OBSERVATIONS ON ERYTHROBLASTOSIS FOETALIS: A CLINICAL AND PATHOLOGICAL STUDY OF THIRTEEN CASES.

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by

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INTRODUCTION.

The epoch making discovery of Minot and Murphy has led to the elucidation of many of the mysteries surrounding the physiology and pathology of the blood; it has led to an immense amount of intensive work, not only on disorders of the blood per se but also on the reactions of the blood to disease over a very wide field. It must be admitted that before the advent of the many recent advances in haematology the conception of erythropoietic disorders in childhood was very confused. There are still many aetiological problems to be solved but the classification of these disorders has been placed on a scientific basis, largely as a result of the clarification of erythropoietic physiology.

During the last decade there have been many valuable contributions to the literature on the pathology of the blood in infancy and childhood. Thanks to the excellence of some of these and the opportunities afforded by my association with the Royal Maternity and Simpson Memorial Hospital in this city, I have, in the course of the last year, become particularly interested in the blood disorders of the neonatal period.

Much /
Much the most frequent blood disorder in the early days of life is "haemorrhagic disease of the newborn." The next most frequent major disorder presents several clinical syndromes, but it is uncommon, though not rare; I refer to the condition which is now known as "erythroblastosis foetalis." Congenital nutritional anaemia of more than a minor degree is very rare in the neonatal period, I cannot recall having seen a definite case until later in infancy, when it is frequently encountered: this type is due to a deficient store of iron in the liver at birth, owing to gross hypochromic anaemia of the mother (Neale and Hawksley, 1933). Leukaemia in the newborn is extremely rare, it is now recognised that most of the cases hitherto described have really been cases of erythroblastosis; the confusion can easily be understood when it is recalled that, in both conditions, there is an excess of nucleated blood cells and an infiltration of them in the liver and spleen. Other blood conditions, such as family acholuric jaundice, are extremely rare in early infancy.

In submitting an account for the Thomson Memorial Medal of original investigation in the field of disorders in children, I have elected to record /
record my observations on erythroblastosis. I think that a study of a disorder which presents jaundice as its major symptom is particularly appropriate, as one of the most important of the many contributions of the late Dr. John Thomson to paediatric literature was that on congenital obliteration of the bile ducts.

In the course of the last sixteen months I have personally observed thirteen cases of erythroblastosis, nine of them have been concentrated in the last seven months. I have consulted the records of many more cases which have been seen during recent years, but thought it advisable to confine this paper to a personal study. I am greatly indebted to those colleagues who have given me every facility in this investigation. The cases occurred in hospital and nursing homes as follows:

- Royal Maternity Hospital - 6
- Royal Hospital for Sick Children - 4
- Private cases - 2
- Elsie Inglis Maternity Hospital - 1

The cases were representative of the various clinical syndromes as follows:

- Hydrops Foetalis - 1
- Icterus Gravis - 9
- Anaemia Haemolytica Neonatorum - 3

This /
This paper is not intended to be an exhaustive study of erythroblastosis but rather a preliminary report of the observations made up to the present time. The importance of following up the recovered cases has been borne in mind, and blood examinations are still being carried out at regular intervals in those cases whose blood counts have not yet attained the normal level. A prolonged follow-up will, of course, be necessary for the assessment of the incidence of mental and nervous sequelae. I propose to discuss briefly the salient features of the condition as I see them and to supplement my comments with references to the literature. A considerable part of this paper will, therefore, be comprised of case records and I have elaborated these with tables and charts where a series of blood counts has been done; while photographs, mostly histological, have been incorporated in a few instances.
DEFINITION OF "ERYTHROBLASTOSIS."

Erythroblastosis is not an ideal designation for the condition under consideration as extra-medullary erythropoiesis also occurs in other conditions in early infancy. It is likely to occur in any condition featuring severe anaemia prior to the atrophy of the foetal extra-medullary erythropoietic foci in the liver and spleen, this atrophy is usually complete at the age of about nine months. Thus, erythroblastosis frequently occurs in congenital syphilis which may closely simulate erythroblastosis foelatis, in family acholuric jaundice which may rarely occur in early infancy, in congenital malformation of the heart and possibly in other pathological states.

It is important to remember that small erythropoietic foci are not infrequently seen in the liver of full time infants, but they are absent in the majority of cases. They are more frequently seen in premature infants, the incidence increasing with the degree of prematurity. I have referred to the liver here because the erythropoietic foci are easily seen in that organ, it is, therefore, per the liver that estimation of the degree of extra-medullary erythropoiesis /
erythropoiesis is always made.

Withal, erythroblastosis foetalis is the only condition exhibiting really extensive extra-medullary erythropoiesis and it is, therefore, entitled to annex the name of "erythroblastosis." The qualification "foetalis" denotes that the process is always initiated in utero.
Fig. I. - The Relationship of the Various Clinical Types of Erythroblastosis.
CLINICAL FEATURES.

The striking clinical dissimilarities of the various syndromes comprising erythroblastosis have been the principal reasons for the failure to realise, until recently, that they are merely different manifestations of one underlying pathological state. It is now believed that severe haemolysis is chiefly responsible for the gross oedema of hydrops foetalis, for the profound icterus of icterus gravis and the waxen pallor of anaemia haemolytica neonatorum; the names of the three clinical syndromes which comprise erythroblastosis foetalis. In these days, when so many clinical syndromes are being subdivided into a number of definite conditions, it is refreshing to find an instance of several syndromes being merged into one pathological concept. Fig. I illustrates the clinical association of the various types, but it must always be remembered that all degrees of intermediate variation may occur.

Incidence of Erythroblastosis.

As the condition of erythroblastosis foetalis becomes better known, following a better understanding of its nature, it is being realised that it is a
by no means uncommon condition. The fact that I have been able to collect thirteen cases in sixteen months, without causing my interest in the condition to become widely known, shows that it is really one of the important major disorders of the neonatal period.

There are, of course, no reliable statistical data of a disease which is so often unrecognised. Hampson (1929) has estimated from the returns for England and Wales for a seven year period, that 1,800 infants died as a result of what was, in all probability, icterus gravis. During the last 2½ years at the Simpson Maternity Hospital there have been at least ten cases, an incidence of about one in five hundred.

**Familial Incidence.**

The occurrence of icterus gravis in siblings is well known; sometimes there is a phenomenal sequence of such cases, there are many examples of this recorded in the literature Macklin, (1937). In my series there were nine cases of icterus gravis and siblings had been similarly affected in two instances.

Hydrops foetalis frequently occurs in more than one /
one pregnancy, and occasionally occurs in several. Case 1 with hydrops was the second instance in the family. Anaemia haemolytica has also been recorded in siblings on numerous occasions.

The occurrence of more than one clinical type of erythroblastosis in a family is not very infrequent. Icterus gravis and hydrops foetalis is the commonest association; Macklin found this association in eleven per cent of the families which she reviewed. De Lange (1932) observed an instance of twins, one of which was affected with icterus gravis and the other with hydrops foetalis, two earlier infants in the same family had icterus gravis. In my series, Case 1 is of special interest in regard to the association of different clinical types in one family, the family history is as follows:- the parents appear healthy, the first child was a healthy infant and is now a robust youth, the second child died of icterus gravis aged 1½ days, the third child was dead-born and exhibited hydrops foetalis, while the fourth, Case 1, was born alive with hydrops foetalis and only lived for fifteen minutes. I have recounted this family history because it is typical of numerous others which have been placed on record. A sibling of Case 9 was a premature dead-born /
dead-born infant with hydrops foetalis. Prior to this there had been a miscarriage, while the child before that, the first, was healthy. Anaemia haemolytica and hydrops would appear to be the most unusual association though it has been recorded.

It is the not infrequent association in siblings of these three clinical syndromes which constitutes the strongest reason for regarding them as different manifestations of the same disorder. It affords much stronger evidence than a similar pathology which is not necessarily indicative of an identical aetiology.

I think that the familial incidence of icterus gravis has been over-stressed. Probably an undue proportion of the published cases have been familial because that fact points to the diagnosis, in the absence of a familial clue the sporadic cases are rarely recognised. I have not been interested in the condition long enough, and, therefore, have not followed up the affected families of this series for sufficient length of time, to be justified in expressing an opinion on this point; but I expect to find that sporadic cases constitute the majority.
11.

**Position in Family.**

It is traditional that first babies in families afflicted by icterus gravis are always healthy. This is not so, for there are numerous instances on record of first babies being affected; however, it is a fact that the incidence in the first born is very much lower than in those born subsequently. There are no first babies in my series; the great preponderance of second babies emphasizes the absence of first born infants and inspires reflection, a possible explanation will be discussed under aetiology. Six of the thirteen cases of my series were second babies, while the second child in three other instances had died of icterus gravis, in all nine cases the first born was healthy.

**Heredity.**

There is no sound evidence to show that erythroblastosis is inherited, although a few authors have suggested that it would appear to be so in some cases. There are two instances on record of a parent having been affected and two of parents with affected siblings.

Macklin (1937) believes that the anomaly has the characters of a dominant hereditary mutation. She has /
has based her conclusion on material the authenticity of some of which is doubtful, while she has assumed that the majority of miscarriages occurring in affected families are caused by the same underlying error.

**Miscarriages.**

The high incidence of miscarriages in some of the affected families suggests that a proportion of these are due to a similar error in the earlier months of foetal life. Macklin points out that "in families in which hydropic children have been born, there is almost always a history of an undue number of miscarriages, premature births, still-births, births of macerated foetuses and similar anomalies." There is, however, no proof that miscarriages in such families are caused by the early death of similarly affected foetuses; but it seems likely that some of the miscarriages may be due to a similar anomaly.

**Hydrops Foetalis.**

Universal oedema of the foetus is another name often applied to cases of hydrops. These infants are usually premature and dead-born, and they display a condition of anasarca of varying degree, but often extreme./
extreme. Sometimes, as in Case 1, there may be little external evidence of oedema, and the diagnosis may not be apparent as in this instance. A large oedematous placenta is the rule. Maceration is often present though it is frequently only slight. A large placenta, hydrops with maceration, and a history of similar births and miscarriages, constitute a picture of syphilis in most peoples' minds, and rightly so; but erythroblastosis is seldom thought of because it is less well-known.

In the less severe cases live births sometimes occur, but death always supervenes in a few minutes or, more rarely, in a few hours. Case 1 was born alive but died after about fifteen minutes. A point of great interest is that the obstetrician noticed respiratory difficulty - "it appeared as though there was no inspiratory difficulty but an obstruction to expiration". The interest lies in the fact that oedema of the glottis demonstrated at autopsy appeared to be the cause of this embarrassment and of death. This may be a cause of the short survival not infrequently in severe cases.

Jaundice is sometimes present in a mild degree.

Anaemia, often gross, is the rule. The blood picture is similar to that in the other clinical types of /
of the disorder but the various abnormalities are often more extreme, the high proportion of erythroblasts being particularly striking as in Case 1. As few as under half a million red cells have been recorded in this condition.

