked preponderance of homozygous fathers in families affected by haemolytic disease of the new-born.

Similarly Cappell (1946) gave figures for the father's genotype in 38 cases; of these 22 were homozygous and 16 heterozygous. These figures, then, appear to have established the point 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 does not explain, however, why some Rh-negative women/

women react more quickly than others to the Rh antigen, while some apparently are not affected by it at all, whether the antigen is in the blood cells of a foetus or in the cells of transfused Rh-positive blood.

Cappell (1946), quoting Race, says there is some evidence that this aptitude to become immunised may also be an inherited character. Unger and Wiener (1945) also consider that the hereditary constitution of the patient is important, and they say, in addition, that the wide spacing of a few transfusions has been shown to be more apt to give rise to sensitization than a larger number of transfusions within a shorter period of time. They believe that the analagous situation is true also of pregnancies. They believe, also, that in pregnancy the maximum amount of foetal blood escapes to the maternal bloodstream at the time of labour; hence the reason the first child usually escapes.

The great length of time that may elapse between sensitization and the subsequent occurrence of a haemolytic reaction has been emphasized by Young and Karher (1945) who describe cases of proved retention of sensitivity nearly eight to sixteen years respectively after the last immunisation by pregnancy. Mollison (1943) believes that the factors to be considered are (1) failure of the Rh antigen to cross the placenta in adequate amount to stimulate the formation of anti-Rh agglutinins, and (2) failure of the mother to respond to the stimulus.

Another/

Another factor that is apparently of importance in regard to this question is the compatibility or otherwise of the ordinary blood groups of the mother and foetus. If the bloods are compatible, the pregnancy is known as "homospecific"; if incompatible, "heterospecific". It is known (Race, Taylor, Cappell and McFarlane, 1943) that in normal random matings one pregnancy in five is heterospecific, but these workers found, on analysis of their 50 cases, that the Rh-positive child of an Rh-negative mother was more likely to suffer from Erythroblastosis Foetalis where the ABO groups were compatible than otherwise. For various reasons, however, their records were incomplete, and a definite conclusion could not be drawn.

Plaut, Barrow, and Abbott (1945) published the results of their investigations of 136 cases of haemolytic disease of the newborn. Cappell (1946), in an analysis of their table, states that their figures show a significant deficiency of group O mothers and an excess of group A; whereas among the husbands there is an excess of group O and a deficiency of group A. Cappell further shows that among the 103 families for which sufficient data were given by Plaut et al., 92 pregnancies were homospecific and only 11 were heterospecific, while of these, 7 were in Rh-positive mothers. In his own series of cases of proved Rh-negative mothers, 90 in all, Cappell (1946) found that there were only 8 heterospecific pregnancies to 82 homospecific, whereas the expected random distribution among 90 pregnancies would be approximately 18 and 72 respectively.

It/

It is evidently not at all clear yet why the compatibility or otherwise of the ABO group should affect sensitization with the Rh factor. Wiener (1945) also noted the fact, and he discussed what he called the "competition of antigens" in man. He stated that the properties A and B were good antigens, whereas only 1:25 to 1:50 Rh-negative individuals respond to transfusion of Rh-positive blood, or pregnancy with an Rh-positive foetus, by producing Rh antibodies. From this he deduced that it would be expected that an Rh-negative woman would be more apt to become sensitized to the Rh factor present in her foetus if the foetus belonged to a compatible group than otherwise. He gave figures, showing that in 96 families, 71.9% were compatible and 28.1% were incompatible.

Smith (1945) investigated the titres of anti-A and anti-B in the mother's serum in relation to confinements where the pregnancies were heterospecific. He found that the infants who produced iso-immunisation in the mothers were secretors, those not causing it being non-secretors. Commenting on these results, Smith is of the opinion that the rise in maternal iso-agglutinins may be due to the diffusion of soluble A or B substance from the foetus into the maternal circulation, and that escape of foetal red cells is not usually concerned. On the other hand, according to Cappell (1946), the relative absence of soluble Rh substance in the plasma had lead to the general acceptance of the view that escape of foetal red cells themselves into the maternal blood was the probable mechanism of/

of iso-immunisation against Rh.

It is obvious from the above that there must be some further factor (or factors) as yet unknown which fortunately keeps down the incidence of Erythroblastosis Foetalis.

Clinical Manifestations of Erythroblastosis Foetalis.

According to Cappell (1946) Haemolytic Disease of the New-born 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, he states, is highly suspicious. The characteristic blood picture shows the haemoglobin to be below the normal birth level, and the red cells are reduced in number although reticulocytes are numerous. The nucleated red cell count is often over 20,000, and normoblasts, megalo-blasts and primitive cells are all present. Cappell maintains that the presence of primitive cells is especially significant. He also states that Rh incompatibility is by far the most important genetic cause of foetal death, and it far outweighs congenital Syphilis as a factor in neonatal mortality.

Skelton and Tovey (1945) have shown 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 affirm that certain cases of so-called "congenital" obliteration of the bile ducts occur as a sequel of Icterus Gravis Neonatorum. Drummond and Watkins (1946) believe/

believe that certain cases of hepatomegaly and splenomegaly in children and adolescents result from haemolytic disease of the newborn, and they emphasize that Rh incompatibility must be excluded in the diagnosis of these conditions. They produce evidence in support of their view.

It will thus be seen from the foregoing survey that the Rh factor is of tremendous importance as a cause of human suffering and disease, apart altogether from the nervous and mental conditions which will now be dealt with.

Relationship of Erythroblastosis Foetalis to Kernicterus.

The relationship between Erythroblastosis Foetalis and Kernicterus has been clearly brought out by Zimmerman and Yannet (1933). These authors summarised the literature on the subject of Kernicterus up to that date, and commented on the cases that had already been described. 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, the mammillary bodies, the 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. Jaundice of the above-named structures, these authors continued, is not a disease sui generis, but occurs as one of the lesions that may be found in newborn infants with severe/

severe jaundice, and only in a comparatively 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, after summarizing the cases already in the literature. Of the four cases, which were described in detail, two died shortly after birth and the post mortem findings were described, proving the presence of Kernicterus. The other two cases survived, although Kernicterus was suspected, and in both cases athetosis, spasticity, and mental deficiency were present.

These writers compared Kernicterus with Wilson's disease (Progressive Lenticular Degeneration) and they came to the conclusion there were more differences than similarities between the two conditions. In this connection it is interesting to note that Wilson (1912), in his Thesis on the disease which now bears his name, observed and commented on a certain similarity between it and Kernicterus, although, as he said, he did not wish to overestimate the value of the analogy.

As regard the causation of Erythroblastosis Foetalis, Zimmerman et al. discussed several theories, but did not mention that of iso-immunisation. They themselves favoured the theory of septic infection as the most likely cause of Icterus Gravis Neonatorum, although they admitted this theory did not explain all the facts, e.g. the familial incidence of the disease. The cases they presented showed typical family histories, and it is interesting to find them groping for an explanation which is now/

now so clear in the light of recent discoveries.

Hawksley and Lightwood (1934) describe 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 say that the condition occurs comparatively rarely in Icterus Gravis Neonatorum, and the quote Schmorl who found six cases in 120 autopsies on cases of Icterus Gravis.

On the other hand, McIntosh (1941) discussing Haemolytic Disease of the Newborn, gives the proportion of cases of this disease who will eventually show serious retardation of mental and behaviour development as not over 10%. This incidence is double that quoted by Hawksley and Lightwood.

Cappell (1947) is also of the opinion that in infants surviving icterus gravis into later childhood, evidence of nervous damage is found in 10% to 12%. He believes that the damage to nerve cells must occur after birth, or at the most, not long before birth, for in infants dying in the first few days, the damaged tissue shows no sign of disintegration or removal.

Regarding sequelae of Erythroblastosis, Hawksley et al. suggest that some cases of cirrhosis of the liver might be the result. They admit that permanent sequelae in the nervous system can result from cases of Kernicterus which do not die, and they give evidence that Icterus Gravis is one of the causes of subdural haemorrhage. They state that mental deficiency/

deficiency is the most important of the nervous sequelae of Icterus Gravis Neonatorum. They, too, discuss the relationship between Kernicterus and Wilson's disease, and they believe they may have found a connection between the two if their conclusion is correct that hepatic cirrhosis is an occasional result of Icterus Gravis.

