Papers and Originals

Immunological Diseases and Pregnancy*

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To appreciate the happenings when an immunological disease occurs in pregnancy it is necessary to have some information on placental and foetal physiology in relation to antibodies, which has been extensively studied in recent years (see Freda (1962) for review). Though the foetus progressively acquires immunological competence *in utero* (Epstein, 1965), it does not reach full immunological maturity until some time after birth, and most of the foetal gamma-globulin appears to be of maternal origin. This gradually disappears in the weeks following birth and the total gamma-globulin reaches a minimal level at about four months, whereafter the level slowly rises again from the infant's own production. While antibodies of the gamma-globulin group of relatively small molecular size and low sedimentation constants (7-Svedberg (S) units) traverse the placenta particularly readily, it seems to be only those belonging to the gamma-2-globulin group that are readily transferred—others of comparable size do not pass, or they pass only in very small amounts. There is in fact an impressive accumulation of evidence that the important factor controlling a protein molecule's transfer is its configuration rather than its size; for example, 4S proteins, which happen to be responsible for thyroxine-binding, apparently do not cross the placenta (Robbins and Rall, 1960).

On purely theoretical grounds, based on what is known about antibody behaviour, it would be reasonable to predict the occasional occurrence in the foetus of a transient form—lasting up to about four months—of a maternal disease when that disease happened to be due to a circulating antibody of the IgG globulin component. The transient nature of the neonatal manifestations would, of course, be dependent upon no irreversible destruction of vital tissue taking place. Furthermore, it would not be expected that neonatal manifestations would be evident in a disease due to cellular or "fixed" antibodies.

It is customary to divide diseases on which there is evidence of primary immunological mechanisms into isoimmune and autoimmune, according to whether the antagonistic effect is against an antigen of another individual of the same species ("iso") or a "self" antigen ("auto"). These are, however, not mutually exclusive groups of disease processes, as is pointed out below.

Current medical interest is centred upon autoimmunization rather than isoimmunization. The mechanisms of isoimmunity have been to a large extent established, but it so happens that their main manifestations concern red blood cells, and for a variety of reasons we know vastly more about red-cell antigens and their antibodies than we do about the immunology of any other system. In addition, the fact that the antibodies are produced by one individual and exert their effect in the system of another has made it possible to elucidate their effects with greater precision than in autoimmunity. It may therefore be of some value to those whose thoughts are largely concerned

with diseases which are possibly autoimmune to contemplate afresh our state of knowledge with regard to isoimmune processes.

Isoimmunization

Rhesus Isoimmunization

Though rhesus sensitization is the most important immunological disease in obstetric practice, I shall not discuss it in detail but merely consider it in general terms, for it is of course almost exclusively a problem of obstetric and paediatric practice. It is the most classical example of an immunological disease known today; it represents, as Medawar (1960) succinctly put it, the "immunological repudiation by the mother of her unborn child." Since the discovery of the rhesus factor and its association with haemolytic disease the exact immunological system has been worked out with elegant precision (Fig. 1). A rhesus-negative mother carrying a child of a rhesus-positive father may be sensitized to the rhesus factor if a significant leak of foetal cells occurs across the placental barrier, as can be demonstrated by the Kleihauer technique (Kleihauer, Braun, and Betke, 1957). Even if a significant foeto-maternal haemorrhage occurs, however, sensitization of the mother will be very unlikely to occur if the foetal blood is of an ABO group unacceptable for donation to the mother.

This effect, first noted by Levine (1943), has formed the basis of the attempts at prevention of rhesus sensitization introduced in this country by Clarke and his colleagues in Liverpool (Clarke, Finn, McConnell, and Sheppard, 1958; Finn, 1960; Finn, Clarke, Donohoe, McConnell, Sheppard, Lehane, and

FIG. 1.—Diagrammatic representation of the usual mechanism of production of rhesus haemolytic disease in which at least four individuals are involved.

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Kulke, 1961; Clarke, Donohoe, McConnell, Woodrow, Finn, Krevans, Kulke, Lehane, and Sheppard, 1963; Woodrow, Clarke, Donohoe, Finn, McConnell, Sheppard, Lehane, Russell, Kulke, and Durkin, 1965; Clarke and Sheppard, 1965) and in the United States by Freda and his associates (Freda and Gorman, 1962; Gorman, Freda, and Pollack, 1962, 1965; Freda, Gorman, and Pollack, 1964, 1965) on the assumption that the naturally occurring ABO antibodies affected the foreign red cells in such a way as to prevent the rhesus (D) antigen expressing itself to the extent of causing sensitization. They have developed the apparently paradoxical approach of giving anti-D to the rhesus-negative mother to render immunologically inactive any foreign D-positive cells in her circulation, thus preventing active production of the very anti-D antibody which has been injected. The passively acquired antibody gradually clears from the circulation in a few months and is unlikely to have any ill effect on a subsequent child. This approach has brought very encouraging preliminary results (Clarke and Sheppard, 1965; Freda *et al.*, 1965), and there seems every reason to expect that it is capable of reducing the incidence of rhesus sensitization very considerably. It is not to be expected, however, that this will prevent rhesus sensitization in pregnancy completely.