The liver and spleen are usually grossly enlarged but not invariably so, occasionally they are of a normal size. These organs were not enlarged in the hydropic twins mentioned later but they were greatly enlarged in Case 1.

In looking through the records of the Elsie Inglis Maternity Hospital I found that, four years ago, post-mortem examinations were made on a pair of premature dead-born twins, one of which had hydrops foetalis and the other no oedema; both displayed the typical histological appearances of erythroblastosis foetalis. A similar instance of such an association occurred in the Royal Maternity Hospital two years ago, unfortunately the non-hydropic foetus was not examined.

Although recognised for centuries one is proud to find that Ballantyne (1892), whose name is so gloriously associated with the Royal Maternity Hospital in this city and of world-wide fame, was the author of the best known early work on hydrops foetalis.
foetalis. He did not associate the condition with the other syndromes constituting erythroblastosis. Haemopoietic foci in the liver, spleen and kidneys were first observed by Swart (1905) but their significance was not understood. Schridde (1910) was the first to describe an underlying causative disturbance of the haemopoietic organs, but it was Rautmann, two years later, who termed the underlying condition erythroblastosis.

The Dead-born Non-hydropic Type.

The association of a hydropic and a non-hydropic foetus in a twin pregnancy, such as I have mentioned above, has been recorded in the literature on eight occasions (Macklin, 1937). This leads one to infer that probably the dead-born type of case, without oedema or other striking features, is usually unrecognised and may be much commoner than is supposed. At autopsy the naked-eye appearances may not appear grossly abnormal, as in the first of the two instances which I have mentioned, but the liver and spleen of this infant displayed very active erythropoiesis.

Icterus gravis.

Oedema. - This, which may be said to link icterus gravis /
16.

Gravis and hydrops, occasionally occurs but is usually of a slight degree.

Jaundice. — A minority of the cases of icterus gravis show jaundice at birth, but in such cases it nearly always becomes deeper thereafter. The outlook is usually regarded as being worse when this is so and Case 3, the most rapidly fatal of the five cases of icterus gravis which died, would seem to bear this out; however, the mild jaundice exhibited at birth by Case 11 with anaemia haemolytica cleared up in two days. In those instances of marked jaundice at birth the vernix caseosa has a "guinea-gold" colour and the liquor amnii is bile-stained, these phenomena were observed in Case 2 in which the vernix was "mustard" coloured. In the majority of cases jaundice is first noticed a while after birth but appears much earlier than the normal physiological type, it is often noticed on the first day, may be a few hours after birth — it was noticed within an hour of birth in Case 8. In all cases the jaundice rapidly becomes intense, the tongue, buccal mucosa and conjunctivae all sharing in the discolouration. The urine contains urobilin in all cases and sometimes urobilinogen, while in the more severe cases it is also bile-stained. The stools are normally pigmented. The van den Bergh reaction gives a biphasic response.

In /
In those cases which survive the first few days of life the jaundice often begins to fade after about a week or ten days and finally disappears at the age of 3-6 weeks. Occasionally exacerbations of jaundice occur as in Case 7.

Anaemia.—This apparently occurs in all cases of icterus gravis. In those cases which die before the jaundice begins to fade it is often not observed clinically unless it is severe and causes the fatal termination as in Cases 5 and 6. As in these cases a fatal and untreated anaemia is apparently most common in the second week of life. Some degree of anaemia probably occurs in all cases from birth, though in the first few days it is usually not extreme; it was of moderate degree, though quite definite, in the three cases of this series which died within three days of birth. In Case 7, which survived, slight anaemia was found on the third day when examinations were begun, and it rapidly became severe early in the second week. It is important to bear in mind the normal high levels of the erythrocytes and haemoglobin at birth. It is apparent then, that unless looked for, anaemia, unless profound, is not observed until the jaundice begins to fade and it often seems to become severe in the course of a few days. A blood transfusion, sometimes several, may be /
be required to save the lives of such cases but I believe that a spontaneous recovery usually occurs; transfusions almost certainly saved the life of Case 7 and probably would have saved that of Case 5, but Cases 8 to 10 inclusive all recovered spontaneously. During the course of recovery, the rate of which varies a good deal, two or three relapses are of frequent occurrence; pauses in the course of recovery, sometimes lasting a week or more, occur in most cases. Usually there is little clinical evidence of anaemia at three months of age, but the haemoglobin and erythrocytes do not usually reach the normal levels until the age of four or five months, as a study of my cases will show.

Blood.—The blood picture is essentially the same in all these cases, the anaemia is always macrocytic and therefore hyperchromic and erythroblastaemia is the rule; the latter occurred in all my patients whose blood was examined but it was slight in five of the seven cases of icterus gravis whose blood was studied. In the other two cases nucleated red cells were very numerous, they amounted to seven per cent in Case 2. Where they are few in number the normoblasts form the great majority, there being a few megaloblasts also.
also. Those cases with a high proportion of immature red cells exhibit a greater number of immature forms, and basophilic pro-erythroblasts may occur in small numbers as in Case 2. Even in the latter cases, however, normoblasts predominate and sometimes, as in Case 2, there is a great diversity of karyorrhectic forms while karyokinesis is sometimes seen. Large numbers of nucleated red cells, especially of the more immature types, is apparently a feature of some of the more severe cases which rapidly prove fatal. I have not seen severe erythroblastaemia in any case which recovered and believe that cases which exhibit this feature usually prove fatal. The common mild erythroblastaemia often persists until the fourth, or even the fifth week of life. Polychromasia is usually a marked feature as the foregoing remarks suggest. The presence of numerous macrocytes, some of them very large, is chiefly responsible for the pronounced anisocytosis. Poikilocytosis is seldom a prominent feature though usually present in slight degree.

Reticulocytosis, often extreme, occurs in all cases with the possible exception of some of those which die early of nervous or haemorrhagic complications. I have made a careful study of this feature /
feature because I feel that by following the reticulocyte level one has a good grasp of the reactivity of the erythropoietic tissues throughout the illness. A glance at the charts of the seven cases in which this feature was followed will show that in 3 of them the reticulocytes reached a very high percentage - well over fifty per cent in Case 9. Marked reticulocytosis, of varying degree, persists in all cases for several weeks until considerable improvement has occurred. It often remains slightly raised up to about three months of age or longer, probably indicating that a mild degree of haemolysis is still occurring.

The fragility of the erythrocyes in hypotonic saline is not increased. It was normal in the two cases of this series which were tested.

It might be well to recall here that nucleated red cells only occur in a minority of infants after birth and, if present, there are very few which only persist for two or three days. Polychromasia and reticulocytosis are both considerable at birth, the reticulocytes usually number about eight per cent but rapidly fall to the adult level of under one per cent in a week or ten days (Krumbhaar, 1932).
A considerable degree of anisocytosis is a normal feature in the new-born, a slight degree of poikilocytosis is also found.

Apart from intercurrent infection I did not find a raised white count as a rule, though it is supposed usually to be raised slightly in the early stages when the myelocyte count is increased. I was struck, however, by the considerable eosinophilia in the early stages of recovery which is a well recognised feature of the disease; less constantly a slight monocytosis is also said to occur at a similar phase of the illness but I have not done a sufficient number of differential counts to confirm this. The essential feature of the white blood picture is that it is not notably abnormal.

The Spleen.—Splenomegaly is an almost constant feature although the spleen is frequently impalpable, it was palpable in only four of the nine cases of icterus gravis. It extended to as much as two inches below the costal margin in Case 9. In the rapidly fatal Case 2 the spleen was easily felt at birth. In Cases 7 and 9 it first became palpable at about three weeks old and, after attaining a maximum of one and two finger-breadths respectively below the costal margin, it receded and became impalpable /
impalpable again in a few weeks. In Cases 3 and 5 which died and in Cases 8 and 10 which recovered, it was never palpable. According to some authors there is no splenomegaly in a small minority of cases.

Liver. - Hepatic enlargement was usually not demonstrable clinically but was present to a slight degree in a minority. Sometimes, however, it is greatly enlarged. It was most pronounced in those cases with the largest spleens as is usually the case.

Nervous Manifestations. - Symptoms of this order are unusual but occur in a considerable minority of cases, they are caused by intracranial haemorrhage or focal degeneration in the brain, the latter complication is termed kernicterus owing to the excessive bile-staining of the degenerate nuclear areas.

In this series nervous features were only observed in the two cases which were proved at sectio to have kernicterus. Case 2 displayed twitchings of the face, generalised starting movements, prolonged coma and hypopnoea which appeared to be of central origin. Case 4 was excessively drowsy, had a similar type of sighing respiration and displayed bradycardia. Convulsions and spasticity are other nervous /
nervous symptoms described at this early stage.

These intracranial complications may not be suspected clinically but when they do give rise to symptoms they are usually not differentiated. Owing to the nervous phenomena exhibited I provisionally diagnosed kernicterus in Case 2, it was confirmed at autopsy. Neither of these complications necessarily prove fatal, and the mental and nervous sequelae which may occur in those which recover will be briefly referred to under prognosis.

Haemorrhage.—This is a frequent and often a fatal complication. It does not often occur after the first two weeks of life. Apart from intracranial haemorrhage which is frequently traumatic, much the commonest site of bleeding is the umbilicus, usually after separation of the cord. A fatal haemorrhage of the latter type occurred in Case 6. Local treatment is of little avail. Probably the next most frequent source of haemorrhage is the lung, the epistaxis in Case 2 came from this source. Haematuria of renal origin may occur or haemorrhage from the mucous and serous surfaces while those of a purpuric nature are not infrequent.

Not until the end of the last century did icterus gravis become separated from other forms of neonatal /
neonatal jaundice. Ashley, in 1884, was one of the first to describe the condition in this country, he reported a family of five children in which the last three died of this condition. De Lange and Arntzenius in 1929 were the first to call attention to the significance of golden vernix caseosa at birth. Attention has focused more and more on the fundamental importance of the blood in icterus gravis since Buchan and Comrie, in 1909, described the pathology of the condition so admirably. They laid particular stress on the extensive extra-medullary haemopoiesis. One is proud to know that work which emanated from this School has achieved such universal acclamation, and is everywhere acknowledged as the first account of the occurrence of extra-medullary blood formation in icterus gravis.

Anaemia Haemolytica Neonatorum.

This term includes not only those cases which have never shown any jaundice but also those exhibiting mild jaundice resembling the physiological type. A completely anicteric course is unusual which adds to the interest of Case 13, there are not many cases of this type on record. The mild jaundice of Case 12 was thought to be physiological, while that of /
of Case 11 is of special interest in that it was observed at birth and cleared in two days. The nature of the jaundice in Case 11 and the severe degree of anaemia at birth demonstrate the close relationship between icterus gravis and "anaemia gravis". It would seem logical to argue that in this case the icterus may have run most of its course in utero, and that the jaundice had almost disappeared at birth: the state of the icterus and the blood which rapidly improved thereafter did, in fact, closely resemble that seen in recovering cases of icterus gravis at the age of two or three weeks.