Pasachoff (1935) described a case that was clinically Erythroblastosis Foetalis at the beginning of the illness, and then obstructive jaundice. The post mortem findings showed the presence of Icterus Gravis Neonatorum, 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 in 1935 followed up their earlier work. They discussed the possible pathogenic factors that might cause Kernicterus to follow Icterus Gravis, and suggested it might be either (1) a post-infectious encephalitic process, (2) cerebral birth trauma or asphyxia, or (3) cerebral cellular maldevelopment. They reported in full the case of a child who had severe icterus during the first four weeks of life, with irregular high temperature. This cleared up, but at the age of five months spasticity and athetosis developed. At twenty months, the patient was mal-nourished and mentally retarded. During her third year she went steadily downhill, having frequent/

frequent high temperatures, and she died when three years old.

The post mortem findings were illuminating. There were no signs of cerebral inflammatory reaction, and no macroscopic changes in the basal ganglia. The substantia nigra was absent, but the cyto-architecture of the cerebral cortex was normal. In the cornu ammonis, the fascia dentata and the end plate of the lamina parietalis were completely destroyed. Of the nuclear masses, the claustrum and the amygdaloid nucleus alone presented a normal microscopic appearance. The corpus striatum was lacking in large nerve cells, and the globus pallidus was completely devoid of both large and small ganglion cells and of myelinated fibres. The lateral thalamic nucleus was also the seat of necrobiotic changes in the ganglion cells. No pathological glial cells were found.

The authors compared the pathological findings in this case with those ending fatally from Kernicterus during the first two weeks of life, and showed that the similarity was so striking that it could hardly be accidental.

The evidence produced by these workers is so conclusive that it seems established beyond all reasonable doubt that an infant surviving Icterus Gravis Neonatorum, even without developing definite signs of Kernicterus during the period of generalised jaundice, may yet become a mental defective with signs and symptoms of involvement of the basal ganglia.

Fitzgerald, Greenfield and Kounine (1939) also discussed cases/

cases of Kernicterus that have appeared in the literature, and described the pathology. They said they disagreed with Zimmerman et al. that Kernicterus is solely associated with Icterus Gravis, and, in support of their contention, they cited Pasachoff (1935) as reporting a case of congenital atresia of the bile ducts with Erythroblastosis and Kernicterus.

In my opinion this criticism is unwarranted, because, in the first place, Zimmerman et al. (1933) stated that Kernicterus was most frequently, if not exclusively, associated with Icterus Gravis Neonatorum, 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. Furthermore, he stated categorically that Kernicterus does not occur in obstructive jaundice. In addition, as I have already 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 Neonatorum.

After severe jaundice has developed, Fitzgerald et al. maintained that symptoms referable to involvement of the central nervous system manifest themselves within twenty four 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/

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 some evidence of involvement of the extra-pyramidal system, such as chorea-athetoid movements and rigidity. Invariably, also, there was a marked degree of mental retardation, in many cases approaching the idiot class. In the pathological examination of these cases, degeneration was limited to the nuclei most deeply affected in Kernicterus, i.e. the subthalamic nuclei, the lenticular nuclei, and the cornu ammonia.

Rh Incompatibility as a cause of
Mental Deficiency associated with Kernicterus.

It was thus quite 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, as described in the first part of this review, that the Rh factor was responsible for about 90% 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.

Theory that Rh Incompatibility may cause
Undifferentiated Mental Defect.

Yannet/

Yannet, collaborator of Zimmerman in the 1933 and 1935 articles, and now in collaboration with Lieberman (1944), was the first worker to wonder if a more direct relationship between the Rh factor and mental deficiency could be established. In their article, these authors said that since the cerebral changes in Kernicterus were most frequently described in cases of Erythroblastosis Foetalis, it appears as a reasonable corollary that the pathogenesis of the cerebral pathology was in some way related to the mechanism of iso-immunisation.

On the basis of present knowledge, they continued, the aetiological importance of iso-immunisation in Rh-positive individuals with severe mental retardation, clinical evidence of basal Ganglion involvement, a neonatal history suggesting Erythroblastosis Foetalis and an Rh-negative mother, would appear reasonably well established. However, they said, if this specific syndrome were the only manifestation of iso-immunisation, its importance in the overall picture of mental deficiency would be slight. Thus, of approximately 1200 admissions to a mental defective institution, only one child fulfilled all the above criteria.

They stated, however, that there was some evidence which suggested the possibility that iso-immunisation, as an aetiological factor, might conceivably 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. This idea was based on two series of/
of/

of observations. 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 ganglion 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 certain 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.

As a result of the above considerations, the authors 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-immunisation during pregnancy.

Results of Investigations of the New Theory.

With this idea in mind, they 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 recognised diagnostic groups (mongols, spastic diplegias, post-natal infective cases, birth traumas, cranial/

cranial anomalies, etc.), and 56 were regarded as undifferentiated, cases where the cause of the mental deficiency could not be ascertained. The former group were used as a control, and the findings were as follows. Control group, 6 mothers Rh-negative, giving a % of 11.3. Of these mothers, 4 had an Rh-positive defective child, giving 7.5% as the incidence of Rh-incompatibility in the control group. In the undifferentiated group, however, 14 mothers were Rh-negative (25%) and of these, 11 had an Rh-positive defective child, giving 19.6% as the incidence of Rh incompatibility.

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

In analysing their results, they point out that 5 cases of the incompatibility would be the result of random distribution, and that the remaining cases would represent 10% of the undifferentiated group studied. This would give an incidence of 3 to 4% for iso-immunisation as an aetiological factor in institutionalized mental defectives, and this is about half the incidence of mongolism.

Commenting/

Commenting on the results quoted above, Cook (1944) agrees that they are striking, but rightly adds the note of warning that the series is too small for definite conclusions to be drawn. As an explanation of the mechanism whereby the defect might result if Rh-incompatibility were indeed proved to be a cause, he suggests that anoxaemia of the brain tissues is so simple and obvious a reason that it is almost sure to be wrong. As a measure of treatment he advises that there should be frequent checking of the mother's blood, with induction of labour whenever the antibody titre begins to rise.

The work of Yannet et al. was soon checked by Snyder, Schonfield and Offerman (1945a). 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.

In an editorial discussion of these results, the British Medical Journal (August 11th 1945) admits that the evidence in favour of the hypothesis propounded by Yannet et al. is very strong, although the figures were not yet sufficient to allow any close estimate to be made as to how much mental deficiency is due to this cause. The Journal emphasizes the need for much further work and co-operative research by many mental defective institutions, in collaboration with the experts of a serological laboratory.

Snyder/

Snyder et al. (1945b) added some further figures to their previous total. They obtained blood from 47 additional cases of undifferentiated mental deficiency and their mothers, but they found that the high frequencies of Rh-negative mothers and of Rh-positive children from Rh-negative mothers were not maintained. Of the 47 mothers, 7 were Rh-negative, only slightly higher than expectation, and of the 47 children, 5 were Rh-positive from Rh-negative mothers, again only slightly higher than expectation. Their combined results, 113 mothers and 115 mentally defective children, with 24 mothers Rh-negative and 16 children Rh-positive from the Rh-negative mothers, are still in excess of those expected, although only significantly so instead of highly significantly so.

Dr. Snyder, in a personal communication, tells me that he and his co-workers have not been able to add to their figures since the above article was published, although they had hoped to do so. This is particularly unfortunate in view of the smallness of the total series of figures as yet available.

Yannet and Lieberman (1946), however, have 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 well-defined categories (mongols etc.) and the remaining 119 were regarded as being undifferentiated. In the control group 22 (14%) of the mothers were Rh-negative, and in 12 cases there was an Rh-positive child with an Rh-negative mother, or a 7.6% incidence of Rh incompatibility.

Among/

Among the undifferentiated cases, however, 26 (22%) of the mothers were Rh-negative, and there were 19 Rh-positive children from these mothers, giving an incidence of 16% for Rh incompatibility in this group. The difference between the two ratios (7.6% and 16%) is stated to be statistically significant.