Furthermore, the difficulties of applying this procedure on a wide scale are not small. It has been estimated that a matter of considerably more than 120,000 donations per annum of the appropriate quality of high titre anti-D would be necessary to apply this technique on a general scale in this country (W. d'A. Maycock, personal communication, 1965). In addition, the problem remains of dealing with the proportion of women who become sensitized by transplacental bleeds in the course of pregnancy rather than at parturition, and it has been suggested that antibody may be given during pregnancy in a form which will not cross the placenta or in a dosage that will not harm the foetus (Gorman *et al.*, 1965). Should prophylactic treatment with anti-D in pregnancy become the rule the demand for anti-D serum would become even greater. In these circumstances there would be considerable saving if, in cases in which the father was rhesus-positive but was thought to be heterozygous for "D," it could be predicted whether the foetus *in utero* was rhesus-positive or rhesus-negative. Ducos (1958) has claimed to be able to predict this with accuracy on specimens of amniotic fluid by means of an indirect antibody-adsorption technique applied to the centrifuged cell deposit. We have experimented with this technique over a prolonged period, but, while the ABO group of the foetus could be predicted with accuracy by the method, we were unable to achieve results with regard to the D factor (Scott and Coulson, 1966). If, however, it can by this technique be discovered that the foetus is incompatible with the mother on an ABO basis, there would be no indication to give anti-D, as the natural protection afforded by the ABO incompatibility would be adequate.

Prophylactic Approaches

We still do not know what factors other than ABO incompatibility influence the chance of sensitization occurring when a given quantity of D-positive cells enters the d-negative individual's circulation. It may be, as suggested by Banner (1964), and as supported by the observations of Callender and Race (1946), Collins, Sanger, Allen, and Race (1950), and Creger, Choy, and Rantz (1961), that when there are other immunological disorders present the individual is excessively reactive to antigens of all sorts.

A recent patient was pregnant for the first time at 30 years. She had a history of diabetes since the age of 10 years, hypertension and albuminuria from 18 years, severe thyrotoxicosis from 20 years, and diabetic retinopathy diagnosed at 21 years, when an incomplete hypophysectomy was performed and followed by relief of the thyrotoxicosis. She had had no previous transfusions or blood injections. When her first blood specimen was tested at 25 weeks

she was found to be group O, Rh positive (phenotype CcDee), with anti-c antibodies present. Her husband was group O, Rh negative (genotype cde/cde). A baby weighing 4 lb. 13 oz. (2,183 g.) was delivered by caesarean section and required two exchange transfusions.

Advances on this front may open the way to other prophylactic approaches. It may be, for example, that, at certain times of life, if introduced to the rhesus factor the individual is not only unresponsive but could be rendered tolerant. It has long been assumed that intramuscular injection of rhesus-positive blood to rhesus-negative babies given in the neonatal period, as it used to be for a variety of reasons, was a potent source of sensitization. Data on this point are remarkably hard to obtain, but we have failed to find any instance from following up individuals given such injections 20 to 30 years ago. For example, a child born on 4 December 1940 was given 12 ml. of its mother's blood at 60, 62, and 64 hours. At 72 hours 12 ml. of its father's blood was given. Twenty years later the blood groups were checked; mother, A rhesus positive; father, B rhesus positive; child, AB rhesus negative, no antibodies present. It is not beyond the bounds of possibility that immunological tolerance to the rhesus factor could be induced with a series of injections, beginning at birth, of rhesus-positive blood to rhesus-negative babies.

If I may be permitted a prediction in this field it would be to the effect that the ultimate solution to this problem will be to administer chemical substances similar to those which inactivate anti-D *in vitro*. Boyd and Reeves (1961) showed that colominic acid, a polymer of *N*-acetylneuraminic acid, was an inhibitor of rhesus antibodies. Dodd, Bigley, Nancy, Johnson, and McCluer (1964) reported the potent inhibitory effect of certain brain gangliosides, the chemical structures of which had previously been suggested (Kuhn and Wiegandt, 1963). These pieces of knowledge permit consideration of the chemical interaction of the inhibitors at molecular level. For inhibitory potency it appears probable that at least three chemically reactive substituent groups are required—the acetylamino group of *N*-acetylglucosamine plus the carboxylic and *N*-acetylamino groups of *N*-acetylneuraminic acid. Construction of a Catalin model revealed that the three substituent groups are so located spatially that a similar arrangement could be achieved with three groups as substituents in a hypothetical six-membered ring system. We are currently investigating the inhibitory properties of readily available chemicals of related structure, and preliminary results suggest that the effect is possibly one of interference with the organization of the antigens on the erythrocyte surface (Good, Scott, Speight, and Wood, 1966).

Maternal Effects

My last comment on the rhesus problem is to refer to the facet which first aroused my own interest in it—namely, that the influence of rhesus isoimmunization upon pregnancy is not entirely confined to the child. Analysis of a series of cases of hydrops foetalis showed a 50% incidence of a maternal illness indistinguishable from the pre-eclamptic syndrome (Scott, 1958). This has been confirmed in other series both before and since (Table I) (Kloosterman, 1947; Jann, 1954; John and Duncan, 1964). It is likely that this association will be seen less in the future, for with improved guides to the degree of severity of the haemolytic disease and the more radical lines of treatment adopted, such as intrauterine transfusion (Liley,

TABLE I.—Reported Incidence of Pre-eclampsia or a "Pre-eclamptic-like Syndrome" in Mothers of Hydropic Foetuses

Authors	No.	Incidence
Kloosterman (1947)	35	23 (65%)
Jann (1954)	162	117 (72%)
Scott (1958)	52	26 (50%)
John and Duncan (1964)	34	20 (59%)
Total	283	186 (66%)

1963), foetuses are rarely allowed to become hydropic or, if they do so, left to languish pointlessly *in utero*.

For the purposes of this discussion I draw attention to it only as an example of the way in which disease of one partner in a pregnancy can have ill effects upon the other and as a demonstration of the complex ramifications of even the simplest immunological process. In this particular case analysis of the situation suggested not that the immunological factor caused the pre-eclampsia directly but that the changes occurring in the placenta of the hydropic foetus consequent upon the haemolytic anaemia produced the pre-eclamptic effects, the principal evidence being that the pre-eclamptic state also tends to develop in mothers carrying hydropic babies *not* apparently due to immunological factors (Table II), while there is no evidence of an increased incidence of pre-eclampsia in pregnancies with rhesus isoimmunization in which the foetus is not hydropic (Scott, 1958; Jeffcoate and Scott, 1959; John and Duncan, 1964).