There is no need to say much of the clinical features in these cases because they do not differ essentially from those of icterus gravis. Apart from the jaundice the main points of difference are the infrequency of cerebral complications and of haemorrhage while erythroblastaemia does not assume the severe degrees found in the more severe types of the disease; it was never observed in Case 12. Anaemia Haemolytica neonatorum is relatively benign and is the mildest manifestation of erythroblastosis foetalis. Even so, it is doubtful whether Case 13 would have survived without active treatment as the erythrocytes fell rapidly to 700,000, the lowest count met /
met with in this series of cases. It is of interest to observe that the splenic and hepatic enlargement in this case surpassed that in any of the others. The pallor was extreme, giving a waxen appearance, as is apt to occur in those without any masking jaundice. One was struck by the vitality of this case throughout, a feature of this less serious form of erythroblastosis which other authors emphasise.

Anaemia haemolytica neonatorum is of comparatively recent recognition, it was first described by Ecklin in 1919. Its association with the other clinical types of erythroblastosis has only been acknowledged within the present decade.
PATHOLOGY.

I will describe the post-mortem appearances of the various types of the disease separately; but owing to its identical nature in most of the organs there will be no need to describe the histology separately, except in those organs where differences occur.

**Morbid Anatomy.**

**Hydrops Foetalis.**

The frequency of maceration has been referred to already, the morbid anatomical appearances are distorted thereby while histological evidence is usually worthless.

Oedema.— The cause of the oedema in hydrops foetalis is uncertain but it is usually assumed to be due to increased capillary permeability resulting from toxic degenerative changes of the endothelium. Others believe that anoxaemia, resulting from the severe anaemia, is responsible for the damage to these cells leading to the same result. Sometimes the ascites is so extreme that the abdomen has to be perforated before delivery can be affected.

Clinical reference to Case 1 has demonstrated the fact that oedema may be marked in the serous sacs and /
and interstitial tissues but only slight subcutaneously. I think this observation, that hydrops may not be diagnosed until autopsy is performed, is a most important one.

Jaundice.- This is usually absent but occasionally slight icterus occurs.

Liver and Spleen.- Typically the liver and spleen are enormously enlarged, but occasionally there is no perceptible change in size as in the twins referred to earlier.

The Heart.- Cardiac hypertrophy is a constant and interesting feature, sometimes the ventricular walls are very thick; the reason for this is obscure but interstitial oedema may be a contributory factor.

Blood.- The blood is usually noticeably thin.

Icterus Gravis.

Oedema.- Sometimes there is an excess of fluid in the serous sacs such as occurred in Case 2.

Jaundice.- There is bile-staining of most of the tissues, the chief exception being the central nervous system which usually does not show any: the liver is often bile-stained but one is sometimes struck by its slight degree as in Case 2.

The Liver.- The liver is usually enlarged, sometimes /
sometimes greatly but more often only moderately. In some of the cases it is stated that there was no enlargement, but this statement cannot be relied on as the organ was not weighed and one cannot estimate small variations in the size of it without doing so. The consistence of the liver is normal. A bright brown colour of the cut surface has been a notable feature in some of the cases, particularly Cases 1 and 2. There is no defect of the bile ducts.

The Spleen.— Although not always detected clinically the spleen was greatly enlarged in all the cases which came to autopsy. The consistence was usually unaltered but sometimes it was rather soft. No Malpighian bodies were ever seen on the cut surface.

The Brain.— In the seven cases of this series which came to autopsy only one, Case 5, had an intracranial haemorrhage which arose from small bilateral tears of the tentorium cerebelli from which a moderate degree of subdural bleeding had occurred. Hawksley and Lightwood (1934) encountered intracranial haemorrhage five times in fifteen autopsies, it was either subdural or subarachnoid - more commonly the former. The same authors observed kernicterus in two /
two of their cases, it was a feature in Cases 3 and 5 of this series. Bile-staining of the central nervous system was first described by Schmorl in 1905, he observed two types, one in which a diffuse pale yellow pigmentation of all the brain tissue occurred and a much commoner type in which the pigmentation was circumscribed and confined to the nuclear areas. The nuclear type is usually of a bright yellow hue. Bile-staining of cerebral elements is said not to occur in other forms of jaundice. Schmorl coined the term kernicterus by which the nuclear type is known. In my two cases the pigmentation was most intense in the medullary nuclei but was also marked in the others of the brain stem, the cerebellar nuclei, and in the corpus striatum. The brain of Case 3 was not examined very carefully but that of Case 2 was carefully sectioned after hardening, in addition to the above features a bright yellow staining of the corpora Luysii and the hippocampal cortex were noticed. The pigmentation was very striking in Case 3 in which it was a very vivid yellow. In the rare diffuse type foci of softening, appearing as pale yellow flecks, are distributed symmetrically in the medullary layers of the hemispheres lateral to the central ganglia and only /
only exceptionally do they occur outside of this region. Bile-staining of the spinal cord has not been a matter of comment, it was not looked for in the worse of these two cases but was not present in the other - Case 3.

The Blood. The blood usually looks thin and may be extremely so when the anaemia is intense, in such cases the tissues may look extremely blanched. Case 5 displayed these features in a severe degree.

Other Organs. There are no other morbid anatomical appearances worthy of much comment. The not infrequent occurrence of haemorrhage has been referred to, there was slight pulmonary haemorrhage in Case 3 and small renal haemorrhages were seen in Case 5.

Anaemia Haemolytica. Apart from the slight degree or absence of jaundice and therefore of bile-staining of cerebral elements, and the lower incidence of haemorrhage from the various sites, the appearances are the same as in icterus gravis. The three cases of this series all recovered.

**Histology.**

The presence of extra-medullary foci of erythropoiesis in the liver and spleen is the essential /
essential histological feature in cases of erythroblastosis. It varies greatly in degree from a massive infiltration of erythroblastic cells to a slight excess of these elements over that sometimes seen in normal infants. The liver and spleen are the organs constantly involved in this process. An occasional focus is sometimes seen in the kidneys as in Case 1, it is very unusual for erythropoiesis to be observed in other organs but there was slight evidence of it in the pancreas of Case 1. The process has been described in the following additional organs: Suprarenal, thyroid, parathyroid, pituitary, ovary, testis, intestine, lung, skeletal muscle and in the skin. These constitute a great variety of situations; the predilection, however, is for glandular tissue. These main histological features are the same in all forms of the disease.

The Liver.-- This is the organ of greatest histological value in erythroblastosis because the presence and extent of haemopoietic cells are easily seen, thus the liver affords the most convenient and the usual medium for estimating the degree of extra-medullary blood formation. In view of its key position it is essential to bear in mind the histological /
Fig. 2. Liver. X 70.
Normal full-time infant.
Three haemopoietic foci are seen.

Fig. 3. Liver. X 80.
Foetus of 14 ozs.
Active haemopoiesis is seen.
histological appearance of the liver in the normal full-time and in the premature infant. In a considerable minority of full-time infants there are small widely scattered foci of erythropoiesis which are conspicuous on account of the pyknotic nature of most of the nuclei. Fig. 2 shows three small foci in a very low power field, such an appearance represents about the maximum amount of erythropoiesis normally seen in full-time infants. There is more active erythropoiesis in the liver of premature infants, the amount roughly corresponding to the degree of immaturity, but there is sometimes no trace of it in those as small as four pounds in weight.

I cannot be more definite about this point as I have not examined a large series of livers of premature infants, such an investigation would give valuable control data. For interest I have included a photomicrograph of a section of liver from a fourteen ounce foetus - Fig. 3. It shows a diffuse infiltration of erythroblastic elements in the sinusoids but these are much less numerous than I expected to find them and than in the worst cases of erythroblastosis - Figs. 4 and 17. I may mention here that the reticulocyte count in this fourteen ounce foetus was twenty-five percent but I was surprised to find that /
Fig. 4. Liver. X 80.
Confluent haemopoietic foci are seen in most areas.

Fig. 5. Liver. X 70.
Normal full-time infant. Three small haemopoietic foci are seen.
that nucleated red cells were few and far between.

The degree of erythroblastosis varies greatly, there may be little more than the maximum normal amount as seen in Fig. 5, or it may be of a massive character as in Fig. 4 which is a section of the liver of a case of icterus gravis which died in the Royal Maternity Hospital two years ago. The erythroblastic elements have a characteristic focal distribution. When the degree of infiltration is considerable there may be a thin diffuse distribution of them as well - Fig. 6. In the most extreme form the erythroblastic elements may be thickly infiltrated throughout most areas of the liver in which case the usual focal appearance is lost - Fig. 4. The cells comprising the foci are situated in the hepatic sinusoids which are distended at the expense of the parenchymal cells in the larger foci.

The erythroblastic foci are composed of erythroblasts at various stages of development and also a small proportion of pro-erythroblasts which have basophilic cytoplasm. The proportion of the different types varies, the pyknotic forms always predominate but in the more severe cases where the process is more active, the more immature cells are numerous. The pro-erythroblasts appear as large undifferentiated /
undifferentiated cells with a pale staining nucleus and a basophilic cytoplasm, their nature may be surmised from their association with the more mature haemoglobin containing erythroblasts. It is possible to distinguish between pro-erythroblasts and myeloblasts chiefly owing to a different disposition of the chromatin network in the two series; considerable cytological experience and technical skill are required for this however. For all practical purposes it is sufficient to rely on the evidence afforded by the more mature cells associated with them. I make no apology for discussing the problem of the undifferentiated cell because it is now recognised that many of the cases in the past, in which these cells were numerous, were diagnosed as leukaemia. In looking through post-mortem records for the last few years I have come across several instances of this error which is due to an unusually large number of these very immature red cells and megaloblasts. The infant whose liver is depicted in Fig. 4, which has already been referred to, was diagnosed histologically as a case of leukaemia; it was a typical case of erythroblastosis of the icterus gravis type. There is no need to describe the features of the various types of erythroblasts as they are so well known, sometimes karyorrhectic forms /
forms are numerous.

There is usually evidence of slight leucopoiesis also, this is more noticeable in the portal tract. The number of eosinophil myelocytes is sometimes definitely increased particularly in the portal tract; after allowance has been made for their conspicuous character I have been struck by this fact.

Slight degenerative changes are often seen in the liver cells, but sometimes there is a considerable degree of fatty degeneration and occasionally small areas of necrosis. The worst changes are seen in hydrops but they may occasionally be quite severe in icterus gravis. Only slight degenerative changes were seen in the six cases of this series. As in my cases, deposits of bile pigment are usually seen in many of the parenchymal and Kupffer cells. Occasionally large globules are seen in the liver cells as though occupying distended bile canaliculi. Bile thrombi sometimes occupy the smallest extra-cellular ducts, but I did not observe this phenomenon. Haemosiderin is usually present in considerable amounts, special staining methods for its demonstration were not carried out in these cases.

An early fine fibrosis was observed by Hawksley and Lightwood (1934) in seven out of nine cases of icterus /
icterus gravis which died after the fifth week of life. It was most conspicuous among the polygonal cells of the atrophic areas and in the neighbourhood of the portal tracts, it was seldom pronounced however.