In the course of this article, Yannet et al. discuss possible theories as to the mechanism whereby mental deficiency could result from iso-immunisation of the mother by the foetus. The suggested theories are (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 (of Cook, 1944); and (3) the possibility that the products of extensive red cell destruction per se may be injurious to the developing neurone.

In a second editorial comment, the British Medical Journal (August 10th 1946) remarks that the results of the above workers might have even higher figures if cases of high grade defect and minor neurological abnormalities had been studied.

Criticisms of the New Theory.

The theories of Yannet and Lieberman have been criticised 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 immunisation and feeblemindedness would require immunological confirmation and

a systematical experiment on a larger scale than hitherto carried out. For such an experiment to be conclusive they maintain 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 feeblemindedness 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 go on to give the results of a careful restudy of the cases reported by Snyder, Schonfield and Offerman (1945a and b). The combined figures from the two papers by Snyder et al. were 16 Rh-positive children from Rh-negative mothers. Thirteen of the original sixteen mothers were located, and of these one was found on re-testing to belong to group Rho (cDe), while the defective child of another was found to be a Cretin. These two cases were therefore eliminated from the series/

series and the remaining eleven cases were further assessed. Only two mothers gave an obstetric history suggestive of Rh immunisation, and in only one of these could anti-Rh antibodies be demonstrated.

All the children studied were over 12 years old. The authors say that the incomplete antibody, present in all mothers with erythroblastotic children, is quite stable and may be present many years after the last immunising experience. They are not invariably so present, however, as the authors had a case where it declined and was absent after a year.

From the above consideration they maintain that failure to demonstrate anti-Rh antibody suggests that the mother never was immunised against the Rh factor, but is not proof that she was not so immunised.

These authors conclude that this restudy of their cases offers no support to the theory of Yannet and Lieberman, but they admit that it does not disprove it. They also admit that the data on which the relationship was originally postulated are statistically significant.

Cappell (1947) is much more severe in his criticism. He agrees it is 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 admits 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./

kernicterus.

He then goes on to criticise Yannet and Lieberman's figures and says that they are unsound for they include in the undifferentiated group six cases of undoubted Icterus Gravis and Kernicterus. If these cases were placed in the specific group, then the difference in the incidence of Rh negative mothers between the two groups disappears.

He states that in a series of about 200 mothers with defective children, examined from his Department, there was no significant difference in the percentage of Rh-negative mothers in a group of Rh-positive children suffering from simple mental deficiency, as compared with a group of defective children of specific types, and both groups showed no significant difference from an unselected group of normal school children. He concludes that it seems improbable that Rh incompatibility can cause mental deficiency in the absence of overt haemolytic disease in the neonatal period.

Conclusion of Literature Review.

In concluding this review of the literature, I would like to emphasize that I have tried to correlate all the aspects of the Rh factor and its effect on the human being, physical and mental, and to show by reference to as many articles as possible to which I have been able to gain access, and by freely quoting from a number of them, the various steps through which our knowledge has advanced. Only in this way is it possible to obtain a clear idea of how Rh incompatibility came ultimately to/

to be considered as a possible factor in the aetiology of some cases of mental deficiency, apart from those associated directly with Kernicterus; and the purpose of my own investigations has been to test this theory under as stringent conditions as possible, and to see whether any definite conclusions can be drawn as to its truth or otherwise.

PERSONAL INVESTIGATION.

Method of Investigation.

The method adopted in this investigation was the simplest that I could devise in the circumstances. The research was begun in the summer of 1946 while I was working in Nottingham, but after I had examined only a comparatively small number of cases, I came to Birmingham and I have been able to continue the research among the mental defective population of this City. As I was engaged in full time work otherwise during the whole period of the research, progress has of necessity been slow, and other workers have made contributions to the subject since I first began my own work on it.

My methods were approximately the same in the two cities and the one description of technique covers both phases of the research unless it is specifically stated otherwise.

The case records of all the mental defectives on the books of the local authority concerned were examined and those whose mothers were still alive were picked out. At first, in Nottingham, I limited the cases to those who had both parents alive, as I had the idea of having all the fathers accurately genotyped, but I found that this scheme was impracticable for two reasons. Firstly, because it limited the number of cases I could do too severely, and secondly because the anti-sera for genotyping purposes was too scarce for it to be used routinely in an investigation of the size which I hoped to make it. I therefore/

therefore abandoned this aspect of the work and have investigated cases irrespective of whether the father was alive or not.

I drafted a letter, which briefly explained the nature and purpose of the investigation, and this letter was sent out to all the mothers, inviting their cooperation. In Nottingham, institutionalised cases were investigated first, and then cases which were under guardianship or statutory supervision, but in Birmingham it was more convenient to reverse the procedure. This made no difference to the end result, as in the final assessment I have not attempted to distinguish between institutionalised cases and others. I did not consider that the point was material, although I know that the Americans in their work stressed the fact that all their cases were institutionalised defectives of low grade (I.Q. below 50%).

At this stage of the investigation, I would like to emphasise that the type and degree of defect were not considered; it was enough that the individual concerned was on the books of the Mental Deficiency Authority. Not all the mothers in either city agreed to cooperate; in fact the response was disappointingly small. Some parents were actively antagonistic and responded with letters of abuse, but the majority of those who failed to respond were simply indifferent and did not reply at all, even when reminders were sent out. Those who did agree, on the other hand, I found to be courteous, polite and very willing to do anything I wanted.

I/

I was able in this way to examine 427 cases altogether, 112 in Nottingham, and 315 in Birmingham. I actually tested 317 mothers in Birmingham, but could not complete the investigations in two cases, and so withdrew them from my total. The cases examined were quite a random selection, within the limits set for the investigation, and there was no picking or choosing of cases. In fact, at this stage I deliberately kept myself entirely in ignorance of the degree and type of defect present in the offspring of the mother from whom I was taking the blood. I was able to do this the more easily because in neither city was I directly associated with the Mental Deficiency Department, and I personally knew very few of the women I tested.

As complete histories as possible were obtained in every case irrespective of whether the mother proved to be Rh-negative or not, as it was felt that to make the investigation complete it was necessary to know as much detail as possible and to take into account all other definite causes of mental deficiency that might be operating in any given case. 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 necessary, as it was found that parents were prone to blame the slightest extraneous factor as being the cause of their child's defectiveness.

I prepared a special history form setting forth all the points on which I wanted information, as I found that the case records, quite understandably, were incomplete from my point of view. Every mother was therefore requested when she attended the/



the centre to have her blood taken or when I went to the home, as I did on quite a number of occasions. These visits that I paid to the homes of the people, however, were usually to take blood from a defective who was too severely handicapped to be brought to the centre.

With all the facts of each case before me, I finally decided into which category each defective was to be placed. At this stage, I kept the records of the Rh investigation separate so that I was in ignorance as far as possible, when making my decisions as to type of defect, etc. of whether Rh incompatibility was present or not in any given case. In this way it has been my aim 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 has been quite impossible to obtain evidence of any other cause of the defect. It should be noted that in the type of case where another possible cause has been present, but reasonable doubt has existed as to its actual responsibility in producing the defect, such a case has been included in the undifferentiated group.

Further, a fair proportion of the defectives I 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/

mongol or one of the other recognised types, he or she was placed in the undifferentiated group. The number of cases where this occurred, however, was very small indeed, and as a rule I had little difficulty in classifying the defective. I do not therefore consider that this factor has influenced my results to any significant degree, particularly as any one case had a proportionate chance of showing Rhesus incompatibility or not.

In order to obtain comparable figures with the American workers, I decided to use the specific group of defectives as a control against the undifferentiated group, but, owing to the limited time at my disposal for carrying out this work, I was unable to test a control series of normal children and their mothers. I therefore had to accept as my base line the figures which have been published as the result of investigations on large numbers of cases and which have come to be accepted as the normal standards for the general population of this country.

The specific, or control, group, consisted of 152 cases, divided as follows; mongols 56, organic nervous disease (excluding spastics) 29, spastics 26, microcephalics 11, birth and early childhood injuries 3, 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 in the undifferentiated group, as did the Americans, for in my opinion Cappell's criticism is justified/

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 Haemolytic Disease of the New-born. These were the conditions laid down by Yannet and Lieberman themselves in their original article and therefore they ought to be adhered to strictly.