This fascinating "rebound" phenomenon in association with rhesus hydrops, illustrated diagrammatically in Fig. 2, highlights the fallacy inherent upon assuming a unique aetiology for every syndrome we clinicians regard as a disease and also the opposite pitfall of assuming that whenever a pathological factor operates it should produce the same effect. Though many

TABLE II.—Incidence of Pre-eclampsia in cases of Hydrops Foetalis Not Due to Rhesus or Other Detectable Forms of Isoimmunization Compared with Incidence of Pre-eclampsia in Pregnancies with Rhesus Isoimmunization but Foetuses not Hydropic—Data from Scott (1958) and Jeffcoate and Scott (1959)

	No.	Incidence of Pre-eclampsia
Non-rhesus hydrops cases	11	9 (82%)
Pregnancies with rhesus isoimmunization, but foetus not hydropic	172	8 (4.7%)

FIG. 2.—Diagrammatic representation of the interrelationship of rhesus isoimmunization, hydrops foetalis, and the pre-eclamptic syndrome.

babies are affected by rhesus antibodies *in utero*, only a minority show obvious effects at birth in the shape of hydropic change. On clinical examination the other affected babies do not even appear to be suffering from the same disease, and, but for our advanced serological techniques in this field, many affected cases would never be diagnosed clinically. While most cases of hydrops are caused by rhesus antibodies, a substantial minority are not so caused, and there is little to suggest that these have an immunological basis. All the cases of hydrops, whether due to isoimmunization or not, have this strong tendency to produce in the mother the pre-eclamptic syndrome; yet, of all the cases of the pre-eclamptic syndrome, only a very small proportion are so caused.

Here then is a three-stage disease process: (1) rhesus antibody production→(2) hydrops foetalis→(3) pre-eclamptic syndrome; only a proportion of cases make the progression at each stage, and at stages 2 and 3 they are joined by a small and a large group of cases, respectively, in which the aetiology of the state is different and almost certainly non-immunological. The tertiary effect (Fig. 3) represents a "feedback" from the site of effect of the antibodies (foetus) to their site of production (mother).

FIG. 3.—Diagrammatic representation of the materno-foetal relationship in cases of rhesus sensitization in which the rhesus antibodies lead to hydrops foetalis, and this, in turn, leads to a maternal pre-eclamptic syndrome.

Because of the distinction between the maternal and foetal systems, it has proved possible to define these various processes precisely; it may prove worth while to bear in mind this relatively concrete but complex situation when considering the apparently confusing data with regard to some autoimmune diseases.

Other Forms of Isoimmunization

The real wonder about the rhesus problem is not that foetal disease should occur as a result of maternal isoimmunization to this particular blood factor but that similar reactions do not occur to many of the paternally inherited genetic factors which the conceptus carries. It is not the case, however, that rhesus haemolytic disease is the sole example of isoimmune disease. Isoimmune disease involving the platelets (Harrington, Sprague, Minnich, Moore, Aulvin, and Dubach, 1953; Shulman, Aster, Pearson, and Hiller, 1962; Pearson, Shulman, Marder, and Cone, 1964) and also the leucocytes (Jensen, 1960) is recorded. These diseases are quite undramatic in their presentation and have relatively little clinical significance, but their existence means that foeto-maternal isoimmune disease occurs in relation to virtually all the circulating cells of the blood.

Autoimmune Diseases

In passing from the field of isoimmunity to autoimmunity, we move from relatively well-mapped territory to an area where

landmarks are few and unreliable. As in any developing area, disputation is rife and border controversies are common. I would, however, ask from you the one indulgence that in the meantime you accept as *possibly* autoimmune the diseases to which I shall refer. It must be admitted that the evidence cannot be regarded as conclusive with regard to any, but I hope to demonstrate that, viewed from the standpoint of the obstetrician, these diseases have certain remarkable features in common, consideration of which may be of some help in deciding the disease mechanism.

The relationship of autoimmune diseases to pregnancy may be considered with regard to the effect of the pregnancy upon the disease and the disease upon the pregnancy. In general most attention has been focused upon the former influence; for long the general uncritical assumption was that pregnancy could do nothing but harm, and this view received support from isolated case reports—recorded almost invariably because something untoward had happened.

This was corrected by Hench's (1938) observation of the high frequency of remission of rheumatoid arthritis in a significant series of cases, and only then was active consideration given to the possibility that anything beneficial to the maternal disease might happen in pregnancy. This of course led to the development of compound E by Hench, Kendall, Slocumb, and Polley (1949)—the classic example in modern times of an advance in medical knowledge brought about by observation of the happenings when pregnancy and a particular disease were associated. The impact of this on modern medicine cannot be disputed even though it is now seriously questioned whether the adrenocortical hormone changes are in fact responsible for the effect in pregnancy (Kaplan and Diamond, 1965; Nelson, 1965). Hench's observation of frequent improvement in pregnancy has been confirmed in the case of many diseases now thought to be immunological; in some there seems to be no obvious tendency to remission or relapse, but in virtually all a strong tendency to relapse in the puerperium has been recorded.

To take just one example, the cases of ulcerative colitis under the care of my colleague Professor John Goligher have recently been reviewed (de Dombal, Watts, Watkinson, and Goligher 1965) and when studied in conjunction with other reports and a control series of non-pregnant patients it was found that the relapse incidence was not increased in those who had pregnancies. When the timing of the relapses which did occur in association with pregnancy was considered it was found that these were particularly common in the three months post partum. It was suggested that steroids in gradually decreasing dosage in the puerperium may be of value to ward off these relapses.