The Spleen.— The most striking feature is the reduction in size of the Malphigian bodies, which is usually marked, while in some they are quite indistinguishable — Fig. 8. The spleen is diffusely infiltrated with the same erythroblastic and pro-erythroblastic elements as are found in the liver. Sometimes there is a tendency to focal formation but this is never pronounced. The degree of erythroblastosis in the spleen is very difficult to assess owing to the structure of that organ, it usually runs parallel with that seen in the liver but not infrequently it is less active. The same may be said of the leucoblastic elements. Deposits of bilirubin and haemosiderin occur as in the liver.

The Kidney.— In a small percentage of cases erythroblastic foci occur in the kidney, they are said usually to be found near the pelvis or at the cortico-medullary junction. In Case 1, Fig. 12, the few small foci seen were in the latter situation and the cortex.
The Blood and Bone-marrow.— The cytology of the blood has been studied clinically. There are no striking changes in the histology of the bone-marrow as erythropoiesis is always active there in the newborn.

The Brain.— Histological sections of Case 1 with kernicterus have not yet come to hand, while those of Case 3 were not specially stained and showed nothing in particular. The usual appearance is a bile-staining of the glial elements around the ganglion cells of the pigmented nuclei, the nerve cells themselves showing signs of injury; occasionally the cytoplasm of these cells is also stained. In the small areas of softening which are found in the hemispheres lateral to the central ganglia, in the rare diffuse form of bile-staining, fat granules and numerous extra- and intra-cellular pigment granules are seen.
DIAGNOSIS.

Foetal hydrops may be caused by congenital anomalies, tumours and, most important of all, congenital syphilis. Unless there is a family history of syphilis or erythroblastosis foetalis, the diagnosis can usually only be made at autopsy; it can never be made with certainty without such an investigation. In some cases, owing to atypical appearances of the organs, the diagnosis can only be made histologically if maceration has not rendered this impracticable. The type of hydrops without subcutaneous oedema, as found in Case 1, can only be diagnosed at post-mortem examination unless a large oedematous placenta gives a provisional indication. The case just referred to suggests the importance of routine autopsies on still- and dead-births, which might also reveal an occasional example of the anhydric type already referred to.

In early and profound neonatal jaundice, icterus gravis is the likely diagnosis when there is a familial incidence of erythroblastosis of any type; however, as sporadic cases are more frequent the condition must always be borne in mind. In my limited experience icterus gravis is the commonest form /
form of profound neonatal jaundice nowadays, since that arising from umbilical sepsis seldom occurs. The presence of jaundice at birth and of golden vernix caseosa renders the diagnosis of icterus gravis virtually certain, as does the onset of jaundice within the first few hours of life. Its onset between the ages of twelve and thirty-six hours is suggestive of that condition. Examination of the blood clinches the diagnosis in the worst cases, but in others it may not show any gross abnormality although the red count will usually be reduced as in Case 7. The development of a sudden profound anaemia renders the diagnosis certain in the absence of haemorrhage.

The sudden development of a waxy pallor in an infant who has had no jaundice, or only a slight degree of it, can only be anaemia haemolytica; examination will reveal the typical blood picture. Severe nutritional anaemia is very rare so early in life, while it is of gradual onset and hypochromic in type.

The following are the conditions with which icterus gravis may be confused in the order of their importance:

1. Physiological jaundice.
2. Physiological jaundice with haemorrhagic disease of the newborn.
3. Congenital syphilis.
4. /
41.

4. Septicaemia from umbilical sepsis.
5. Congenital obliteration of the bile ducts.
6. Physiological jaundice with intracranial haemorrhage.
7. Physiological jaundice with congenital malformation of the heart.
8. Family acholuric jaundice.

I do not propose to discuss the differential diagnosis of each of these conditions as the means of doing so are known to all interested in infants. The most difficult to differentiate may be congenital syphilis which sometimes mimics all the important clinical features of both hydrops foetalis and icterus gravis: the family history may help but serological tests put the diagnosis beyond doubt, as does demonstration of the treponema pallidum in the event of death. Physiological jaundice complicating congenital malformation of the heart may be troublesome if the abdominal organs are enlarged.

One finds in practice that the condition of congenital obliteration of the bile ducts occupies a much too prominent position in the minds of many people, and is more readily thought of than icterus gravis which is much more frequent. The jaundice in /
in atresia of the bile ducts does not usually appear for several days, progresses more slowly than that of icterus gravis and is accompanied by acholic stools.
PROGNOSIS.

In hydrops foetalis death always occurs in a few minutes or hours if it has not preceded birth.

In icterus gravis, as the name implies, the prognosis is serious but it is far from hopeless. Since the conception of the condition as a blood disease and the advent of transfusions in its treatment, the mortality has been reduced, but not by a great deal. There are no statistics of much value but the mortality is often estimated at about eighty per cent: four of the nine cases in this series recovered. The worst cases of icterus gravis which die within a few days would appear to die of toxaemia or intracranial complications; medullary failure seems to be the cause of death in kernicterus, both of my cases showed marked signs of respiratory failure. Severe jaundice at birth and severe erythroblastaemia are probably of ill omen in most cases as in Case 2. The greatest dangers to life after the first few days are haemorrhage and profound anaemia. Infections are apt to occur, particularly those of a respiratory nature: three of the seven cases of this series which survived had quite severe naso-pharyngitis /
naso-pharyngitis with a purulent nasal discharge. Green stools were a troublesome feature in three instances but were apparently due to indigestion.

**Sequelae.**

The ultimate prognosis in this disease is usually regarded unfavourably, some authorities maintain that active measures to save the lives of these infants is scarcely justified on this account. There has been too little follow-up work of sufficient duration to justify such pessimistic conclusions. As I have not already done so and, in view of their importance, I propose to discuss the sequelae of icterus gravis briefly at this juncture.

**Hepatic Cirrhosis.**—I think it is very doubtful whether the slight hepatic cirrhosis already referred to ever becomes a harmful factor.

**Sub-chronic Haemolytic Anaemia.**—The duration of the haemolytic process in icterus gravis and anaemia haemolytica varies greatly as has already been observed. Parsons, Hawksley and Gittins (1933) showed that those cases in which haemolysis continues for several months develop all the features of what used to be termed Von Jaksch's anaemia. They prefer to call such cases "sub-chronic haemolytic anaemia," which /
which is more descriptive. These authors gave details of the development of the last named condition in a case of erythroblastosis foetalis. Hawksley and Lightwood (1934) described a similar case.

**Nervous Sequelae.** These are the most important sequelae and may result from cerebral haemorrhage or kernicterus. Owing to its much greater frequency the former is probably the more potent cause of these residual effects. Mental defect is the chief symptom, the other principal features are muscular hypotonia and inco-ordination or, sometimes, hypertonia with a picture of spastic diplegia. Chorea-a-thetotic movements are sometimes seen and they tend to be associated with the flaccid inco-ordinate type of case; these symptoms are probably the result of the degenerative changes associated with kernicterus and icterus gravis. Unless these symptoms are present, particularly the striatal symptoms, I do not think one is justified in assuming that nervous manifestations are necessarily of this nature. I think that there is much too great a tendency for those interested in the nervous sequelae of icterus gravis to attribute the symptoms, in too high a proportion of cases, to the effects of kernicterus. In many cases the symptoms do not differ in any way from those resulting from intracranial /
intracranial haemorrhage. At the Clinic for mentally defective children held at the Royal Hospital for Sick Children there are four cases of mental defect, in boys under five years of age, all of whom exhibited severe and prolonged neonatal jaundice. Three of these patients are of the flaccid inco-ordinate type which makes it very difficult for them to learn to walk; two of them who can now walk are very ataxic; one of them displays slight chorea-like movements. The mental defect is not severe in these cases, and their progress leads one to believe that the prognosis regarding this aspect of matter is better than in most other forms of mental defect in children. The course of the mental defect and the nature of the nervous signs, in these three cases, makes it seem very probable that they suffered from the kernicteric type of degenerative change in infancy. It is now thought to be unlikely that such cases have any connection with Wilson's disease. One must not forget that kernicterus is an infrequent complication of icterus gravis and may not always be followed by untoward effects, while intracranial haemorrhage quite often leaves no ill effects whatever. I would prefer to be more optimistic than many about the ultimate prognosis in those cases of icterus gravis which recover /
recover from the acute phase of the illness. However, this belief is not based on reliable data and is, therefore, of little value.

I would expect anaemia haemolytica to have a fairly low mortality. Owing to the lower incidence of haemorrhage in these cases and the probable absence of cerebral degenerative changes, serious sequelae will probably prove to be very infrequent in those which recover.

I am convinced that as a knowledge of this disease spreads and more of the less severe cases of icterus gravis and anaemia haemolytica are recognised, and I am sure that many are not, the prognosis will come to be looked upon with less apprehension.
TREATMENT.

As the aetiology of erythroblastosis is obscure no logical prophylactic measures can be taken.

Blood Transfusion.- My contact with the disease has convinced me that, apart from general nursing measures such as free administration of glucose and saline, the only useful form of treatment is blood transfusion which is a very valuable and often a life-saving measure. The principal indication for transfusion is the development of severe anaemia; a less frequent but equally important indication is the occurrence of severe haemorrhage. There is no reason to believe that the transfused blood has any beneficial effect other than the replacement of haemolysed red cells, thus maintaining adequate oxygenation of the tissues until spontaneous recovery of the anaemia sets in.

I have pointed out elsewhere that frequent estimations of the haemoglobin and reticulocyte levels enables one to follow the activity of the haemolytic and regenerative processes and to feel that one has control of the case. In severe cases this must /
must be done daily owing to the possibility of sudden exacerbations of haemolysis. By taking these precautions there is no urgency for transfusion unless the haemoglobin falls below thirty per cent, but a suitable donor should be prepared to give a transfusion without delay should a severe exacerbation occur. I have mentioned thirty per cent as the haemoglobin level below which transfusion should be performed without delay. I know that many will criticise this figure as being much too low but my experience has shown that at such a level the vitality is usually good, and that rapid spontaneous improvement, as in Cases 8 and 9, is more likely to occur than further deterioration. Diamond, Blackfan and Baty (1932) and Hawksley and Lightwood (1934) and others recommended repeated blood transfusions, as required, to maintain the red count at over four millions. I think such active treatment in the less severely anaemic cases is quite unnecessary, and scarcely justified for such a doubtful advantage. There is always a slight risk attached to blood transfusions, the technique in infants is difficult in inexperienced hands.

The haemoglobin danger level is below twenty per /
per cent, so if it is not allowed to fall much below thirty per cent the safety margin is ample if adequate vigilance is observed. The amount of transfusate usually recommended is 10-15 c.c. per lb. of body weight; I think the former amount is needlessly small and that 15 c.c. per lb. should usually be given.

My observations on the indications for transfusion may sound unduly conservative, but prolonged and careful observation of the last seven cases of this series has crystallised the indications for treatment in my mind. One would rather have had a larger series of cases on which to be so dogmatic but further observation will show whether my conclusions are justified.