I want to mention particularly the cases of otherwise undifferentiated mental defect where the family history was such that I felt I had to take into account the factor of Heredity as a possible cause of the deficiency. At first I was definitely of the opinion that these cases should be classed along with the control 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 still did not feel satisfied, however, because now my undifferentiated group would not fulfil all the conditions I had laid down for it.

I decided therefore 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 group. I conceived the idea that, since the Rh factor is inherited on Mendelian lines, and since it has been suggested/

suggested that the tendency for an Rh negative woman to become immunised against the Rh antigen is also inherited, possibly Rh incompatibility might be a factor in the inheritance of otherwise undifferentiated mental defect. I realised that a comparison between the two series of results might at least show whether this theory was worth pursuing or not.

Result of Investigation.

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

Table I.

Total number of cases investigated	427
Total number 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
Number of 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
Number of Rh negative mothers	35 = 23.0% (s)
Rh negative mothers with Rh positive children	20 = 13.2%
s = significant.	

Tables/

Tables IV to IX show the results for the test group. I divided the test group into two classes, (1) The Feeble-minded, or high grade cases of mental defect, (2) The Imbeciles and Idiots, or low grade cases of mental defect. I give the results 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
Number of 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
Number of 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
Number of Rh negative Mothers	21 = 18.6%
Rh negative Mothers with Rh positive children	15 = 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/

Table VIII
Imbecile & 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 & Idiot Cases (Including "Heredity" Cases)

Number of Cases Investigated	153
Number of Rh negative Mothers	25 = 16.3%
Rh negative Mothers with Rh positive children	15 = 9.8%

For the purposes of comparison I have summarised all the above results, giving percentages only, in Table X.

Analysis of Results and Case Material.

As I have already indicated, I have not been able to examine a series of normal children and their mothers to get normal control figures of my own and I must therefore define exactly the basis I have taken for comparing my results with the normal average figures for the general population.

Race, Mourant, Lawler and Sanger (1948) in an article on "The Rh Chromosome Frequencies in England" give the results of their observed and the expected genotype frequencies, based on 2000 cases. The expected frequencies (based on the Chromosome Frequencies calculated by Professor Fisher) and the observed frequencies agree closely, and I have therefore taken as my normal standards the expected frequencies as given in this paper.

The frequency of the genotype rr (ode/ode) is expected to be/

be 15.102%. To these I have added the expected frequencies of the genotypes made up from combinations of r^1 , r^2 and r , and I find that the expected frequency of all genotypes lacking the antigen D is 16.84%. Apart from the theoretical considerations already discussed justifying the inclusions of R^1 and R^2 amongst the Rh negative group from the point of view of pregnancies and receiving blood transfusions, there is the very practical one

Table X

	%		%	
	Rh negative Mothers		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%
Feebleminded Cases	18.6%	19.7%	13.3%	13.9%
Imbecile & Idiot Cases	15.3%	16.3%	10.2%	9.8%

* = Significant

that amongst my series of 427 two mothers were found to be of the genotype r^1r (Cases 28 and 36, Appendix B). The figure of 16.84% for all Rh negative cases expected agrees closely with the observed figure of 17.07% in Race et al's paper and I am therefore taking it as the normal standard.

As regards the expected frequency of Rh positive children from Rh negative mothers, I am not sufficiently mathematically minded/

minded to be able to calculate this from the gene frequencies given by Race et al. Dr. J.A.H. Waterhouse, of the Department of Medical Statistics, Birmingham University had kindly done this calculation for me, and he finds that the expected frequency is 9.92%. This figure agrees very closely with the one of 10% mentioned by Cappell (1946) and I am therefore taking it as my normal standard. I realise that this figure is slightly higher than the observed one should be owing to the occurrence of iso-immunisation and the fatalities at various stages of foetal and post-natal life caused by it, but Dr. Waterhouse assures me that this difference is relatively insignificant statistically. Dr. Waterhouse has in addition subjected all my figures to statistical analysis.

(a) Whole Group of Mental Defectives.

It will be seen from Table 1, that out of a total of 427 mothers of mental defectives of all types and grades, 84 or 19.7% were Rh negative, while 52 or 12.2% 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 11 and 111 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% Rh negative mothers and 23 or 13.0% Rh negative mothers with Rh positive/

positive children, whereas out of 152 cases (heredity ones excluded) there were 35 or 23.0% Rh negative mothers, and 20 or 13.2% negative mothers with Rh positive children. It will be seen that the inclusion or exclusion of the heredity cases give almost identical percentages in the control group.

The figures of 23.7% Rh negative mothers on 177 cases, and 23% Rh negative mothers on 152 cases are both statistically significant, the probability due to chance being in the first cases 60:1, and in the second case 20:1, against.

In Table XI, the control group (excluding heredity cases) is further analysed.

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 (Excluding Cretin)	5	2	2
Cretins	4	1	-
Congenital G.P.I.	2	-	-
Kernicterus & Icterus Gravis.	4	4	4
Total	152	35	20

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/

in Columns 2 and 3.

The clinical histories of the "control" cases in which Rh Incompatibility has occurred are described in Appendix A (Cases 1 - 20).

The six cases amongst the Spastics in which Rh incompatibility occurred are described in Appendix A, nos. 7 - 12. The very high incidence of incompatibility even in this very small series of 26 cases could lead to the supposition that possibly it had 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 mother's serum. Case 9 had meningitis at the age of 6 months, and this may have caused the paralysis. Case 11 showed tremor and incoordination of all movements, but no true athetosis was present. Case 12 did have a history of neo-natal jaundice which lasted intermittently for three months, and paralysis, involving the right side, developed subsequently. There was no athetosis. The family history did not definitely suggest that iso-immunisation had occurred, and so I did not class this case as one of erythroblastosis neonatorum, although it may possibly have been.

The case histories of both the Microcephalics in which Rh incompatibility occurred (Nos. 13 and 14 Appendix A) in each case suggest that the mother was in fact immunised 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 is rather typical of iso-immunisation, and in case 14 the/

the child was very anaemic when born. In neither case, however, did I feel justified in classifying them as erythroblastosis foetalis.

There were four definite cases of Erythroblastosis Foetalis (nos. 17 - 20, Appendix A) and in three of these (nos. 18, 19, 20) there is no doubt whatever of the presence of Kernicterus. In all four cases there was a history of neo-natal jaundice and the family histories are typical of iso-immunisation 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 from 1:200 to 1:250 births. Further, of the cases surviving erythroblastosis, not more than 10% may be expected to show the clinical signs of Kernicterus. This means that in the general population Kernicterus occurs in not more than 1:2000 to 1:2500 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 recognised 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./

cases.

As I have shown, the percentage of negative mothers and of negative mothers with positive children in my 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.

I therefore re-calculated the control group, omitting the three cases of Kernicterus, but leaving in the case of Erythroblastosis Foetalis without Kernicterus. The control group 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
Number of 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 is now brought below the level of statistical significance, the opportunities due to chance being reduced now to 16:1, and 8:1 against, respectively. The figures for the incidence of Rh incompatibility are now reduced practically to the normal average for the general population.

(c) Test Group of Undifferentiated Mental Defectives.

Table IV/

IV shows that there were 250 cases of all grades of defect excluding the "heredity" cases. Of these 42 mothers, or 16.8% were Rh negative while 29 of these mothers, or 11.6% had Rh positive defectives. 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, or 17.8% mothers were Rh negative, and of these, 32 or 11.6% had Rh positive defective children. Again neither figures is significant, and in fact, the percentage figures for the cases showing Rh incompatibility are identical.

For convenience I append here Table XIII showing how the "heredity" cases are divided.

Table XIII
"Heredity" Cases

	<u>Total</u>	<u>Total Rh negative Mothers</u>	<u>Rh negative mothers with Rh positive children</u>
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 mental deficiency) and Imbecile and Idiot cases (low grade mental deficiency) 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, or 18.6% mothers were Rh negative, and of these mothers 15 or 13.3% had Rh/

Rh positive defective children. There is no statistical significance in these figures.

Even when the "heredity" cases are added (Table VII) out of a total of 122, 24 or 19.7% mothers were Rh negative, while of these 17 or 13.9% had Rh positive defective children. Although these figures are very slightly higher than those in Table VI, they are still within normal limits, and not statistically significant.