I would like to direct your attention in more detail to three disease groups in which there appears to be a specific effect upon the pregnancy.

1. Idiopathic Thrombocytopenic Purpura

When an obstetrician is faced with a mother who shows a disorder manifesting a haemorrhagic tendency his immediate concern tends to be with the risk of her having a serious haemorrhage from the placental site. The main clinical point I wish to make in relation to idiopathic thrombocytopenic purpura is that there lurks in the shadow a much more sinister danger against which the obstetrician may fail to take all possible steps because of his morbid fear of post-partum haemorrhage.

My remarks on this disease are mainly based on a study by my colleague Dr. R. F. Heys (1966), in which 50 women of child-bearing age having the disease were reviewed. In this group 44 pregnancies occurred without maternal fatality. Thirty-eight of the pregnancies were in women who had previously had splenectomy performed; one splenectomy was carried out in the ante-partum period and one immediately after

delivery, so four patients completed pregnancy and puerperium without splenectomy. Pregnancy did not seem to affect the maternal prognosis in any particular way with regard to the frequency of relapse and remission.

The maternal risk is clearly not a large one and consideration of the literature confirms that this is so particularly in cases where splenectomy has preceded pregnancy. A different picture emerges if one considers the pregnancies that have not been preceded by splenectomy. When the maternal mortality rate of 7–11% (Robson and Davidson, 1960; Tancer, 1960; Goodhue and Evans, 1963) is contrasted with the death-rate in series of similar non-pregnant patients it is found to be about twice that in the non-pregnant group—4% (Heys, 1966).

Critical analysis reveals three specific and distinct maternal risks: (a) deterioration in late pregnancy unresponsive to medical treatment, leaving splenectomy as the last resort; in these circumstances the patient is usually seriously ill before splenectomy is undertaken and the operation is technically very difficult because of the presence of the large uterus; (b) massive purpura occurring consequent upon the straining efforts of the second stage of labour; the haemorrhages could conceivably involve a vital intracranial site; and (c) troublesome bleeding from tears or incisions in the lower genital tract—apart from this there is no increased tendency to post-partum haemorrhages, which is as one would expect in view of the fact that the main haemostatic mechanism is uterine retraction, independent of capillary and coagulation factors.

The practical inferences to be drawn from these are that "splenectomy before pregnancy" is a wise policy, that forceps delivery should be performed to avoid the straining of the second stage of labour, and that any perineal tears or incisions should be sutured expeditiously and carefully.

Table III shows the perinatal mortality in recorded series—which gives an overall rate of 16% in 210 cases. Here, unexpectedly, appears to lie the major risk of idiopathic thrombocytopenia in pregnancy. A possible explanation comes to light if the condition of the surviving infants is considered. Purpuric manifestations are common in the newborn of thrombocytopenic mothers and the observed incidence of thrombocytopenia has varied from 34 to 68% (Robson and Davidson, 1950; Peterson and Larson, 1954; Heys, 1966). The actual incidence of neonatal thrombocytopenia was almost certainly higher than this, as many of the babies did not have platelet counts performed. This evidence of involvement of the infant gradually disappears between 4 and 12 weeks after birth, and thereafter the children are haematologically normal. From an analysis of seven dead infants (Heys, 1966) it transpired that three upon whom necropsies were performed had intracranial haemorrhages, while one other had intracranial haemorrhagic signs attributed to asphyxia. It seems that when the baby is afflicted by the transient form of the maternal disease, minor, otherwise self-limiting, intracranial bleeds are apt to progress into major and fatal haemorrhages.

TABLE III.—Recorded Perinatal Mortality in Pregnancies Complicated by Maternal Idiopathic Thrombocytopenic Purpura

	Viable Infants	Deaths	Mortality Rate
Robson and Davidson (1950) ..	32	8	25%
Peterson and Larson (1954) ..	66	10	15%
Tancer (1960)	70	9	13%
Heys (1966)	42	7	17%
Total	210	34	16%

A striking feature is the fact that, in cases in which the mother has been apparently cured symptomatically and haematologically by splenectomy, infants are frequently born showing manifestations of transient neonatal thrombocytopenic purpura (Peterson and Larson, 1964; Heys, 1966).

This represents a most remarkable situation—a maternal disease with haemorrhagic manifestations has unexpectedly as its main risk in pregnancy not maternal haemorrhage but intra-

cranial haemorrhage in the child associated with a transient neonatal form of the disease; furthermore, this transient form may occur in a child born long after the mother is apparently cured by splenectomy.

The practical points to be taken from this are that all babies born to mothers who *have ever had* idiopathic thrombocytopenic purpura should be brought into the world with the greatest of gentleness—usually by low forceps delivery—and that they should all have platelet counts.

When one seeks understanding of these remarkable phenomena the only tenable explanation is that there is a humoral factor involved which predisposes to thrombocytopenia, which persists in the maternal system after splenectomy, which crosses the placenta, and which undergoes denaturation in the foetal system in the 12 to 16 weeks following birth.

This period of time, of course, corresponds to that predicted for a disease due to maternal IgG globulins. While there appears to be no proof that the humoral substance involved is an antibody, the suggestion of an autoimmune cause for idiopathic thrombocytopenic purpura (Harrington, 1957) is the only one which seems compatible with the facts as seen from an obstetric viewpoint. It is presumably possible for splenectomy to restore the maternal platelet levels permanently to normal, yet the noxious antibodies persist, cross the placenta, and produce thrombocytopenia in the infant who has a normally functioning spleen. If this be the true explanation we have here a disease process which is both autoimmune and isoimmune.

2. Myasthenia Gravis

Myasthenia gravis is characterized by voluntary muscle weakness increasing after exercise and apparently due to interference with passage of the impulse across the motor end-plate.