The great value of blood transfusion is of comparatively recent recognition. The repeated transfusion method was introduced into this country by Hawksley and Lightwood in 1933, having been advocated in the United States and on the Continent for a few years before that time. Frequent small transfusions in icterus gravis, commenced as soon as possible after birth, have been advocated by various authors; such treatment is not based on any sound principal and it is doubtful whether the cases which recover under it would not have done equally well without.
Multiple Human Blood-serum Injections.- Before the value of transfusion became widely acknowledged injections of whole blood or human blood-serum were reputed to be of value. In Britain little interest was taken in either form of haemotherapy until 1929 when Hampson published an account of the use of human blood-serum by intramuscular injections. In his series of eighteen familial cases of icterus gravis seventeen recovered. He advocated the early commencement of treatment and the injection of 5-15 c.c. of serum on successive days. Hampson believed that some anti-haemolytic agent, which was absent from the infant's blood and present in the adult serum, was responsible for the beneficial effect. He has since modified his views and agrees with the advisability of blood transfusion when the condition is seen after the first few days of life. Darrow (1938), whose views on aetiology will be discussed later, attributes the apparently beneficial effect to a desensitisation mechanism.

Liver Therapy.- The high reticulocyte counts usually found contra-indicate liver therapy, even where the reticulocyte count is relatively low there is no evidence to show that the specific anti-
anti-anaemic factor is deficient. Short trials of liver therapy were given by those in charge of four of the seven cases which recovered but it did not appear to affect the course of the disease, as a study of the charts of these four cases and the other three of the series will show.

Iron Therapy.- This is quite illogical in the early stages of the disease but it may sometimes be of value towards the end of the illness, after the age of about three months, in helping to restore the haemoglobin to the normal level. It did not seem to be indicated in any of the cases of this series, although some of them had courses of iron without any apparent effect.

Apart from the occurrence of gross nutritional anaemia in the mother or prematurity of the infant, iron therapy is seldom indicated for several months after birth. The ample store of iron normally present in the liver of full-time infants at birth may be lacking in the foregoing circumstances, while physiological haemolysis following birth leads to an augmentation of the store derived from the mother in the latter weeks of pregnancy. In this disease the massive haemolysis leads to the deposition of additional /
additional large amounts of haemosiderin, waiting to be called up as soon as blood formation outpaces haemolysis. Apart from these facts a study of the colour index, which greatly exceeds unity for several weeks until recovery is well advanced, shows that the low haemoglobin level is dependent on the low erythrocyte count. Even when spontaneous recovery is complete the colour index is at the normal level for the age so far as I have observed. Case 11 which did not receive any treatment, that in the first two weeks being of no value, had the following blood counts at five months of age:- R.B.C. 5,540,000, Hb. 98%, C.I. .88.

Oxygen Administration.- The use of oxygen is advocated by some who believe in the injurious effect of anoxaemia on the liver. Darrow believes that the chief beneficial effect of blood transfusion is to improve the oxygenation of the hepatic tissue. Various workers claim to have demonstrated the value of oxygen and repeated transfusions in relieving the anoxaemia associated with hepatic disease. I think that further evidence is required before the beneficial effect of oxygen or transfusion on the liver can be acknowledged in this disease.

Intercurrent Infection.- /
AETIOLOGY.

There have been many theories on the causation of icterus gravis as is usually the case in obscure diseases. An excellent review of the literature on the aetiology of icterus gravis has recently been written by Darrow (1938); she has herself brought forward a new and intriguing hypothesis which I will discuss at some length later.

I propose to refer briefly to the various theories regarding the causation of this disease and will divide them into two main groups:

Theories not connected with the blood.

Theories connected with the blood.

I may repeat here that since the work of Buchan and Comrie in 1909 attention has been focussed more and more on the fundamental importance of the blood in the condition, and for the last twenty years has been chiefly concerned with it. I will merely mention the less important and out-of-date theories, it can be assumed that they are easily exposed as untenable. I will say a little about those which have attracted the most attention.

Theories not connected with the blood:

Toxaemia of pregnancy. - Toxaemia cannot be demonstrated in the great majority of mothers.

Nutritional /
Nutritional disturbances in the mother.

Disease in the mother.- Syphilis was often thought to be a factor before the demonstration of the causal organism of that disease.

Intensification of Physiological Jaundice.-

Blocking of the bile ducts or canaliculi with inspissated bile.

Food allergy.- Cases have been described in which there was an idiosyncrasy to the mother's milk.

Septicaemia.- In former days septicaemia of umbilical origin was common and it is not surprising that cases of icterus gravis were connected with it.

Endogenous intoxication from the bowel.

Hepatic dysfunction.- Hepatic dysfunction has been regarded by I.A. Abt and others as of fundamental importance, their view being that the toxic products and acidosis arising therefrom cause anoxaemia and compensatory erythrobastosis. A number of observers have related the degenerative changes in the brain sometimes found in icterus gravis, to the toxic action of products of hepatic injury. Ligation of the common bile duct in dogs and rats has been followed by the necrosis of cerebral tissue, particularly in the striate body and the brain stem nuclei. Darrow believes that a pathological insufficiency exists in the /
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the liver in icterus gravis, even though histological evidence of injury may often be absent, and I think that this is probably the cause of the cerebral degeneration as mentioned above. Darrow does not believe, however, that the primary cause of the disturbance lies in the liver but agrees that the erythroblastosis may be secondary to it.

Theories connected with the blood:-

A primary constitutional anlage defect of the Haemopoietic System.- This was a conception advanced by Gierke and supported by Clifford and Hertig and others. However, when recovery occurs there is no evidence of such a defect.

A Metabolic disturbance of the Haemopoietic System.- This was postulated by Diamond, Blackfan and Baty and is widely supported in the United States.

"Embryonal Haematopoietic Persistence".- This was regarded as the error by A.F. Abt but his argument is not convincing.

Deficiency of an Anti-haemolytic factor.- This was postulated by Hampson and has been referred to under treatment.

Erythronoclastic Anaemia of toxic origin.- This is the theory of Parsons, Hawksley and Gittins and is the most popular in this country. The term indicates /
indicates that not only the circulating blood but also the other haemopoietic elements are adversely affected. No suggestions as to the nature of the injurious toxins are made. The erythroblastosis is regarded as a compensatory effect.

Passive immunisation and passive sensitisation of the Infant to its own Erythrocytes.—This is the recent theory of Darrow which I propose to discuss at some length. As the hypothesis of hepatic dysfunction does not explain cases of anaemia haemolytica in which the liver appears to be healthy, Darrow endeavoured to formulate an hypothesis which might explain all forms of erythroblastosis foetalis. She elaborated her argument as follows:—The mother is the one constant factor when the disease appears in a series of off-spring and seems to be the primary source of the noxious influence. In anaemia haemolytica there is no apparent intoxication, only severe anaemia, and, therefore, destruction of erythrocytes is the essential pathological change. She argues that haemolysis through some form of immune reaction seems the only possible mechanism which she explains as follows. The mother is actively immunised against foetal haemoglobin which, as shown by Trought, has a different composition from that of adult haemoglobin and is, therefore,
a foreign protein and an adequate antigen. The foetal erythrocytes gain access to the mother's circulation as a result of a placental accident. Antibodies to these pass to the child per the placenta ante-natally and the colostrum and milk post-natally. A delayed onset of the condition, as in Case 12, is attributed to the time taken for the antibodies to become concentrated enough to produce a marked effect. The passive immunity to foetal haemoglobin established in the child, which is responsible for the haemolysis, is relatively short lived. This would account for the rapid spontaneous improvement which occurs after a varying interval in those who recover. Any subsequent children would be similarly affected by the active immunity in the mother and the passive immunity in themselves, while children born before the immunising of the mother would be entirely unaffected. Anderson experimentally produced such a process in guinea-pigs and four successive litters were affected. This hypothesis adequately explains the familial incidence and the tendency of the first-born to escape, while those born after an affected case are usually affected also.

So far the action on the blood only has been considered and Darrow believes that the closely related /
related mechanism of anaphylaxis, due to passive sensitisation, could explain the disturbances in icterus gravis and hydrops foetalis. In anaphylaxis liver damage occurs and is often severe, and this as already explained might lead to extra-medullary blood formation. Other effects of anaphylaxis are increased capillary permeability, the effects of vagal stimulation, gastro-enteral disturbances, respiratory distress and other nervous symptoms. Darrow thinks that the apparent success of multiple injections of mothers serum, as described by Hampson, might thus be explained on a desensitising basis; also that this conception would appear to give the advice of Rolleston and others, to withhold mothers milk, a new importance.

Conclusion.

It must be acknowledged that the aetiology of erythroblastosis foetalis is unknown. Of the numerous hypotheses which have been offered to account for the condition I find that those of Darrow and Parsons, Hawksley and Gittins are the most satisfying. The latter authors have fallen back on a hypothetical toxin to explain the erythronoclastic process which, in turn, accounts for the other disturbances encountered. One feels that these authors have not taken /
taken sufficient cognisance of the fact that, occasionally, in *Hydrops foetalis* and *icterus gravis* the anaemia has not become severe at a time when the other symptoms are profound and early death has occurred. This suggests that the noxious influence exerts a more widespread effect, injuring the liver, capillary endothelium and other tissues.

Darrow is the first to offer a possible scientific explanation of all the phenomena encountered in *erythroblastosis foetalis*. One cannot altogether disregard the fact that it explains the peculiar type of familial incidence; while the experimental work of Anderson on guinea-pigs, already mentioned, would seem to indicate the possibility of a similar process occurring in man. It should not be impossible to confirm or disprove the occurrence of such an antigen-antibody reaction in the disease under consideration.
A report is given on thirteen cases of erythroblastosis foetalis personally collected in the last sixteen months. It has been elaborated by a study of the condition.

The clinical syndromes of hydrops foetalis, icterus gravis and anaemia haemolytica neonatorum are now acknowledged to be different manifestations of erythroblastosis foetalis. The most convincing evidence is the not infrequent association of these different syndromes in the same family; the pathology is essentially the same in them all.

The thirteen cases of this series belong to the following clinical types:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Count</th>
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<tbody>
<tr>
<td>Hydrops foetalis</td>
<td>1</td>
</tr>
<tr>
<td>Icterus gravis</td>
<td>9</td>
</tr>
<tr>
<td>Anaemia Haemolytica</td>
<td>3</td>
</tr>
</tbody>
</table>

In four instances other infants born in the family had exhibited erythroblastosis in some form, in two of them it was of a different type.

Apart from the striking symptom which gives to each type its name the principal clinical features common to all are splenomegaly, hepatomegaly and erythroblastaemia /
erythroblastaemia with a macrocytic anaemia which is usually severe.

The principal complications are haemorrhage, usually intracranial or umbilical, and focal degeneration in the brain. The common type of cerebral degeneration is known as kernicterus owing to its location and the concomitant bile-staining.

Active extra-medullary erythropoiesis is the essential pathological feature. It is usually confined to the liver and spleen but is occasionally seen in the kidneys and other tissues.

The differential diagnosis has been discussed. Icterus gravis is the most difficult of the three clinical types to separate from the other causes of neonatal jaundice; but severe jaundice, particularly if of early onset, is usually of this type. Congenital syphilis may mimic hydrops foetalis and icterus gravis very closely and should always be excluded by serological tests.