The figures for the low grade group of undifferentiated defectives are even more striking. From Table VIII, "heredity" cases excluded, it is seen that of 137 cases, 21, or 15.3% mothers were Rh negative, and of these, 14 or 10.2% had Rh positive defective children.

Addition of the "heredity" cases (Table IX) shows that out of 153 cases, 25, or 16.3% mothers were Rh negative, and of these 15, or 9.8% had Rh positive defective children. All the percentages in Tables VIII and IX are so close to the average that it was not necessary to do a statistical calculation on them to decide that there was no significant difference in them from the normal.

The clinical histories of the cases of undifferentiated defect in which Rh incompatibility is present 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 I regarded this jaundice as physiological and nothing more.

Case/

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 that this was not a case of undifferentiated mental defect.

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 ending in still birth followed by four siblings all alive and well, then the defective, and finally two more siblings alive and well, it is reasonable to suppose that if the still births had been due to iso-immunisation, the effect on the defective would have been much more serious. I therefore felt justified in regarding the jaundice in his case 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 and there was no history of a threatened miscarriage at the time of the fall, so that it is highly unlikely it had anything whatever to do with the defect in the child.

The family history in case 32 rather suggests that iso-immunisation 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 foetalis, and so I classed him 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-immunisation would occur in his case. Atypical agglutinins/

agglutinins were found in the mother's serum, however, proving that she was sensitive and had been immunised. In spite of this there were no grounds for labelling the defective other than undifferentiated.

Case 42 is interesting because of the treatment he received on the day of his birth. In the light of present day knowledge his father would have been the last person chosen to give him blood, but as it has been proved that the mother had never been immunised, no harm was done. In any case, this was a first pregnancy.

Case 45. The early history of this defective and the family history are suggestive that Syphilis was the operating factor in the still-births and miscarriages, although the family history is not strictly typical. In view of my inability to obtain confirmation from the hospital where the defective was supposed to have been treated, and of the fact that she now shows no stigmata of Syphilis, I have had to classify her as undifferentiated.

Case 46. The family history in this case is strongly suggestive that iso-immunisation had occurred in the mother, although no confirmation could be obtained. As there was no history of erythroblastosis in the defective (second pregnancy), however, I have classed him as undifferentiated.

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

(d)/

(d) Homospecific and Heterospecific Pregnancies.

It was noted in the review of the literature that some evidence had been produced that iso-immunisation to the Rh factor was favoured by a homospecific pregnancy rather than a heterospecific one. It was shown that in a series of pregnancies where iso-immunisation had been proved to have occurred the proportion of homospecific pregnancies was unduly high. It was also shown that there was an undue proportion of Group A bloods amongst the Rh negative mothers.

In Table XLV there is listed the distribution of the ABO groups amongst the mothers and defectives, in the 52 cases where Rh incompatibility occurred.

Table XLV.

	<u>Mothers</u>	<u>Defectives</u>
Group O	24	27
Group A	23	21
Group B	2	1
Group AB	3	3
Total	52	52

It will be seen that the ABO 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% of cases, or one in five. Table XV shows the proportion in my series of cases of Rh incompatibility.

Table XV.

	<u>Total Pregnancies</u>	<u>Homospecific Pregnancies</u>	<u>Heterospecific Pregnancies</u>
Whole Group	52	41	11
Control Group	20	16	4
Test Group (all cases)	32	25	7
Feebleminded Cases	17	15	2
Imbecile & Idiot Cases	15	10	5

For the whole group, the control group, and the test group (all cases) the frequency of the homospecific pregnancies as compared with the heterospecific could scarcely be more normal, and for the subdivision of the test group, the numbers are so small that the slight variation may be disregarded.

DISCUSSION AND CONCLUSIONS.

Since Rh incompatibility occurs in practically 10% 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 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 my own work, I have adhered strictly to the conditions laid down by these writers, so that my results would bear an exact comparison and any conclusions I drew could not be criticised on the grounds of a difference in these conditions. One difference, a fundamental one, has appeared, namely the conception of what is the base line or normal control figure for the general population, and I shall discuss this more fully presently.

Snyder, Schonfield and Offerman carried out comparable investigations and their results appeared to confirm these of Yannet/

Yannet et al, but again the series of cases was small. Later, Scholl, Wheeler and Snyder re-examined the cases previously dealt with by Snyder et al, and felt that the results were inconclusive. They also laid down certain principles to be observed in the conduct of such an experiment. These I have already quoted, (page 45) and I must acknowledge that I have not been able to fulfil them all, although I have done so as far as possible.

My number of cases of undifferentiated defect showing Rh incompatibility is 32 thus exceeding the 25 stipulated by Scholl et al as a minimum. I have not been able to examine any case within a year of birth, but quite an appreciable number were quite young children, although many of my 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 I examined had been certified under the M.D. Acts of this country, and earlier on in this work I have stated how I finally decided which cases were truly undifferentiated or not. Finally in my clinical histories, given in the Appendices, I have noted any neurological abnormalities found to be present.

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 my series. Table XVI shows the results of the two total series.

Table/

Table XVI

	<u>Total Cases</u>	(1) <u>Total Rh negative Mothers</u>	(2) <u>Total Rh negative Mothers with positive child- ren.</u>
Yannet & Lieberman	386	68 (17.6%)	46 (11.9%)
Gilmour	427	84 (19.7%)	52 (12.2%)

It will be seen that my percentages are actually very slightly higher in both columns (1) and (2) than those of the American workers, and it is also seen that for the whole group of defectives in the American work, there is no statistical significance in their figures.

When the two groups are divided into "control" and "undifferentiated" the comparison is as follows. I have included the "heredity" cases in my series for this purpose in the undifferentiated group.

Table XVII

	<u>Total Cases</u>	<u>Total Rh negative Mothers</u>	<u>Total Rh negative Mothers with positive children.</u>
Yannet et al. "Control"	211	28 (13.2%)	16 (7.6%)
Gilmour "	152	35 (23.0%)	20 (13.2%)
Yannet et al. "Undifferentiated"	175	40 (22.9%)	30 (17.1%)
Gilmour "	275	49 (17.8%)	32 (11.6%)

The difference in the two sets of figures, both as regards total cases and in the percentages in columns (1) and (2) is at/

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 feebleminded cases. Amongst my controls, the big majority were low grade (3.34:1) whereas amongst the undifferentiated, the numbers much more nearly equal (1.25:1).

The reason for the marked difference in the percentage figures is undoubtedly that mentioned by Cappell (1947), and which I have already 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 my figures and those of the Americans is the question of what are the normal base-line figures on 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) state unequivocally that in the general population, 87% are Rh positive and 13% Rh negative and that the proportion of Rh positive children from Rh negative mothers works out at about 8%. They obtain this figure of 13% for the incidence of Rh negative individuals by regarding as negative only those who are completely so (cde/cde). Cook in the Journal of Heredity (1944) states that conception in Rh negative women will/

will average 60% incompatible. If this figure is applied to the 13% the percentage of Rh positive children from Rh negative mother certainly works out at about 8% (actually 7.8%).

I have already discussed, however, why this conception of what should be regarded as Rh-negative is not correct when applied to the question of incompatible pregnancies. If the figure of 15% for the incidence of Rh-negative individuals is taken as the normal, the expected percentage of incompatible pregnancies then becomes exactly 9% 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%, 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%. Cook's formula applied to this gives the expected proportion of incompatible pregnancies as 10.1%.

The figure on which my results have been statistically assessed is actually a shade lower, however, (9.9%), as this figure was calculated from the gene frequencies of the elementary antigens as given in the paper by Race et al.

I have taken some trouble to emphasise this point, because if my figures had been assessed on the American percentages, some of them, apart from the total number of Rh negative mothers in my control group (see Tables 11 and 111) would have been just statistically significant.

Finally, it should be observed that the percentages for my test group of imbecile and idiots, the group comparable to Yannet/

Yannet and Lieberman's test group, could scarcely be more normal. In my series there were 153 cases, against the Americans' 175, and the respective percentages were 16.3% against 22.9%, and 9.8% against 17.1%.

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-immunisation. I 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, because both the distribution of the ABO groups and the proportion of homospecific to heterospecific pregnancies agree very closely with the percentages of Rh incompatible pregnancies found in my groups of cases, as they are both within normal limits.