In pregnancy the evidence suggests little change in the myasthenic relapse incidence (Osserman, Kornfeld, Cohen, Genkins, Medelow, Goldberg, Windsley, and Kaplan, 1958; Osserman, 1960), though myasthenic crises, if they occur, may be more difficult to manage, and dosage of anticholinesterase preparations may require frequent adjustment. There is no general indication for therapeutic abortion nor is there anything to suggest that the usual anticholinesterase preparations administered increase the tendency to spontaneous abortion, though this is a theoretical risk. Edrophonium chloride (Tensilon) is a short-acting anticholinesterase which can be used to decide whether the patient requires more or less anticholinesterase drug; and McNall and Jafarnia (1965) suggest that it should not be used intravenously in the early stages of pregnancy lest abortion be provoked. The first stage of labour is usually entirely normal, but low forceps delivery under local anaesthesia is desirable to relieve the mother of the voluntary muscle effort required in the second stage.

I make no apology for referring particularly to the occurrence of myasthenia in the offspring of myasthenic mothers, for in a recent authoritative British text in obstetrics appears the statement that infants born to myasthenic mothers are *never* affected. In fact the first report was in 1942 by Strickroot, Schaeffer, and Bergo, and by 1964 Stern, Hall, and Robinson found 34 cases recorded and added two of their own, while McNall and Jafarnia (1965) quote an incidence of 20%. Of 11 pregnancies in myasthenics in my own experience, two cases were of the neonatal form. The duration may vary from 10 days to 13 weeks, with an average of three weeks (Stern *et al.*, 1964). It may occur in babies of women who have undergone thymectomy (van der Geld, Feltkamp, van Loghem, Oosterhuis, and Biemond, 1963).

The practical importance of appreciating the occurrence of this neonatal form of the condition is considerable in that, if diagnosis is promptly made and the infant appropriately treated for a few weeks, it will subsequently lose the myasthenic taint

and become normal. If the existence of the condition is *not* appreciated then attempts at maintaining artificial respiration may be abandoned on the assumption that there is irreversible cerebral damage.

General lack of muscle tone is the main feature of neonatal myasthenia, with shallow or absent respirations and relative inability to swallow, suck, or cry, with a weak or absent Moro response; unlike the adult form, ptosis is not a feature. The onset may be delayed for up to one or two days after birth, presumably owing to the influence of the anticholinesterase preparations administered to the mother; these drugs are also apt to produce an excess of tenacious mucus. Immediate management should be to suck out the mucus, establish an airway, and apply artificial respiration. The appropriate procedure is to test the baby's response to edrophonium chloride 0.5 mg. (0.05 ml.) subcutaneously. If the infant shows return of muscle tone with this, then maintenance dosage with one of the longer-acting preparations should be given, together with atropine to counteract the muscarine effects. The delayed onset of the muscle-weakness is a great pitfall, and it is vital that any apparently unaffected baby should be observed closely for the first 48 hours of life lest respiratory failure should develop.

Here, then, is a second disease showing the theoretical type of foetal effects postulated in a maternal disease caused by immune globulins, and, in this case also, much independent evidence has accumulated, pointing to an immune mechanism, since Simpson (1960) presented a hypothesis that myasthenia gravis was an autoimmune disease. It is probably a fair simplification to say that there is now a great deal to suggest that immunological processes are involved to a major extent, but no single antigen-antibody system has been defined which in itself can account for all cases (Beutner, Witebsky, Ricken, and Adler, 1962; Simpson, 1964; *Brit. med. J.*, 1965; Sahay, Blendis, and Greene, 1965). Beutner *et al.* (1962) suggested that the neonatal form might be due to passive transfer of maternal antibodies, and, although van der Geld *et al.* (1963) and Stern *et al.* (1964) failed to detect antibodies, it seems on the evidence to be the most likely mechanism.

3. Thyroid Disease

The exact role of autoimmunity in thyroid disease is as yet undefined, and the classic example of an autoimmune process—Hashimoto's disease (Roitt, Doniach, Campbell, and Hudson 1956)—is not often found in association with pregnancy. I have seen only one case, and that was remarkable for the fact that there was also evidence of true Addisonian pernicious anaemia—the only example of that disease, now itself suspected to be an autoimmune one, which I have encountered in association with pregnancy. Myxoedema, in the aetiology of which autoimmunity apparently plays at least a part, is commonly associated with infertility, and little information is available about it in relation to pregnancy except for a suggestion that chromosomal non-dysjunction abnormalities occur with increased frequency—one postulate being that the autoantibody may react with complementary deoxyribonucleo-protein, interfering with chromosomal separation at cell division (Fialkow, 1964; Burch, Burwell, and Rowell, 1964; Fialkow, Uchida, Hecht, and Motulsky, 1965).

Thyrotoxicosis, on the other hand, is a relatively common clinical syndrome of the child-bearing years and is not infrequently seen in association with pregnancy. Hawe and Francis (1962) reported on 70 cases seen in Liverpool in 15 years, and much of my own experience of the disease was with this case material. A number of important physiological changes occur in relation to thyroid activity in pregnancy, but the overall result is that effective thyroxine activity is often less in the pregnant woman. Reports of elevation of the basal metabolic rate almost certainly reflect foetal metabolism rather than thyroxine over-

activity (Freedberg, Hamolsky, and Freedberg, 1957). This interpretation of the physiological changes is supported by the clinical improvement of many cases of thyrotoxicosis in mid-pregnancy.

Also relevant is the evidence that thyroxine does cross the placenta, at least to some extent, in late pregnancy (Myant, 1958); that thyroid stimulating hormone probably does not cross the placenta (Peterson and Young, 1952; McKenzie, 1964); and that antithyroid drugs not only cross the placenta but are excreted in the milk (Williams, Kay, and Jandorf, 1944). While the antithyroid drugs are capable of causing complete suppression of the foetal thyroid, with resultant cretinism (Keynes, 1952; Hawe and Francis, 1962) and also foetal goitres (Keynes, 1952; Piper and Rosen, 1954), there is nothing to suggest that, used in moderate dosage in pregnancy, they are likely to cause serious harm to the foetus. It is, however, sensible to avoid breast-feeding.