The prognosis is hopeless in hydrops foetalis. It is unusual for live-birth to occur but when it does death follows almost immediately. The mortality /
mortality in icterus gravis is reputed to be about eighty per cent but I believe that more general recognition of the milder cases will reduce the figure considerably. The outlook in anaemia haemolytica is good if it is treated adequately in the worst cases. The mortality in the cases of this series was as follows:-

<table>
<thead>
<tr>
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The principal sequelae in those which recover from the acute phase of the illness are those resulting from the intracranial complications. It is often difficult to be sure whether they are due to haemorrhage or kernicterus, but hypotonia, ataxia and chorea-athetosis suggest the nuclear type of involvement. Mental defect usually accompanies other nervous sequelae but may occur independently.

The only valuable form of treatment is blood transfusion which is often a life-saving measure and may have to be repeated several times. The principal indications are severe anaemia - below thirty /
thirty per cent - and severe haemorrhage.

Spontaneous recovery of the anaemia will occur in a majority of those cases which survive the first week of life. The rapid improvement, in the absence of treatment, in some of the cases of this series was particularly striking.

A good grasp of the progress of these cases is best achieved by means of frequent blood examinations. The reticulocytes and haemoglobin afford the most helpful information.

The aetiology of erythroblastosis foetalis is unknown. The numerous theories brought forward have been mentioned and the more important of them discussed. Of latter years the fundamental importance of the blood in all manifestations of the disease has been increasingly realised. The most attractive theories are those of Darrow and Parsons et. al. The latter postulate an erythronoclastic anaemia of toxic origin and believe that the erythroblastosis and other changes are secondary phenomena. Darrow believes that the cause of the disease is an antigen-antibody reaction which leads to immunological and anaphylactic disturbances.
REFERENCES


- "The Diseases and Deformities of the Foetus." Oliver & Boyd, Edin.


CASE RECORDS.
CASE No. 1.

Professor Johnstone. Private Case.

Hydrops Foetalis.

Baby X. Female. Born 12.5.38.
DIED, aged 15 minutes.

Clinical Notes.- Fourth child.

Family History.- First child born alive and well and now quite healthy. Second child died, aged two days, of icterus gravis. Third child born dead and slightly macerated, it exhibited signs of universal oedema of moderate degree. No history of miscarriages.

Birth.- Spontaneous delivery following a normal pregnancy. Birth weight 6 lbs. 6 ozs. The infant never breathed with any regularity and died in 15 minutes. "The breathing was peculiar in that inspiration appeared unembarrassed but there appeared to be an obstruction to expiration."

Pathological Notes.-

Autopsy.- The abdomen was slightly distended and tense. There was very slight oedema of the limbs, especially of the legs. No icterus was perceptible.

Head.- /
Head.— There was no evidence of disease or injury within the skull.

Thorax.— Both pleural sacs contained a small quantity of clear fluid and the pericardial sac contained a considerable excess of similar fluid. Heart was distinctly above the average size in proportion to that of the body. This was the result of hypertrophy as the chambers were not dilated. There was no developmental abnormality of the valves, septa or vessels. Lungs were well expanded but very oedematous. No pneumonia was present and there was no haemorrhage except a few subserous petechiae. The mediastinal tissues were extremely oedematous and the areolar tissue of the neck shared in this. There was quite severe oedema of the larynx, especially of the epiglottis and ary-epiglottic folds, which had produced a definite narrowing of the aperture; this condition was indeed more pronounced than is often seen post-mortem. Thymus gland was rather small.

Abdomen.— Peritoneal sac contained a fairly large amount of clear, bright yellow fluid. The abdominal distension was mostly due to this. Liver was distinctly enlarged, its lower border being well /
Fig. 6. Liver. X 80.
Haemopoietic foci are very numerous.

Fig. 7. Liver. X 70.
Three small haemopoietic foci are seen.
well below the iliac crest on the right side. It was bright brown, not obviously bile stained, fairly firm but not tough. It showed no visible fibrosis or infiltrations.

Spleen was much enlarged measuring about 3" in length and being proportionately increased in its other dimensions. It was moderately firm, uniformly dull red with no visible lymphoid elements, not tough to cut.

None of the other viscera showed anything of interest. All the areolar tissues of the abdomen were extremely oedematous.

Blood. - The blood was watery and poorly coloured and the muscles were pale, suggesting the presence of anaemia of some severity.

Histology. -

Liver. - Shows haemopoietic activity in excess of the normal. Erythroblastic activity is particularly prominent; many of the cellular foci are composed almost entirely of nucleated red cells, while there are a few in which large palely staining and undifferentiated cells predominate. The epithelial liver cells contain a considerable quantity of bile pigment. There is no fibrosis.

Spleen. - Also shows excessive haemopoietic activity, /
Fig. 13. Blood. X. 550. Post-mortem film. Many nucleated red cells are seen.
Fig. 10. Spleen. X 250.
Note the homogeneous structure and increased cellularity.

Fig. 11. Spleen. X 250.
Normal appearance. Note the Malpighian body and smaller number of large cells.
Fig. 8. Spleen. X 45.
Note the absence of Malpighian bodies.

Fig. 9. Spleen. X 45.
Normal appearance. The Malpighian bodies are conspicuous.
activity, particularly as regards erythroblastic elements. There is no fibrosis.

Kidney.- Contains a few foci of haemopoietic cells in the cortex and at the cortico-medullary junction. Otherwise it shows nothing of interest.

Other organs examined showed nothing of special interest. In all sections the blood in the vessels contains remarkably large numbers of nucleated red corpuscles.

Blood film— The striking feature is the very large number of nucleated red blood corpuscles. About two-thirds of all nucleated cells are erythroblasts. They show great variation in size, many being over-sized. Many show polychromatic staining. Some primitive forms of white cells are present also, but are not particularly remarkable.
CASE No. 2.

Simpson Maternity Hospital.

Severe Jaundice: Haemolytic Anaemia.

Baby S. Female. Born 10.5.38.
DIED, aged 1½ days.

Clinical Notes.-- Second child.

Family History.-- First child apparently normal in infancy. No miscarriages.

Birth.-- Spontaneous delivery following a normal pregnancy. Birth weight - 8 lbs. The placenta was not unduly large, weighing 1 lb. 10 ozs. Large quantities of meconium were passed with the liquor amnii, so it was not noticed whether it was very bile stained. The vernix caseosa was "mustard coloured".

Jaundice.-- Fairly deeply jaundiced at birth, a few hours later it was seen to be deep, particularly on the face: the conjunctiva, tongue and buccal mucosa were all yellow. Van den Bergh reaction -

Anaemia.-- At 10 hours old the lips were slightly paler than normal. A blood examination at that time revealed a marked anaemia, the red cells numbering barely half the normal for the first day of life: the /
Fig. 16. Blood. X. 750.
Vital staining.
Many nucleated red cells and reticulocytes are seen.
Fig. 14. Blood. X. 450.
Many nucleated erythrocytes are seen. Karyorrhexis is a prominent feature.

Fig. 16. Blood. X. 1100.
Several nucleated erythrocytes are seen. The larger ones with a reticulated nucleus are megaloblasts while those with pyknotic nuclei are normoblasts.
proportion of nucleated red cells, the figure having risen to 7% and the nucleated cell count to 240,000.

The results of the blood examination are recorded in the table. Photographs of blood films illustrate some of the points I have mentioned.

Spleen.- Enlarged, extending one finger breadth below the cortical margin.

Liver.- Not enlarged.

Nervous Symptoms.- At 29 hours old occasional generalised jerking movements, like a shiver, were seen; also a sighing type of respiration at times, and murmuring muttering noises "like someone trying to speak." Three hours later became collapsed and had twitchings of the facial muscles and a temperature of 103°F. For the last six hours, at least, the child was in coma with an apnoeic sighing type of respiration.

Haemorrhage.- Slight epistaxis, apparently of pulmonary origin, occurred five hours before death.

Progress.- Partly described already. The general condition was quite good for the first 24 hours, the child appearing comfortable and taking the bottle well, he then began to seem uncomfortable, making muttering noises and writhing movements occasionally, as if uncomfortable. For the last six /
Fig. 19. Liver. X. 450.
Note cells constituting the haemopoietic foci, most of them are normoblasts, a few are more immature and palely stained.
Fig. 17. Liver. X. 70.
Many haemopoietic foci are seen.

Fig. 18. Liver. X. 70.
Normal full-time appearance.
Note three small haemopoietic foci.
the pons and midbrain, and the dentate nuclei of the cerebellum were stained a fairly bright yellow with bile pigment; also the hippocampal cortex, the corpora Luysii and corpus striatum were stained a paler yellow.

Lungs.- Extremely oedematous and contained small patches of haemorrhage.

Histology.-

Liver.- Shows very excessive haemopoiesis and is crowded with blood-forming cells. Many are of primitive type. Erythroblastic activity is prominent; there are little nests of nucleated red cells, conspicuous among the general cellularity. There is probably leucoblastic activity also to some extent, though many of the unpigmented cells may be primitive erythroblasts. The epithelial cells do not contain much bile pigment. There is no fibrosis.

Spleen.- Haemopoiesis is present but not comparable to that in the liver. There are areas of haemorrhage and much of the tissue has undergone autolytic softening. The conspicuous feature is infiltration by polymorph leucocytes, many of which are pyknotic. This occurs under the capsule and throughout the substance in areas resembling the Malpighian bodies but larger and more diffuse. This suggests an infective element, but there is no other evidence /
CASE No. 3.

Simpson Maternity Hospital District.

Severe Jaundice: Haemolytic Anaemia.

Baby McC. Female. Born 4.2.38.

DIED, aged 2½ days.

Clinical Notes.- Seventh child.

Family history.- None of the other six children apparently had severe neonatal jaundice. One miscarriage between the fifth and sixth children. The second child died aged two hours and the third aged 4½ months.

Birth.- Spontaneous delivery following "one of the worst pregnancies." A full time infant of average weight.

Jaundice.- Present at birth, rapidly became intense and baby died at home aged 2½ days.

Pathological Notes.-

Autopsy.- Intense jaundice with staining of most of the tissues.

Brain.- No visible kernicterus.

Liver.- A little enlarged, bile stained.

Spleen.- Enlarged to about twice the normal size.

It was deep red and very soft - the pulp was diffuent /
diffluent, the Malpighian bodies were invisible.

Blood.— Rather thin.

Histology.—

Liver.— Showed very much more active haemopoiesis than is usual in full time babies. The haemopoietic cells were found not only in foci in the sinuses, but also in the portal tract, where eosinophil myelocytes were conspicuous. Most of the cells in the foci were normoblasts and erythroblasts, but there were a few larger lightly stained more primitive undifferentiated cells.

Spleen.— Also contained many haemopoietic cells.

Blood.— A few nucleated red cells, about 2%. Polychromasia marked and an abnormal degree of anisocytosis especially macrocytosis.
1.

CASE No. 4.

Simpson Maternity Hospital.

Severe Jaundice: Haemolytic Anaemia.

Baby M. Male. Born 15.4.37.