Effect of "Heredity" Cases

Although throughout this work I have referred to the 25 cases in which mental defect was found in the family history apart from the defective as "heredity" cases, I have not meant to imply thereby that I considered these cases of defect to be due solely to a bad heredity. What I have felt is that in these cases the hereditary factor must at least be taken into consideration.

It will be seen from a study of Table X where I have summarised all my percentages that the inclusion or exclusion of/

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.

From a careful consideration of all my figures, taken on their own, and compared with the American ones, and from the study of all the factors I have detailed in this Thesis, I have come definitely to the conclusion that Rh incompatibility, apart from when it causes Haemolytic Disease of the Newborn and Kernicterus, due to iso-immunisation of the mother during pregnancy, does not have any effect of the mental state of the child. There was no significant difference in the percentage number of cases of Rh incompatibility either in my 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, as compared with the percentage for the general population of this country; nor was there any significant difference between the figures for my control group and my test group.

Further, the ordinary blood group distribution was perfectly normal as was the proportion of homospecific and heterospecific pregnancies. In my opinion, 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 population, and for this reason it has, I feel, been conclusively proved that Rh incompatibility as such 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 investigations into the incidence of Rh incompatibility in 427 cases of Mental Deficiency has been described.

The conclusion has been drawn that Rh incompatibility, apart from the production of Erythroblastosis Foetalis and Kernicterus, is not a factor in the production of Mental Deficiency.

APPENDIX A.

Control Group of Cases showing Rh Incompatibility.

1. Mongols.

Case (1). R.C. aet 12. Third of three pregnancies, homo-specific. Mother's Group A, Rh negative. Defective's Group A, Rh positive.

Pregnancy and confinement were normal, and there was no history suggestive of Erythroblastosis Foetalis. No atypical agglutinins found in mother's serum. Defective was always delicate and is a typical mongol.

Family History. Eldest sibling is alive and well. Second pregnancy ended in a still-birth, but details not known.

Father's sister had a mental breakdown.

Case (2). D.J.O. aet 4. First of two pregnancies, hetero-specific. Mother's Group A, Rh negative. Defective's Group AB, Rh positive.

Pregnancy was normal, but child was premature, although otherwise normal. No history suggestive of Erythroblastosis. No atypical agglutinins in mother's serum. Defective is a typical mongol.

Family History. Younger sibling is alive and well.

Otherwise nil.

Case (3). M.W. aet 11. Sixth of six pregnancies. Homo-specific. Mother's Group B, Rh negative. Defective's Group O, Rh positive.

Pregnancy and confinement normal, and no history suggestive of/

of Erythroblastosis. No atypical agglutinins in mother's serum. Defective a typical mongol.

Family History. The three eldest siblings are alive and well. They were followed by two miscarriages and then the defective. Cause of miscarriages not known. Otherwise nil.

11. Organic Nervous Disease.

Case (4). D.T.C. aet 4. Second of three pregnancies. Hetero-specific. Mother's Group, O Rh negative. Defective's Group, A, Rh positive. Defective a twin.

Pregnancy normal, but child and twin were three weeks premature. An instrumental delivery. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Defective a very small child. Has never developed properly. Is practically blind. Has optic atrophy. 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 alive and well, and youngest child is alive and well. Otherwise nil.

Case (5). J.N.S. aet 24. Third of six pregnancies. Homospecific. Mother's Group, A, Rh negative. Defective's Group, O, Rh positive.

Pregnancy normal, prolonged labour, with convulsions at birth. No history of Erythroblastosis. No atypical agglutinins in mother's serum. Meningitis aet two weeks, as a result of which he is paralysed on the left side. Pneumonia aet $1\frac{3}{12}$ years/

years. Operation to eye aet three months. He is a feeble-minded epileptic, undoubtedly the result of the meningitis.

Family History. First pregnancy ended in miscarriage, second in stillbirth. Fourth child died of pneumonia aet three months and the fifth child of T.B. Sixth is alive and well. 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 negative. Defective's Group O, Rh positive.

Pregnancy and confinement normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Defective developed Encephalitis Lethargica when a few years old, since when she has never been right. She is feebleminded.

Family History. Eldest three siblings alive and well. Fourth died aet 3 years of measles. Sixth and seventh siblings alive and well. Otherwise nil.

III. Spastics.

Case (7). N.D.F. aet 20. Fourth of four pregnancies. Homospecific. Mother's Group B, Rh negative. Defective's Group O, Rh positive.

Pregnancy and confinement normal, although he was one month premature. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Spasticity noticed when he did not begin to walk. Now walks with difficulty and cannot go far from home.

Family History. Eldest sibling alive and well, second died/

died aet 16 months of measles. Third alive and well. Otherwise nil.

Case (8). R.F. aet 31. Seventh of eight pregnancies. Homospecific. Mother's Group, A. Rh negative. Defective's Group, A. Rh positive.

Pregnancy and confinement normal as far as known. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Defective paralysed from birth and helpless and bedridden.

Family History. Eldest five siblings alive and well. Sixth died aet 1 year, cause unknown. Eighth is alive and well. Otherwise nil.

Case (9). R.E.A. aet 23. Third of seven pregnancies. Heterospecific. Mother's Group, O. Rh negative. Defective's Group, A. Rh positive.

Pregnancy and confinement normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Defective had meningitis at six months and suffers from spastic paralysis.

Family History. Eldest sibling alive and well. Second died aet 18 months, thought to be food poisoning. Fourth child aet two days, cause unknown. Fifth and sixth alive and well. Seventh a miscarriage at 3 months. Otherwise nil.

Case (10). J.W. aet 10. Second of two pregnancies. Homospecific. Mother's Group, A. Rh negative. Defective's Group, A. Rh positive.

Pregnancy/

Pregnancy and confinement normal. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Spasticity first observed when defective due to start walking. Requires calipers. Shows incoordination of hands but no true athetosis.

Family History. Elder sibling died aet 14 months of Bronchitis. Mother suffers from mild form of epilepsy and her sister is also an epileptic.

Case (11). J.A.W. aet 11. Only pregnancy. Homospecific. Mother's Group A, Rh negative. Defective's Group O, Rh positive.

Pregnancy normal. Breech birth. Six weeks overdue it is stated by Mother. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Defective is a spastic and all movements show tremor and incoordination.

Family History. nil.

Case (12). B.J.R. aet 17. Fourth of four pregnancies. Homospecific. Mother's Group AB, Rh negative. Defective's Group A, Rh positive.

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. No atypical agglutinins in mother's serum. Defective is an epileptic also, fits having occurred since age of 10.

Family/

Family History. Eldest two siblings alive and well. Third pregnancy ended in miscarriage at three months. Otherwise nil.

IV. Microcephalics.

Case (13). J.H.W. aet 35. Second of fourteen pregnancies. Homospecific. Mother's Group O, Rh negative. Defective's Group O, Rh positive.

Pregnancy was normal, but birth premature, $6\frac{1}{2}$ months. Defective very delicate and blind for six months. No definite history of jaundice. No atypical agglutinins in mother's serum.

Family History. Eldest sibling died aet 24, of Bright's disease. Third alive and well, fourth died 14 months, was paralysed. Pregnancies 5 to 9 all ended in still-births. Tenth sibling died within a few hours. Pregnancy eleven ended in still-birth. Pregnancies twelve and thirteen ended in miscarriages. Fourteenth sibling alive and well. 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 negative. Defective's Group O, Rh positive.

Pregnancy normal, extended breech birth. Child very anaemic when born and no finger or toe nails. No jaundice. No atypical agglutinins in mother's serum.

Family History. Eldest two siblings alive and well. Third pregnancy ended in miscarriage. Fifth sibling alive and well. Otherwise nil.

V. Endocrine Disorders.

Case/

Case (15). F.B. aet 20. Third of seven pregnancies. Hetero-specific. Mother's Group, A, Rh negative. Defective's Group, AB Rh positive.

Pregnancy and confinement normal. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. This defective did not develop normally physically owing to endocrine imbalance for which he was treated in hospital.

Family History. First sibling died aet nine months of meningitis. The second and fourth alive and well. Fifth died 10 months of Mastoid. Sixth and Seventh (illegitimate) alive and well. Mother not very bright intellectually.