The main point of debate with regard to management is the place of surgery as opposed to medical treatment. This must of course reflect the policy of those concerned with thyrotoxicosis in their treatment of the non-pregnant patient. If surgery after a short course of medical "preparation" is favoured there seems to be a great deal to support the argument of Hawe and Francis (1962) that pregnancy is a good rather than a bad time for it, and in particular the "peaceful middle trimester" is opportune both from the point of view of the thyrotoxicosis and from that of the pregnancy. If surgery is delayed until after delivery deterioration is likely to take place, and the mother has the additional worry of organizing the care of the young addition to the family.

There is little call for alteration in the obstetric management, but the possibility of foetal goitre causing hydramnios or abnormality of presentation should be borne in mind.

Thyrotoxicosis and Pregnancy

The most intriguing aspect of the relationship of thyrotoxicosis and pregnancy is the occasional occurrence of transient thyrotoxicosis in the newborn baby. The late Clifford White (1912) observed that a baby born to a thyrotoxic mother exhibited all the signs of the maternal disease; not only that, he recorded evidence of this situation before birth by the presence of a foetal tachycardia of the order of 200 beats a minute. By so doing he presented clinical workers in the thyroid field with a lead regarding the mechanisms operating in the disease—a lead which was not profitably integrated with other observations until half a century later.

In the interval the correctness of White's original observation was confirmed by at least 16 unequivocal reports of the same neonatal form of the disease (McKenzie, 1964), and another 20 probable examples (Paatela, 1960; Landucci-Rubini, and Battistini, 1962; Saxena, Crawford, and Talbot, 1964; Patterson, 1964; Adams, Lord, and Stevely, 1964; Mahoney, Pyne, Stamm, and Bakke, 1964; Zaidi, 1965).

Transient neonatal thyrotoxicosis is, however, rare; Hawe and Francis (1962) found only one case in 70 births to thyrotoxic mothers, while Saxena *et al.* (1964) found only one out of 70 cases of childhood thyrotoxicosis. Cases usually present at birth as underweight "jittery" babies with tachycardia, tachypnoea, goitre, exophthalmia, and diarrhoea; some show cardiac failure, which may of course prove fatal, the recorded mortality being of the order of 25%. If antithyroid drugs have been given to the mother the appearance of thyrotoxic manifestations can be delayed for up to eight days (Riley and Sclare, 1957; Sclare, 1960). The delay in onset in babies born to women receiving drug therapy, together with the fact that the condition may occur in women whose disease has been clinically completely cured by surgery (Koerner, 1954—in this case the mother had been rendered myxoedematous) or drugs, represent the main diagnostic pitfalls. These are of course features

reminiscent of neonatal thrombocytopenia and myasthenia gravis, and the duration—usually less than three months (Adams *et al.*, 1964)—is also similar.

The above are not the only features of similarity in these diseases. Thrombocytopenia has been recorded in a case of neonatal thyrotoxicosis by Mahoney *et al.* (1964) and in two cases by Zaidi (1965). These three infants also had hepatosplenomegaly, which, with jaundice, has also been recorded in at least three other affected infants (Mahoney *et al.*, 1964). Woodruff (1940) has discussed thrombocytopenia in relation to adult thyrotoxicosis and suggested a toxic action on the platelets.

Keynes (1952) delivered a Blair Bell lecture to the Royal College of Obstetricians and Gynaecologists on thyrotoxicosis and myasthenia gravis in pregnancy; his reason for associating the two conditions was that he was interested in the surgery of thyroid and of thymus, but he did observe that the thymus was often enlarged in thyrotoxicosis. In recent years, however, the frequent occurrence of the two diseases in the same patient has received much attention (Simpson, 1960; Sahay *et al.*, 1965), as also has the similarity of the thymus changes (Irvine, 1964), and while much elucidation is still required there can be little doubt that the two diseases are in some way related.

Sinclair and Silverman (1964) have suggested that if information on neonatal cases is strictly recorded it may be possible to obtain data on the influence of thyroid activity on foetal growth. Fig. 4 shows the birth weights of cases recorded by them, together with others, with adequate data plotted against maturity in relation to the Colorado standards of weight distribution (Lubchenco, Hansman, Dressler, and Boyd, 1963), and it will be seen that the weights in general fall short of the expected. This is not invariably so with babies of thyrotoxic mothers, as demonstrated by a recent case. This patient, pregnant for the second time, developed apparent eclamptic convulsions at 26 weeks' gestation. After control of the fits with bromethol an unexplained tachycardia persisted, and it eventually became clear that this was due to thyrotoxicosis. Long-acting thyroid stimulator was not detected in the maternal serum. Under medical treatment the thyrotoxicosis settled, as did all signs of toxæmia, and eventually a baby was delivered weighing 11 lb. 11 oz. (5,300 g.), showing no signs of thyrotoxicosis. Glucose tolerance was normal. The cause of the fits was eventually demonstrated to be a cerebral astrocytoma.

FIG. 4.—Birth-weights in relation to maturity of infants recorded in the literature as having neonatal thyrotoxicosis (after Sinclair and Silverman, 1964) shown in relation to the Colorado weight standards (Lubchenco *et al.*, 1963).

White's observation of foetal tachycardia prior to delivery has been confirmed by Javett, Senior, Braudo, and Heymann (1959) and Mahoney *et al.* (1964). Keynes (1952) recorded a case in which the maternal thyrotoxicosis had been treated surgically but the baby was born with obvious exophthalmos though euthyroid.