DIED, aged 2½ days.

Clinical Notes.- Third child.

Family history.- The other two children were not jaundiced in infancy. No miscarriages.

Birth.- Spontaneous delivery following a normal pregnancy. Full time, weight 6½ lbs.

Jaundice.- Deep jaundice was noticed on the second day of life; it rapidly became intense.

Blood.- Not examined during life.

Spleen.- Impalpable.

Liver.- Not enlarged.

Progress.- On the third day when seen about six hours before death the baby was very drowsy, the respirations were of a slow sighing character but no twitching or convulsions were seen; there was also bradycardia.

Treatment.- Maternal blood, 14 c.c., was given intramuscularly six hours before death.

Pathological /
Pathological Notes.-

Autopsy. - Deep jaundice with staining of most of the tissues which, however, were not blanched.

Brain. - Severe kernicterus; the corpus striatum and the nuclei of the brain stem were deeply bile stained; the latter particularly being a bright yellow colour - the olivary nuclei were notably conspicuous. Unfortunately a more careful examination of the brain for signs of pigmentation was not made. It is a pity that no coloured photographs of this beautiful specimen were not taken and also more care with its preservation.

Liver. - Not appreciably enlarged.

Spleen. - Enlarged, about twice the normal size. Normal consistence. The Malpighian bodies were indistinguishable.

Stomach. - Multiple pin-head ulcerations of the mucosa with vivid yellow borders, fewer in the pyloric antrum.

Histology.-

Liver. - Haemopoietic activity definitely above the normal though not very active. Smallish erythropoietic foci numerous, with a slight diffuse infiltration of small numbers of immature red cells elsewhere in the sinuses. Most /
Most of these cells contained haemoglobin and had darkly staining nuclei. Both the hepatic and the Kupffer cells contained bile pigment; in some of the former the deposits were large as though lying in distended bile canaliculi. Eosinophils were fairly numerous.

Spleen. - Extremely congested. Haemopoietic activity considerably increased, there being a diffuse infiltration with nucleated red blood cells, the normoblasts being the most conspicuous. Bile pigment conspicuous in the reticulo-endothelial cells.

Blood. - An increased number of nucleated red cells forming 2%. Polychromasia increased, otherwise not abnormal.

Remarks. -

The histological findings indicate that a clinical examination of the blood would probably have shown a moderate degree of haemolytic anaemia.
1.

CASE No. 5.

Simpson Maternity Hospital.

Severe Jaundice: Acute Haemolytic Anaemia.

DIED, aged 8 days.

Clinical Notes. - Fifth child.

Family History. - None of the other four children had severe neonatal jaundice. No miscarriages.

Birth. - Spontaneous delivery following a normal pregnancy. Birth weight 9 lbs.

Jaundice. - None noticed at birth, unusually deep jaundice attracted attention on the third day, it became deeper and was very intense at a week old. Urine was bile stained on the last two days of life and the stools were a little pale. On the day of death the icteric index was 40 and the Van den Bergh reaction gave a direct biphasic response.

Anaemia. - On the eighth day extreme pallor, particularly noticeable in the lips, was observed; it seemed to have developed very suddenly. The haemoglobin estimated just before death was about 15%. A film showed the presence of a few nucleated red cells,
cells, with polychromasia marked, and anisocytosis - there being many very large macrocytes.

Spleen.- Impalpable.
Liver.- Not enlarged.

Feeding.- Breast. Fed well until day of death, a test feed the previous day showed a gain of 2½ ozs.

Progress.- The baby's general condition seemed quite good until the day of death when she suddenly seemed very ill. She did not lose an excessive amount of weight but failed to gain.

Pathological Notes.-

Autopsy.- There was severe jaundice and most of the tissues were bile stained and very blanched.

Intracranial haemorrhage.- Small tears on both sides of the tentorium cerebelli involving only the upper layer, a little haemorrhage therefrom on both sides.

Brain.- No kernicterus was observed.
Liver.- Slightly enlarged and deeply bile stained.

Spleen.- Greatly enlarged, it was fully 3" long. Very soft. The Malpighian bodies were not visible.

Kidneys.- A few small haemorrhages in some of the pyramids.

Blood /
Blood.—Thin and watery, the plasma was bright yellow.

**Histology.**—

Liver.—Showed abnormally active haemopoiesis. There were frequent foci in the sinuses, many of them small, these consisted of nucleated red cells and an unusually high proportion of larger pale staining undifferentiated cells with large round vesicular nuclei. These cells preponderated in the larger foci, they were probably very primitive red cells. The portal tract was infiltrated with similar cells and also contained many eosinophil myelocytes. Many liver cells contained bile pigment.

Spleen.—Showed similar but more striking haemopoietic activity, the sinuses were crowded with large primitive haemoblastic cells. Eosinophil myelocytes were also numerous. Many of the reticuloendothelial cells contained bile pigment.
Severe Jaundice: Acute Haemolytic Anaemia.

DIED, aged 10 days.

Clinical Notes.- Second child.

Family history.- First child apparently a healthy infant. Matter of miscarriages uncertain.

Birth.- Spontaneous delivery following a normal pregnancy. A full time infant of average weight.

Jaundice.- First noticed on second day of life, it soon became deep but after the third day was thought to become less intense. When admitted aged ten days in a moribund state there was still a deep icterus.

Anaemia.- The lips were very pale. Owing to the infant's state a blood count was not done but the blood was seen to be "very watery", the haemoglobin was about 18% and there were many nucleated red cells.

Haemorrhage.- Umbilical bleeding occurred on the ninth day but had ceased before admission.

Spleen.- "Easily felt".
Liver.- Not enlarged.
Feeding /
Feeding.- Breast.

Progress.- The infant died four hours after admission.

Pathological Notes.-

Autopsy.- There was a small red umbilical polyp which had been the source of the haemorrhage, there was no evidence of infection. There was deep jaundice with widespread bile staining of the tissues.

Brain.- No kernicterus was seen.

Liver.- Slightly enlarged and deeply bile stained.

Spleen.- Greatly enlarged; it was 4" long, dark red, softish and the lymphoid follicles were indistinguishable.

Blood.- Very thin.

Histology.-

Liver.- Evidence of brisk haemopoiesis, many fairly large foci of erythroblastic cells. The liver cells contained bile pigment and showed fatty changes. The reticulo-endothelial cells also contained bile pigment.

Spleen.- Also showed evidence of brisk haemopoiesis and deposits of bile pigment in the reticulo-endothelial cells.

Blood /
Blood. - Very numerous nucleated red cells, mostly normoblasts; many polychromatic erythrocytes and slight anisocytosis. White cells showed no abnormality.
CASE No. 7.

Dr. McNair Murray, R.H.S.C.

Severe Jaundice: Acute Haemolytic Anaemia.

Baby J. Male. Born 11.2.38. RECOVERED.

Clinical Notes. - Fourth child.

Family History. - First child apparently a healthy infant. Second child very jaundiced at birth, and died with icterus gravis aged four days. Third child had "recurrent attacks of mild jaundice through infancy". Incidence of miscarriages not determined. The mother had "jaundice from the sixth month onwards" with the third pregnancy and "again with this latest one;" it never prevented her from attending to her household duties.

Birth. - Spontaneous delivery. A large 9 lb. baby. Nothing abnormal was noticed about the infant or the placenta.

Jaundice. - None seen at birth, but was marked the next day. In view of the family history the doctor sent him into hospital on the third day. On admission he was deeply jaundiced, the conjunctiva and buccal mucosa also. On the fifth day of life the /
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<th>Age in Days</th>
<th>R.B.C. Millions per Cu: Mm.</th>
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--- = Transfusion.
the van den Bergh reaction gave a direct biphasic response and the icteric index was 153. The jaundice remained intense for a few days but when ten days old it showed considerable improvement: on the ninth day the icteric index had fallen to 40 and the van den Bergh was the same as before. There was a marked but transient exacerbation of the jaundice at two weeks old, the day following the first transfusion: fading then proceeded but there was another slight exacerbation ten days later, it finally cleared at six weeks old. The fragility of the red blood cells was within normal limits.

Anaemia.— The infant did not look at all anaemic on admission, but the red count was considerably below the normal high level for the first few days of life and was, therefore, considered abnormal. There was a puzzling rise in the red count towards the end of the first week, but that done on the seventh day would appear to have been faulty. This improvement shook my belief in the likelihood of a severe anaemia developing in this case, and I did not see the child until three days later when there were signs of slight but definite anaemia—particularly in the lips. He looked worse the next day and a blood examination demonstrated /
demonstrated a fairly severe macrocytic anaemia; the erythrocytes had fallen to considerably less than half and the haemoglobin approached half in the short space of four days. The steep fall continued and the first transfusion given on the thirteenth day only caused a slight temporary improvement of the red cell count, however, it was immediately followed by a marked reticulocytosis and in a few days by a considerable rise of erythrocytes. This was short lived and at 2½ weeks the erythrocytes fell steeply to just over one million, the count being almost halved in two days: this accompanied a sudden increase in pallor which was now severe. The anaemia was worse next day and another transfusion was given; this and a third transfusion, given two days later, coincided with a sudden turn of the tide for there was a great improvement in the blood picture during the next week as a glance at the chart will show. This was followed by two slight relapses in the fifth and seventh weeks respectively, after which the improvement of the anaemia was steady and unusually rapid for the later stages of recovery. The blood picture had returned to normal at the age of three months, an unusual attainment in this condition.
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CASE No. 8.

Professor McNeil. Private Case.

Severe Jaundice: Acute Haemolytic Anaemia.

Baby P. Female. Born 16.1.38. RECOVERED.

Clinical Notes.— Third child.

Family History.— First child apparently a normal infant. Second child died with icterus gravis aged three days. I do not know about miscarriages.

Birth.— Spontaneous delivery following a normal pregnancy. Full time and average weight.

Jaundice.— Noticed half an hour after birth, it rapidly deepened and reached its maximum intensity at about three days old; it then faded gradually and had almost vanished when I first saw the child aged two weeks.

Anaemia.— A severe degree of anaemia became apparent in the second week as the jaundice faded. When I first saw the child it was very blanched, the pallor of the lips being particularly striking; an examination of the blood demonstrated a severe macrocytic anaemia. The subsequent blood findings are recorded in the accompanying table and chart. The doubling of the haemoglobin percentage and an almost /
almost corresponding rise of the red cell count in the course of six days was truly astounding, almost equally so was the dramatic improvement in the child's colour. This was followed by a slight check but no true relapse, and the steep upward rise was soon resumed. The fifth haemoglobin reading was probably erroneous. The erythrocyte count rose from 1,190,000 to 3,630,000 in 3 1/2 weeks. Thereafter the rise was gradual and when last seen at 13 weeks old the count was just under four millions. The very high reticulocyte count, which was maintained for several days, in the early days of recovery preceded the rapid red cell rise.

Spleen.- Never palpably enlarged.

Liver.- Never enlarged.

Feeding.- Breast feeding with complimentary feeds, then weaned at two weeks owing to inadequate lactation. The baby fed slowly for several weeks and had his feeds changed, but one felt that a rather unpractical mother had a good deal to do with this.