Case (16). J.W.J. aet 24. First of two pregnancies. Homospecific. Mother's Group, O, Rh negative. Defective's Group, O, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. This individual is a moral rather than an intellectual defective. He is a dwarf, and has been in trouble on many occasions for slitting girls' mackintoshes.

Family History. Younger sibling alive and well.
Otherwise nil.

VI. Haemolytic Disease of Newborn and Kernicterus.

Case (17). P.S. aet 20. Third of six pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group, A, Rh positive.

Pregnancy and birth normal. Defective developed jaundice on/

on day of birth and this persisted for about a fortnight. He had fits just after birth, and again between ages of two and three. There is now no evidence suggestive of Kernicterus. No atypical agglutinins in mother's serum. Defective is feebleminded.

Family History. Eldest sibling died aet 21, of T.B. Second alive and well. Fourth alive and well. Fifth and sixth pregnancies ended in still-births. Otherwise nil.

Case (18). R.B. aet 18. Third of five pregnancies. Homospecific. Mother's Group AB, Rh negative. Defective's Group B, Rh positive.

Pregnancy and birth normal. Jaundice stated to have developed about the third day, but its duration is uncertain. When the child was young, she was stated to have a doubtful positive W.R. and she and her mother attended hospital for injections. The 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 in poor health. The Defective is an imbecile. No abnormal agglutinins in mother's serum.

Family History. Eldest sibling (by first husband) alive and well. Second (by second husband) alive and well. Fourth pregnancy ended in still-birth. Fifth alive and well. 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 negative. Defective's Group

O. Rh positive.

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 form of school. His speech is imperfect. No abnormal agglutinins now in mother's serum.

Family History. First two siblings alive and well. Third died aet two days of jaundice. Otherwise nil.

Case (20). J.T. aet 15. Seventh of seven pregnancies. Homospecific. Mother's Group, O, Rh negative. Defective's Group O, Rh positive.

Pregnancy and birth normal. Jaundice, which was severe and lasted for about three months, developed on the third day. The child was not expected to live, and she subsequently developed athetosis. In this case, the mother's serum agglutinated saline suspended rhesus positive cells, and the reaction was greatly enhanced when the cells were suspended in albumin and a titre of 1:8 was 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 siblings died aet nine months of meningitis. Second alive and well. The fourth pregnancy ended in a miscarriage. Fifth and sixth siblings alive and well. All the children were slightly jaundiced at birth. Otherwise nil.

APPENDIX B.

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

1. Feebleminded Cases.

Case (21). R.H. aet 20. First of two pregnancies. Homospecific. Mother's Group, O. Rh negative. Defective's Group, O. Rh positive.

Pregnancy normal. No qualified help available at birth. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Defective at first attended an ordinary school, then special school.

Family History. Second pregnancy ended in miscarriage during 7th 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 negative. Defective's Group A. Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Nothing of note in subsequent development, apart from the fairly mild mental defect.

Family History. Second and third siblings alive and well. No history of jaundice. Otherwise nil.

Case (23). J.S. aet 48. Fifth of nine pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group, A. Rh positive.

Early/

Early details rather vague, but no history obtained of Erythroblastosis and no atypical agglutinins in mother's serum. Nothing of note in subsequent development apart from defect.

Family History. First two siblings died in infancy, third, fourth and sixth alive and well. Seventh, eighth and ninth (by second husband) alive and well. Otherwise nil.

Case (24). C.A. aet 36. First of two pregnancies. Homospecific. Mother's Group O. Rh negative. Defective's Group, O. Rh positive.

Pregnancy normal. Breech birth. Slight jaundice immediately after birth, duration unknown. No atypical agglutinins in mother's serum. Nothing of note in subsequent development, apart from mental defect. Physically she is in fair health, with no stigmata suggesting that the early jaundice was of the Icterus Gravis type.

Family History. Second sibling alive and well. A cousin of the defective, on father's side is also a defective.

Case (25). A.M.W. aet 38. Sixth of ten pregnancies. Homospecific. Mother's Group, O. Rh negative. Defective's Group, O. Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Backward development generally from early age. Fell downstairs and broke leg aet four years, with doubtful head injury. Defective always delicate, but on examination no stigmata of Icterus Gravis or Kernicterus.

Family/

Family History. Eldest sibling died aet 10 weeks, cause unknown. Second and third alive and well. Fourth died aet $1\frac{1}{2}$ years, and fifth died aet three years, both of meningitis. Seventh alive and well. Eighth pregnancy ended in still-birth, mother being unwell due to worry and lack of food, ninth and tenth alive and well. Otherwise nil.

Case (26). W.H.H. aet 41. Eighth of ten pregnancies. Homospecific. Mother's Group O, Rh negative. Defective's Group O, Rh positive.

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

Family History. Eldest sibling alive and well. Second and third pregnancies ended in still-births. Fourth to seventh and ninth and tenth siblings alive and well.

Case (27). A.L.W. aet 54. Only pregnancy. Homospecific. Mother's Group A, Rh negative. Defective's Group O, Rh positive.

Pregnancy normal. Confinement very difficult, and it was feared child would be lost. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Nothing of note in subsequent history apart from mental defect apparent from early age, and the later development of mental illness requiring admission/

admission to a mental hospital.

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 negative, the genotype being in this case, r'r (Cde/cde). Defective's Group, AB, Rh positive.

Pregnancy and birth normal. Nothing of note in history till he was aged 23 when he developed Epilepsy. No atypical agglutinins in mother's serum. Mental defect evident from an early age.

Family History. Eldest three siblings alive and well. Otherwise nil.

Case (29). J.B. aet 12. First of two pregnancies. Homospecific. Mother's Group, O, Rh negative. Defective's Group, O, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Nothing of note in subsequent history apart from mental defect.

Family History. Younger sibling alive and well. Otherwise nil.

Case (30). D.E.M. aet 23. Third of six pregnancies. Heterospecific. Mother's Group, O, Rh negative. Defective's Group, A, Rh positive.

Mother had a bad fall during early stages of the pregnancy, but she carried on to term. Birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum.
Epilepsy/

Epilepsy began at one year and has continued since.

Family History. All the other five siblings are alive and well. Otherwise nil.

Case (31). F.B. aet 29. Sixth of fifteen pregnancies. Homospecific. Mother's Group O, Rh negative. Defective's Group, O. Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Backward from an early age.

Family History. The first, fourth, fifth, seventh, ninth and thirteenth siblings all died at an early age of definite physical illness. The rest of the family eight in all, alive and well; no defectives among them.

One grandparent on each side of the family said to be backward. The father was a heavy drinker.

Case (32). J.G.P. aet 31. Second of eight pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group A, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Nothing of note in subsequent history apart from mental defect.

Family History. Eldest sibling died at two years, cause unknown. Third died at two years of meningitis. Fourth and Fifth alive and well. Sixth, seventh and eighth died at one week, two and three days respectively, cause not known.

An uncle of the Defective's mother was ill mentally for some years.

Case/

Case (33). R.L.S. aet 18. Third of three pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group A, Rh positive.

Pregnancy and birth normal. Nothing of note in history from birth onwards, apart from mental defect. No atypical agglutinins in mother's serum.

Family History. Eldest sibling died aet 13 of Cerebral Tumour. Second alive and well.

Mother is a patient in a mental hospital and her father died of mental trouble (almost certainly senility or comparable disease).

Case (34). J.H.W. aet 34. Third of three pregnancies. Homospecific. Mother's Group O, Rh negative. Defective's Group O, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Developed epilepsy at age of three and a half years and fits have continued ever since.

Family History. Eldest two siblings alive and well. Otherwise nil.

Case (35). K.J.W.D. aet 21. First of ten pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group O, Rh positive.

Pregnancy normal. Instrumental delivery, but child normal, and no history of Erythroblastosis and nothing of note in subsequent development apart from mental defect. In this case, atypical agglutinins were found in the mother's serum. The serum/

serum did not agglutinate saline suspended cells, but it agglutinated strongly all the albumin suspended rhesus positive test cells. The indirect Coombs test was also strongly positive. This finding occurred five years after birth of the mother's youngest child but it was impossible to obtain specimens from the rest of the children owing to lack of further cooperation.