Thyroid Stimulation

Within the past decade information has been accumulating concerning a thyroid stimulator found in the blood of thyrotoxic patients, distinguishable from thyroid stimulating hormone by a number of features, including its more prolonged action (Adams and Purves, 1956; McKenzie, 1958, 1960, 1961; Munro, 1959; Major and Munro, 1960; Adams, 1961, 1965), and this has been called "long-acting thyroid stimulator" (Adams, 1961). The present evidence is that it is an IgG globulin and possibly an antibody (Kriss, Pleshakov, and Koblin, 1964; Adams, 1965); that it crosses the placenta (McKenzie, 1964) and stimulates thyroid activity in an identical way to thyroid stimulating hormone but for a longer period. If this be the case, then, by being the first metabolically active gamma-globulin, it opens a new field of clinical pathology. It is of course similar to the type of antibody action postulated by Simpson (1960) for myasthenia gravis, but in that case the effect is depressant rather than stimulant.

The evidence with regard to the occurrence of long-acting thyroid stimulator in thyrotoxicosis is that it has been demonstrated in 30% hyperthyroid sera (Major and Munro, 1962) and in 65% gamma-globulin concentrates (Purves and Adams, 1961). McKenzie (1961) recorded it in 78% of 76 cases with thyrotoxicosis or exophthalmos. The sensitivity of the assay is such that long-acting thyroid stimulator is almost certainly present in a higher proportion of cases than is detectable with present techniques. With transient neonatal thyrotoxicosis, assays on the baby's serum have been reported positive in four cases by McKenzie (1964); in a fifth case no long-acting thyroid stimulator activity was detected, but the sample of infant blood was insufficient for the usual assay technique. The evidence is strong that long-acting thyroid stimulator is a cause (Adams, 1965) if not *the* cause of thyrotoxicosis.

Thus in each of the three considered conditions which show the predicted pattern in relation to pregnancy for a disease mediated by a gamma-globulin, there is independent evidence for such a mechanism, this being particularly strong in relation to thyrotoxicosis.

Transient Neonatal Diabetes

If the idea be accepted that the occurrence of a transient neonatal form of a disease such as has been considered is suggestive of an immunological mechanism, the question arises whether any other diseases present this feature and whether its occurrence might be taken to suggest the possibility of an immunological basis. One example comes to mind—transient neonatal diabetes. Hutchison, Keay, and Kerr (1962) described a group of four newborn infants with this condition. There had been previous reports of isolated cases (Kitselle, 1852 ;

FIG. 5.—Birth-weights in relation to maturity of infants recorded in the literature as having transient neonatal diabetes, shown in relation to the Colorado weight standards (Lubchenco *et al.*, 1963).

Ramsey, 1926; Lawrence and McCance, 1931; Strandqvist, 1932; Nawrocka-Kańska, 1952; Arey, 1953; Keidan, 1955; Engleson and Zetterqvist, 1957), and a further case was described by Sweetnam and Sykes (1962). These babies were born to normal women with no significant family history of diabetes; they were under weight at birth in relation to maturity (Fig. 5) and failed to thrive: the picture, in fact, of what the obstetrician often refers to as "placental insufficiency" and the paediatrician as "dysmaturity." The presentation is such a non-specific one, and obtaining urine for testing from newborns was such a difficult procedure until the recent introduction of "tape" testing, that there can be little doubt that the diagnosis has often been overlooked, and death attributed to such causes as prematurity, post-maturity, inanition, marasmus (Hutchison *et al.*, 1962), or placental insufficiency.

These infants, if adequately treated with insulin, not only survived but shortly became non-diabetic. In 10 of the 13 cases with adequate data the glycosuria cleared or insulin treatment was stopped within three months of birth; in three others the administration of insulin was continued for 7, 8, and 18 months (Fig. 6), but it is possible that it was not appreciated that the diabetic condition might be a temporary one and that insulin was continued unnecessarily. The common duration of this transient form of neonatal diabetes, then, corresponds with that of transient neonatal forms of diseases which seem likely to be due to a gamma-globulin. No rational explanation of the aetiology of this bizarre form of diabetes has been forthcoming, and, until one is, it would seem reasonable to suspect that the mechanism involved is transfer of an antibody from the mother which has this diabetogenic effect on the infant. The situation is of course different from the other diseases mentioned in that the mother in these cases is apparently healthy, but in thyrotoxicosis and idiopathic thrombocytopenic purpura neonatal forms can occur when the mother has been clinically completely cured.

FIG. 6.—Duration of glycosuria or insulin treatment in recorded cases of transient neonatal diabetes. It is probable that in some cases treatment was continued for longer than was strictly necessary.

Variable Incidence of Neonatal Involvement

On reviewing the spectrum of neonatal involvement in possible autoimmune diseases—running from frequent in thrombocytopenic purpura to rare in thyrotoxicosis—the question immediately poses why, assuming that the antibodies are globulins with similar characteristics, this disparity in the frequency of neonatal manifestations exists. A number of explanations suggest themselves.

1. It could be that more-prolonged stimulation is necessary to produce frank manifestations of thyrotoxicosis than thrombocytopenia, but the great majority of mothers with thyrotoxicosis have

the disease before the onset of pregnancy, and therefore the period of exposure will nearly always involve the whole pregnancy.

2. It could be that a higher level of antibody is required to produce the clinical manifestations in one disease than in another, but if this were so it would be expected that the occasional case of transient neonatal thyrotoxicosis which occurs would be a mild one. This does not seem to be the case, though McKenzie (1964) suggests that biochemical thyrotoxicosis may be commoner in newborns than the clinical syndrome.