Weight and General Progress.- Probably owing to the above facts the child was rather thin and a little under weight when last seen. The vitality was good throughout even when profoundly anaemic.

Treatment.- None. Spontaneous recovery.
No further emphasis need be laid on this child's dramatic improvement, the inferences to be drawn from the fact that it was spontaneous are obvious. I would like to mention, however, that I consider the evidence presented by this case gives very definite therapeutic indications to be followed in similar cases.
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CASE No. 92.

Professor McNeil, R.H.S.C.

Severe Jaundice: Acute Haemolytic Anaemia.

Baby S. Female. Born 18.2.38. RECOVERED.

Clinical Notes.- Third child.

Family History.- First child apparently a normal infant. A miscarriage occurred between the two first babies. The second baby was dead-born and hydropic.

Birth.- Spontaneous delivery following a normal pregnancy. Weight 7 lb.s

Jaundice.- Severely jaundiced in first week, time of onset not determined. It finally disappeared at about one month old.

Anaemia.- First noticed at two weeks as the jaundice faded; "first the nails and hands, and then the lips, gums and ears." Very pale on admission aged 24 days with a tinge of jaundice still present. Investigation of the blood showed a severe macrocytic anaemia with a very high reticulocytosis. The course of the blood condition is recorded in the accompanying table and chart. The anaemia got slightly worse for a week at the end of which time the infant looked a little paler and not so well. This was probably a /
Fig. 20. Blood. X. 1000. Vital staining. Reticulocytes 45%.
2.

a relapse as there were signs of improvement the day after admission. After a week in hospital there was a fairly rapid sustained improvement. When last seen at three months the red count was almost four millions. The high reticulocytosis was unusually prolonged in this case as a glance at the chart will show: during the first three weeks of observation reticulocytes the\text{\textemdash}always numbered more than one third of the total red count, and they exceeded 50\% on two occasions.

Spleen.- Greatly enlarged. When first seen at 24 days it was just palpable, extending barely one finger breadth below the costal margin. During the next three days it became much larger, extending down two finger breadths. Three weeks later it had receded considerably and when next seen after a further five weeks it was impalpable.

Liver.- Slight enlargement coincided with the maximal splenic enlargement.

Feeding.- Breast fed throughout.

Weight and General Progress.- During the fortnight's stay in hospital the weight remained stationary but when last seen at three months the baby was quite plump and looking very well.

Treatment.- None. Spontaneous recovery.
<table>
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<th>Age in Days</th>
<th>R.E.C. Millions per Cu: Mm.</th>
<th>H.B. % (Sahli)</th>
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Severe Jaundice: Haemolytic Anaemia.

RECOVERED.

Clinical Notes.- Second child.

Family History.- First child apparently normal in infancy. No miscarriages.

Birth.- Spontaneous delivery following a normal pregnancy. A full time infant of average weight.

Jaundice.- This was first noticed the day after birth and rapidly deepened during the next three days. The child was drowsy and the urine a dark brown colour. On admission at two weeks old the baby was still deeply jaundiced, the conjunctivae and the tongue and buccal mucosa showed considerable icterus also. The urine contained a little bile and the van den Bergh reaction was "direct, strong biphasic". At the age of one month the jaundice had faded to a lemon yellow tint and the conjunctivae was still quite yellow. At six weeks old, the time of writing, there is only a faint tinge remaining.

Anaemia.- No pronounced anaemia was noticed on admission but the lips showed a definite though not severe /
severe degree of pallor. An examination of the blood demonstrated a macrocytic anaemia of moderate degree. The course of the anaemia is indicated in the accompanying table and chart. During the first few days there was a considerable improvement of the blood condition, but during the next ten days there was a slow deterioration. This was followed by a sharp temporary improvement, after a slight check which lasted a few days there was a marked and steady improvement. After being in progress for a week this improvement was still continuing at the time of writing when the colour index had just fallen below unity. The child was then six weeks old.

Spleen.— Never palpably enlarged.

Liver.— Never demonstrably enlarged.

Feeding.— Artificial.

Weight and General Progress.— At the age of one month the infant developed an upper respiratory infection which was accompanied by a profuse nasal discharge. At the time of writing two weeks after its onset this respiratory complication has almost cleared up. This infection may have contributed to the prolonged pause in the improvement of the blood. There was only half a pound gain in weight during the /
the first three weeks in hospital but during the last week the infant has gained one pound. During the fifth week the stools were loose and green for a few days apparently owing to indigestion.

Treatment.— Ferri et. ammon. cit. gr. 6 daily for the first sixteen days. A steam tent and other measures for the respiratory infection.
<table>
<thead>
<tr>
<th>Age in Days</th>
<th>R.B.C. Millions per Cu. Mm.</th>
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CASE No. 11.

Elsie Inglis Maternity Hospital.

Slight Jaundice: Haemolytic Anaemia.

Baby D. Male. Born 9.11.37. RECOVERED.

Clinical Notes.— Second child.

Family History.— First child apparently normal in infancy. No miscarriages.

Birth.— Spontaneous delivery following a normal pregnancy. Full time and average weight.

Jaundice.— Said in hospital to have been slightly jaundiced at birth which faded in a day or two.

Anaemia.— Pallor was noticed when the jaundice faded. Such a severe degree of anaemia at birth is unusual, the red count at one day old was about two millions. When I first saw the baby at nine days old it was said to have improved considerably, but there was still a marked degree of anaemia. The progress of the blood condition is recorded on the accompanying table and chart. It will be seen that after the first few days there was a rapid improvement followed by a check in the third week. During the /
the next few weeks the anaemia was only slowly repaired. At the age of 23 weeks, however, the erythrocytes and haemoglobin were well above the normal level. The reticulocytes reached a high figure in the second week and it was a matter of surprise that the red count did not show any rise in the next two weeks. This points to the continuation of a more severe haemolysis than even the check in the erythrocyte curve suggests. The state of the curves at $6\frac{1}{2}$ weeks indicates that haemolysis was still proceeding at that time.

Spleen.- Never palpably enlarged.
Liver.- Never enlarged.
Feeding.- Breast fed. Not weaned when last seen at 23 weeks.

Weight and General Progress.- General condition and weight course good throughout, when last seen a picture of health. The slow improvement of the anaemia appeared to have no retarding influence.

Treatment.- Paternal blood, 10 c.c. intramuscularly, on day of birth. The liver and iron therapy of the first fortnight and the lack of any therapy thereafter would seem to be reflected in the curves on the chart, but a study of some of those which never had any treatment makes this seem doubtful.
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<th>Age in Days</th>
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CASE No. 12.

Simpson Maternity Hospital.

Mild Jaundice: Haemolytic Anaemia.

Baby T. Female. Born 21.10.37. RECOVERED.

Clinical Notes.— Second child.

Family History.— First child showed no evidence of gross neonatal disorder. No miscarriages.

Birth.— Spontaneous delivery following a normal pregnancy. Weight 6 lb. 2 oz.

Jaundice.— Appeared at a few days old, apparently of the normal physiological type and attracted no particular attention; it vanished at a fortnight old.

Anaemia.— When the jaundice disappeared a definite degree of anaemia was noticed, during the first few days it became more severe, the pallor of the lips being particularly striking. The first blood examination was done on the sixteenth day and revealed a fairly severe macrocytic anaemia. The progress of the blood condition is given in the accompanying table and chart. It will be seen that a /
a slight relapse occurred in the eighth week, and that the red count and haemoglobin had attained a normal level at the age of four months. The reticulocyte kick associated with relapse is interesting; I do not think it was the result of the liver extract so much as a physiological response to the relapse.

Spleen.—Never palpably enlarged.

Liver.—Never enlarged.

Feeding.—Breast milk by bottle during jaundiced period when appetite poor and drowsy. Supplementary feeding from third to eighth weeks when finally weaned.

Weight and General Progress.—Gain slow until two and a half weeks, satisfactory thereafter, the appetite and vitality being good. Weight at 16 weeks was 14 lbs.

Treatment.—Indicated on the chart. Iron was continued for another month. No therapy until one month when spontaneous recovery well established: subsequent administration of liver and iron appeared to have little influence on the course of events.
<table>
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<tr>
<th>Age in Days</th>
<th>R.B.C. Millions per Cu. Mm.</th>
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- Transfusion.
CASE No. 13.

Simpson Maternity Hospital.

Acute Haemolytic Anaemia.

Baby P. Male. Born 7.6.38. RECOVERED.

Clinical Notes.- Second child.

Family History.- First child apparently normal in infancy. No miscarriages.

Birth.- Spontaneous delivery following a normal pregnancy. Weight 6 lbs. 9 ozs.

Jaundice.- None.

Anaemia.- Pallor first noticed when six days old, it rapidly became extreme, the red count falling to 700,000 two days later when a highly macrocytic anaemia was demonstrated. The waxen pallor at that stage was alarming; even the lips were almost white; the strength and vigour and the loud lusty cry afforded a great contrast to the infant's appearance and compelled attention. The progress of the blood condition is recorded in the accompanying table and chart. Barely a week after the initial transfusion a slight improvement was evident but this was quickly followed by a sharp relapse which prevented the second transfusion.
transfusion from raising the erythrocyte level. After two weeks there was a sharp rise of reticuloocytes and a steady rise of haemoglobin, followed in a few days by a rapid augmentation in the number of red cells. A lag occurred in the sixth week and around three months; no count was made between the ages of thirteen weeks and thirty-two weeks, at the latter age the blood picture was normal in all respects.

Spleen.—Greatly enlarged, it was three finger breadths below the costal margin at one month old; it reached to the umbilicus and the iliac crest. The spleen did not recede to the costal margin for another six weeks.

Liver.—Slightly enlarged, it extended to two finger breadths below the costal margin at the age of a month.

Feeding.—Breast fed for five weeks, when weaned owing to mother developing acute rheumatic fever.

Weight and General Progress.—The weight began to rise on the fourth day and with the exception of a slight lag at a week rose steadily until the eleventh day; thereafter there was a loss of a few ounces which was not made good for almost a fortnight, after /
Fig. 21. Case 13 at 7½ months.
Weight 19 lbs.
after which there was a satisfactory steady gain in weight. At 32 weeks the child weighed 19 lbs. and was a picture of health (see photograph). Upper respiratory catarrh and a muco-purulent rhinorrhea developed at two weeks old and persisted for about ten days; there was considerable oedema around the external nares, but the infant's vitality remained unimpaired. Could this have been responsible for the check of the initial improvement and the relapse which followed?

Treatment.- Indicated on the chart. Note the striking result of the first transfusion, which was a life saving measure, might have been larger; also the apparent ineffectiveness of the second transfusion owing to its coinciding with a relapse, and the doubtful value of liver therapy.
I wish to express my gratitude to Professor Charles McNeil for his interest and encouragement during this investigation. My thanks are also due to the Staff of The Royal Maternity Hospital, The Royal Hospital for Sick Children, The Elsie Inglis Maternity Hospital and to all who have so willingly given their assistance at all times. My special thanks are due to Miss Hamilton for her secretarial skill.