Family History. Second, fourth, fifth, seventh, ninth and tenth siblings alive and well. Third died aet $2\frac{5}{4}$ years of Pneumonia. The sixth and eighth pregnancies ended in stillbirths. Otherwise nil.

11. Imbecile and Idiot Cases.

Case (36). J.G.D. aet 20. First of two pregnancies. Homospecific. Mother's Group O, Rh negative, the genotype being in this case r'r (Cde/cde) or r'r' (Cde/Cde) Defective's Group O, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Fits began when he was six months and ceased at age of $2\frac{1}{2}$ years. Nothing else in history apart from mental defect.

Family History. Second sibling alive and well.

Otherwise nil.

Case (37). E.A.S. aet 42. First of four pregnancies. Homospecific. Mother's Group, A. Rh negative. Defective's Group, A, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Epilepsy developed/

Epilepsy developed at age of 13 and has continued since, but mental defect was evident from an early age.

Family History. Difficult labours, and instrumental deliveries at all confinements after first. Second and third sibilings alive and well. Fourth pregnancy resulted in twins, one being alive and well, the other dying aet 6 of Diphtheria. No jaundice in any of these sibilings at birth.

Otherwise nil.

Case (38). S.H. aet 15. Only pregnancy. Homospecific. Mother's Group O, Rh negative. Defective's Group O, Rh positive.

Pregnancy normal. Umbilical haemorrhage at birth. Prolonged instrumental labour. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Epilepsy began at age of two years and has continued since.

Family History. nil.

Case (39). M.B. aet 34. First of three pregnancies. Heterospecific. Mother's Group, O. Rh negative. Defective's Group, A, Rh positive.

Pregnancy normal. Normal birth at seven months, no jaundice developed, but defective was anaemic and delicate. No atypical agglutinins in mother's serum. Defective fell out of bed when a few weeks old and injured the forehead, but no evidence that this had any bearing on the mental defect.

Family History. Second sibilng died aet ten weeks, said to be due to T.B. of bowel. Third sibilng alive and well. No history of jaundice in either case. Otherwise nil.

Case/

Case (40). E.M.G. aet 36. Second of six pregnancies. Hetero-specific. Mother's Group O, Rh negative. Defective's Group A. Rh positive.

Pregnancy and birth normal. Nothing of note in life history apart from mental defect. No atypical agglutinins in mother's serum.

Family History. All the other five siblings alive and well with no history suggestive of Erythroblastosis.

Otherwise nil.

Case (41). B.M.B. aet 7. First of four pregnancies. Hetero-specific. Mother's Group O, Rh negative. Defective's Group A, Rh positive.

Mother had chronic Nephritis, and pregnancy was terminated four weeks early. Normal birth and no history of Erythroblastosis. No atypical agglutinins in mother's serum. Defective had blood transfusions from mother at age of two months because of attack of gastro-enteritis. Normal subsequent history apart from mental defect.

Family History. Induced labours for all the siblings owing to the Nephritis. The three younger children alive and well, but last child was slightly jaundiced at birth. This was probably physiological as atypical agglutinins would almost certainly otherwise have been found. (Mother's blood examined less than three years after this birth). Otherwise nil.

Case (42). P.E.B. aet 9. First of two pregnancies. Hetero-specific. Mother's Group O, Rh negative. Defective's Group A, Rh/

Rh positive.

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. No atypical agglutinins in mother's serum. Defective said to have had meningitis at age of three years, but there is no evidence that defect was due to this.

Family History. Younger child aet 5 alive and well. He also is Rh positive, with no history suggestive of Erythroblastosis, so that defective's condition at birth can in no way be related to iso-immunisation. Otherwise nil.

Case (43). A.F. aet 12. Second of three pregnancies. Hetero-specific. Mother's Group O, Rh negative. Defective's Group A, Rh positive.

Pregnancy and birth normal. Nothing of note in history from birth onwards apart from mental defect. No atypical agglutinins in mother's serum.

Family History. First and Third siblings alive and well. Mother has suffered from Thyrotoxicosis.

Case (44). C.R.H. aet 16. Seventh of eight pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group A, Rh positive.

Mother had a fall while pregnant and this caused a large "lump on the privates". This was removed in hospital and baby was born a few days later, a fortnight prematurely. Normal birth and no history of Erythroblastosis. No atypical agglutinins in/

in mother's serum. Epilepsy began at age of $4\frac{1}{2}$ years, and continued till age 12.

Family History. First pregnancy ended in still-birth, $7\frac{1}{2}$ months. Second third and fourth siblings alive and well. Fifth died aet 11 years said to be diabetes. Sixth pregnancy ended in miscarriage, $4\frac{1}{2}$ months. Eighth sibling alive and well. Otherwise nil.

Case (45). B.D.J. aet 26. Fourth of six pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group, O. Rh positive.

Normal pregnancy. Caesarean birth, at 8 months. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Defective was always delicate and for first twelve months was stated to be in hospital receiving blood tests and injections. Although she now shows no stigmata of Syphilis, I checked up with the hospital in question and they could find no trace of this individual in their records. Nothing of note in subsequent history apart from mental defect.

Family History. First pregnancy ended in still-birth, second sibling died aet ten weeks, cause unknown. Third pregnancy ended in still-birth (eight months) Fifth pregnancy ended in miscarriage (four months) Sixth sibling alive and well. Otherwise nil.

Case (46). W.J.R. aet 21. Second of five pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group O, Rh positive.

Pregnancy/

Pregnancy and birth normal. No history of Erythroblastosis. No atypical agglutinins in mother's serum. Defective fell downstairs at eight months but no evidence of head injury. Nothing of note in subsequent history apart from mental defect.

Family History. First sibling alive and well. Third, fourth and fifth pregnancies ended in miscarriage.

Otherwise nil.

Case (47). L.M.S. aet 11. Only pregnancy (twin). Defective homospecific with mother. Mother's Group O, Rh negative. Defective's Group O, Rh positive.

Pregnancy normal. Birth normal, eight months. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Defective had severe diarrhoea at ten weeks, but nothing else of note in subsequent history apart from mental defect.

Family History. The other twin is alive and well.

Otherwise nil.

Case (48). G.J.P. aet 17. First of two pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group O, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis, and no atypical agglutinins in mother's serum. Nothing of note in subsequent history apart from mental defect.

Family History. Second sibling alive and well.

Great-Aunt of defective was mentally ill and his grand-uncle was said to have committed suicide. Both were on father's side.

Case/

Case (49). J.C.A. aet 32. First of two pregnancies. Homospecific. Mother's Group O, Rh negative. Defective's Group O, Rh positive.

Pregnancy normal. Instrumental delivery at eight months, caused bruising on head. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Defect first noticed at about two years. Nothing else of note in subsequent history.

Family History. Second sibling alive and well. Otherwise nil.

111. "Heredity" Cases.

Case (50). B.G.C. aet 11. Sixth of seven pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group A, Rh positive.

Mother had kidney trouble during last six weeks of pregnancy. Birth normal. Defective a twin, dissimilar. No history of Erythroblastosis. No atypical agglutinins in mother's serum. Nothing of note in subsequent history, apart from mental deficiency. Defective is an imbecile.

Family History. Other seven siblings alive and well including the twin.

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 fifteen pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group A, Rh positive.

Mother had pneumonia during late pregnancy, and was very ill during and after birth of child. As far as is known there was no jaundice, and there are no atypical agglutinins in mother's serum. Nothing of note in subsequent history apart from defect.

Defective/

Defective is feeble-minded.

Family History. First sibling alive. Is a discharged defective. Details of rest of family not clear. Three died in infancy of physical illness, there was a still-birth about the tenth pregnancy, and there was a miscarriage, position in family sequence not known.

The mother herself appeared not very bright intellectually. Eldest sister of defective is feeble-minded. Two cousins, brothers, are both feeble-minded with superadded Schizophrenia, and one of these committed suicide.

Case (52). C.Y. aet 30. First of two pregnancies. Homospecific. Mother's Group A, Rh negative. Defective's Group O, Rh positive.

Pregnancy and birth normal. No history of Erythroblastosis and no atypical agglutinins in mother's serum. Defective and mother were knocked down by a motor cycle when he was two years, since when he has not spoken, but there is no evidence that this was the cause of the defect. Nothing of note in subsequent history.

Family History. Younger sibling alive and well. The mother in this case 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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