3. It could be dependent upon the antibody configuration being specific for both mother and child and that the chance of this occurring depends upon genetic factors variable between the diseases under consideration. Yet, in thyrotoxicosis the evidence with regard to the antibody's nature—long-acting thyroid stimulator—and its prolonged stimulant action upon the thyroid is that it is *not* specific. In the case of transient neonatal diabetes, however, the most likely immunological explanation seems to be that if an antibody is concerned it has a special configuration specific for a foetal antigen and different from the mother's.

4. Possibly we are dealing not with diseases but with symptom-complexes of variable aetiology. I have not presented all the evidence, much of it apparently conflicting, on the immunological background of these diseases; in none of them has a specific antibody been demonstrated which would account for all cases. The possibility is that all of these conditions have a variable aetiology, sometimes immunological.

My tentative suggestion, bearing in mind the known situation I have referred to with regard to hydrops foetalis and iso-immunization, is that not only is the occurrence of a transient neonatal form of a maternal disease suggestive that the disease may on occasion be due to a humoral immunological factor, but also the frequency of the neonatal involvement may give some guide to the relative frequency with which such a factor is involved as compared with other aetiological mechanisms. It might be profitable to abandon the idea that each of the syndromes considered has a unique aetiology.

Runt Syndrome

The presentation in at least two of these neonatal conditions in which there is evidence suggestive of an immunological aetiology is similar to what is often loosely termed "placental insufficiency" or "dysmaturity"—with a baby, born underweight for the period of gestation, that fails to thrive. It seems far from improbable that there are other cases at present placed in these categories in which an immunological basis is responsible. As an alternative to the unsatisfactory "placental insufficiency" there would seem much to be said for the adoption of the term "runt syndrome" as used by Elliott (1964). "Runt" has a variety of social and biological connotations, but in general it carries a strong implication of a poorly developed offspring, and has recently come to imply an immunological disorder.

While, as already mentioned, it would not be likely that foetal effects would result from a maternal disease due to cellular or "fixed" antibodies, evidence is now being formulated that in certain exceptional circumstances cellular immune processes may operate to the detriment of the foetus. Recently A. D. Bain and I described the first case of XX/XY mosaicism or chimerism recorded in this country in a singleton (Bain and Scott, 1965). This bizarre chromosomal anomaly is remarkable for the fact that it cannot be explained on the basis of non-dysjunction or anaphase lag, as is the case with other chromosome mosaics and abnormalities in number. At that time what seemed the possible aetiological mechanisms were reviewed, and, as birth records revealed no possibility of a foetus-papyraceus co-twin, it was suggested that this was probably the result of a bizarre accident of fertilization whereby two sperms—one X-bearing and one Y-bearing—fertilized an ovum nucleus, together with an unexpelled second polar body. Following this, however, Taylor and Polani (1965) suggested, on the basis of their findings of XX/XY mosaicism in blood

and thymus of an abortion, that an escape of maternal (XX) cells into the circulation of a male (XY) foetus had occurred, with colonization of the embryo and its death by a form of graft-versus-host reactions—in other words, "runt disease" as known to the experimental immunologists (Billingham, 1959). Kadowaki, Thompson, Zuelzer, Woolley, Brough, and Gruber (1965) have since described another example of XX/XY chimerism, apparently restricted to immunologically competent cells in a phenotypically male child of low birth-weight who failed to thrive and died at 16 months. There was thymic aplasia with dysgammaglobulinaemia and relative lymphoid hyperplasia with lympho-histiocytic infiltration of the spleen. This picture—even more typical of runt disease—could be attributed to an intrauterine graft of maternal cells reacting against the infant host, a possibility forecast by Billingham (1964).

Conclusion and Summary

The theoretically predictable behaviour in pregnancy of an autoimmune disease due to an IgG globulin capable of crossing the placenta—namely, a transient neonatal form of the adult disease—is found in some cases of idiopathic thrombocytopenic purpura, myasthenia gravis, and thyrotoxicosis. The cases showing this may be examples of these three clinical syndromes which have such an aetiology, while others may have a different, possibly non-immunological, basis. Support for this concept is obtained from consideration of rhesus isoimmunization in relation to hydrops foetalis and pre-eclampsia, which also suggests that it is inappropriate to expect the same clinical effects in all cases with a particular antibody. It is suggested that transient neonatal diabetes may also represent an immunological process.

The temporary failure of the infants to thrive in these conditions may be regarded as a form of runting, and, as other cases of so-called "placental insufficiency" or "dysmaturity" may have a similar basis, the use of the term "runt syndrome" in these circumstances is suggested.

While cellular rather than humoral runting is probably uncommon in humans, evidence is put forward from chromosomal and other studies that it may occur, possibly by a mother-to-foetus transfer of immunologically competent cells. Further search for such occurrences may help to elucidate hitherto unexplained failure of growth and development of the foetus and newborn.

There seems good reason to believe that future studies of disease states in pregnancy conducted with a realization of the potential of immunological anomalies presenting distinct effects at this time will reveal further secrets of the scope and mode of action of immunological processes.

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Intrahepatic Typhoid Carriers

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Cholecystectomy was first advocated in the treatment of the biliary typhoid carrier by Dehler (1907). Whipple (1929) thought that it was successful in approximately 70% of cases, and this has been confirmed in other series reported from Europe and the United States of America (Browning, 1933; Humbert, 1959; Tynes and Utz, 1962). Wilson and Miles (1964), in explanation of the failure, stated: "It is not clear

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in what part of the intestinal tract the focus of infection persists, though there is reason to believe that it is in the biliary passages of the liver." Erlik and Reitler (1960) reported that bile from the hepatic ducts of four carriers contained *Salmonella typhi*, and that, following cholecystectomy, bile obtained through a T-tube inserted into the common bile-duct of three of these carriers contained the same organism. They concluded that their patients were intrahepatic carriers. Tynes and Utz (1962) included in their series two patients in whom